Multistate Outbreak of *Fusarium* Keratitis Associated With Use of a Contact Lens Solution

Douglas C. Chang, MD
Gavin B. Grant, MD, MPH
Kerry O'Donnell, PhD
Kathleen A. Wannemuehler, MSc
Judith Noble-Wang, PhD
Carol Y. Rao, PhD
Lara M. Jacobson, MD
Claudia S. Crowell, MD
Rodlescia S. Sneed, MPH
Felicia M. T. Lewis, MD
Joshua K. Schaffzin, MD, PhD
Marion A. Kainer, BS, MS, MPH
Carol A. Genese, MBA
Eduardo C. Alfonso, MD
Dan B. Jones, MD
Arjun Srinivasan, MD
Scott K. Fridkin, MD
Benjamin J. Park, MD
for the *Fusarium* Keratitis Investigation Team

Context *Fusarium* keratitis is a serious corneal infection, most commonly associated with corneal injury. Beginning in March 2006, the Centers for Disease Control and Prevention received multiple reports of *Fusarium* keratitis among contact lens wearers.

Objective To define the specific activities, contact lens hygiene practices, or products associated with this outbreak.

Design, Setting, and Participants Epidemiological investigation of *Fusarium* keratitis occurring in the United States. A confirmed case was defined as keratitis with illness onset after June 1, 2005, with no history of recent ocular trauma and a corneal culture growing *Fusarium* species. Data were obtained by patient and ophthalmologist interviews for case patients and neighborhood-matched controls by trained personnel. Available *Fusarium* isolates from patients' clinical and environmental specimens were genotyped by multilocus sequence typing. Environmental sampling for *Fusarium* was conducted at a contact lens solution manufacturing plant.

Main Outcome Measures Keratitis infection with *Fusarium* species.

Results As of June 30, 2006, we identified 164 confirmed case patients in 33 states and 1 US territory. Median age was 41 years (range, 12-83 years). Corneal transplantation was required or planned in 55 (34%). One hundred fifty-four (94%) of the confirmed case patients wore soft contact lenses. Forty-five case patients and 78 controls were included in the case-control study. Case patients were significantly more likely than controls to report using a specific contact lens solution, ReNu with MoistureLoc (69% vs 15%; odds ratio, 13.3; 95% confidence interval, 3.1-119.5). The prevalence of reported use of ReNu MultiPlus solution was similar between case patients and controls (18% vs 20%; odds ratio, 0.7; 95% confidence interval, 0.2-2.8). *Fusarium* was not recovered from the factory, warehouse, solution filtrate, or unopened solution bottles; production of implicated lots was not clustered in time. Among 39 isolates tested, at least 10 different *Fusarium* species were identified, comprising 19 unique multilocus genotypes.

Conclusions The findings from this investigation indicate that this outbreak of *Fusarium* keratitis was associated with use of ReNu with MoistureLoc contact lens solution. Contact lens users should not use ReNu with MoistureLoc.

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Among the estimated 34 million contact lens wearers in the United States,[1] microbial keratitis (corneal infection) is a rare but serious complication that may lead to permanent vision loss or the need for corneal transplantation. The risk of microbial keratitis among contact lens wearers is about 80-fold greater than among healthy nonwearers.[2] Risk factors for contact lens–associated microbial keratitis

See also p 985.

Author Affiliations: Mycotic Diseases Branch (Drs Chang, Rao, Fridkin, and Park), Respiratory Diseases Branch (Dr Grant), and Biostatistics Office (Ms Wannemuehler), Division of Bacterial and Mycotic Diseases, and Epidemiology and Laboratory Branch (Drs Noble-Wang and Srinivasan), Division of Healthcare Quality Promotion, National Center for Infectious Diseases and Epidemic Intelligence Service (Drs Chang, Grant, Lewis, and Schaffzin) and Epidemiology Elective Program (Drs Jacobson and Crowell), Career Development Division, Office of Workforce and Career Development, Centers for Disease Control and Prevention, Atlanta, Ga; Microbial Genomics Research Unit, National Center for Agricultural Utilization Research, Agricultural Research Service, US Department of Agriculture, Peoria, Ill (Dr O'Donnell); Miami-Dade County Health Department, Miami, Fla (Ms Sneed); Philadelphia Department of Health, Philadelphia, Pa (Dr Lewis); New York State Department of Health, Albany, NY (Dr Schaffzin); Tennessee Department of Health, Nashville, Tenn (Dr Kainer); New Jersey Department of Health and Senior Services, Trenton, NJ (Ms Genese); Bascom Palmer Eye Institute, University of Miami School of Medicine, Miami, Fla (Dr Alfonso); and Cullen Eye Institute, Baylor College of Medicine, Houston, Tex (Dr Jones).
Corresponding Author: Douglas C. Chang, MD, 1600 Clifton Road, MS C-09, Atlanta, GA 30333 (DChang@cdc.gov).

include extended wear soft lenses, overnight contact lens wear, and suboptimal adherence to recommended lens wear and care regimens.[2-8] Annual incidence of microbial keratitis is estimated to be 4 to 21 per 10 000 soft contact lens wearers depending on overnight wear.[9-11]

Fungal keratitis is usually limited to tropical or subtropical climates; in southern Florida, fungal keratitis comprises up to 35% of microbial keratitis cases compared with 1% in New York.[12,13] *Fusarium* is a filamentous fungus commonly found in soil, plants, and aqueous environments[14,15] and is the major cause of fungal keratitis in certain tropical or subtropical regions including Singapore[16] and southern Florida.[12,17] Fungal keratitis among contact lens wearers is rare, even in regions where noncontact lens–associated fungal keratitis is more common, comprising less than 5% of microbial keratitis among contact lens wearers.[18-23]

In February 2006, clusters of patients with *Fusarium* keratitis were reported from Singapore[24,25] and Hong Kong.[26] Initial findings indicated that a high proportion of affected patients were contact lens wearers who used a Bausch & Lomb ReNu (Rochester, NY) brand contact lens solution. As a result, the manufacturer agreed to voluntarily suspend sales of its ReNu brand solutions in these locations in late February.

On March 8, 2006, the Centers for Disease Control and Prevention (CDC) received a report from an ophthalmologist in New Jersey about 3 patients with contact lens–associated *Fusarium* keratitis during the preceding 2 months. This article details the multistate investigation undertaken in collaboration with ophthalmologists and state and local health departments, and describes the results of our epidemiological and laboratory investigations.

METHODS

Case Definition and Case-Finding

A case patient was defined as a US resident with clinically consistent fungal keratitis reported by the treating ophthalmologist and without a history of ocular trauma during the 30 days before presentation. *Ocular trauma* was defined as trauma resulting in exposure to soil, organic, or vegetable matter. A confirmed case patient was required to have a positive culture for *Fusarium* from a corneal specimen (eg, corneal scrape or biopsy). *Possible case patients* were defined as those cases not fulfilling the confirmed criteria but where *Fusarium* species was cultured from contact lenses or lens cases, or demonstrating other laboratory evidence for fungal infection on corneal specimen (eg, histopathology). Patients with illness onset after June 1, 2005, were followed up by local and state health departments to determine case status.

Potential case patients were identified through both active and passive case finding. Reporting of suspected fungal keratitis cases was requested through CDC's Epidemic Information Exchange (a public health listserv), Keranet (a listserv for corneal specialists), and ClinMicronet (a listserv for clinical microbiology laboratory directors). Publication of a *Morbidity and Mortality Weekly Report* (*MMWR*) dispatch on April 10, 2006, encouraged clinicians and patients to report cases to the CDC or state and local health departments.[27] To confirm the presence of an outbreak, we contacted clinical microbiology laboratories, mostly associated with large eye care centers, to identify numbers of positive *Fusarium* cultures from eye specimens. The secular trend of these cultures was evaluated to determine whether an increase in *Fusarium* occurred in these centers.

Interviews were attempted for every potential case of *Fusarium* keratitis. Interviews with patients and ophthalmologists and review of medical records were performed by the state and local health officials or CDC staff. A standardized questionnaire was used to obtain demographic and clinical data, as well as information on contact lens hygiene practices and use of specific eye care products.

Contact lens products were classified according to the US Food and Drug Administration (FDA) lens group criteria.[28]

Case-Control Study

A case-control study was conducted to determine exposures associated with disease. To minimize the potential bias associated with media coverage of this outbreak, the case-control study was limited to a subset of confirmed case-patients identified before the April 10, 2006, *MMWR* dispatch.[27] Eligible case patients were soft contact lens wearers aged 18 years or older. Neighborhood-matched controls, identified using a reverse telephone directory, were adult (≥18 years) soft contact lens wearers during March 2006 with no history of fungal keratitis. Trained personnel, using standardized questionnaires, obtained a detailed history of exposures, including contact lens type, solutions, and hygiene practices, by telephone interview.

Statistical Analysis

All statistical analysis was performed using SAS 9.1 (SAS Institute Inc, Cary, NC). The descriptive and univariate analyses of potential risk factors were completed on confirmed cases only. Exact conditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for univariate analysis. These results led to a multivariable model, limited to single-solution users only, that focused on the comparisons of ReNu with MoistureLoc and MultiPlus solutions against all other solutions, respectively, while controlling for possible confounders. In other words, solution exposure for this model was defined as having exposure to only MoistureLoc, only MultiPlus, or neither of these. Both ReNu MultiPlus and private-label MultiPlus (ie, generic, store-brand solution formulaically equivalent to ReNu MultiPlus and manufactured at the same facility) were grouped together for this purpose.

A sensitivity analysis was conducted that addressed the misclassifi-

cation issues involved when individuals reported unspecified ReNu or private-label Bausch & Lomb solution (which may be either a saline product or private label MultiPlus). This provided an ad hoc method for assessing whether the results from the multivariable analysis would remain consistent if cases reporting these unspecified solutions were classified as exposed or unexposed, whereas controls were classified oppositely.

Environmental Assessment

Evaluation of Contact Lens Products. When available, case-patients' contact lenses, lens cases, and contact lens solution bottles were collected and sent to CDC. Lot numbers were obtained from available bottles or per patient interview. We requested that Bausch & Lomb provide unopened containers of relevant lots from its retained storage for sterility testing.

To culture contact lens solution bottle closures, we sampled the flip cap, cap tip, cap threads, and inside bottle necks by using sterile swabs premoistened with Dey Engley neutralizing broth (Becton Dickinson, Sparks, Md). The swabs were cultured on potato dextrose agar (Becton Dickinson), Sabouraud's dextrose agar, Emmons with chloramphenicol (dextrose agar; Becton Dickinson) and neutralizing broth.

Unopened contact lens solution bottles were tested for sterility by a modified membrane filtration method (0.45-µm, 47-mm mixed cellulose ester membrane filters; Millipore Corp, Billerica, Mass) as described per United States Pharmacopeia.[29] Membrane filters were rinsed with Fluid D (Becton Dickinson), and the filtrate portions were cultured on potato dextrose agar, trypticase soy broth (Becton Dickinson) and fluid thioglycollate medium (Becton Dickinson).

Filtrates from opened bottles were cultured only on potato dextrose agar. The potato dextrose agar, dextrose agar, neutralizing broth, and trypticase soy broth media were incubated at ambient room temperature (20°-25°C) for 7 (opened bottles) to 14 days (unopened bottles). The fluid thioglycollate medium (unopened bottles) was incubated at 35°C for 14 days. All agar plates were sealed with shrink seals (Scientific Device Laboratory, Maywood, Ill) prior to incubation.

For used contact lens cases, lenses (if present) were rinsed with 2.0 mL of neutralizing broth and cultured on potato dextrose agar. The lens case fluid and lens rinse were inoculated in neutralizing broth and 0.1-mL aliquots were cultured on potato dextrose agar and dextrose agar. Premoistened swabs were also used to sample the lens case wells and lids and cultured on potato dextrose agar and dextrose agar. Unused contact lens cases were inoculated with 1.5 mL of Sabouraud's dextrose broth (dextrose broth; Becton Dickinson) and incubated at ambient room temperature for 7 days. Contact lenses were cultured in dextrose broth. Neutralizing broth, dextrose broth, potato dextrose agar, and dextrose agar media were incubated at ambient room temperature for 7 days. All media were observed for fungal growth consistent with *Fusarium* species. Presumed *Fusarium* isolates were confirmed by molecular methods.

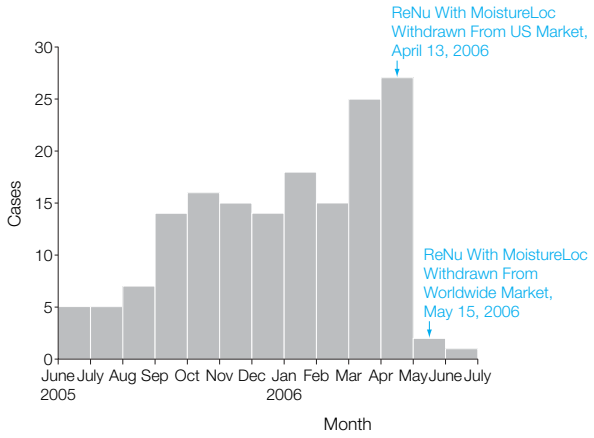
Evaluation of the Manufacturing Plant. The manufacturing plant in Greenville, SC, that produces all Bausch & Lomb contact lens solutions used in the United States, Singapore, and Hong Kong, as well as other countries, was visited April 19 and 20, 2006, by CDC investigators who observed manufacturing processes and interviewed quality control personnel. Targeted air and dust sampling was performed by the CDC using 0.8 µm of pore size, 37-mm closed-faced, polycarbonate filters housed in 2-piece cassettes (Zefon, Ocala, Fla). Air filter cassette samples were collected at a flow rate of 3 L per minute. Surface dust filter cassette samples were collected by microvacuum of a flat surface (ranging in area from 25-80 in^2 [162-516 cm^2]) for 2 minutes at a flow rate of 20 L per minute. Also, 1-L samples of municipal water and water at various points in the purification system were collected in containers with sodium thiosulfate added to neutralize residual chlorine.

The air and surface sample filters were extracted in 20 mL phosphate buffer with 0.01% Tween 80. For air samples, the extraction fluid was centrifuged at 4000 × g for 10 minutes, the final volume was adjusted to 2.5 mL, and 0.1 mL of full-strength extraction fluid and 10^{-1} dilution were spread on dextrose agar. For surface samples, 0.1 mL of the full-strength extraction fluid and 10^{-2}, 10^{-4}, and 10^{-6} dilutions were spread on dextrose agar. The water samples (200-mL aliquots) were filtered through 0.45 µm pore-size, 47-mm mixed cellulose ester membrane filters (Millipore Corp). The filters were cultured on dextrose agar. Culture plates were incubated at ambient room temperature at the CDC.

Confirmation of *Fusarium* species and Nucleic Acid Sequencing

Isolates from corneal specimens that were available at clinical microbiology laboratories were sent to the CDC for confirmation. All presumed *Fusarium* species from environmental assessments or corneal cultures were examined using morphological methods.[30] All isolates consistent with *Fusarium*, including *Fusarium* isolates from Singapore and Hong Kong, were genotyped by the US Department of Agriculture using multilocus DNA sequence typing as previously described,[31] with the exception that sequence data from the second largest RNA polymerase subunit was also included.[32] Nucleotide-to-nucleotide Basic Local Alignment Search Tool (BLAST) searches of the Fusarium-ID database, using partial translation *elongation factor (EF-1α)* sequences as the query, were used as an initial screen to place fusaria within species and/or species complexes.[33] Sequencher version 4.1.2 (Gene Codes, Ann Arbor, Mich) was used to edit and align DNA sequence data, followed by maximum parsimony analysis using the phylogenetic program (PAUP).[34] All sequence data have been deposited in

Figure 1. Confirmed Cases of *Fusarium* Keratitis in the United States, June 2005-July 2006



Month of illness onset of confirmed cases of *Fusarium* keratitis reported to the Centers for Disease Control and Prevention.

GenBank under accession numbers DQ790471-DQ790602.

The National Center for Infectious Diseases, CDC, determined that these activities were a combination of surveillance and public health response, not research. As such, the CDC determined that our investigation was not human-subjects research and not subject to review and approval by an ethics committee. Patient identifiers and protected health information remained confidential throughout the conduct of the study. Verbal assent was provided by case patients and controls prior to interview, and participation in all interviews was voluntary.

RESULTS

Descriptive Epidemiology

Ten clinical microbiology laboratories, excluding Florida laboratories where recovery of *Fusarium* is common,[35] reported the number of cultures from ocular specimens from which *Fusarium* was recovered. The secular trend of these positive cultures increased from 12 in 2004, to 51 in 2005, thereby supporting the presence of an increase beginning approximately in June 2005.

As of June 30, 2006, 318 reports of *Fusarium* keratitis had been received by the CDC; investigation of these reports identified 164 confirmed case patients, 32 possible case patients, 58 who did not meet the case definition (eg, recent ocular trauma, illness onset before June 1, 2005), and 12 with keratitis of other etiology. Information was not available to classify the remaining 52. Of the 164 patients included in this analysis, 12 were reported previously in the 2 articles by Alfonso et al[35,36] and 4 were reported previously in the article by Bernal et al.[37] Thirty-three states and 1 US territory reported at least 1 confirmed case patient.

The number of case patients identified through active and passive case finding steadily increased beginning in June 2005 and peaked in April 2006, and then declined in May and June 2006 (FIGURE 1). Confirmed case patients were mostly adults, with 16 (10%) younger than 18 years (TABLE 1). The overall median age was 41 years (range, 12-83 years). Twelve (7%) had bilateral infection. At the time of the case report, 37 patients (23%) reported that their infections had resolved with topical or systemic antifungal therapy alone; 65 patients (40%) were still receiving antifungal therapy but no corneal transplant had been performed or planned; and 55 patients (34%) had a corneal transplant performed or planned due to active disease, a residual corneal scar, or both (Table 1).

Six confirmed case patients (4%) reported not using contact lenses. Of the remaining 158, contact lens data were available on 154, all of whom reported wearing soft contact lenses (Table 1). Case patients reported wearing contact lenses produced by multiple manufacturers. Of the 81 case patients for which the specific contact lens brand was reported, 43 (53%) wore lenses made of nonsilicone hydrogel, high-water content, ionic polymers (FDA Lens Group 4).[28] Four (5%) wore lenses made of nonsilicone hydrogel, low-water nonionic polymers (FDA Lens Group 1), 1 (1%) wore high-water content, nonionic polymers (FDA Lens Group 2), 31 (38%) wore silicone hydrogel lenses, and 2 (2%) wore multiple lenses belonging to more than 1 FDA Lens Group. Other than contact lens use, other established risk factors for fungal keratitis, such as immunosuppression or diabetes, were uncommon (Table 1).

Of the 164 confirmed case-patients, 8 (5%) denied any contact lens solution use during the month prior to infection onset, 10 (6%) did not report which solution was used, and 116 (71%) reported using a single type of Bausch & Lomb contact lens solution: 94 (57%) reported using MoistureLoc only, and 10 (6%) reported ReNu MultiPlus only. One (1%) single-solution user reported a private-label solution, which may have been saline or private-label MultiPlus. Of 164 confirmed case patients, multiple solutions were reported by 28 (17%; Table 1). Overall, 15 of the case patients who reported a single solution and 7 case patients who reported multiple solutions denied any use of MoistureLoc (22 of 164, 13%).

Twenty-seven bottles of solution were submitted by 20 case patients. Fourteen case patients submitted 19 bottles of MoistureLoc from 14 different lot numbers. Five case patients who denied using any MoistureLoc submitted solution bottles; the solution bottle received at the CDC for 2 of these was

a partially used bottle of MoistureLoc. Solutions associated with the 14 different MoistureLoc lot numbers were produced using several different compounding tanks and all 4 of the production lines, which are also used to make non-MoistureLoc solutions. Production of traceback lots of MoistureLoc bottles occurred throughout late 2004 and 2005. Six bottles of MultiPlus with 6 different lot numbers were submitted by 5 confirmed case patients; production months for these 6 bottles were from 4 different years (data not shown).

Case-Control Study

Of 66 case-patients identified before April 10, 2006, 55 were adults who exclusively used soft contact lenses; 10 of the 55 did not have matched controls. The case-control study thus involved 45 case patients matched to 1 or 2 of 78 eligible controls. Three thousand five hundred five telephone numbers were called to obtain the 78 eligible controls. Of 1414 calls that were answered, 308 (22%) refused participation (ie, hung up) before initial assessment for eligibility could be completed, 977 (69%) reported that no one in the household wore contact lenses, and 51 (4%) did not otherwise meet the control definition.

Case patients were older than controls though similar with respect to sex (TABLE 2). On univariate analysis, case patients were more likely than controls to store lenses by reusing contact lens solution already in the lens case (OR, 3.2; 95% CI, 1.2-9.4) and were less likely than controls to never clean their lenses by rubbing (OR, 0.4; 95% CI, 0.2-0.9; Table 2). Other established risk factors for microbial keratitis, such as sleeping overnight with lenses, hand washing, and lens case age were similar among case-patients and controls (Table 2).

Cases (69%) were significantly more likely to report using MoistureLoc than controls (69% vs 15%, respectively; OR, 13.3; 95% CI, 3.1-119.5; Table 2). Other products, including ReNu MultiPlus (18% vs

Table 1. Demographic and Clinical Characteristics of 164 Confirmed Case-Patients With *Fusarium* Keratitis—June 1, 2005, to June 30, 2006, US

Characteristic	No. (%) (n = 164)
Age category, y	
<18	16 (10)
18-34	40 (24)
35-49	51 (31)
>50	57 (35)
Sex	
Women	112 (68)
Diabetes or immunosuppression	11 (7)
Affected eye(s)	
Right only	81 (49)
Left only	71 (43)
Both	12 (7)
Rewetting eye drops	35 (21)
Clinical status at time of report	
Resolved after antifungal treatment; no corneal transplant performed or planned	37 (23)
Antifungal treatment ongoing; no corneal transplant performed or planned	65 (40)
Corneal transplant performed or planned	55 (34)
Unknown status	7 (4)
Contact lens wear	
Noncontact lens wearers	6 (4)
Soft contact lens wearers*	154 (94)
Unknown soft contact lens wearers	4 (2)
Contact lens solutions	
Did not use contact lens solution due to being a noncontact lens wearer	6 (4)
Did not use contact lens solution despite being a contact lens wearer†	2 (1)
Unknown solution in contact lens wearers	10 (6)
Contact lens solution reported in contact lens wearers	146 (89)
Single solution used, Bausch & Lomb	116 (71)
ReNu with MoistureLoc	94 (57)
ReNu MultiPlus (brand)	10 (6)
ReNu multipurpose (older formula)	2 (1)
ReNu unspecified	9 (5)
Private-label saline or private-label MultiPlus‡	1 (1)
Single solution used, non–Bausch & Lomb	2 (1)
Multiple solutions used	28 (17)
ReNu with MoistureLoc with other solutions	21 (13)
ReNu MultiPlus with other solutions§	14 (9)
Private label MultiPlus with other solutions§	3 (2)
Non–Bausch & Lomb with other solutions	11 (7)
Wear and replacement schedule (n = 154)	
7-Day extended wear	8 (5)
30-Day extended wear	36 (23)
Daily disposable	6 (4)
2-Week daily wear	74 (48)
Frequent or planned replacement	20 (13)
1-Year conventional, daily wear	4 (3)
Unknown schedule despite contact lens wearer	6 (4)

*Two of 154 known soft contact lens users also reported using hard contact lenses within 30 d prior to illness onset.
†Two patients reported using daily disposable contact lenses and hence did not use contact lens solution. Other patients may use daily disposable contact lenses but may not dispose of them every day and hence use contact lens solution.
‡May be saline or a solution with equivalent formula to ReNu MultiPlus, produced in the same US manufacturing plant as ReNu MultiPlus; for this case-patient exact solution is unknown.
§Of the 17 patients reporting ReNu MultiPlus or private-label MultiPlus, 11 also reported using ReNu with MoistureLoc.

20%, respectively; OR, 0.7; 95% CI, 0.2-2.8), private label MultiPlus (0% vs 6%, respectively; OR, 0.3; 95% CI, 0.0-2.5) were not associated with *Fusarium* keratitis (Table 2).

The multivariable model of single-solution users (22 case patients, 32 controls), when controlling for the practice of reusing old solution, identified only the use of MoistureLoc in the month before symptom onset as significantly associated with having *Fusarium* keratitis (adjusted OR, 22.3; 95% CI, 3.1-∞ [infinity]) compared with persons using neither MoistureLoc nor MultiPlus. Case patients were not significantly associated with using MultiPlus vs non-MoistureLoc non-MultiPlus (adjusted OR, 2.4; 95% CI, 0.2-∞). The sensitivity analysis resulted in consistent findings.

Table 2. Comparison of Demographics and Exposures of 45 Confirmed Case-Patients With Soft Contact-Lens Associated *Fusarium* Keratitis (June 2005 to April 2006) and 78 Neighborhood-Matched Control-Patients Wearing Soft Contact Lenses (March 2006)

Demographic or Exposure*	No. (%) Cases (n = 45)	No. (%) Controls (n = 78)	Odds Ratio (95% CI)†
Demographics			
Age category, y			
18-34	12 (27)	27 (36)	1.0
35-49	15 (33)	27 (36)	1.2 (0.5-3.6)
>50	18 (40)	21 (28)	2.3 (0.7-7.9)
Sex			
Women	35 (78)	65 (83)	0.7 (0.3-2.0)
Smoker, active	8 (18)	13 (17)	1.1 (0.4-3.3)
Extended-wear contact lens	16 (39)	21 (31)	1.5 (0.5-4.4)
Contact lens usage habits			
≥5 y as contact lens wearer	41 (91)	67 (86)	2.2 (0.5-13.5)
Wear more than 5 d/wk	36 (82)	70 (92)	0.5 (0.1-1.6)
Sleep overnight with contact lenses	7 (16)	18 (24)	0.7 (0.2-1.9)
Swim with lenses	3 (7)	12 (16)	0.4 (0.1-1.7)
Contact lens hygiene practices			
Do not ever clean lenses by rubbing‡	13 (30)	41 (54)	0.4 (0.2-0.9)
Do not rub contact lenses everyday	31 (72)	50 (68)	1.2 (0.5-3.1)
Do not use enzymatic cleaner	40 (93)	63 (85)	2.0 (0.5-11.8)
Reuse solution in contact lens case	18 (44)	17 (24)	3.2 (1.2-9.4)
Do not always rinse lenses	13 (30)	18 (24)	1.3 (0.5-3.3)
Do not always wash hands before putting in contact lenses	10 (24)	18 (25)	1.0 (0.3-3.0)
Do not always recap solution bottle after use	9 (22)	17 (24)	0.9 (0.3-3.0)
Lens case			
Do not rinse lens case ≥1/wk	12 (28)	20 (28)	1.1 (0.4-2.7)
Lens case more than 3 mo old	16 (42)	36 (56)	0.6 (0.2-1.4)
Contact lens solution			
ReNu with MoistureLoc only	20 (69)	7 (15)	13.3 (3.1-119.5)
ReNu MultiPlus (brand) only	5 (18)	9 (20)	0.7 (0.2-2.8)
Private-label MultiPlus	0 (0)	4 (6)	0.3 (0.0-2.5)
ReNu MultiPlus or private label MultiPlus	4 (16)	11 (30)	0.4 (0.1-1.8)
Alcon only	0 (0)	8 (13)	0.1 (0.0-0.8)
AMO only	0 (0)	3 (5)	0.5 (0.0-4.8)
CIBA Vision only	0 (0)	8 (12)	0.2 (0.0-1.1)
Other private-label (non–Bausch & Lomb) only	0 (0)	8 (12)	0.0 (0.1-1.0)

Abbreviations: AMD, Advanced Medical Optics Inc; CI, confidence interval.
*For case patients, the exposures period was 1 month prior to illness onset. For controls, the exposures pertain to March 2006.
†Exact conditional logistic regression where a median unbiased estimate was reported as needed.
‡Not statistically significant after controlling for reuse of solution in contact lens case.

Environmental Assessments

Evaluation of Contact Lens Products. *Fusarium* species were not recovered from any unopened product, including contact lens solutions, lenses, or lens cases provided by case patients (TABLE 3). *Fusarium* species were recovered from the caps of opened bottles of contact lens solutions in 1 of 17 bottles of MoistureLoc, and 1 of 5 bottles of MultiPlus, but not from the solution filtrates (Table 3). *Fusarium* species were also recovered from 6 of 11 used contact lens cases (Table 3). No fungal growth was recovered from relevant retained lots of MoistureLoc (3 lots), MultiPlus (1 lot), and private label MultiPlus (1 lot).

Evaluation of the Solution Manufacturing Plant. Air and dust samples were analyzed for culturable *Fusarium* species in 2 clean-room areas (the pharmacy area and upper-mix rooms of the manufacturing plant) and in 3 non-clean-room areas (1 packaging line at the manufacturing plant and 2 areas in the warehouse distribution center). Several environmental mold species were detected in the samples collected in the nonclean-room areas but not in the clean-room areas; *Fusarium* species were not detected in any specimen. *Fusarium* species were not recovered from water samples obtained from taps delivering municipal water, de-ionized water, or distilled water.

Multilocus Sequence Typing

Thirty-nine isolates representing 38 case patients from 14 US states were available for DNA sequence-based multilocus genotyping, as were 10 corneal isolates from each of the Singapore and Hong Kong outbreaks. Phylogenetic analysis of the 39 US isolates revealed great genotypic diversity. At least 10 different *Fusarium* species were represented, including 19 unique multilocus genotypes, 14 of which were singletons (FIGURE 2).

Except for 2 of the US isolates, 30 (77%) were nested within the *Fusarium*

solani species complex (FSSC)[31] and 7 (18%), in the *Fusarium oxysporum* species complex (FOSC). *F solani* species complex isolates were of 6 species (ie, genotype groups 1-4, 6, and 7) comprising 12 multilocus genotypes, and FOSC representatives were from clades 3 and 4, which collectively comprised a total of 5 multilocus genotypes.[38] All of the FSSC and FOSC groups or clades with 2 or more isolates were strongly supported as monophyletic by parsimony bootstrapping (98%-100%). Approximately two thirds of the corneal isolates either belonged to FSSC group 1 (n=13) or FSSC group 2 (n=12). These groups also contained the 2 most common genotypes: FSSC 1-a represented by 11 isolates and FSSC 2-d with 7 isolates.

Multilocus genotyping of corneal isolates from Singapore and Hong Kong showed that all 20 were nested within FSSC group 2, and the FSSC 2-d genotype was predominant in both regions (n=7 Singapore, n=9 Hong Kong). Furthermore, 2 unique multilocus genotypes that were not represented among the confirmed US case-patient isolates were present in Singapore (FSSC 2-e and 2-f), as was one strain of the FSSC 2-f genotype in Hong Kong.

COMMENT

This outbreak of *Fusarium* keratitis identified 164 patients in 33 states and 1 US territory. In our study, *Fusarium* keratitis was associated with the use of MoistureLoc solution, although the mechanism for the association is still uncertain. ReNu with MoistureLoc was introduced in the fall of 2004, increasing US market share through 2005 (FIGURE 3). The MultiPlus formula has been on the market without changes for about 10 years; ReNu MultiPlus and private-label MultiPlus market share has been stable or decreased during 2004 and 2005. (data not shown; Alan Wilson, Bausch & Lomb Inc, written communication, July 7, 2006). In mid April 2006, based on the preliminary findings of this investigation,[27] Bausch & Lomb suspended shipments of MoistureLoc and instructed US retailers to halt sales of the solution.[39,40] On May 15, 2006, after additional preliminary findings were shared with the company, it permanently withdrew this solution from the worldwide market.[41]

Our data suggest that some potential explanations are unlikely. Although the MoistureLoc distributed to the United States, Hong Kong, and Singapore all originate from a common manufacturing plant, the evidence suggests that it is unlikely that these cases were caused by intrinsic contamination of the solution itself. Samples of unopened bottles of relevant lots were tested by the CDC during this investigation and all were sterile. Additionally, the manufacturer reported that none of the product sterility tests had positive cultures for *Fusarium* during 2004 to February 2006 (Alan Wilson, Bausch & Lomb Inc, written communication, July 7, 2006). In addition, our multilocus genotyping scheme revealed high genetic diversity among infecting strains. Collectively, these findings suggest, but do not prove definitely, that a common point source during production is unlikely.

Extrinsic contamination originating at the manufacturing plant or nearby warehouse also appears to be unlikely as the cause of this outbreak. Although it is possible that low-level intermittent extrinsic contamination from multiple sources could have yielded this degree of genetic diversity, this type of contamination would probably affect all solutions made by this manufacturer, including the private-label solutions and those for hard contact lenses because all of these products were produced, packaged, and stored in the same facilities. In addition, after sampling potential areas of extrinsic contamination at the plant and the distribution center, we were unable to identify any *Fusarium* species from these areas.

Results of the multilocus genotyping analysis favors extrinsic contamination through case patients' local environments. In contrast to an earlier study, in which FSSC group 3 isolates were most often associated with ocular infections,[31] only 2 (5%) of 39 case-patient isolates were from this group and 30 (77%) isolates were from FSSC groups 1 and 2. *F solani* species complex groups 1 and 2, along with the FOSC 3-a clonal lineage (also found among our case-patient isolates), have been identified by previous studies as most prevalent in sink and shower drains.[14,31,38] *F solani* species complex group 2 has also been associated with diverse marine animal sources.[31] The genetic diversity of US *Fusarium* isolates likely reflects the local ecologic diversity of *Fusarium* in water systems in case-patients' homes or communities. Although Singapore and Hong Kong isolates are narrower in diversity (20 of 20 isolates were FSSC group 2 and predominantly genotype 2-d), they come from more geographically limited areas. Additionally, if on-going intermittent contamination over a long period did exist, we would expect the genotyping results of isolates from Hong Kong and Singapore to have a similarly high degree of genetic diversity as US isolates.

Our findings, together with the results of environmental testing, suggest that exposure to *Fusarium* was likely the result of extrinsic contamination of con-

Table 3. Positive *Fusarium* Cultures From Contact Lens Supplies Submitted by Confirmed Case-Patients

Sample	*Fusarium*/ Total Tested
Contact lens solution	
ReNu with MoistureLoc, opened	1/17*
ReNu with MoistureLoc, unopened	0/2
ReNu MultiPlus, opened	1/5*
ReNu MultiPlus, unopened	0/1
Non–Bausch & Lomb, opened	0/2
Contact lenses, with case, used	6/11
Contact lenses, no case, opened	0/2
Contact lenses, no case, unopened	0/33
Contact lens case, no lenses, opened	0/3
Contact lens case, no lenses, unopened	0/1

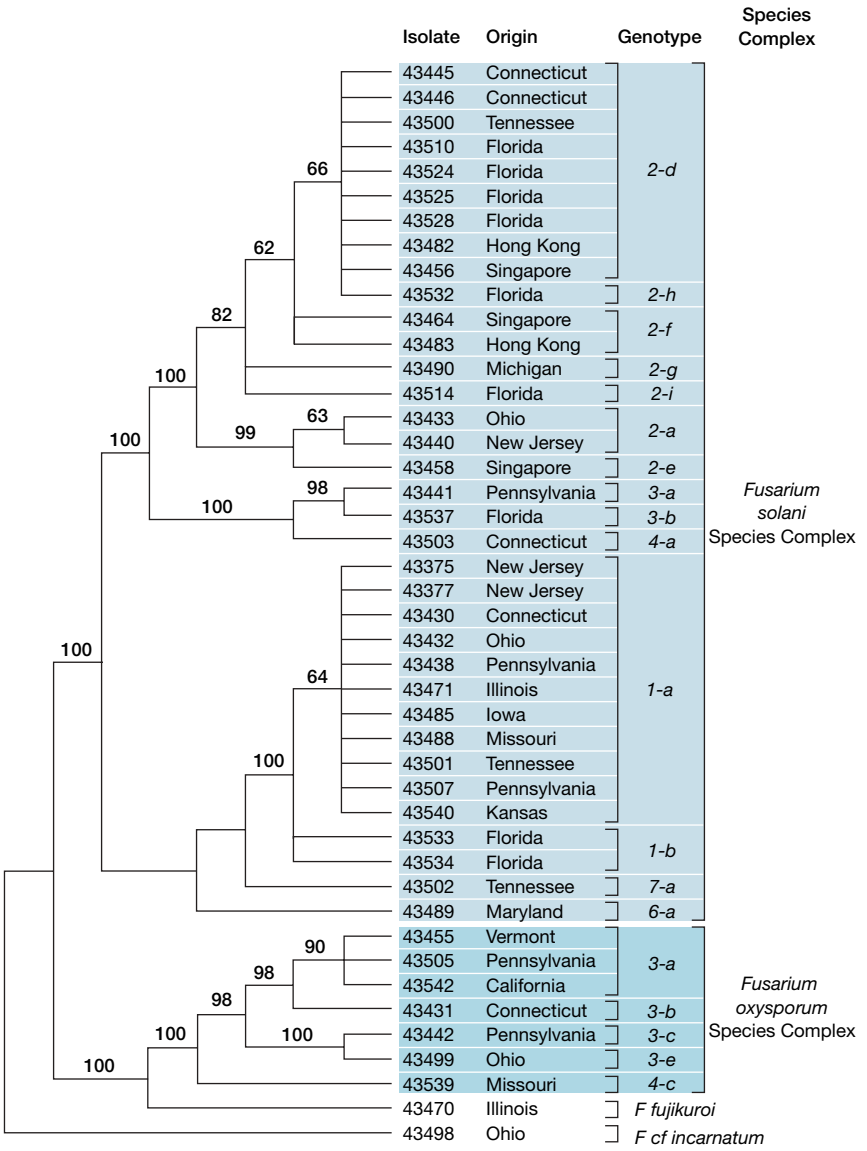
**Fusarium* was isolated only from the caps from these contact lens solution bottles.

tact lens solution bottles or lens cases occurring outside of the manufacturing or storage processes, perhaps in patients' homes. However, suboptimal contact lens hygiene practices appear unlikely as the major explanation for the outbreak. No single hygiene practice was independently associated with disease in our multivariable model, and our case-control study revealed that suboptimal hygiene practices were common and similar among case patients and controls. One practice that was statistically significant on univariate analysis was storing lenses by reusing contact lens solution already in the lens case; exploring how this practice may promote *Fusarium* growth in lens cases merits further study.

It appears that this outbreak may have been caused by a complex and, as yet, undetermined interaction between MoistureLoc, *Fusarium*, and possibly the lens case or contact lens. Unique properties of MoistureLoc formula may have contributed to fungal infection following this type of contamination. The MoistureLoc formula contains 2 ingredients not found in other soft contact lens solutions currently on the market: alexidine (a disinfectant) and polyquarterium 10 (a moisture-retaining polysaccharide that holds water close to the contact lens surface). In addition, MoistureLoc contains a high content of poloxamer 407, a surfactant that in combination with other ingredients helps to inhibit deposits on the lens (Jim Saviola, FDA, written communication, August 3, 2006). Although in vitro studies have demonstrated that the formulation meets all current biocidal standards against *Fusarium*, persistence of this activity in a variety of environments, including simulated noncompliant use, is not customarily tested and is currently unknown. In addition, the effect of the polysaccharides and surfactants on the growth or survival of *Fusarium* is not well understood.

Biofilm formation on contact lenses or lens cases and *Fusarium*'s ability to penetrate soft contact lenses also may have played roles in this outbreak.[42,43] Some hygiene practices, such as storing lenses by reusing contact lens solution already in the lens case, may have facilitated the growth of such biofilms, therefore rendering the solution less efficacious.[44] It is also possible that *Fusarium* has specific adaptations promoting adherence and penetration into contact lenses that allow survival within lens cases with MoistureLoc solution. These possibilities require further study.

Figure 2. Phylogenetic Diversity of 59 Isolates Inferred From Multilocus DNA Sequence Data



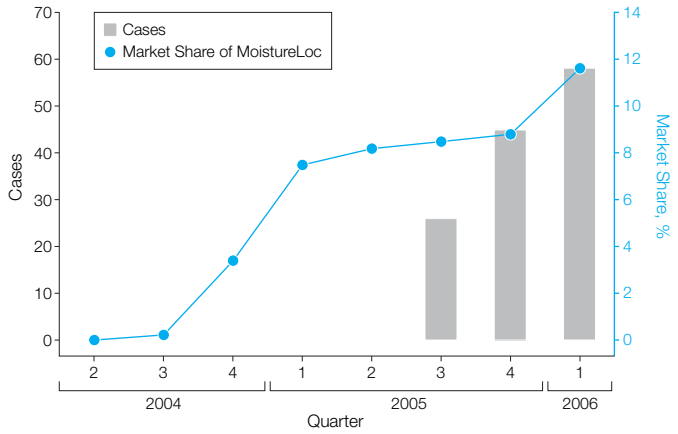
The data include 39 corneal isolates from 38 US confirmed case patients, and 20 isolates from the keratitis outbreaks in Singapore and Hong Kong. US isolates represent 19 unique genotypes: 12 genotypes (30 isolates) within the *Fusarium solani* species complex (FSSC), 5 genotypes (7 isolates) within the *Fusarium oxysporum* species complex (FOSC), 1 genotype (1 isolate) was *Fusarium fujikuroi*, and 1 genotype (1 isolate) was *Fusarium cf incarnatum*. Although 20 isolates (10, Hong Kong; 10, Singapore) were genotyped, only 1 exemplar genotype is shown: FSSC 2-d (7 Singapore isolates, 9 Hong Kong isolates), FSSC 2-e (1 Singapore isolate), FSSC 2-f (2 Singapore isolates, 1 Hong Kong isolate). Although the dominant genotype FSSC 2-d in Asia was shared by the United States, 2 additional unique genotypes were represented in Asia (FSSC 2-e and 2-f). Numbers on nodes indicate bootstrap support.

Although exposure to MoistureLoc was the most significant risk factor for infection, 14% of confirmed case-patients did not report using this product. There may be several explanations for this observation. Some of these patients may have had exposure to MoistureLoc earlier than 30 days before illness onset that would not have been assessed in the interview. Because the incubation period for contact lens–associated *Fusarium* keratitis is largely unknown, these exposures may have played a part. Also, some case patients may simply represent background disease; about 5% of case patients denied using any contact lens solution, a proportion similar to the proportion using only the MultiPlus solution. Additionally, MultiPlus packaging and labeling during the outbreak period was similar to that of MoistureLoc; therefore, patients may have confused the 2 products. In fact, 2 patients who denied MoistureLoc use provided MoistureLoc bottles to the CDC for testing. In addition, patients may not have reported occasional use of MoistureLoc (eg, free travel-size sample).

This outbreak had a high degree of morbidity. Most patients were young and had no immune compromising illness, yet corneal transplantation was required or planned for 55 patients (34%). The US rate of corneal transplantation was higher than what was reported in the study of *Fusarium* keratitis from Singapore,[25] in which 5 of 68 cases required transplant for active disease only, probably because we also counted those who required transplantation for corneal scarring.

Our investigation and analysis had several limitations. To be stringent in the multivariable analysis of the case-control study, we included only patients reporting use of a single-product line, which reduced the number of study participants. As a result, we were unable to evaluate other potential confounding variables except for reuse of contact lens solution. However, confounding by other hygiene practices would seem unlikely since these exposures were comparable between case patients and controls.

Figure 3. Illness Onset of Confirmed Cases of *Fusarium* Keratitis in the United States and Market Share by Quarter



Cases were reported to the Centers for Disease Control and Prevention.

Recall bias may have limited the accuracy of case patients' responses because interviews occurred weeks or months after infections occurred. Media attention may have also influenced ascertainment of case patients, although we attempted to limit this in our case-control study by including only those case patients reported before widespread report of *Fusarium* keratitis outbreaks in the United States. In attempting to obtain controls, we were not able to determine whether those refusing telephone participation were significantly different from those who agreed to participate because this refusal prohibited collection of data for comparison.

In addition, inability to recover *Fusarium* from environmental sampling of the manufacturing plant and warehouse should be interpreted cautiously because sampling occurred several months after the lots associated with case patients had been produced and standard methods to recover *Fusarium* may have been insufficiently sensitive.

Conclusions

In summary, we describe an outbreak of *Fusarium* keratitis with substantial morbidity that was associated with use of a specific contact lens solution, MoistureLoc. On-going studies may help to determine if the infections were caused by an interaction of its ingredients with *Fusarium* that might have permitted growth of the organism. In the meantime, clinicians should be vigilant in diagnosing and treating fungal keratitis,[36] and users of MoistureLoc should discontinue the use of this product.[45] Soft contact lens users should follow the instructions of their ophthalmologist or other eye-care professional and continue to pay careful attention to optimal hygiene practices, including washing and drying hands prior to handling lenses, storing lenses in new contact lens solution after each use, and carefully following directions for use of contact lens and contact lens solution products.

Author Contributions: Dr Chang had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Chang, O'Donnell, Noble-Wang, Jacobson, Lewis, Schaffzin, Kainer, Alfonso, Jones, Srinivasan, Fridkin, Park.
Acquisition of data: Chang, Grant, O'Donnell, Noble-Wang, Rao, Jacobson, Crowell, Sneed, Lewis, Schaffzin, Kainer, Genese, Alfonso, Jones, Park.
Analysis and interpretation of data: Chang, Grant, O'Donnell, Wannemuehler, Noble-Wang, Kainer, Srinivasan, Fridkin, Park.
Drafting of the manuscript: Chang, Grant, O'Donnell, Noble-Wang, Rao, Crowell, Srinivasan, Fridkin, Park.
Critical revision of the manuscript for important intellectual content: Chang, Grant, Wannemuehler, Noble-Wang, Jacobson, Sneed, Lewis, Schaffzin, Kainer, Genese, Alfonso, Jones, Srinivasan, Fridkin, Park.
Statistical analysis: Chang, O'Donnell, Wannemuehler, Kainer, Fridkin, Park.

Administrative, technical, or material support: Chang, Grant, O'Donnell, Jacobson, Crowell, Sneed, Lewis, Genese, Fridkin, Park.
Study supervision: Chang, O'Donnell, Noble-Wang, Genese, Alfonso, Srinivasan, Fridkin, Park.

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Fusarium Keratitis Investigation Team: Lauren Burwell, Melissa Gerhart, Lynette Benjamin, Shirley McClinton, Mark Lindsley, Matthew J. Arduino, Mary E. Brandt, Centers for Disease Control and Prevention, Atlanta, Ga; Cheng Leng Chan, Health Sciences Authority, Singapore; Pak-Leung Ho, University of Hong Kong, Hong Kong, China; Sue Chen, California Department of Health Services, Richmond, Calif; Lynn E. Sosa, CDC and Connecticut Department of Public Health, Hartford; Kathleen A. Ritger, CDC and Illinois Department of Public Health, Chicago; Corwin A. Robertson, New Jersey Department of Health and Senior Services, Trenton; L. Rand Carpenter, CDC and Tennessee Department of Health, Nashville; Neil Pascoe, Texas Department of State Health Services, Austin; Brandon D. Ayres, Wills Eye Institute, Philadelphia, Pa; Darlene Miller, Jorge Cantu-Dibildox, Bascom Palmer Eye Institute, Miami, Fla; David G. Hwang, Maria D. Bernal, University of California, San Francisco; David S. Chu, University of Medicine and Dentistry of New Jersey, New Jersey Medical School, Newark; Geraldine Johnson, Madhu Anand, New York State Department of Health, Albany, NY; Ellen D. P. Salehi, Ohio Department of Health, Columbus; David Bruckner, University of California, Los Angeles; Francis S. Mah, University of Pittsburgh Medical Center, Pittsburgh, Pa; and Ose Emasealu, Orange County Department of Health, Goshen, NY.

Disclaimer: Product names are necessary to report factually on available data; however, the USDA neither guarantees nor warrants the standard of the product, and the use of the name by the USDA implies no approval of the product to the exclusion of others that may also be suitable. The use of product names in this manuscript does not imply their endorsement by the US Department of Health and Human Services. The findings and conclusions in this article are those of the author(s) and do not necessarily represent the views of the CDC.

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Yes, writing can be complicated, exhausting, isolating, abstracting, boring, dulling, briefly exhilarating; it can be made to be grueling and demoralizing. And occasionally it can produce rewards. But it's never as hard as, say, piloting an L-1011 into O'Hare on a snowy night in January, or doing brain surgery when you have to stand up for ten hours straight, and once you start you can't just stop. If you're a writer, you can stop anywhere, any time, and no one will care or ever know. Plus, the results might be better if you do.
—Richard Ford (1944-)