California Surveillance Update: Enhanced laboratory-based meningococcal disease surveillance: November 2004 - June 2006

KEY FINDINGS

- During the enhanced laboratory surveillance study period (Nov 2004-June 2006), we identified 321 meningococcal disease case-patients (282 confirmed, 39 probable).
- The corresponding 2005 meningococcal disease incidence rate was 0.5 cases per 100,000 Californians. Cases were associated with serogroups A (1,<1%), B (127, 43.3%), C (105, 35.8%), Non-groupable (1, <1%), Other (5, 1.7%), W-135 (5, 1.7%) and Y (49, 16.7%).
- Nine percent (28/321) of cases and 48% (28/59) of tested suspect-patients had detection of *N. meningitidis* solely based on the state's PCR assay. Negative PCR assays provided an additional line of evidence to help rule out disease in 31 other suspect-patients. These rapid results have helped several local health departments in managing heightened public concerns.
- During this study period, one organizational outbreak was identified in California. One suspected community outbreak was ruled out based on MLVA strain typing results.
- MLVA strain typing results confirmed two epidemiologic clusters. Results linked one previously (presumed) unrelated case to an epidemiologic cluster.
- MLVA strain typing helped to establish the non-relatedness of at least three case clusters of the same serogroup that appeared within a short time within each county.

Background *Neisseria meningitidis* is a leading cause of community-acquired bacterial meningitis and sepsis in the United States and California. In 2005, a conjugate vaccine (Menactra® or MCV4) covering four of five pathogenic *N. meningitidis* serogroups was licensed for use in persons 11-55 years of age. In November 2004, the California Department of Health Services (CDHS) initiated a pilot, statewide laboratory-based surveillance project to (i) improve laboratory detection and public health management of individual meningococcal disease cases, case clusters, and outbreaks by providing centralized rapid testing and molecular strain typing and (ii) monitor the potentially changing epidemiology of meningococcal disease in California following introduction of the MCV4 vaccine. We describe here enhanced laboratory-based surveillance results from November 1, 2004 through June 30, 2006 with emphasis on improved laboratory detection of cases and detection and management of meningococcal case clusters and outbreaks.

Enhanced laboratory-based surveillance and surveillance case definitions CDHS maintains a mandatory, passive reporting system for meningococcal disease. Health care providers are required to report invasive meningococcal disease suspect-patients to their local health departments (LHDs); LHDs forward reports of confirmed and probable cases to CDHS. In November 2004, CDHS asked physicians and clinical laboratories to voluntarily submit (via the local public health laboratory) clinical specimens from clinically-suspicious culture-negative patients and isolates from culture-positive patients. We identified the presence of *N. meningitidis* in clinical specimens using a *ctr*A TaqMan polymerase chain reaction (PCR) assay (96% sensitivity, 100% specificity). We assigned molecular strain types to serogroup B, C and Y isolates and PCR-positive specimens using multilocus variable number tandem repeat analysis (MLVA), a PCR-based subtyping method.

We defined a **confirmed** case of meningococcal disease as one with clinically compatible illness and isolation of *N. meningitidis* from a normally sterile site. A **probable** case was one with clinically compatible illness and either (a) evidence of *N. meningitidis* antigen in cerebrospinal fluid or (b) detection of *N. meningitidis* DNA from a normally sterile site by a validated PCR assay. A **suspect** patient was one with clinically compatible illness in the absence of confirmatory laboratory tests. We defined a **genotyping cluster** as two or more patients whose specimens shared the same MLVA pattern. We defined an **epidemiologic link** as an association between cases by known direct contact. We defined an **organizational outbreak** as a genotyping cluster of ≥ 2 patients with a common affiliation (but no direct contact) occurring within a 90 day period and resulting in a primary attack rate of 10 per 100,000 persons. We defined a **community outbreak** as a genotyping cluster of ≥ 3 patients who resided in the same geographic area or in the same social network (but no direct contact) occurring within a 90 day period and resulting in a primary attack rate of 10 per 100,000 persons.

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Results Summary of laboratory participation

We tested 361 samples (233 isolates, 128 specimens) from laboratories in Alameda (15,4), Butte (0,1), Contra Costa (7,5), El Dorado (1,5), Fresno (3,1), Humboldt (2,0), Kern (4,6), Los Angeles including Long Beach (56,4), Marin (3,0), Mendocino (7,0), Merced (2,0), Monterey (1,0), Orange (9,35), Placer (3,0), Plumas (1,0), Riverside (6,0), Sacramento (10,17), San Bernardino (0,4), San Diego (12,11), San Francisco (8,13), San Joaquin (20,3), San Luis Obispo (2,0), San Mateo (2,0), Santa Barbara (5,3), Santa Clara (5,2), Santa Cruz (6,2), Shasta (2,1), Solano (1,4), Sonoma (8,0), Stanislaus (15,2), Tulare (3,0), Tuolumne (0,1), Ventura (5,0), Yolo (9,0), out of state (0,2), and not stated (0,2). Fifty-five percent (71/128) of clinical specimens tested by PCR were positive.

Summary of laboratory and epidemiologic data

We electronically matched the project's laboratory records to Meningococcal Case Reports submitted to CDHS. We identified 321 case-patients: 282 confirmed and 39 probable. Of 80 suspect-patients who had no evidence of *N. meningitidis* using hospital-based test methods, our PCR assay provided the sole source of laboratory diagnosis in 28 patients and helped rule out disease in 31 patients. We did not receive specimens for 21 additional suspect-patients thereby missing the opportunity to potentially confirm disease.

Of 321 confirmed or probable cases, 293 (91%) had a serogroup identified and included serogroups A (1,<1%), B (127, 43.3%), C (105, 35.8%), non-groupable (1, <1%), other (5, 1.7%), W-135 (5, 1.7%) and Y (49, 16.7%). Cases resided in the counties of Alameda (12), Amador (2), Butte (2), Calaveras (2), Contra Costa (9), El Dorado (4), Fresno (3), Humboldt (3), Kern (9), Lake (1), Los Angeles including Long Beach (62), Marin (4), Mendocino (6), Merced (2), Modoc (2), Monterey (4), Napa (1), Nevada (2), Orange (20), Placer (1), Plumas (1), Riverside (8), Sacramento (23), San Bernardino (11), San Diego (23), San Francisco (15), San Joaquin (10), San Luis Obispo (3), San Mateo (3), Santa Barbara (4), Santa Clara (14), Santa Cruz (4), Shasta (1), Solano (4), Sonoma (9), Stanislaus (15), Sutter (1), Tulare (5), Tuolumne (8), Ventura (5), Yolo (1), and not listed (2).

Eighty-four percent (236/281) of serogroup B, C, or Y case-patients had a sample available for genotyping (Table 1). While more than half of B and Y cases tested had unique MLVA genotypes, only 40% of serogroup C cases had a unique MLVA genotype suggesting that serogroup C samples were somewhat less diverse. More complete epidemiologic analyses of these strain data will be completed as the cohort size increases.

Application of MLVA typing results to the detection and public health management of suspected clusters

In the 20 month period of enhanced surveillance, LHDs reported to CDHS three serogroup B disease clusters prior to MVLA typing. Cluster B-1 (4 patients) and B-2 (3 patients) were each epidemiologically-linked; case patients within each cluster demonstrated identical MLVA patterns. In cluster B-2, MLVA testing identified an additional case-patient previously presumed to be unrelated but later determined to be a probable contact. Cluster B-3 (initially 4 patients) had no epidemiologic link, or common organizational or community settings identified. While 3 of 4 patients had identical MLVA patterns, the community outbreak threshold was not met. The LHD heightened surveillance; no additional cases occurred within the 90 day period.

LHDs also reported 3 serogroup C clusters prior to MLVA typing. Cluster C-1 (2 patients) and C-2 (2 patients) occurred in two nursing homes among patients with no known contact; case-patients within each cluster demonstrated identical MLVA patterns. In Cluster C-1, the attack rate was above the outbreak threshold; all staff and patients were prophylaxed. One additional case with the cluster C-1 pattern occurred in the county with no known association to the institution. That patient's close contacts were prophylaxed and no additional cases occurred. In cluster C-2, the index patients were considered co-primary; targeted prophylaxis was used in the institution and no additional cases occurred. Cluster C-3 (initially 4 patients) occurred in a small, remote community setting. Two patients had identical and two had distinct MLVA patterns. Based on 2 MLVA matches, the community outbreak threshold was not met and mass prophylaxis of the community was called off. No additional cases were identified. CDHS identified Cluster C-4 (4 patients) by review of genotyping results. Patients were predominantly Hispanic adolescents in 2 adjacent counties with onsets within 18 days. Further investigation identified no epidemiologic link, or common organizational or community setting.

Comment Our preliminary findings suggest that rapid PCR testing has increased laboratory detection of meningococcal disease in California. Strain typing provided rapid confirmation of one organizational outbreak and two epidemiologic clusters and rapidly ruled out one suspected community outbreak. Strain typing also linked one previously (presumed) unrelated case to an epidemiologic cluster. These findings improved our understanding of the potential usefulness of MLVA strain typing in the identification and management of case clusters and outbreaks.

Table 1. Enhanced laboratory-based meningococcal disease surveillance in California: Nov 2004 - June 2006
Strain typing results using multilocus variable number tandem repeat analysis (MLVA)

	Serogroup			
Attribute	**B**	**C**	**Y**	**Total**
Number of patients	127	105	49	281
Number patients with a sample genotyped by MLVA (percent of patients with a reported sero-group)	107 (84%)	84 (80%)	45 (92%)	236 (84%)
Number of distinct MLVA genotypes (e.g. patterns) identi-fied	79	47	37	163
Number of unique MLVA geno-types, e.g., MLVA patterns that occurred in only one case-patient. (percent of patients tested).	64 (60%)	33 (40%)	32 (71%)	129 (55%)
Number of MVLA genotyping clusters (e.g. clusters of two or more case-patients with identical MLVA patterns)	15	14	5	34
Median duration of genotyping clusters in days (range in days)	201 (13-575)	127 (0-517)	133 (9-409)	139.5 (0-575)
Median number of case-patients per genotyping cluster (range)	3 (2-5)	3 (2-9)	3 (2-3)	3 (2-9)
Number of genotyping clusters involving ≥3 patients within a 90 day period and	5	6	0	11
• an epidemiologic link was established	2	0	0	2
• the organizational outbreak threshold was met (10/100K)	0	1[a]	0	1
• the community outbreak threshold was met (10/100K)	0	0	0	0
• No epidemiologic, or com-mon organizational or com-munity settings were identi-fied and cases occurred				
• Within 1 county	1	0	0	1
• Across ≥2 counties	2	5[c]	0	7

[a]2 serogroup C genotyping clusters were identified in 2 different organizational settings; Cluster C-1 (2 patients) met the outbreak threshold and cluster C-2 did not (the 2 patients involved were considered co-primary cases). See narrative for details.

[b]Includes cluster C-2; cluster C-2 was embedded within a larger genotyping cluster that extended over a large geographic area for a period of 517 days . See narrative for details

Health Care Providers and Laboratories

Healthcare providers

- Maintain a high level of clinical suspicion for meningococcal disease.
- Promptly **report suspect** meningococcal disease cases to your local public health department.
- Urge your clinical lab to **send isolates** for patients with culture confirmed invasive disease to the local public health laboratory
- Urge your lab to **send specimens** for cases that meet high clinical suspicion for invasive disease but are culture-negative to your public health laboratory. The **criteria for high clinical suspicion** will depend on individual assessment but may include:
    - Fever or septic shock AND petechial or purpuric rash,
    - Purpura fulminans,
    - Suspected bacterial meningitis or sepsis and preliminary laboratory evidence of invasive disease (e.g., positive Gram stain with visualization of gram-negative diplococci)
- Further PCR testing of these culture negative cases by the State's Microbial Diseases Laboratory (MDL), especially those cases who may have received antibiotic treatment prior to specimen collection, maybe useful for epidemiologic investigations and outbreak detection.
- The **preferred specimen** for patients with suspected meningococcemia is blood and for patients with suspected meningitis is CSF. However, if the preferred specimen is unavailable, either specimen is acceptable. If CSF or blood are unavailable, serum (0.5 ml) can be tested.

Clinical/hospital laboratories

- Forward to the local public health laboratory an **isolate** for patients with culture confirmed invasive disease.
- Forward to the local public health laboratory **blood or CSF specimens** for cases that meet high clinical suspicion for invasive disease but are culture-negative. The criteria for high clinical suspicion are described above.
- When submitting isolates or specimens to the public health lab, please provide as much demographic information on the patient as possible (most especially age and county of residence) AND indicate the clinical syndrome (meningococcemia, meningitis, or both).
- Details for specimen/isolate shipping are described under *Public Health Laboratories.* **Please ship samples to your LOCAL public health laboratory and do not ship directly to the state's laboratory.**

Local Health Departments

Communicable disease programs

- Coordinate with clinicians and clinical laboratories to forward to your local public health lab an invasive meningococcal isolate for culture-confirmed cases of meningococcal disease.
- Coordinate with clinicians and clinical laboratories to forward to the public health lab a blood or cerebrospinal fluid (CSF) specimen for culture-negative cases for which there is a high level of clinical suspicion for meningococcal disease.
- Complete the revised (DHS8469 version 10/05) Meningococcal Disease Case Report Form (CRF) for cases of meningococcal disease that are culture confirmed or are positive by PCR or CSF antigen.

Public health laboratories

- Forward to the state's MDL an isolate for culture-confirmed invasive disease cases. Please submit the isolate on an appropriate agar slant (such as chocolate agar) in a screw cap tube with MDL form 446 "Bacterial Culture for Identification". Use standard shipping protocol for bacterial cultures. Please provide as much demographic information on the patient as possible (most especially age and county of residence).
- Forward to MDL a blood or CSF specimen for culture-negative cases with high clinical suspicion. Please submit a minimum of 0.5 ml of CSF or 0.5 ml of blood (EDTA treated—purple top) and MDL form 420 'Miscellaneous Examination' requesting *N. meningitidis* PCR. Preferred specimens are described under *HealthCare Providers*. Ship refrigerated for overnight delivery. For short term storage of clinical specimens prior to shipping, please freeze CSF and serum at minus twenty, and hold blood at refrigerated temperatures. Please indicate the clinical syndrome.
- Cultures or clinical specimens can be batched for shipment and sent to:

Specimen Receiving—Attn: Special Pathogens Unit
California Department of Health Services
Microbial Diseases Laboratory
850 Marina Bay Parkway
Richmond, CA 94804

Thank you for your interest and continued participation in this important enhanced surveillance project.