Invasive meningococcal infections despite immunization - California

Kathleen Winter, MPH, Kathleen Harriman, PhD, MPH, RN, John Semerdjian, Chann Sang, Robert Schechter, MD, and John Talarico, DO, MPH
California Department of Public Health (CDPH)

Kathleen Winter, MPH
850 Marina Bay Parkway
Richmond, CA 94804
T: (510) 620-3770
F: (510) 620-3949

INTRODUCTION

Most cases of invasive meningococcal disease in the world are caused by five serogroups of the bacterium *N. meningitidis,* four of which (B, C, Y and W-135) are most common in the United States. The current quadrivalent polysaccharide vaccine (MPSV4) was licensed in the US in 1978 and two quadrivalent conjugate vaccines (MCV4) were licensed in 2005 and 2010. All three vaccines protect against serogroups A, C, Y and W-135. The immunogenicity of MCV4 and MPSV4 in adolescent and adults is lowest against serogroup Y and highest against serogroup W-135 (Table 1).

Since 2005 meningococcal conjugate vaccines have been recommended for young adolescents aged 11-12 years, college freshmen living in dormitories and others aged 11-55 years at increased risk (e.g., military recruits, travelers to areas in which meningococcal disease is hyperendemic or epidemic, microbiologists who are routinely exposed to isolates of *N. meningitidis*, patients with anatomic or functional asplenia, and patients with terminal complement deficiency). In 2010, ACIP recommended a booster dose after ~5 years for adolescents as well as a two-dose primary series in high-risk persons aged 2-54 years.[3]

Since their licensure, meningococcal conjugate vaccines have largely replaced MPSV4 because of their anticipated advantages in providing immunity and reducing asymptomatic carriage of *N. meningitidis*.[1] According to estimates from the 2009 National Immunization Survey, approximately 58.4% adolescents aged 13-17 years in California and 53.6% nationally had received at least one dose of meningococcal conjugate vaccine.[2] Although safe and immunogenic, the efficacy of conjugate vaccines in preventing invasive meningococcal disease has not been established, and cases in vaccinated people are known to occur.

ESTIMATED VACCINE IMMUNOGENICITY

Table 1. Percent of adolescents (11-18y) and adults (18-55y) with >4-fold rise of bactericidal antibody at day 28 following vaccination with Menactra® (MCV4) and MPSV4

	MCV4				MPSV4			
	Adolescents (11-18y)		Adults (18-55y)		Adolescents (11-18y)		Adults (18-55y)	
Serogroup	%	95% CI	%	95% CI	%	95% CI	%	95% CI
A	92.7	(89.8, 95.0)	80.5	(78.2, 82.6)	92.4	(89.5, 94.8)	84.6	(82.3, 86.7)
C	91.7	(88.7, 94.2)	88.5	(86.6, 90.2)	88.7	(85.2, 91.5)	89.7	(87.2, 91.4)
Y	81.8	(77.8, 85.4)	73.5	(71.0, 75.9)	80.1	(76.0, 83.8)	79.4	(76.9, 81.8)
W-135	96.7	(94.5, 98.2)	89.4	(87.6, 91.0)	95.3	(92.8, 97.1)	94.4	(92.8, 97.1)

Package insert for Menactra, Sanofi Pasteur. 24 Aug 2010.

METHODS

Invasive meningococcal infections are reportable by laboratories and clinicians in California. We reviewed all cases that occurred in California residents and were reported to the California Department of Public Health from January 1, 2006 through March 1, 2011. Vaccination histories were obtained on cases that were reported to have received at least one dose of meningococcal vaccine. We compared the serogroup distribution among the vaccinated and non-vaccinated cases of the same age range of 11-28 years.

RESULTS

Of 790 total cases of invasive meningococcal disease, vaccination status was known for 518 (66%). Of these, 24 had been vaccinated with at least one dose of meningococcal vaccine; the median time from vaccination to onset of invasive disease was 6.5 months (range 6 days to 8.8 years). All vaccinated cases were adolescents or young adults; the median age among the vaccinated cases was 19 years (range 11-28 years). Of the 23 cases with known serogroup, 9 (39%) had a vaccine-preventable serogroup: Y (5), C (3), W-135 (1) (Figure 1A). The remaining cases were serogroup B (11), ungroupable (3) or unknown (1). Three deaths occurred among the previously-vaccinated cases: C (1), W-135 (1), and ungroupable (1).

98 cases, including 4 deaths, were reported in unvaccinated persons of the same age (11-28 years). Of the 91 with known serogroup, 45 (49%) were a vaccine-preventable serogroup (Figure 1B). Among the vaccinated cases, there were disproportionately fewer cases of serogroup C and more cases of serogroup B. However, the distribution of serogroups was not significantly different between immunized and non-immunized cases of the same age.

Figure 1A. Vaccine-preventable serogroup of previously-vaccinated cases (n=9)

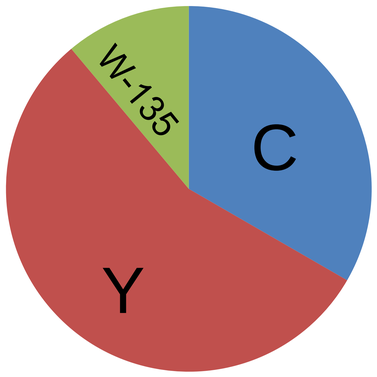

Figure 1B. Vaccine-preventable serogroups of unvaccinated cases aged 11-28 years (n=45)

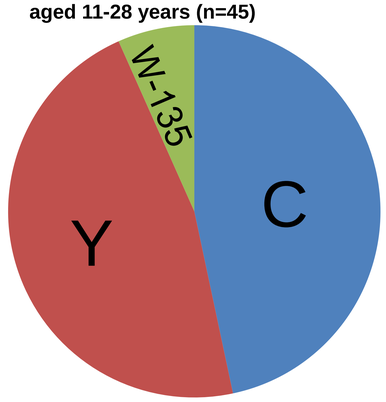

Table 2. Vaccine-preventable serogroup distribution of among previously-vaccinated cases, by vaccine type

	Total		MCV4	MPSV4	Unknown
Serogroup	n	%	n	n	n
A					
C	2	22%	1 (fatal)	1	
Y	6	67%	4	1	1
W-135	1	11%			1 (fatal)

Cases in MCV4 recipients

Five cases of vaccine-preventable invasive meningococcal disease occurred in patients previously immunized with Menactra® (the study's timing precluded frequent use of Menveo®); 4 were serogroup Y, 1 was serogroup C. All were previously-healthy males whose median age was 19 years (range 18-21 years); 3 were military recruits, 2 were college students. The median time from immunization to illness onset was 151 days (9 days-3 years).

Case 1:
21 year-old previously-healthy male college student who resided in a student apartment. Received MCV4 2 years and 11 months prior to onset of headache, nausea, fever, chills and right knee pain. The patient's knee was irrigated and debrided and *N. meningitidis*, serogroup Y was isolated from the synovial fluid. The patient improved and was discharged home on hospital day 4.

Case 2:
19 year-old previously-healthy male college student who resided at home with family and coached a youth sports team. Received MCV4 2 years and 7 months prior to onset of headache, fever, altered mental status and petechial rash. *N. meningitidis*, serogroup C was isolated from both blood and CSF. Patient experienced diffuse cerebral edema and expired on hospital day 20.

Case 3:
18 year-old previously-healthy male military recruit who resided in barracks. Received MCV4 151 days prior to onset of fever, upper respiratory tract symptoms, nausea, vomiting, diarrhea and altered mental status. *N. meningitidis*, serogroup Y was isolated from both blood and CSF. The patient survived and was discharged home.

Case 4:
19 year-old previously-healthy male military recruit who resided in barracks. Received MCV4 9 days prior to onset of headache, stiff neck, nausa, shaking chills, joint pain and petechial rash. *N. meningitidis*, serogroup Y DNA was detected in CSF by polymerase chain reaction. Patient received 14 days of IV ceftriaxone, improved and was discharged to his unit on hospital day 15. Six weeks after discharge, patient presented with fever, headache, stiff neck and muscle aches and was determined to have recurrent meningococcal meningitis, confirmed by detection of *N. meningitidis*, non-groupable strain DNA by PCR from CSF. Immunologic testing was conducted and patient was diagnosed with terminal complement deficiency. The patient survived and was discharged to home.

Case 5:
20 year-old previously-healthy male military recruit who resided in barracks. Received MCV4 vaccine 40 days prior to onset of headache, fever and nausea and petechial rash. *N. meningitidis*, serogroup Y was isolated from blood. Patient was hospitalized for 18 days, improved and was discharged to his unit.

Cases in MPSV4 recipients

Two cases of vaccine-preventable invasive disease occurred in MPSV4 recipients:

- A 19-year old previously-healthy military recruit residing in barracks was vaccinated 6 months prior to onset. *N. meningitidis*, serogroup C was isolated from CSF. He improved and was discharged home on hospital day 9.
- A 15 year-old asplenic male high school student was vaccinated 2 years, 3 months prior to symptom onset. *N. meningitidis*, serogroup Y was isolated from blood and CSF. He was hospitalized for 5 months and discharged to rehabilitation.

Cases in vaccine recipients – vaccine type unknown

Two cases with vaccine-preventable serogroups had incomplete vaccine histories. However. the dates of vaccination suggest that both received MCV4. Neither resided in a congregate setting or was attending college at onset of illness:

- A 27 year-old male was vaccinated after splenectomy 3 years, 8 months before illness onset. Vaccine formulation and lot number were not recorded in the chart or pharmacy records. He expired within several hours of hospital admission. *N. meningitidis*, serogroup W-135 was isolated from his blood.
- A 26 year-old previously-healthy male was vaccinated 3 years, 4 months prior to onset. *N. meningitidis*, serogroup C, was isolated from both blood and CSF. The patient improved and was discharged home on hospital day 7.

CONCLUSIONS

This is the largest population-based review of meningococcal disease in vaccinated persons. Although rare, invasive meningococcal disease can occur in immunized people. Of 9 vaccinated cases with a vaccine-preventable serogroup in our cohort; 6 (67%) were serogroup Y, including 4 of 5 (80%) cases who received MCV4. Serogroup Y is the least immunogenic serogroup after immunization with MCV4 or MPSV4 in either adolescents or adults. Although there were disproportionately fewer cases of serogroup C and, not unexpectedly, more cases of serogroup B and among the vaccinated cases, the serogroup distribution was not significantly different between immunized and non-immunized cases of the same age.

There were 3 (13%) deaths among vaccinated cases and 4 (4%) deaths among unvaccinated cases in this time period. The case-fatality rate may be higher among vaccinated persons since vaccine is recommended for individuals that are more susceptible to invasive meningococcal disease and these individuals may also be less responsive to immunization and may also have poorer disease outcomes. More than half (55%) of the cases were vaccinated ≥1 year prior to illness onset. Because of concerns about waning immunity, in 2010 ACIP recently recommended an additional booster dose of MCV4. More studies are needed to determine if waning immunity versus primary vaccine failure contributes to disease in vaccinated persons.

As with Case 4, persons with invasive meningococcal disease after immunization warrant investigation of possible immunodeficiency .

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