Phase I/II, Open-Label Trial of Safety and Immunogenicity of Meningococcal (Groups A, C, Y, and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine in Human Immunodeficiency Virus-Infected Adolescents

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Abstract

Background: Quadrivalent meningococcal polysaccharide conjugate vaccine (MCV4) is routinely recommended for healthy youth in the United States, but there are no data about its use in HIV-infected people.

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Methods: P1065 is a Phase I/II trial of MCV4 safety and immunogenicity in HIV-infected children and youth performed at 27 US sites of the IMPAACT network. All youth (11–24 years old) received 1 dose of open-label MCV4 at entry. Standardized questionnaires were used to evaluate safety. Baseline protective immunity was defined as rabbit serum bactericidal antibody (rSBA) titer ≥1:128. Immunogenic response was defined as a ≥4-fold rise in rSBA against each meningococcal serogroup. Multivariable logistic regression analysis was used to evaluate the association of demographic and clinical characteristics on immunogenic response to serogroup C.

Results: Among 319 subjects who received MCV4, 10 (3.1%) reported immediate adverse events which were local and mild, and 7 (2.2%) experienced Grade ≥3 adverse events, unrelated to vaccine. The 305 subjects with serologic data had a median age of 17 years and were 59% male, 50% Black, and 38% Latino. Subjects were stratified by entry CD4%: 12%, CD4 <15%; 40%, 15% to 24%; and 48%, ≥25%. Baseline protective immunity varied by serogroup: A, 41%; C, 11%; W-135, 15%; Y, 35% The immunogenic response rates to serogroups A, C, W-135, and Y were 68%, 52%, 73%, and 63%, respectively. In multivariable logistic regression models, lower entry CD4%, higher entry viral load, and CDC Class B/C diagnosis were associated with significantly lower odds of response to serogroup C.

Conclusion: Many HIV-infected youth naturally acquire meningococcal immunity. MCV4 is safe and immunogenic in HIV-infected youth, but response rates are lower than in healthy youth, particularly for those with more advanced HIV clinical, immunologic, and virologic status.

A quadrivalent meningococcal polysaccharide conjugate vaccine (MCV4, Menactra) containing *Neisseria meningitidis* serogroups A, C, Y, and W-135 capsular polysaccharide antigens individually conjugated to diphtheria toxoid protein, was approved by the US Food and Drug Administration in 2005 for people aged 11 to 55 years and, then, in 2007 for children aged 2 years and older.[1] Since 2005, the CDC Advisory Committee on Immunization Practices (ACIP) has recommended MCV4 as part of the routine immunization schedule for adolescents (11 years of age and older) in the United States.[2] This recommendation was extended to 2 to 10-year-old children with conditions (eg, anatomic or functional asplenia) that increase their risk of meningococcal infection.[1] Healthy youth make an immunogenic response to MCV4 at high rates (80%–97%), varying by meningococcal sero-group.[3] Although acceptable rates of anticipated local and systemic adverse effects were observed during vaccine trials, cases of Guillain-Barré syndrome (GBS) reported in postmarketing surveil-lance raised concern for a potential association of MCV4 with GBS.[4] Adolescent recipients of MCV4 appear to have a small increase in the rate of GBS as compared with the general population, but ongoing surveillance and analyses have not confirmed that MCV4 is causally related to these GBS cases; at present, pending additional results of those ongoing analyses, MCV4 is not recommended for people with a history of GBS.[5]

The ACIP has acknowledged the potential benefit of giving MCV4 to HIV-infected children and adolescents, since HIV infection likely increases the risk of meningococcal disease.[1,2] In addition, most perinatally acquired and all new adolescent cases of HIV infection in the United States are age-eligible for MCV4. However, there are no data regarding the use of MCV4 in HIV-infected patients of any age. In HIV-infected patients, nonlive vaccines are generally safe and immunogenic but response to vaccines can be less reliable, of lower titer, qualitatively abnormal or of shorter duration, especially if HIV infection is advanced or poorly controlled.[6-13] The objective of IMPAACT Protocol P1065 was to evaluate the safety and immunogenicity of MCV4 in HIV-infected children and youth. The short-term

safety and immunogenicity results following administration of a single dose of MCV4 to HIV-infected youth are presented here.

PATIENTS AND METHODS

P1065 Study Population

P1065 is a Phase I/II safety and immunogenicity trial of MCV4 in HIV-infected children and youth performed at 27 clinical sites of the IMPAACT network in the United States. Eligibility criteria for Version 2.0 of the protocol were: (1) age of 11 to 24 years; (2) on stable antiretroviral therapy (ART) or not receiving ART for at least 90 days prior to vaccination; (3) no personal or family history of GBS; and (4) no meningococcal polysaccharide vaccine within last 2 years and no MCV4 at any time. Additional exclusion criteria included pregnancy, breastfeeding, receipt of other killed vaccines within 2 weeks before entry, receipt of live vaccines within 4 weeks before entry, planned receipt of other vaccines 2 weeks after entry, use of systemic immunosuppressant or immunomodulatory drugs, malignancy, hypersensitivity to MCV4 components, bleeding problems precluding intramuscular injection, or signs/symptom suggestive of GBS including areflexia in all 4 extremities, and presence of any new and unresolved grade ≥3 laboratory or clinical toxicity. Subjects of reproductive potential were required to commit to avoiding pregnancy for the duration of the study. At the time of enrollment, subjects were stratified by CD4% into 3 groups: <15%, 15% to 24%, and ≥25%. Subjects were enrolled between July and October of 2007. A later version (Version 3.0) of P1065 subsequently opened in September 2008 to 2 to 10-year-old HIV-infected children with CD4 ≥15%; this study of younger children is ongoing and therefore these results will not be reported here.

P1065 Study Protocol

All sites received approval for the study through their local Institutional Review Board (IRB). Subjects or their parents/guardians signed an informed consent prior to participation; written assent was obtained as required by local IRBs.

All eligible subjects were administered the MCV4 vaccine (Meningococcal [Groups A, C. Y and W-135] polysaccharide diphtheria toxoid conjugate vaccine - Menactra, Sanofi-Pasteur, Swiftwater, PA; 0.5 mL intramuscular injection) at study entry. At 24 weeks, all eligible subjects with entry CD4 <15% received a second dose of MCV4; eligible subjects within the CD4 15% to 24% and CD4 ≥25% strata were randomly assigned to receive a second dose of MCV4 or no additional vaccine in 1:1 proportion.

Safety

The outcome measures for safety objectives included the number and percent of subjects with documented reactions to the vaccine, with ≥grade 3 adverse events (AEs) and with suspected or proven GBS. AEs were graded according to the December 2004 DAIDS AE Grading Table[14] and were based on laboratory evaluations, signs and symptoms, local vaccine reactions, and adverse event reports. Subjects were observed for 30 minutes postvaccination and were contacted by telephone at 3, 7, and 42 days after each vaccine administration. In addition, standardized questionnaires were administered during the study visits at 4, 24, 28, and 72 weeks after initial immunization. Signs and symptoms suggestive of GBS were collected on case report forms. The safety assessment reported here is limited to the 42-day period after initial MCV vaccine dose and includes all enrolled subjects who received at least 1 MCV4 administration.

Immunogenicity

The primary criterion for an immunogenic response was a ≥4-fold rise in functional serum bactericidal antibody (SBA) titer against each meningococcal serogroup (A, C, W-135, and Y). Serum was obtained at entry (prevaccine) and at weeks 4, 24, 28, and 72 on all subjects. SBA assays using a baby rabbit complement source (rSBA) were performed at Sanofi Pasteur, Inc., as previously described.[3] This report presents 4-week immunogenicity results for all subjects who received the first MCV4 dose and had entry and 4-week sera available. The immunogenicity results at 24, 28, and 72 weeks and the effect of a second dose of vaccine will be reported at a later time. Absolute rSBA titer correlates of immunity were classified as: ≥1:128 immune; <1:8 susceptible; and 1:8 to 1:64 indeterminate.[15,16]

Statistical Methods

Response rates for each serogroup were calculated based on at least a 4-fold rise in rSBA titer from prevaccine level. In addition, rates of absolute rSBA titer of at least 1:128 and geometric mean titers (GMT) were calculated for each serogroup. Standard errors for response rates were based on the binomial distribution. The target sample size for subjects with CD4 ≥15% in this study (N = 117 per arm) was chosen to provide a power of 80% to detect an odds ratio of 2.5 between 72-week immunogenic response rate in recipients of 1 dose versus 2 doses of MCV4 with a 2-sided significance level of 0.05, given an anticipated response to serogroup-C in the 1-dose arm of 70%.

Univariate logistic regression analysis was used to assess the association of subject characteristics with the immunogenic response to each serogroup. ART status was determined based on whether a subject was on a regimen classified as highly active ART (HAART) or not on HAART at the time of study enrollment; HAART was defined as a regimen containing at least 3 antiretroviral drugs from at least 2 drug classes. Multivariable logistic regression modeling was used to evaluate the association of the above factors on immunologic response to serogroup C. All factors with $P < 0.20$ in univariate models were included as candidate predictors; the final model retained only those covariates with $P < 0.10$.

Statistical analyses were conducted using SAS Version 9 (SAS Institute, Cary, NC). A level of 0.05 was used for statistical significance. All analyses are based on data submitted by January 5, 2009.

RESULTS

P1065 Study Population

Of 324 participants enrolled in the study between July and October of 2007, 319 received the first MCV4 dose and contributed to safety analyses. Two subjects were later found to be ineligible. Of the 317 eligible participants who received the first dose of MCV4, 305 had entry and week 4 serology results and are included in the immunogenicity analyses. Subjects included in the immunogenicity analysis (n = 305) were similar to those not included (ineligible or without serology results, n = 14), except that those not included were less likely to be receiving HAART (50% vs. 82%, Fisher exact test $P = 0.008$). Baseline characteristics for all 319 subjects who received MCV4 are displayed in Table, Supplemental Digital Content 1, http://links.lww.com/INF/A305.

Safety

Of 319 subjects, 10 (3.1%) reported immediate local vaccine reaction adverse events (AEs) after the initial MCV4 administration, predominantly pain and tenderness at the injection site; all local AEs were mild (grade 1). The overall rate of subjects experiencing grade 3 or

higher AEs within 42 days of immunization was 2.2%, with AE rates inversely related to entry CD4% category (Table 1). Grade ≥3 laboratory abnormalities were reported in 2 (0.6%) subjects, including one subject with neutropenia and leucopenia and another with neutropenia, leucopenia and thrombocytopenia; both had a prestudy history of lower-grade neutropenia. Grade ≥3 signs or symptoms were reported by 5 subjects (1.6%), who reported headache (n = 2), fever (n = 1), pain (n = 1), and psychiatric symptoms (n = 1). All grade ≥3 AEs were judged not related to vaccine. There were no deaths and no cases of GBS or meningitis within 42 days of immunization.

Serum Bactericidal Antibody Activity and Response Rates

At study entry, 62% of subjects had baseline immunity (rSBA titer ≥1:128) to at least 1 serogroup, but baseline immunity to individual serogroups ranged from 11% to 41% (Fig. 1). Baseline CD4% and VL categories were not associated with baseline immunity to any serogroup; factors that were associated with baseline immunity to some serogroups were: CDC stage B/C (serogroups C, W-135, Y), older age (serogroups C and Y), and nonperinatal HIV acquisition (serogroups A, C, Y) (data not shown).

The proportions with ≥4-fold SBA titer rise to individual serogroups ranged from 52% to 73% (Table 2); 88% had ≥4-fold rSBA titer rise to at least 1 serogroup. When subjects with baseline immunity were excluded, the proportions with ≥4-fold rSBA titer rise were similar for serogroups C, W-135, and Y (51% [±3%], 73% [±3%] and 65% [±3%], respectively), but higher for sero-group A (76% [±3%]). For all serogroups, the median rSBA titer was <1:8 at baseline but at 4 weeks exceeded the 1:128 titer associated with protective immunity (Table 2). Serogroups with higher baseline GMT consistently had higher 4-week GMT (Table 2). By all measures, serogroup C demonstrated the lowest rates of response and immunity.

Univariate Predictors of MCV4 Vaccine Response

For all 4 serogroups, lower baseline CD4% (OR: 0.03–0.24 for CD4 <15% and OR: 0.35–0.48 for CD4 15 to <25% compared with CD4 > = 25%; *P* < 0.001 for each serogroup) and higher baseline VL category (OR: 0.08–0.25 for VL >10,000 copies/mL and OR: 0.44–0.78 for 400–10,000 copies/mL compared with VL <400 copies/mL; *P* < 0.001 for each serogroup) were strongly associated with lower odds of serologic response 4 weeks after immunization (Table, Supplemental Digital Content 2, http://links.lww.com/INF/A306). More advanced HIV clinical disease (CDC stage B or C) at study entry was also associated with lower odds of serologic response but not as strongly (OR: 0.41–0.58, *P* < 0.001–0.03). There was no association between response to any serogroup and route of acquisition of HIV infection, use of HAART at entry, duration of HAART, or demographic characteristics.

Predictors of MCV4 Vaccine Response for Serogroup C

Because the correlation of serologic titers and protective immunologic response are most clearly established for serogroup C, response to this serogroup was chosen a priori for multivariable analysis of predictors of response to MCV4.15 Characteristics with *P* < 0.20 in univariate logistic regression analyses of a 4-fold response were examined in the multivariable analysis: screening CD4% stratum, entry VL, entry CDC clinical class (classes B/C vs. A/N) and sex. After adjustment for CD4%, viral load, and CDC class, sex was no longer significantly associated with response and was removed from the final model. In the final reduced multivariable model, response rates were found to be significantly decreased in subjects with entry CD4% <25 (adjusted OR [AOR] of 0.61 for CD4% of 15–24, AOR of 0.14 for CD4% <15, *P* = 0.003), HIV viral load ≥400 copies/mL (AOR of 0.62 for VL 400–10,000 copies/mL, AOR of 0.33 for VL >10,000 copies/mL, *P* = 0.005), or having CDC

Class B or C at study entry (AOR 0.38, *P* < 0.001) (Table 3). Multivariable models for response to other serogroups showed similar findings (data not shown).

DISCUSSION

A single dose of MCV4 was safe and immunogenic for HIV-infected youth in this trial. The higher rate of AEs in the most immunocompromised group was not surprising, as this group has high rates of laboratory and clinical abnormalities in the absence of immunization.[17,18] The local AEs following MCV4 administration were less common and milder than those reported following administration of MCV4 to healthy youth in previous studies.[3] There were no cases of GBS. However, in this small study, we can only conclude that the rate of GBS following MCV immunization of HIV-infected youth is not more than 7600/100,000 person-months, leaving us unable to detect differences from or increases over the historical rate, either with (0.2/100,000 person-months) or without (0.11/100,000 person months) MCV4 immunization.[5]

Levels of baseline immunity (attributed to naturally acquired immunity) in this population varied by serogroup. Rates of preexisting immunity were especially high for serogroups A (41%) and Y (35%) but much lower for serogroups C (11%) and W-135 (15%). In one study of HIV-uninfected US youth, pre-existing immunity was extremely low for serogroup A (1%) but more common (13%–24%) for the other serogroups; however, immunity in that study was defined as SBA ≥1:8 with an assay using human-derived complement which may be less directly comparable to the current study.[19] In another study of healthy youth using the rSBA assay, pre-existing immunity as measured by GMT was also highest for serogroups A and Y, but lower for serogroup W-135 than for serogroup C.[3] In addition, baseline GMT for each serogroup in these healthy youth[3] was higher than the baseline GMT for the corresponding serogroup in the current study of HIV-infected youth. Naturally acquired immunity to meningococcal serogroups normally increases through adolescence and young adulthood, though the age and rate of acquisition vary by study location, population and time period as well as methods used.[20-23] It is hypothesized that colonization—by meningococci or nonpathogenic commensal organisms with cross-reactive antigens—without symptomatic infection or disease accounts for development of immunity in the absence of immunization or disease.[20] It is reassuring that HIV-infected youth, regardless of their immunologic status and degree of virologic control, appear to acquire natural immunity to meningococci at a similar rate, though perhaps at a lower antibody titer.

Immunogenicity was evaluated with a standardized SBA, using baby assay serum as a complement source (rSBA), as recommended by the World Health Organization[15] and as used in a similar immunogenicity study of MCV4 in healthy (HIV-uninfected) youth.[3] For each serogroup, the majority of HIV-infected youth in this study developed a 4-fold or greater increase in rSBA titer at 28 days after immunization, regardless of whether they were HIV-infected perinatally or through high-risk behaviors. The response rates to each serogroup, however, were lower than the corresponding rates reported for similarly aged HIV-uninfected youth (Fig. 2).[3] There were high rates of protective immunity (≥1:128) to serogroups A, W-135, and Y 4 weeks after immunization. However, the rates of 4-fold antibody response and postimmunization titer of ≥1:128 for serogroup C were substantially lower than for other serogroups, a concern for protecting these youth during serogroup C outbreaks. Lower response rates and lower postimmunization titers compared with those in studies of healthy peers are consistent with findings of other studies of HIV-infected children (reviewed in reference).[6,24]

The association of higher VL, lower CD4% and more advanced HIV disease stage with lower odds of vaccine response was consistent across all 4 serogroups contained in the

MCV4 vaccine and all remained independently and strongly associated with vaccine nonresponse in the multivariable model. Severe immunosuppression (CD4 <15%) was associated with the greatest reduction in odds of responding to the vaccine, suggesting that immunization in this group is unlikely to produce protective immunity.[7,8] These factors were also independent predictors of vaccine response in studies of conjugated pneumococcal, pertussis booster, and hepatitis A vaccines in HIV-infected children.[7,8,25] In other studies, however, there was no correlation between baseline VL or CD4 count and response of HIV-infected children to conjugated pneumococcal vaccine,[26] and a strong association of baseline VL but not CD4% with high-titer antibody response to hepatitis A vaccine in HIV-infected children.[9] However, these studies[9,26] were limited to children without severe immunosuppression at baseline. Studies, like the current one, which include patients with the full range of CD4 values, can more readily demonstrate the negative impact of low baseline CD4% on vaccine response.[7,8,25] The contribution of lifetime CD4 nadir, independent of CD4% at immunization, to predicting vaccine response has been inconsistent across other studies and was not evaluated in the present study.

There are some additional limitations of this study. The main outcome measure was a serologic correlate of protective immunity without a true trial of efficacy, which is the only practical approach for a disease as uncommon as meningococcal disease. This study was not able to assess the contribution of HAART to subjects' responses to immunization, since HAART was not randomly assigned and thus estimates of the association between HAART and vaccine response are likely to be confounded by subject characteristics that influence treatment in a clinical setting. HAART may disproportionately be given to patients with more advanced disease which may make them less likely to respond to vaccines, but HAART may also preserve or restore immunologic function, thus increasing ability to respond to vaccines.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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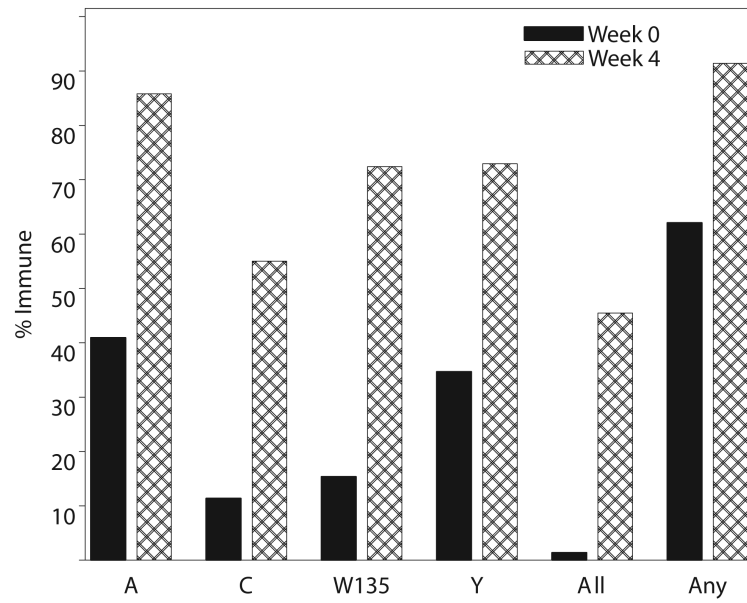**FIGURE 1.**
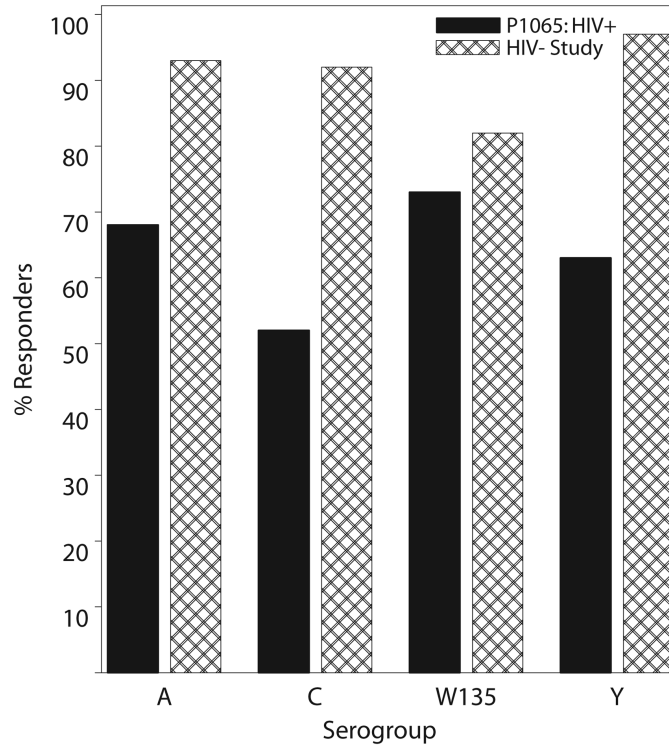Percentage of subjects immune (≥1:128) at baseline and week 4 by serogroup.

FIGURE 2.
Rates of response (≥4-fold increase in rSBA titer) at week 4 by serogroup in current study and in published study of healthy youth.3

TABLE 1

Study Participants With Adverse Events Occurring Within 42 d After Immunization, by CD4% Stratum at Screening (N = 319)

Adverse Event (AE)	CD4% Stratum at Screening			Overall (n = 319)
	<15% (n = 39)	15%–24% (n = 127)	≥25% (n = 153)	
Death or GBS	0	0	0	0
Laboratory AEs, grade ≥3	2 (5.2%)	0	0	2 (0.6%)
Signs and symptoms AEs, grade ≥3	1 (2.6%)	3 (2.4%)	1 (0.7%)	5 (1.6%)
Any of above	3 (7.9%)	3 (2.4%)	1 (0.7%)	7 (2.2%)
Any of above, possibly related to MCV4 vaccine	0	0	0	0

TABLE 2

Response Rates and rSBA Titers by Serogroup

Serogroup	Geometric Mean Titer (95% Confidence Limits)		Median (Interquartile Range[*]) Titer		≥4-Fold Increase in rSBA Titer at Week 4	rSBA Titer ≥128	
	Week 0	Week 4	Week 0	Week 4		Baseline	Week 4
A	39 (28, 53)	1424 (1039, 1951)	<8 (<8, 512)	2048 (512, 8192)	68%	41%	86%
C	8 (6, 9)	107 (75, 154)	<8 (<8, <8)	256 (<8, 2048)	52%	11%	55%
W-135	9 (8, 11)	239 (179, 318)	<8 (<8, <8)	512 (64, 2048)	73%	15%	72%
Y	28 (22, 36)	303 (227, 403)	<8 (<8, 128)	512 (64, (2048)	63%	35%	73%

[*]Due to assay limitations, exact titers could not be provided for results <8 or >131,072. For purposes of calculating medians and geometric mean titers, results <8 were set equal to 4 and those > 131,072 were set equal to 262,144. Interquartile range: 25th percentile to 75th percentile.

TABLE 3

Multivariable Logistic Regression Results for Immunogenicity Response to Serogroup C as Predicted by Clinical Characteristics

Predictor	Adjusted Odds Ratio for Response	95% Confidence Interval	P
CD4 stratum			0.003
<15%	0.14	(0.04, 0.45)	
15−≤25%	0.61	(0.36, 1.04)	
≥25%	1.00	(Ref.)	
Viral load: (copies/mL)			0.005
<400	1.00	(Ref.)	
400–10,000	0.62	(0.33, 1.17)	
>10,000	0.33	(0.17, 0.64)	
CDC clinical classification			<0.001
Class N/A	1.00	(Ref.)	
Class B/C	0.38	(0.23, 0.64)	