Published in final edited form as:
J Pediatr Gastroenterol Nutr. 2010 May ; 50(5): 481–485. doi:10.1097/MPG.0b013e3181bab2ee.

Exposure to *Helicobacter pylori*-positive Siblings and Persistence of *Helicobacter pylori* Infection in Early Childhood

Diana Cervantes, M.S., M.P.H.[*],
The University of North Texas Health Science Center

Lori A. Fischbach, M.P.H, Ph.D.,
The University of North Texas Health Science Center

Karen J. Goodman, Ph.D.,
University of Alberta

Carl Phillips, Ph.D.,
University of Alberta

Shande Chen, Ph.D., and
The University of North Texas Health Science Center

Cheryl Broussard, Ph.D.
The University of Texas Health Science Center at Houston, School of Public Health

Abstract

Objectives—Cross-sectional studies suggest that *Helicobacter pylori* may be transmitted between siblings. The present study aimed to estimate the effect of a *Helicobacter pylori* infected sibling on the establishment of a persistent *Helicobacter pylori* infection.

Methods—The authors used data collected from a Texas-Mexico border population from 1998–2005 (the "Pasitos Cohort Study"). Starting at age 6-months, *Helicobacter pylori* and factors thought to be associated with *Helicobacter pylori* were ascertained every six month for participants and their younger siblings. Hazard ratios were estimated from proportional hazards regression models with household dependent modeling.

Results—Persistent *Helicobacter pylori* infection in older siblings always preceded persistent infection in younger siblings. After controlling for mother's *Helicobacter pylori* status, breastfeeding, antibiotic use and socioeconomic factors, a strong effect was estimated for persistent *Helicobacter pylori* infection in an older sibling on persistent infection in a younger sibling [Hazard Ratio (HR): 7.6, 95% Confidence Interval (CI): 1.6, 37], especially when the difference in the age of the siblings was less than or equal to 3 years (HR: 16, 95% CI: 2.5, 112**).**

[*]Corresponding author: Diana Cervantes, Tarrant County Public Health, 1101 S. Main St, Rm, 2205, Fort Worth, Texas 76104. Cervantes@unt.edu; Phone: (817), 321-5376 Fax: (817) 321-5353.

Conflict of Interest Statement: The funder played no role in designing this study and the authors are not aware of any preference for particular results that either the funder or investigators have. None of the authors have a financial interest in the results of this study, but those who have authored previous publications from this cohort study acknowledge an often overlooked conflict of interest arising from an investment in previous work. In particular, they have an incentive to demonstrate the value of the methods and core findings of the Pasitos Cohort Study, which some commentators have challenged in the past, and this analysis contributes to doing so. However, no particular result from this analysis would tend to do that better than any other result, and so there is no incentive to favor particular results.

The Pasitos Cohort Study was funded by the National Institute of Diabetes and Digestive and Kidney Diseases [Grant RO1-DK053664].

Conclusions—These results suggest that when siblings are close in age, the older sibling may be an important source of *Helicobacter pylori* transmission for younger siblings.

Keywords

Helicobacter pylori; siblings; cohort studies; disease transmission

INTRODUCTION

Helicobacter pylori (*H. pylori*) is one of the most common chronic bacterial infections worldwide; it is estimated that more than half of the world's population is infected with *H. pylori* (1). It is widely accepted that a persistent *H. pylori* infection may lead to serious disease outcomes such as gastric cancer, peptic ulcers and other gastrointestinal diseases (2). A persistent *H. pylori* infection is characterized by long-term colonization of the stomach, often for decades, up to a lifetime, regardless of developing an acquired immune response in the absence of antibiotic therapy (3). Newly acquired *H. pylori* infections often appear to be transient in very young children (4,5), and it is not known what causes many *H. pylori* infections to persist into adulthood in the absence of directed treatment.

H. pylori's mode of transmission is not well understood. Person-to-person is the most likely mode of transmission and evidence has demonstrated that oral-oral, fecal-oral and gastric-oral may be significant transmission routes (2). Previous cross-sectional studies have suggested that siblings may be a source of *H. pylori* transmission, although none of these studies have followed a large cohort of children throughout the first years of life (6–8). Few studies have longitudinally examined factors which influence *H. pylori* transmission. Past studies have been conducted on *H. pylori* transmission in children (6,7) and *H. pylori* persistence (9,10), but studies which prospectively examine sibling-to-sibling transmission and its role in acquiring a persistent infection are lacking. Therefore, our objective was to estimate the effect of exposure to a *H. pylori* infected (or persistently infected) sibling on the acquisition of a persistent *H. pylori* infection in early childhood.

MATERIALS AND METHOD

Data utilized in this analysis was collected from the Pasitos Cohort Study, a previously described prospective birth cohort study conducted from April 1998 through December 2005 at sites along the United States-Mexico border (11). Pasitos Cohort Study participants were drawn from Juarez, Chihuahua, Mexico and the communities of Socorro and San Elizario located in El Paso County, Texas. These sites were selected to investigate how diet, hygiene, socioeconomic and other household factors may play a role in the incidence and persistence of *H. pylori* infection in developed and developing countries (11,12). Additional details pertaining to the study design have previously been reported elsewhere (11,12).

The Pasitos Cohort Study began by recruiting pregnant women who were receiving Women, Infants and Children government assistance at San Elizario and Socorro clinics in El Paso County or who were seeking prenatal benefits at the Mexican Social Security Institute maternal-child clinics in Juarez (11).

The study and the informed consent was approved by the Committee for the Protection of Human Subjects at the University of Texas Health Science Center at Houston, and the institutional review boards at the Mexican Social Security Institute, the University of Texas at El Paso, and the Texas Department of Health. Upon informed consent, baseline information was collected by questionnaire; blood samples and breath samples were also collected as previously described (4,11). Briefly, a questionnaire was administered to the

pregnant women to ascertain basic demographic information as well as factors relating to socioeconomic status and hygiene. Questionnaires were available both in Spanish and English to allow for the language preference of the mother. While the index child was *in utero*, *H. pylori* status of the mother was assessed using the commercially available enzyme immunoassay kit HM-CAP (High-molecular-mass cell-associated protein enzyme immunoassay) previously described (12), which tests for IgG (Immunoglobulin G) antibodies against *H. pylori*.

The first follow-up visit was targeted at six months after the birth of the index child, the main subject of the study; follow-up visits were conducted at target intervals of six months thereafter. All younger siblings born during the study were invited to enroll. At all follow-up visits for index children and younger siblings, a questionnaire was administered to ascertain study factors, including illness history, antibiotic use and dietary intake during the preceding six month interval (12). *H. pylori* status was determined during each follow-up visit using the ^{13}C urea breath test with Klein's correction as previously described (4).

For younger siblings, information regarding baseline study factors was obtained via a baseline questionnaire adapted for younger siblings. Younger siblings' follow-up visits occurred concurrently with the older siblings, rather than at targeted six month age multiples.

Survival analysis was utilized to estimate the effect of having a *H. pylori* infection (or a persistent *H. pylori* infection) in the older (index) sibling on the rate of acquiring an incident (or persistent) infection in a younger sibling. The direction of effect from younger to older siblings was not examined for reasons explained in further detail below. The proportional hazards regression model was used to obtain hazard ratios and 95% confidence intervals (CI). Since the observations within a household are not independent, we used the method proposed by Lee EW and colleagues (13) to adjust for the dependence within the household. This model uses a working independent model with a general estimation equation approach.

The first incident *H. pylori* infection and persistent infection in the younger sibling were used as the outcome variables in our models. An incident case was defined as a positive *H. pylori* breath test result after a previous negative test (or birth, if the first test was positive). Persistence was defined as three consecutive positive *H. pylori* breath test results with no subsequent negative test results. All breath test results including the first and last results were counted and utilized in the analysis. In relation to each outcome, the main exposures of interest were any *H. pylori* positivity and persistent positivity in the older (index) siblings. In households with three or more siblings in the study, these exposure variables (any *H. pylori* positivity and persistent positivity) came from the index subjects, and not from the second or subsequent siblings.

The time at risk (or time to event) variable was defined for the initial acquisition of *H. pylori* infection and persistent infection in the younger siblings. Given interval-censored infection onsets, time of initial acquisition of infection was estimated as the midpoint between the immediately preceding negative breath test and the first positive breath test. For younger siblings who tested positive at their first follow-up visit, the time of risk for the initial acquisition was defined as the midpoint between birth and the first visit. Time of acquisition of a persistent infection was defined as the midpoint between the first and third consecutively positive breath tests. For subjects who did not become infected (or persistently infected), the sum of all time intervals in which data was collected was defined as the time at risk of infection (or persistence). The proportionality assumption was checked by plotting the hazard of each exposure by person-time in months.

Several variables were included as possible confounders in the regression models. Socioeconomic status was controlled for based on *a priori* knowledge of which socioeconomic variables are associated with *H. pylori* frequency, and therefore included the variables of mother's years of education and household size (14). The mother's baseline *H. pylori* status (seropositivity) (15), the number of months the child was breastfed (14) and number of antibiotic courses taken (14) were also adjusted for based on *a priori* information. The difference in age between the siblings and the country of residence (United States or Mexico) were treated as effect modifiers by stratifying the models on these factors.

RESULTS

In the Pasitos Cohort Study, 472 index subjects and 143 younger siblings returned for follow-up and had one or more breath tests. A total of 3,114 follow-up visits were conducted, with index children attending an average of 5.5 visits and younger siblings attending an average of 3.7 visits. The mean follow-up time, starting at 3–9 months of age, was 3.8 years for index children and 2.5 years for younger siblings. Among index subjects with younger siblings, the average age at last follow-up was 5.6 years. One or more valid ^{13}C urea breath test results were obtained from 468 index subjects (99%). Of these, 212 (45%) acquired *H. pylori* at least once during follow-up and 34 (7%) became persistently infected, while of 136 siblings with complete data for the current analysis, 49 (36%) acquired *H. pylori* and 10 (7%) became persistently infected.

H. pylori seropositivity status at baseline was obtained for 454 (96%) mothers in the Pasitos Cohort Study. Of these mothers, antibodies against *H. pylori* were detected in 283 (63%). Maternal *H. pylori* seropositive status occurred in 135 (64%) households with an infected index child and 30 (88%) households with a persistently infected index child.

Of 212 index subjects who acquired *H. pylori*, there was no instance in which the younger sibling's *H. pylori* acquisition preceded that of the index subject. In all instances except four, the first incident infection in the older index sibling was acquired prior to the first incident infection in a younger sibling; in the other four occasions, the first incident infection was acquired simultaneously. All 34 cases of persistent *H. pylori* infection in the index subject preceded the acquisition of a persistent infection in the younger sibling. Therefore, we only present the results of analyses examining the effect of incident and persistent infections of *H. pylori* in the direction of the older index sibling's status affecting incident and persistent infections of *H. pylori* in the younger sibling.

Results of survival analysis controlling for mother's *H. pylori* status, mother's education, household size, number of antibiotic courses, and months breastfed revealed that younger siblings whose older sibling was infected with *H. pylori* were roughly just as likely to be infected with *H. pylori* as those who did not have an infected older sibling (HR: 1.1, 95% CI: 0.61, 1.8) (Table 1). However, a younger sibling was nearly three times more likely to acquire an *H. pylori* infection when their older index sibling had a persistent infection compared to younger siblings whose older index sibling did not have a persistent *H. pylori* infection (HR: 2.8, 95% CI: 1.6, 4.9) (Table 1). Stratified analysis showed that the effect of exposure to a persistently infected older sibling on the acquisition of *H. pylori* in younger siblings was greater in the United States (HR: 3.5, 95% CI: 1.4, 9.1) than in the Mexico (HR: 2.5, 95% CI: 1.0, 5.9), and among siblings close in age (≤3 years apart) (HR: 3.7, 95% CI: 1.5, 8.7) versus those farther apart in age (HR: 2.4, 95% CI: 0.92, 6.2) (Table 1).

Younger siblings were at an even greater risk of acquiring a persistent infection if their older index sibling had a persistent infection. Younger siblings whose older index sibling had a persistent infection were roughly eight times more likely to become persistently infected

compared to those whose older index sibling was not persistently infected with *H. pylori* (HR: 7.6, 95% CI: 1.6, 37) (Table 2). The effect of exposure to an older persistently-infected sibling on persistent infection in a younger sibling was greater in Mexico (HR: 37, 95% CI: 6.0, 224) than in the United States (HR: 8.9, 95% CI: 0.74, 107), and greater among siblings close in age (≤3 years) (HR: 17, 95% CI: 2.5, 113) than those farther apart in age (HR: 1.8, 95% CI: 0.15, 21).

In considering the other covariates in our model for the effect of exposure to an older infected sibling on the incident infection of a younger sibling, none of the covariates appeared to have an independent effect on the incident infection in the younger sibling (Table 3). These results are similar when evaluating other covariates in estimating the effect of exposure to a persistently infected older sibling on the incident infection of a younger sibling (Table 3).

When taking into account the effect of exposure to an persistently infected older sibling on the persistent *H. pylori* infection of a younger sibling, other covariates in the model indicate that increasing household size (HR: 0.86, 95% CI: 0.58, 1.3) and years of education obtained by the mother (HR: 0.74, 95% CI: 0.50, 1.1) appeared somewhat protective (Table 3). We observed that a younger sibling was almost four times more likely to become persistently infected with *H. pylori* if the mother was seropositive for *H. pylori* at the beginning of the study compared to a younger sibling whose mother was seronegative for *H. pylori* at the beginning of the study, however the confidence interval was wide and the direction of the association less certain (HR: 3.9, 95% CI: 0.69, 22.7) (Table 3).

DISCUSSION

Due to the role children are thought to play in *H. pylori* transmission, our aim was to estimate the effect of exposure to *H. pylori* infection (or a persistent infection) in siblings on the establishment of a persistent *H. pylori* infection. Our findings are consistent with person-to-person transmission occurring from older to younger siblings living in the same household. We found that the establishment of an *H. pylori* infection occurred first in the older sibling and later in the younger sibling, but never vice versa. Having an *H. pylori*-infected older sibling was associated with an increased rate of acquiring a persistent *H. pylori* infection in a younger sibling, and having a persistently infected older sibling increased the rate of acquiring a persistent infection in a younger sibling by approximately eight-fold. Further, persistent infections were most likely to be transmitted between siblings closer in age. A 17-fold increased rate of persistent infection was observed when the difference in the age of the siblings was three years or less. All of these effects were observed after controlling for the mother's *H. pylori* infection and other potential confounders.

Previous cross-sectional studies have also suggested that family composition, specifically siblings, may influence *H. pylori* transmission (6,8). In the study by Goodman and Correa, the odds of a prevalent *H. pylori* infection in Aldana, Colombia increased as the number of two to nine year-old siblings in the household increased, and *H. pylori* infection was especially likely when siblings were less than four years apart in age (6). In the study by Kivi et al, shared strains of *H. pylori* were most commonly observed among siblings, followed by mother-child relationships (8). These studies were limited by their cross-sectional design, and therefore were not able to evaluate the time sequence for *H. pylori* transmission or persistence.

The present prospective cohort study provides evidence to suggest that transmission occurs from the older to the younger siblings. It also estimates rate ratios for the effect of an older

sibling's infection on the incidence and persistence of a younger sibling's infection. *H. pylori* transmission between siblings was the focus of the present analysis as mother's *H. pylori* status was not associated with the incident infection of the older index sibling in previous Pasitos Cohort analyses (16). Although in the current study the seropositivity status of the mother was associated with the persistent *H. pylori* status of the younger sibling, the effect estimate was not as large as observed for the persistently infected older (index) sibling and the direction of effect was less certain. While there have been reports examining populations in which strong associations between mother's and children's infection status was observed, this is not consistent across populations and study designs (6).

We should mention that the wide confidence intervals for the hazard ratios from the stratified analyses indicate a lack of precision for stratum-specific estimates (Tables 1 and 2). Thus, though the results strongly support the claim of association, which we believe is causal, estimates of the strength of associations are imprecise. We were not able to simultaneously stratify on country of origin and the siblings' age difference due to sparse numbers and the resulting instability of the models. Additionally, we did not have bacterial genotype information to examine the specific strain of *H. pylori* in the siblings to provide further evidence to support the hypothesis that the older sibling was the source of the younger siblings' infection. As such, we cannot rule out the influence of other household members besides the mother and siblings enrolled in our study.

This study contributes to the overall knowledge regarding transmission patterns of *H. pylori* and provides evidence to suggest possible unilateral transmission of *H. pylori* in early childhood from older sibling to younger siblings, particularly when they are close in age. Although further cohort studies that examine the specific strain of *H. pylori* in household members may provide more direct evidence of transmission routes within families, our study provides a strong basis and direction for additional research possibly leading to more effective treatment and prevention strategies.

References

1. Kato S, Sherman PM. What is new related to *Helicobacter pylori* infection in children and teenagers? Arch Pediatr Adolesc Med 2005;159(5):415–21. [PubMed: 15867113]
2. Miyaji H, Azuma T, Ito S, et al. *Helicobacter pylori* infection occurs via close contact with infected individuals in early childhood. J Gastroenterol Hepatol 2000;15(3):257–62. [PubMed: 10764025]
3. Algood HM, Cover TL. *Helicobacter pylori* persistence: An overview of interactions between *H. pylori* and host immune defenses. Clin Microbiol Rev 2006;19(4):597–613. [PubMed: 17041136]
4. Goodman KJ, O'Rourke K, Day RS, et al. Dynamics of *Helicobacter pylori* infection in a US-Mexico cohort during the first two years of life. Int J Epidemiol 2005;34(6):1348–55. [PubMed: 16076858]
5. Phillips CV, Goodman KJ. Interpreting data in the face of competing explanations: assessing the hypothesis that the observed spontaneous clearance of *Helicobacter pylori* was all measurement error. Int J Epidemiol 2009:1–8.
6. Goodman KJ, Correa P. Transmission of *Helicobacter pylori* among siblings. Lancet 2000;355(9201):358–62. [PubMed: 10665555]
7. Tindberg Y, Bengtsson C, Granath F, et al. *Helicobacter pylori* infection in Swedish school children: Lack of evidence of child-to-child transmission outside the family. Gastroenterology 2001;121(2):310–16. [PubMed: 11487540]
8. Kivi M, Tindberg Y, Sorberg M, et al. Concordance of *Helicobacter pylori* strains within families. J Clin Microbiol 2003;41(12):5604–08. [PubMed: 14662948]
9. Perez-Perez GI, Sack RB, Reid R, et al. Transient and persistent *Helicobacter pylori* colonization in Native American children. J Clin Microbial 2003;41(6):2401–07.

10. Okuda M, Miyashiro E, Booka M, et al. *Helicobacter pylori* colonization in the first 3 years of life in Japanese children. Helicobacter 2007;12(4):324–27. [PubMed: 17669105]
11. Goodman KJ, O'Rourke K, Day RS, et al. Establishment of a binational cohort to study *Helicobacter pylori* infection in children. Ethn Dis 2003;13(3):387–94. [PubMed: 12894964]
12. O'Rourke K, Goodman KJ, Grazioplene M, et al. Determinants of geographic variation in *Helicobacter pylori* infection among children on the US-mexico border. Am J Epidemiol 2003;158(8):816–24. [PubMed: 14561672]
13. Lee, EW.; Wei, LJ.; Amato, DA. Cox-type regression analysis for large numbers of small groups of correlated failure time observations. In: Klein, JP.; Goel, PK., editors. Survival Analysis, State of the Art. Dordrecht: Kulwer Academic Publishers; 1992. p. 237-47.
14. Magalhaes Queiroz DM, Luzza F. Epidemiology of *Helicobacter pylori* infection. Helicobacter 2006;11(Suppl 1):1–5. [PubMed: 16925604]
15. Weyermann M, Adler G, Brenner H, et al. The mother as source of *Helicobacter pylori* infection. Epidemiology 2006;17(3):332–34. [PubMed: 16452833]
16. Wang C, Goodman KJ, Day RS, et al. Mother's infection status and H. pylori incidence in a US-Mexico birth cohort. Am J Epidemiol 2003;157:S85.

Table 1

Effect of exposure to an *H. pylori*-infected older sibling on a younger sibling acquiring an incident *H. pylori* infection, Pasitos Cohort, Juarez, Mexico/El Paso, Texas, 1998–2005.

Exposure variable	Incident Infections (n)[a]	Person Time (Months)[b]	Hazard Ratio[c]	95% CI[c,d]
Overall	49	3113		
Infected older sibling[e]	31	1911	1.1	0.61, 1.8
Uninfected older sibling	18	1202	1.0	
Persistently infected older sibling[f]	13	307	2.8	1.6, 4.9
Not persistently infected older sibling	36	2806	1.0	
≤3 years of age between siblings	25	1885		
Infected older sibling[e]	14	1064	1.4	0.54, 3.6
Uninfected older sibling	11	821	1.0	
Persistently infected older sibling[f]	6	140	3.7	1.5, 8.7
Not persistently infected older sibling	19	1745	1.0	
> 3 years of age between siblings	24	1228		
Infected older sibling[e]	17	847	1.2	0.53, 2.6
Uninfected older sibling	7	381	1.0	
Persistently infected older sibling[f]	7	167	2.4	0.92, 6.2
Not persistently infected older sibling	17	1061	1.0	
Mexico	34	1972		
Infected older sibling[e]	19	1301	0.80	0.41, 1.6
Uninfected older sibling	15	671	1.0	
Persistently infected older sibling[f]	6	144	2.5	1.0, 5.9
Not persistently infected older sibling	28	1828	1.0	
United States	15	1141		
Infected older sibling[e]	12	610	2.0	0.62, 6.7
Uninfected older sibling	3	531	1.0	
Persistently infected older sibling[f]	7	163	3.5	1.4, 9.1
Not persistently infected older sibling	8	978	1.0	

[a] Number of incident infections in the numerator of the crude rate

[b] Person months used in the denominator of the crude rate

[c] Confidence Interval

[d] Adjusted for mother's *H. pylori* status, mother's years of education, household size, number of months of breastfeeding, and number of antibiotic courses.

[e] One or more urea breath tests positive for *H. pylori* during follow-up.

[f] Three or more consecutive urea breath tests positive for *H. pylori* during follow-up.

Table 2

Effect of exposure to a persistently *H. pylori*-infected older sibling on a younger sibling acquiring a persistent *H. pylori* infection, Pasitos Cohort, Juarez, Mexico/El Paso, Texas, 1998–2005.

Exposure variable	Persistent Infections (n)[a]	Person Time (Months)[b]	Hazard Ratio[c,d]	95% CI[c,d]
Overall	10	3906		
Persistently infected older sibling[e]	6	552	7.6	1.6, 37.0
Not persistently infected older sibling	4	3354	1.0	
≤3 years of age between siblings	6	2265		
Persistently infected older sibling[e]	4	237	17	2.5, 113
Not persistently infected older sibling	2	2028	1.0	
> 3 years of age between siblings	4	1641		
Persistently infected older sibling[e]	2	315	1.8	0.15, 21
Not persistently infected older sibling	2	1326	1.0	
Mexico	5	2466		
Persistently infected older sibling[e]	4	228	37	6.0, 224
Not persistently infected older sibling	1	2238	1.0	
United States	5	1440		
Persistently infected older sibling[e]	2	324	8.9	0.74, 107
Not persistently infected older sibling	3	1116	1.0	

[a] Number of persistent infections in the numerator of the crude rate

[b] Person months used in the denominator of the crude rate

[c] Confidence Interval

[d] Adjusted for mother's *H. pylori* status, mother's years of education, household size, number of months of breastfeeding, and number of antibiotic courses.

[e] Three or more consecutive urea breath tests positive for *H. pylori* during follow-up.

Table 3

Hazard ratios for the effect of exposure to an *H. pylori*-infected older sibling on a younger sibling acquiring an incident or persistent *H. pylori* infection and model covariates.

	Younger sibling acquiring incident infection - Model A		**Younger sibling acquiring incident infection Model - B**		**Younger sibling acquiring persistent infection**	
	Hazard Ratio[b]	**95% CI[a, b]**	**Hazard Ratio[b]**	**95% CI[a, b]**	**Hazard Ratio[c]**	**95% CI[a, c]**
Infected older index sibling	**1.1**	**0.61, 1.8**				
Persistently infected older index sibling			**2.8**	**1.6, 4.9**	**7.6**	**1.6, 37.1**
Mother's Education(per year increase)	0.95	0.83, 1.1	0.96	0.85, 1.1	0.74	0.50, 1.1
Household Size(per person increase)	1.1	0.94, 1.3	1.1	0.96, 1.3	0.86	0.58, 1.3
Mother's *H. pylori* Seropositivity (baseline)	1.2	0.62, 2.2	0.98	0.52, 1.9	3.9	0.69, 22.7
Antibiotic Courses(per course increase)	0.92	0.69, 1.2	0.95	0.73, 1.2	1.1	0.53, 2.3
Months Breastfed(per month increase)	1.0	0.95, 1.0	1.0	0.96, 1.0	0.93	0.72, 1.2

[a] Confidence Interval

[b] Overall person-time was 3,113 person months

[c] Overall person-time was 3,283 person months