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Predicting the Probability of Chlamydia Reinfection in African-American Women using Immunologic and Genetic Determinants in a Bayesian Model

Kristin M. Olson, PhD[*,†], **William M. Geisler, MD**[*,†], **Rakesh K. Bakshi, PhD**[*,†], **Kanupriya Gupta, PhD**[*,†], **Hemant K. Tiwari, PhD**[‡]

[*]School of Medicine, University of Alabama at Birmingham, Birmingham, AL, USA

[†]Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, USA

[‡]Department of Biostatistics, University of Alabama at Birmingham, Birmingham, AL, USA

Abstract

Background: African Americans have the highest rates of *Chlamydia trachomatis* (CT) infection in the U.S. and also high reinfection rates. The primary objective of this study was to develop a Bayesian model to predict the probability of CT reinfection in African-American women using immunogenetic data.

Methods: We analyzed data from a cohort of CT-infected African-American women enrolled at the time they returned to a clinic in Birmingham, AL, for treatment of a positive routine CT test. We modeled the probability of CT reinfection within 6 months after treatment using logistic regression in a Bayesian framework. Predictors of interest were presence or absence of an HLA-DQB1*06 allele and CT-specific CD4+ IFN-γ response, both of which we had previously reported were independently associated with CT reinfection risk.

Results: Among 99 participants evaluated, the probability of reinfection for those with a CT-specific CD4+ IFN-γ response and no HLA-DQB1*06 alleles was 14.1% (95% credible interval [CI]: 3.0% – 45.0%), whereas probability of reinfection for those without a CT-specific CD4+ IFN-γ response and at least one HLA-DQB1*06 allele was 61.5% (95% CI: 23.1% – 89.7%).

Conclusions: Our model demonstrated that presence or absence of an HLA-DQB1*06 allele and CT-specific CD4+ IFN-γ response can have an impact on the predictive probability of CT reinfection in African-American women.

SUMMARY

In a Bayesian model, we demonstrated that presence or absence of an HLA-DQB1*06 allele and *Chlamydia trachomatis*-specific CD4+ IFN-γ response can impact the probability of chlamydia reinfection in African-American women.

Corresponding author: William M. Geisler, Department of Medicine, University of Alabama at Birmingham, 703 19th St. South, 242 ZRB, Birmingham, AL 35294; phone: 205-934-4376; wgeisler@uabmc.edu;.

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Keywords

chlamydia; reinfection; HLA; interferon; model

INTRODUCTION

Chlamydia trachomatis (CT) causes the most common sexually transmitted bacterial infection. In the United States in 2018 alone, there were over 1.75 million reported cases of CT infection.[1] Women are disproportionately impacted. Over 1 million of the CT cases reported in the U.S. in 2018 were in women,[1] and CT commonly causes infection of the reproductive organs in women, leading to severe sequelae, including pelvic inflammatory disease (PID) and tubal factor infertility (TFI).[2,3] CT-associated reproductive complications occur even in the absence of genital or pelvic symptoms; almost 80% of CT-infected women do not have symptoms of infection.[4] CT reinfection (i.e. repeat CT infection acquisition after a CT infection has cleared) is a common outcome after treatment of CT infection, occurring in up to 20% of infected women within a year after treatment.[5] Reinfection is concerning because it can lead to reproductive morbidity and transmission of infection to sexual partners. It remains unclear why some women are more susceptible to reinfection than others, and therefore an understanding of predictors of reinfection could be useful in developing strategies to prevent reinfection.

Demographic predictors of CT infection include sex and age.[1] Not only do women account for the majority of reported cases in the U.S., but more specifically, women under the age of 25 account for nearly two-thirds of reported CT cases.[1] Furthermore, African Americans have a nearly six-fold higher rate of infection than Caucasians.[1] However, data has shown sexual behaviors and practices are inconsistent predictors.[6]

While human studies of immune responses associated with CT incidence and reinfection are sparse, findings have been consistent. We and others have demonstrated that a CT-specific CD4+ IFN-γ response is associated with lower rates of CT incidence and reinfection,[7–9] an association that is consistent with murine chlamydia model findings.[10–12] A CD4+ T-cell response is influenced by the human leukocyte antigen (HLA) class II antigens on host antigen presenting cells.[13] Studies that have evaluated for an association between CT-related outcomes and HLA class II variants have been inconsistent, with the exception of findings associated with one allele of the *HLA-DQB1* gene, HLA-DQB1*06, which we have found to be associated with CT reinfection in two separate cohorts.[14–15] We reported an association of HLA-DQB1*06 with CT reinfection in a cohort of high risk, predominately HIV-infected adolescents.[14] We then validated this association of HLA-DQB1*06 with CT reinfection in a cohort of HIV-negative African-American women recruited from a STD clinic in Birmingham, AL.[15] HLA-DQB1*06 has also been associated with CT-related tubal factor infertility,[16] as has other HLA-DQ alleles.[17]

To our knowledge, all previously published studies investigating predictors of CT reinfection have been association studies. However, assessing the predictive probability of potential predictors of reinfection may also provide important knowledge that could be useful in guiding CT testing strategies and possibly CT vaccine development. The number of

statistical models focusing on urogenital CT infection are limited, and none have focused on the impact of immunologic and genetic predictors on the predictive probability of CT reinfection. Of the papers modeling CT urogenital infection, only one by Tu et al. used a Bayesian model and it focused on determining the probability of CT infection acquisition (from a male partner to a female) per sexual encounter, primarily using sexual behavior data.[18]

The purpose of our study was to investigate the effect of a CT-specific CD4+ IFN-γ response and an HLA-DQB1*06 allele on the predictive probability of CT reinfection. We focused on these two immunogenetic markers because our previous studies on this cohort did not identify associations of CT reinfection with other CT-specific CD4+ or CD8+ responses or HLA-DQB1 alleles that we investigated.[8,15] We hypothesized that the subset of women with absence of a CD4+ IFN-γ response and presence of at least one HLA-DQB1*06 allele would have the highest predictive probability of CT reinfection; conversely, we hypothesized that women with presence of a CD4+ IFN-γ response and absence of HLA-DQB1*06 alleles would have the lowest predictive probability of CT reinfection. Thus, we expected that knowledge of CD4+IFN-γ response and status of HLA-DQB1*06 alleles would be highly informative for knowing which patients have a high probability of CT reinfection, and such knowledge could be used in clinical management decisions in the future; for instance, these markers could be measured in women at the time of CT infection treatment and used to make decisions on frequency and timing of repeat CT testing to evaluate for reinfection.

MATERIALS AND METHODS

Data Source

This study evaluated participants from a study cohort described in our previous work.[8,15] Briefly, women ≥16 years of age returning to a STD clinic in Birmingham, AL, for treatment of a recent positive routine CT nucleic acid amplification test (NAAT) were enrolled in a CT study. Exclusion criteria for the study included pregnancy, prior hysterectomy, co-infection with HIV, syphilis, or gonorrhea, immunosuppressed, or use of antibiotics with anti-CT activity in the prior 30 days; these exclusion criteria were chosen because these factors could impact immunogenetic markers being measured or CT test results. At enrollment, participants were interviewed for demographic, clinical, and sexual history information and had a vaginal swab, cervical swab, and blood collected (for immunologic and genetic studies). All participants received azithromycin 1g orally (directly observed) and were advised to refer all sexual partners for treatment if not already treated. All participants were scheduled for 3- and 6-month follow-up visits, at which time they had an interview, a cervical swab collected for CT NAAT to evaluate for CT reinfection, and repeat blood collection (for immunologic studies). HLA-DQB1 genotyping was performed on the DNA (extracted from whole blood) by polymerase chain reaction and Sanger sequencing methods as previously described.[15] Presence of a CT-specific CD4+ IFN-γ response was determined by intracellular cytokine staining combined with flow cytometry as previously reported.[8]

This study included 99 African-American women from our previously described cohort[8,15] who had both HLA-DQB1 genotyping and testing for a CT-specific CD4+ IFN-γ response

performed; HLA typing in this cohort focused on African-American women because women from other race groups accounted for a very small proportion and therefore meaningful analyses accounting for reported race would not be possible. CT reinfection was defined as a participant having a positive CT NAAT at either of their follow-up study visits. If a study participant had a positive CT NAAT at one follow-up study visit but did not complete the other follow-up study visit, she was still categorized as having CT reinfection. Absence of CT reinfection was defined as a study participant completing both follow-up study visits and not having a positive CT NAAT at either follow-up visit. There was limited sexual behavior data collected from participants, including unprotected sex after treatment, that were available for consideration for inclusion in the model.

Conceptual Model

We based our model on the Bayesian framework proposed by Tu et al.[18] The Tu et al. model focused on using sexual behavior data to model probability of CT infection acquisition per sexual encounter, while our model used immunologic and genetic factors to predict acquisition of CT reinfection after treatment (Fig. 1). Since the publication of the Tu et al. paper, a randomized controlled trial investigating the efficacy of CDC recommended CT treatment regimens has been published,[19] showing that the microbiological cure rate for a single dose of azithromycin 1g in women with urogenital CT was 99%. Due to this newly published data and due to the fact that all women in our cohort received directly observed treatment of azithromycin 1g, we did not include a variable for treatment failure in our model. Regarding including sexual behavior variables in our model, we previously found in this cohort that neither reported partner treatment nor a reported new sexual partner since treatment were associated with reinfection.[8] Because we previously found in this cohort a significant association of unprotected sex after treatment with reinfection[8] and a possible trend towards an association of sexual partner number in the prior 3 months with reinfection,[15] we conducted a univariate analysis with these two variables and reinfection in this dataset and did not find any association of unprotected sex or number of sexual partners with CT reinfection (Table 1). Therefore, we did not include a variable for behavior in our model.

Our model preserves the underlying mathematical framework proposed by Tu et al. and then adds immunologic and genetic variables using the proposed logistic model to evaluate their impact on the predictive probability of CT reinfection. In our cohort, all women had confirmed CT infection at baseline; therefore, we narrow the focus to develop a model that predicts the probability of CT reinfection after confirmed CT infection at baseline based on our immunologic and genetic markers of interest.

Data Analysis

Univariate analyses were performed to assess the association between baseline characteristics and CT reinfection using Wilcoxon rank sum test, Fisher’s exact test, or chi-square test of independence, as appropriate. Complete details of the Bayesian models shown in Fig 1. are provided in the Supplemental Methods. Briefly, for Bayesian estimation, we used a logistic regression model and a hierarchical model structure. We estimated three models that included data from all 99 participants (Fig 1.): (a) a baseline model for the

effect of at least one HLA-DQB1*06 allele; (b) a baseline model for the effect of a positive CD4+ IFN-γ response; and (c) the full model to include both the effect of a positive CT-specific CD4+ IFN-γ response and the effect of at least one HLA-DQB1*06 allele. In Bayesian analysis, we need to specify prior probability distributions on all the parameters to be estimated in the model. An informative prior can be useful if there is a large literature from similar studies. In recent years, weakly informative priors are recommended in absence of other known similar studies.[20] We did not use any informative priors due to absence of prior studies modeling CT reinfection using immunologic and genetic predictors; rather, we chose weakly informative priors.[21] In particular, we chose weakly informative priors such that $\beta_0 \sim Cauchy(0,10)$, $\beta_i \sim Cauchy(0, 2.5)$. We based prior distributions on previous work by Gelman et al. (Ann Appl Stat 2008; 2:1360–1383) (see the Supplemental Methods). We used the rstanarm package[22] to fit the model and obtain posterior estimates for the model parameters. To estimate parameters of the regression models in the Bayesian framework, typically it involves to draw a representative sample from the prior distribution for the target posterior distribution. Bayesian software packages such as rstanarm employs simulation techniques known as Markov chain Monte Carlo (MCMC) to obtain a sample consisting of many draws. We used the defaults, such that each model was fit using 4 MCMC chains with 2,000 iterations per chain, of which 1,000 iterations were used as a burn-in. We ran 4 MCMC chains to check that they all converge to the same distribution even if initialized at different starting values. We also used the rstanarm package[22] to calculate the leave-one-out information criteria (LOOIC), the Watanabe-Aikeke information criteria (WAIC), and Bayes R^2 in order to compare model fit.

RESULTS

Participant characteristics at enrollment are shown in Table 1. None of the baseline characteristics were significantly associated with CT reinfection in univariate, non-Bayesian analyses, as was consistent with our previous studies.[8,15] Of the 99 participants, 50 (50.5%) had at least one HLA-DQB1*06 allele and 52 (52.5%) had a CT-specific CD4+ IFN-γ response. Of the 35 participants with reinfection, 23 (65.7%) had at least one HLA-DQB1*06 allele and 13 (37.1%) had a CT-specific CD4+ IFN-γ response. Of the 50 participants with at least one HLA-DQB1*06 allele, 23 (46%) had reinfection. Of the 52 participants with a CT-specific CD4+ IFN-γ response, 13 (25%) had reinfection. Of the 29 participants with both at least one HLA-DQB1* 06 allele and a CT-specific CD4+ IFN-γ response, 10 (34.5%) had reinfection.

We used the posterior estimates (Supplemental Table 1) to calculate the predictive probability of CT reinfection under the HLA-DQB1*06 baseline model (Fig. 2). Specifically, the probability of reinfection for those with at least one HLA-DQB1*06 allele was 45.5% (95% credible interval (CI): 14.9% – 78.8%), whereas probability of reinfection for those without an HLA-DQB1*06 allele was 24.4% (95% CI: 13.8% – 37.5%); the 95% credible interval is a Bayesian 95% confidence interval (i.e., there is a 95% probability that the true [unknown] estimate would lie within the interval, given the evidence provided by the observed data).

Similarly, we used the posterior estimates (Supplemental Table 2) to calculate the predictive probability of CT reinfection under the CD4+ IFN-γ baseline model (Fig. 3). The probability of reinfection for those with a CT-specific CD4+ IFN-γ response was 24.8% (95% CI: 7.1% – 57.8%), whereas probability of reinfection for those without a CT-specific CD4+ IFN-γ response was 46.0% (95% CI: 31.9% – 60.3%).

We built the full model with both a CT-specific CD4+ IFN-γ response and at least one HLA-DQB1* 06 allele. Using the posterior estimates (Supplemental Table 3), we observed that the highest predicted probability of CT reinfection occurred in those without a CT-specific CD4+ IFN-γ response and with at least one HLA-DQB1*06 allele (Fig. 4). The probability of reinfection for those without a CT-specific CD4+ IFN-γ response and at least one HLA-DQB1* 06 allele was 61.5% (95% CI: 23.1% – 89.7%), whereas probability of reinfection with neither a CT-specific CD4+ IFN-γ response nor an HLA-DQB1*06 allele was 33.8% (95% CI: 19.3% – 51.5%). The probability of reinfection for those with both a CT-specific CD4+ IFN-γ response and at least one HLA-DQB1*06 allele was 33.8% (95% CI: 3.8% – 87.0%), whereas probability of reinfection with a CT-specific CD4+ IFN-γ response and no HLA-DQB1*06 alleles was 14.1% (95% CI: 3.0% – 45.0%).

We found that the full model, which included both CD4+ IFN-γ and HLA-DQB1*06, had the lowest leave-one-out information criteria (LOOIC), the lowest Watanabe-Aikeke information criteria (WAIC), and the highest Bayes R^2, of all three models (Supplemental Table 4). This indicates that the full model is a better fit than either baseline model.

DISCUSSION

The objective of our study was to develop a model for predicting the probability of CT reinfection in young African-American women using immunologic and genetic data. We built our model on the flexible Bayesian framework published by Tu et al.[18] and used their proposed logistic structure to include variables for HLA-DQB1*06 and CT-specific CD4+ IFN-γ, both of which we have previously found to be associated with CT reinfection risk. This is the first Bayesian model, to our knowledge, to evaluate the impact of immunologic and genetic predictors on the predictive probability of urogenital CT reinfection.

The major finding from our study was that there was a distinct separation of the predicted probability of CT reinfection in young African-American women based on presence or absence of a CT-specific CD4+ IFN-γ response and HLA-DQB1*06. Specifically, women without a CD4+ IFN-γ response and at least one HLA-DQB1*06 allele had the highest predicted probability of reinfection (61.5%). Conversely, women with a CD4+ IFN-γ response and no HLA-DQB1*06 alleles had the lowest predicted probability of reinfection (14.1%). These findings agreed with our hypothesis. However, in both the scenarios, the credible intervals were wide, showing the range of uncertainty in prediction given the data. The wider CIs could be due to our study's small sample size, implying this was a potential limitation of the study. Furthermore, if we had a much larger sample, the prior would have had a much larger influence on the shape of the posterior distribution, possibly with narrower credible intervals. Notably, the Tu et al. paper discussed the potential importance of unmeasured immune responses in influencing the probability of CT infection

acquisition per sexual encounter in their own model.[18] Indeed, our results showed that an individual's immune response along with an individual genetic variant is an important predictive component of the CT reinfection model. While the mechanism by which HLA-DQB1*06 imparts increased risk for CT reinfection and CT-associated complications is unknown, it is likely related to the adaptive cellular immune response to CT given that HLA-DQB presents exogenous antigens to CD4+ T helper cells.

While we built our model on the Bayesian framework published by Tu et al.,[18] our model had distinct differences from the Tu et al. model. Our model used immunogenetic data to predict probability of CT reinfection after treatment and there was limited behavioral data collected from our cohort, while the Tu et al. model used primarily sexual behavior data to study probability of CT acquisition from a male to a female per sexual encounter and had more comprehensive behavioral data. The study populations were also different. Our population were young adult African American women (median age 22) attending an STD clinic who had CT infection at enrollment; most had unprotected sex after receiving CT treatment and over half reported prior CT infection. In contrast, the Tu et al. study cohort were adolescent females (ages 14–17), mostly African American, who were recruited from primary care clinics, had a diverse range of sexual experience, and most did not have CT infection at enrollment. Thus, our study population was behaviorally less diverse and a higher STI risk cohort than the population in the Tu et al. model,[18] and this may account in part for why behaviors were not a discriminating factor in CT reinfection risk in this cohort. Also, because over half of the women in our cohort reported having CT infection prior to our study, it is possible this could further diminish the influence of CT exposure by behavior, since prior infection may impart some degree of protective immunity against CT exposures as evidenced by its association with decreased reinfection risk[23] and a previous finding that there is a lower CT organism load with repeat CT infection.[24]

While our full model differed from the Tu et al.[18] model, it still preserved their underlying mathematical framework and it illustrated the importance of including immunologic and genetic data as important biological variables in modeling the probability of acquiring CT infection. Future studies interested in modeling CT infection scenarios could consider incorporating both the behavioral variables from Tu et al.[18] and the biological variables we propose in order to best fit their own cohort data. Additionally, future studies could expand on this framework to further clarify the biomarker phenotype of CT infection risk in women, including investigating the role of other immunologic response markers, such as neutralizing antibodies, and conducting more comprehensive genotyping methods in order to evaluate the role of other genetic variants (outside of HLA-DQB1) that may impact the probability of acquiring CT infection.

As with the Tu et al. model,[18] our model is contingent upon some implicit assumptions. First, as discussed above, we assumed that exposure by behavior did not appreciably affect CT reinfection probability in this model. Second, we assumed that our diagnosis of CT reinfection status was accurate, which we felt confident it was due to the use of highly effective, directly observed CT therapy[19] at the time of initial treatment (making the possibility of treatment failure unlikely and its impact on the model negligible) and a highly sensitive CT NAAT for CT detection. There are two potential limitations worth noting. The

strength of the findings in this study was limited by the sample size, which contributed to the credible intervals being large. We also do not know if our reinfection probability estimates will be generalizable to non-African-American women, in whom the frequency of HLA-DQB1*06 and a CT-specific CD4+ IFN-γ response could differ.

In conclusion, our model illustrated the utility of predicting the probability of CT reinfection using immunologic and genetic biomarkers. We found that African-American women had a higher predicted probability of CT reinfection based on an absent CT-specific CD4+ IFN-γ response and the presence of at least one HLA-DQB1*06 allele. A better understanding of immunogenetic predictors of reinfection could influence CT prevention and control strategies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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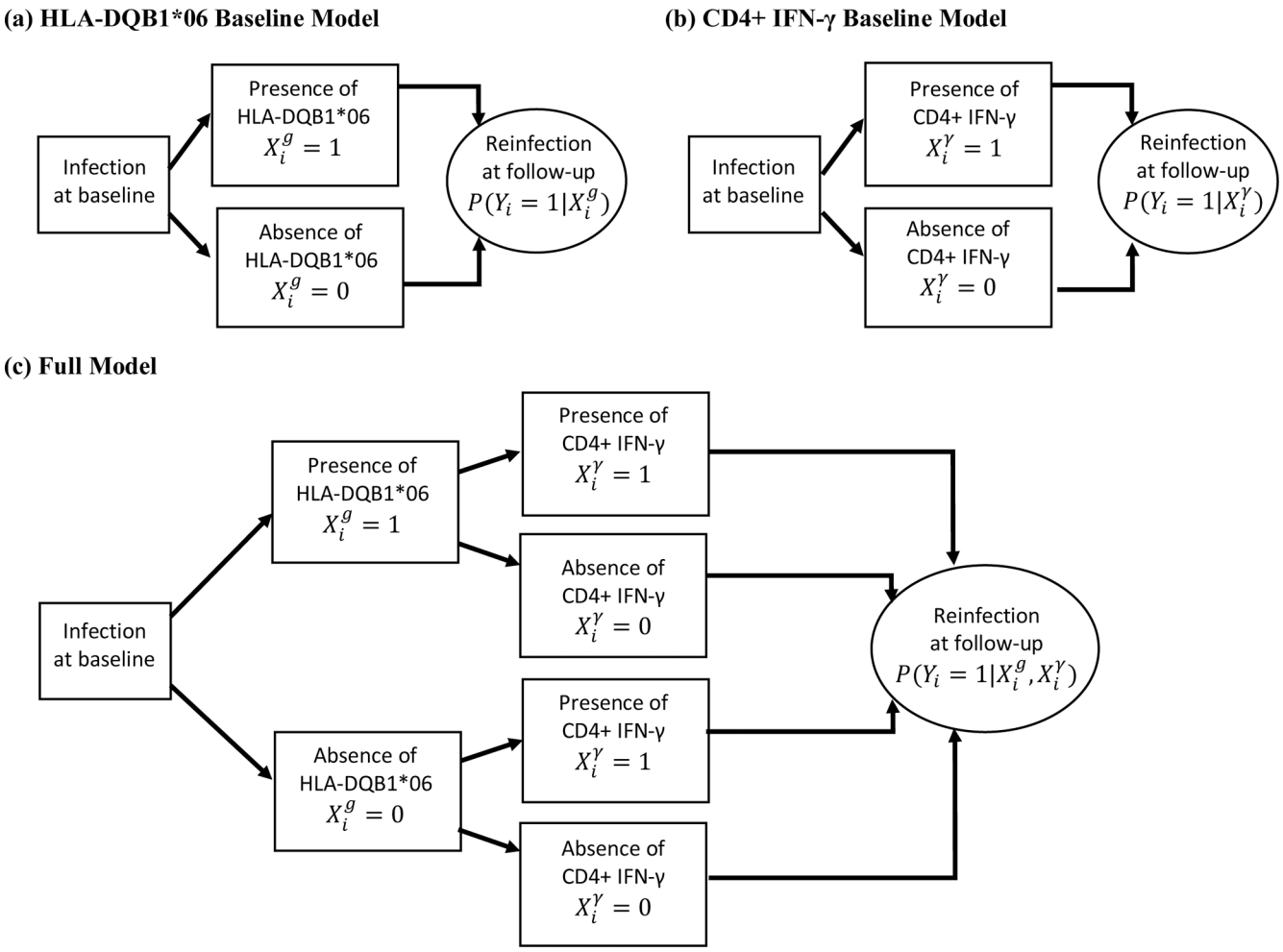

Figure 1.

Conceptual models for predicting the probability of *Chlamydia trachomatis* (CT) reinfection: (a) a baseline model for presence or absence of at least one HLA-DQB1*06 allele; (b) a baseline model for presence or absence of a CT-specific CD4+ IFN-γ response; and (c) a full model incorporating both HLA-DQB1*06 and CT-specific CD4+ IFN-γ variables. X_i^g denotes the presence or absence of at least one HLA-DQB1*06 allele; X_i^γ denotes the presence or absence of a CT-specific CD4+ IFN-γ response; and Y_i denotes the presence or absence of CT reinfection.

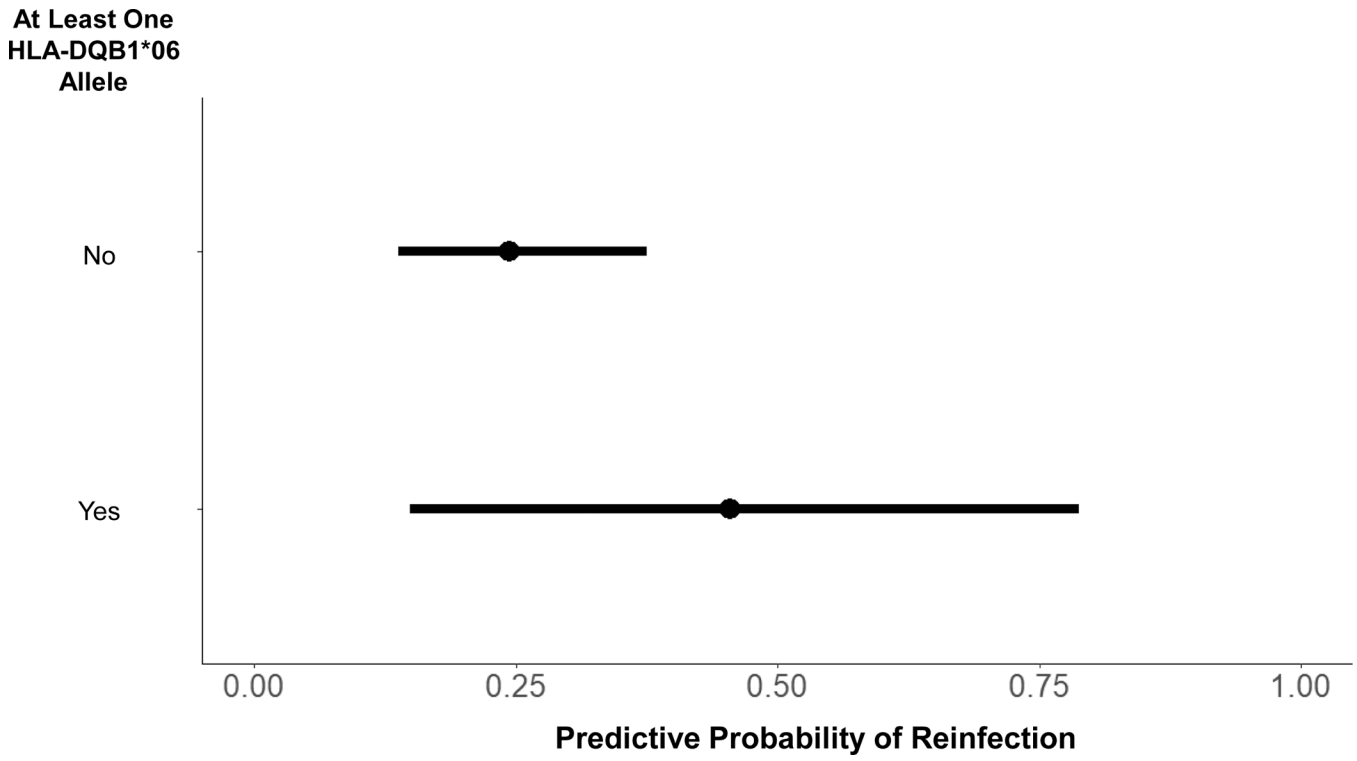

Figure 2.

In the HLA-DQB1*06 baseline model, women without any HLA-DQB1*06 alleles had a lower predictive probability of *Chlamydia trachomatis* (CT) reinfection than women with at least one allele.

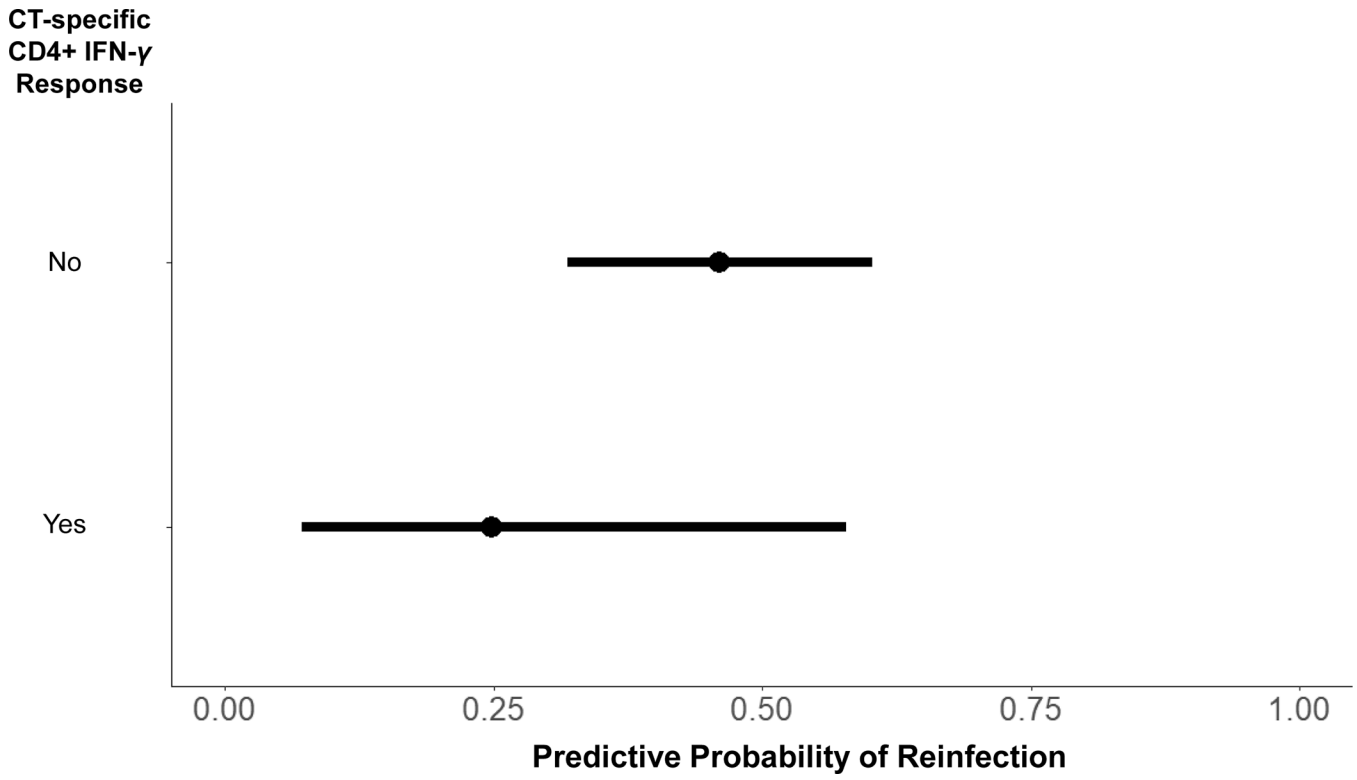

Figure 3.

In the *Chlamydia trachomatis* (CT)-specific CD4+ IFN-γ baseline model, women with a CT-specific CD4+ IFN-γ response had a lower predictive probability of CT reinfection than women in whom the response was absent.

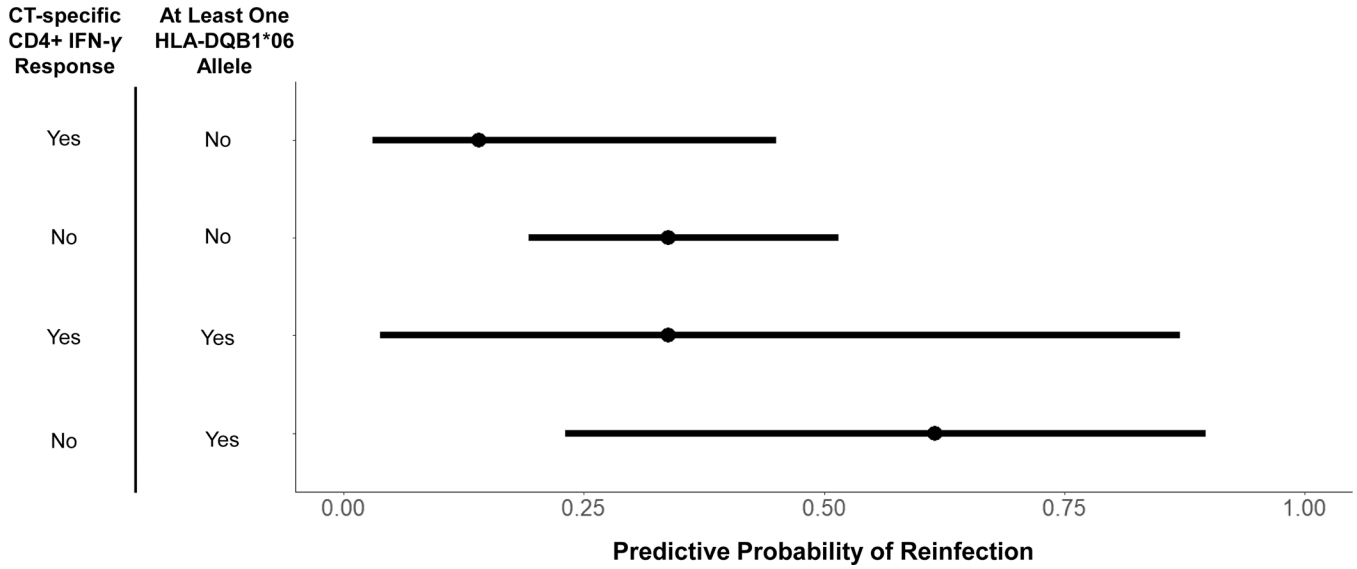

Figure 4.

In the full model, women with an absent *Chlamydia trachomatis* (CT)-specific CD4+ IFN-γ response and at least one HLA-DQB1*06 allele had the highest predictive probability of CT reinfection. Conversely, women with a CT-specific CD4+ IFN-γ response and lacking any HLA-DQB1*06 alleles had the lowest predictive probability of reinfection.

TABLE 1.

Select Participant Characteristics by *Chlamydia trachomatis* Reinfection Status

Characteristic	Total (n = 99)	CT Positive (n = 35)	CT Negative (n = 64)	*P*
Age, median (range)	22 (16–32)	22 (16–32)	22 (16–29)	0.52
No symptoms, N (%)	56 (56.6%)	19 (54.3%)	37 (57.8%)	0.74
Prior CT, N (%)	57 (58.2%)	23 (65.7%)	34 (54.0%)	0.26
Partner number last 3 months, median (range)	1 (1 – 5)	2 (1 – 5)	1 (1 – 5)	0.27
Unprotected sex, N (%)	79 (79.8%)	30 (85.7%)	49 (76.6%)	0.28
Hormonal contraceptive use, N (%)	45 (45.5%)	19 (54.3%)	26 (40.6%)	0.19
Candidiasis, N (%)	13 (13.3%)	3 (8.6%)	10 (15.6%)	0.37
Bacterial vaginosis, N (%)	28 (28.3%)	9 (25.6%)	19 (29.7%)	0.67
Trichomoniasis, N (%)	5 (5.1%)	2 (5.7%)	3 (4.7%)	1.00
Cervicitis, N (%)	19 (19.4%)	8 (23.5%)	11 (17.2%)	0.45

CT, *Chlamydia trachomatis*