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Methods

Statistical adjustment of culture-independent diagnostic tests for trend analysis in the Foodborne Diseases Active Surveillance Network (FoodNet), USA

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Abstract

Background: Culture-independent diagnostic tests (CIDTs) are increasingly used to diagnose *Campylobacter* infection in the Foodborne Diseases Active Surveillance Network (FoodNet). Because CIDTs have different performance characteristics compared with culture, which has been used historically and is still used to diagnose campylobacteriosis, adjustment of cases diagnosed by CIDT is needed to compare with culture-confirmed cases for monitoring incidence trends.

Methods: We identified the necessary parameters for CIDT adjustment using culture as the gold standard, and derived formulas to calculate positive predictive values (PPVs). We conducted a literature review and meta-analysis to examine the variability in CIDT performance and *Campylobacter* prevalence applicable to FoodNet sites. We then developed a Monte Carlo method to estimate test-type and site-specific PPVs with their associated uncertainties.

Results: The uncertainty in our estimated PPVs was largely derived from uncertainty about the specificity of CIDTs and low prevalence of *Campylobacter* in tested samples. Stable CIDT-adjusted incidences of *Campylobacter* cases from 2012 to 2015 were observed compared with a decline in culture-confirmed incidence.

Conclusions: We highlight the lack of data on the total numbers of tested samples as one of main limitations for CIDT adjustment. Our results demonstrate the importance of adjusting CIDTs for understanding trends in *Campylobacter* incidence in FoodNet.

Key words: Sensitivity, specificity, false-positive, positive predictive value, uncertainty, trend

Key Messages

- Increased use of CIDT complicates comparison with historical incidence based only on culture.
- Our estimated number of cases based on modelling positive predictive values for CIDTs shows a different trend compared with those based on culture only or on culture plus unadjusted CIDTs, and highlights the importance of an adjustment for CIDTs.
- Substantial uncertainty resulted from limited information about the specificity of CIDT and low prevalence of *Campylobacter* in tested samples.
- We demonstrate the need for the total number of samples tested by CIDT, for better adjustment.

Background

The Foodborne Diseases Active Surveillance Network (FoodNet) is a collaboration among the Centers for Disease Control and Prevention (CDC), 10 state health departments, the U.S. Department of Agriculture's Food Safety and Inspection Service (USDA-FSIS) and the Food and Drug Administration (FDA). FoodNet has conducted active, population-based surveillance for laboratory-confirmed infections of *Campylobacter* since 1996. *Campylobacter* is the most common bacterial diarrhoeal infection in the USA, causing an estimated 1.3 million illnesses per year.[1]

Campylobacter infection is typically diagnosed by isolating the organism using selective media and incubation for 48–72 h at 42°C in a microaerobic atmosphere, followed by confirmatory tests resulting in high specificity of the diagnosis. However, in FoodNet there has been a recent increase in the use of culture-independent diagnostic tests (CIDTs) that detect pathogen-specific antigens or DNA markers for diagnosis of campylobacteriosis.[2] Advantages of CIDTs over culture-based methods include lower cost, faster turnaround time and the ability to simultaneously test for multiple pathogens with a single test.[3]

Culture-confirmation is part of the definition of a *Campylobacter* case in FoodNet, and culture-confirmed cases have been used to monitor changes in incidence over time.[4] In 2010, FoodNet began tracking the use of CIDTs in its surveillance area, which has dramatically increased since 2012[2,5] In 2016, nearly a third of *Campylobacter* infections were diagnosed only by CIDT.[6] CIDTs vary in test performance (e.g. sensitivity and specificity); some tests are more and some are less sensitive than culture. In addition, because of the advantages of CIDTs, it is possible that more patients with gastrointestinal illness are being tested. All of these factors make it difficult to compare current case counts (culture-confirmed only or culture-confirmed plus CIDT) with historical cases (culture-confirmed only) and to assess changes in incidence over time. Thus, some adjustment for the effects of CIDTs is needed.

Our goal was to apply the epidemiological principles of diagnostic tests [i.e. sensitivity, specificity, positive predictive value (PPV)] and negative predictive value (NPV)], to adjust *Campylobacter* CIDT-based results as compared with culture as 'gold' standard.[7] These principles have previously been applied outside diagnostic test evaluation, e.g. estimating the sensitivity and specificity of a surveillance system.[8,9] In this study, we extended these concepts to adjust *Campylobacter* incidence rates in a surveillance setting based on a variety of CIDTs to enable us to assess changes in incidence over time.

Materials and Methods

CIDTs used for diagnosing *Campylobacter* in FoodNet

Adjustment for the effect of CIDTs on FoodNet surveillance is challenging because the prevalence of *Campylobacter* infection varies across the 10 sites, CIDT practices differ by laboratory and no requirements exist for confirmation of diagnosis based only on CIDT using culture-based methods. Furthermore, the types of CIDTs used in FoodNet sites have changed over time and the performance characteristics of the tests vary. For example, in 2014–15 increased use of nucleic acid amplification tests (NAAT), a newer-generation test thought to have good sensitivity and specificity, was noted in FoodNet sites even though antigen-based tests, which have variable performance characteristics, remained predominant.[5]

Several brands of FDA-approved CIDTs were used in FoodNet sites. During 2012–15, the vast majority were antigen-based although there was an increase in the use of NAAT in 2015. One antigen-based test, ImmunoCard STAT! CAMPY (ICS) (Meridian Bioscience Inc., Cincinnati, OH), accounted for 58% of CIDTs cases, and our literature review suggested it has different performance characteristics compared with other antigen-based tests

(Supplementary Appendix Table 1, available as Supplementary data at *IJE* online). Therefore, we grouped CIDTs into three categories for our analysis: ICS, Non-ICS antigen-based tests and NAAT.

The framework of CIDT adjustment

For adjustment of CIDT results using culture as the gold standard, there are two kinds of errors to consider, i.e. false-positives and false-negatives. Since the prevalence of *Campylobacter* infection in clinical samples was generally low, false positivity was a much greater concern than false negativity. For example, a CIDT with 95% sensitivity and 95% specificity performed on 400 samples with a true prevalence of 5% would result in 19 false positives but only one false negative.[10] In fact, a CIDT evaluation study conducted in the USA found a *Campylobacter* prevalence ranging from 2% to 5% across the eight included FoodNet sites, and out of 2681 stool samples that they tested by culture, enzyme-linked immunosorbent assay (EIA) and polymerase chain reaction (PCR), there were 196 false positives (EIA+, culture- and PCR-negative) and only nine false negatives (EIA+ and PCR+, culture-negative).[11] Therefore, we only adjusted for false positives because false negatives were expected to have a negligible effect on our point estimate and other sources of uncertainty overwhelm the uncertainty associated with false negatives.

To correct for false positives, we need to calculate the positive predictive value (PPV), defined as the probability of culture-confirmed infection given a positive CIDT. In a diagnostic setting, PPV is calculated to evaluate the likelihood of illness given a positive CIDT based on sensitivity and specificity as well as prevalence in a population.[12] However, prevalence in this instance is unknown because our goal is to estimate the prevalence in the surveyed population. In the Supplementary Appendix B, available as Supplementary data at *IJE* online, we demonstrate that the total number of samples tested, including the number of both CIDT positives and CIDT negatives, is needed to estimate PPV, and we provide the necessary formulas to do so in the surveillance setting. However, clinical and public health laboratories currently do not report the total number of samples tested, and we had to estimate prevalence based on published studies to estimate PPV although we recognize the limitations of this approach.

Literature review

Using results from a meta-analysis of published studies, we developed parametric models for sensitivity, specificity and prevalence that account for the variability in the diagnostic practices of *Campylobacter* infection across FoodNet sites. We generated a comprehensive list of the *Campylobacter*-specific CIDT literature using search terms composed of relevant keywords in PubMed/Medline (Supplementary Appendix Table 1, available as Supplementary data at IJE online). In total, 42 studies/reports were identified and reviewed; many had multiple evaluations of different combinations of test types, culture methods and sample collection (prospective or retrospective samples). We evaluated studies of test performance and prevalence separately. For test performance, we excluded studies of non-FDA-approved CIDTs, extremely low performance (sensitivity and specificity <0.7), those aimed at testing the limit of detection and those focused on cost savings. This resulted in 28 published studies with 62 test performance scenarios, i.e. pairs of sensitivity and specificity data for the various classes of CIDT used in our study. For prevalence estimation, we excluded studies that used retrospective stool specimens with known *Campylobacter* culture-positive results. This yielded 21 studies with 30 scenarios using different media or different sample collection methods (Supplementary Appendix Table 1, available as Supplementary data at IJE online).

Bivariate copula model of sensitivity and specificity

Because our goal was to compare recent estimates of the incidence of *Campylobacter* including a combination of culture-confirmed and CIDT-based cases with previous estimates based only on culture-confirmed cases, we used culture as the gold standard to define the sensitivity and specificity of the CIDTs. In general, sensitivity and specificity are assumed to be independent of prevalence based on a dichotomous disease status. In many situations, however, the disease status is a continuum of traits on which a diagnostic classification is based, and the distribution of underlying traits affects diagnostic accuracy and prevalence in the population.[13] There are studies describing trivariate models of the dependence of sensitivity and specificity on prevalence,[14–16] but we did not adopt this approach because our data were too sparse to be fitted by such models. Instead, we applied a bivariate copula model of sensitivity and specificity with an assumption that prevalence was independent of these measures.

Sensitivity and specificity are inversely related as the threshold used for classifying cases changes: sensitivity decreases with high thresholds while specificity increases, and vice versa.[17,18] To model the correlation between sensitivity and specificity, we used a copula beta-binomial distribution based on the data collected from our literature review.[19] In brief, the observed true positives (TP) are assumed to be a binomial random variate conditional on latent sensitivity, whereas true negatives (TN) are assumed to be a binomial

random variate conditional on latent specificity. The marginal latent sensitivity and specificity are modelled as a bivariate copula with a correlation parameter. We used CopulaREMEDA package[19] in R[20] to estimate the mean (μ) and variance (γ) of latent sensitivity and specificity and Kendall τ based on maximum likelihood method.[19] This estimation was conducted separately for each type of CIDT.

Bayesian hierarchical model of prevalence

We developed a Bayesian hierarchical model (mixed-effects model) to estimate site-specific prevalences because the method allowed improved estimation by borrowing strength across sites.[21]

$$g_s \sim Binomial(p_s, n_s)$$

$$\log\left(\frac{p_s}{1-p_s}\right) = \alpha + \beta_s$$

$$\alpha \sim Normal(0, \tau_\alpha)$$

$$\beta_s \sim Normal(0, \tau_\beta)$$

where g_s was the number of culture-positive cases, n_s was total samples from site s and p_s was the prevalence at site s. α was a random intercept, and β_s was the random effect for site s. s was the index of individual testing scenarios where g and n could be obtained from prospective samples at FoodNet sites[11] or published studies (Table 1; Supplementary Appendix, available as Supplementary data at *IJE* online). τ_α and τ_β were precision parameters, i.e. the reciprocal of variance. We assumed weakly informative priors on α and β by setting $\tau_\alpha = 1$ and $\tau_\beta = 5$ to allow borrowing strength across sites. Four FoodNet sites (New Mexico, Oregon, Tennessee and New York) were not included in the evaluation studies. At these sites, we assumed that the total number of tests at each was the same as the smallest observed at any FoodNet site ($n = 157$).[11] The missing positive numbers of CIDTs at these sites were estimated as missing values in the Bayesian hierarchical model.

We conducted Gibbs sampling for Markov Chain Monte Carlo (MCMC) simulation from posterior distribution of prevalence using WinBUGS with three chains and 5000 burn-in samples.[22]

Estimate PPV and uncertainty from bootstrap samples

Site and test-type specific $PPV_{s,T}$'s were estimated in the usual fashion:[12]

$$PPV_{s,\ T} = \frac{S_{e,T} \times p_s}{S_{e,T} \times p_s + (1 - S_{p,T})(1 - p_s)} \quad (1)$$

where $S_{e,T}$ was sensitivity and $S_{p,T}$ was specificity of test type T (ICS, Non-ICS or NAAT), and p_s was the prevalence of *Campylobacter* infection in clinical samples at site s. Note we assumed that each $PPV_{s,T}$ was constant over time.

Based on (1), we generated 1000 samples of site- and type-specific $PPV_{s,T}$'s by taking bootstrap samples from the bivariate copula of sensitivity and specificity of test type T and the posterior prevalences from the Bayesian hierarchical model at site s. Then, the calculated $PPV_{s,T}$'s were applied to observed numbers of CIDT-positives of type T at site s in year y to calculate annual sums of adjusted cases N_adj_y

$$N\_adj_y = \sum_s \sum_T (D_{s,T,y} \times PPV_{s,T}) + CC_y \quad (2)$$

where $D_{s,T,\ y}$ is the number of positive cases by test type T in site s and year y. CC_y is the number of culture confirmed cases in year y.

Sensitivity analysis

We conducted two sensitivity analyses. First, we examined how the uncertainties in estimated PPV changed as we replaced the variable estimates of sensitivity and specificity with the fixed means. Fixed prevalence is equivalent to a scenario where total number of cases tested with CIDT is available (Supplementary Appendix B, available as Supplementary data at *IJE* online). Second, some states perform reflex culture at their public health laboratories on some or all of the CIDT-positive results. These data could provide a direct measure of misclassification for the CIDTs, although several factors complicate the interpretation of negative reflex cultures. For example, reflex culture is usually not simultaneously performed with CIDTs, and delays in testing and effects of transportation on samples affect the viability of the pathogen. Nevertheless, we examined the agreement between the observed positives from reflex culture and predicted cases of those CIDTs where reflex culture was available.

Results

Reported CIDT use in FoodNet

Application of NAAT has increased over the years, especially in California where there was a substantial shift in 2015 from culture-based tests to NAAT: from less than 1% in 2012 to 53% in 2016 (Figure 1). ICS use has remained stable overall, but increased dramatically in Minnesota from 2014 to 2015.

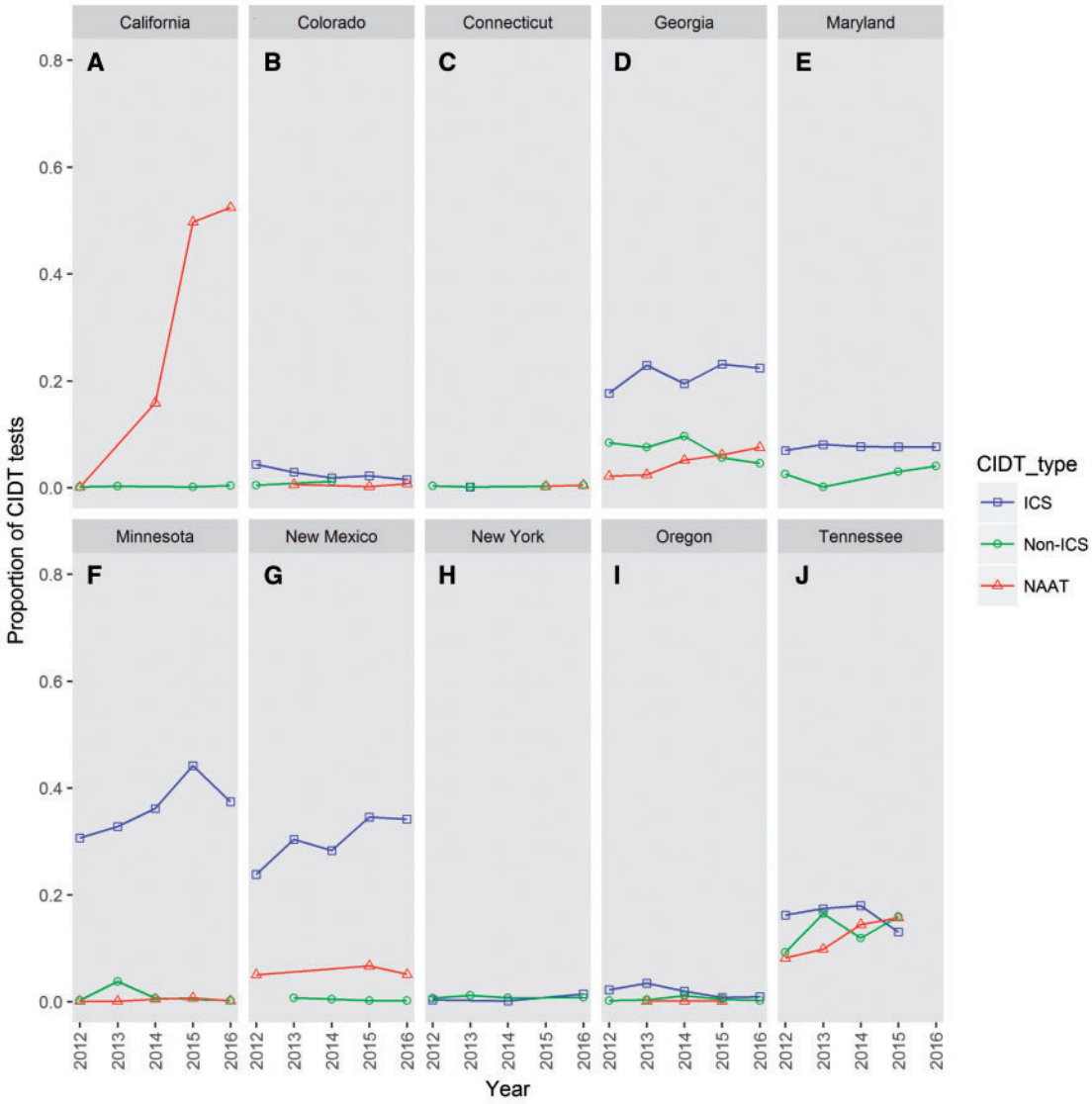

Figure 1. The proportions of *Campylobacter* cases diagnosed by three types of culture-independent diagnostic tests with ICS (open square), Non-ICS antigen based (open circle) and NAAT (open triangle) in FoodNet. ICS = ImmunoCard STAT! CAMPY. NAAT = nucleic acid amplification test.

Table 1. Estimates of maximum likelihood of bivariate beta-binomial model of joint sensitivity and specificity

	Sensitivity		Specificity		
	μ	γ	μ	γ	Kendall τ
ICS	0.862 (0.049)	0.103 (0.067)	0.972 (0.006)	0.02 (0.013)	−0.067 (0.219)
Non-ICS	0.914 (0.018)	0.054 (0.021)	0.97 (0.004)	0.02 (0.005)	−0.013 (0.166)
NAAT	0.956 (0.009)	0.016 (0.015)	0.98 (0.003)	0.009 (0.004)	−0.4 (0.333)

Estimation of sensitivity, specificity and prevalence

Parameter estimation for the three test types indicated that the sensitivity and specificity of ICS were lower compared with Non-ICS and NAAT types (Table 1). Sensitivity was negatively correlated with specificity as expected. NAAT had the highest estimates of sensitivity, specificity and Kendall τ correlation. Predictions from the bivariate models were consistent with the observed values for three test types (Figure 2).

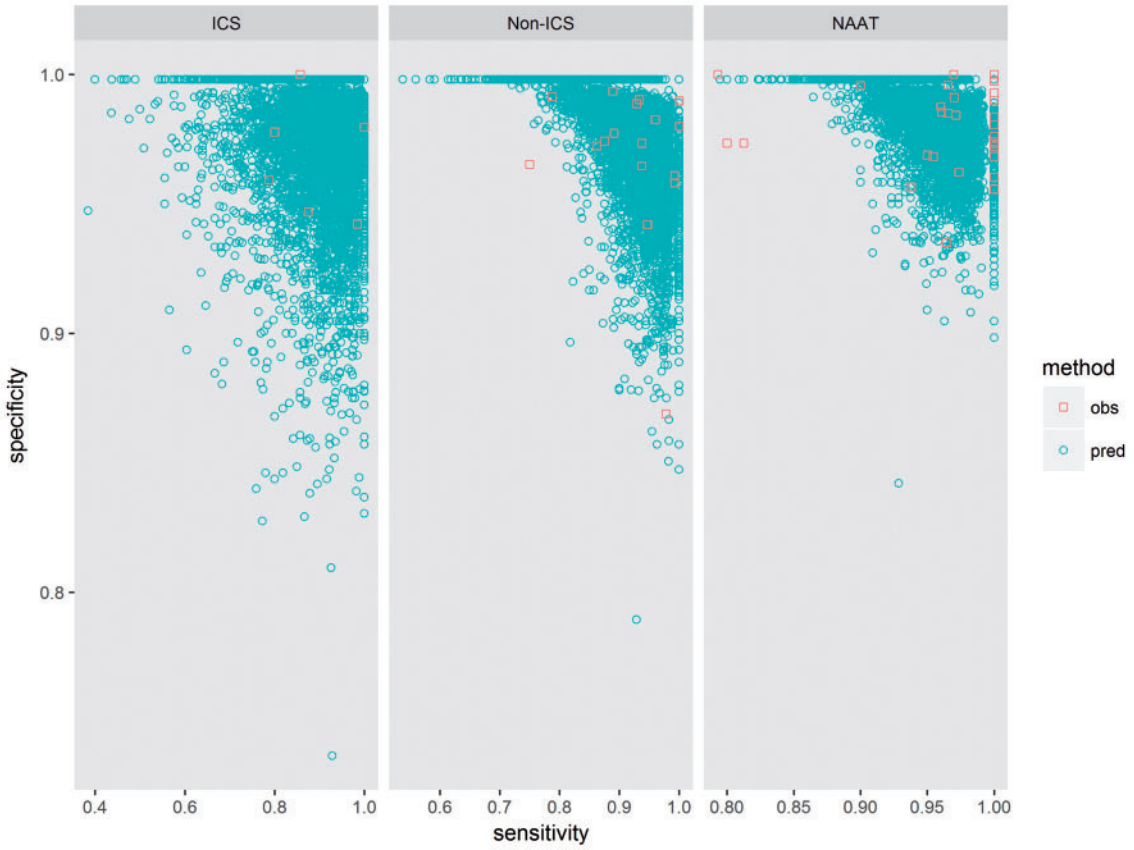

Figure 2. Comparison of estimated joint sensitivity and specificity between observed values (open square) from the literature review and predicted ones (open circle) from bivariate copula model for different culture independent diagnostic test types.

The estimated site-specific prevalence varied between sites, with the highest prevalence in Minnesota and California. Uncertainty in the prevalence was highest at the four sites without observed data (Figure 3A). Prevalence estimated by the Bayesian hierarchical model shows the expected shrinkage of estimates toward the grand mean. Deviations between the estimated and observed prevalence increased as sample size was decreased and the prevalence deviated further from the grand mean (Figure 3B).

Sensitivity analysis

The uncertainties in sensitivity, specificity and prevalence led to wide confidence intervals for estimated PPV, especially for the four sites without prevalence data (Figure 4). Differences in estimated PPV were observed among FoodNet sites. Uncertainty was relatively smaller for Minnesota and California, which had higher prevalence. Reducing uncertainty in specificity markedly reduced the uncertainty in estimated PPV. Interestingly, fixed prevalence (based on knowing the total number of CIDTs performed) had little influence on estimated uncertainty except in the four sites with no observed prevalence. The same was true for fixed sensitivity. In contrast, the estimates were similar for different test types, reflecting similar specificities seen in published studies (Table 1).

Based on estimated PPVs, we predicted the number of adjusted cases for those with both a positive culture and a positive CIDT. The numbers of adjusted cases were higher than the observed reflex culture, although the 95% confidence intervals generally enclosed the observed culture-confirmed case count (Table 2).

Estimated trends

Figure 5 shows the different patterns of the number of culture-confirmed cases, unadjusted total number of cases (sum of culture-confirmed cases and positive CIDT reports without confirmatory culture) and adjusted total number of cases with associated uncertainty. Trends in *Campylobacter* incidence over time differed drastically between the three measures. The incidence rate of culture-confirmed *Campylobacter* shows a consistent decline, whereas unadjusted and adjusted rates incorporating CIDT were relatively stable with a slight increase in 2015 (Figure 5). Estimates of CIDT-adjusted cases suggest no changes in infection rates in FoodNet from 2012 to 2015.

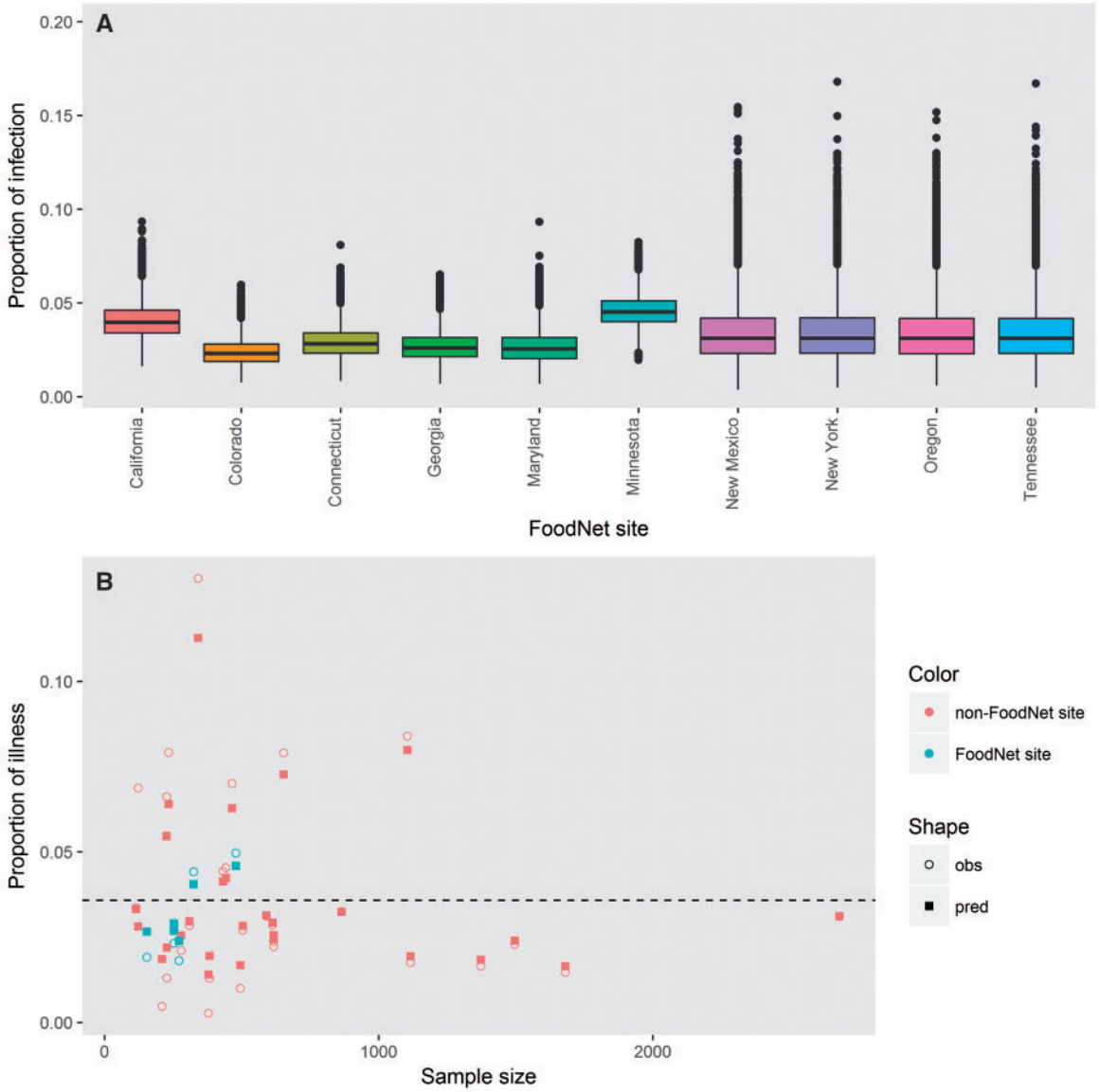

Figure 3. Estimated prevalence of *Campylobacter* in FoodNet sites based on the Bayesian hierarchical model. Note that prevalences in New Mexico, New York, Oregon and Tennessee were imputed as missing values (A). Predicted average of prevalence (solid square) are compared with observed ones (open circle) as a function of sample size (dotted line—the grand mean).

The uncertainty in the CIDT-adjusted number of cases was higher after 2014 as more CIDT cases were reported.

Discussion

Although the concept of PPV is well known in diagnostic settings, it has not generally been used for adjustment of testing practices in surveillance programmes. We demonstrate that PPV was useful for adjusting the number of CIDT cases for monitoring of changes in *Campylobacter* incidence over time. It is essential to collect the total number of cases tested by CIDT for statistical adjustment in surveillance programmes. Given the lack of a total number of CIDTs, we applied a Bayesian hierarchical model to estimate site-specific prevalence for adjustment. We estimated uncertainty in our CIDT adjustment using Monte Carlo simulation by incorporating variations in CIDT practices and prevalence in target populations across FoodNet sites.

Our choice of culture as the gold standard for adjustment was based on our wish to compare current case counts arising from mixed testing approaches with past counts based only on culture-confirmed infections, which have been used for trend analysis of campylobacteriosis in FoodNet.[4] Therefore, we did not attempt to adjust culture-confirmed case counts to account for cultures' own imperfections in detection even though we recognize that culture represents an imperfect gold standard. For example, Scallan *et al.*[1] used 70% sensitivity as an adjustment of

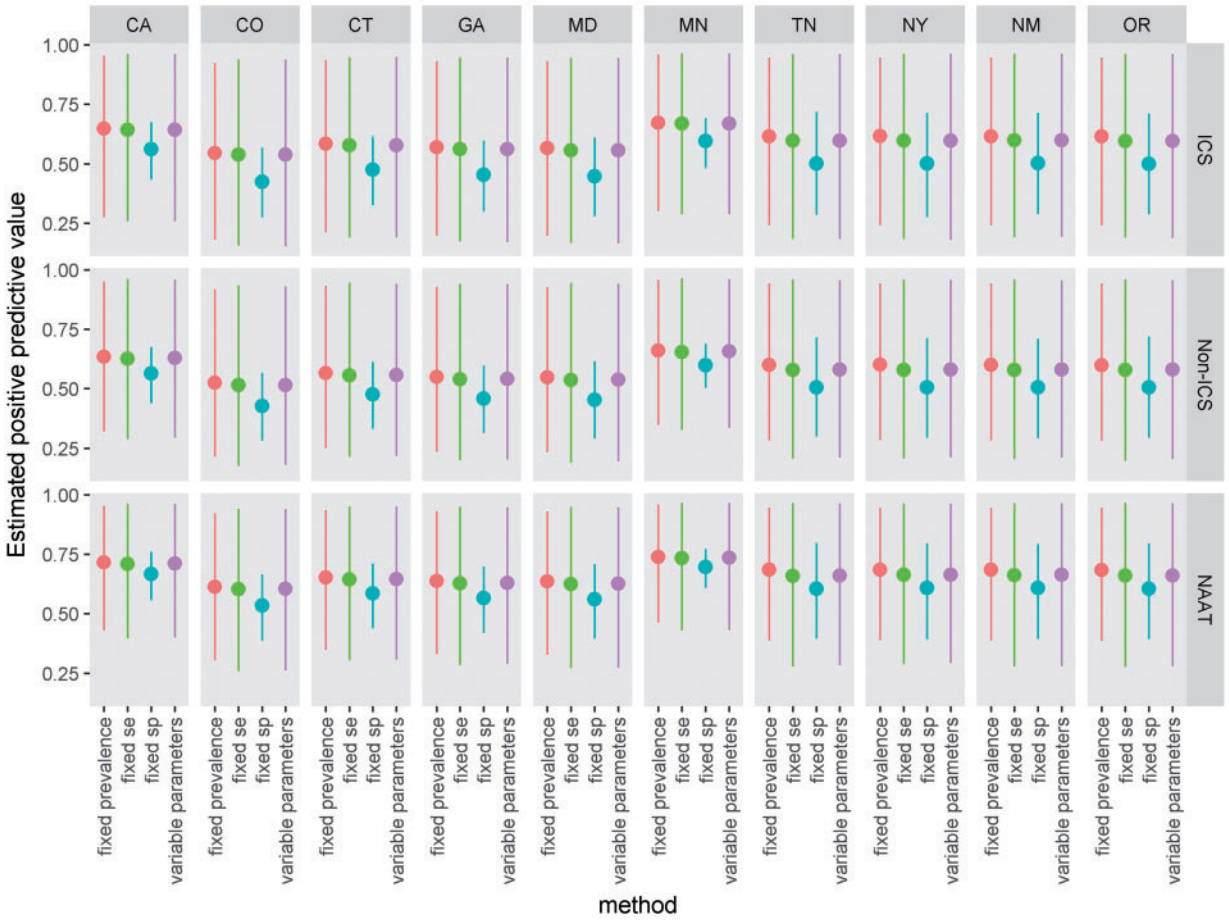

Figure 4. Influence of fixed estimates of sensitivity, specificity and prevalence (equivalent to available volume data of culture independent diagnostic test) as compared with variable estimates of the parameters on estimated PPV.

Table 2. Total numbers of *Campylobacter* cases of reflex culture and CIDTs as compared with predicted average cases (95% confidence interval) based on adjustment of positive CIDT

Category	Observed cases based on reflex culture	Predicted cases based on CIDT adjustment (95% confidence interval)
ICS	1221	2425 (972–3756)
Non-ICS	120	230 (79–405)
NAAT	207	309 (149–457)

culture-confirmed cases for true infections. Studies have shown that CIDTs, especially DNA-based NAATs, have higher sensitivity compared with culture for diagnosing *Campylobacter* infections.[23] With the increased use of CIDTs in the future, there may be a need to consider one of the CIDTs as a reference standard and adjust culture-confirmed counts for comparison, or to apply latent class models for evaluating test performance of multiple tests on individuals in the absence of a gold standard.[24]

Reported sensitivity of CIDTs from published studies varied considerably due to small sample sizes, especially in prospective studies. In 14 test scenarios, sensitivity was estimated with less than 10 cases. Because sensitivity and specificity are generally considered properties of a CIDT which are not related to the prevalence of the test (but see[13,17]) the inclusion of test scenarios from retrospective samples with more cases could improve sensitivity estimation. For the adjustment of false positives, however, accurate specificity is more important than sensitivity for estimating PPV. Prospective sample collection appeared to yield sufficient numbers of culture-negative results for estimating specificity. Our estimated PPVs for the three types of CIDTs were, in general, consistent with the evaluation study of CIDTs performed in many FoodNet sites in which overall estimated PPVs for antigen-based tests were about 50%.[11] It should be noted that antigen-based tests were phased out by NAAT, which had higher sensitivity and specificity for diagnosis of campylobacteriosis and resulted in improved estimates of PPV.

Our method has several limitations. First, we assumed that performance data from published studies are directly

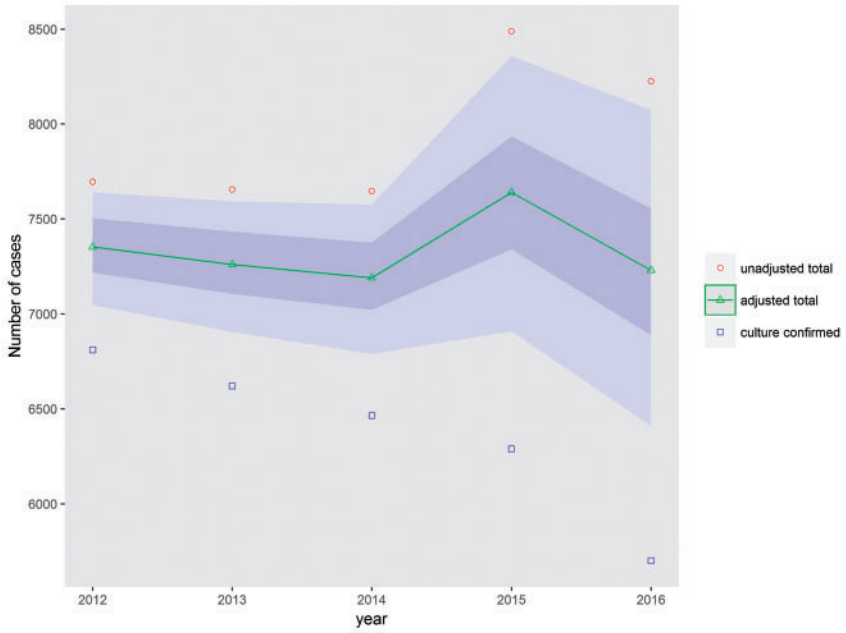

Figure 5. Estimated adjusted culture-independent diagnostic test cases (open triangle) and interquartile (25–75% dark shade) and 95% confidence intervals (light shade) as compared with unadjusted total cases (open circle) and culture positive cases (open square).

applicable to FoodNet sites. These studies were conducted in different countries and in different settings which may differ from FoodNet. In addition, the variety of settings in which the studies were performed also resulted in substantial variability in reported sensitivities and specificities of the CIDTs, which had an impact on our estimated PPV and subsequent incidence estimate. Our previous study[11] showed a 95% confidence interval for ICS's specificity of 0.95 to 0.97 compared with 0.94 to 1 in other published studies. Since we applied CIDT adjustment at the state level, the variability of CIDT performance in FoodNet might be lower than that seen in published data. As we have shown, reduced variability in specificity would significantly reduce the uncertainty in PPV estimation (Figure 4). Second, historical prevalence data were used for estimation of PPV due to the lack of data on the total number of CIDTs performed, a practice somewhat circular to our ultimate goal of estimating incidence. The assumption that site prevalence did not change over time may also be invalid. The increased availability of CIDTs, lower cost, faster turnarounds and ability to simultaneously test for multiple pathogens may encourage physicians to order more tests, and without data on the number of tests performed over time we are unable to address this possibility. Finally, prevalence for four FoodNet sites were estimated as missing values with the smallest sample size observed, increasing the uncertainty in our estimate. However, the influence of this assumption was likely relatively small because these four sites were not among the top three contributors of CIDT cases.

Our results show that adjustment of CIDT cases is critical for evaluating change in *Campylobacter* incidence as the use of CIDTs increases in FoodNet. Adjustment of CIDT-based incidences could be improved by systematic collection of data on the total number of CIDTs performed to track the changes in proportions of positive samples and changes in testing practices of patients with enteric diseases. The proposed method can be adapted to the trend analyses of other pathogens that increasingly rely on CIDT for clinical diagnosis.[5,25]

Supplementary Data

Supplementary data are available at *IJE* online.

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Conflict of interest: V.D. is currently an employee at bioMerieux Inc. (the parent company of Biofire Inc.). Peer-reviewed data from one of Biofire products, Film Array GI panel, were used for reference during this study. V.D. was not associated with either bioMerieux Inc. or Biofire Inc. when this study was conducted.

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