BIAS CORRECTION METHODS FOR TEST-NEGATIVE DESIGNS IN THE PRESENCE OF MISCLASSIFICATION

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ABSTRACT

The test-negative design has become a standard approach for vaccine effectiveness studies. However, previous studies suggested that it may be more sensitive than other designs to misclassification of disease outcome caused by imperfect diagnostic tests. This could be a particular limitation in vaccine effectiveness studies where simple tests (e.g. rapid influenza diagnostic tests) are used for logistical convenience. To address this issue, we derived a mathematical representation of the test-negative design with imperfect tests, then developed a bias correction framework for possible misclassification. Test-negative design studies usually include multiple covariates other than vaccine history to adjust potential confounders; our methods can also address multivariate analyses and be easily coupled with existing estimation tools. We validated the performance of these methods using simulations of common scenarios for vaccine efficacy and were able to obtain unbiased estimates in a variety of parameter settings.

Keywords  Test negative design · Vaccine effectiveness · Misclassification · Bias correction · Statistical methods · Sensitivity · Specificity

Abbreviations  VE, vaccine effectiveness; TND, test-negative design; TD, target disease; ND, non-target disease; PCR, polymerase chain reaction; MLE, maximum likelihood estimate; MO, multiple overimputation; EM, expectation-maximisation.

1 Introduction

Vaccine effectiveness (VE) is typically estimated as the vaccine-induced risk reduction of the target disease (TD) and has been traditionally studied by the cohort or case-control designs. However, the test-negative design (TND) is becoming a popular alternative design for vaccine effectiveness (VE) studies [1,2]. This is a modified version of the case-control study with an alternative definition of the control group; traditional case-control studies usually define controls as non-disease individuals in the study population, while the TND studies use individuals with similar symptoms to the target disease but presenting negative test results (i.e., patients of non-target diseases; ND). The test-negative design can therefore minimise ascertainment bias by including only medically-attended patients in both case and control groups. Many TND studies have focused on influenza vaccination, but recent studies have also targeted other diseases including pneumococcal disease [3,4] and rotavirus disease [5,6,7].

Despite its increasing popularity, TND can be more sensitive than other study designs to misclassification of disease outcome. Multiple studies have shown that VE is underestimated when the diagnostic tests used in the study are imperfect (i.e. have a sensitivity and/or a specificity less than 100%) [8,9,10]. This can be a particular issue when simple tests (e.g. rapid diagnostic tests) are used for logistical convenience, as simple tests tend to have lower diagnostic
performance than more advanced tests (e.g. polymerase chain reaction; PCR). Previous studies evaluated the expected degree of bias and concluded that specificity had a more important effect on bias than sensitivity \[8,9,10\]. These findings appear to support the use of rapid tests, despite limited sensitivity, because the specificity of these tests is typically high \[2\]. However, theoretical studies to date have been based on specific assumptions about efficacy and pathogen epidemiology; it is therefore unclear whether such conclusions hold for all plausible combinations of scenarios.

If a study is expected to generate a non-negligible bias in estimation, such bias needs to be assessed and—if possible—corrected before the estimate is reported. Greenland \[11\] proposed a bias correction method for cohort studies where the sensitivity and specificity of the test are known (or at least assumed). However, this method cannot apply to case-control studies because of differential recruitment, whereby the probability of recruiting (test-positive) cases and (negative) controls may be different. Although TND studies are often considered to be special cases of case-control studies, they are free from the issue of differential recruitment because the recruitment and classification are mutually-independent. This means that, while Greenland’s method does not apply to TND, another type of bias correction may still be possible. For example, De Smedt et al. have characterised the misclassification bias in VE in the test-negative design in a simulation study \[3\]. One limitation of this approach is it relies on the unobserved “true” disease risk being known, where in reality this is not usually measurable in field studies. As a result, bias correction methods for TND studies that are directly applicable to field data have not yet been proposed. Moreover, previous analysis of misclassification bias has not considered the impact of multivariate analysis, where potential confounders (e.g. age and sex) are also included in the model used to estimate VE.

To address these issues, we develop a bias correction method for the test-negative VE studies that uses only data commonly available in field studies. We also apply these methods to multivariate analyses. As our approach uses the so-called multiple overimputation framework (generalisation of multiple imputation) \[12\], it can easily be coupled with a wide range of estimation tools without modifying their inside algorithms. Finally, we evaluate the performance of our methods by simulations of plausible epidemiological scenarios.

## 2 Methods and results

### 2.1 Characterising bias in test negative design studies

First, we consider the case where only vaccination history is included as a risk factor of acquiring the TD (i.e. the univariate setting). In this case, the (true) case counts can in theory be summarised in a two-by-two table as shown below:

<table>
<thead>
<tr>
<th></th>
<th>Vaccinated</th>
<th>Unvaccinated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target disease</td>
<td>(x_V)</td>
<td>(x_U)</td>
</tr>
<tr>
<td>Non-target</td>
<td>(y_V)</td>
<td>(y_U)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>(S_V)</td>
<td>(S_U)</td>
</tr>
</tbody>
</table>

Following the approach of Haber et al. (2015) \[13\], we consider four steps in the case reporting process: vaccination, onset of symptoms, seeking of medical care, and diagnosis. For simplicity, let us assume that occurrence of TD and ND are mutually independent, where their prevalences are represented as \(r_1\) and \(r_0\), respectively. Let \(v\) be the vaccination coverage; in observational studies, vaccinated and unvaccinated population can have different likelihoods of seeking medical treatment (we denote such probabilities as \(m_V\) and \(m_U\), respectively). As our focus in the present study is the bias in VE estimation caused by imperfect tests, we made two key assumptions following Haber et al \[13\]: vaccination does not affect the risk of ND or the relative probability \(\mu\) of medical attendance between TD and ND (which may reflect different disease severity between TD and ND). Namely, the study was assumed to be able to provide an unbiased VE estimate if tests are perfect. Based on these assumptions, we can classify the expected incidence in population \(N\) into four categories:

<table>
<thead>
<tr>
<th></th>
<th>Vaccinated</th>
<th>Unvaccinated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target disease</td>
<td>(v\gamma\mu m_Vr_1N)</td>
<td>((1-v)\mu m_Ur_1N)</td>
</tr>
<tr>
<td>Non-target</td>
<td>(vm_Vr_0N)</td>
<td>((1-v)m_Ur_0N)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>(vm_V(\gamma \mu r_1 + r_0)N)</td>
<td>((1-v)m_U(\mu r_1 + r_0)N)</td>
</tr>
</tbody>
</table>

\[1\] It has been suggested that a possible violation of this assumption occur as a result of virus interference \[14\], but conclusive evidence for this is currently lacking \[15,16\] and the effect on VE estimates may be limited in any case \[17\].
Suppose that the true data in a TND study \((x_V, y_V, x_U, y_U)\) is as described in the above tables. However, due to imperfect tests, we would instead expect to obtain the following observations:

<table>
<thead>
<tr>
<th>Test positive</th>
<th>Test negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccinated</td>
<td>Unvaccinated</td>
</tr>
<tr>
<td>(\alpha x_V + (1 - \beta)y_V)</td>
<td>(\alpha x_U + (1 - \beta)y_U)</td>
</tr>
<tr>
<td>((1 - \alpha)x_V + \beta y_V)</td>
<td>((1 - \alpha)x_U + \beta y_U)</td>
</tr>
</tbody>
</table>

where \(\alpha\) and \(\beta\) are the sensitivity and specificity of the test, respectively. Denoting observed case counts with misclassification by \(X\) and \(Y\), the process of diagnosis can be represented by the following matrix expression:

\[
\begin{bmatrix}
X_V & X_U \\
Y_V & Y_U
\end{bmatrix} = \begin{bmatrix}
\alpha & 1 - \beta \\
1 - \alpha & \beta
\end{bmatrix} \begin{bmatrix}
x_V & x_U \\
y_V & y_U
\end{bmatrix}.
\]

(1)

Matrix \(C = \begin{bmatrix}
\alpha & 1 - \beta \\
1 - \alpha & \beta
\end{bmatrix}\) describes the conversion from the true disease state to the observed result. We hereafter refer to \(C\) as the classification matrix.

The observed odds ratio (subject to the misclassification bias) is therefore given as

\[
\frac{X_V}{Y_V} = \frac{X_U}{Y_U} = \frac{\alpha x_V + (1 - \beta)y_V}{(1 - \alpha)x_V + \beta y_V} / \frac{\alpha x_U + (1 - \beta)y_U}{(1 - \alpha)x_U + \beta y_U} = \frac{\alpha \gamma \mu r_1 + (1 - \beta)\mu r_0}{(1 - \alpha)\gamma \mu r_1 + \beta \mu r_0} \frac{(1 - \alpha)\alpha \mu r_1 + (1 - \beta)\mu r_0}{\alpha \gamma \delta + (1 - \beta)((1 - \alpha)\delta + \beta)}
\]

\(\delta = \frac{\gamma \mu r}{\mu m}\) is the odds of the (medically-attended) target disease in the unvaccinated population.

We define bias in the VE estimate to be the absolute difference between the (raw) estimate and the true value. The expected bias \(B\) is a function of \(\alpha, \beta, \gamma\) and \(\delta\):

\[
B(\alpha, \beta, \gamma, \delta) = \text{VE}_{\text{raw}} - \text{VE}_{\text{true}} = \gamma - \frac{\alpha \gamma \delta + (1 - \beta)((1 - \alpha)\delta + \beta)}{(1 - \alpha)\gamma \delta + \beta}(1 - \beta).
\]

(3)

This suggests that the influence of sensitivity/specificity on the degree of bias varies depending on the case ratio \(\delta/(1 + \delta)\), i.e. the ratio between incidence of medical attendance for TD and ND in the study population (Figure 1). The degree of bias also depends on \(\gamma\) but is independent of \(m_V\) and \(m_U\). The degree of bias is largely determined by the test specificity when the case ratio is small, but the influence of sensitivity and specificity is almost equivalent with a case ratio of 0.6. It is notable that high specificity does not always assure that the bias is negligible. This may be true if specificity is strictly 100% and the case ratio is low to moderate, but a slight decline to 97% can cause a bias up to 10-15 percentage points. The effect of sensitivity is also non-negligible when the case ratio is high.

When the expected bias is plotted against the case ratio with various combinations of test performance, we find that VE estimates can be substantially biased for certain case ratios (especially when the ratio is far from 1:1), even with reasonably high sensitivity and specificity (Figure 2A). In TND studies, researchers have no control over the case ratio because the study design requires that all tested individuals be included in the study. We found that the proportion of TD-positive patients in previous TND studies (retrieved from three systematic reviews [18][19][20]) varied considerably, ranging from 10% to 70% (Figure 2B). Because of this large variation in the case ratio, it would be difficult to predict the degree of bias before data collection. Post-hoc assessment and correction therefore need to be considered.

(Further analysis of the relationship between the degree of bias and parameter values can be found in the supplementary information.)

Strictly speaking, proportion positive is a different quantity from case ratio, but it should serve as a reasonable proxy of the case ratio in most settings.
2.2 Bias correction in univariate analysis

2.2.1 Model and statistical analysis

To develop a correction method that can address the bias presented in the previous section, we first model the case reporting process in the univariate setting as follows. Let us assume that incidence of TD and ND both follow Poisson-distributions. As presented in Section 2.1, the mean total incidence in the unvaccinated population is given as

\[ \lambda_U = (1 - v) m_U (r_1 \mu + r_0) N. \]

Let \( \lambda_V = \frac{\lambda_U}{m_U} \) so that \( \lambda_V \) corresponds to the mean total incidence in the vaccinated population (\( = N v \)) when \( \gamma = 1 \), i.e. VE=0. This definition is to ensure that parameters \( \gamma \) and \( \lambda_V \) are mutually independent. Let \( \delta = \frac{r_1 \mu}{r_0} \) be the odds of the (medically-attended) target disease in the unvaccinated population. Using these four parameters \( \gamma, \delta, \lambda_V, \lambda_U \), we get the following table for (potentially mis-classified) mean case counts:

<table>
<thead>
<tr>
<th></th>
<th>Vaccinated</th>
<th>Unvaccinated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test positive</strong></td>
<td>( \frac{\alpha \gamma \delta + (1 - \beta) \lambda_V}{1 + \delta} )</td>
<td>( \frac{\alpha \delta + (1 - \beta) \lambda_U}{1 - \alpha \delta + \beta} )</td>
</tr>
<tr>
<td><strong>Test negative</strong></td>
<td>( \frac{1 + \gamma \delta + \beta \lambda_V}{1 + \delta} )</td>
<td>( \frac{1 + \delta}{1 + \delta} \lambda_U )</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>( \frac{1 + \gamma \delta + \beta \lambda_V}{1 + \delta} )</td>
<td>( \lambda_U )</td>
</tr>
</tbody>
</table>

Figure 1: Bias in VE estimates caused by misclassification for different combinations of parameter values. (A) – (C) Estimated VE plotted against sensitivity. (A) True case ratio = 0.2 (B) 0.4 (C) 0.6. Each two sets of lines respectively correspond to different true VEs (80% and 40%, denoted by the dotted lines). (D) – (F) Estimated VE plotted against specificity. (D) True case ratio = 0.2 (E) 0.4 (F) 0.6.
Figure 2: Biased VE estimates with varying case ratio and the observed proportion of positive patients. (A) The proportion of test positive patients in TND studies from systematic reviews. The proportions were retrieved from three systematic reviews [18, 19, 20]. (B) Estimated VE plotted against case ratio. Two sets of lines respectively correspond to different true VEs (80% and 40%, denoted by the dotted lines). The histogram in Panel (A) is overlaid on the x axis.

When data $D = (X_V, Y_V, X_U, Y_U)$ is obtained following this misclassified pattern, we can construct the likelihood of obtaining such data, given underlying parameters, as

$$
\mathcal{L}(\gamma, \delta, \lambda_V, \lambda_U; D) = \text{Pois}\left( X_V; \frac{\alpha \gamma \delta + (1 - \beta)}{1 + \delta} \lambda_V \right) \text{Pois}\left( Y_V; \frac{(1 - \alpha) \gamma \delta + \beta}{1 + \delta} \lambda_V \right) \\
\text{Pois}\left( X_U; \frac{\alpha \delta + (1 - \beta)}{1 + \delta} \lambda_U \right) \text{Pois}\left( Y_U; \frac{(1 - \alpha) \delta + \beta}{1 + \delta} \lambda_U \right).$$

(4)

By maximising this likelihood over all parameters, we can obtain a maximum likelihood estimate (MLE) of the odds ratio $\gamma^*$ that accounts for misclassification. Let us refer to

$$
\gamma^* = \frac{X_V - \frac{1-\beta}{\beta} Y_V}{Y_V - \frac{1-\alpha}{\alpha} X_V} \cdot \frac{X_U - \frac{1-\alpha}{\alpha} Y_U}{Y_U - \frac{1-\beta}{\beta} X_U},
$$

(5)

as the "corrected odds ratio", which gives an unbiased estimate of $\gamma$. Comparing $\gamma^*$ with the "raw" odds ratio $\frac{X_V Y_U}{Y_V X_U}$, we find that the estimate can be corrected using the following substitution

$$
X_V \rightarrow X_V - o_\beta Y_V \\
Y_V \rightarrow Y_V - o_\alpha X_V \\
X_U \rightarrow X_U - o_\beta Y_U \\
Y_U \rightarrow Y_U - o_\alpha X_U
$$

(6)

where $o_\alpha = \frac{1-\alpha}{\alpha}$ and $o_\beta = \frac{1-\beta}{\beta}$ are the odds of diagnostic errors corresponding to sensitivity and specificity, respectively, which take 0 when sensitivity/specificity is perfect. Also note that the same odds ratio is obtained by taking the odds ratio of the reconstructed data table where the inverted classification matrix is applied:

$$
C^{-1} \begin{bmatrix} X_V & X_U \\ Y_V & Y_U \end{bmatrix} = \frac{1}{\alpha + \beta - 1} \begin{bmatrix} \beta & 1 - \beta \\ 1 - \alpha & \alpha \end{bmatrix} \begin{bmatrix} X_V & X_U \\ Y_V & Y_U \end{bmatrix}.
$$

(7)

The determinant $c = \alpha + \beta - 1$ is the Youden index of the test and satisfies $0 < c \leq 1$ (if $c < 0$, the test is not predictive and the definitions of positive/negative should be swapped).
In some (relatively rare) cases, one or more quantities in Eq. (6) may become negative due to random fluctuations in observation. Theoretically, negative values are not permitted in as true case counts, and thus such negative quantities would need to be truncated to 0. As a result, the corrected odds ratio can be either 0 or infinity. Such an estimate would suggest that the study does not have a sufficient sample size to properly evaluate VE and that the study design itself might need to be reconsidered.

The confidence interval for VE can be obtained by assuming log-normality of the odds ratio $\gamma$, i.e.,

$$\gamma = \gamma^* \exp(\pm 1.96\sigma^*)$$

where $\sigma$ is the shape parameter of the log-normal distribution and is empirically given as

$$\sigma^* = \text{SD}(\log(\gamma^*))$$

$$= \sqrt{\frac{1}{S_V^2} \left[ \frac{\pi_V(1 - \pi_V)}{(1 - \pi_V - (1 - \alpha))^2(\pi_V - (1 - \beta))^2} + \frac{1}{S_U^2} \cdot \frac{\pi_U(1 - \pi_U)}{(1 - \pi_U - (1 - \alpha))^2(\pi_U - (1 - \beta))^2} \right]^{\text{1+}}},$$

where $\pi_V$ and $\pi_U$ are observed (uncorrected) TD frequency ($\pi_V = \frac{X_V}{X_V + Y_V}$ and $\pi_U = \frac{X_U}{X_U + Y_U}$). (See Appendix for details of the MLE and confidence intervals.)

### 2.2.2 Simulation

To assess the performance of the corrected odds ratio given in Equation (22), we used simulation studies. TND study datasets were generated based on the likelihood presented in Equation (4), where the mean total sample size $\left(\frac{1+\gamma}{1+\beta}\cdot\lambda_V + \lambda_U\right)$ was set to be 3,000. Parameter values were chosen according to a range of scenarios shown in Table 1, and the true vaccine effectiveness $VE = 1 - \gamma$ was compared with the estimates obtained from the simulated data. For each scenario, simulation was repeated 500 times to yield the distribution of estimates. Reproducible codes (including those for simulations in later sections) are reposited on GitHub (https://github.com/akira-endo/TND-biascorrection/).

<table>
<thead>
<tr>
<th>ID</th>
<th>Scenario</th>
<th>True VE ($\gamma$)</th>
<th>$\lambda_V/\lambda_U$</th>
<th>Case ratio ($\frac{\lambda_V}{\lambda_U}$)</th>
<th>Sensitivity ($\alpha$)</th>
<th>Specificity ($\beta$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Baseline: low VE</td>
<td>0.4</td>
<td>0.5</td>
<td>0.5</td>
<td>0.8</td>
<td>0.95</td>
</tr>
<tr>
<td>2</td>
<td>Baseline: high VE</td>
<td>0.8</td>
<td>0.5</td>
<td>0.5</td>
<td>0.8</td>
<td>0.95</td>
</tr>
<tr>
<td>3</td>
<td>High quality test: low VE</td>
<td>0.4</td>
<td>0.5</td>
<td>0.5</td>
<td>0.95</td>
<td>0.97</td>
</tr>
<tr>
<td>4</td>
<td>High quality test: high VE</td>
<td>0.8</td>
<td>0.5</td>
<td>0.5</td>
<td>0.95</td>
<td>0.97</td>
</tr>
<tr>
<td>5</td>
<td>Low quality test: low VE</td>
<td>0.4</td>
<td>0.5</td>
<td>0.5</td>
<td>0.6</td>
<td>0.9</td>
</tr>
<tr>
<td>6</td>
<td>Low quality test: high VE</td>
<td>0.8</td>
<td>0.5</td>
<td>0.5</td>
<td>0.6</td>
<td>0.9</td>
</tr>
<tr>
<td>7</td>
<td>High TD incidence: low VE</td>
<td>0.4</td>
<td>0.5</td>
<td>0.7</td>
<td>0.8</td>
<td>0.95</td>
</tr>
<tr>
<td>8</td>
<td>High TD incidence: high VE</td>
<td>0.8</td>
<td>0.5</td>
<td>0.7</td>
<td>0.8</td>
<td>0.95</td>
</tr>
<tr>
<td>9</td>
<td>Low TD incidence: low VE</td>
<td>0.4</td>
<td>0.5</td>
<td>0.3</td>
<td>0.8</td>
<td>0.95</td>
</tr>
<tr>
<td>10</td>
<td>Low TD incidence: high VE</td>
<td>0.8</td>
<td>0.5</td>
<td>0.3</td>
<td>0.8</td>
<td>0.95</td>
</tr>
<tr>
<td>11</td>
<td>High vaccine coverage: low VE</td>
<td>0.4</td>
<td>0.7</td>
<td>0.5</td>
<td>0.8</td>
<td>0.95</td>
</tr>
<tr>
<td>12</td>
<td>High vaccine coverage: high VE</td>
<td>0.8</td>
<td>0.7</td>
<td>0.5</td>
<td>0.8</td>
<td>0.95</td>
</tr>
<tr>
<td>13</td>
<td>Low vaccine coverage: low VE</td>
<td>0.4</td>
<td>0.3</td>
<td>0.5</td>
<td>0.8</td>
<td>0.95</td>
</tr>
<tr>
<td>14</td>
<td>Low vaccine coverage: high VE</td>
<td>0.8</td>
<td>0.3</td>
<td>0.5</td>
<td>0.8</td>
<td>0.95</td>
</tr>
</tbody>
</table>

We found that the uncorrected estimates, directly obtained from the raw case counts that were potentially misclassified, exhibited substantial underestimation of VE for most parameter values (Figure 3). On the other hand, our bias correction method was able to yield unbiased estimates in every setting, whose median almost correspond to the true VE. Although the corrected and uncorrected distributions were similar (with a difference in median $\sim 5\%$) when VE is relatively low ($40\%$) and the test has sufficiently high sensitivity and specificity ($95\%$ and $97\%$, respectively), they became distinguishable with a higher VE ($80\%$). With lower test performances, the bias in the VE estimates can be up to $10\%$-$20\%$, which may be beyond the level of acceptance in VE studies.

### 2.2.3 Bias correction of VEs reported in previous studies

We have seen that the degree of bias for uncorrected VE estimates depends on parameter values. To explore the possible degree of bias in existing VE studies, we extracted the reported crude VEs (i.e. VEs without adjustments of potential confounders) from two systematic reviews [18, 20] (Young et al. [19] was not included because they did not report case counts) and applied our bias correction method assuming different levels of test sensitivity and specificity. The
Figure 3: Bias correction for simulated data in the univariate setting. The distributions of bias-corrected VE estimates (boxplots in blue) are compared with those of raw VE estimates without correction (red). Five hundred independent datasets were randomly generated for each set of parameter values, and the corrected and uncorrected VE estimates are compared with the true value (black solid line).

case counts for each study summarised in the reviews were considered eligible for the analysis if the total sample size exceeded 200. Varying the assumed sensitivity and specificity, we investigated the possible discrepancy between the reported VE (or crude VE derived from the case counts if unreported in the reviews) and bias-corrected VE. We did not consider correcting adjusted VEs because it requires access to the original datasets.

Figure 4 displays the discrepancy between the reported VE and bias corrected VE corresponding to a range of assumptions on the test performance. Many of the extracted studies employed polymerase chain reaction (PCR) for the diagnostic test, which is expected to have a high performance. However, the true performance of PCR cannot be definitively measured as there is currently no other gold-standard test available. Figure 4B suggests that even a slight decline in the test performance can introduce a non-negligible bias in some parameter settings. Our bias correction methods may therefore also be useful in TND studies using PCR, which would enable a sensitivity analysis accounting for potential misdiagnosis by PCR tests. In this light, it is useful that the corrected odds ratio

\[ \gamma^* = \frac{X_U - \frac{1 - \beta}{\beta} X_V}{Y_U - \frac{1 - \alpha}{\alpha} X_V} \]

is a monotonic function of both \( \alpha \) and \( \beta \) (given that all the four components are positive). The possible range of VE in a sensitivity analysis is obtained by supplying \( \gamma^* \) with the assumed upper and lower limits of sensitivity and specificity.

### 2.3 Bias correction in multivariate analysis

#### 2.3.1 Theoretical framework

TND studies often employ a multivariate regression framework to address potential confounding variables such as age. The most widespread approach is to use linear models (e.g., logistic regression) and include vaccination history as well as other confounding variables as covariates. The estimated linear coefficient for vaccination history can
Figure 4: Bias correction method applied to published VE estimates assuming various test sensitivity and specificity. Case count data were extracted from two systematic reviews [18, 20]. Each connected set of dots show how (crude) VE estimates reported in the review varies when imperfect sensitivity and specificity are assumed. Black dots on the grey diagonal line denote the original VEs reported in the reviews (where sensitivity = specificity = 1) and coloured dots show the estimated VE considering potential misclassification.

Then be converted VE (in the logistic regression model, the linear coefficient for vaccination history corresponds to \( \log(1 - \text{VE}) \)).

In this situation, the likelihood function now reflects a regression model and thus the bias-corrected estimate in the univariate analysis (Equation (5)) is no longer applicable. We therefore need to develop a separate multivariate TND study framework to correct for bias in multivariate analysis. Suppose that covariates \( \xi = (\xi_1, \xi_2, ..., \xi_n) \) are included in the model, and that \( \xi_1 \) corresponds to vaccination history (1: vaccinated, 0: unvaccinated). \( \xi \) is expected to have a certain distribution over the total population \( N \), and let us denote the frequency density of covariates \( \xi \) by \( N(\xi) \), where \( \int N(\xi)d\xi = N \). Let \( \rho_1(\xi) \) and \( \rho_0(\xi) \) be the conditional probabilities that an individual is included in the study with TD and ND, respectively, given covariates \( \xi \). Incorporating misclassification, the probability of an individual \( i \) with covariates \( \xi_i \) being included and tested positive/negative will be

\[
\begin{align*}
\rho_+ (\xi_i) &= \alpha \rho_1 (\xi_i) + (1 - \beta) \rho_0 (\xi_i) \\
\rho_- (\xi_i) &= (1 - \alpha) \rho_1 (\xi_i) + \beta \rho_0 (\xi_i)
\end{align*}
\]

Assuming that disease incidences follow Poisson distributions, as in the univariate case, we can obtain the probability density of observing data \( D = \{Z_i, \xi_i\}_{i=1,2,...,S} \) (\( Z_i \) denotes the test result of individual \( i \)) as

\[
P(D) = \text{Pois}(S_+; \lambda_+) \text{Pois}(S_-; \lambda_-) \prod_{i \in \{+\}} \frac{\rho_+(\xi_i)N(\xi_i)}{\lambda_+} \prod_{i \in \{-\}} \frac{\rho_-(\xi_i)N(\xi_i)}{\lambda_-}.
\]

where \( \lambda_+ \) and \( \lambda_- \) are the mean incidence of being included in the study and tested positive/negative: \( \lambda_+ = \int \rho_+(\xi)N(\xi)d\xi \). The first two Poisson distributions on the right-hand side of Eq. (10) give the probability that the study yields \( S_+ \) positive and \( S_- \) negative subjects. The products that follow represent the probability density for covariates \( \xi_i \) observed in the positive/negative group.
Suppose that we model this system using a parameter set \( \theta \). We could directly model \( p_1(\xi; \theta) \) and \( p_0(\xi; \theta) \); however, it is often more convenient to model the binomial probability for the true outcome \( p_1(\xi) = \frac{\rho_1(\xi)}{\rho(\xi)} \) and \( p_0(\xi) = \frac{\rho_0(\xi)}{\rho(\xi)} \), where \( \rho(\xi) = \rho_1(\xi) + \rho_0(\xi) = \rho_+ (\xi) + \rho_- (\xi) \) is the probability density of being included in the study given covariates \( \xi \), because the absolute scale of incidence is rarely of a primary concern. The binomial probabilities for the respective observed outcomes (with errors) are then given by:

\[
\begin{align*}
\pi_+ (\xi; \theta) &= \alpha p_1(\xi; \theta) + (1 - \beta) p_0(\xi; \theta) \\
\pi_- (\xi; \theta) &= (1 - \alpha) p_1(\xi; \theta) + \beta p_0(\xi; \theta)
\end{align*}
\]  

(11)

Let us use parameter set \( \theta \) to model the binomial probabilities \( \pi_+ \) (and \( \pi_- \)) and assume that another set of parameters \( \eta \) (nuisance parameters) characterise \( \rho(\xi) \). Then our objective is reduced to the estimation of \( \theta \) and \( \eta \).

Rearranging Equation (10), we get the joint likelihood for \( \theta \) and \( \eta \):

\[
\mathcal{L}(\theta, \eta; D) = \left( \sum_{S_+} \text{Pois}(S; \lambda(\eta)) \prod_{i=1}^{S} \frac{\rho(\xi_i; \eta)N(\xi_i)}{\lambda(\eta)} \prod_{i \in S_+} \pi_z_i(\xi_i; \theta),
\]

(12)

where \( \lambda(\eta) \) is the overall mean incidence: \( \lambda(\eta) = \int \rho(\xi; \eta)N(\xi)d\xi \). The factor outside the products on the right-hand side of Eq. (12) is the probability that the study yields \( S \) subjects of which \( S_+ \) are positives and \( S_- \) are negatives. The first product is the probability density for covariates \( \xi_i \) observed in data \( D \), and the second product is the binomial probabilities for the test results \( Z_i \). When only \( \theta \) is of our concern, we can obtain the MLE for \( \theta \) by maximising

\[
\mathcal{L}(\theta; D) = \prod_{i=1}^{S} \pi_z_i(\xi_i; \theta) = \prod_{i \in (+)} \left[ \alpha p_1(\xi_i; \theta) + (1 - \beta) p_0(\xi_i; \theta) \right] \prod_{i \in (-)} \left[ (1 - \alpha) p_1(\xi_i; \theta) + \beta p_0(\xi_i; \theta) \right],
\]

(13)

as \( \theta \) and \( \eta \) are separate in the likelihood (12). With the estimate \( \theta^* \), the VE estimate for an individual with covariates \( \xi^{2:n} = (\xi^2, \xi^3, \ldots , \xi^n) \) is given as (1-odds ratio):

\[
\text{VE}(\xi^{2:n}) = 1 - \frac{p_1(\xi^1 = 1, \xi^{2:n}; \theta^*)}{p_0(\xi^1 = 1, \xi^{2:n}; \theta^*)} / \frac{p_1(\xi^1 = 0, \xi^{2:n}; \theta^*)}{p_0(\xi^1 = 0, \xi^{2:n}; \theta^*)}.
\]

(14)

2.3.2 Direct likelihood method for the logistic regression model

The logistic regression model is well-suited for modelling binomial probabilities \( p_1 \) and \( p_0 \). The log-odds (log\((\frac{p_1}{p_0})\)) is characterised by a linear predictor as:

\[
\log \left( \frac{p_1(\xi; \theta)}{p_0(\xi; \theta)} \right) = \theta_0 + \theta_1 \xi^1 + \cdots + \theta_n \xi^n.
\]

(15)

In the logistic regression model where covariate \( \xi_1 \) indicates vaccination history, the corresponding coefficient \( \theta_1 \) gives the VE estimate: \( \text{VE} = 1 - \exp(\theta_1) \). Due to the assumed linearity, the estimated VE value is common across individuals regardless of covariates \( \xi^{2:n} \).

We can employ the direct likelihood method by combining Equations (13) and (15). The usual logistic regression optimises \( \theta \) by assuming that the test results follow Bernoulli distributions \( Z_i \sim \text{Bernoulli}(p_1(\xi_i; \theta)) \) (\( Z_i = 1 \) for positive test results and \( 0 \) for negative). To correct the misclassification bias, we instead need to use the modified probabilities given by Eq. (11) to construct the likelihood accounting for diagnostic error, i.e.,

\[
Z_i \sim \text{Bernoulli}(\alpha p_1(\xi_i; \theta) + (1 - \beta) p_0(\xi_i; \theta)).
\]

(16)

Parameter \( \theta \) is estimated by directly maximising the probability of observing \( \{Z_i\} \) based on Eq. (16).

Note that as long as the binomial probability is the modelling target, other type of models (e.g. probit model) could also be employed under a similar framework.
The direct likelihood method presented in the previous section is the most rigorous MLE approach and would therefore be preferable whenever possible. However, it is often technically-demanding to implement such approaches as it involves re-defining the likelihood; if we wanted to use existing tools for logistic regression (or other models), for example, we would need to modify the internal algorithm specifying the likelihood computation. To ensure that researchers are able to employ correction methods without reprogramming the underlying software algorithms, we also propose another method, which employs a multiple overimputation (MO) framework [12] to account for misclassification. Whereas multiple imputation only considers missing values, MO is proposed as a more general concept which includes overwriting mismeasured values in the dataset by imputation. In our multivariate bias correction method, test results in the dataset (which are potentially misclassified) are randomly overimputed.

Let \( M \) be an existing estimation software tool whose likelihood specification cannot be reprogrammed. Given data \( d = \{ z_i, \xi_i \}_{i=1,2,...,S} \), where \( z_i \) denotes the true disease state (\( z = 1 \) for TD and \( z = 0 \) for ND), \( M \) would be expected to return at least the following two elements: the point estimate of VE (\( \varepsilon_d \)) and the predicted binomial probability \( \hat{p}_1(\xi_i) \) for each individual \( i \). From the original observed dataset \( D \), imputed datasets \( \{ \tilde{D}^j \} = \{ \tilde{D}^1, \tilde{D}^2, ..., \tilde{D}^J \} \) are generated by the following procedure.

1. For \( i = 1, 2, ..., S \), impute disease state \( \tilde{z}_i^j \) based on the test result \( Z_i \). Each \( \tilde{z}_i^j \) is sampled from a Bernoulli distribution conditional to \( Z_i \):
   \[
   \tilde{z}_i^j \sim \begin{cases} 
   \text{Bernoulli}(1 - \tilde{\varphi}_{i+}) & (Z_i = 1) \\
   \text{Bernoulli}(\tilde{\varphi}_{i-}) & (Z_i = 0) 
   \end{cases}
   \tag{17}
   \]

   \( \tilde{\varphi}_{i+} \) and \( \tilde{\varphi}_{i-} \) are estimated probabilities that the test result for individual \( i \) is incorrect (i.e., \( z_i \neq Z_i \)) given \( Z_i \).

   The sampling procedure [17] is therefore interpreted as the test result \( Z_i \) being "flipped" at a probability \( \tilde{\varphi}_{i+} \) or \( \tilde{\varphi}_{i-} \). Later we will discuss possible procedures to obtain these probabilities.

2. Apply \( M \) to \( \tilde{D}^j = \{ \tilde{z}_i^j, \xi_i \} \) to yield a point estimate of VE (\( \varepsilon^j \)).

3. Repeat 1., 2. for \( j = 1, 2, ..., J \) to yield MO estimates \( \{ \varepsilon^j \}_{j=1,...,J} \).

Once MO estimates \( \{ \varepsilon^j \} \) are obtained, the pooled estimate and confidence intervals of VE are obtained by appropriate summary statistics, e.g., Rubin’s rules. As long as the estimated “flipping” probabilities \( \tilde{\varphi}_{i\pm} = (\tilde{\varphi}_{i+}, \tilde{\varphi}_{i-}) \) are well chosen, this MO procedure should provide an unbiased estimate of VE with a sufficiently large number of iterations \( J \).

There can be multiple candidates for the flipping probability estimate \( \tilde{\varphi}_{i\pm} \). Here we discuss two possible options: parametric bootstrapping and the expectation-maximisation (EM) algorithm. Our simulation showed that parametric bootstrapping is preferable (see the supplementary document).

(i) Parametric bootstrapping

The simplest option to estimate \( \tilde{\varphi}_{i\pm} \) is to use Bayesian probability

\[
\mathcal{P}(z_i = Z_i | Z_i) = \left\{ \begin{array}{ll}
\frac{\alpha P(z_i = 1)}{\alpha P(z_i = 1) + (1 - \beta) P(z_i = 0)} & (Z_i = 1) \\
\frac{\beta P(z_i = 0)}{(1 - \alpha) P(z_i = 1) + \beta P(z_i = 0)} & (Z_i = 0)
\end{array} \right.
\]

The true binomial probabilities \( p_0(\xi_i), p_1(\xi_i) \) are not known, but their estimators are derived with the inverted classification matrix in the same manner as Eq. (7). By substituting \( \begin{bmatrix} p_1(\xi_i) \\ p_0(\xi_i) \end{bmatrix} \) with \( C^{-1} \begin{bmatrix} \pi_+(\xi_i) \\ \pi_-(\xi_i) \end{bmatrix} \), we get

\[
\tilde{\varphi}_{i+} = 1 - \mathcal{P}(z_i = 1 | Z_i = 1) = \frac{1 - \beta}{\alpha + \beta - 1} \begin{bmatrix} \alpha & \pi_-(\xi_i) \\ \pi_+(\xi_i) & 1 - (1 - \alpha) \end{bmatrix}
\]

\[
\tilde{\varphi}_{i-} = 1 - \mathcal{P}(z_i = 0 | Z_i = 0) = \frac{1 - \alpha}{\alpha + \beta - 1} \begin{bmatrix} \beta & 1 - (1 - \beta) \\ \pi_+(\xi_i) & \pi_-(\xi_i) \end{bmatrix}
\]

These probabilities can be computed provided the odds of the test results \( \frac{\pi_+(\xi_i)}{\pi_-(\xi_i)} \). We employ a parametric approach and approximate this odds by applying estimation tool \( M \) to the original data \( D \); i.e., the predicted binomial probability
\(\hat{p}_1(\xi_i)\) obtained from \(D\) is used as a proxy of \(\pi_+(\xi_i)\). Generally it is not assured that true and observed probabilities \(p_1(\xi_i)\) and \(\pi_+(\xi_i)\) have the same mechanistic structure captured by \(M\); however, when our concern is limited to the use of model-predicted probabilities to smooth the data \(D\), we may expect for \(M\) to provide a sufficiently good approximation with realistic test sensitivity and specificity. The above framework can be regarded as a variant of parametric bootstrapping methods as MO datasets are generated from data \(D\) assuming a parametric model \(M\). The whole bias correction procedure is presented in pseudocode (Algorithm 1); a sample R code is also available on GitHub (https://github.com/akira-endo/TND-biascorrection/).

Algorithm 1 Multiple imputation with parametric bootstrapping

\textbf{Input:} \(D = \{Z_i, \xi_i\}_{i=1,2,...,S}\)

Fit model \(M\) to \(D\) to obtain a predictive model \(\pi_+ = \hat{p}_1(\xi)\)

\textbf{for} \(j = 1, 2, ..., J\) \textbf{do}

\textbf{for} \(i = 1, ..., S\) \textbf{do}

\(\pi_+ \leftarrow \hat{p}_1(\xi_i)\)

\(\tilde{z}_i^j \leftarrow Z_i\)

\textbf{if} \(Z_i = 1\) \textbf{then}

\(\varphi \leftarrow \frac{1-\beta}{\alpha+\beta-1} \left[ \alpha \cdot \frac{1-\pi_+}{\hat{p}_1(\xi)} - (1-\alpha) \right]\)

\(u \leftarrow \text{Unif}(0, 1)\)

\textbf{if} \(u < \varphi\) \textbf{then}

\(\tilde{z}_i^j \leftarrow 0\)

\textbf{end if}

\textbf{else}

\(\varphi \leftarrow \frac{1-\alpha}{\alpha+\beta-1} \left[ \beta \cdot \frac{\pi_+}{\hat{p}_1(\xi)} - (1-\beta) \right]\)

\(u \leftarrow \text{Unif}(0, 1)\)

\textbf{if} \(u < \varphi\) \textbf{then}

\(\tilde{z}_i^j \leftarrow 1\)

\textbf{end if}

\textbf{end if}

\textbf{end if}

\textbf{end for}

Fit model \(M\) to \(\tilde{D}^j = \{\tilde{z}_i^j, \xi_i\}_{i=1,2,...,S}\) to estimate parameter \(\epsilon^j\)

\textbf{end for}

\textbf{Output:} MO estimates \(\{\epsilon^j\}_{j=1,2,...,J}\)

(ii) EM algorithm

Another possible approach is to use EM algorithm as proposed by Magder et al. [21], where \(\hat{\varphi}_{i+}\) can be estimated by iterations (see the supplementary document for details). However, in our simulation we found that the performance of EM algorithm was inferior to the other two alternatives (direct likelihood and parametric bootstrapping). The three methods all provided effectively identical distributions of estimates in most settings, but in some settings the EM algorithm produced extreme estimates (VE < 0 or > 1) slightly more often than the other two. We therefore recommend parametric bootstrapping as the first choice of bias correction method when the direct likelihood approach is inconvenient.

2.3.4 Simulation of bias correction with parametric bootstrapping

To assess the performance of this method, we used the same simulation framework as in the univariate analysis (Table 1). In addition to vaccination history (denoted by \(\xi_1\)), we consider one categorical and one continuous covariate. Let us assume that \(\xi_2\) represents the age group (categorical; 1: child, 0: adult) and \(\xi_3\) the pre-infection antibody titre against TD (continuous). Suppose that the population ratio between children and adults is 1:2, and that \(\xi_3\) is scaled so that it is standard normally distributed in the population. For simplicity, we assumed that all the covariates are mutually independent with regard to the distribution and effects (i.e., no association between covariates and no interaction effects).

The relative risk of children was set to be 2 and 1.5 for TD and ND, respectively, and a unit increase in the antibody titre was assumed to halve the risk of TD (and not to affect the risk of ND). The mean total sample size \(\lambda\) was set to be 3,000, and 500 sets of simulation data were generated for each scenario. VE estimates were corrected by the parametric bootstrapping approach (the number of iterations \(J = 100\)) and were compared with the raw (uncorrected) VE estimates.
Figure 5 shows the distributions of estimates with and without bias correction in the multivariate setting. Our bias correction (parametric bootstrapping) provided unbiased estimates for all the scenarios considered. Overall, biases in the uncorrected estimates were larger than those in the univariate setting. In some scenarios, the standard error of the bias-corrected estimates was extremely wide. This was not because of the failure of bias correction, but because of the uncertainty already introduced before misclassification. The standard errors in those scenarios were very large even with perfect test sensitivity and specificity as can be seen in Figure 6. Larger sample size is required to yield accurate estimates in those settings, as the information loss due to misclassification will be added on top of the inherent uncertainty in the true data.

2.3.5 Increased uncertainty introduced by misclassification

Although our bias correction methods provide unbiased VE estimates from potentially misclassified test results, the resulting uncertainty is larger than that which would be obtained from estimates using the true disease status. In Figure 6, we compared bias-corrected estimates obtained from misclassified data (by the direct likelihood method) with those obtained from the true data (i.e., 100% sensitivity and specificity). Although both estimates are unbiased around the true value, the results from the misclassified data exhibit higher variability (by a factor of 1.1-3.0) due to the loss of information caused by misdiagnosis. Increased uncertainty due to misclassification should be carefully considered when one calculates the power of test-negative design studies. Overestimated test performance may not only underestimate the true VE but also lead to overconfidence.

2.3.6 The number of confounding variables

We investigated how the bias in uncorrected VE estimates can be affected by the number of confounding variables. In addition to the vaccine history $\xi^1$, we added a set of categorical/continuous confounding variables to the model and assessed the degree of bias caused by misclassification. The characteristics of the variables were inherited from those in Section 2.3.4: categorical variable "age" and continuous variable "pre-infection antibody titre". That is, individuals were assigned multiple covariates (e.g., "categorical variable A", "categorical variable B", ..., "continuous variable..."
A", "continuous variable B", ...) whose distribution and effect were identical to "age" (for categorical variables) and "antibody titre" (for continuous variables) in Section 2.3.4. No interaction between covariates was assumed. The covariate set in Section 2.3.4 being baseline (the number of covariates: (vaccine, categorical, continuous) = (1, 1, 1)), we employed two more scenarios with a larger number of covariates: (1, 3, 3) and (1, 5, 5).

The simulation results are presented in Figure 2. Overall, additional confounding variables led to more severe bias in the uncorrected VE estimates towards underestimation. As shown in Figure 2A, the degree of bias is strongly affected by the case ratio: the ratio between the risk of TD and ND. More confounding variables in a population result in higher heterogeneity in individuals’ risk of TD and ND. This may account for the association between the degree of bias and the number of confounding variables; more individuals in a highly heterogeneous population may fall in the outer range of the case ratio shown in Figure 2A, substantially contributing to the misclassification bias.

3 Discussion

Misclassification caused by imperfect diagnostic tests can potentially lead to substantial biases in TND studies. By considering the processes involved in VE estimation, we have characterised the degree of bias potentially caused by diagnostic misclassification in different parameter settings, finding that VE can be noticeably underestimated, particularly when the ratio between TD and ND cases in the study data is unbalanced. To address this potential bias, we developed multiple bias correction methods that address test misclassification and provide unbiased VE estimates in both univariate and multivariate settings. When the test sensitivity and specificity are known or assumed, those values can be used to restore the true VE estimate by a relatively simple statistical procedure. Using simulations, we showed that our methods could successfully eliminate the bias in VE estimates obtained from misclassified data, although some uncertainty was introduced as a result of the information loss.

We believe that our methods could therefore enable researchers to address possible misclassification in their data and report unbiased VE estimates even when imperfect tests had to be used. Such methods could also help in the scaling up of TND studies, as tests with limited performance are usually inexpensive and logistically convenient. Even
Figure 7: Bias in raw VE estimates from simulated data in the presence of different numbers of confounding variables. The distributions in red, purple and blue correspond to uncorrected VE estimates in the presence of 2, 6 and 10 confounding variables in addition to the vaccination history.

when high-performance diagnostic tests including PCR techniques are available, the risk of misdiagnosis may not be negligible in certain settings, and our methods could further be used to perform sensitivity analysis to properly address the possibility of bias in such cases.

Although TND is a relatively new study design, first appearing in a publication in 2005 [22], it has gained broad popularity and is becoming a standard approach in VE studies. TND is believed to minimise the bias caused by different health seeking behaviour of individuals, but one of the largest factors that have contributed to its widespread use is the fact that data collection can be completed within clinical setups [1]. Whereas cohort or case-control studies usually require additional efforts including follow up or recruitment of non-patients, TND studies only involve patients visiting healthcare facilities with suspects of certain diseases and thus routinely collected clinical data can be easily adapted for analysis. For diseases of which suspected patients routinely undergo lab tests, TND may be one of the most convenient options to generate epidemiological insights into the effect of specific prevention/treatment. VE studies of influenza, for which TND is most frequently used, often use PCR as a diagnostic tool for better data quality [20]. However, such studies usually involve intensive effort and cost, and thus may only be feasible by large-scale research bodies. Our bias correction methods may open a possibility of wider use of clinical data, which could potentially provide rich epidemiological insights, especially in settings where rapid tests are routinely used for diagnosis. For example, rapid influenza diagnostic tests are routinely used for inpatient clinics and hospitals in Japan, and such clinical data have facilitated a number of TND studies [23, 24, 25, 26, 27, 28]. Such studies based on rapid tests could benefit from our methods, as it would provide strong support for the validity of their estimates. Our methods may also be useful in resource limited settings or for diseases without high-performance diagnostic tools. Even in resourceful settings where high-performance tests are available, the slight possibility of misclassification might not always be neglected.

Although PCR tests are currently used as a gold-standard for influenza diagnosis, their sensitivity and specificity may not be exact 100%; especially, the sensitivity of the test depends not only on microbiological technique but also on the quality of swab samples from patients. In addition, it is suggested that the sensitivity of PCR tests may change during the time course of infection [29] and be sufficiently high only during a limited time window. Our simulation study also indicated that a high heterogeneity in individual characteristics in study samples might increase the bias in the
VE estimate. Our methods could enable researchers to implement sensitivity analysis by assuming the possible test sensitivity and specificity in such cases.

Our bias correction methods are also intended to be reasonably straightforward for researchers to introduce. Existing estimation tools including software libraries and packages are often used in epidemiological analyses, and most of them have specific requirements for data input and output. Modifying the procedure employed by such tools in a way which is unexpected by the authors is usually impossible or requires advanced technical skills including reprogramming of the underlying algorithms. Incorporating the MO approach, our parametric bootstrapping bias correction method only involves data manipulation and does not require modification of the estimation algorithm. The only inputs required to produce MO datasets are the assumed test sensitivity and specificity ($\alpha, \beta$) and the model-predicted binomial probability for the test result ($\pi_+ \gamma$) for each individual. Once multiple sets of data are randomly generated, any type of analysis can be performed as long as they produce numerical estimates to be summarised over the MO datasets. Of particular note is that our methods for multivariate analysis (including the direct likelihood method) allow stratification of sensitivity and specificity among individuals. Therefore, the users can employ more complex misclassification mechanisms including time-varying test performance or test performance affected by individual characteristics. Datasets with a mixture of different diagnostic tools [3, 30] can also be handled by applying different values for each test.

There are some limitations to our study. We only focused on misclassification of diagnosis (i.e., misclassified outcomes) and did not consider potential misclassification of covariates (e.g., vaccine history and other confounding variables), which is another important type of misclassification in TND studies [10]. Further, it is generally not easy to plausibly estimate the sensitivity and specificity for measurement of covariates (e.g. recall bias), which must be known or assumed to implement bias correction. However, if reliable estimates are available, an extension of our approach may yield bias-corrected VE estimates in the presence of covariate misclassification. Such consideration remains to be discussed in future work. Moreover, to keep our focus only on diagnostic misclassification, our methods rested on the assumption that other sources of bias in TND studies are nonexistent or properly addressed. Potential sources of bias in TND studies have been discussed elsewhere [13, 31], and the researchers conducting TND studies need to carefully consider the possibility of such biases in addition to the diagnostic misclassification. Lastly, it must be noted that our methods depend on the assumed test sensitivity and specificity, and that misspecifying those values can result in an improper correction. The sensitivity and specificity of tests are usually reported by manufacturers in a comparison of the test results with gold-standard tests; however, when such gold-standard tests themselves are not fully reliable or when no available test has satisfactory performance to be regarded as gold-standard, specifying sensitivity and specificity of a test is in principle impossible. Further, test performances reported by manufacturers might lack sufficient sample size or might not be identical to those in the actual study settings. Use of composite reference standards [32, 33] or external/internal validation approaches [34] may help overcome these problems.

Although the presence of imperfect diagnosis limits the quality of clinical data, data with such uncertainty can still hold useful information, and this information can be transformed into useful insights by appropriate statistical processing. Our bias correction methods were developed primarily for TND studies, but a similar approach could be applied to broader classes of estimation problems with misclassification. The value of routinely collected data in healthcare settings has become widely recognised with the advancement of data infrastructure, and we believe our methods could help support the effective use of such data.

4 Conclusion

Bias correction methods for the test-negative design studies were developed to address potential misclassification bias due to imperfect tests.

Appendix

Maximum likelihood estimates and confidence intervals in the univariate setting

Expanding Equation (4) in the main text, we get

$$
L(\gamma, \delta, \lambda_V, \lambda_U; D) = \frac{\alpha \gamma \delta (1 - \beta) [X_V (1 - \alpha) \gamma \delta + \beta] Y_V (\alpha \delta + (1 - \beta)) [X_U (1 - \alpha) \delta + \beta] Y_U \lambda_V \lambda_U^{S_U} (1 + \delta)^{S_V} (1 + \delta)^{S_U} X_V Y_V X_U Y_U \exp \left( \frac{1 + \gamma \delta}{1 + \delta} \lambda_V \right) \exp \lambda_U }{
(1 + \delta)^{S_V} X_V Y_V X_U Y_U \exp \left( \frac{1 + \gamma \delta}{1 + \delta} \lambda_V \right) \exp \lambda_U },
$$

(20)

where $S_V = X_V + Y_V$ and $S_U = X_U + Y_U$. 

For mathematical convenience, we change the variable $\lambda$ to $\lambda' = \frac{1+\delta}{1+\beta} \lambda$. Let $l = \log \mathcal{L}(\gamma, \delta, \lambda'; X)$. Partial derivatives of $l$ are

\[
\frac{\partial l}{\partial \gamma} = \frac{\alpha \delta X_V}{\alpha \gamma \delta + (1 - \beta)} + \frac{(1 - \alpha) \delta Y_V}{(1 - \alpha) \gamma \delta + \beta} - \frac{\delta S_V}{1 + \gamma \delta} \\
\frac{\partial l}{\partial \delta} = \frac{\alpha \gamma X_V}{\alpha \gamma \delta + (1 - \beta)} + \frac{(1 - \alpha) \gamma Y_V}{(1 - \alpha) \gamma \delta + \beta} + \frac{\alpha X_U}{\alpha \delta + (1 - \beta)} + \frac{(1 - \alpha) Y_U}{(1 - \alpha) \delta + \beta} - \frac{\gamma S_V}{1 + \gamma \delta} - \frac{S_U}{1 + \delta}
\]

(21)

Equation (21) gives the maximum likelihood estimates:

\[
\gamma^* = \frac{X_V - \frac{1-\beta}{\alpha} Y_V}{Y_V - \frac{1-\alpha}{\alpha} X_V} \\
\delta^* = \frac{X_U - \frac{1-\beta}{\alpha} Y_U}{Y_U - \frac{1-\alpha}{\alpha} X_U} \\
\lambda_{V'}^* = S_V \\
\lambda_{U'}^* = S_U
\]

The confidence intervals for parameters can be constructed using the Fisher's information matrix from Equation (21). $\lambda_{V'}^*$ and $\lambda_{U'}^*$ are independent from other parameters and

\[
\text{Var}(\lambda_{V'}) = -\frac{\partial^2 l}{\partial \lambda_{V'}^2} = S_V - \frac{\partial^2 l}{\partial \lambda_{U'}^2} = S_U
\]

(23)

We log-transform $\gamma$ and $\delta$ for mathematical convenience. Noting that $\frac{\partial y}{\partial (\log y)} = x \frac{\partial y}{\partial x}$, we get

\[
-\frac{\partial^2 l}{\partial \log(\gamma)^2} = \frac{\gamma \delta}{(1 + \gamma \delta)^2} S_V - \frac{\alpha (1 - \beta) \gamma \delta}{(\alpha \gamma \delta + (1 - \beta))^2} X_V - \frac{(1 - \alpha) \beta \gamma \delta}{[(1 - \alpha) \gamma \delta + \beta]^2} Y_V \\
-\frac{\partial^2 l}{\partial \log \gamma \partial \log \delta} = \frac{\gamma \delta}{(1 + \gamma \delta)^2} S_V - \frac{\alpha (1 - \beta) \gamma \delta}{(\alpha \gamma \delta + (1 - \beta))^2} X_V - \frac{(1 - \alpha) \beta \gamma \delta}{[(1 - \alpha) \gamma \delta + \beta]^2} Y_V \\
-\frac{\partial^2 l}{\partial \log y^2} = \frac{\gamma \delta}{(1 + \gamma \delta)^2} S_V - \frac{\alpha (1 - \beta) \gamma \delta}{(\alpha \gamma \delta + (1 - \beta))^2} X_V - \frac{(1 - \alpha) \beta \gamma \delta}{[(1 - \alpha) \gamma \delta + \beta]^2} Y_V + \frac{(1 - \alpha) \beta \gamma \delta}{[(1 - \alpha) + \beta]^2} Y_V
\]

(24)

With the parameter values estimated in Eq. (22), we get the following information matrix

\[
\begin{bmatrix}
\frac{x_{V,V'}}{S_V} \left[ 1 - S_V \left( \frac{\alpha (1 - \beta)}{\lambda_V} + \frac{(1 - \alpha) \beta}{Y_V} \right) \right] & x_{V,V'} S_V \left[ 1 - S_V \left( \frac{\alpha (1 - \beta)}{\lambda_V} + \frac{(1 - \alpha) \beta}{Y_V} \right) \right] \\
\frac{x_{V,V'}}{S_V} \left[ 1 - S_V \left( \frac{\alpha (1 - \beta)}{\lambda_V} + \frac{(1 - \alpha) \beta}{Y_V} \right) \right] & \frac{x_{V,V'}}{S_V} \left[ 1 - S_V \left( \frac{\alpha (1 - \beta)}{\lambda_V} + \frac{(1 - \alpha) \beta}{Y_V} \right) \right] + x_{U,U'} S_V \left[ 1 - S_V \left( \frac{\alpha (1 - \beta)}{\lambda_V} + \frac{(1 - \alpha) \beta}{Y_V} \right) \right]
\end{bmatrix}
\]

where $x_{V} = \frac{1}{\alpha} [\beta X_V - (1 - \beta) Y_V]$ and $y_{V} = \frac{1}{\alpha} [\alpha Y_V - (1 - \alpha) X_V]$ are the true case counts (without misclassification) for $\xi = V, U$. Let $p_{V'} = x_{V}/(x_{V} + y_{V})$ and $p_{U'} = x_{U}/(x_{U} + y_{U})$ be the corresponding true binomial probabilities.
The inverse of the information matrix provides variance of estimates: in particular, for \( \log \gamma \) we get

\[
\text{Var}(\log \gamma^*) = \frac{S_V}{x_V y_V} \left[ 1 - \left( \frac{\alpha(1-\beta)}{\pi_V} + \frac{(1-\alpha)\beta}{1-\pi_V} \right) \right] + \frac{S_U}{x_U y_U} \left[ 1 - \left( \frac{\alpha(1-\beta)}{\pi_U} + \frac{(1-\alpha)\beta}{1-\pi_U} \right) \right] \\
= \frac{S_V}{x_V y_V} \frac{\pi_V(1-\pi_V)}{(1-\pi_V - (1-\alpha)) \pi_V (1 - \beta)} + \frac{S_U}{x_U y_U} \frac{\pi_U(1-\pi_U)}{(1-\pi_U - (1-\alpha)) \pi_U (1 - \beta)}
\]

or to the observed standard error (without correction),

\[
\text{SD}(\log \gamma_{\text{true}}) = \sqrt{\frac{1}{S_V \pi_V (1 - \pi_V)} + \frac{1}{S_U \pi_U (1 - \pi_U)}} = \sqrt{\frac{\Sigma_V^2}{S_V} + \frac{\Sigma_U^2}{S_U}},
\]

where \( \sigma_V = \lbrack p_V (1 - p_V) \rbrack^{1/2} \) and \( \sigma_U = \lbrack p_U (1 - p_U) \rbrack^{1/2} \) are the components of the true standard error and \( \Sigma_V = \lbrack \pi_V (1 - \pi_V) \rbrack^{1/2} \) and \( \Sigma_U = \lbrack \pi_U (1 - \pi_U) \rbrack^{1/2} \) are those of uncorrected standard error. We get

\[
\sigma^* = \text{SD}(\log(\gamma^*)) = \sqrt{\frac{\Sigma_V^2}{S_V} \left( \frac{1}{1 - \frac{1-\alpha}{\pi_V}} \right) \left( \frac{1}{1 - \frac{1-\beta}{\pi_V}} \right) + \frac{\Sigma_U^2}{S_U} \left( \frac{1}{1 - \frac{1-\alpha}{\pi_U}} \right) \left( \frac{1}{1 - \frac{1-\beta}{\pi_U}} \right)}
\]

This equation indicates that the confidence intervals diverge when the true outcome is bipolarised (\( p_V, p_U \approx 0 \) or 1).

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**References**


