Package 'iDOVE'

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Type Package

Title Durability of Vaccine Efficacy Against SARS-CoV-2 Infection

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Description Implements a nonparametric maximum likelihood method for assessing potentially time-varying vaccine efficacy (VE) against SARS-CoV-2 infection under staggered enrollment and time-varying community transmission, allowing crossover of placebo volunteers to the vaccine arm.

License GPL-2

Encoding UTF-8

Suggests rmarkdown

VignetteBuilder utils, knitr

Imports Rcpp (>= 1.0.4.6), methods, stats, graphics, knitr

LinkingTo Rcpp, RcppArmadillo

RoxygenNote 7.1.1

Collate 'VEplot.R' 'VEcal.R' 'postProcess.R' 'CoxReg.R' 'EMmeth.R' 'RcppExports.R' 'idove.R' 'idoveData.R' 'intCens.R' 'plot.iDOVE.R' 'print.iDOVE.R'

NeedsCompilation yes

Depends R (>= 3.5.0)

R topics documented:

idove *Durability of Vaccine Efficacy Against Asymptomatic SARS-CoV-2 Infection*

Description

Assesses potentially time-varying vaccine efficacy (VE) against SARS-CoV-2 infection under staggered enrollment and time-varying community transmission, allowing crossover of placebo volunteers to the vaccine arm. The infection time data can be either interval- or right-censored, with the latter being a special case of the former.

Usage

```
idove(
  formula,
  data,
  constantVE = FALSE,
  rightCens = FALSE,
  plots = TRUE,
  changePts = NULL,
  timePts = NULL,
  tol = 1e-04,
  maxit = 2000
)
```

Arguments

formula	A formula object, with the response (all the time information) on the left hand side of a '~' operator and the covariates on the right. The response must be specified through the intCens() function. See ?intCens and Details for further information.
data	A data.frame object. The data.frame in which to interpret the variable names in formula. Must contain the entry time, the left interval, time, the right interval time, the vaccination time, and the covariates. See Details.
constantVE	A logical object. If TRUE, VE is assumed to be constant. If FALSE (default), VE is assumed to be waning. Note that constant versus waning VE pertains only to the period after ramping VE.
rightCens	A logical object. If TRUE, the standard Cox model will be fitted, by treating the time of first positive test as a potentially right-censored event time and performing maximum partial likelihood estimation. If FALSE (default), the interval-censored event time method will be applied. When examinations are completed daily or every two days, this input is ignored and a standard Cox regression is performed. See Details.
plots	A logical object. If TRUE (default), plots of the estimated VE in reducing attack rate, the estimated VE in reducing the hazard rate, and their 95% confidence intervals will be automatically generated. If FALSE, plots will not be generated.

changePts	An integer vector object or NULL. The potential change points (in days) of the piece-wise log-linear hazard ratio. See Details for further information. If NULL, AIC will be used to select one change point from {28, 35, 42, 49, 56} (weeks 4, 5, 6, 7, 8).
timePts	An integer vector object or NULL. The endpoints (in days) of the time periods for which the VE in reducing the attack rate are to be estimated. The estimated VE in reducing the hazard rate at these endpoints are also returned. If NULL, a default sequence $t_1, 2t_1, 3t_1, \ldots$ will be used, where t_1 be the first change point. The sequence ends at the maximum of the left and and right ends of the time intervals from all participants. This input is ignored when constantVE = TRUE.
tol	A numeric scalar. The convergence threshold for the EM or Newton-Raphson algorithm. The default value is 0.0001.
maxit	A positive integer. The maximum number of iterations for the EM or Newton-Raphson algorithm. The default value is 2000.

Details

The information required for an analysis is

Entry Time: The time when the participant enters the trial in whole units days.

Left Interval Time: The last examination time when the test is negative in whole units days.

Right Interval Time: The first examination time when the test is positive in whole units days. If the participant does not test positive during the trial, use NA or Inf.

Vaccination Time: The time when vaccination takes place in whole units days. If the participant is not vaccinated during the trial, use NA or Inf.

Covariates: Baseline covariates (e.g., priority group, age, ethnicity).

The covariates can include categorical variables, for which all other categories are compared to the first category.

Note that all the time variables are measured from the start of the clinical trial and are specified in whole units of days. Though they need not be provided as integer, all non-NA and finite values must be able to be cast as integers without loss of information. For each individual, the entry_time, left_time, and right_time satisfy entry_time $\leq$ left_time $\leq$ right_time.

The general structure of the formula input is

```
intCens(entry_time, left_time, right_time, vaccination_time) ~ covariates
```

The response variable contains all of the time information. It must be specified through function 'intCens()'. Specifically,

```
intCens(entry_time, left_time, right_time, vaccination_time)
```

If entry_time > left_time, or left_time > right_time, the case will be removed from the analysis and a message will be generated.

When right_time - left_time ≤ 2 for all individuals whose infection times are truly interval-censored (i.e., right_time is finite and less than the end of the trial), idove() assumes that examinations are

completed daily or every two days and performs a standard Cox regression, regardless of the value specified for input rightCens.

The log hazard ratio with respect to vaccination, denoted by $\eta(t)$, is approximated by linear splines. Specifically, in K-piece linear splines,

$$\eta(t) = \gamma_1 t + \gamma_2(t - t_1)_+ + \gamma_3(t - t_2)_+ + \ldots + \gamma_K(t - t_{K-1})_+,$$

where $t_1, \ldots, t_{K-1}$ are the $K - 1$ pre-specified change points and $\gamma_1, \ldots, \gamma_K$ are the K spline parameters. The first $K - 1$ spline parameters are always estimated from the data, whereas the treatment of the last parameter γ_K depends on the value of input constantVE. If constantVE = TRUE, the slope of the last piece is assumed to be zero, that is, $\gamma_K = -\sum_{k=1}^{K-1} \gamma_k$. Thus, γ_K is a redundant parameter and is not estimated. If constantVE = FALSE, the slope of the last piece can be nonzero and γ_K is also estimated from the data.

Value

An S3 object of class iDOVE containing a list with elements

`call` The unevaluated call.

`covariates` A matrix containing the estimated (log) hazard ratio of each covariate, together with the estimated standard error, the 95% confidence intervals, and the two-sided p-value for testing no covariates effect. NA if only an intercept is given as the right hand side in input formula.

`vaccine` A list containing one or three elements, depending on the value of constantVE. If constantVE = TRUE, the only element is named 'VE' and is a vector containing the estimate of constant VE, its standard error estimate, and the 95% confidence interval. If constantVE = FALSE, three matrices are returned. The first matrix named 'VE_a' contains the estimates of the VE in reducing the attack rate at all time points given in timePts, together with the 95% confidence intervals. The second matrix named 'VE_h' contains the estimates of the VE in reducing the hazard rate at timePts. The third matrix named 'VE_period' contains the estimates of VE in reducing the attack rate over successive time periods according to timePts, together with the 95% confidence intervals.

Objects of class iDOVE have additional attributes, knots, tau, gamma, and covgamma, which are included for plotting capabilities

References

Lin, D-Y, Gu, Y., Zeng, D., Janes, H. E., and Gilbert, P. B. (2021). Evaluating Vaccine Efficacy Against SARS-CoV-2 Infection. Submitted.

Examples

```
data(idoveData)

set.seed(1234)
smp <- sample(1L:nrow(x = idoveData), size = 500L)

# Fit the model with default settings
```

```
idove(formula = intCens(entry.time, left.time, right.time, vaccine.time) ~ 1,
      data = idoveData[smp,])

# Specify Week 4 as the change point
# Assume a potentially waning VE after 4 weeks
# Estimate VE_a over 0-4, 4-16, 16-28, 28-40 weeks
idove(formula = intCens(entry.time, left.time, right.time, vaccine.time) ~ 1,
      data = idoveData[smp,],
      changePts = 4*7,
      timePts = c(4, 16, 28, 40)*7)

# Specify multiple change points at Weeks 4 and 8
# Assume a constant VE after 8 weeks
idove(formula = intCens(entry.time, left.time, right.time, vaccine.time) ~ 1,
      data = idoveData[smp,],
      changePts = c(4, 8)*7,
      constantVE = TRUE)
```

`idoveData` *Toy Dataset For Illustration*

Description

This data set is provided for the purposes of illustrating the use of the software. It was simulated under a blinded, priority-tier dependent crossover design.

Usage

```
data(idoveData)
```

Format

idoveData is a data.frame containing 40,000 participants. The data.frame contains 6 columns,

entry.time The entry time in days

left.time The left end of the time interval in days

right.time The right end of the time interval in days

vaccine.time The time of vaccination in days

priority A composite baseline risk score taking values 1-5

sex A binary indicator of sex (male/female)

intCens *Specify Time Variables*

Description

This function is used in the model statement of idove() to specify the entry time, left interval time, right interval time, and vaccination time.

Usage

```
intCens(entry_time, left_time, right_time, vaccination_time)
```

Arguments

entry_time	The variable for the time when the participant enters the trial.
left_time	The variable for the last examination time when the test is negative
right_time	The variable for the first examination time when the test is positive; Inf or NA if the participant is never tested positive during the follow-up
vaccination_time	The variable for the time when vaccination takes place.

Value

This function is intended to be used only in the model statement of idove(). The result, a matrix, is used internally.

plot *Plot Estimated Vaccine Efficacy*

Description

Generates plots of the estimated vaccine efficacy in reducing attack rate, the estimated vaccine efficacy in reducing the hazard rate, and their 95% confidence intervals.

Usage

```
## S3 method for class 'iDOVE'
plot(x, ...)
```

Arguments

x	An iDOVE object. The value object returned by idove().
...	ignored

Value

No return value, called to produce graphical elements.

Examples

```
data(idoveData)

set.seed(1234)
smp <- sample(1L:nrow(x = idoveData), size = 500L)

# Fit the model with default settings
result <- idove(formula = intCens(entry.time, left.time, right.time, vaccine.time) ~ 1,
                data = idoveData[smp,])

plot(x = result)
```

`print` *Print the Primary Results of an idove() Analysis*

Description

Print the primary results of an idove() analysis.

Usage

```
## S3 method for class 'iDOVE'
print(x, ...)
```

Arguments

`x`	An iDOVE object. The value object returned by a call to idove()
`...`	ignored

Value

No return value, called to display key results.

Examples

```
data(idoveData)

set.seed(1234)
smp <- sample(1L:nrow(x = idoveData), size = 500L)

# Fit the model with default settings
result <- idove(formula = intCens(entry.time, left.time, right.time, vaccine.time) ~ 1,
```

```
                  data = idoveData[smp,])

print(x = result)
```

Index