L05 Vaccination[1]

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Outline

Overview

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Vaccine efficacy (1)

- Vaccine efficacy is defined as the reduction in the attack rate attributable to the vaccine, i.e.

$$\mathrm{VE} = \left(\frac{p_u - p_v}{p_u} \right),$$

  where p_u and p_v denote the risk of infection in unvaccinated and vaccinated individuals over the observation period $[0, t]$, respectively,
- Alternatively, this is often written as

$$\mathrm{VE} = 1 - \mathrm{RR},$$

  where RR is the relative risk of infection, i.e. p_v/p_u, also known as risk ratio.

Vaccine efficacy (2)

- A hazard rate based definition of VE is in terms of the hazard ratio (HR) of infection in a survival context:

$$\mathrm{VE} = 1 - \mathrm{HR} = 1 - \frac{\lambda_v}{\lambda_u},$$

  where λ_u and λ_v are the constant hazard rates in the unvaccinated and vaccinated, respectively.
- If $\lambda_u t$ – and hence also $\lambda_v t$ – is small, the RR and HR based measure of VE do not differ much as seen from

$$p_u = F_u(t) = 1 - \exp(-\lambda_u t) \approx \lambda_u t \quad \text{and}$$
$$p_v = F_v(t) = 1 - \exp(-\lambda_v t) \approx \lambda_v t.$$

Vaccine efficacy (3)

- One often differs between *vaccine efficacy* for measures of the effect of vaccine in controlled clinial trials and *vaccine effectiveness* of the effect under field conditions
- Vaccine effects under field conditions are – in addition to biological factors – also influenced by
  - Vaccine storage
  - Vaccination schedules
  - Herd immunity

Estimating vaccine efficacy and effectiveness

- Vaccine efficacy and effectiveness can be estimated by the classical *cohort* and *case-control* designs known from epidemiology.
- Vaccination status of individuals is the exposure variable and outcome is whether individuals developed the disease.
- Furthermore, a regression contexts allows adjusment for possible confounders as in standard cohort or case-control analysis.
- In this course only the basic theory is shown, see Halloran et al. (2010) for a more thorough treatment of how to estimate analyse vaccine effects from study data.

Estimating vaccine efficacy from cohort studies

- In cohort design, assume n_v and n_u vaccinated and unvaccinated individuals, respectively, are subject to follow-up without censoring. Suppose y_v and y_u individuals cases arise during the observation period.
- An estimate of vaccine efficacy is then:

$$\widehat{\mathrm{VE}} = 1 - \frac{y_v/n_v}{y_u/n_u}$$

- Confidence intervals for VE are derived from transforming confidence intervals for the RR.
- Poisson regression including person-years as offset can be used to adjust for additional confounders.

Salk polio vaccine field trial (1)

- 1954 randomized controlled trial to investigate polio vaccination in the USA (Francis 1955)
- Incidence of polio at that time was about 50 per 100,000 children
- Vaccination of childrens in 1st to 3rd grade:

Vaccination \ Poliomyelitis	Yes	No
Yes	57	2.00745×10^5
No	142	2.01229×10^5

- One of the largest controlled trials ever
- Question: Does the vaccination work?

Salk polio vaccine field trial (2)

- The function `Epi::twoby2` can be used to compute the relative risk and associated CIs from simple 2×2 tables:

```
salk <- t(matrix(c(57,200745,142,201229),2,2))
dimnames(salk) <- list(c("vacc","non-vacc"),c("case","nocase"))
require("Epi")
tab <- twoby2(salk,F.lim=1e9,print=FALSE)
(RR <- tab$measures["             Relative Risk:",])
##           95% conf.  interval
## 0.4025459 0.2960563 0.5473391
(VE <- 1-RR[c(1,3,2)])
##            interval 95% conf.
## 0.5974541 0.4526609 0.7039437
```

Estimating vaccine efficacy from case-control studies

- One can also use case-control studies to estimate VE, i.e. let n_{cases} and $n_{controls}$ be the number of cases and controls, respectively, and let p_{cases} and $p_{controls}$ be the proportions vaccinated in the two groups.
- Here, one uses the odds ratio of vaccination in cases and controls, which is equal to the odds ratio of disease in vaccinated and unvaccinated
- Provided that the attack rate is low (i.e. $RR \approx OR$) one obtains

$$\widehat{\mathrm{VE}} \approx 1 - \frac{p_{cases}/(1-p_{cases})}{p_{controls}/(1-p_{controls})}$$

- Logistic regression can be used to adjust the estimates for additional confounders.

Catalytic model and vaccination

- Catalytic models (and transmission models) can be used to evaluate required vaccine effects – again R_0 is the key quantity.
- Let V denote the minimum proportion to be vaccinated for eradication if vaccination induces complete protection:

$$V = 1 - \pi \approx 1 - \frac{A}{L} \approx 1 - \frac{1}{\overline{\lambda} L}.$$

- Note that it is not necessary to vaccinate the entire population in order to eradicate the disease

Herd immunity

Vaccination does not only protect vaccinated individuals, but also induces indirect protection to unvaccinated by reducing the circulation of the infection in the population

Screening method (1)

- Farrington (1993) describes a retrospective method to assess the effectiveness of a vaccine under field conditions.
- This *screening method* requires only data on the cases – together with an estimate of vaccine coverage from sources external to the study (e.g. vaccination register data).
- Since the method is fitted within a GLM framework control for confounders (e.g. age, geographic location) is immediate by adding them as covariates.

Screening Method (2) – Notation

Random sample of disease cases in a given period from a defined population.

- Use sample to estimate the proportion cases vaccinated (PCV)
- Assume that the proportion of the population vaccinated (PPV)
- Vaccine effectiveness (VE) is given by

$$\mathrm{VE} = 1 - \frac{\mathrm{PCV}}{1-\mathrm{PCV}} \cdot \frac{1-\mathrm{PPV}}{\mathrm{PPV}}$$

- Note that $1 - \mathrm{VE}$ corresponds to the odds ratio of vaccination in cases and the population.

Stratification by GLM (1)

- We now consider n strata with θ_i and π_i denoting PCV and PPV in the cohort, respectively.
- Let $R_i = 1 - \mathrm{VE}_i$ be the relative risk of disease in vaccinated relative to unvaccinated individuals in each stratum.
- Assume k covariates are also available in each stratum, i.e. let $\boldsymbol{x}_i = (x_{i1}, \ldots, x_{ik})'$.
- Log-linear model to control for confounding by stratification

$$\log(R_i) = \alpha + \boldsymbol{x}_i'\boldsymbol{\beta}, \quad i = 1, \ldots, n$$

Stratification by GLM (2)

- In case of a rare disease $R_i = \mathrm{OR}_i$. Hence,

$$\log(R_i) = \log\left(\frac{\theta_i}{1-\theta_i}\frac{1-\pi_i}{\pi_i}\right) = \alpha + \boldsymbol{x}_i'\boldsymbol{\beta}$$

- Re-arranging terms yields:

$$\begin{aligned}\log\left(\frac{\theta_i}{1-\theta_i}\right) &= \log\left(\frac{\pi_i}{1-\pi_i}\right) + \alpha + \boldsymbol{x}_i'\boldsymbol{\beta} \\ &= o_i + \alpha + \boldsymbol{x}_i'\boldsymbol{\beta}\end{aligned}$$

- This corresponds to a binary GLM with logit-link and offset o_i

$$\text{No. vaccinated cases} \sim \mathrm{Bin}(\text{No. cases}, \theta_i).$$

Sample size (1)

- The user should specify: V_T anticipated true effectiveness, V_L the lower threshold effectiveness value as well as $PPV = \pi$, the power $1 - \beta$ and the significance level α
- Standard arguments for computing sample sizes for difference in proportion in $2\times$ 2 tables yield

$$N = \frac{(z_{\alpha/2} + z_{1-\beta})^2(1 - \pi V_L)^2(1 - V_T)}{\pi(1 - \pi)(V_T - V_L)^2}, \tag{1}$$

  where, e.g., $z_{\alpha/2}$ is the $\alpha/2$ quantile of the standard normal distribution.
- Alternatively, if $\beta = 0.5$ then $V_T - V_L$ can be thought of as anticipated lower half-width of the corresponding $(1 - \alpha/2) \cdot 100\%$ CI.

Sample size (2)

- R function implementing the sample size equation (1)

```
N <- function( VT, VL, pi, alpha=0.05, beta=0.2) {
  (qnorm(alpha/2) + qnorm(1-beta))^2 * (1-pi*VL)^2 * (1-VT) / ( pi*(1-pi)*(VT-VL)^2)
}
```

- Reproducing the first 3 rows of Table 2 in Farrington (1993):

```
VT<-seq(0.5,0.9,by=0.1)
t(sapply(c(0.05,0.1,0.15), function(delta) {
  structure(round(N( VT=VT,VL=VT-delta, pi=0.5,alpha=0.05,beta=0.5)),names=VT)
}))
##       0.5  0.6 0.7 0.8 0.9
## [1,] 1846 1292 840 480 203
## [2,]  492  346 226 130  55
## [3,]  232  164 108  62  27
```

Measles in Leeds 1980–1986

- Farrington (1993) illustrates the screening method using measles notification from two districts in Leeds 1980–1986.

```
#Load data on measles notifications and vaccine coverage in Leeds
(measles <- read.csv2(file=file.path("Data", "farrington1993-table1.csv")))
##   Birth.cohort Cases Vaccinated Coverage
## 1         1980    82          5     70.0
## 2         1981    98          9     70.9
## 3         1982   180         28     76.0
## 4         1983   177         37     81.0
## 5         1984   112         22     83.7
## 6         1985   140         27     84.5
## 7         1986   151         27     83.1
#Create offset from PCV
measles$o <- with(measles, log(Coverage / (100-Coverage)))
#Create factor representing the birth cohort
measles$bc <- as.factor(measles$Birth.cohort)
m <- glm( cbind(Vaccinated, Cases-Vaccinated) ~ offset(o), family=binomial,data=measles)
m.bc <- glm( cbind(Vaccinated, Cases-Vaccinated) ~ offset(o) + bc, family=binomial,data=measles)
#Compare models
(p <- anova(m, m.bc,test="Chisq")$"Pr(>Chi)"[2])
## [1] 0.5758264
#Vaccine coverage
(VE <- (1-exp(as.numeric(coef(m)))))
## [1] 0.950991
#Confidence intervals
sort(1-exp(confint(m)))
## Waiting for profiling to be done...
##    97.5 %     2.5 %
## 0.9419066 0.9589255
```

Other methods to assess vaccine effectiveness (1)

- Vaccine effectiveness can also be quantified using time series models for disease incidence.
  - One option is to define periods before and after the introduction of vaccination and analyse the difference in model parameters for the two periods (Anderson et al. 1984; Antunes et al. 2007; Girard 2000).
  - A second option is to include vaccination coverage as a (time-varying) covariate in the time series model (Herzog et al. 2011; Höhle et al. 2011).
  - Usually, coverage proportions are only available for certain age groups.
- Instead of a time series model one can also use a SIR transmission model with an extra "vaccinated" department.
- In either case it is important to realize that vaccine effects can be a combination of short term effects and long term effects.

Other methods to assess vaccine effectiveness (2)

- Time series regression model in Höhle et al. (2011) for the logarithm of the incidence containing intercept, trend and seasonal terms:

$$\log(y_t) = \beta_0 + \beta_1 \cdot t + f(t) + \epsilon_t, \quad t = 1, 2, \ldots, n,$$

$$\mu_t = E(y_t) = \exp\left(\beta_0 + \beta_1 \cdot t + f(t) + \frac{1}{2}\sigma^2\right),$$

  where $f(t)$ is a periodic function and ϵ_t is described by an $\mathrm{ARMA}(p, q)$ model with variance σ^2.

- Using $\beta_1 \cdot \text{coverage}_t$ instead of $\beta_1 \cdot t$ in the above model leads to

$$\mathrm{VE} = 1 - \frac{\mu_{\text{100\% coverage}}}{\mu_{\text{0\% coverage}}} = 1 - \exp(\beta_1)^{100}.$$

Literature I


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