BIOST/STAT 578 A
Statistical Methods in Infectious Diseases
Lecture 5
January 20, 2009

Vaccine efficacy and models of vaccine mechanisms; time-to-event and final value data

From Barack Obama’s Inauguration Speech today:

“……. Our health care is too costly; our schools fail too many; and each day brings further evidence that the ways we use energy strengthen our adversaries and threaten our planet.

These are the indicators of crisis, subject to data and statistics. Less measurable but no less profound is a sapping of confidence across our land - a nagging fear that America's decline is inevitable, and that the next generation must lower its sights. ……”

SURVIVAL ANALYSIS IN A NUTSHELL

T - random variable for time to the event

PDF: $f(t) = \lim_{dt \to 0} P[t < T \leq t + dt]/dt$

CDF: $F(t) = P[T \leq t]$

Survival function: $S(t) = P[T > t] = 1 - F(t)$

Hazard function: $\lambda(t) = \frac{f(t)}{S(t)}$

Integrated hazard function: $\Lambda(t) = \int_0^t \lambda(\tau) d\tau$

$$S(t) = e^{-\Lambda(t)}$$

$$F(t) = AR(t) = 1 - S(t)$$

FOR AN INFECTIOUS DISEASE

$$\lambda(t) = cp\frac{I(t)}{n}$$

SIR EPIDEMIC

$$\frac{dS(t)}{dt} = -cp\frac{I(t)}{n}S(t) = -\lambda(t)S(t)$$

$$\frac{dI(t)}{dt} = cp\frac{I(t)}{n}S(t) - \gamma I(t)$$

$$\frac{dR(t)}{dt} = \gamma I(t),$$

$$S(t) + I(t) + R(t) = n, \text{ for all } t,$$

$$S(0) = n - a, I(0) = a > 0, R(0) = 0.$$

$$\frac{dI(t)}{dt} = \left[\frac{cp}{\gamma}\frac{S(t)}{n} - 1\right]\gamma I(t)$$

Basic Reproductive Number:

$$R_0 = \frac{cp}{\gamma}$$

DYNAMICS OF SIR EPIDEMIC

$$\frac{dI(t)}{dt} = \left[R_0 \frac{S(t)}{n} - 1\right] \gamma I(t)$$

$$\text{if } R_0 \frac{S(t)}{n} \leq 1, \text{ then } \frac{dI(t)}{dt} \leq 0$$
$$\text{if } R_0 \frac{S(t)}{n} > 1, \text{ then } \frac{dI(t)}{dt} > 0$$

near $t = 0$, $\frac{S(t)}{n} \approx 1$, and

$$\frac{dI(t)}{dt} \Big|_{t=0^+} = \left[R_0 - 1\right] \gamma I(t)$$

if $R_0 \leq 1$, then no epidemic occurs
if $R_0 > 1$, then an epidemic occurs

SURVIVAL FUCTION

Let $a = 0^+$ and $S(0) = n^-$

$$\frac{dS(t)}{dt} = -\lambda(t)S(t)$$

solving yields

$$\frac{S(t)}{n} = e^{-\Lambda(t)}$$

where

$$\Lambda(t) = \frac{cp}{n}\int_0^t I(\tau)d\tau$$

Let $\mathrm{AR}(t) = 1 - \frac{S(t)}{n}$, then

$$\mathrm{AR}(t) = 1 - e^{-\Lambda(t)}$$

THE VACCINE MODEL

Force of infection to an unvaccinated person

$$\lambda_0(t) = Z_0 c\pi p(t)$$

$$\text{where } p(t) = \left[\frac{n_0 p_0(t) + n_1 \phi p_1(t)}{n} \right] ,$$

and to a vaccinated person,

$$\lambda_1(t) = Z_1 \theta c\pi p(t).$$

$$S_\upsilon(t) = E\{\exp[-Z_\upsilon \Lambda_\upsilon(t)]\} = L_{Z_\upsilon}[\Lambda_\upsilon(t)] .$$

where $\Lambda_0(t) = c\pi \int_0^t p(\tau)d\tau$ and $\Lambda_1(t) = c\pi\theta \int_0^t p(\tau)d\tau$.

$$P(Z_\nu = 0) = \alpha_\nu,$$

and

$$Z_\nu | Z_\nu > 0 \sim f_\nu(\cdot), \text{ with probability } 1 - \alpha_\nu,$$

where $E(X_\nu) = 1$ and $Var(X_\nu) = \delta_\nu$

$$E(Z_\nu) = 1 - \alpha_\nu \text{ and } Var(Z_\nu) = (1 - \alpha_\nu)(\delta_\nu + \alpha_\nu)$$

$$L_{Z_\nu}(s) = \alpha_\nu + (1 - \alpha_\nu)L_{X_\nu}(s).$$

MIXING MODEL (GAMMA DISTRIBUTION)

X_υ gamma with scale and shape parameters $1/\delta_\upsilon$.

$$L_{Z_\upsilon}(s) = \alpha_\upsilon + (1 - \alpha_\upsilon)\left[\frac{1}{1 + s\delta_\upsilon}\right]^{1/\delta_\upsilon}$$

$$S_\upsilon(t) = \alpha_\upsilon + (1 - \alpha_\upsilon)\left[\frac{1}{1 + \Lambda_\upsilon(t)\delta_\upsilon}\right]^{1/\delta_\upsilon}$$

When $\alpha_\upsilon = 0$,

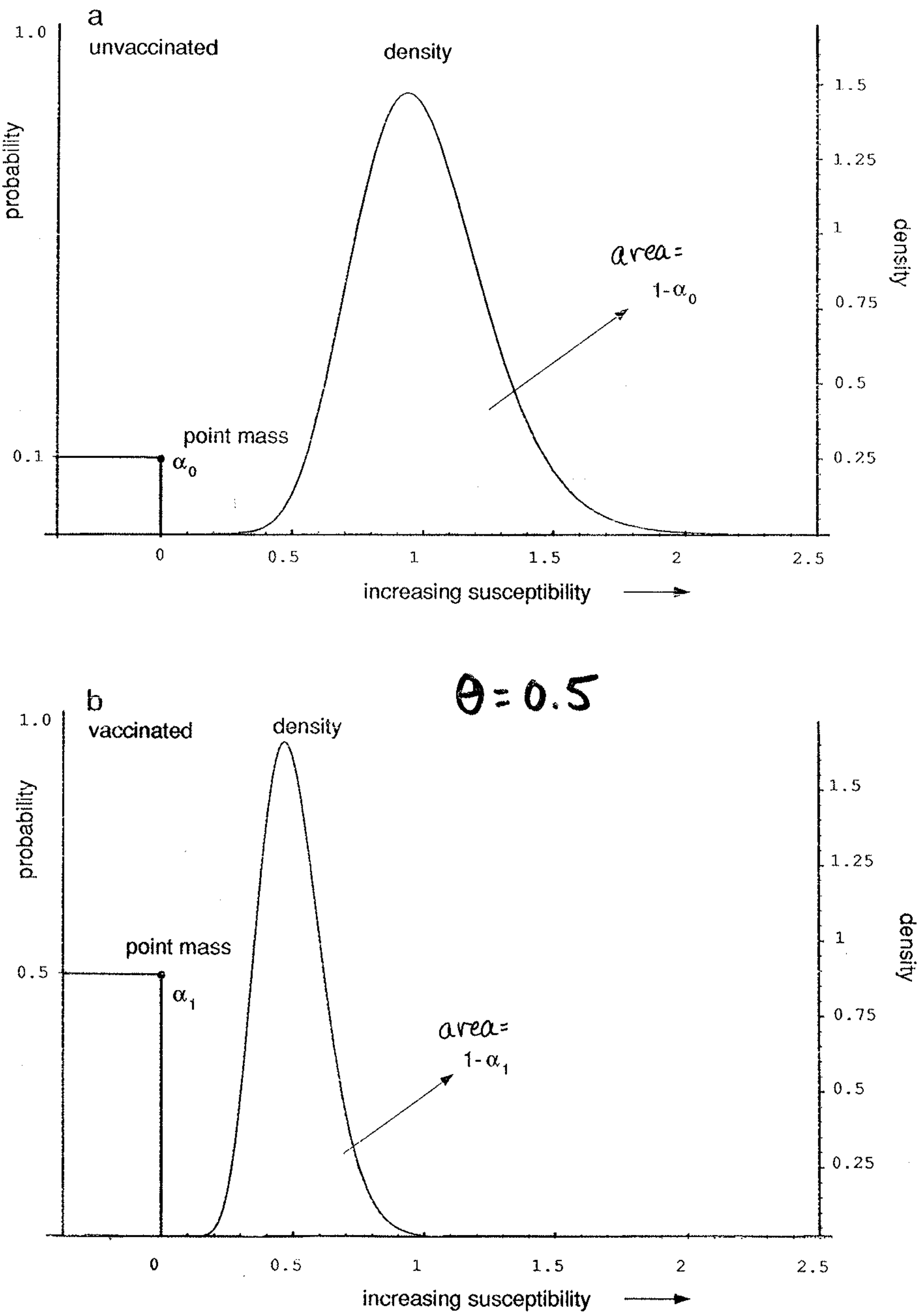
$$S_\upsilon(t) = \left[\frac{1}{1 + \Lambda_\upsilon(t)\delta_\upsilon}\right]^{1/\delta_\upsilon}.$$

When $\delta_\upsilon = 0$,

$$S_\upsilon(t) = \alpha_\upsilon + (1 - \alpha_\upsilon)\exp[- \Lambda_\upsilon(t)]$$

$$S_0(t) = \alpha_0 + (1 - \alpha_0)\exp[- \Lambda_0(t)]$$

$$S_1(t) = \alpha_1 + (1 - \alpha_1)\exp[- \theta\Lambda_0(t)]$$


a
unvaccinated
density
probability
density
1.0
0.1
1.5
1.25
1
0.75
0.5
0.25
area=
1-α0
point mass
α0
0
0.5
1
1.5
2
2.5
increasing susceptibility
θ=0.5
b
vaccinated
density
probability
density
1.0
0.5
1.5
1.25
1
0.75
0.5
0.25
point mass
α1
area=
1-α1
0
0.5
1
1.5
2
2.5
increasing susceptibility

MODEL OF AALEN (COMPOUND POISSON)

(Annals of Applied Probability, 1992)

$$L_{Z_\upsilon}(s) = \exp\left\{\frac{\alpha_\upsilon}{(1-\alpha_\upsilon)\delta_\upsilon}\left[1 - \{1 + (s\delta_\upsilon/\alpha_\upsilon)\}^{1-\alpha_\upsilon}\right]\right\},\ \alpha_\upsilon \neq 1,\ \alpha_\upsilon > 0$$

$$P(Z_\upsilon = 0) = \exp\left\{\frac{\alpha_\upsilon}{(1-\alpha_\upsilon)\delta_\upsilon}\right\}$$

$$S_\upsilon(t) = \exp\left\{\frac{\alpha_\upsilon}{(1-\alpha_\upsilon)\delta_\upsilon}\left[1 - \{1 + (\Lambda_\upsilon(t)\delta_\upsilon/\alpha_\upsilon)\}^{1-\alpha_\upsilon}\right]\right\}$$

When $\alpha_\upsilon = 1$,

$$S_\upsilon(t) = \left[\frac{1}{1 + \Lambda_\upsilon(t)\delta_\upsilon}\right]^{1/\delta_\upsilon}.$$

VACCINE EFFICACY

$$VE_S = 1 - \frac{(1 - \alpha_1)\theta\pi}{(1 - \alpha_0)\pi} = 1 - \frac{(1 - \alpha_1)}{(1 - \alpha_0)}\,\theta$$

Special cases:

$\alpha_0 = 0, \quad VE_S = 1 - (1 - \alpha_1)\,\theta$

$\alpha_0 = \alpha_1, \quad VE_S = 1 - \theta$ "leaky"

$\alpha_0 = 0,\ \theta = 1, \quad VE_S = \alpha_1$ "all-or-none"

Halloran, *et al.*(1992)

$VE_I = 1 - \phi$

RELATIONSHIPS AMONG MODEL PARAMETERS AND VE MODELS

Model name	α_0	α_1	θ	VE
General	$\alpha_0 > 0$	$\alpha_1 > 0$	$\theta \neq 1$	$1 - \frac{(1 - \alpha_1)}{(1 - \alpha_0)} \theta$
Relative all-or-none	$\alpha_0 > 0$	$\alpha_1 > 0$	$\theta = 1$	$\frac{\alpha_1 - \alpha_0}{1 - \alpha_0}$
All-or-none*	$\alpha_0 = 0$	$\alpha_1 > 0$	$\theta = 1$	α_1
All-or-partially susceptible*	$\alpha_0 = 0$	$\alpha_1 > 0$	$\theta \neq 1$	$1 - (1 - \alpha_1)\theta$
Partially susceptible*	$\alpha_0 = \alpha_1$		$\theta \neq 1$	$1 - \theta$
Risk difference all-or-none**	$\alpha_0 > 0$	$\alpha_1 > 0$	$\theta = 1$	$\alpha_1 - \alpha_0$

*Model previously described by Halloran, *et al.*(1992). Note that "leaky" has been changed to "partially susceptible."

**Model not contained in the general model.

ESTIMATING VE FROM FINAL VALUE DATA
PARTIALLY SUSCEPTIBLE CASE ($\delta_0 = \delta_1 = 0,\ \alpha_0 = \alpha_1 = 0$)

$$AR_v(t) = 1 - S_v(t).$$

$$\ln[1 - AR_0(t)] = -\Lambda_0(t)$$

$$\ln[1 - AR_1(t)] = -\theta\Lambda_0(t)$$

$$\theta = \ln[1 - AR_1(t)]/\ln[1 - AR_0(t)]$$

$$VE_S = 1 - \theta$$

$$\lambda_1(t) = \theta\lambda_0(t)$$

$$\theta = e^{\beta}$$

$\hat{VE} = 1 - \frac{\hat{AR}_1}{AR_0}$ PARTIALLY SUSCEPTIBLE CASE (CONTINUED)

$$\hat{VE}_S = 1 - [\ln(1 - \hat{AR}_1(t))/\ln(1 - \hat{AR}_0(t))] \gtrsim 1 - \frac{\hat{AR}_1}{\hat{AR}_0}$$

Note that

$$\mathrm{Var}[\hat{AR}_\nu(t)] \cong AR_\nu(t)\,[1 - AR_\nu(t)]/n_\nu,$$

and that $AR_0(t)$ and $AR_1(t)$ are conditionally independent.

Then use the delta method to yield

$$\mathrm{Var}[\hat{VE}] \cong [AR_1(t)/n_1 + \theta^2 AR_0(t)/n_0]\,[\log_e(1 - AR_0(t))]^{-2} \quad \text{(Becker, 1982)}$$

Regression model: $[1 - AR_1(t)] = [1 - AR_0(t)]^\theta$ proportional hazards model

ALL-OR-NONE $(\delta_0 = \delta_1 = 0,\ \alpha_0 = 0,\ \alpha_1 = \alpha,\ \theta = 1)$

$$[1 - AR_0(t)] = \exp\{-\Lambda_0(t)\}$$

$$[1 - AR_1(t)] = \alpha + (1 - \alpha) \exp\{-\Lambda_0(t)\} = \alpha + (1 - \alpha)[1 - AR_0(t)]$$

$$AR_1(t) = (1 - \alpha)\ AR_0(t)$$

$$\alpha = 1 - [AR_1(t)/AR_0(t)]$$

Variance of $\hat{\alpha} = 1 - [\hat{AR}_1(t)/\hat{AR}_0(t)]$

Let $a = \log_e(1 - \alpha)$, then

$$\hat{a} = \ln[\hat{AR}_1(t)] - \ln[\hat{AR}_0(t)].$$

Then by the delta method,

$$Var[\hat{a}] = [(1 - AR_1(t))/(n_1 AR_1(t))] + [(1 - AR_0(t))/(n_0 AR_0(t))]$$

(O'Neill, 1988)

Regression Model: $AR_0(t) = [1 + \exp(b_0)]^{-1}$, $AR_1(t) = [1 + \exp(b_0 + b_1)]^{-1}$.

$$\hat{VE} = 1 - \frac{1 + \exp(\hat{b}_0)}{1 + \exp(\hat{b}_0 + \hat{b}_1)}$$

$ROR = e^{b_1}$

$\hat{VE} \neq 1 - e^{\hat{b}_1}$

LOG-LOG PLOTS

Plot $\ln\{-\ln[S_\nu(t)]\}$ vs. t

e.g., pure leaky model ($\delta_0 = \delta_1 = 0,\ \alpha_0 = \alpha_1 = 0$)

$$S_0(t) = \exp[-\Lambda_0(t)]$$

$$S_1(t) = \exp[-\theta\Lambda_0(t)]$$

$$-\ln[S_0(t)] = \Lambda_0(t)$$

$$-\ln[S_1(t)] = \theta\Lambda_0(t)$$

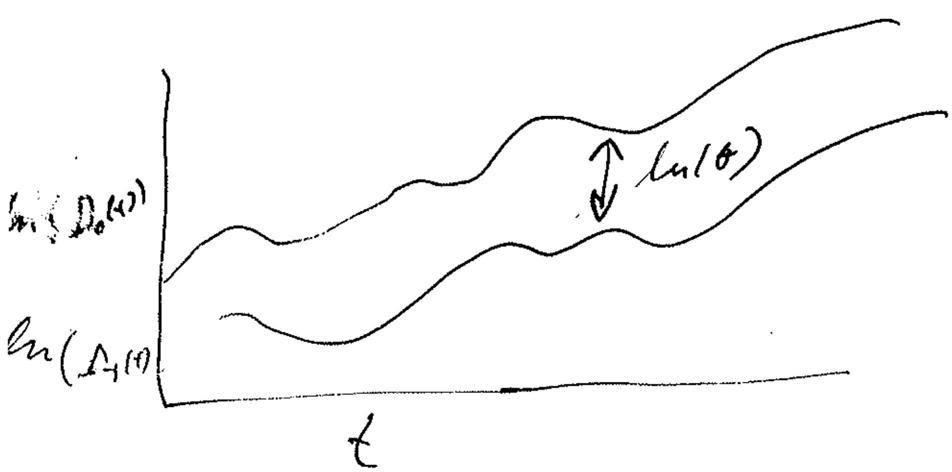
$$\ln\{-\ln[S_0(t)]\} = \ln[\Lambda_0(t)]$$

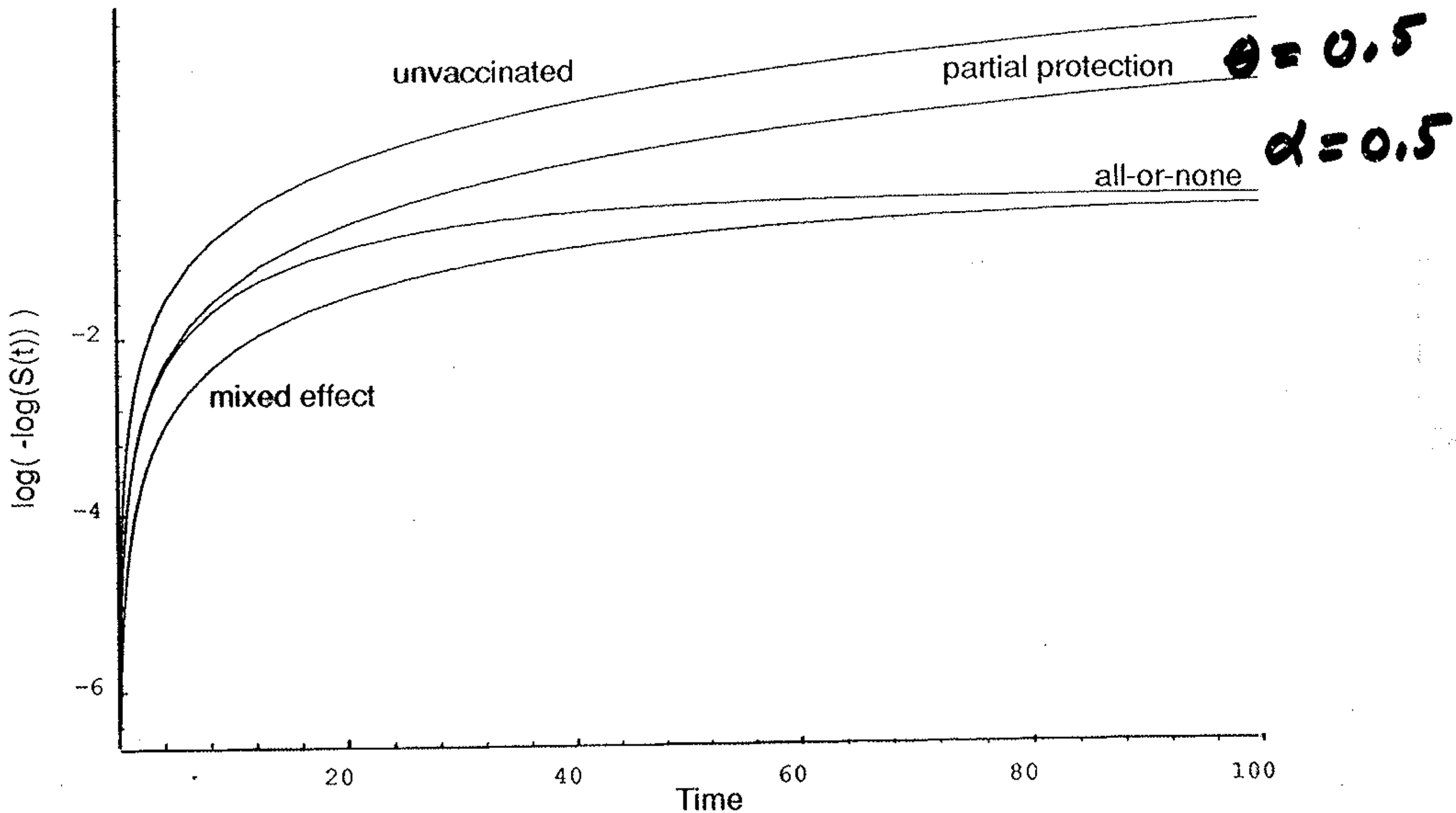
$$\ln\{-\ln[S_1(t)]\} = \ln[\Lambda_0(t)] + \ln(\theta)$$

e.g., pure all-or-none model ($\delta_0 = \delta_1 = 0,\ \alpha_0 = 0,\ \alpha_1 = \alpha,\ \theta = 1$)

$$S_0(t) = \exp[-\Lambda_0(t)]$$

$$S_1(t) = \alpha + (1 - \alpha)\exp[-\Lambda_0(t)]$$

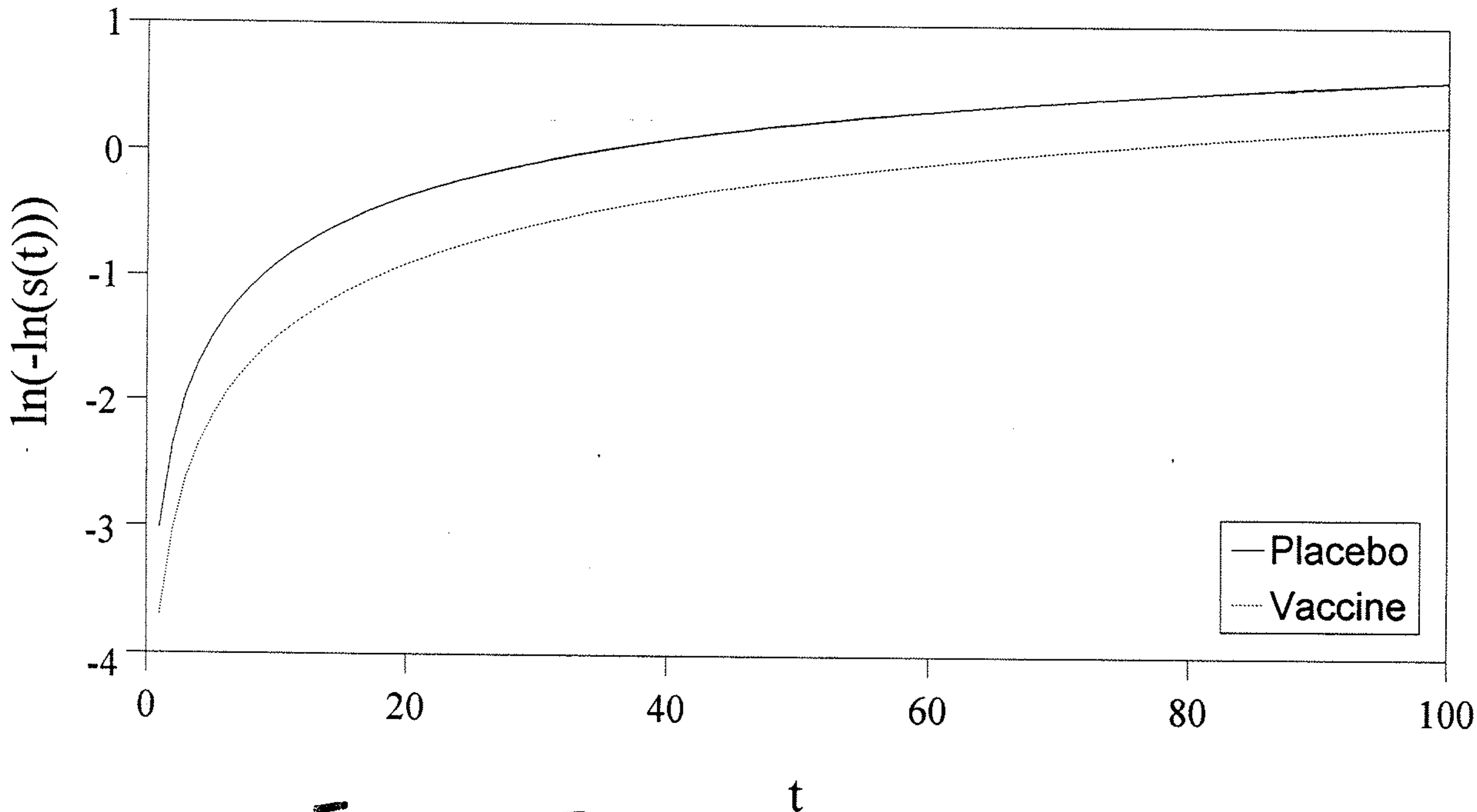




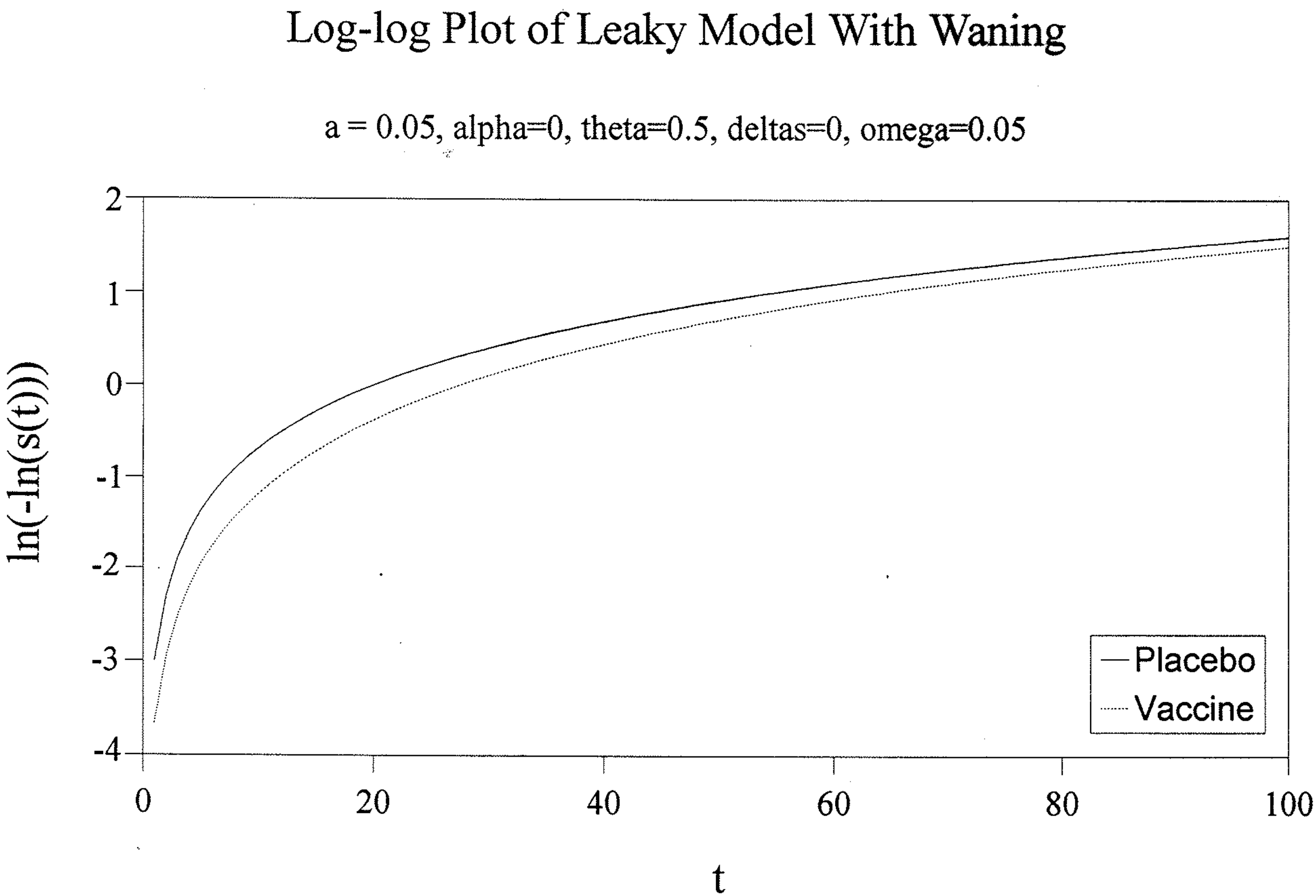
unvaccinated
partial protection
all-or-none
mixed effect
θ = 0.5
α = 0.5
log(-log(S(t)))
-2
-4
-6
20
40
60
80
100
Time

Log-log Plot Of Leaky Model With Heterogeneity

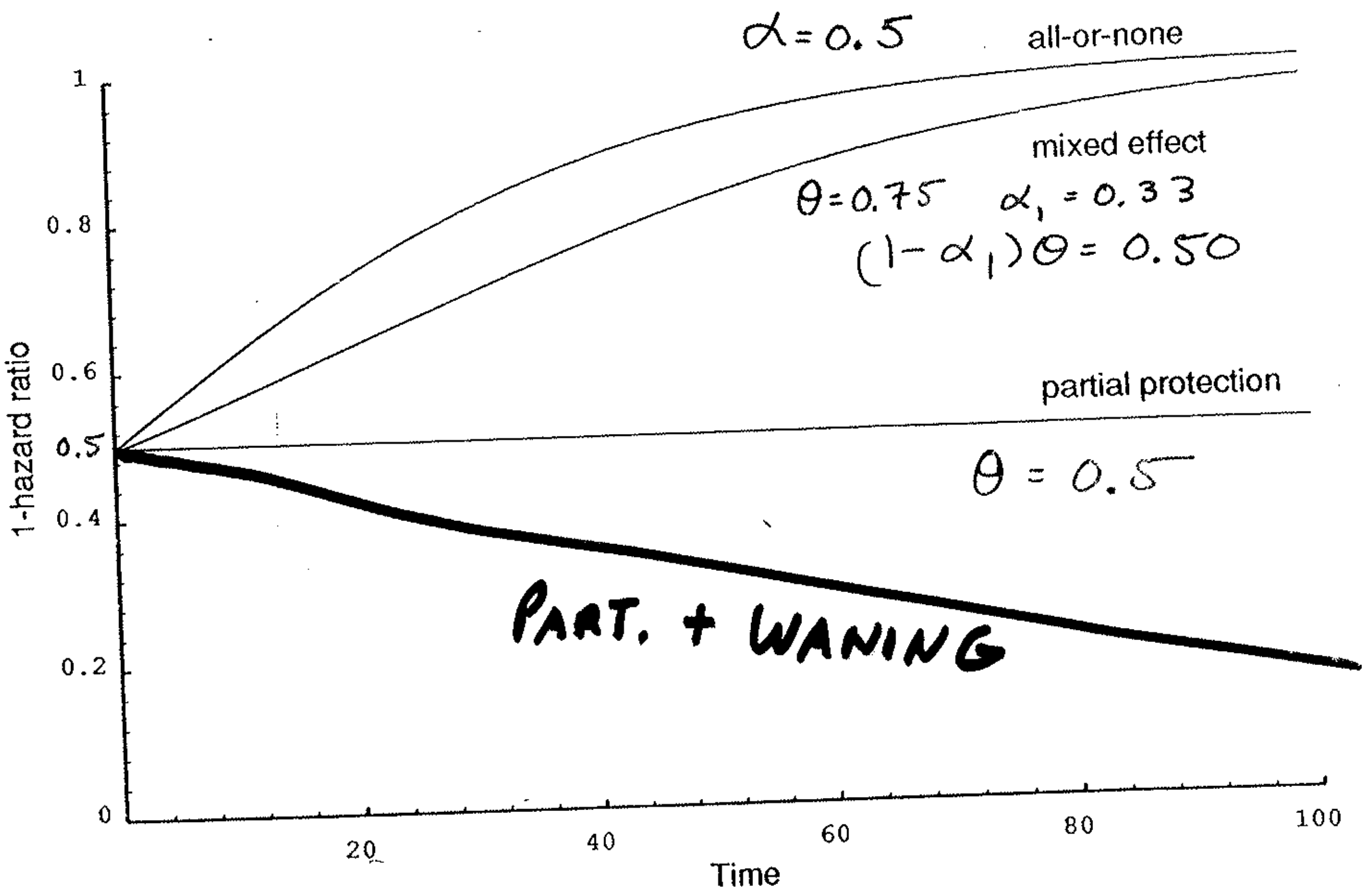
a=0.05, alpha=0, theta=0.5, deltas=1



$$S_0(t) = \left[\frac{1}{1+at}\right] \qquad S_1(t) = \left[\frac{1}{1+a\theta t}\right]$$


Log-log Plot of Leaky Model With Waning
a = 0.05, alpha=0, theta=0.5, deltas=0, omega=0.05
ln(-ln(s(t)))
2
1
0
-1
-2
-3
-4
0
20
40
60
80
100
t
Placebo
Vaccine

$$1 - \frac{\lambda_1(t)}{\lambda_0(t)}$$



STATISTICAL INFERENCE ON GROUPED DATA, $\phi = 1$

Parameters: $\alpha_0, \alpha_1\ \delta_0, \delta_1\ \theta$, and $a = c\pi$

Data: Observations are made at times $t_0(=0), t_1, \ldots, t_k$.

Define the time intervals, $[t_{i-1}, t_i)$, $i = 1, \ldots, k$.

$p(t) = p_i$ in interval i,

$$\Lambda_0(t) = c\pi\int_0^t p(\tau)d\tau = c\pi\kappa\Big[\sum_{j=1}^{i} (t_j - t_{j-1})p_j + (t-t_i)p_i\Big],\ t \in [t_i, t_{i+1}).$$

$r_{i\upsilon}$ number at risk at beginning of i

$m_{i\upsilon}$ number infected during i

Likelihood function:

$$L = \prod_{i=1}^{k} \prod_{\upsilon=0}^{1} \{S_\upsilon(t_i)/S_\upsilon(t_{i-1})\}^{(r_{i\upsilon}-m_{i\upsilon})} [1 - \{S_\upsilon(t_i)/S_\upsilon(t_{i-1})\}]^{m_{i\upsilon}},$$

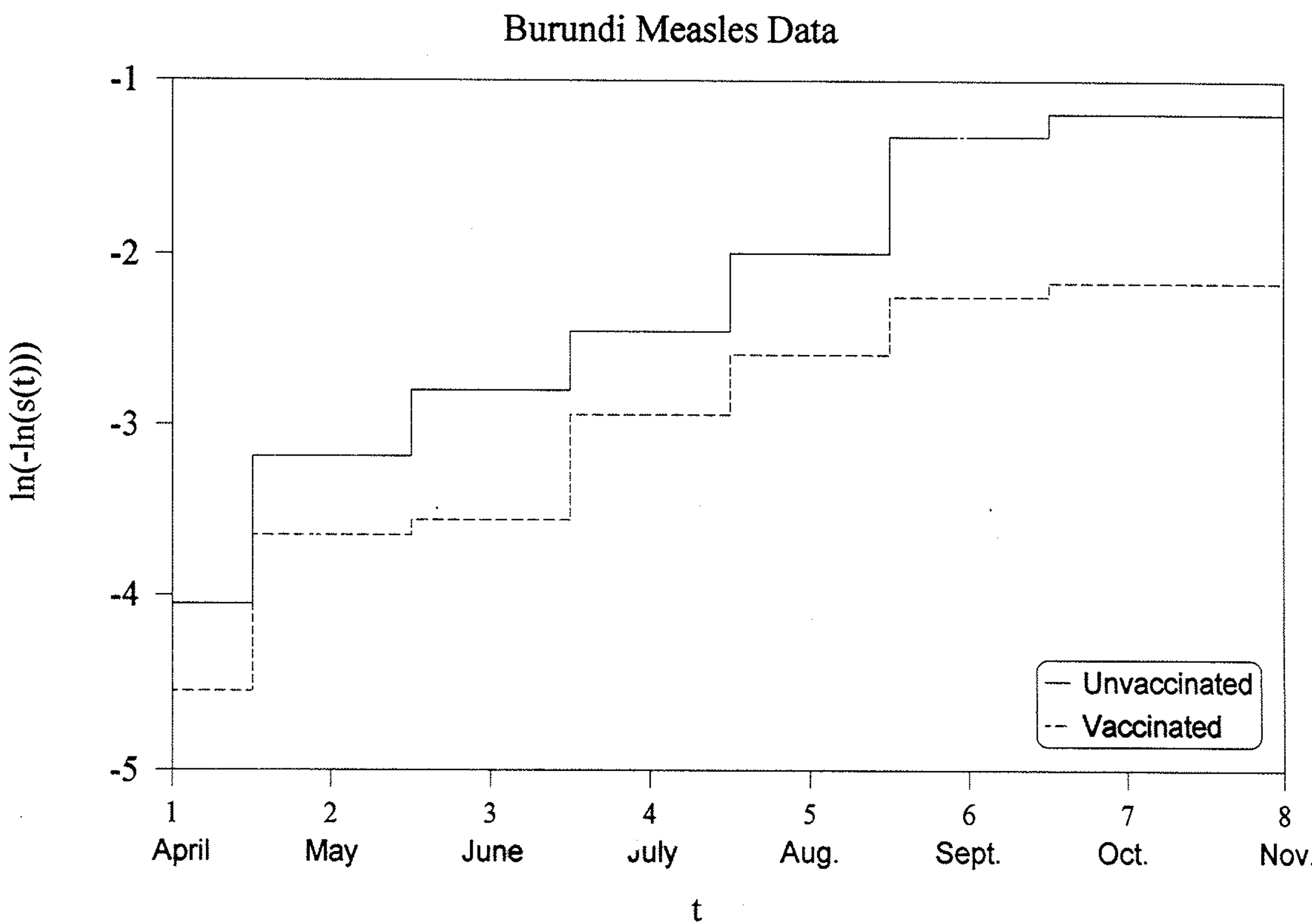
Table 1.
Numbers at risk, ill, and monthly exposure for the measles epidemic Muyinga, Burundi, April - November, 1988

i	Month	Unvaccinated			Vaccinated			Exposure
		At Risk*	Ill	Percent	At Risk	Ill	Percent	p_i x 100 Percent
1	April	579	10	1.7	857	9	1.1	1.3
2	May	551	13	2.4	848	13	1.5	1.9
3	June	517	10	1.9	835	2	0.2	0.9
4	July	483	12	2.5	833	20	2.4	2.4
5	Aug.	451	22	4.9	813	18	2.2	3.2
6	Sept.	408	50	12.3	795	24	3.0	6.4†
7	Oct.	337	12	3.6	771	7	0.9	1.7
8	Nov.	317	0	0.0	764	0	0.0	0.0
	Total		129			93		

* 140 initially at-risk unvaccinated children were vaccinated during the epidemic, and their vaccination times were treated as right censoring times for measles illness

† Includes three individuals who were vaccinated and who contracted measles in September. These individuals were treated as being unvaccinated with right-censored times for the purpose of estimation.

Ln-ln Plot of Observed Data



MEASLES OUTBREAK IN MUYINGA, BURUNDI, MARCH - DECEMBER, 1988 (CONTINUED)

$m = 7, \alpha_0 = \delta_0 = \delta_1 = 0$

Estimates: $\hat{a} = c\pi\kappa = 1.658 \pm 0.137, \quad \hat{\alpha}_1 = 0.805 \pm 0.060,$

$\hat{\theta} = 2.764 \pm 1.235$

$\hat{VE}$ all-or-none = 0.805 [0.687,0.924]

$\hat{VE}$ part. = -1.765 [-4.185,-0.657]

$\hat{VE}$ gen. = 0.462 [0.318,0.671]

Ln-ln Plot of Observed and Expected Data

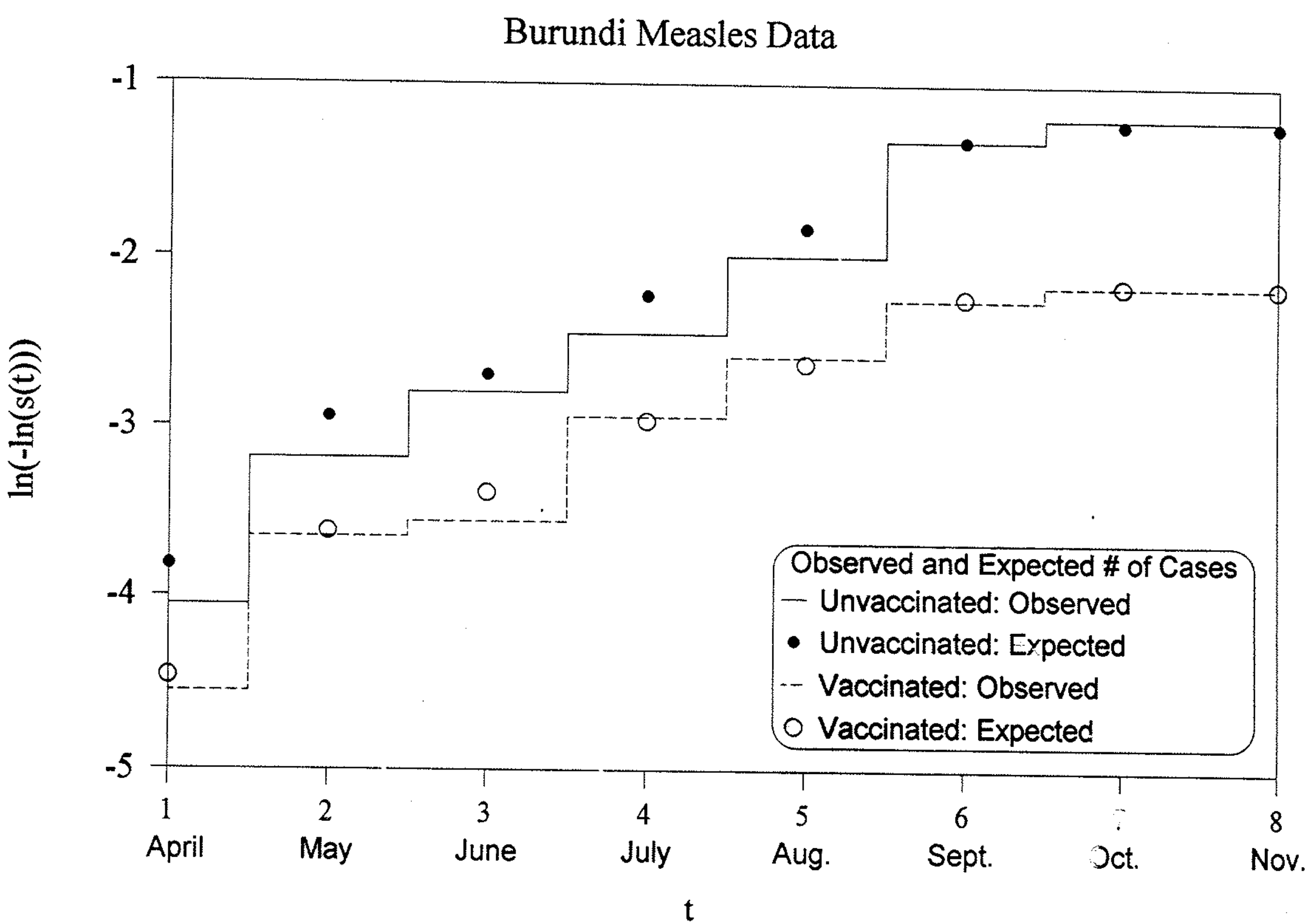


Table 2.

Observed and expected frequencies for the model fitted to the data from the measles outbreak in Muyinga, Burundi, April - October, 1988

i	Month	Unvaccinated		Vaccinated	
		Observed	Expected	Observed	Expected
1	April	10	12.6	9	9.8
2	May	13	16.7	13	12.8
3	June	10	7.6	2	5.8
4	July	12	19.1	20	14.7
5	Aug.	22	23.0	18	16.7
6	Sept.	50	41.0	24	27.2
7	Oct.	12	9.4	7	6.0
	Total	129	129.3	93	93.0

χ_{11}^2 - 12.8 (p-0.3)

Observed and Expected Number Ill Using
Degenerate Model with Estimates:
a=1.98761, alpha1=0.59442, theta=0.78174

Month	Unvaccinated At Risk	Unvaccinated Obs. Ill	Unvaccinated Exp. Ill	Vaccinated* At Risk	Vaccinated* Obs. Ill	Vaccinated* Exp. Ill	p(t)
1	1865.0	30.	31.6901	490.0	3.	2.6448	.00862
2	1835.0	132.	155.3851	487.0	14.	13.0952	.04452
3	1703.0	167.	169.4726	473.0	13.	14.3584	.05274
4	1536.0	108.	92.5926	460.0	6.	8.0008	.03128
5	1428.0	90.	77.4975	454.0	9.	6.8868	.02807

Chi-Square=9.6139
* Vaccinated with card   d.f. = 6   p = 0.14

MEASLES OUTBREAK IN CHAD, FEBRUARY - JUNE, 1993
(CONTINUED)

$m = 5, \alpha_0 = \delta_0 = \delta_1 = 0$

VE_{AN}

Estimates: $\mathbf{a} = c\pi\kappa = 1.988 \pm 0.084, \alpha_1 = 0.594 \pm 0.111,$
$1 - VE_S = \theta = 0.782 \pm 0.238$

VE all-or-none = 0.594 [0.378,0.811]

VE part. = 0.218 [-0.248,0.684]

VE gen. = 0.683 [0.504,0.925]

Table 2. Estimated vaccine efficacy using the summary model (VE_{SUM}), partial protection model (VE_{PP}) and all-or-none model (VE_{ALL}) for data simulated with 10,000 people in both the vaccinated and unvaccinated groups, 60 time periods, 5% right censoring in the unvaccinated group, baseline hazard $\lambda_a(t)= 0.05$ and $\delta_0=\delta_1=0$.

α_1*	Model	Point estimate and empirical 95% confidence interval for vaccine efficacy†			
		$1-\theta$‡ = 0.2	$1-\theta = 0.4$	$1-\theta = 0.6$	$1-\theta = 0.8$
0.2	Preset§	0.36	0.52	0.68	0.84
	VE_{SUM}	0.36 (0.34-0.38)ǁ	0.52 (0.50-0.54)	0.68 (0.67-0.69)	0.84 (0.83-0.85)
	VE_{PP}	0.52 (0.50-0.53)	0.61 (0.60-0.62)	0.72 (0.71-0.73)	0.85 (0.84-0.86)
	VE_{ALL}	0.23 (0.22-0.24)	0.29 (0.28-0.30)	0.40 (0.39-0.41)	0.61 (0.60-0.62)
0.4	Preset	0.52	0.64	0.76	0.88
	VE_{SUM}	0.52 (0.50-0.54)	0.64 (0.62-0.66)	0.76 (0.75-0.77)	0.88 (0.87-0.89)
	VE_{PP}	0.71 (0.70-0.72)	0.75 (0.74-0.76)	0.81 (0.81-0.82)	0.89 (0.89-0.90)
	VE_{ALL}	0.42 (0.41-0.43)	0.47 (0.46-0.48)	0.55 (0.54-0.56)	0.71 (0.70-0.72)
0.6	Preset	0.68	0.76	0.84	0.92
	VE_{SUM}	0.68 (0.66-0.70)	0.76 (0.74-0.77)	0.84 (0.83-0.85)	0.92 (0.91-0.93)
	VE_{PP}	0.84 (0.83-0.84)	0.86 (0.85-0.86)	0.89 (0.88-0.89)	0.93 (0.93-0.94)
	VE_{ALL}	0.62 (0.61-0.63)	0.65 (0.64-0.66)	0.70 (0.69-0.71)	0.81 (0.80-0.82)
0.8	Preset	0.84	0.88	0.92	0.96
	VE_{SUM}	0.84 (0.83-0.85)	0.88 (0.87-0.89)	0.92 (0.91-0.93)	0.96 (0.96-0.96)
	VE_{PP}	0.93 (0.93-0.93)	0.94 (0.93-0.94)	0.95 (0.95-0.95)	0.97 (0.97-0.97)
	VE_{ALL}	0.81 (0.80-0.82)	0.82 (0.82-0.83)	0.85 (0.85-0.86)	0.91 (0.90-0.91)

* α_1 = proportion completely protected in vaccinated group.

† Average point estimate based on 1,000 simulations per α_1, $1-\theta$ combination.

‡ θ = relative residual susceptibility of vaccinated susceptibles compared to the unvaccinated group.

§ Preset value of VE_{SUM} in the simulation model = $1-(1-\alpha_1)\theta$.

ǁ Empirical 95% confidence intervals based on 1,000 simulations per α_1, $1-\theta$ combination.

SUMMARY

* - Meaningful estimates of vaccine efficacy parameters can be obtained

* - Depends on correctly specified model
  - fit several models

* - Underlying assumptions → keep in mind!

* - At high censoring (rare disease), most misspecified models estimate close to summary VE_{sum}.

* - Sample size calculations → possibility of being under powered

* - Identifiability → use of dependent happening structure

Cholera Vaccines

Durham, L.K., Longini, I.M., Halloran, M.E., Clemens, J.D., Nizam, A. and Rao, M.: Estimation of vaccine efficacy in the presence of waning: Application to cholera vaccines. *American Journal of Epidemiology* **147**, 948-959 (1998).

Durham, L.K., Halloran, M.E., Longini, I.M. and Manatunga, A.K.: Comparing two smoothing methods for exploring waning vaccine effects. *Applied Statistics* **48**, 395-407 (1999).

Longini, I.M., Nizam, A., Ali, M., Yunus, M., Shenvi, N. and Clemens, J.D.: Controlling endemic cholera with oral vaccines. *Public Library of Science (PloS), Medicine* **4** (11) 2007: e336 doi:10.1371/journal.pmed.0040336.

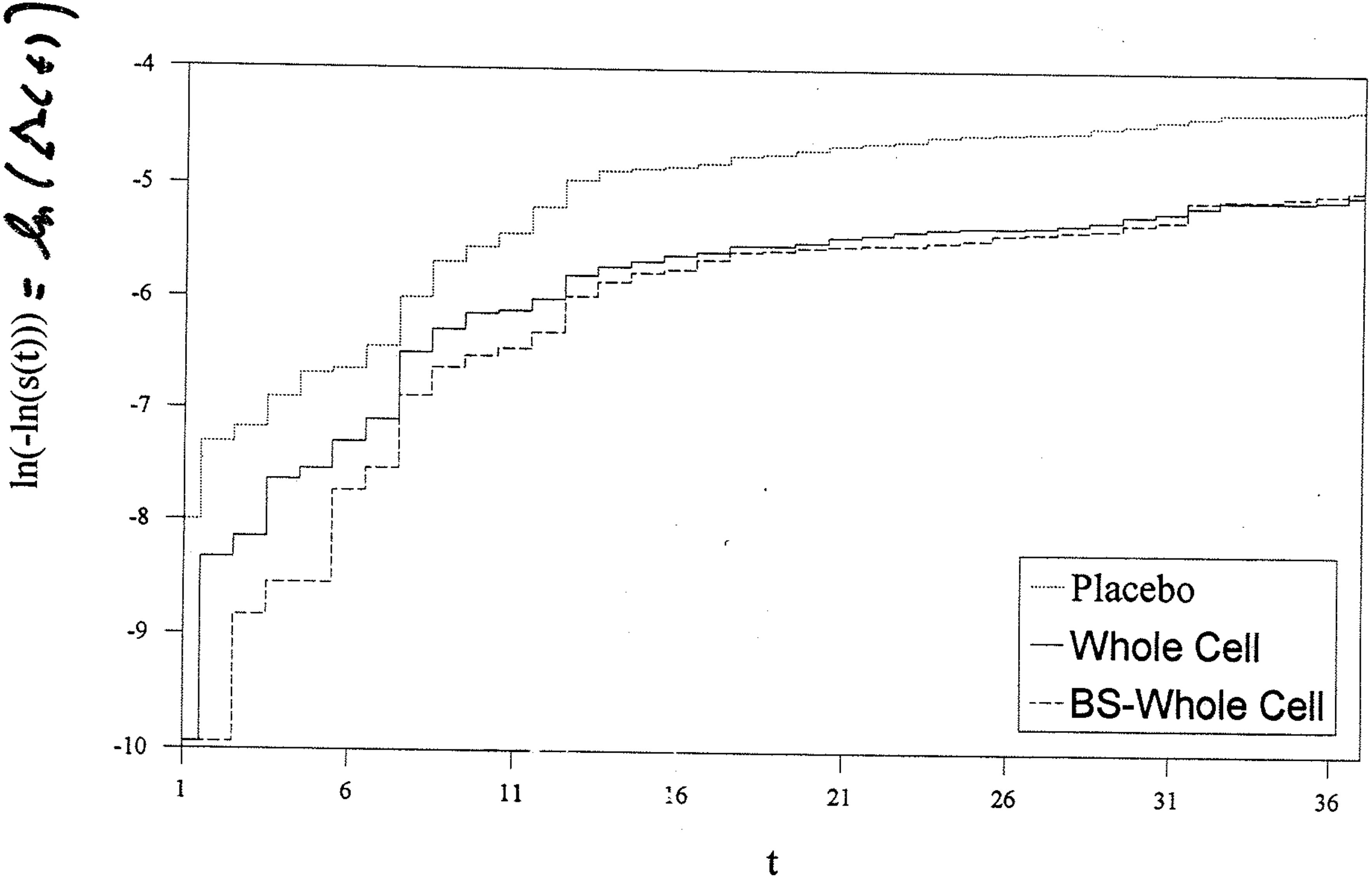
Table 1

Data from the Bangladesh cholera vaccine trial (Clemens, et al., 1990)

	Vaccine Group v									
	Placebo $v=0$			WC $v=1$			BS-WC $v=2$			
Month i	At Risk r_{i0}	Ill d_{i0}	Lost	At Risk r_{i1}	Ill d_{i1}	Lost	At Risk r_{i2}	Ill d_{i2}	Lost	p_i
0 Initial	20837			20743			20705			
1 May '85	20822.0	7	30	20723.5	1	39	20689.5	1	31	0.00014
2 Jun	20777.0	7	46	20681.5	4	43	20649.0	0	48	0.00032
3 Jul	20722.0	2	50	20633.5	1	45	20600.0	2	50	0.00040
4 Aug	20677.0	5	36	20589.0	4	42	20547.0	1	52	0.00056
5 Sep	20612.5	5	83	20530.0	1	58	20485.0	0	70	0.00066
6 Oct	20536.5	1	59	20466.0	3	58	20423.0	5	54	0.00081
7 Nov	20484.5	6	43	20414.5	3	39	20374.0	2	34	0.00099
8 Dec	20442.5	18	29	20375.5	14	33	20337.5	10	35	0.00167
9 Jan '86	20360.5	19	99	20307.0	7	76	20265.5	6	89	0.00220
10 Feb	20252.5	10	79	20219.0	6	86	20192.0	3	46	0.00251
11 Mar	20165.5	10	75	20141.0	1	58	20135.5	2	61	0.00273
12 Apr	20090.0	23	56	20080.5	5	61	20075.0	5	56	0.00328
13 May	20020.5	30	37	20023.5	12	43	20021.0	14	42	0.00421
14 Jun	19937.0	12	70	19960.5	5	59	19953.0	7	66	0.00461
15 Jul	19860.0	3	60	19896.5	3	59	19883.5	5	59	0.00479
16 Aug	19791.5	3	71	19836.5	4	55	19815.5	2	67	0.00494
17 Sep	19732.0	5	42	19785.5	2	39	19752.5	6	55	0.00516
18 Oct	19689.5	11	33	19744.0	5	40	19702.0	5	34	0.00552
19 Nov	19650.5	3	23	19702.5	0	33	19663.5	1	[illegible]	0.00559
20 Dec	19614.0	6	44	19671.0	2	30	19626.5	2	39	0.00576
21 Jan '87	19545.0	8	82	19620.5	4	67	19566.0	1	78	0.00598
22 Feb	19464.5	4	63	19552.0	2	62	19498.0	1	56	0.00610
23 Mar	19403.0	3	52	19486.0	3	66	19436.5	0	65	0.00620
24 Apr	19349.5	9	49	19433.5	2	33	19385.0	2	38	0.00642
25 May	19290.0	3	52	19393.0	1	44	19346.5	2	35	0.00653
26 Jun	19233.5	2	55	19348.5	0	43	19299.0	4	56	0.00663
27 Jul	19175.5	2	57	19295.5	1	63	19235.5	1	63	0.00670
28 Aug	19099.5	2	91	19206.0	2	14	19146.0	2	114	0.00680
29 Sep	19028.0	9	48	19118.0	3	58	19054.0	1	66	0.00703
30 Oct	18969.5	5	51	19063.5	5	45	18997.0	5	46	0.00730
31 Nov	18912.5	9	53	19013.0	3	46	18950.0	3	38	0.00756
32 Dec	18863.0	7	28	18972.5	6	29	18909.0	18	38	0.00811
33 Jan '88	18824.0	9	36	18933.0	5	38	18854.5	2	35	0.00839
34 Feb	18786.5	0	21	18900.0	0	18	18822.0	0	26	0.00839
35 Mar	18766.0	1	20	18882.0	0	18	18793.5	3	31	0.00846
36 Apr	18749.5	2	11	18866.5	2	13	18771.5	3	7	0.00858
37 May	18739.0	5	6	18852.0	5	12	18761.5	4	7	0.00883

266 127 131 524

Ln-Ln Plot: Observed Bangladesh Cholera Data



B4671

DURHAM, HALLORAN, LONGINI

1. SCHOENFELD RESIDUALS
2. GEN. ADD. MODELS (GAM)

$$\widehat{VE}(t) = 1 - \widehat{RR}(t) = 1 - e^{\hat{\beta}(t)}$$

SCHOENFELD RESIDUALS

$N_i(t)$ - COUNTING PROCESS

$\lambda_0(t)$ - BASELINE INTENSITY

INTENITY FOR TIME INVARIATNT MOD.

$$Y_i(t)\, e^{\beta' Z_i}\, \lambda_0(t)$$

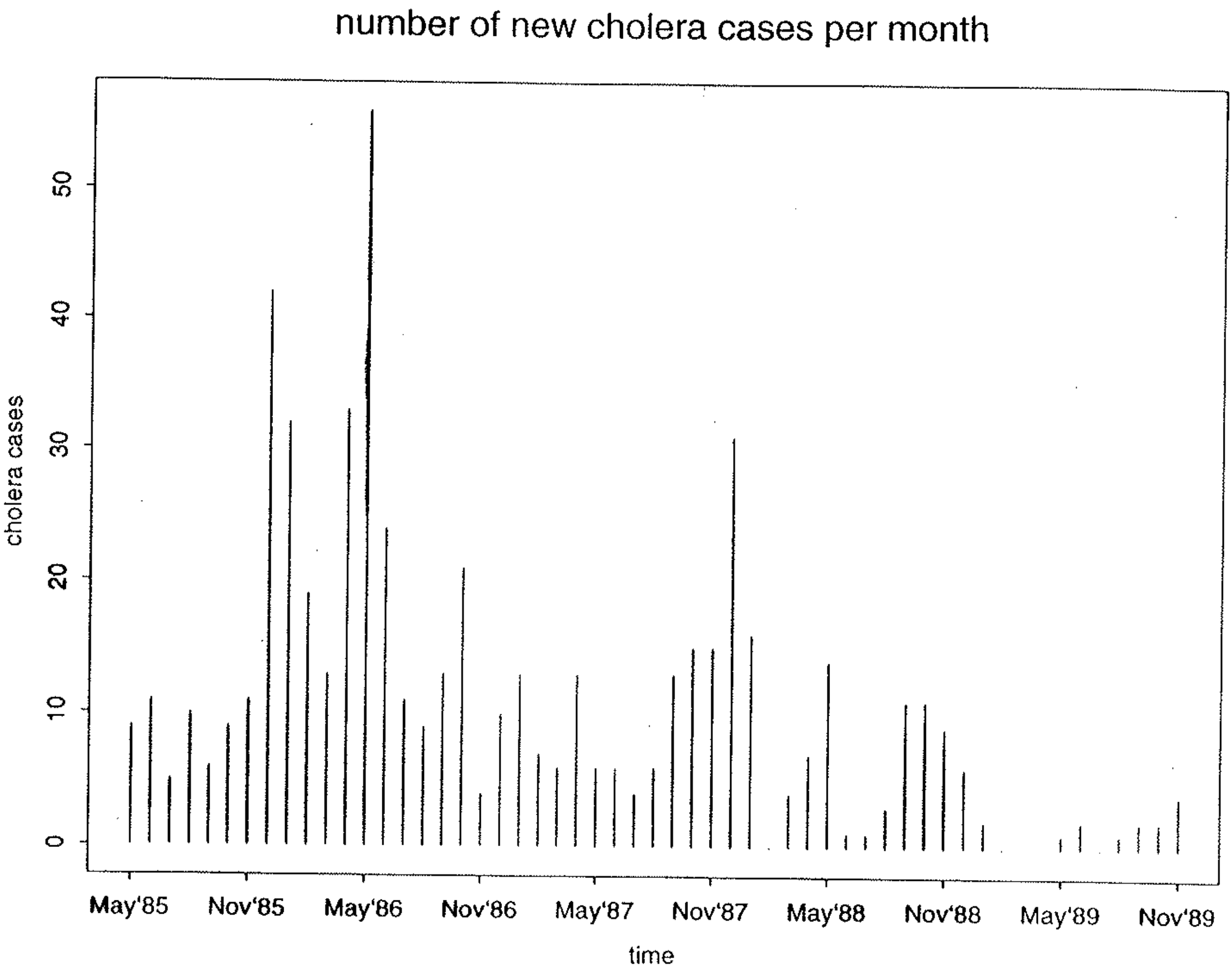
FIT AND GET ESTIMATE OF β

COMPUTE RESIDUAL AT FAILURE TIMES AND CONSTRUCT

$$\hat{\beta}(t) = \hat{\beta} + \hat{\Theta}(t)$$

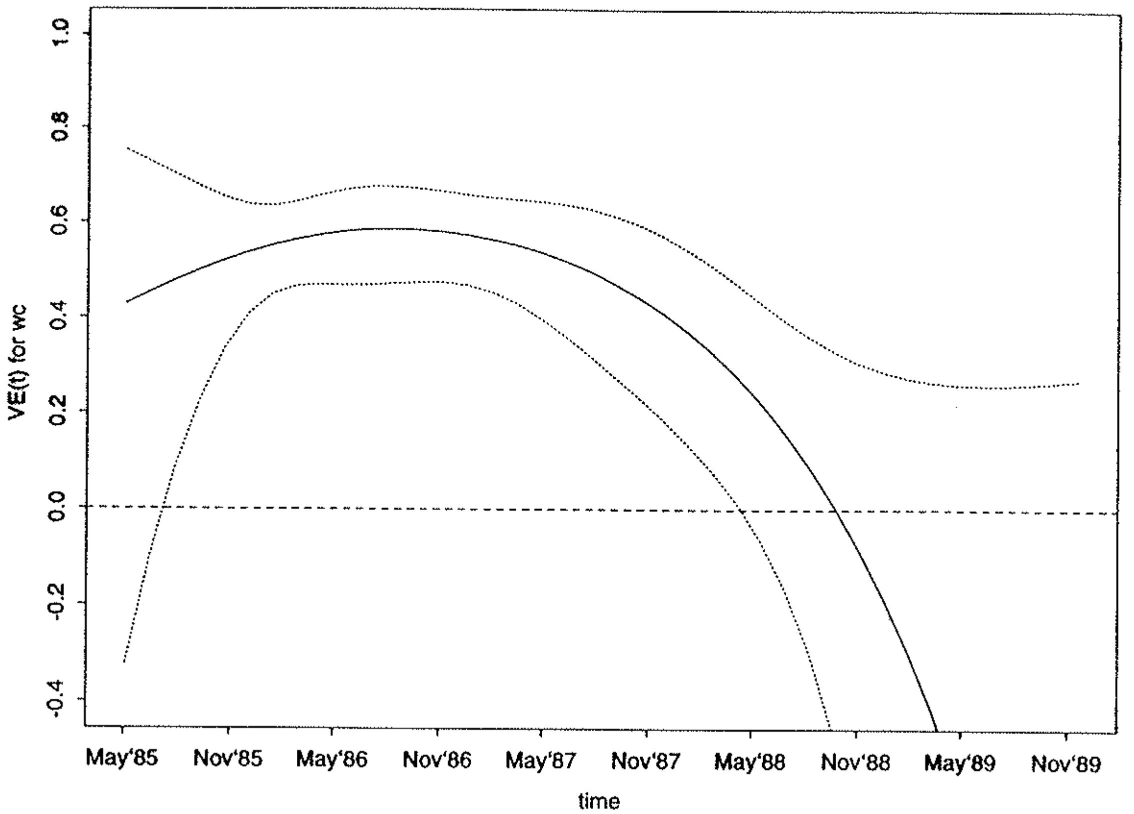
WHICH IS DEFINED AT EACH FAILURE TIME

THEN SMOOTH $\hat{\beta}(t)$


number of new cholera cases per month
cholera cases
0
10
20
30
40
50
May'85
Nov'85
May'86
Nov'86
May'87
Nov'87
May'88
Nov'88
May'89
Nov'89
time

580 CASES

WC vaccine



BS-WC vaccine

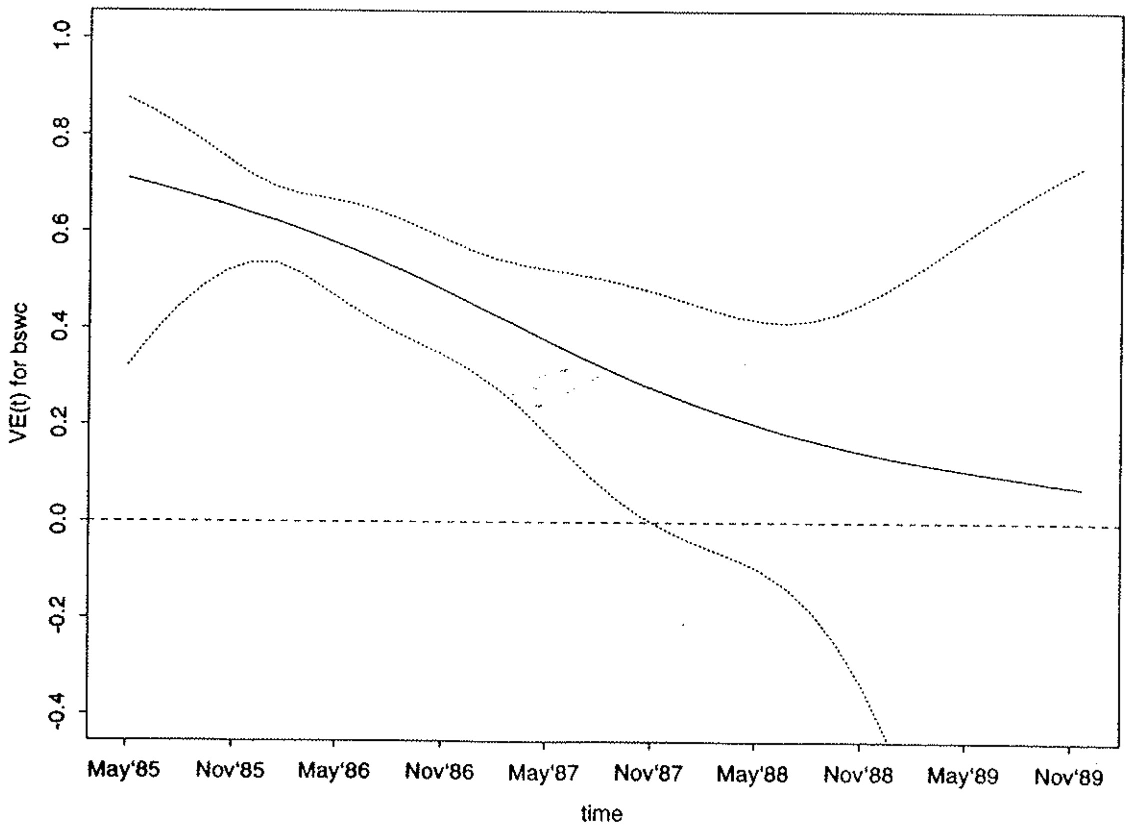


Table 3: Estimates cf VE(t), with 95% confidence intervals, for the WC and BS-WC vaccines, Matlab, Bangladesh, May 1, 1985-November 31, 1989

		whole cell		B-subunit whole cell	
date	day	VE(day)	approx. 95% c.i.	VE(day)	approx. 95% c.i.
May 85	0	0.430	(-0.342, 0.758)	0.713	(0.320, 0.879)
Nov 85	183	0.525	(0.356, 0.650)	0.650	(0.523, 0.743)
May 86	365	0.579	(0.467, 0.667)	0.572	(0.457, 0.662)
Nov 86	548	0.583	(0.478, 0.667)	0.476	(0.344, 0.582)
May 87	730	0.538	(0.394, 0.648)	0.374	(0.176, 0.524)
Nov 87	913	0.433	(0.220, 0.588)	0.280	(0.006, 0.478)
May 88	1095	0.245	(-0.028, 0.445)	0.202	(-0.089, 0.416)
Nov 88	1278	-0.073	(-0.664, 0.308)	0.141	(-0.338, 0.448)
May 89	1460	-0.59)	(-2.40, 0.257)	0.092	(-0.955, 0.578)