Sieve Analysis–If and how does VEs depend on characteristics of HIV?

Xuesong Yu
Department of Biostatistics
University of Washington
March 7, 2006

Questions of Interest

- Is there evidence for differential vaccine efficacy against the different HIV genotypes?
- How does the vaccine efficacy vary across the different genotypes?

Vaccine Trial Data

- HIV genetic variation measured by the neutralizing face core genetic distance of the infecting HIV sequence to the GNE8 HIV strain represented in the vaccine
- HIV genetic distances are missing for non-infected subjects

	# Randomized	# Infected	%Infected
Vaccine	3502	145	4.1%
Placebo	1805	127	7.0%
Total	5307	272	

$\hat{VE} = 42.9\%$

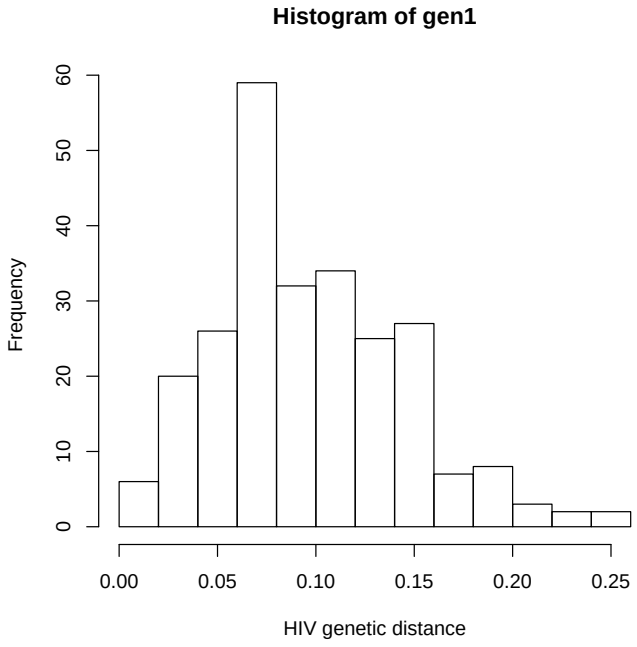
Models for Sieve Analysis

			Endpoint	
			Binary	Failure time
	Contin.		Wald/Score test	Gilbert et al 2006
HIV	Discrete	Nominal	Chi-square	Cause-specific Cox model
			MLR	
type		Ordinal	Trend test	
			Cumulative logit	

Categorization of HIV types

Infecting HIV strains

	0	1	2	3	4	Cohort size
Placebo	15	39	33	20	12	1805
Vaccine	7	16	28	33	48	3502
Total	22	55	61	53	60	5307
V/Total	0.318	0.291	0.459	0.623	0.800	



Strain-Specific Vaccine Efficacy

- Define "per strain-specific contact" vaccine efficiacy by $VE^{pc}(s) = 1 - RR^{pc}(s)$ where

$$RR^{pc}(s) = \frac{\Pr(\text{Inf}|\text{Expos. to strain } s, \text{Vaccine})}{\Pr(\text{Inf}|\text{Expos. to strain } s, \text{Placebo})}$$

- $$e_s^{\beta} = OR(s) = \frac{RR^{pc}(s)}{RR^{pc}(0)}$$

Tests for Differential VE

Null hypothesis: all $OR(s) = 1$

- Nominal categorical: Chi-square test
  $X^2 = 37.2$, df $= 4$, p-value< 0.0001
- Ordinal categorical: Cochran-Armitage trend test
  test score $z^2 = 4536$, df=1, p-value < 0.0001
- Categorical scored models
  $\exp(\beta) = 1.895$, 95% CI =(1.517, 2.367),
  p-value< 0.0001
- All tests show that there is strong evidence for differential vaccine efficacy against the different HIV genotypes.

Estimation of Vaccine Efficacy

- MLR model

$$\text{logit}(Pr(Y = s|x)) = \alpha_s + \beta_s x$$

- Scored MLR model
  log odd ratio is linear with respect to HIV genetic distance
- Cumulative logit

$$OR(> s) = \frac{RR^{pc}(> s)}{RR^{pc}(\leq s)}$$

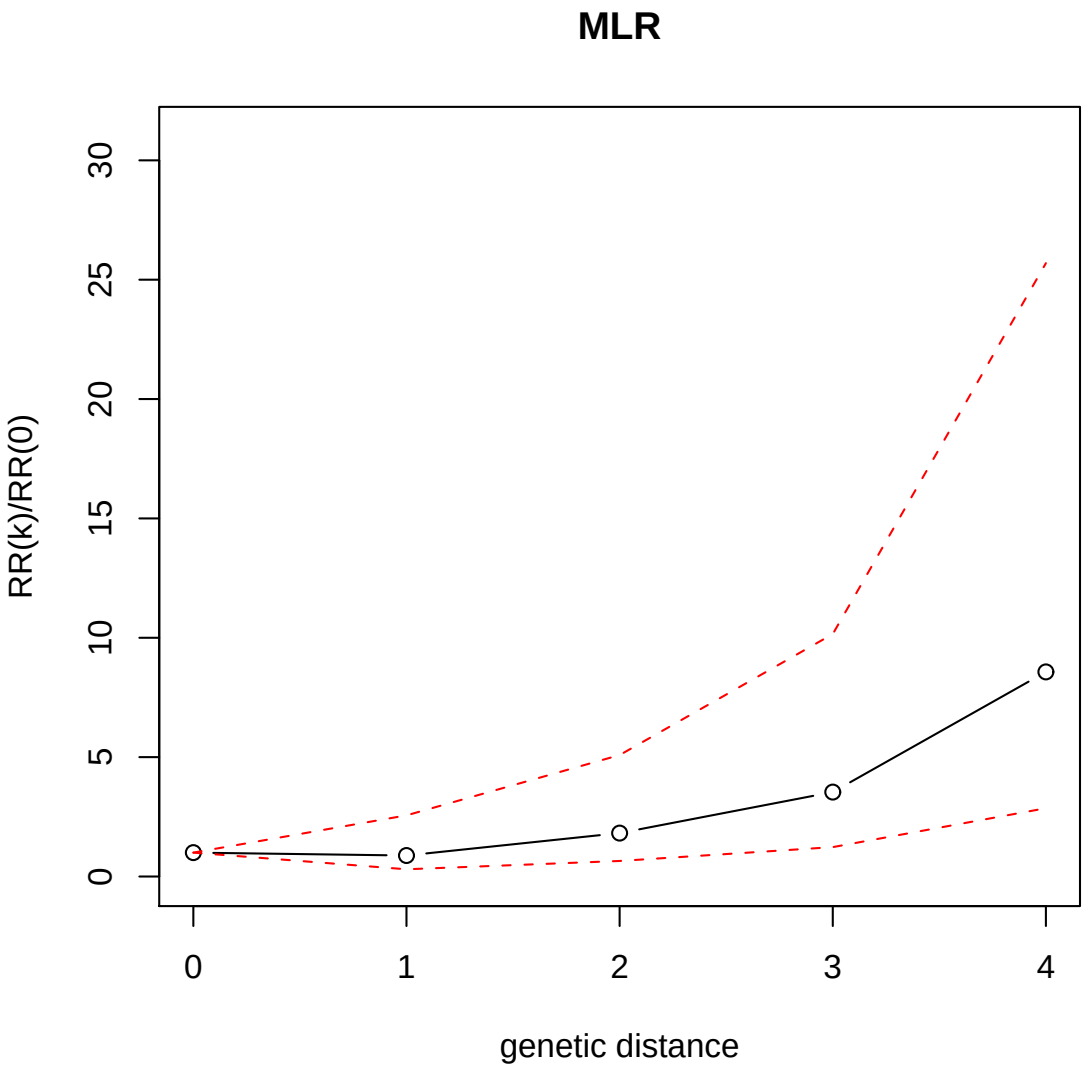
Estimation of Vaccine Efficacy

	$\widehat{OR}$ Point estimate (95%CI)	
Strain	MLR	Scored MLR
1	0.879 (0.302 2.561)	1.895 (1.517 2.367)
2	1.818 (0.650 5.087)	3.591 (2.301 5.604)
3	3.536 (1.231 10.156)	6.805 (3.491 13.265)
4	8.571 (2.860 25.692)	12.895 (5.295 31.403)

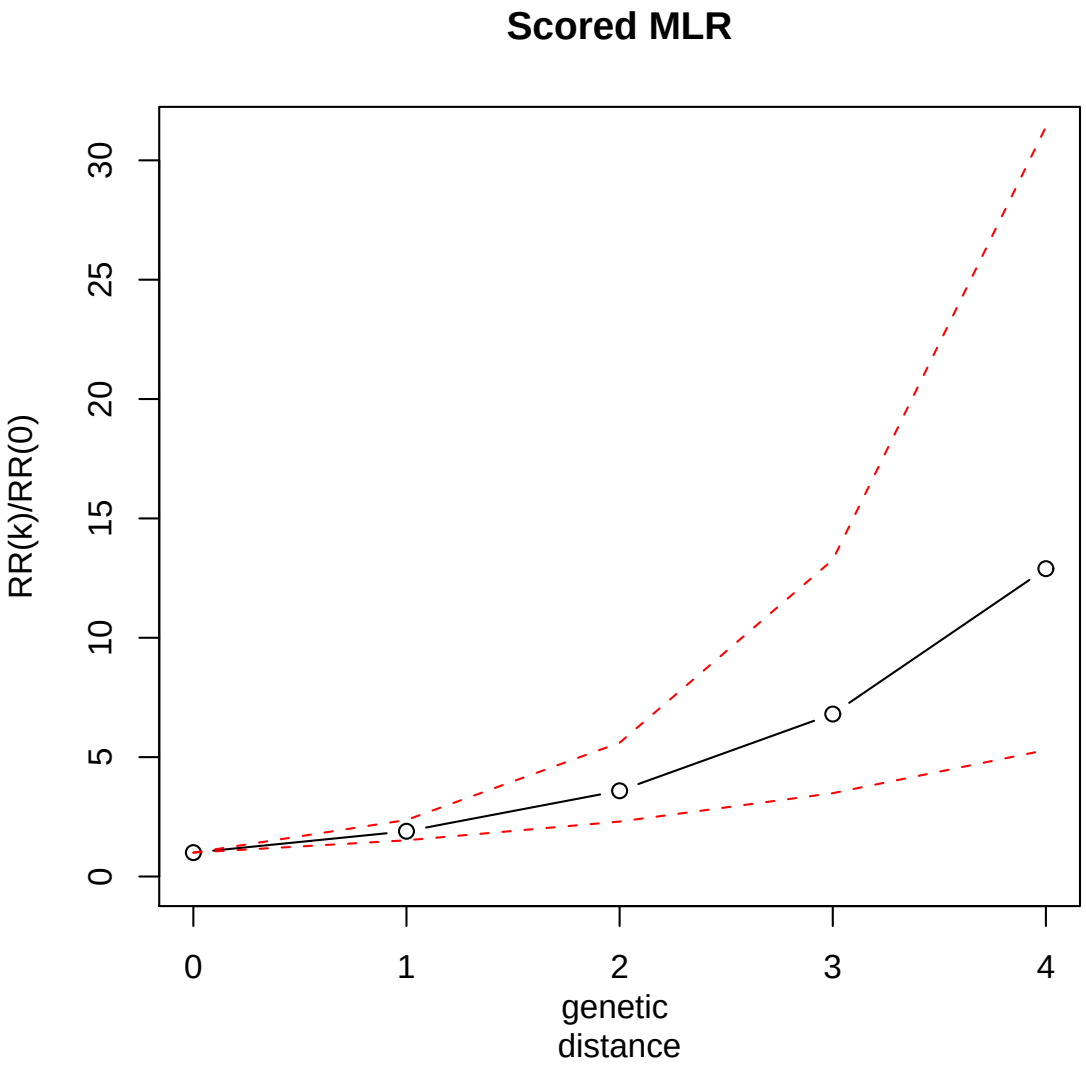
Estimation of Vaccine Efficacy

	$\widehat{OR}$ Point estimate (95%CI)
Strain	Cumultaive logit
> 0	0.688 (0.269 1.759)
> 1	3.487 (1.550 7.845)
> 2	10.957 (4.753 25.258)
> 3	31.968 (13.027 78.452)

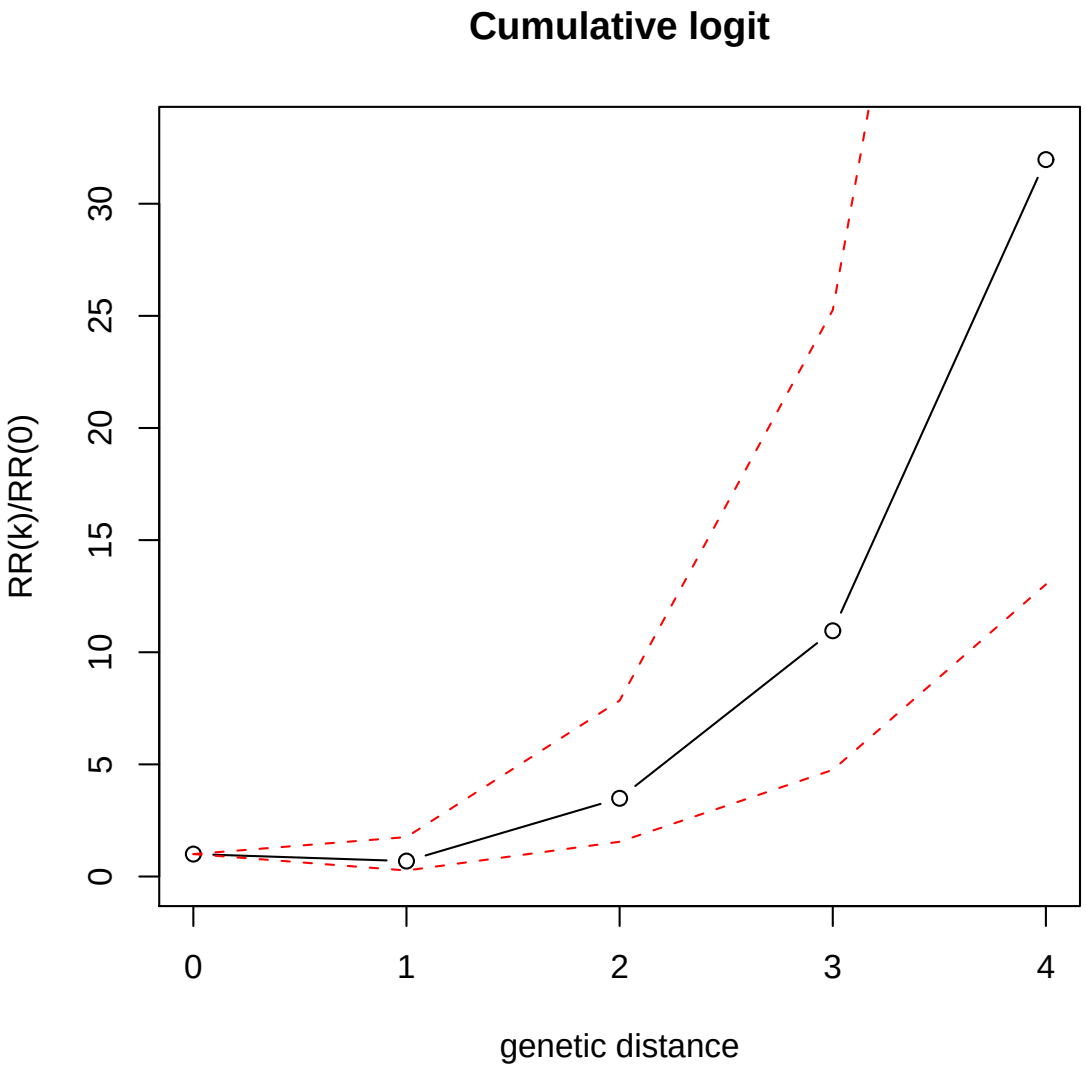
Plot of Relative Risk



Plot of Relative Risk



Plot of Relative Risk



Conclusion

- Vaccine efficacy does depend on infecting HIV strain
- Vaccine efficacy decreased dramatically as the genetic distance of infecting HIV strain increases