

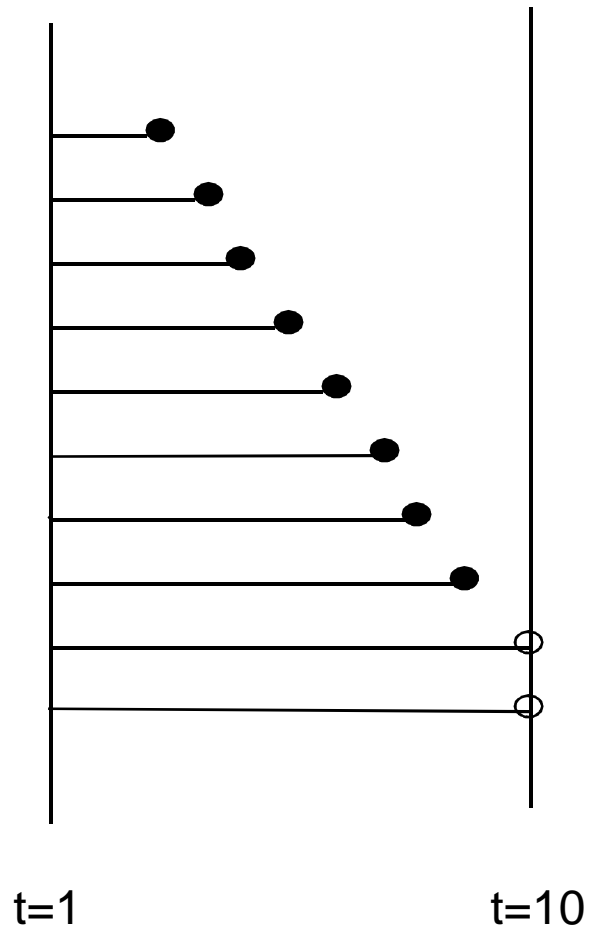
Statistical Methods for Estimating Vaccine Efficacy: Examples

Jingyee Kou, Ph.D.
FDA/CBER/OBE

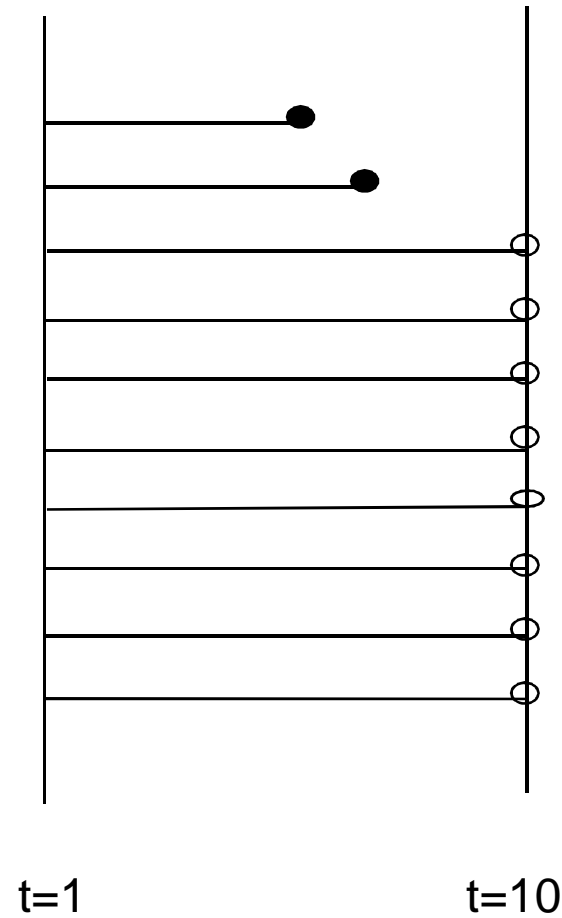
WHO, Geneva
3 June 2008

Equal Follow-up Time Example

Placebo



Vaccine



Equal Follow-up Time Example

Placebo			Vaccine		
t0 (start)	t1 (end)	Outcome (1 = case)	t0 (start)	t1 (end)	Outcome (1 = case)
1	2	1	1	5	1
1	3	1	1	6	1
1	4	1	1	10	0
1	5	1	1	10	0
1	6	1	1	10	0
1	7	1	1	10	0
1	8	1	1	10	0
1	9	1	1	10	0
1	10	0	1	10	0
1	10	0	1	10	0

Equal Follow-up Time Example

- Ratio of Risks (proportions)

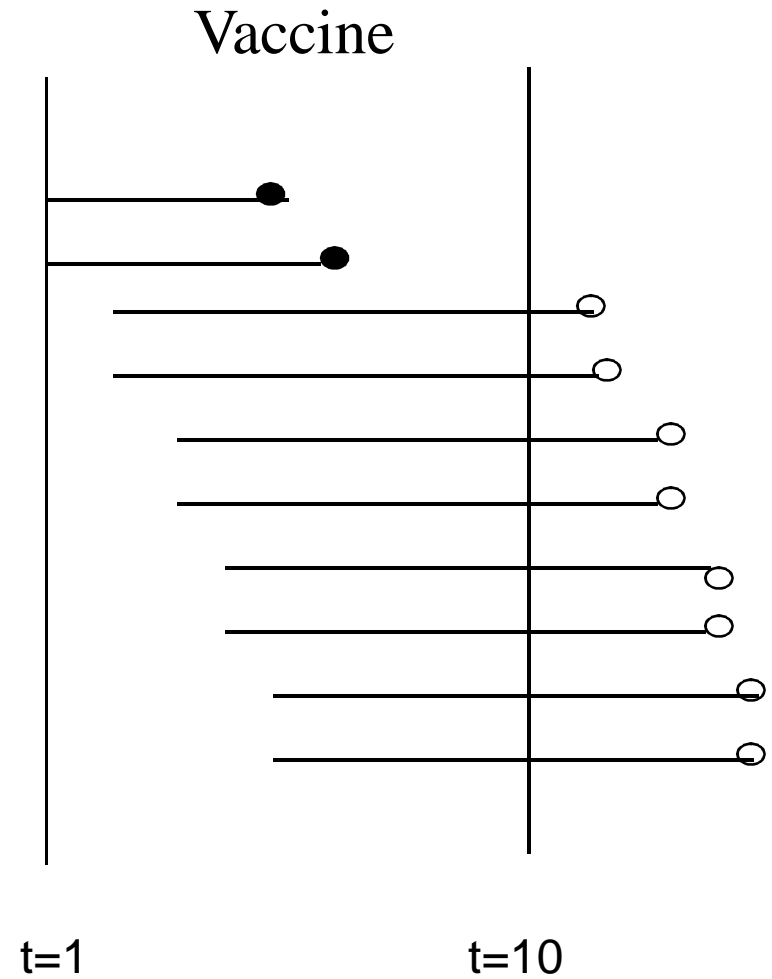
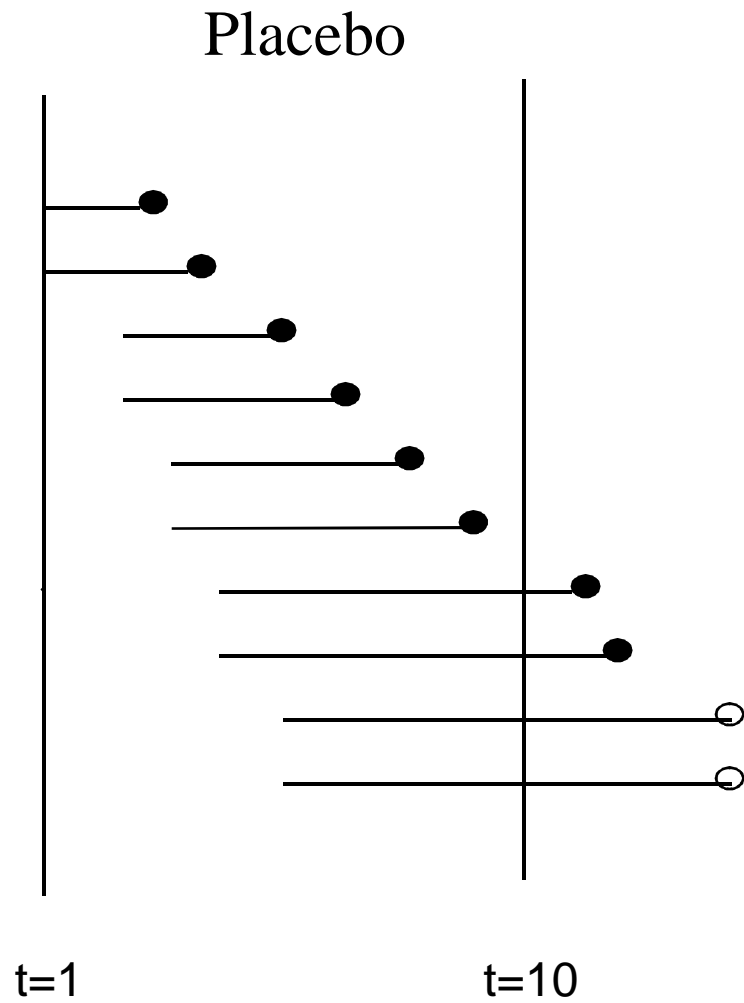
$$R = \frac{(\text{cases}_{\text{vaccine}} / n_{\text{vaccine}})}{(\text{cases}_{\text{placebo}} / n_{\text{placebo}})}$$

$$= (2 / 10) / (8 / 10)$$

$$= 0.25$$

$$95\% \text{ CI} = (0.07, 0.90)$$

Varying Follow-up Time Example



Varying Follow-up Time Example

Placebo			Vaccine		
t0	t1	Outcome	t0	T1	Outcome
1	2	1	1	5	1
1	3	1	1	6	1
2	5	1	2	10	0
2	6	1	2	10	0
3	8	1	3	10	0
3	9	1	3	10	0
4	10	0	4	10	0
4	10	0	4	10	0
5	10	0	5	10	0
5	10	0	5	10	0

Varying Follow-up Time Example

- Ratio of Risks (proportions)

$$R = \frac{(\text{cases}_{\text{vaccine}} / n_{\text{vaccine}})}{(\text{cases}_{\text{placebo}} / n_{\text{placebo}})}$$

$$= (2 / 10) / (6 / 10)$$

$$= 0.33$$

$$95\% \text{ CI} = (0.09, 1.27)$$

Varying Follow-up Time Example

- Incidence Rates Ratio (person-time)

$$R = \frac{\text{cases}_{\text{vaccine}} / \text{person-time}_{\text{vaccine}}}{\text{cases}_{\text{placebo}} / \text{person-time}_{\text{placebo}}}$$

$$= (2 / 71) / (6 / 53)$$

$$= 0.25$$

$$95\% \text{ CI} = (0.02, 1.39)$$

Varying Follow-up Time Example

- Poisson Regression:

$R = 0.25$

95% CI = (0.05, 1.23)

- Cox (proportional hazards) Regression:

$R = 0.25$

95% CI = (0.05, 1.26)

Varying Follow-up Time Example

Method	R	95% CI
Ratio of Risks (proportions)	0.33	(0.09, 1.27)
Incidence Rates Ratio (person-time)	0.25	(0.02, 1.39)
Poisson Regression	0.25	(0.05, 1.23)
Cox Regression	0.25	(0.05, 1.26)

Varying Follow-up Time Example

Method	VE (1 - R)	95% CI
Ratio of Risks (proportions)	0.67	(-0.27, 0.91)
Incidence Rates Ratio (person-time)	0.75	(-0.39, 0.98)
Poisson Regression	0.75	(-0.23, 0.95)
Cox Regression	0.75	(-0.26, 0.95)

Licensed Vaccine Products

Method used	Vaccine Product Examples
Risk Ratio	Flumist™
Incidence Rate Ratio	RotaTeq™
Poisson Regression	Pertussis in DTP vaccine (not for licensure)
Cox Regression	Rotarix™

RotaTeq™ Vaccine Efficacy

	RotaTeq™	Placebo
# vaccinated	2834	2839
# in analysis	2207	2305
Days of follow-up	623,880	622,399
GI cases	82	315

RotaTeq™ Vaccine Efficacy

- Ratio of Risks (proportions)

$$R = (82 / 2207) / (315 / 2305)$$

$$= 0.27$$

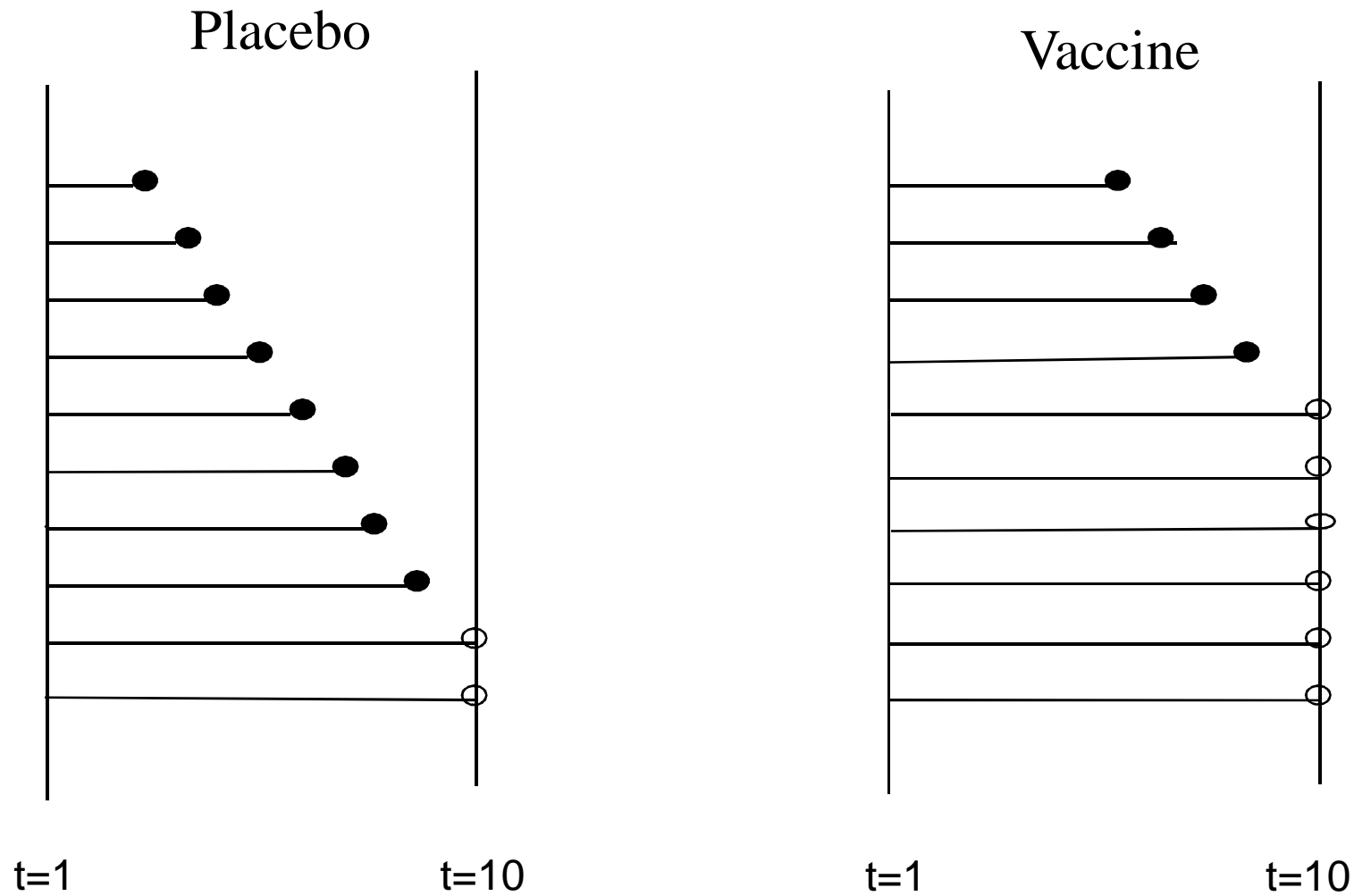
- Incidence Rates Ratio (person-time)

$$R = (82 / 623880) / (315 / 622399)$$

$$= 0.26$$

$$VE = 0.74, \quad 95\% \text{ CI} = (0.67, 0.80)$$

High Background Incidence Rate Example



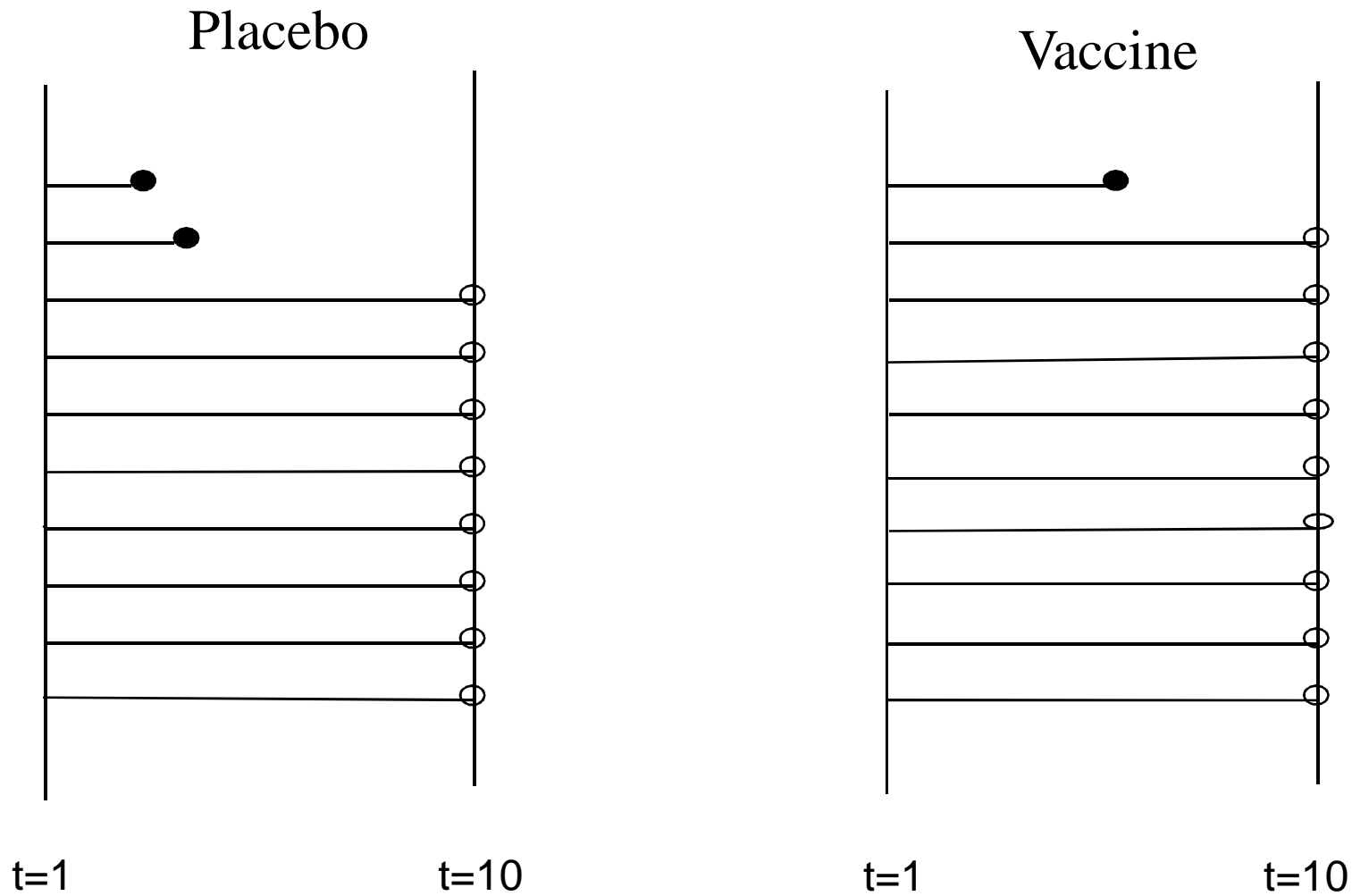
High Background Incidence Rate Example

Placebo			Vaccine		
t0	t1	Outcome	t0	t1	Outcome
1	2	1	1	5	1
1	3	1	1	6	1
1	4	1	1	7	1
1	5	1	1	8	1
1	6	1	1	10	0
1	7	1	1	10	0
1	8	1	1	10	0
1	9	1	1	10	0
1	10	0	1	10	0
1	10	0	1	10	0

High Background Incidence Rate Example

Method	R	VE
Ratio of Risks (proportions)	0.50	0.50
Incidence Rates Ratio (person-time)	0.43	0.57
Cox Regression	0.44	0.56

Low Background Incidence Rate Example



Low Background Incidence Rate Example

Placebo			Vaccine		
t0	t1	Outcome	t0	t1	Outcome
1	2	1	1	5	1
1	3	1	1	10	0
1	10	0	1	10	0
1	10	0	1	10	0
1	10	0	1	10	0
1	10	0	1	10	0
1	10	0	1	10	0
1	10	0	1	10	0
1	10	0	1	10	0
1	10	0	1	10	0

Low Background Incidence Rate Example

Method	R	VE
Ratio of Risks (proportions)	0.50	0.50
Incidence Rates Ratio (person-time)	0.45	0.55
Cox Regression	0.45	0.55

Low Background Incidence Rate

- Assume equal number of subjects in each group ($n_{\text{vaccine}} = n_{\text{placebo}}$)
- Ratio of Risks (proportions)

$$R = \frac{(\text{cases}_{\text{vaccine}} / n_{\text{vaccine}})}{(\text{cases}_{\text{placebo}} / n_{\text{placebo}})}$$

$$= (\text{cases}_{\text{vaccine}}) / (\text{cases}_{\text{placebo}})$$

Low Background Incidence Rate

- $\text{cases}_{\text{placebo}} / \text{person-time}_{\text{placebo}} \ll 1$
- $\text{person-time}_{\text{vaccine}} \approx \text{person-time}_{\text{placebo}}$
- Incidence Rates Ratio (person-time)
$$R = \frac{(\text{cases}_{\text{vaccine}} / \text{person-time}_{\text{vaccine}})}{(\text{cases}_{\text{placebo}} / \text{person-time}_{\text{placebo}})}$$
$$\approx (\text{cases}_{\text{vaccine}}) / (\text{cases}_{\text{placebo}})$$
$$= \text{Ratio of risks}$$

RotaTeq™ Vaccine Efficacy (low background rate)

- Ratio of Risks (proportions)

$$R = (82 / 2207) / (315 / 2305) \\ = 0.27, 95\% \text{ CI} = (0.21, 0.34)$$

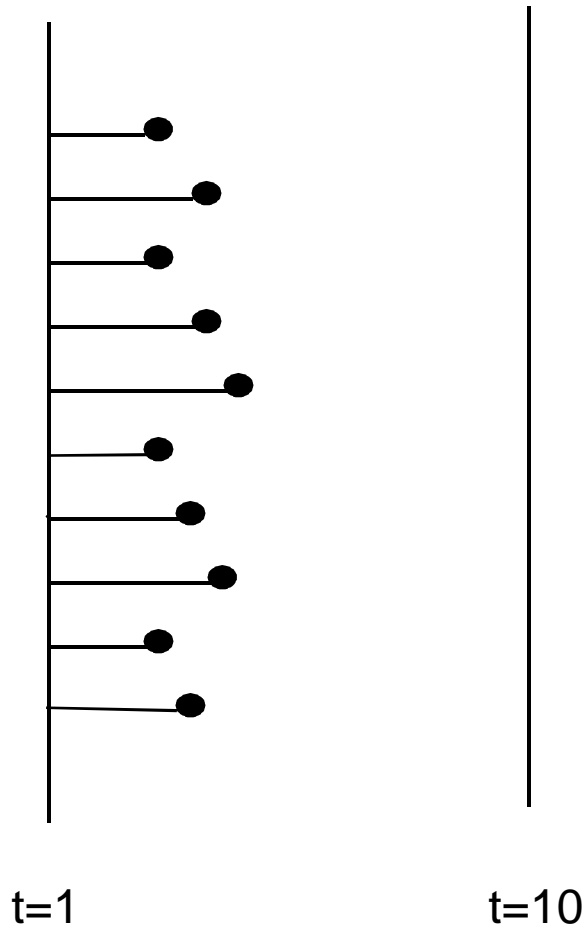
- Incidence Rates Ratio (person-time)

$$R = (82 / 623880) / (315 / 622399) \\ = 0.26, 95\% \text{ CI} = (0.20, 0.33)$$

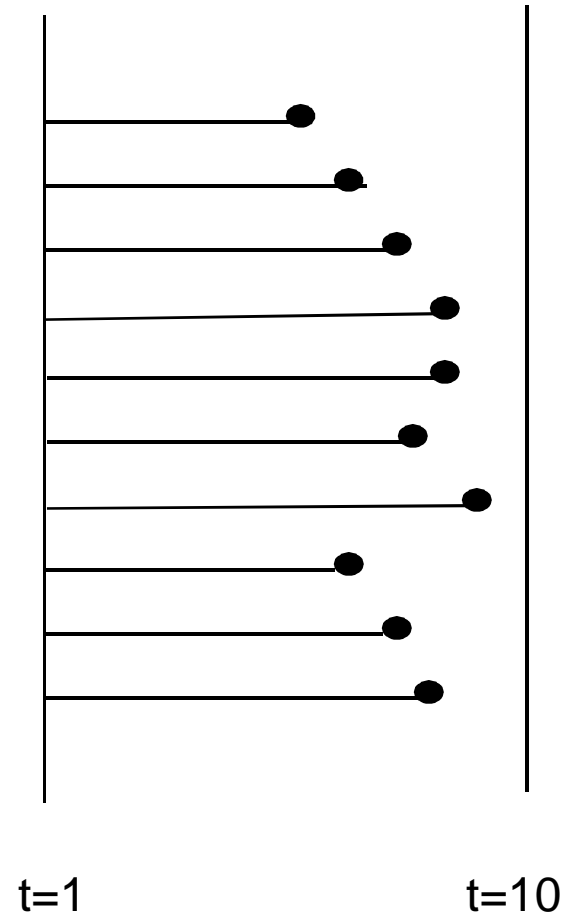
$$VE = 0.74, 95\% \text{ CI} = (0.67, 0.80)$$

Equal Events Example

Placebo



Vaccine



Equal Events Example

Placebo			Vaccine		
t0	t1	Outcome	t0	t1	Outcome
1	2	1	1	5	1
1	3	1	1	6	1
1	2	1	1	7	1
1	3	1	1	8	1
1	4	1	1	8	1
1	2	1	1	7	1
1	3	1	1	9	1
1	4	1	1	6	1
1	2	1	1	7	1
1	3	1	1	8	1

Equal Events Example

Method	R	VE
Ratio of Risks (proportions)	1.00	0.00
Incidence Rates Ratio (person-time)	0.39	0.61

Equal Events

- Assume equal number of subjects
- Equal events: $\text{Case}_{\text{vaccine}} = \text{Case}_{\text{placebo}}$

- Ratio of Risks (proportions)

$$\begin{aligned} R &= (\text{cases}_{\text{vaccine}} / n_{\text{vaccine}}) \\ &\quad / (\text{cases}_{\text{placebo}} / n_{\text{placebo}}) \\ &= 1 \end{aligned}$$

Equal Events

- Incidence Rates Ratio (person-time)

$$\begin{aligned} R &= (\text{cases}_{\text{vaccine}} / \text{person-time}_{\text{vaccine}}) \\ &\quad / (\text{cases}_{\text{placebo}} / \text{person-time}_{\text{placebo}}) \\ &= \text{person-time}_{\text{placebo}} / \text{person-time}_{\text{vaccine}} \end{aligned}$$

- If $\text{person-time}_{\text{placebo}} < \text{person-time}_{\text{vaccine}}$
then $VE > 0$

Summary

- When the follow-up time is unequal for each subject, the time-to-event approaches accumulate the time-at-risk in the denominator.
- When the background incidence rate is low, the vaccine efficacy estimates are similar for all methods

Summary *continued*

- If every subject had an event by the end of the follow-up period, the VE would be 0 according to the risk ratio method. However, the person-time approach can provide a non-zero VE estimate if the time-at-risk numbers are not the same for the two groups.

Multiple Events within a Subject

- Anderson-Gill model with robust variance estimate was the analysis method used for the approval of the Otitis Media indication for the infant pneumococcal vaccine:
Prevnar™

Multiple Events within a Subject

- Cox regression model with Anderson-Gill approach and robust variance estimate
- 2 assumptions:
 - No change in baseline hazard
 - Overall estimate of effect is of interest

Multiple Events within a Subject

- Other methods in handling multiple events within a subject can be found in the following reference:

Therneau, TM & Grambsch, PM. 2000.
Modeling Survival Data: Extending the Cox Model. Springer-Verlag New York