




Analysis of recurrent events: Evaluating treatment effect in vaccine trials

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Outline



- Finnish Otitis Media (FinOM) Vaccine Trial
- Some features of recurrence
- Analysis methods for recurrent outcomes
- Parameter interpretation
- Conclusions



Finnish Otitis Media (FinOM) trial

Ear infections are a common cause of illness during the first 2 years of life and *Streptococcus pneumoniae*, pneumococcus is the most commonly reported bacterial cause.

- FinOM: Randomised, double-blind trial of a pneumococcal conjugate vaccine for prevention of ear infections
- 1662 children received either pneumococcal (Pnc) or control (HBV) vaccine at ages 2, 4, 6 and 12 months
- Primary follow-up from 6.5 months (after the primary series) until 24 months of age
- Primary endpoint: acute ear infection caused by vaccine-preventable pneumococcal serotype (vsAOM)



Main results

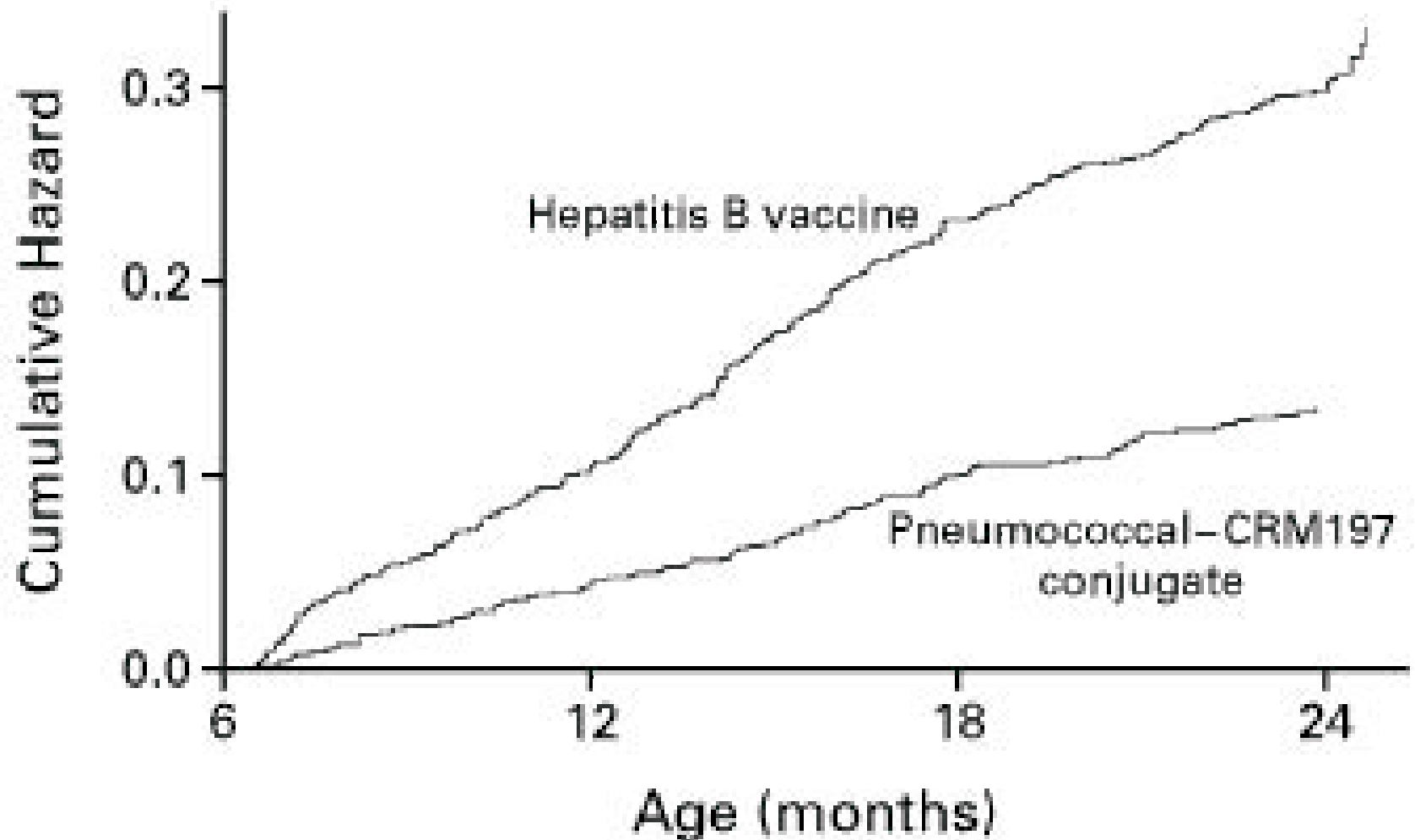
Vaccine Efficacy = 1 - Rate Ratio (*Eskola et. al., NEJM 2001*)

AOM	No. episodes		No./person-year		Vaccine Efficacy (VE)	
	HBV	Pnc	HBV	Pnc	Est	95%CI
vs	250	107	0.21	0.09	0.57	(0.44 to 0.67)
any	1345	1251	1.24	1.16	0.06	(-0.04 to 0.16)

- VE estimates (57% and 6%) frequently cited
- Comparable estimates later produced in another trial (*Prymula et. al., Lancet 2006*)



Cumulative hazard: vaccine type AOM



Main results (cont.)

VE against first and subsequent episodes caused by vaccine serotypes:

vsAOM	No. episodes		No./person-year		Vaccine Efficacy (VE)	
	HBV	Pnc	HBV	Pnc	Est	95%CI
first	177	89	0.17	0.08	0.52	(0.39 to 0.63)
subs.	73	18	0.47	0.25	0.45	(0.05 to 0.69)

- VE estimates (first 52% and subsequent 45%) not cited

Recurrence in the FinOM dataset

No. of episodes	Children with any AOM		Children with vs AOM	
	HBV	Pnc	HBV	Pnc
0	259	301	644	722
1	206	185	124	74
2	141	116	35	13
3	84	86	13	1
4	78	65	4	1
5	36	37	1	0
6	10	17	0	0
7	5	3	0	0
8	1	1	0	0
10	1	0	0	0

Many features of recurrence

Focus on recurrence with low frequency (enumerable events)

Vaccine Efficacy = 1 - Rate Ratio

Rate Ratio of what?

- average rate in treatment group relative to control?
- rate of k^{th} ear infection relative to control?
 - conditional on previous infection(s)?
 - marginal infection-number-specific?



Methods for recurrent outcomes

Generalisations of the Cox proportional hazard model:

For a subject i , infection k , and time t since start of study:

$$\lambda_{ik}(t) = \lambda_{0k}(t) \exp\{\beta_k v_i\} \times Y_{ik}(t)$$

where

- v_i is the treatment (vaccine) indicator
- β_k is the log rate ratio between treatment and control
- $\lambda_{0k}(t)$ is the baseline hazard
- $Y_{ik}(t)$ is the 'at-risk' indicator



Three Cox models

- Andersen-Gill (AG, 1982)
- Prentice-Williams-Peterson (PWP, 1981)
- Wei-Lin-Weissfeld (WLW, 1989)

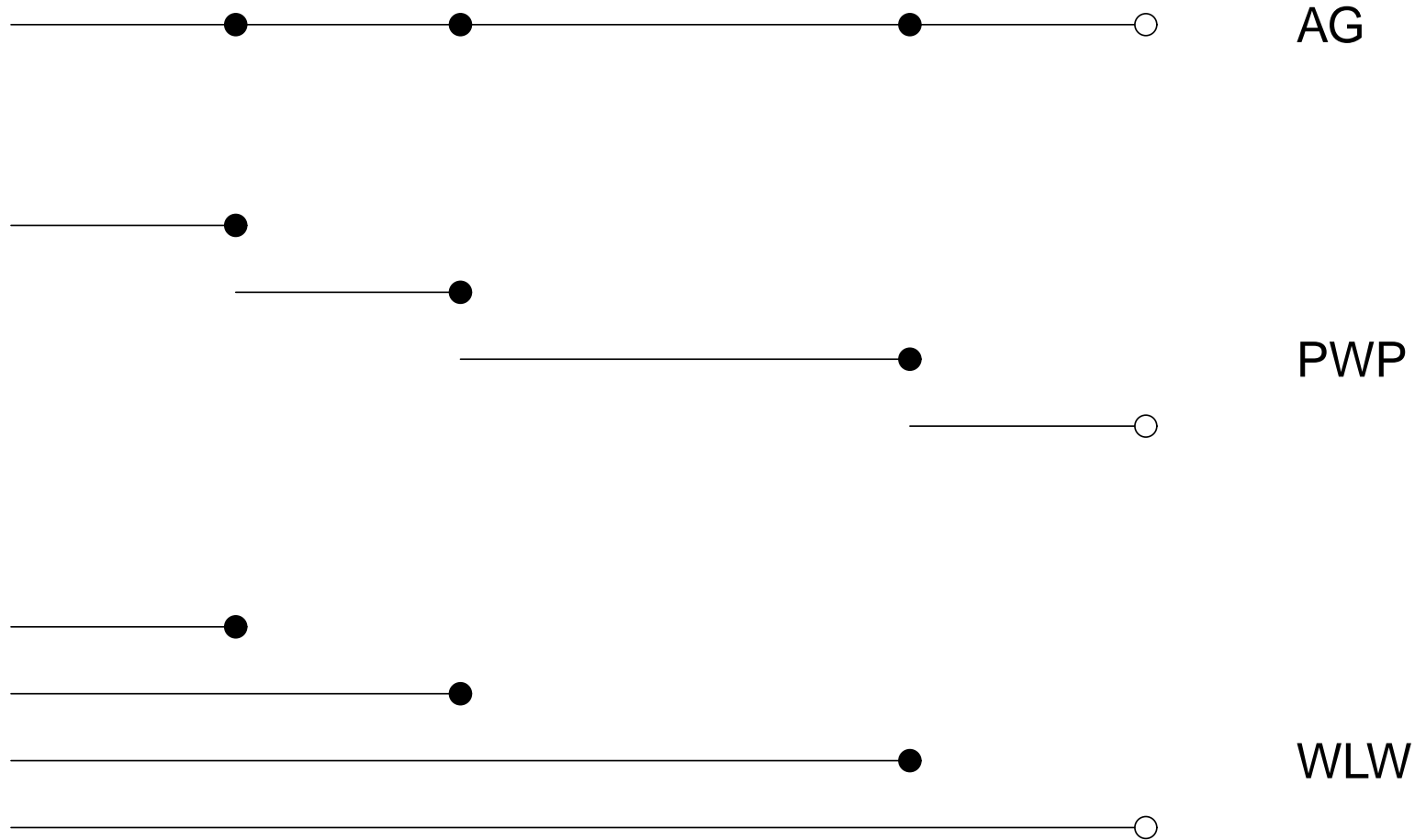
Key difference: the 'at-risk' indicator

- AG : $Y_i(t) = I\{t \leq C_i\}$
- PWP: $Y_{ik}(t) = I\{T_{i(k-1)} < t \leq \min(T_{ik}, C_i)\}$
- WLW: $Y_{ik}(t) = I\{t \leq \min(T_{ik}, C_i)\}$

where T_{ik} is time to k th ear infection and C_i is censoring time

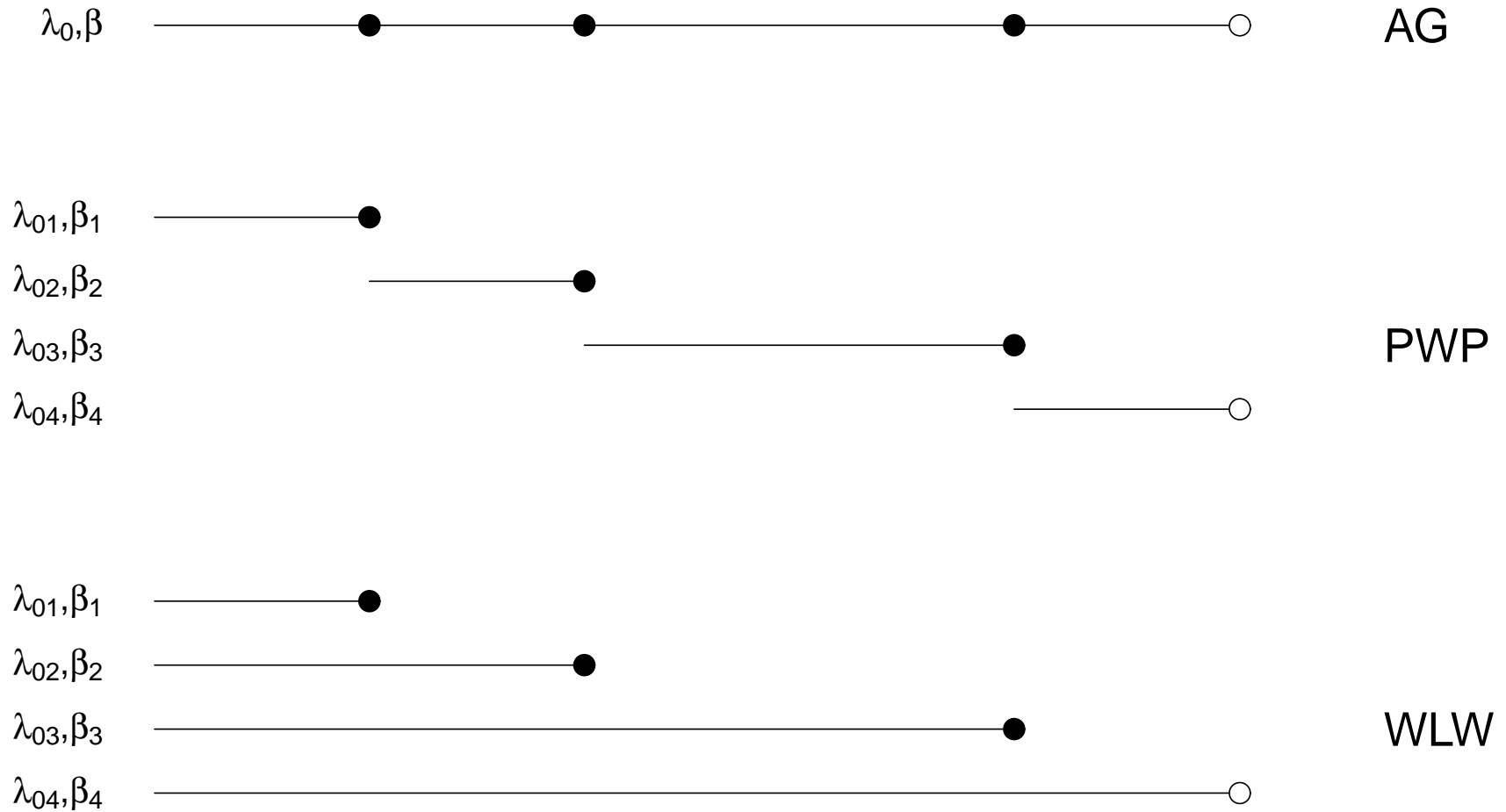


Risk interval illustrations





Risk interval illustrations



One more Cox model

PWP(&AG) -type Cox model (Eerola, 1989):

$$\lambda_i(t) = \lambda_0(t) \exp\{\beta_1 v_i + \beta_2 Y_{i2}(t) + \beta_3 v_i Y_{i2}(t)\} \times I\{t \leq C_i\}$$

where

- $Y_{i2}(t) = I\{T_{i1} < t \leq C_i\}$ PWP-type at-risk indicator
- β_1 log RR between treatment and control
- β_2 log RR between states before and after first infection
- β_3 interaction term parameter

Note: $\beta_1 + \beta_3$ is the treatment effect on subsequent infections, conditional on having the first infection

One more Cox model (cont.)

Comparison of Prentice-Williams-Peterson and Eerola:

PWP:

$$\lambda_{i1}(t) = \lambda_{01}(t) \exp\{\beta_1 v_i\} \times Y_{i1}(t)$$

$$\lambda_{i2}(t) = \lambda_{02}(t) \exp\{\beta_2 v_i\} \times Y_{i2}(t)$$

Eerola:

$$\lambda_i(t) = \lambda_0(t) \exp\{\beta_1^* v_i + \beta_2^* Y_{i2}(t) + \beta_3^* v_i Y_{i2}(t)\} \times I\{t \leq C_i\}$$

where

- $\beta_1 \approx \beta_1^*$ treatment effect on first episodes
- $\beta_2 \approx \beta_1^* + \beta_3^*$ treatment effect on subsequent episodes
- $\lambda_{02}(t)/\lambda_{01}(t) \approx \exp\{\beta_2^*\}$

Dependence due to recurrence

None of the reviewed Cox models (fully) account for possible dependence due to recurrence

- Parameters estimated assuming independence of episodes
- Standard errors adjusted using (robust) sandwich variance estimate (Lin & Wei, 1989)

⇒ Bias of estimates? (and their standard errors?)

Two main mechanisms:

- Time-independent heterogeneity in the population (MIX)
- Time (event)-dependent processes (AR)

A blunt review of reviews

Simplified summary of recommendations in the literature

Authors et.al	Study	Recommendation
Kelly (2000)	Data & simul.	PWP
Box-Steffensmeier (2006)	Data & simul.	PWP(ish)
Metcalfe (2006)	Simulation	mix:AG, ar:PWP
*Jahn-Eimermacher (2007)	Study review	mix:AG, ar:other
Metcalfe (2007)	Data & simul.	WLW
*Jahn-Eimermacher (2008)	Data & simul.	mix:AG, ar:none
Kuramoto (2008)	Simulation	all three
*Cheung (2010)	Data & simul.	AG

* pneumococcal vaccine trials

PWP model fitted to the FinOM trial

PWP-model fitted to the FinOM vsAOM episode data:

Episode	Vaccine Efficacy	95%LCL	95%UCL
first	0.52	0.39	0.63
second	0.40	-0.08	0.67
third or greater	0.56	-0.64	0.88

at-risk indicators:

- $Y_{i1}(t) = I\{0 < t \leq T_{i1}\}$
- $Y_{i2}(t) = I\{T_{i1} < t \leq T_{i2}\}$
- $Y_{i3}(t) = I\{T_{i2} < t \leq C_i\}$

Reminder: Main results (cont.)

VE against first and subsequent episodes caused by vaccine serotypes (Eerola):

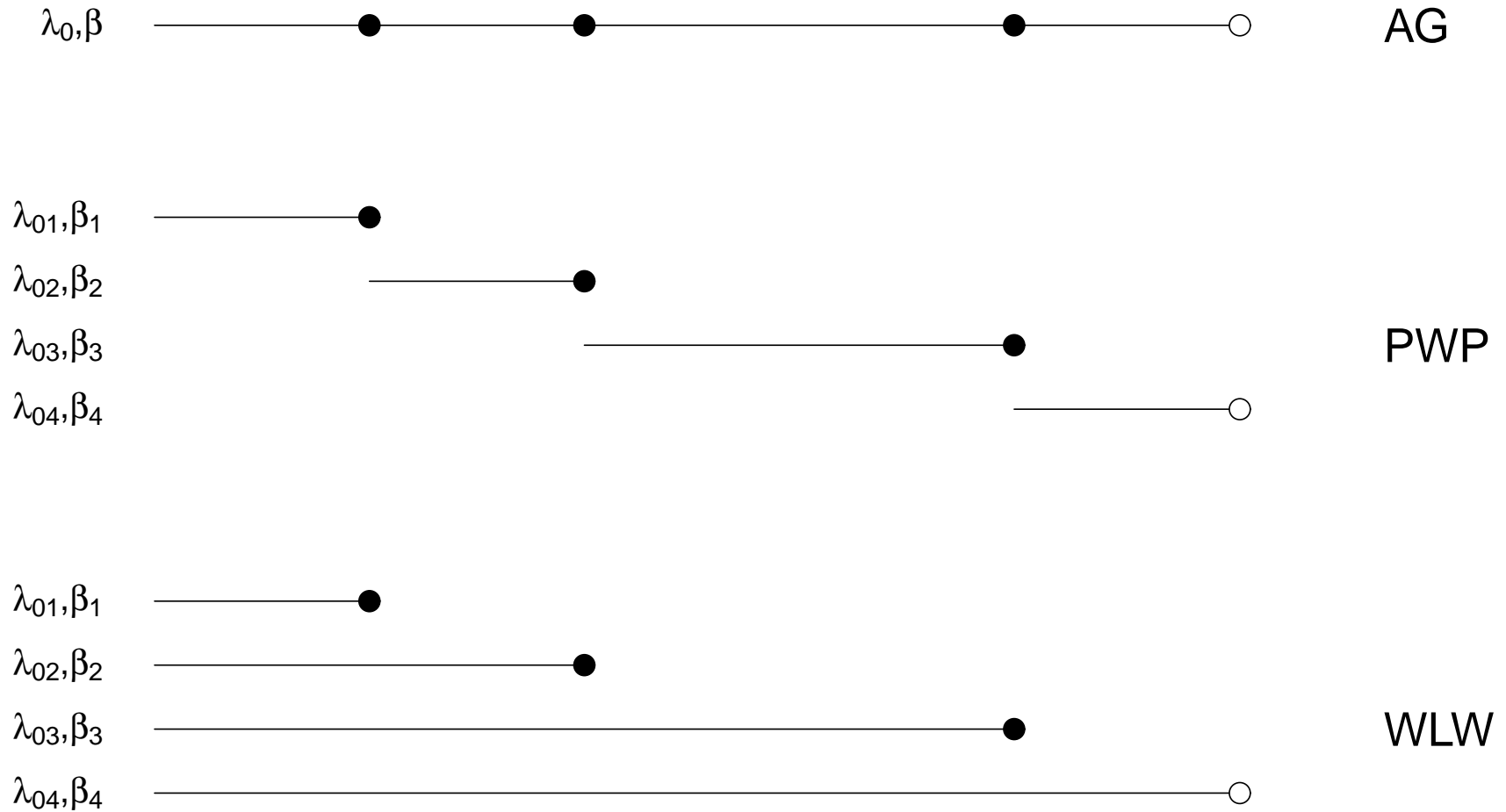
vsAOM	No. episodes		No./person-year		Vaccine Efficacy (VE)	
	HBV	Pnc	HBV	Pnc	Est	95%CI
first	177	89	0.17	0.08	0.52	(0.39 to 0.63)
subs.	73	18	0.47	0.25	0.45	(0.05 to 0.69)

Note the difference between events and rates

⇒ Rates compared after the first infection are no longer based on initially randomised children (informative censoring?)



Reminder: Risk intervals



WLW model fitted to the FinOM trial

WLW-model fitted to the FinOM vsAOM episode data:

	Vaccine Efficacy	95%LCL	95%LCL
first	0.52	0.39	0.63
second	0.71	0.48	0.84
third or greater	0.88	0.49	0.97

at-risk indicators:

$$\bullet Y_{i1}(t) = I\{0 < t \leq T_{i1}\}$$

$$\bullet Y_{i2}(t) = I\{0 < t \leq T_{i2}\}$$

$$\bullet Y_{i3}(t) = I\{0 < t \leq C_i\}$$

⇒ Marginal effect on each ordered event in turn

AG-model: Back to FinOM results

AOM	No. episodes		No./person-year		Vaccine Efficacy (VE)	
	HBV	Pnc	HBV	Pnc	Est	95%CI
vs	250	107	0.21	0.09	0.57	(0.44 to 0.67)
any	1345	1251	1.24	1.16	0.06	(-0.04 to 0.16)

- Several suggestions of bias under event-dependence (Kelly et.al, Box-Steffensmeier et.al, Metcalfe et.al, Jahn-Eimermacher et.al, Kuramoto et.al, Therneau et.al)
- Cheung et al. (2010) showed that there is no bias, there's a difference in parameter interpretation

A little simulation

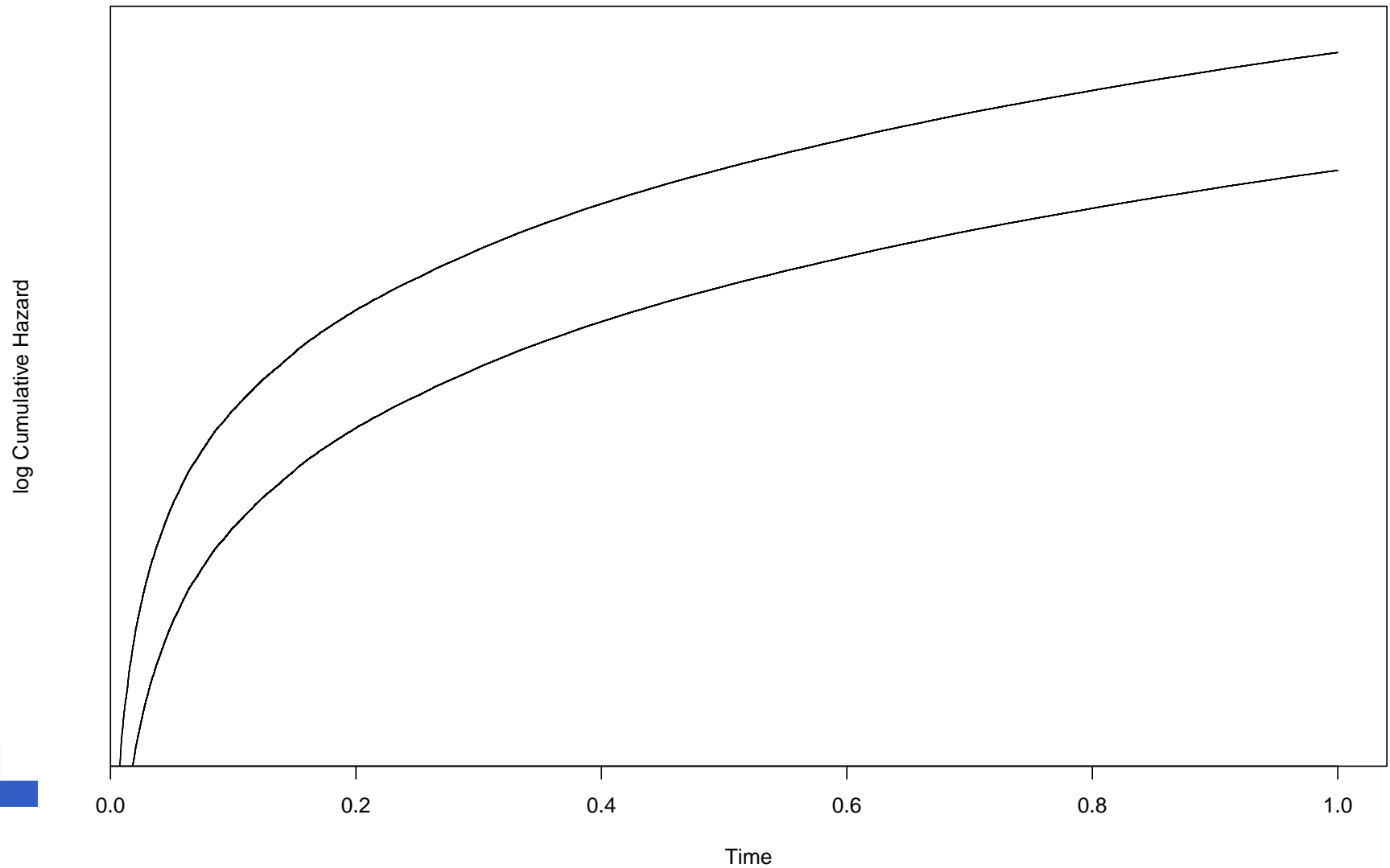
- exp-distributed times: rate=0.5 in Pnc and rate=1 in HBV
- After the first event, a 3-fold rate in both groups
- 30,000 event histories in both groups (censoring at time 1)

AOM	No. episodes		Vaccine Efficacy		Crude estimate
	HBV	Pnc	Est	95%CI	$1-(\#Pnc/\#HBV)$
vs	250	107	0.57	(0.44-0.67)	0.57
simul	52366	21562	0.59	(0.58-0.60)	0.59

Effect on episode $k > 1$:

a sum of direct effect on the risk of episode k and an indirect effect from the first episode (delayed onset)

Simulation: test for proportionality



Summary

Generalisations of Cox models have different interpretation:

- PWP: Conditional effect
- WLW: Marginal effect
- AG: Population-averaged effect

In vaccine trials,

- Under event-dependence, **PWP** gives the subject-specific effect, otherwise the interpretation may be cumbersome
- **WLW** is useful if e.g. recurrence may lead to subsequent interventions (e.g. tube placement in case of AOM)
- **AG** compares the average rates on a population level, often the most important public health estimate

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Acknowledgements



- Mervi Eerola
- Robert Kohberger
- Terhi Kilpi



Epilogue: Robust sandwich estimator

“To advertise as robust a method whose only demonstrated property is consistency is to invite the wrath of SASA, the Statistical Advertising Standards Authority”

Drum & McCullagh (Stat.Sci., 1993)

- Kauermann & Carroll (JASA, 2000) give theoretical justification for an undercoverage of the CI based on the sandwich variance estimator
- Some empirical evidence that “robust” variance may even be smaller than their naïve counterparts
- More research? More simulations?