A modified self-controlled case series (SCCS) method for event-dependent exposures and high event-related mortality, with application to COVID-19 vaccine safety

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COI Disclosure information

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I have no financial relationship to disclose

SCCS method

- It is an alternative to the traditional study designs cohort and case control studies

  - What is the risk of aseptic meningitis in the period 1-14 days after MMR vaccination?
    - Absolute risk

  - Given that an MMR-vaccinated child was diagnosed with aseptic meningitis in the second year of life, how much more likely is it that this diagnosis arose 1-14 days after vaccination rather than at some other time?
    - Relative risk

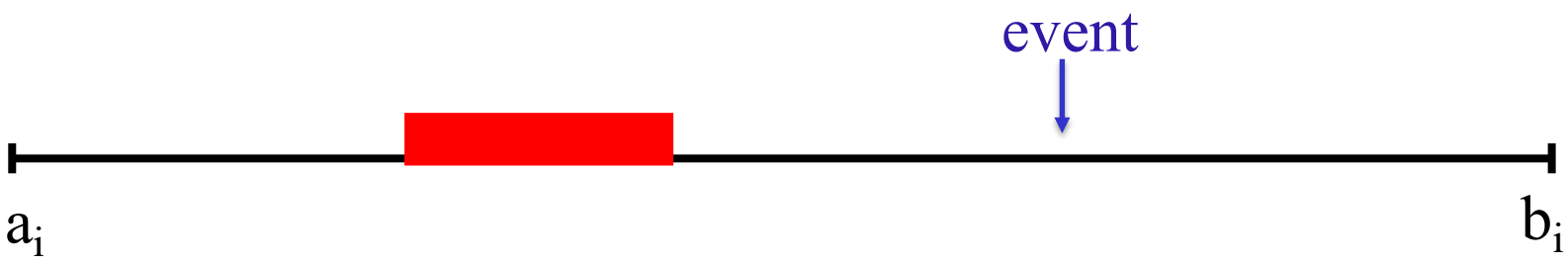
SCCS method

- It is used to investigate the association between exposures such as vaccines or other drugs and an adverse event
- Only cases are required, no controls
- Automatically controls all fixed multiplicative confounders

SCCS method

- It is a conditional cohort method: exposures are regarded as fixed, event times as random
- Follow-up is not censored at event time
- Estimation is self-matched, within-individuals, all fixed confounders factor out
- Events studied can be either independent recurrent, or rare non-recurrent

SCCS method



SCCS method

- Data required

case	sta	end	am	mmr
1	366	730	384	516
2	444	730	517	495
3	366	730	407	487
4	366	730	407	384
5	366	730	380	NA
6	366	730	584	NA
7	366	730	495	477
8	366	730	458	434
9	366	730	503	469
10	366	445	407	382
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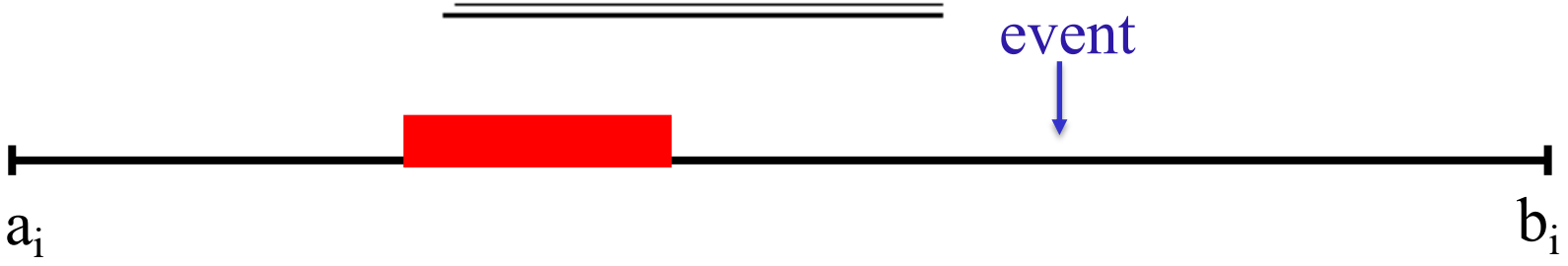


How does it work?

- Fix an observation period, over which events are ascertained; individuals with events are cases.
- Obtain exposure histories over this period.
- Subdivide the observation periods into exposure and age groups.

The case series likelihood

number of events

time spent by individual i in age group j and risk period k

$$l(\alpha,\beta)=\sum_{ijk} n_{ijk}\log\left[\frac{\exp(\alpha_j+\beta_k)e_{ijk}}{\sum_{rs}\exp(\alpha_r+\beta_s)e_{irs}}\right]$$

- Parameters of interest: $\exp(\beta_k)$, relative incidences
- Individual effects factor out, hence self-control
- Use Poisson regression to fit model

Assumptions of SCCS

- Events arise independently within individuals
- Occurrence of an event does not affect the subsequent period of observation
- Occurrence of an event does not influence the timing of subsequent exposures
- Exposures do not influence the ascertainment of events

Event dependent exposures

- There is an extension of the standard SCCS
- Exposures after an event are disregarded and considered as missing
- Model is estimated using unbiased estimation equations
- Risk periods must be known and non-indefinite

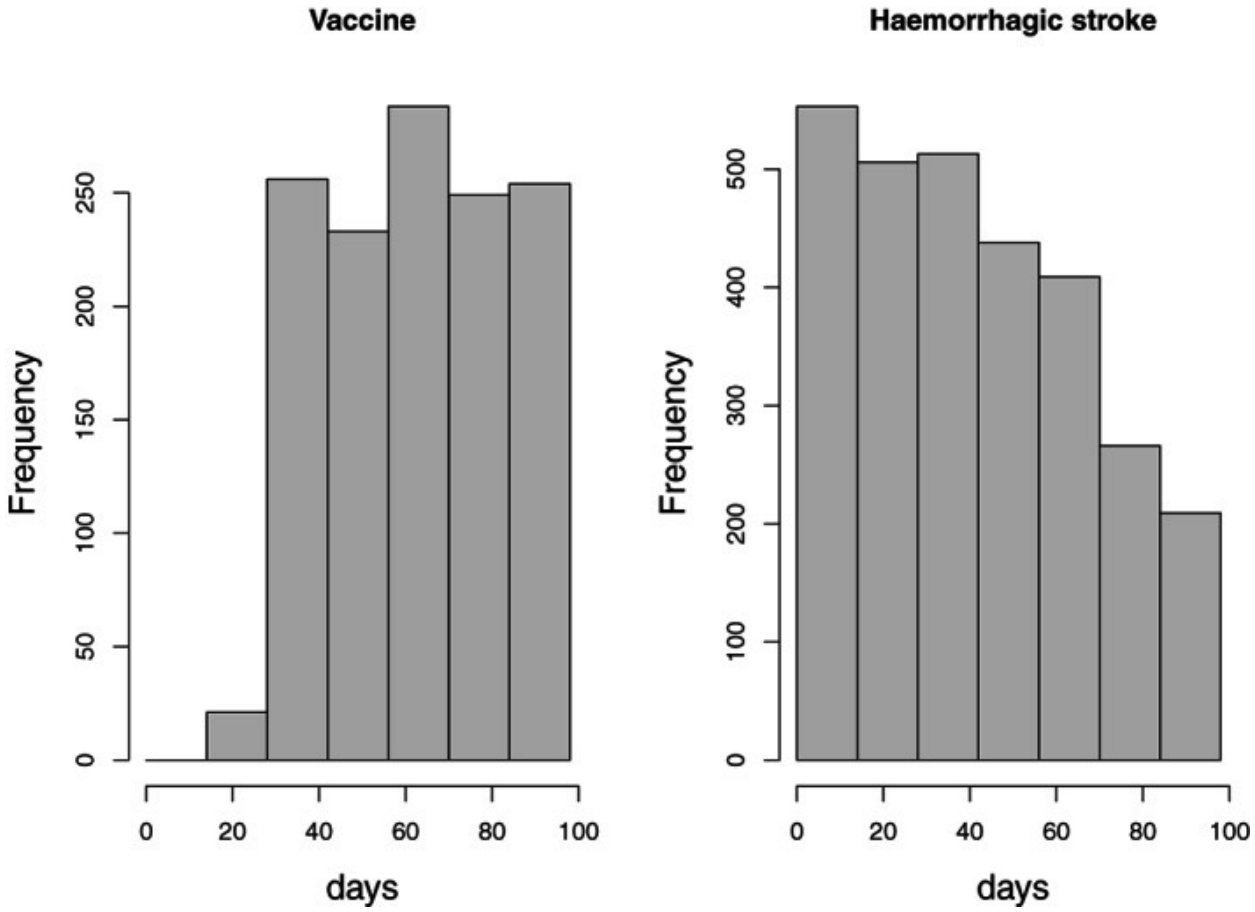
Covid-19 Vaccination and Haemorrhagic stroke

- Relative incidence of stroke after vaccination with the Pfizer-BioNTech Vaccine

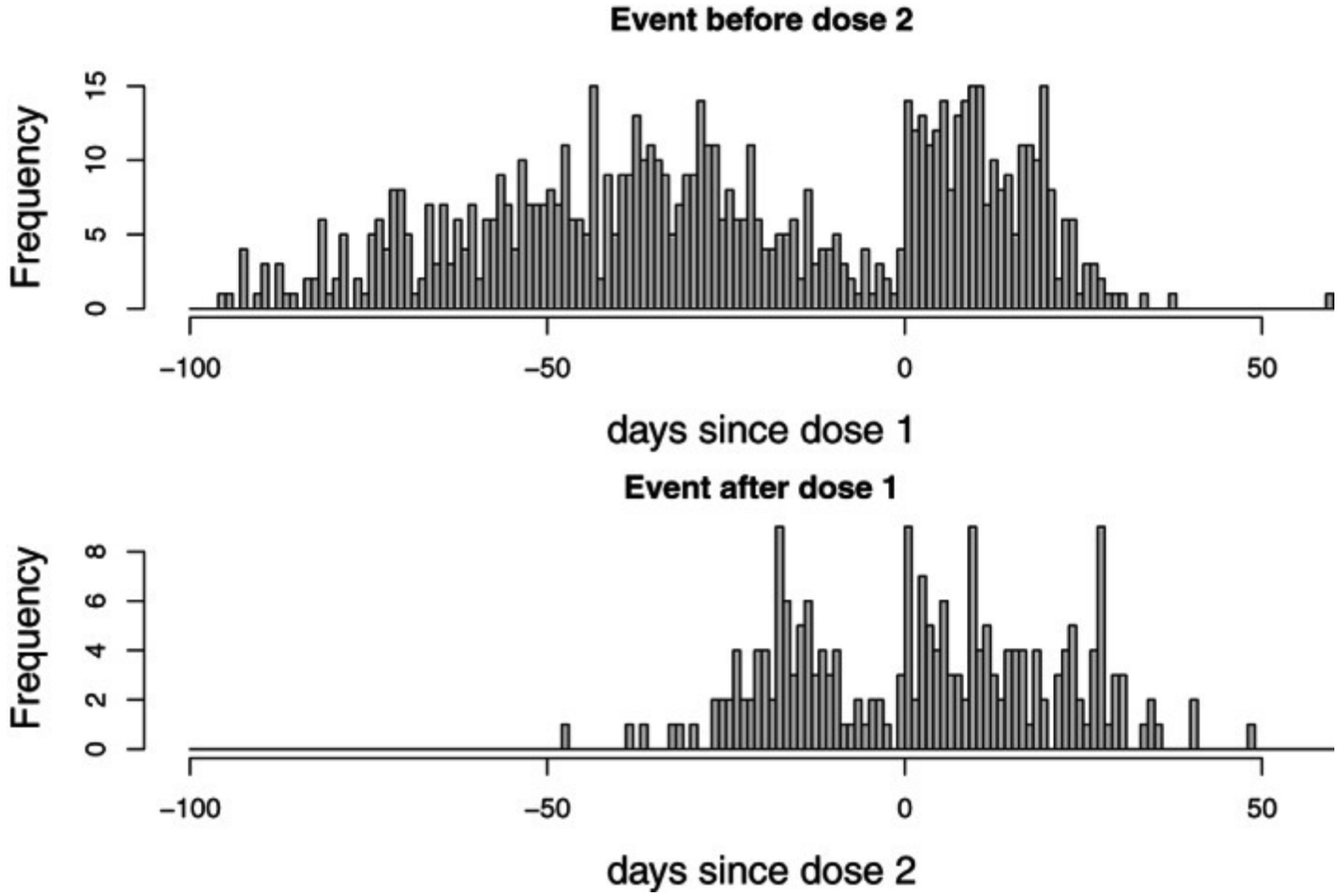
- 2894 events occurring between December 15, 2020 and March 20, 2021

- 894 of them received at least one vaccine dose
  - 407 had received both doses
  - Median interval between doses was 23 days

Event dependent exposures



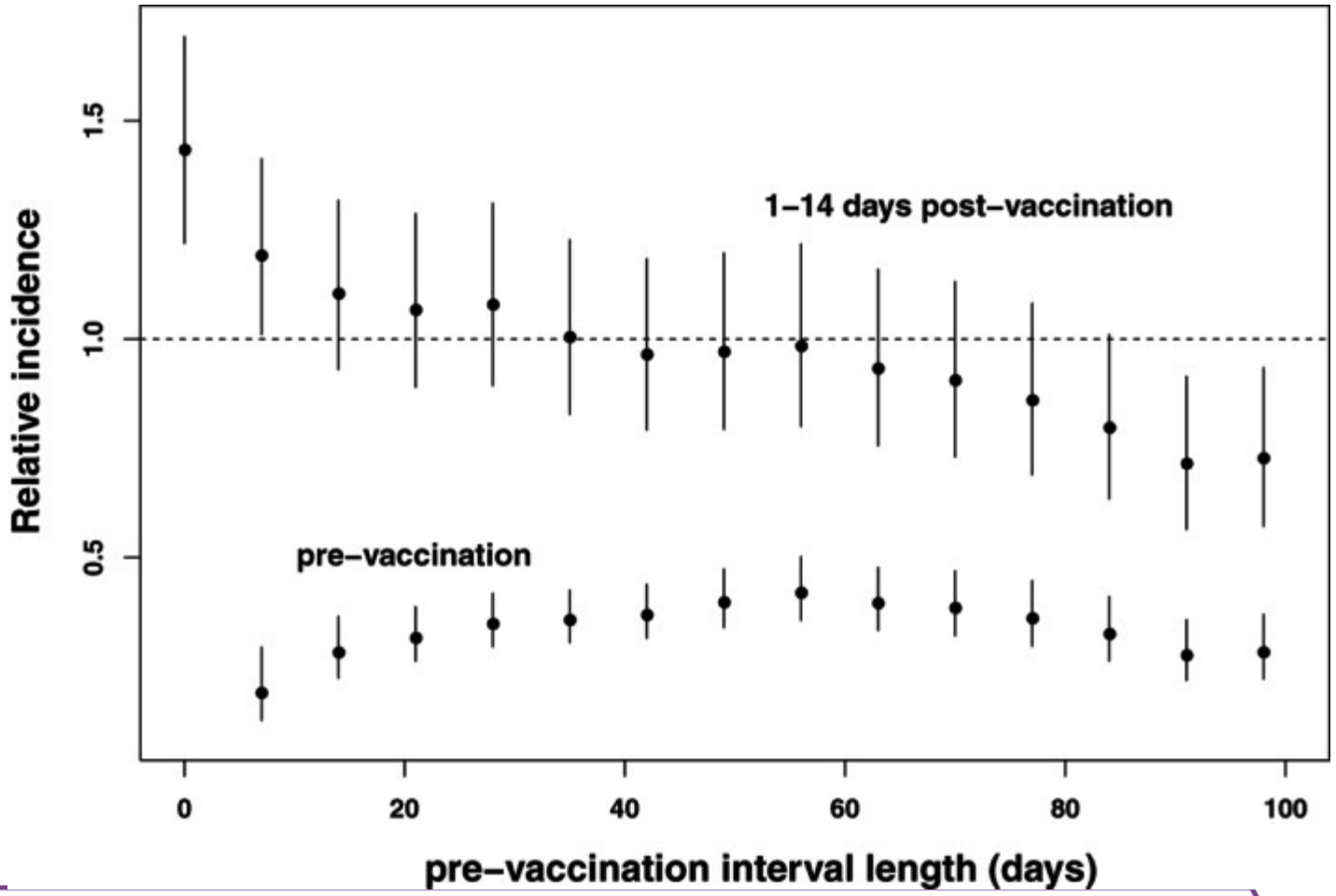
Event dependent exposures



Event dependent exposures

- A dip in the number of events just before each vaccination
- Shows individuals who have had a haemorrhagic stroke are likely to delay or avoid vaccination
- Delaying or cancelling vaccination tend to inflate relative incidence
- A bias by a short delay can be correct within standard SCCS by include preexposure period

Pre-exposure risk periods



Pre-exposure risk periods

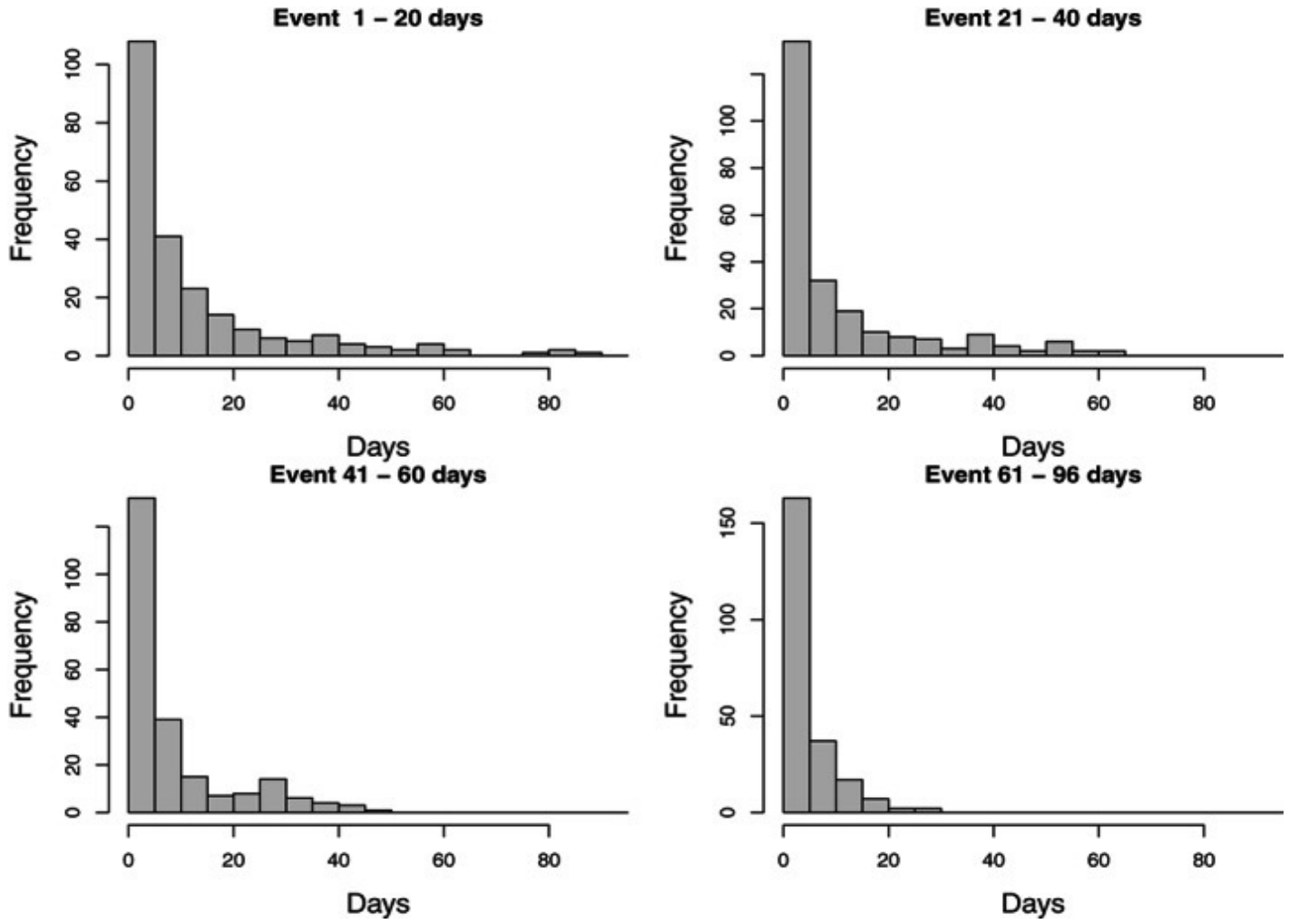
- Relative risk post vaccination changes with the length of pre-vaccine risk period

- Hence a method for event dependent exposures should be used

Deaths caused by event

- 927 of the 2894 cases died after the event during relatively brief observation period
- Others died later
- The median time from event to death was 4 days, for those who died within the observation period

Deaths caused by event



Deaths caused by event

Risk period (days)	Events	RI	95 % CI
Control period	134	1.00	
0 to 4 days	495	8.44	(5.76, 12.4)
5 to 9 days	169	3.44	(2.38, 4.96)
10 to 14 days	84	2.06	(1.43, 2.96)
15 to 19 days	45	1.31	(0.89, 1.94)

Deaths caused by event

- Haemorrhagic stroke induces high short-term mortality up to 14 days after the event
- Deaths censor the observation period
- A model to address this has been developed
- But here exposures are also influenced by event

Proposed model

- When all the deaths are related to event
- Event dependent exposure method can be used
- Use the planned end observation period not date of death
- Deaths due to the event of interest have no impact in the estimation process of the method

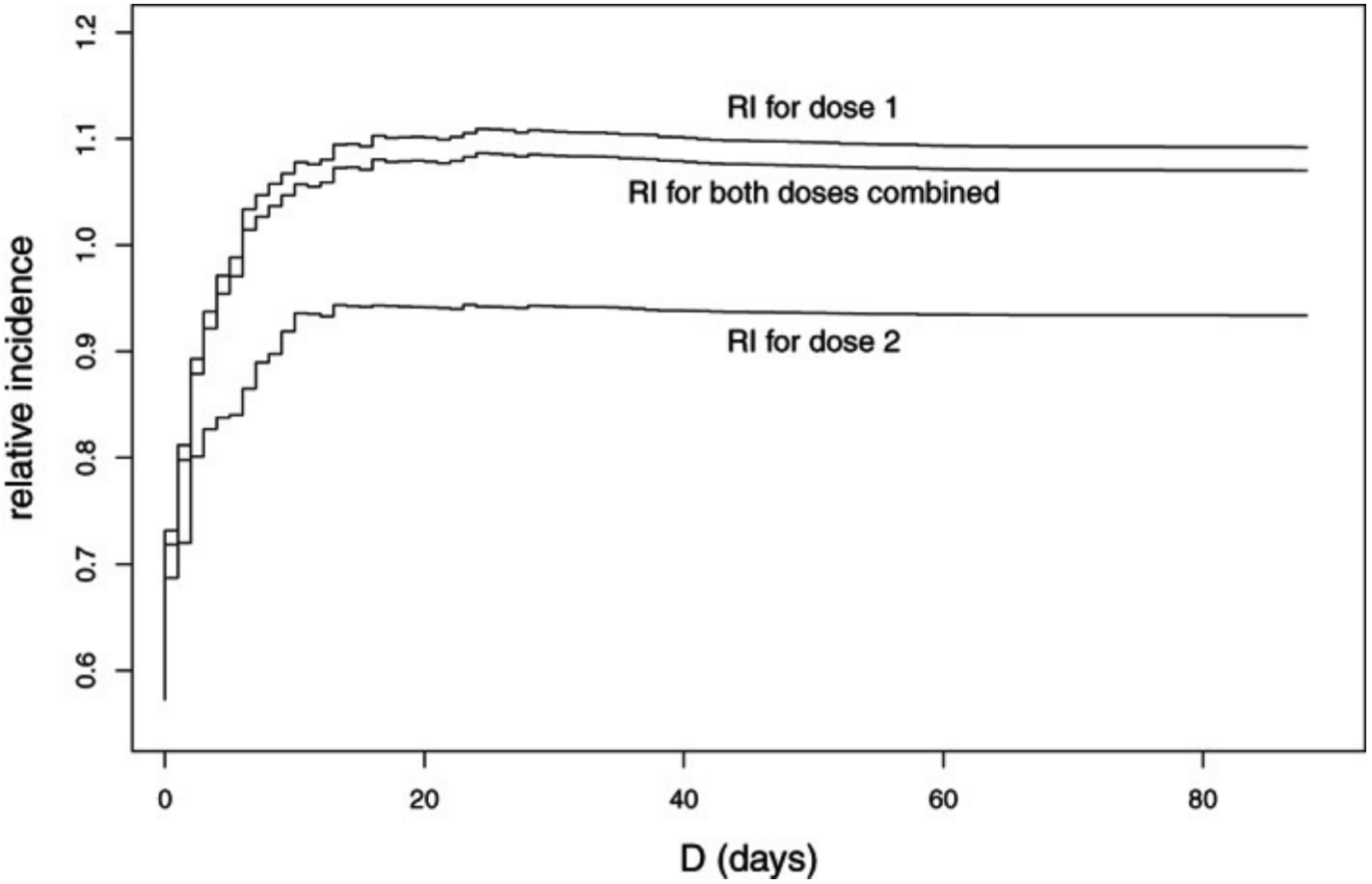
Proposed model

- In practice
  - Set all end of observations as planned if event carry high mortality but not known for certain individuals
  - If the is not known to be associated with high mortality, observation periods should end at the earliest of death and planned end of observation
  - If it is known which deaths are caused by event and which are not use appropriate end of observation period

Proposed model

		Model 1		Model 2	
Risk period (days)	**Events**	**RI**	**95 % CI**	**RI**	**95% CI**
Control period	2657	1.00		1.00	
Dose 1:					
Day 0	4	0.31	(0.11, 0.86)	0.31	(0.11, 0.86)
Days 1 to 14	166	1.09	(0.87, 1.36)	1.10	(0.88, 1.36)
Dose 2:					
Day 0	3	0.49	(0.16, 1.58)	0.50	(0.16, 1.61)
Days 1 to 14	64	0.93	(0.66, 1.33)	0.94	(0.66, 1.34)
Both doses:					
Day 0	7	0.38	(0.18, 0.82)	0.38	(0.18, 0.83)
Days 1 to 14	230	1.07	(0.86, 1.33)	1.07	(0.86, 1.33)

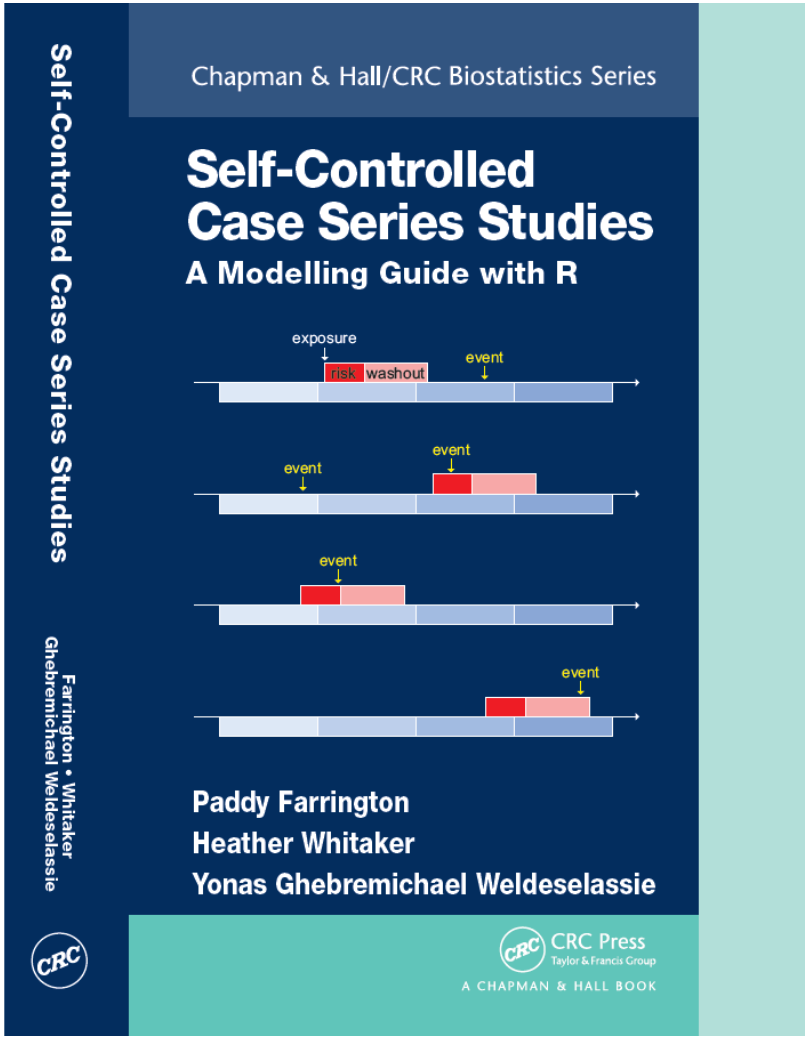
Proposed model



Simulation study

Proportion p		$\rho = 1$	$\rho = 2$	$\rho = 3$	$\rho = 4$
$p = 0$					
	Bias	-0.0021 (0.0028)	-0.0010 (0.0028)	0.0023 (0.0028)	0.0020 (0.0028)
	MSE	0.0079 (0.0004)	0.0076 (0.0003)	0.0077 (0.0003)	0.0076 (0.0004)
$p = 0.1$					
	Bias	-0.0045 (0.0030)	-0.0148 (0.0028)	-0.0219 (0.0027)	-0.0268 (0.0028)
	MSE	0.0089 (0.0004)	0.0081 (0.0004)	0.0077 (0.0004)	0.0086 (0.0004)
$p = 0.2$					
	Bias	-0.0072 (0.0030)	-0.0244 (0.0028)	-0.0302 (0.0028)	-0.0496 (0.0028)
	MSE	0.0088 (0.0004)	0.0085 (0.0004)	0.0085 (0.0004)	0.0102 (0.0004)
$p = 0.3$					
	Bias	-0.0076 (0.0031)	-0.0285 (0.0028)	-0.0526 (0.0029)	-0.0651 (0.0030)
	MSE	0.0096 (0.0004)	0.0085 (0.0004)	0.0110 (0.0005)	0.0133 (0.0005)

Simulation study



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