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# Sequential case series analysis for prospective surveillance

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# Plan of the talk

1. The self-controlled case series method: *description*
2. The self-controlled case series method: *some applications*
3. A case series approach for prospective surveillance
4. Conclusion

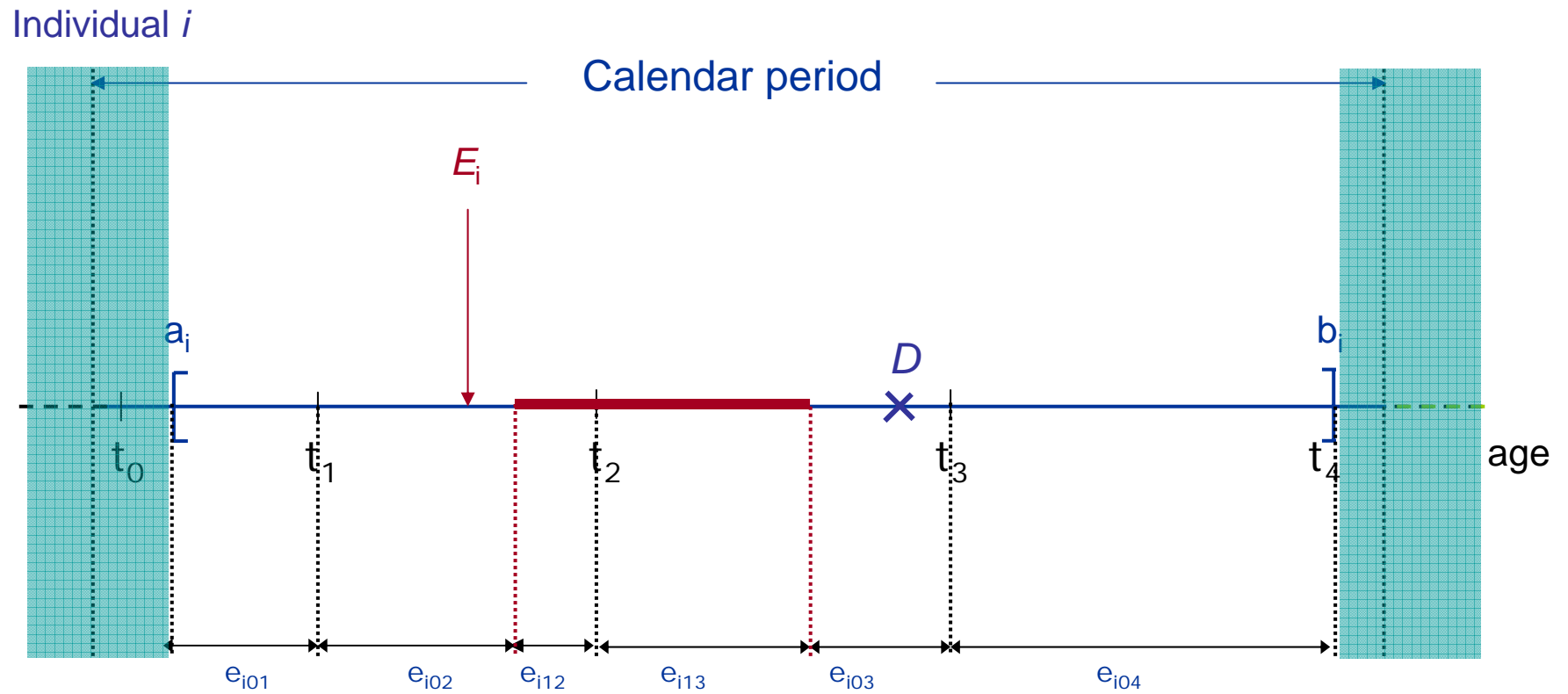
1. The self-controlled case series method:  
Description

## The case series method – *Setting*

The **case series method** is designed to study the association between time-varying exposures  $E$  and rare events  $D$ , potentially recurrent, **using data from cases only.**

- A within-individual estimation of the **relative incidence (RI)**

# The case series method – *Graph*



# The case series method – *Model and likelihood*

## Model

For each individual  $i$ , for each interval of length  $e_{ijk}$ ,

The number of events:  $n_{ijk} \sim P(e_{ijk}\lambda_{ijk})$

$$\lambda_{ijk} = \exp(\underbrace{\varphi_i}_{\text{indiv.}} + \underbrace{\alpha_j}_{\text{age}} + \underbrace{\beta_k}_{\text{exposure}})$$

**ln(RI)**

## Likelihood

After conditioning on the total number of events  $n_i = \sum_{jk} n_{ijk}$  experienced by individual  $i$  over  $[a_i - b_i]$  → multinomial likelihood:

$$L = \prod_i \prod_{j,k} \left( \frac{e_{ijk} \exp(\alpha_j + \beta_k)}{\sum_{r,s} e_{irs} \exp(\alpha_r + \beta_s)} \right)^{n_{ijk}}.$$

# The case series method – *Advantages*

Two main advantages

1. Uses data from **only cases**

→ quick, economic and easy to apply

2. **Adjusts** for all **time-fixed** confounders

→ reduces the bias

## 2. Case series method: Some applications in vaccine safety

# Guillain-Barré Syndrome and flu vaccine (1)

J. Stowe et al. Am J Epidemiol 2008

- In 1976 → **increased risk** of GBS in the US related to flu vaccine
- A case series of 989 cases recorded in the UK from 1990 to 2005
- The relative incidence of GBS was:
  - RI = 0.76 (0.41, 1.40) within 90 days after vaccination,
  - RI = 7.35 (4.36, 12.38) within 90 days of an influenzalike illness

# Guillain-Barré Syndrome and flu vaccine (2)

J. Stowe et al. Am J Epidemiol 2008

- **Consistent** with anecdotal reports of a preceding respiratory illness in GBS.
- It has important implications for **the risk/benefit assessment** that would be carried out should pandemic vaccines be deployed in the future.

## Bleeding disorders and MMR (1)

- In rare instances **MMR vaccine** can cause Idiopathic thrombocytopenic purpura (**ITP**), an uncommon bleeding disorder.
- Case series analysis of **35** children with **44** hospital admissions for ITP.
- Risk period: **0–42 days** post MMR.

## Bleeding disorders and MMR (2)

Farrington & Whitaker. JRSS C 2006

### Semi-parametric analysis:

<i>Risk period (days)</i>	<i>Events</i>	<i>Relative incidence (95% CI)</i>	
Unexposed	31	1	
0–42 post MMR	13	3.01	(1.38, 6.54)

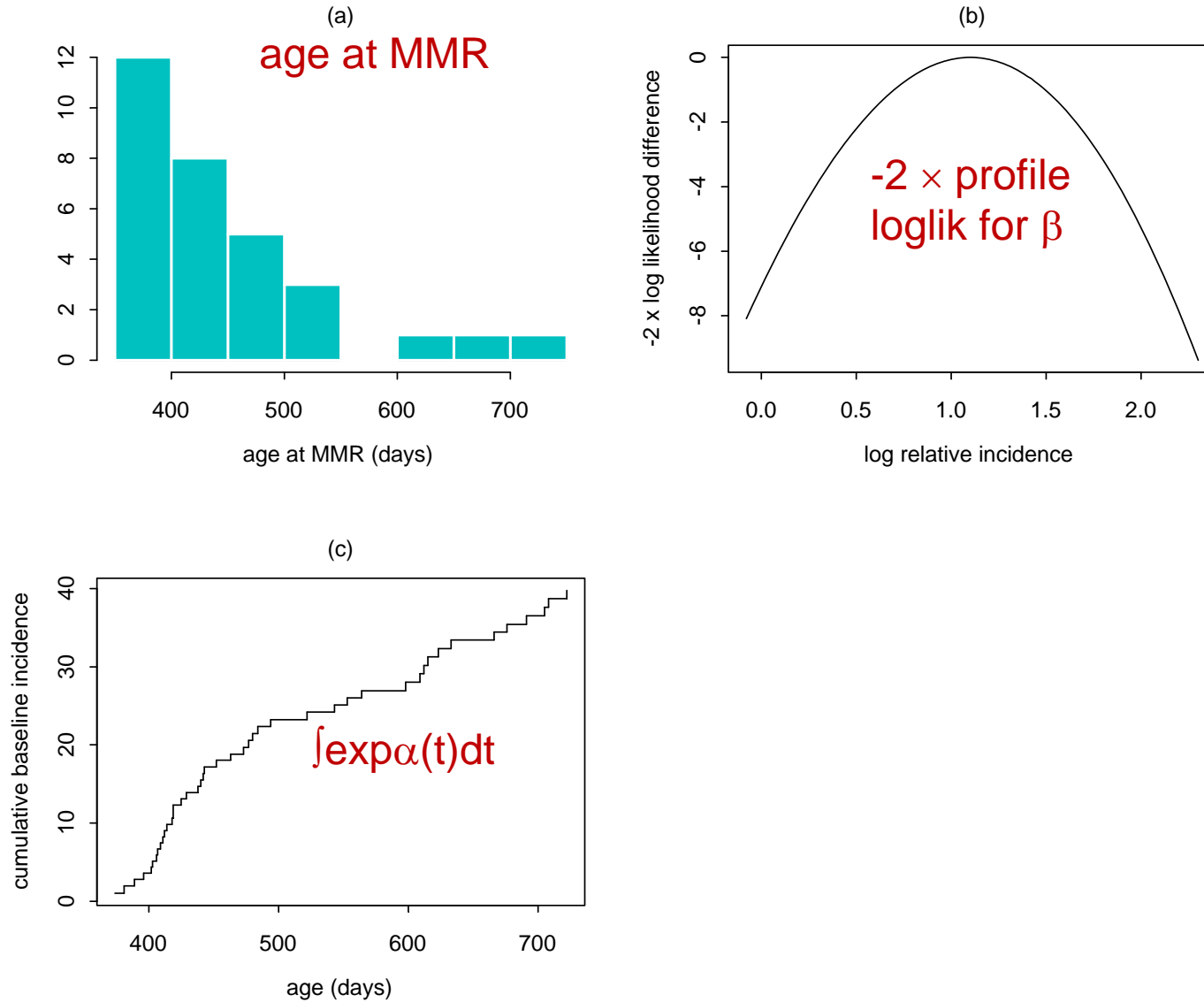
### Analysis of first ITPs:

Case series relative incidence (35 cases) : 3.7 (1.6, 8.7)

Case-control study (23 cases, 116 controls): 6.3 (1.3, 30.1)

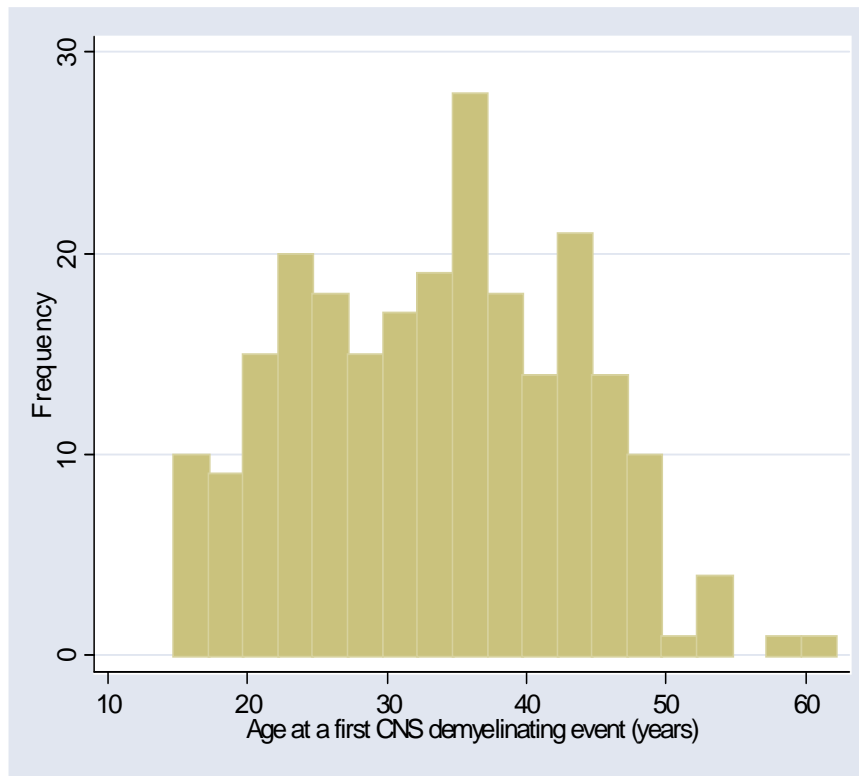
Black, Kaye & Jick 2003

# Bleeding disorders and MMR (3)

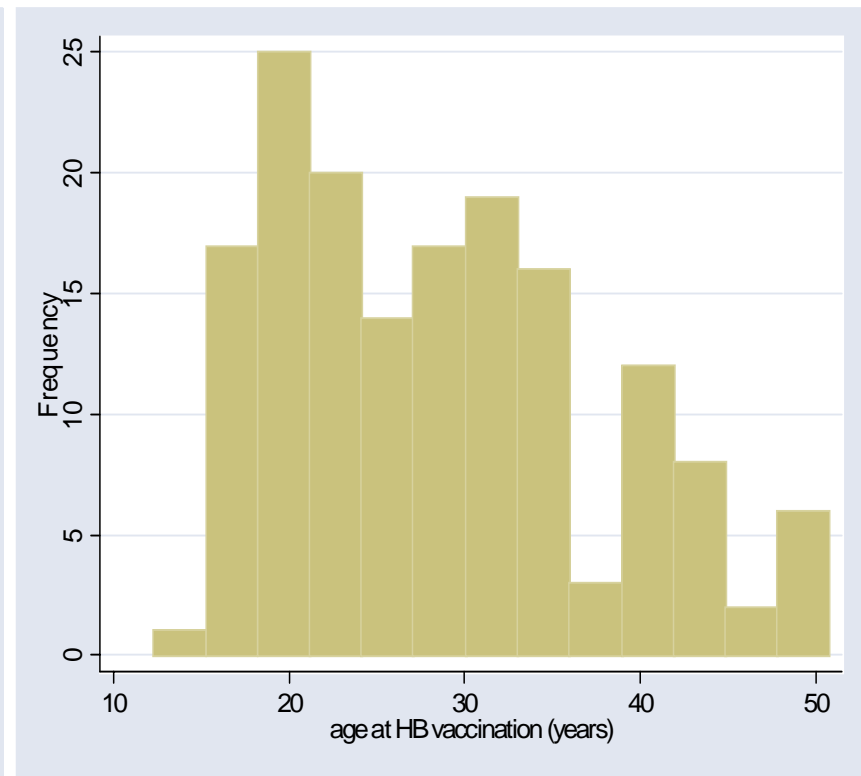


# HB vaccine and first demyelination (1)

A **Case-control** study with 236 cases and 355 matched controls, realised in France in 1995.



Age at event



Age at exposure

## HB vaccine and first demyelination (2)

Hocine et al. Vaccine 2007

**Case-control** study with 236 cases and 355 matched controls.  
Exposure: Hepatitis B vaccination within 60 days.

**Case series** analysis on the same cases. Risk period: 0 – 60 days.

	Case-control	Case series
All cases	1.8 (0.7 – 4.6)	1.7 (0.8 – 3.7)
Probable or definite MS	2.0 (0.8 – 5.4)	1.6 (0.7 – 3.8)

**53 cases** dropped owing to lack of matching controls could have been used in the case series analysis.

# Asthma and flu vaccine (1)

Kramarz *et al.* Arch. Fam. Med 2000.

Cohort and case series studies undertaken in asthmatic children to determine whether **influenza vaccination** precipitates **asthma exacerbations**.

- **Observation period**: influenza months in 1995-6 for asthmatic children aged 1 to 6 years.
- **Temporal effect**: month (i.e. season, not age).
- **Risk period**: 2 weeks after influenza vaccination.

## Asthma and flu vaccine (2)

Method	Sample size	<i>RI</i>	95% CI
Cohort, unadjusted	70 753	3.29	(2.55, 4.15)
Cohort, adjusted	70 753	1.39	(1.08, 1.77)
Case series	2 075	0.98	(0.76, 1.27)

\*adjustment for sex, age, calendar time, asthma severity and preventive care practices

The cohort results are biased owing to **indication bias**. The case series results are **unaffected** by this bias.

# Rotavirus vaccine and intussusception (1)

Murphy *et al.* *NEJM* 2001

Case-control and case series studies to determine whether a new rotavirus vaccine causes **intussusception**.

- **Observation period:** ages 1-12 months
- **Age adjustment:** by month
- **Risk period:** 3-7, 8-14 and 15-21 days after vaccine doses 1 and 2

## Rotavirus vaccine and intussusception (2)

Risk period (days) fffffffffff	Case-control	Case series
3 – 7	37.2 (12.6, 110)	58.9 (31.7, 110)
8 – 14	8.2 (2.4, 27.6)	9.4 (3.9, 22.3)
15 – 21	1.1 (0.2, 5.4)	2.3 (0.5, 10.2)

- **Case control study:** 382 cases and 1657 controls, matched on sex, age, hospital of birth, proxies for socio-economic position.
- **Case series study:** 432 cases.

**Indication bias:** children from poor backgrounds more likely to get intussusception and less likely to get vaccine

### 3. A case series approach for prospective surveillance

Hocine et al. JRSS A 2009

# A prospective approach

- ✓ The case series method is well adapted for prospective surveillance
- ✓ How to use a retrospective method for a prospective surveillance?
- Use a sequential approach at regular time intervals: Adapt the Sequential Probability Ratio Test (SPRT)
- Surveillance of a new vaccine introduced on the market

# The case series SPRT (1)

- ✓ Focus on a **specified adverse event**,
- ✓ Choose the length of the « **monitoring interval** »: regular time intervals  
(example: 6, 12, 24 months),
- ✓ The data on **cases notified** over the monitoring interval are collected and  
**linked to vaccination** records,
- ✓ Apply the SPRT test

## The case series SPRT (2)

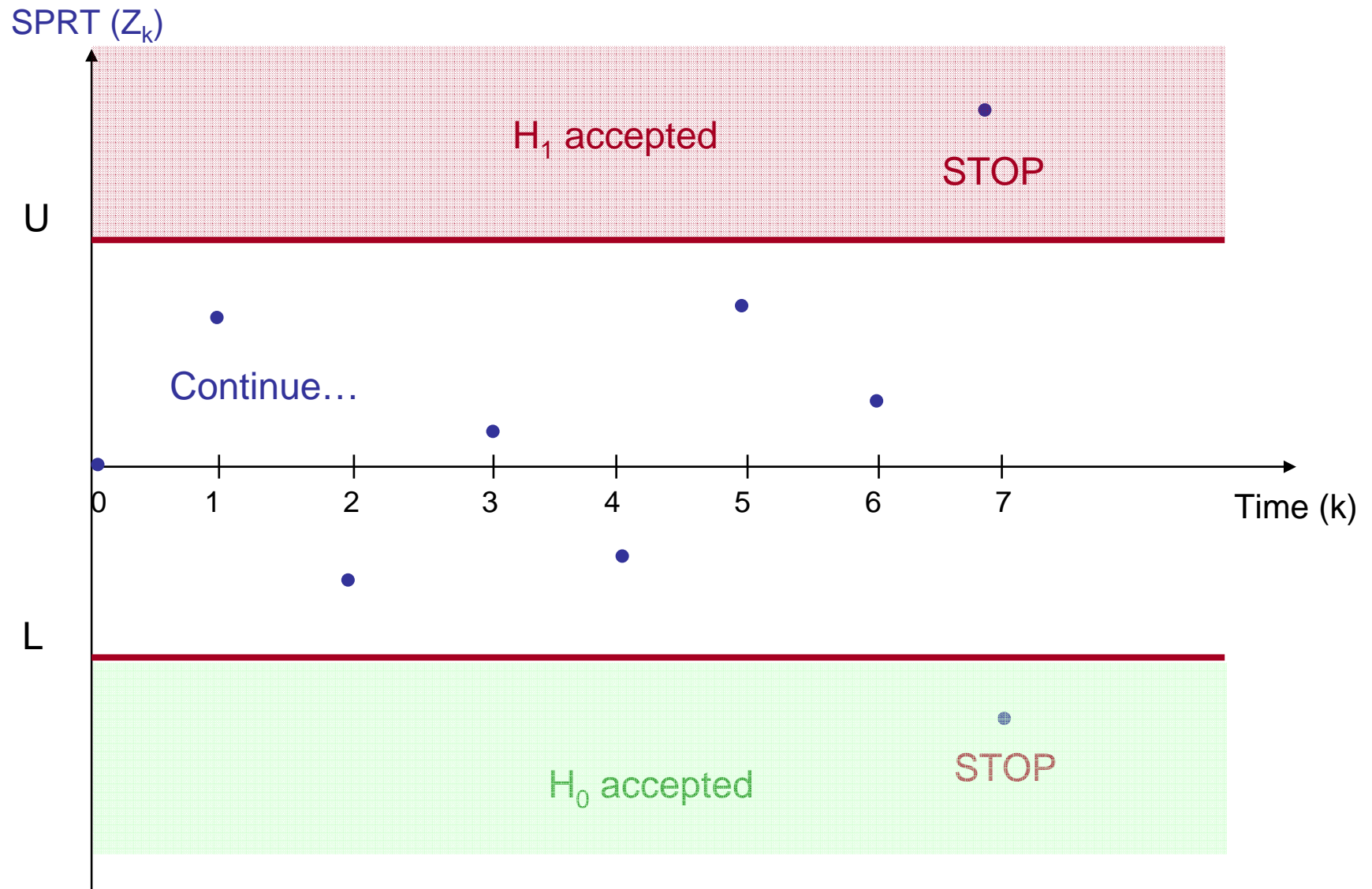
- Define the hypotheses,

$$H_0: \rho = 1 \quad \text{and} \quad H_1: \rho = \rho_A$$

- Using the data collected over the monitoring interval  $k$ :
  - ✓ Fit the case series model under  $H_0$  and under  $H_1 \rightarrow$  the log multinomial likelihoods  $l_{0k}(1)$  and  $l_{1k}(\rho_A) \rightarrow \Lambda_k = l_{1k}(\rho_A) - l_{0k}(1)$
  - ✓ Calculate the value of the SPRT:  $Z_k = Z_{k-1} + \Lambda_k, Z_0 = 0$ .
- Calculate two fixed boundaries:

$$\text{Upper: } U = \log[(1-\beta)/\alpha], \quad \text{Lower: } L = \log[\beta/(1-\alpha)].$$

# The case series SPRT (3)



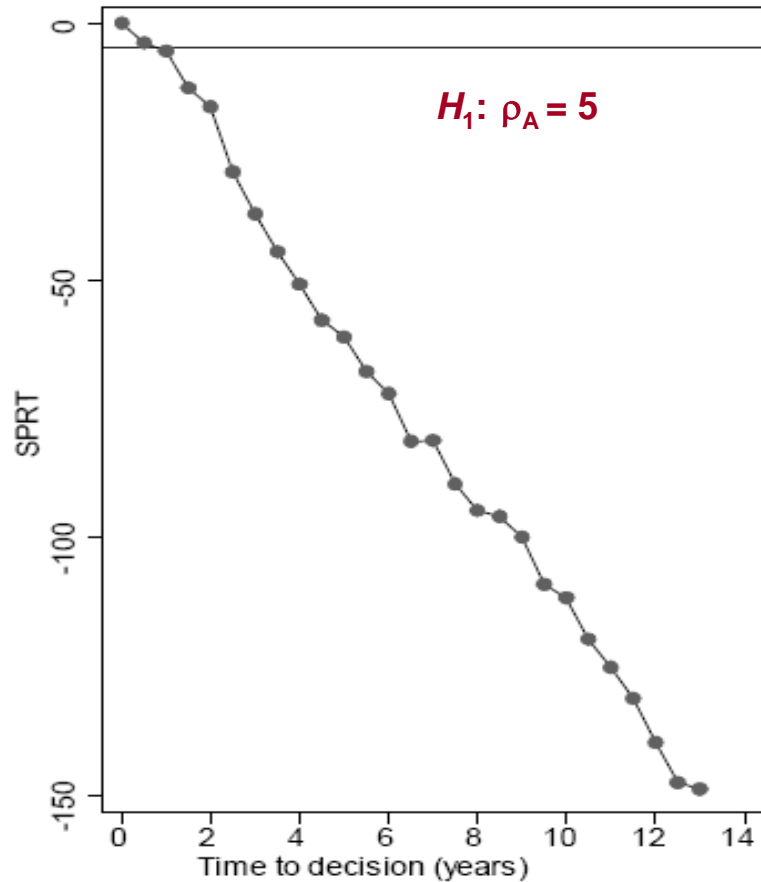
# Bell's palsy and influenza vaccine (1)

- ✓ In Switzerland, a **strong association** was reported between an **intranasal flu vaccine** and Bell's palsy (an acute facial paralysis affecting the 7<sup>th</sup> facial nerve).
- ✓ Further studies undertaken in the **UK** using data on **standard flu vaccine**  
→ no association

## Bell's palsy and influenza vaccine (2)

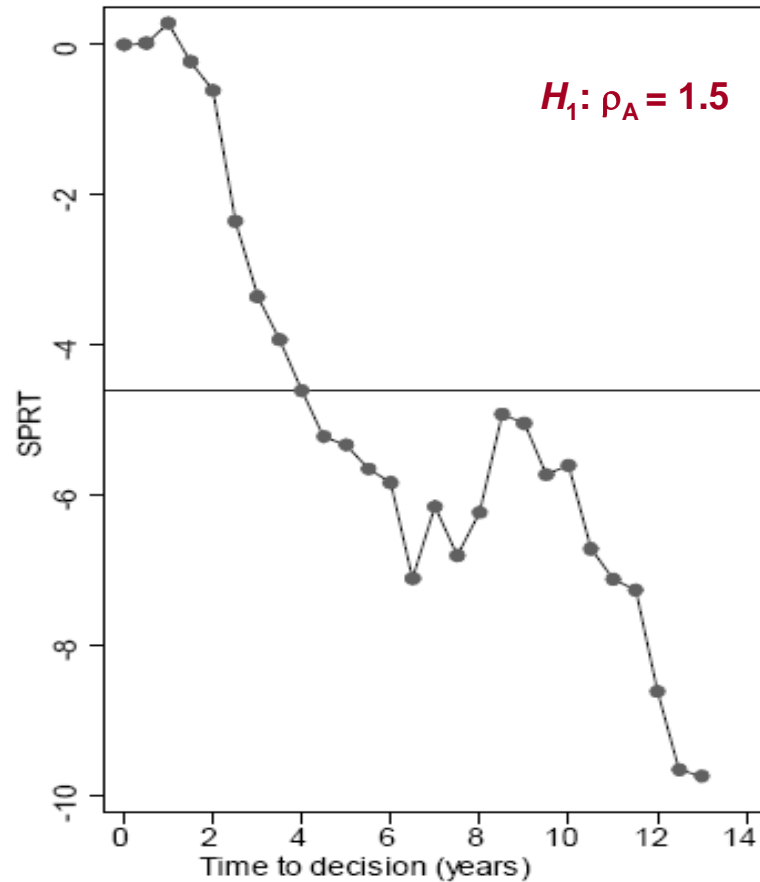
- ✓ Retrospective application of case series SPRT from July 1992
- ✓ Temporal adjustment: by calendar month.
- ✓ Risk period: 1-91 days after any dose of influenza vaccine.
- ✓ Alternative hypothesis:  $\rho_A = 1.5$  and 5
- ✓ Monitoring interval length = 6 months
- ✓ Alarm  $\alpha = \beta = 0.01 \rightarrow L = -4.6$  (lower boundary)

# Bell's palsy and influenza vaccine (3)



$H_1: \rho_A = 5$

(a)



$H_1: \rho_A = 1.5$

(b)

Performance (time to decision) depends on the choice of  $H_1$

# But...

The standard SPRT requires to fix a value of  $\rho_A$ . If this value is not the correct one:

- ✓ Type I error may be inflated,
- ✓ time to decision may be increased

Is it possible to avoid a priori choice of  $\rho_A$  ?

# The Adaptive SPRT (1)

Use a **composite** alternative hypothesis:

$$H_1: \rho \neq 1 \text{ instead of } H_1: \rho = \rho_A$$

- ✓ **Generalized likelihood ratio test:** the likelihood ratio maximised over all possible choices of  $\rho_A$ 
  - Results on bounding the Type I error probability are no longer valid,
  - Need to specify maximum duration of surveillance,
  - Boundary difficult to compute.
  
- ✓ **A stepwise approach of the SPRT:** the value of  $\rho_A$  is updated using data from previous monitoring intervals
  - Excludes data from the current monitoring interval

*Huang, JRSS B (2004)*

## The Adaptive SPRT (2)

We applied the method of Huang

1. Start with a pre-determined value  $\rho_0$
2. After the *first* monitoring interval, obtain:

$$A_1^* = l_{11}(\rho_0) - l_{01}(1), \quad \hat{\rho}_1 = MLE(\rho)$$

$$A_2^* = l_{12}(\hat{\rho}_1) - l_{02}(1),$$

...

$$A_k^* = l_{1k}(\hat{\rho}_{k-1}) - l_{0k}(1),$$

The adaptive SPRT:  $Z_k = Z_{k-1} + A_k^*$ ,  $Z_0 = 0$

# The Adaptive SPRT (3)

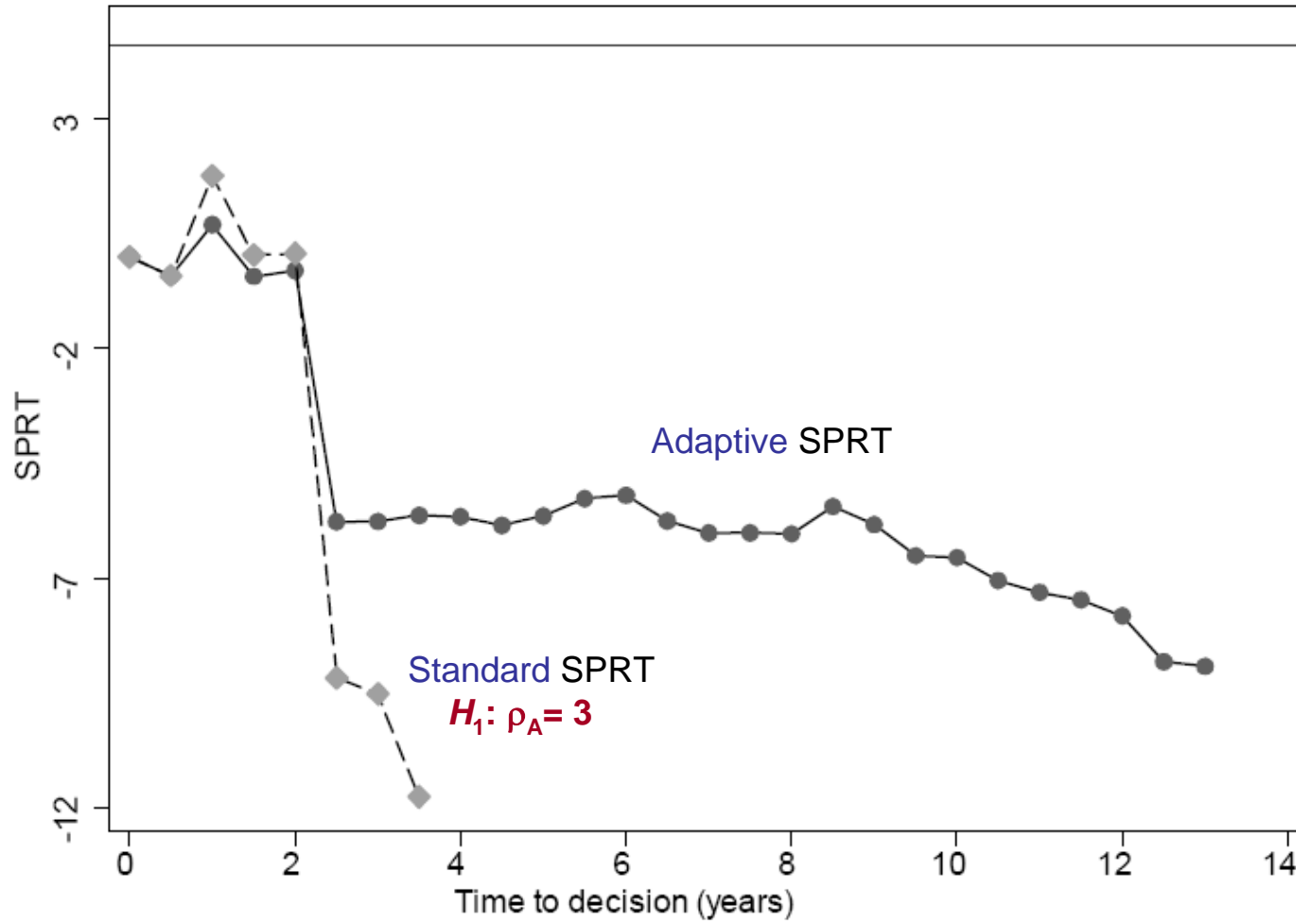
## Properties

- ✓  $H_0$  is never accepted  $\rightarrow$  use a unique boundary at  $\log(1/\alpha)$ ,
- ✓ This uniformly bounds the Type I error probability.

## Age effect

- ✓ *If known*  $\rightarrow \Lambda^*$  is the case series log-likelihood ratio,
- ✓ *If not known*  $\rightarrow \Lambda^*$  is the **profile** log-likelihood ratio.

# Bell's palsy and influenza vaccine (4)



# Adaptive SPRT

## Recommendations

- ✓ Use 6-month monitoring intervals,
- ✓ For multi-dose vaccines, focus on monitoring one dose,
- ✓ Use a single risk period per dose.

## Long-term surveillance

For longer-term surveillance of an established vaccination programme, we proposed the **case series CUSUM**

→ Monitoring vaccine safety using case series cumulative sum charts. Musonda, Hocine et al. *Vaccine* 26 (2008) 5358–5367.

# Conclusion

- ✓ The self-controlled case series method provides a robust and readily implemented method for routine surveillance:
- **Sequential case series for pharmacovigilance.** Hocine, Musonda, Andrews, Farrington. *JRSS A* 172 (2009) 213–236

**Website:** <http://statistics.open.ac.uk/sccs>