

VACCIMUS:
VACCINES AND THE RISK OF
RELAPSE IN MULTIPLE SCLEROSIS

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Hepatitis B vaccination in France

- 1980s: Recommended for at-risk individuals
- 1991: Compulsory for health professionals
- 1994: Recommended for newborn and adolescents
- 1994-95: Vaccination campaign implemented in schools
- In total: 25 million vaccinated 1991-98, including 18 million 1994-96

Pharmacovigilance Alerts in France

- 1991: Publication of 2 cases in the Lancet (Herroelen L, 1991)
- 1991-94: French neurologist/MS specialist reports having observed several cases to l'Agence Française du Médicament
- 1994: First official investigation of spontaneous reports of neurological disorders (1989-1994):
 - Cases were rare
 - Risk assessment not possible
 - Warning about Hep. B vaccination in MS patients
 - Proposal to implement epidemiological approaches

BACKGROUND

1996: New media campaign

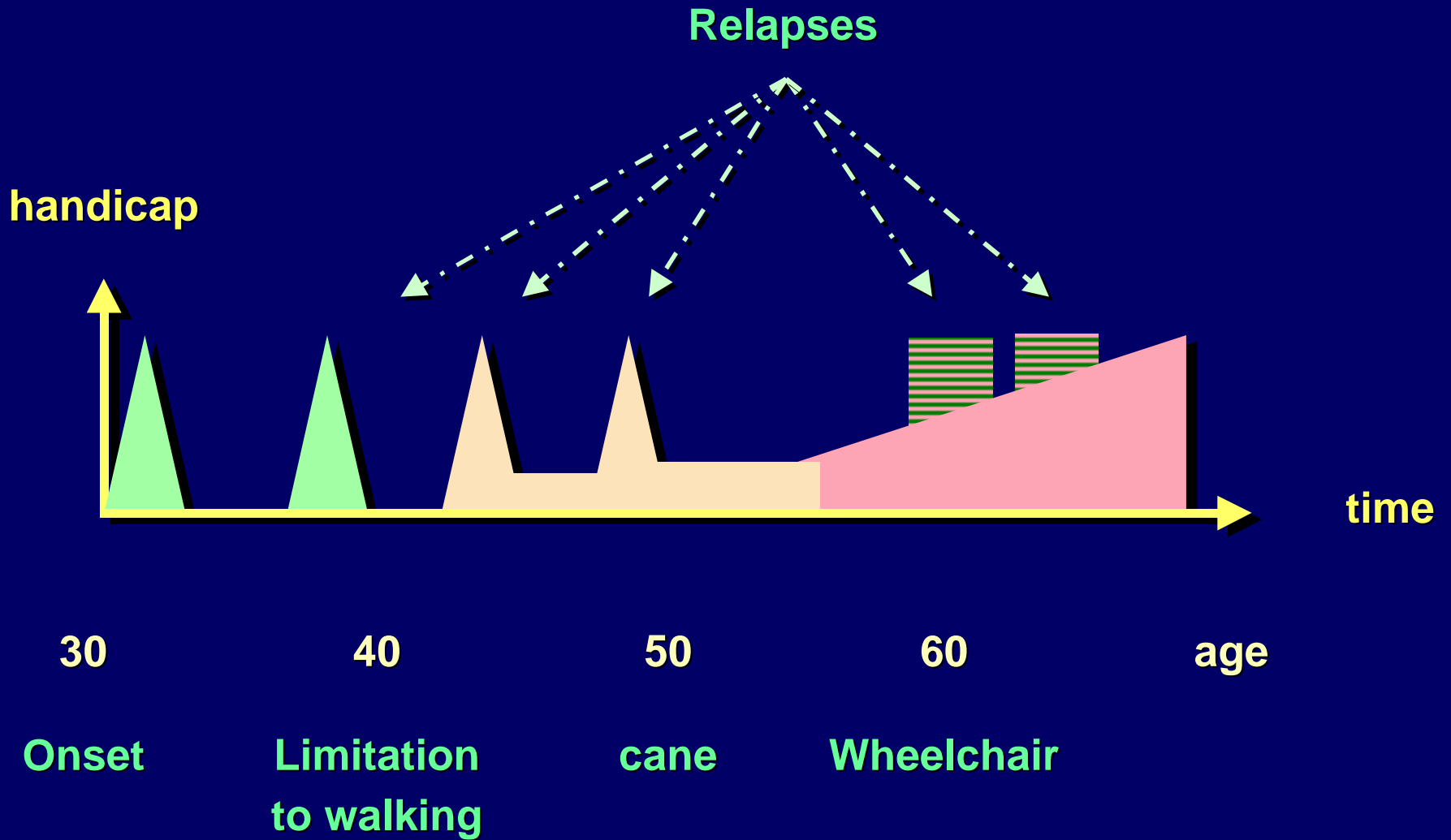
- Additional investigations of spontaneous reports of demyelinating and autoimmune disorders inconclusive

1997: Decision to sponsor epidemiological studies

1998: Several epidemiological studies launched

- GPRD study (Sturkenboom et al, 1999)
- French Agency case-control study (Fourrier et al, 1999)
- Nurses' health cohort study (Ascherio et al, 2001)
- VACCIMUS study (Confavreux et al, 2001)

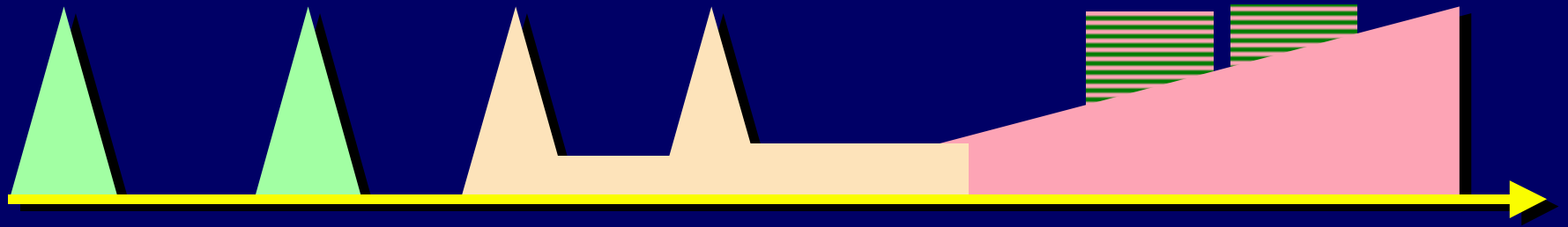
MULTIPLE SCLEROSIS



Vaccines

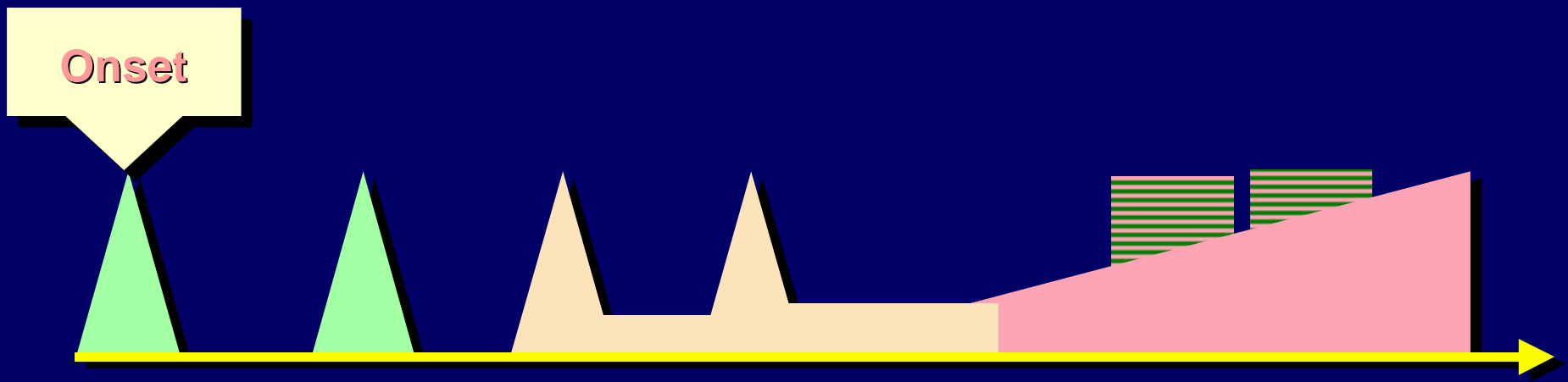
Onset

Relapse



Other epidemiological studies

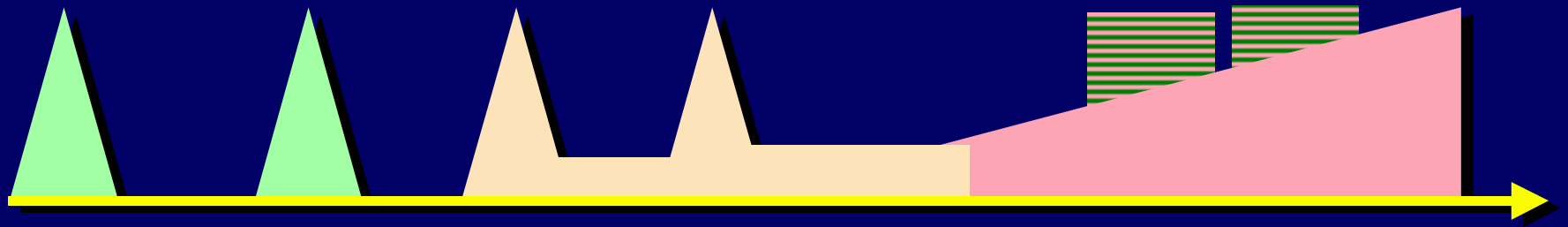
Vaccines



VACCIMUS Project

Vaccines

Relapse



VACCIMUS: Objective

- To assess whether vaccinations increase the risk of a relapse in patients with multiple sclerosis

Confavreux et al: NEJM 2001;344:319-326

VACCIMUS: Organisation

- Principal Investigators:
 - Pr Christian Confavreux (neurologist) CHU, Lyon, France
 - Pr Samy Suissa (epidemiologist), McGill University, Montreal, Canada.
- 6 participating centers (France-4; Spain, Switzerland)
- Monitoring: MAPI Clinical research
- Scientific Advisory Committee:
 - Dr Rachid Salmi, Université de Bordeaux
 - Dr Alastair Compston, Cambridge University, UK
 - Dr Elisabeth Miller, Public Health Laboratory, London, UK
- Funding: Aventis Pasteur and Aventis Pasteur MSD

Confavreux et al: NEJM 2001;344:319-326

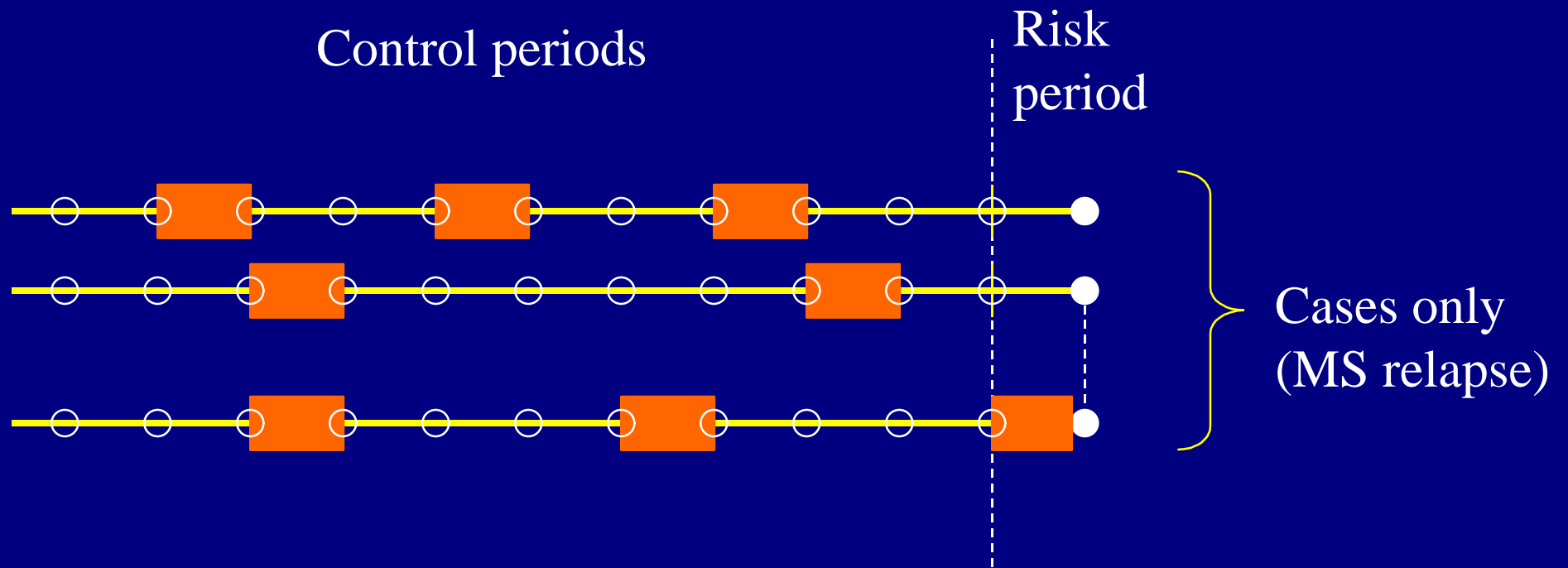
VACCIMUS: Design Challenges

- MS highly variable disease with unknown prognostic factors
- Cases of relapse relatively straightforward to identify
- Controls would be complex (variable relapse times, unmeasured confounding factors)
- Therefore: used a **case-crossover design**, similar to case-control study where cases are used as both cases and as their own controls

Case-crossover design

- Transient exposures (drugs, foods, activities)
- Acute risk: of equal magnitude and known effect-time after each exposure
- Cases only
- Rate ratio estimated by comparing exposures between risk period and control period(s)

Case-crossover design



VACCIMUS: Case identification

- Subjects with MS with a relapse occurring during 1993-1997
- Identified from computerised database from 6 of the European centers in the EDMUS network
- MS relapse definite or probable (Poser criteria)
- Consent letter for inclusion into study

Confavreux et al: NEJM 2001;344:319-326

VACCIMUS: Case definition

- **Index relapse:** First definite or probable MS relapse to occur during 1993-1997
- Medical record obtained to validate MS relapse
- Relapse followed by an outpatient visit or hospitalisation within 2 months of the onset
- Relapse preceded by a relapse-free period of 12 months or more

Confavreux et al: NEJM 2001;344:319-326

VACCIMUS: Exposure information

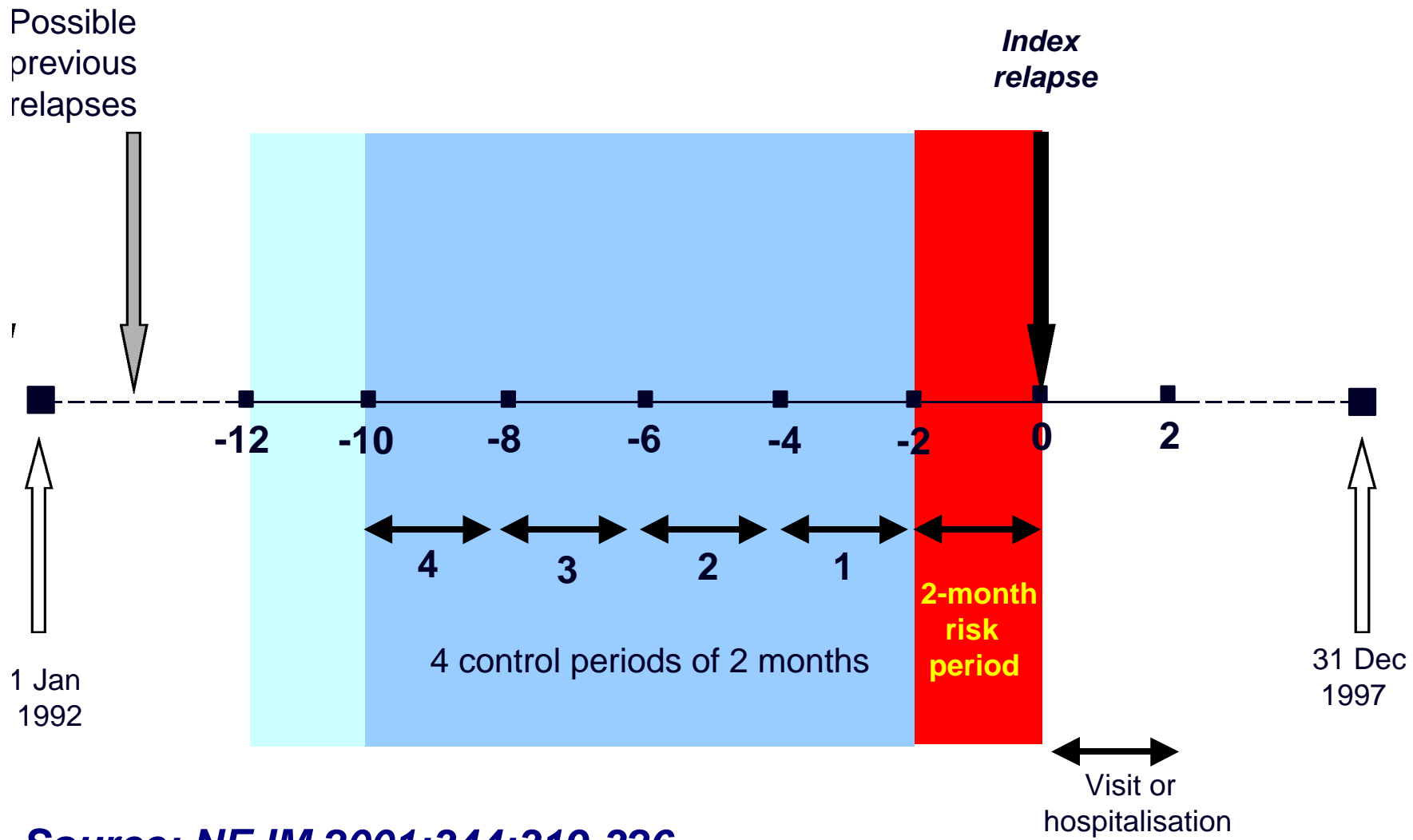
- Interviews and questionnaires to assess vaccination history (1992-97)
- Validation from vaccination records
- Sub-study among random sample of 97 subjects reporting no vaccination to confirm non-vaccination (0/89)

Confavreux et al: NEJM 2001;344:319-326

VACCIMUS: Design

- Case-crossover design
- Target 600 cases (RR=2; $\alpha = .05$; power=90%)
- A 2-month risk period
- Four 2-month control periods per subject (8 months)

VACCIMUS Study: Case-crossover design



Source: NEJM 2001;344:319-326

VACCIMUS: Subjects

- 1,037 eligible subjects identified in EDMUS with a relapse during 1993-97
- 1,009 were requested to participate
- 960 subjects accepted
- First 643 subjects included in the study

Confavreux et al: NEJM 2001;344:319-326

VACCIMUS: Vaccinations

- 260 subjects of the 643 (40%) with 1 or more confirmed vaccination in 1992-97
- 960 vaccinations reported between 1992-97
- 89 (14%) subjects received a vaccination during 12 months prior to onset of index relapse
- These patients received 135 vaccinations

Confavreux et al: NEJM 2001;344:319-326

Characteristics of 643 patients with a relapse of MS by vaccination

Characteristics	None (n=383)	1992-97 (n=260)	Prior year (n=89)
Female sex (%)	68%	72%	78%
Age at index relapse – years	39 \times 10	37 \times 11	37 \times 11
Last know Kutzke disability score			
Median	3	2	1
Range	0 – 8	0 – 9	0 – 7
Type of initial symptoms (%)			
Optic neuritis only	22	24	25
Brain-stem symptoms only	15	13	12
Long tract symptoms only	46	45	45
Mixed symptoms	15	17	16
Other or unknown	2	2	2

Source: NEJM 2001;344:319-326

Characteristics of 643 patients with a relapse of MS by vaccination

Characteristics	None (n=383)	1992-97 (n=260)	Prior year (n=89)
Course of disease – no. (%)			
Relapsing – remitting	73	80	82
Secondary progressive	24	17	16
Progressive relapsing	3	2	2
Years of disease at index relapse	9.5 \times 7.6	8.6 \times 7.4	8.6 \times 7.9
Median	7	6	7
Range	1–43	1–43	1–43
No. Of relapses prior to index relapse	3.9 \times 3.5	3.3 \times 3.0	3.0 \times 2.7
Median	3	2	2
Range	1–25	1-23	1-13


Source: NEJM 2001;344:319-326

Control prevalence of vaccination in the 12 months preceding the index relapse

Periods before the index relapse	Prevalence (%) (N=643)
1 – 2 month (risk period)	??
3 – 4 months (1 st control period)	3.0
5 – 6 months (2 nd control period)	2.8
7 – 8 months (3 rd control period)	4.0
9 – 10 months (4 th control period)	3.0
11 – 12 months	2.6

Source: NEJM 2001;344:319-326

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Source: NEJM 2001;344:319-326

Prevalence of vaccination in the study period preceding the index relapse

Periods before the index relapse	Prevalence (%) (N=643)
1 – 2 month (risk period)	2.3
3 – 4 months (1 st control period)	3.0
5 – 6 months (2 nd control period)	2.8
7 – 8 months (3 rd control period)	4.0
9 – 10 months (4 th control period)	3.0

Source: NEJM 2001;344:319-326

Two-month risk of relapse associated with exposure to specific vaccines

Type of vaccine	% Exposed		Rate ratio	
	Risk period	Control periods	(95 % CI)	
Any vaccine	2.3	3.2	0.71	(0.40–1.26)
Tetanus alone	0.6	0.8	0.75	(0.23–2.46)
Combined tetanus	0.3	1.2	0.22	(0.05–0.99)
Hepatitis B	0.6	0.9	0.67	(0.20–2.17)
Influenza	0.8	0.7	1.08	(0.37–3.10)

Source: NEJM 2001;344:319-326

VACCIMUS: Study limitations

- Study excludes patients with frequent relapses (within 12 months of each other; ~ 25% for a given episode), although must apply throughout entire 1993-97 period
- Study excludes minor relapses
- Power of 90% for rate ratio of 2 for all vaccines, but lower for specific vaccines
- Case-crossover design assumes constancy of exposure (shown) and equality of risk after each exposure (shown)

VACCIMUS: Study strengths

- Case-crossover design uses cases only and avoids difficulties of control selection and confounding often present in case-control studies
- Time-constant confounders adjusted for
- High response rate and validation of vaccination information
- Results unaffected by change in length of effect period
- High power for rate ratio of 2 for all vaccines

CONCLUSION

- Vaccination does not appear to increase the short-term risk of a relapse among patients with multiple sclerosis