Public Health England

Population-based post-licensure safety surveillance

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With thanks to Paddy Farrington, Open University for contributing some SCCS slides and Claudia Vellozzi CDC for some pharmacovigilance slides

ADVAC May 16th 2014

Aims of the lecture

- To cover the role of passive and active vaccine - pharmacovigilance and epidemiological surveillance /studies
- To cover how this is done in different settings
- To understand the main designs used
- To focus on the self controlled case series design and how it was developed in response to a practical problem

Already covered (Neal Halsey)

- Causality assessment
  - Bradford Hill
  - Trials, cohort, case-control, vaccine only, (case only), ecological, case-reports.
  - Individual level causality

- In this lecture we focus on pharmacovigilance and the self controlled case series method for assessing causality.

Vaccine Safety Assessment components

Vaccine Trials
reactogenicity

Licensure

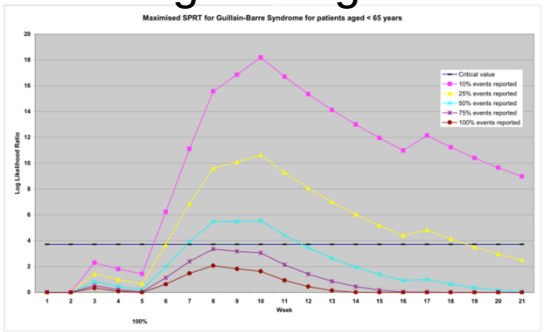
Pharmacovigilance
(passive/active):
hypothesis generation,
RAPID

Individual
causality
assessment

Epidemiological
studies
(hypothesis
testing)

Priority?

Signal
Strengthening

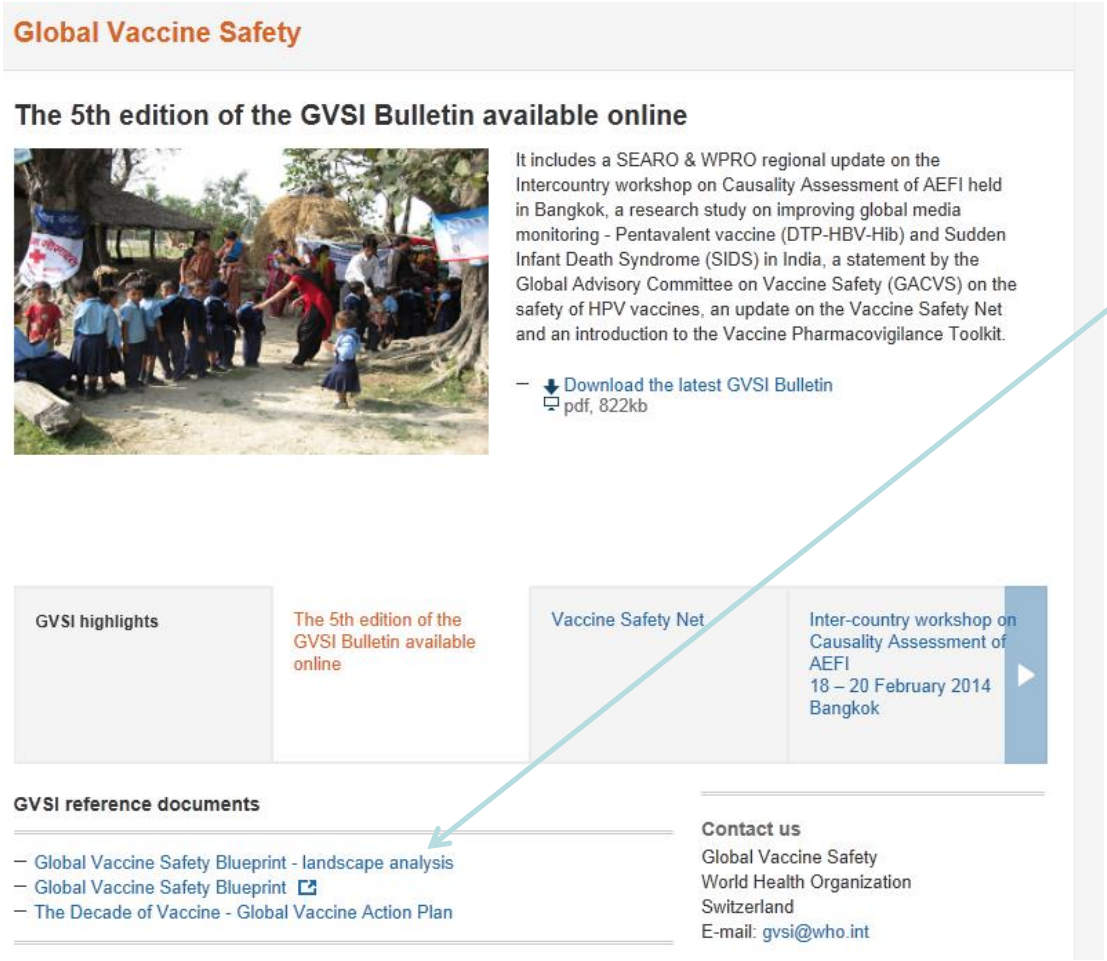


Plausiblility, other data/methods, experts, other risks, interval from vaccine,….

Vaccine Pharmacovigilance

"the science and activities relating to the detection, assessment, understanding, prevention and communication of adverse events following immunization" - Global Vaccine Safety Blueprint

WHO Global Vaccine Safety Initiative: See http://www.who.int/vaccine_safety/en/



Vision

"Effective vaccine pharmacovigilance systems are established in all countries."

Blueprint: Minimal Capacity for Vaccine Safety Surveillance

- A national dedicated vaccine pharmacovigilance capacity
- Health-care workers and others encouraged to report vaccine safety issues
- A reporting form for individual case safety reports
- A national database or system for collating, managing and retrieving AEFI reports
  - For example: signs/symptoms of adverse event coded and entered into database
- Harmonized methods and tools for the monitoring and investigation of AEFI
  - Brighton Collaboration* provides case definition and classification for many AEFIs

WHO/IVB/12.07; *www.BrightoncoIlarboration.org

Blueprint: Enhanced Capacity for Vaccine Safety Surveillance

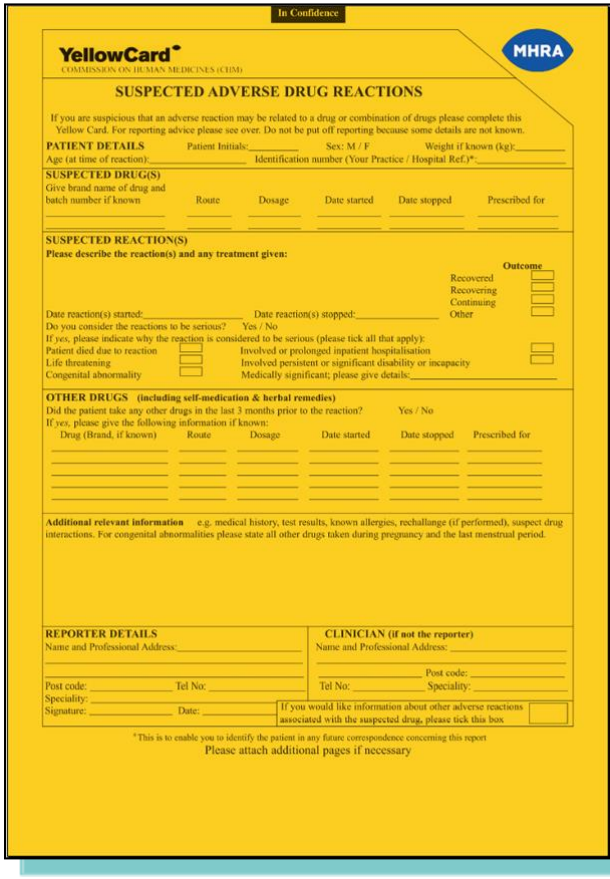
- The ability to carry out active surveillance rather than relying solely on spontaneous reporting of AEFI alone for the purpose of signal detection

- The ability to carry out epidemiological studies to test hypotheses

Detection -in Spontaneous Reporting systems

– **Pros and Cons**

- Real-time, rapid, permanent
- Easily-accessible, anyone can report
- Can detect very rare risks
- Under-reporting, subject to biases
- Cannot confirm causality



In Confidence

YellowCard
COMMISSION ON HUMAN MEDICINES (CHM)

MHRA

SUSPECTED ADVERSE DRUG REACTIONS

If you are suspicious that an adverse reaction may be related to a drug or combination of drugs please complete this Yellow Card. For reporting advice please see over. Do not be put off reporting because some details are not known.

PATIENT DETAILS Patient Initials:_____ Sex: M / F Weight if known (kg):_____
Age (at time of reaction):_____ Identification number (Your Practice / Hospital Ref.)*:_____

SUSPECTED DRUG(S)
Give brand name of drug and batch number if known | Route | Dosage | Date started | Date stopped | Prescribed for

SUSPECTED REACTION(S)
Please describe the reaction(s) and any treatment given:

Outcome
Recovered ☐
Recovering ☐
Continuing ☐
Other ☐

Date reaction(s) started:_____ Date reaction(s) stopped:_____
Do you consider the reactions to be serious? Yes / No
If yes, please indicate why the reaction is considered to be serious (please tick all that apply):
Patient died due to reaction ☐ Involved or prolonged inpatient hospitalisation ☐
Life threatening ☐ Involved persistent or significant disability or incapacity ☐
Congenital abnormality ☐ Medically significant; please give details:_____

OTHER DRUGS (including self-medication & herbal remedies)
Did the patient take any other drugs in the last 3 months prior to the reaction? Yes / No
If yes, please give the following information if known:
Drug (Brand, if known) | Route | Dosage | Date started | Date stopped | Prescribed for

Additional relevant information e.g. medical history, test results, known allergies, rechallange (if performed), suspect drug interactions. For congenital abnormalities please state all other drugs taken during pregnancy and the last menstrual period.

REPORTER DETAILS
Name and Professional Address:_____
Post code:_____ Tel No:_____
Speciality:_____
Signature:_____ Date:_____

CLINICIAN (if not the reporter)
Name and Professional Address:_____
Post code:_____
Tel No:_____ Speciality:_____

If you would like information about other adverse reactions associated with the suspected drug, please tick this box ☐

*This is to enable you to identify the patient in any future correspondence concerning this report

Please attach additional pages if necessary

Examples of vaccine Pharmacovigilance systems

- **UK – Yellow card** – long established system run by MHRA – no electronic and accepts reports from patients and heath care professionals. Publically available reports.
- **USA – VAERS** similar to UK – 30,000 reports per year. Run by CDC / FDA.
- **Brazil** - National system run by the Ministry of Health using 30,000 health centre. Events evaluated at state level and classified at the national level. There is an electronic database.
- To be effective it is essential to have high reporting rates

Detecting signals in Spontaneous Reporting systems

- Case counts – assess frequencies, trends, spikes…
- Careful clinical review (severe events)
- Observed – Expected rates
  - Expected from external data source – can be done sequentially using sequential methods to reduce false positives.
- Data mining – disproportionality analysis*
  - e.g. 10% of all adverse events reported after MMR are convulsions compared to 5% of all adverse events after other vaccinations. Proportional reporting ratio = 2. Test with chi-square.
  - Use Empirical Bayesian Data Mining** to reduce false alerts (from expected small numbers) based on a prior distribution. (Bayesian shrinkage).

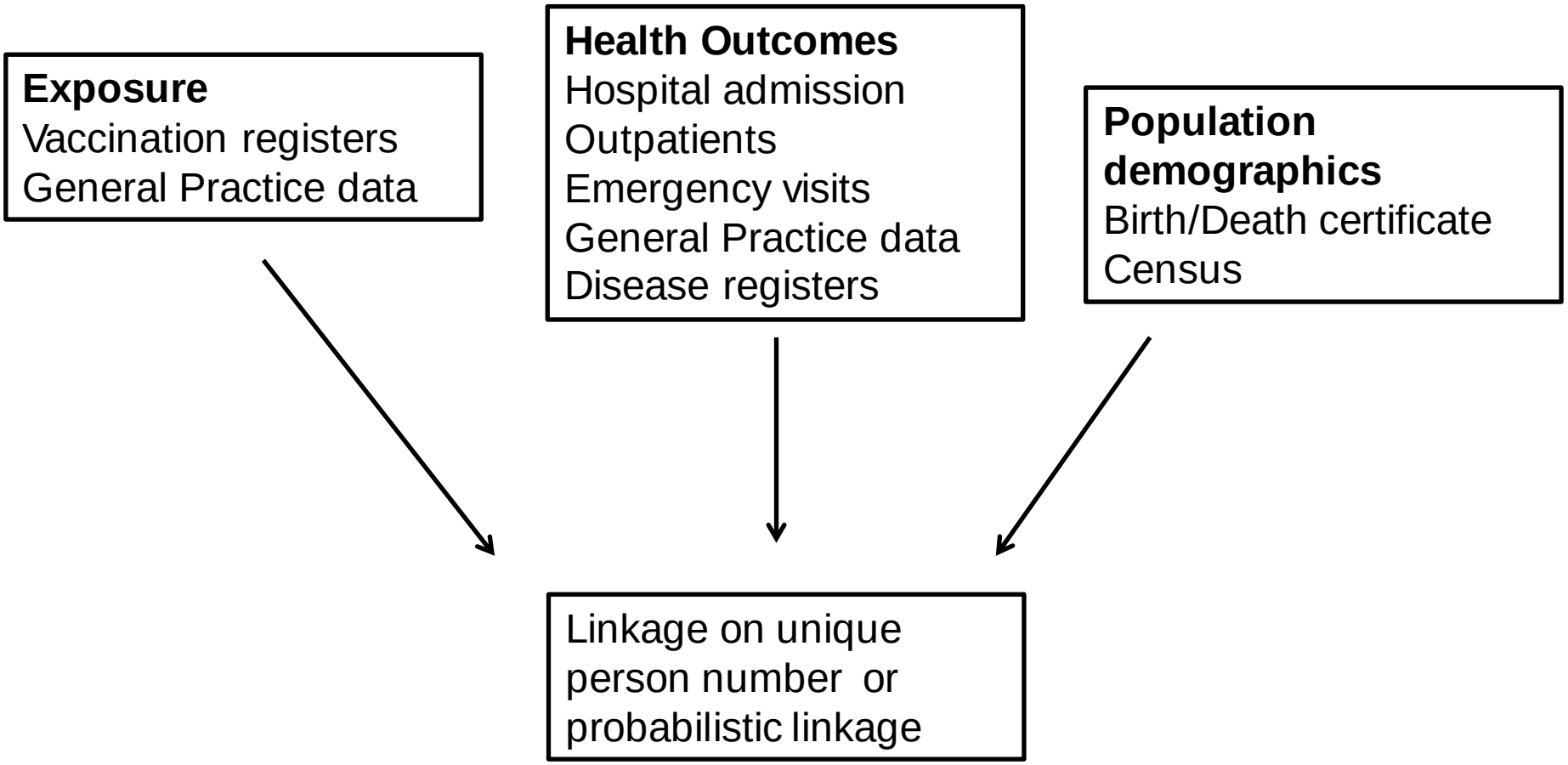
***Evans SJW, Waller PC, Davis S (2001). *Pharmacoepidemiology and Drug Safety* 10:483-6.**

****Banks D, Woo J, Burwen DR, et al (2005). *Pharmacoepidemiology and Drug Safety* 14:601-609.**

Active surveillance

- Large linked databases for active surveillance
  - USA - Vaccine Safety Datalink –
    - rapid cycle analysis using managed care organisation data.
  - UK Clinical Practice Research Datalink (CPRD) –
    - recently used for maternal pertussis
  - Other countries have databases where this might be done (Denmark, Australia, Finland..)
- Hospital based active reporting
  - Canada – IMPACT system
    - Covers 80% of all paediatric admissions
    - Special nurses scrutinise all admissions for possible adverse events (and vaccine preventable diseases)
    - Causality assessment largely based on biological plausibility
- Active follow up of a cohort

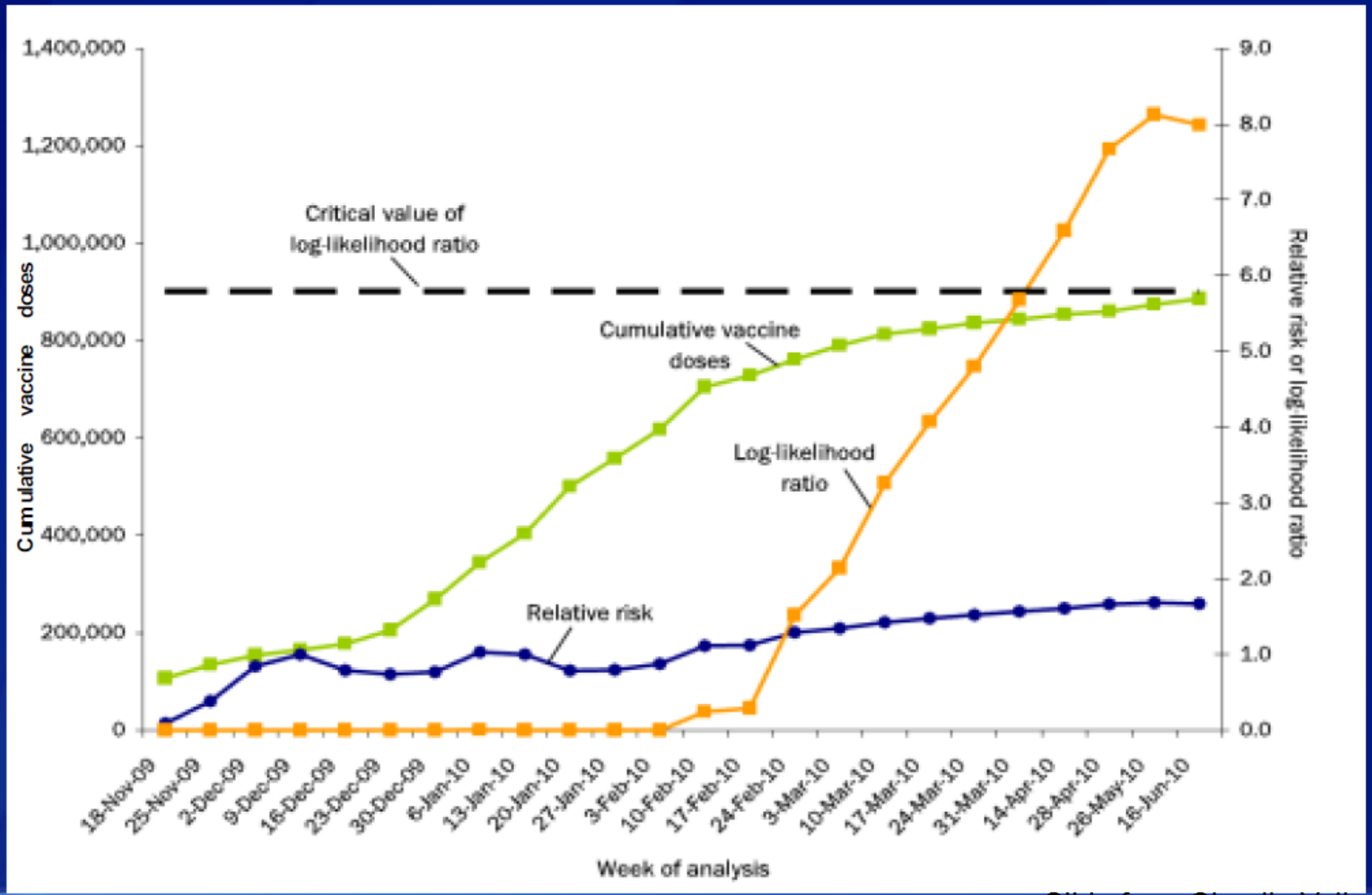
Large Linked Databases



Methods for detection in large linked databases

- Start with a list of events of interest (e.g. 30 events)
- Compare cumulative reports to a comparison group
  - Historical incidence
  - Concurrent cohort (unvaccinated)
  - Self controlled design (see later)
- Use Sequential monitoring (sequential probability ratio tests) – Rapid Cycle Analysis

Statistical test for sequential monitoring: log-likelihood ratio and relative risk following 2009 H1N1 inactivated vaccine of Bell's palsy for adults ≥25 years.



Lee G, et al AJPM 2011

Slide from Claudia Vellozzi

Many other sources of safety signals

- Case-reports (literature, medical specialists, media, internet…)
- Clinical trials
- Biological mechanism
- Ecological studies
- Reports from other countries

Signal assessment

- Most signals will not need a full epidemiological study
- Interim assessment (signal strengthening)
  - Similar data in other countries, other data sources / analysis methods, plausibility, other causes (individual causality), expert review
- Prioritisation and refinement
  - Severe, new, large numbers given vaccine, size of risk, vaccine still in use, public/media/political interest, affect on coverage, alternatives…
  - What exactly is the hypothesis to be tested in a formal study…

Three Examples (from many…)

- Pandemrix and narcolepsy 2010: Sweden - detected in passive reports, Finland by clinicians.
- Hypersensitivity reactions in a national MMR campaign in Brazil – 2004 (Frietas et al vaccine 2013)
  - Detected in passive surveillance
  - Interim assessment
  - Rates compared between manufacturers
  - Manufacturer "A" rate 15.3 per 100,000 doses vs 1.2 and 0.6 for other manufactures
  - Recall of Brand A
- Deaths following PCV7 and Hib Vaccines in Japan 2011
  - Vaccines withdrawn
  - Rates compared to other countries (similar) and expert review of the 7 deaths with no clear causality.
  - Vaccine re-instated after 4 weeks

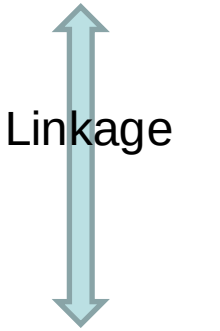
Epidemiological assessment

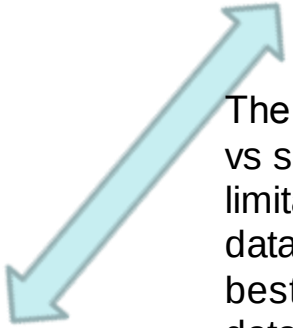
Main epidemiological designs used for safety assessment

- **Cohort**
  - Prospective parallel group, historical
- **Case-control**
  - Usually matched by the date of the event in the case.
- **Case only**
  - Self controlled case-series (SCCS) - MORE DETIALS TO FOLLOW…
  - Case cross-over
- **Case-coverage** (case-cohort) – see extra slides for UK study of pandemrix and narcolepsy – odds of vaccination in cases from all of England compared to the odds of vaccination in the population (matched by time period and risk factors) using data from about 100 general practices across England.

Design and data sources for epidemiological -studies

- The design will depend on the precise question and the data sources available.
- As with all epi-studies it is important to have a precise question (as is possible), case-definition (strict/less strict), exposure risk (and interval post vaccination), population of interest and likely important confounding variables.
- Data sources…..
  - Immunisation registries
  - Disease registers
  - Hospital Episode databases
  - Individual Hospital data
  - General Practice databases
  - Health Maintenance data bases
  - Prospective cohorts (e.g. whole birth cohorts followed up)





The “ideal” design vs strengths/ limitations of datasourses and best design for data available

Same question – different designs – Pandemic flu and narcolepsy / Gullaine Barré Syndrome

- Narcolepsy
  - Finland – cohort using linked national hospital data
  - France – case-control with controls from the same hospitals as cases
  - UK – case-coverage, cases from sleep centres, coverage from GP data
- GBS
  - US – PRISM/VSD - various case only designs
  - UK – SCCS using hospital admissions and GP vaccine records
  - Global collaboration (Dodd et al, 2013 – Global Vaccine Safety datanet) – 10 countries. hospital admission databases, individual hospital logs, neurologist reporting, GP data. SCCS analysis
  - European collaboration (Dieleman et al, 2013) VAESCO) – Case control and SCCS on various data sources (hospital / GP) from 5 countries

Denmark – National linkage

- In Denmark linkage of Disease registers, vaccine registers, hospital data and much more is possible using the Central Person Registry number. The CPR also contains data on demographics and vital status, emigration, disappearance.

- Many vaccine safety cohort studies published (e.g. MMR-Autism – Madsen et al)

- Demonstrates the huge potential of national linked data/

The origins of the SCCS method

- Solving a practical problem by Paddy Farrington

SCCS: Why was the method developed?

- UK 1992: the MMR vaccine has been in use for 5 years.
- Cases of viral meningitis are reported soon after receipt of MMR vaccines containing the Urabe mumps strain.
- Discharge data from the administrative databases of 5 hospitals are searched.
- 32 cases of viral meningitis in children aged 12 – 24 months are identified.
- 13 of these had onsets 15 – 35 days after an MMR vaccine.

Is there an association between MMR vaccine and aseptic meningitis?

What was to be done?

- The catchment areas of the 5 hospitals were ill-defined.
- So a retrospective cohort study did not appear to be possible,
- … and the selection of controls from the cohort was prone to bias.
- A case-control study would have been difficult to undertake.
- And in any case results were needed rapidly.

Could a valid epidemiological study be based only on cases, that is, on children with viral meningitis?

What happened

- The case-series method was developed at PHE (HPA / PHLS) by Paddy Farrington and an increased risk shown.
- Urabe-containing MMR vaccines were withdrawn.
- A confirmatory record-linkage SCCS study was undertaken.

	Cases	*RI* in 15-35 day period after MMR
Febrile Convulsion or Aseptic Meningitis	1062	1.51 (1.21, 1.90)
Aseptic Meninigitis	7	38.1 (4.3, 336)

Farrington *et al* (1995), *Lancet*

What is the case series method?

- It is a conditional cohort method: exposures are regarded as fixed, event times as random.
- Follow-up is not censored at event.
- The method can be used with independent recurrent events, or uncommon non-recurrent events.
- Only cases are required: estimation is within-individuals.
- Cases must clearly be an unbiased set of cases (not any collection of cases!)
- The analysis is self-matched, thus eliminating the effect of fixed confounders.
- It has been programmed in standard statistics packages.

Main advantages

- Only cases are required, hence data are relatively easy and cheap to assemble.
- All fixed confounders are controlled.
- Temporal variation in the event rate is explicitly modelled as in a cohort study.
- Independent recurrences can be handled in the same framework.
- Exposures need not be transient.
- Power is often good.

Main limitations

- Only estimates of relative risk are available - absolute risks are not estimated.
- Occurrence of an event should not appreciably increase mortality.*
- Occurrence of an event should not affect subsequent exposure history.*

* Recent developments extend applicability of the method to situations where these last conditions are not met, but at the cost of greater methodological complexity.

Using only cases:

Relative incidence of convulsions in 2nd week after measles vaccine

USA study (Barlow *et al* 2001)	2.83 (1.44, 5.55)
UK study (Farrington *et al* 1995)	3.04 (2.27, 4.07)

Cohort study, 679 942 kids

Case series, 952 cases

Controlling confounding:

Asthma exacerbation and flu vaccine

Kramarz *et al, Arch. Fam. Med*. 2000, 9: 617 – 623

Cohort and case series studies in asthmatic children aged 1 – 6 years in 1995/6. Risk period: 2 weeks after flu vaccine.

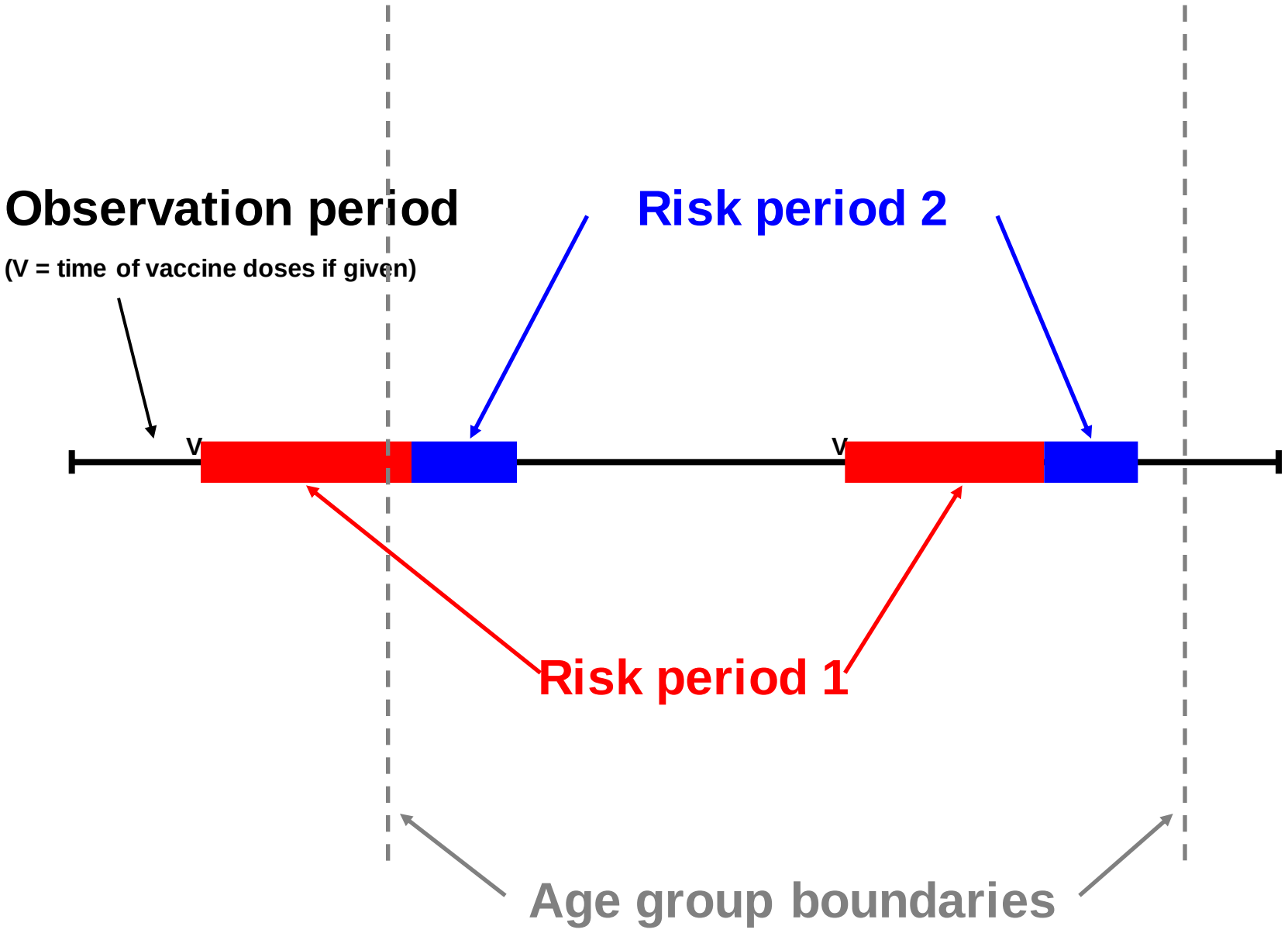
Method	Sample size	*RI*	95% *CI*
Cohort, unadjusted	70 753	3.29	(2.55, 4.15)
Cohort, adjusted	70 753	1.39	(1.08, 1.77)
Case series	2075 cases	0.98	(0.76, 1.27)

The cohort results are subject to indication bias. The case series results are unaffected by this bias.

How does it work?

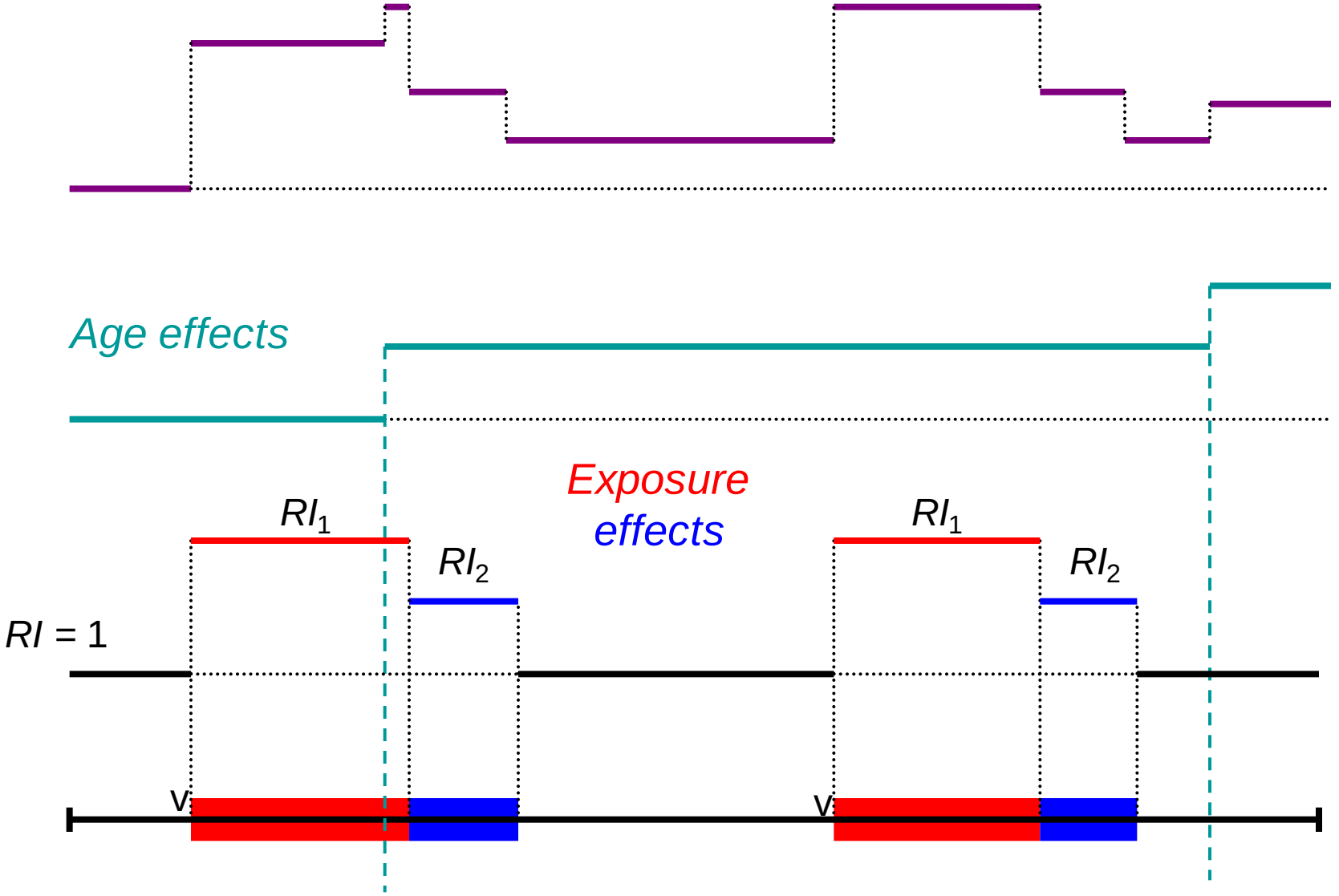
(pictures to follow!)

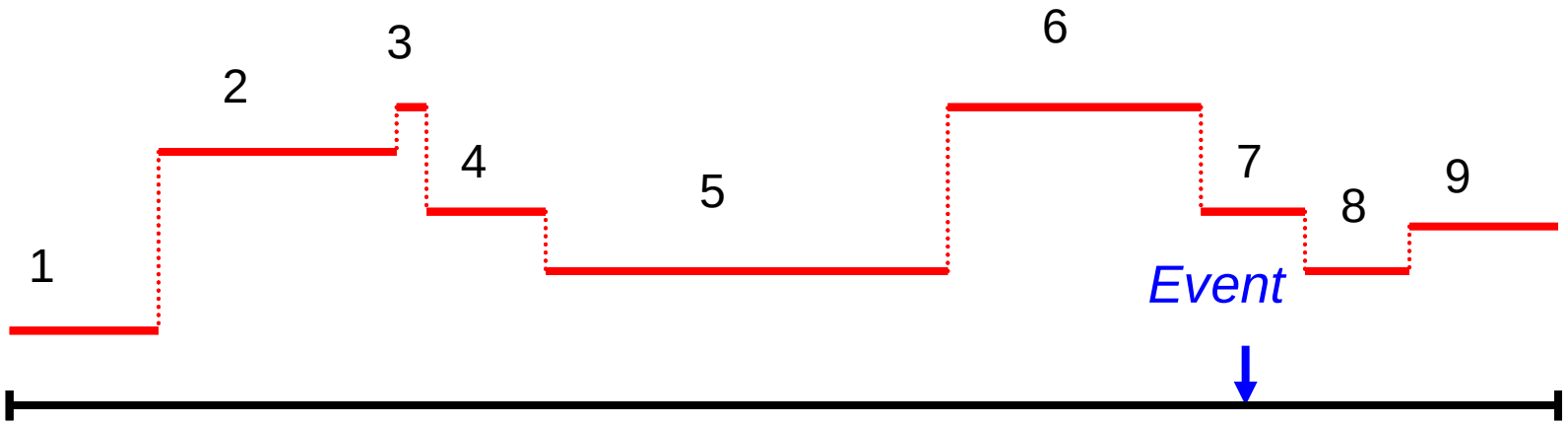
- Fix an observation period, over which events are ascertained; the individuals with events are the cases.
- For each case obtain all exposures within that period.
- Subdivide the observation periods into exposure and age groups (and other time varying confounders).
- As in a cohort study, these are treated as fixed. Unlike most cohort studies, exposures may be post-event.
- For each case, regard the interval in which the event occurs as random.
- The statistical model is product multinomial, which can be fitted by conditional Poisson regression.


Observation period
(V = time of vaccine doses if given)
Risk period 2
V
V
Risk period 1
Age group boundaries

Overall relative incidence profile.

(We estimate RI_1, RI_2 and age effects given time of the events)





Data table for fitting as a conditional Poisson model

Indiv	*Interval*	*Length*	*Age*	*Exposure*	*Events*
1	1	19	1	1	0
1	2	30	1	2	0
…	…	…	…	…	…
1	7	12	2	3	1
1	8	13	2	1	0
1	9	19	3	1	0

Stata code example: xtpoisson events i.exposure i.age, fe i(indiv) offset(log(length))

Example: GBS, flu vaccine and flu-like illness

Stowe *et al*, *Am. J. Epidemiol.* 2008, 169: 382 - 388

Data source: General Practice Research Database (GPRD)

Observation period: all time within GPRD in 1990 – 2005

Two types of exposures: flu vaccination and flu-like illness.

Risk periods: 0-30, 31-60, 61-90 days after vaccine/onset

Pre-exposure risk period: 2 weeks

Age groups: 12 periods over 0 – 115 years

Seasonal groups: calendar month

Repeat episodes: included if > 6 months separation

Results

775 distinct episodes in 690 individuals

Flu vaccine:

0 – 30 days: RI = 0.58 (0.18, 1.86)

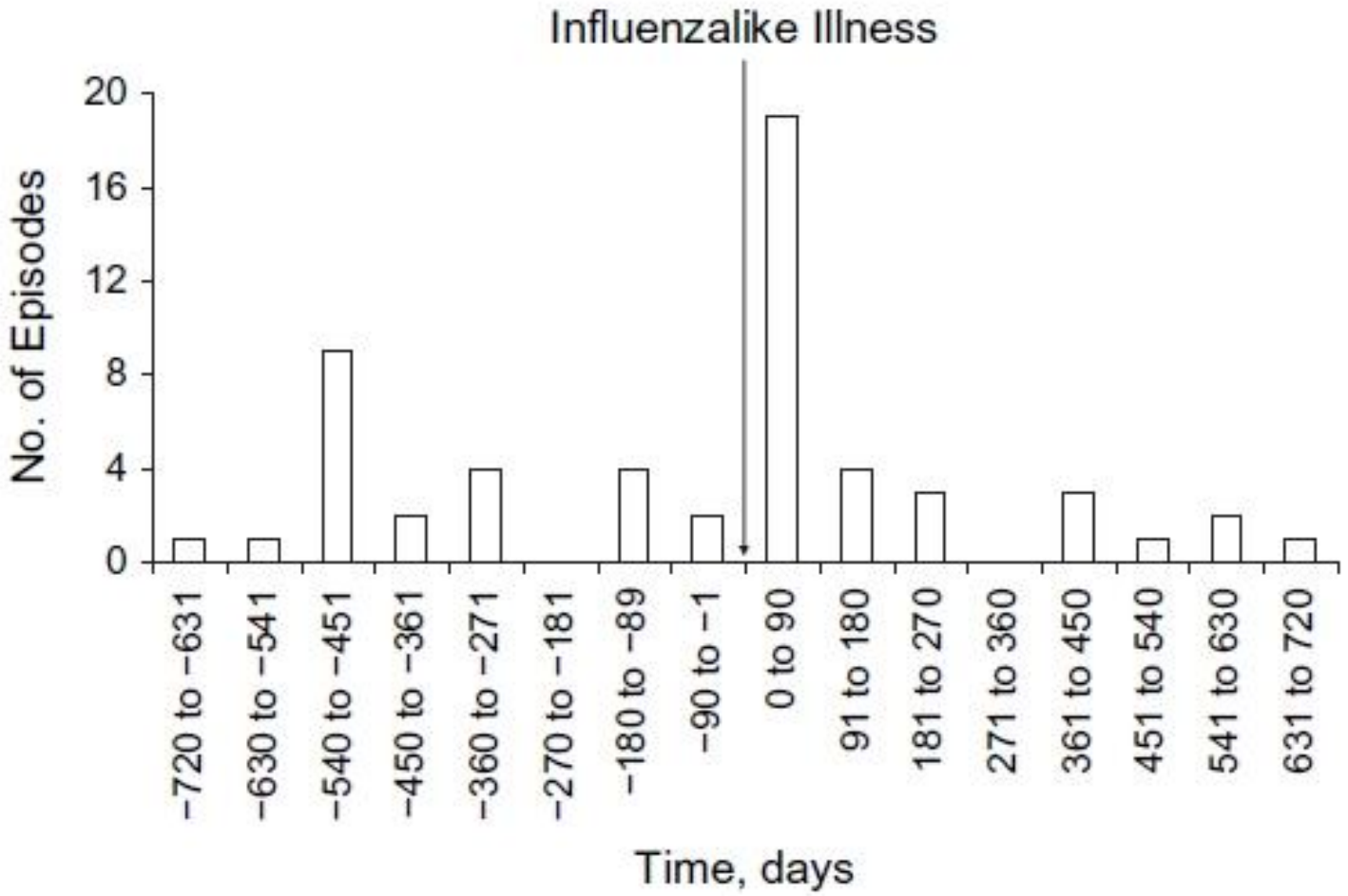
0 – 90 days: RI = 0.76 (0.41, 1.40)

Influenza-like illness:

0 – 30 days: RI = 16.64 (9.37, 29.54)

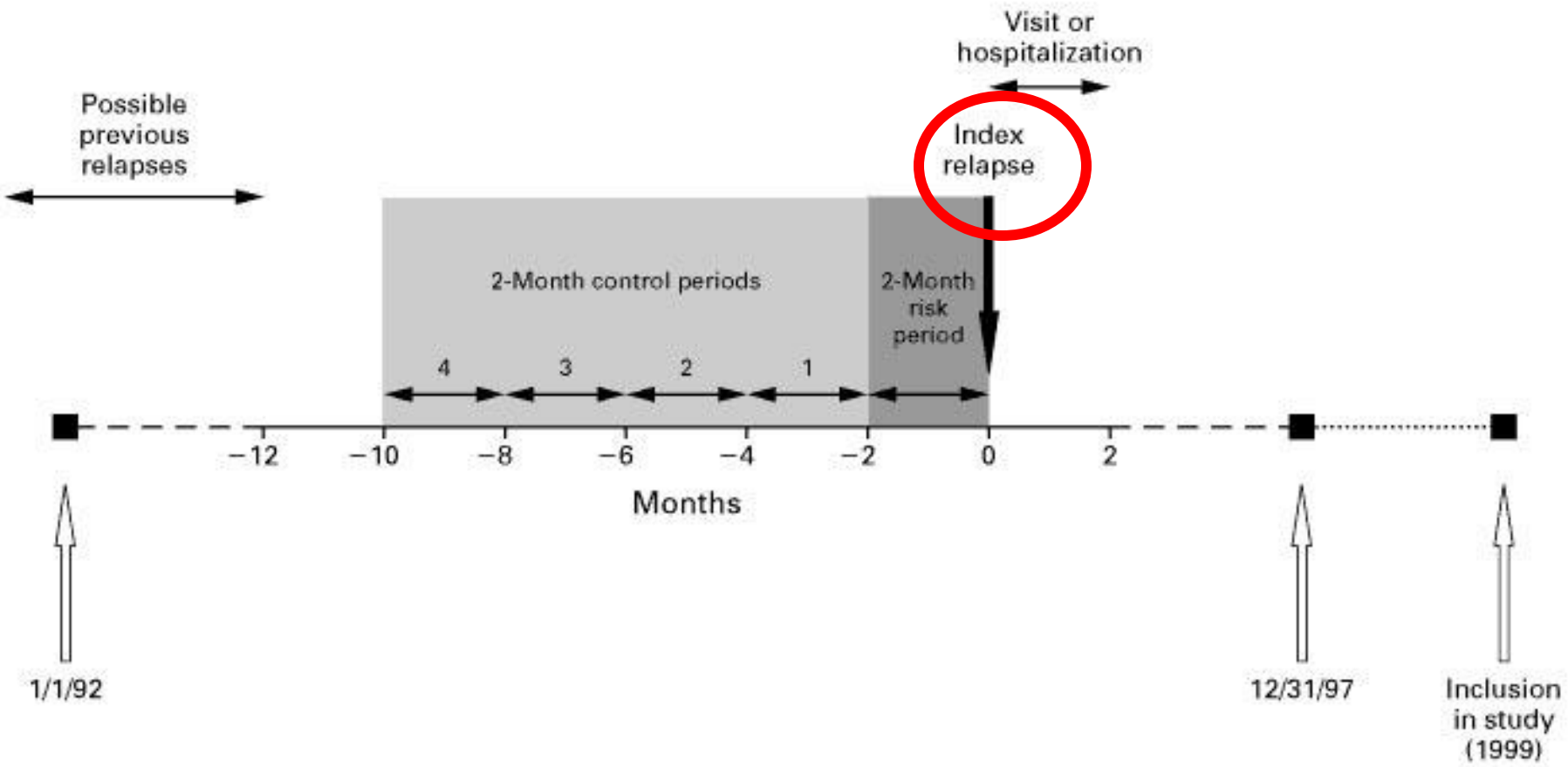
0 – 90 days: RI = 7.35 (4.36, 12.38)

Interval between influenza-like illness and GBS



From: Stowe *et al*, *Am. J. Epidemiol.* 2008, 169: 382 - 388

Case Cross-over study: For people with MS, are relapses associated with vaccines? (slide thanks to Neal Halsey)



Confavreux C et al. N Engl J Med 2001;344:319-326

TABLE 3. RISK OF RELAPSE ASSOCIATED WITH EXPOSURE TO SPECIFIC VACCINES IN THE TWO MONTHS PRECEDING A RELAPSE IN 643 PATIENTS WITH MULTIPLE SCLEROSIS.*

TYPE OF VACCINE	PERCENT EXPOSED		RELATIVE RISK (95 PERCENT CONFIDENCE INTERVAL)
	RISK PERIOD	CONTROL PERIODS	
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)
Monovalent vaccines	2.0	2.3	0.92 (0.49–1.74)
Combined vaccines	0.3	1.1	0.26 (0.06–1.12)

*For each patient there was one risk period and four control periods.

ANALYSIS IS CONDITIONAL LOGISTIC REGRESSION.

The NEW ENGLAND JOURNAL of MEDICINE

Exposures and outcomes investigated using SCCS

Exposure	Outcome
Pregnancy	TB
Infections	Hip fracture
Flying	Stroke
Antipsychotics	Death
Statins	Nephrotic syndrome
Invasive dental treatment	Bells Palsy
Foot ulceration	DVT
Bupropion	Gait disturbance
Strontium ranelate	Bacterial infection
Antidepressants	Asthma
Many vaccines	Convulsions,
	GBS, Autism, ITP, Aseptic Meningitis…..

All need careful consideration of the assumptions of SCCS

Summary

- Pharmacovigilance and individual causality assessments help identify signals and rapidly evaluate them.
- Population based epidemiological studies are important to help assess causality
- Optimal design depends on question and data sources
- Large linked data bases are the future BUT how do we use them best – detection vs testing!

EXTRA SLIDES: Useful resources

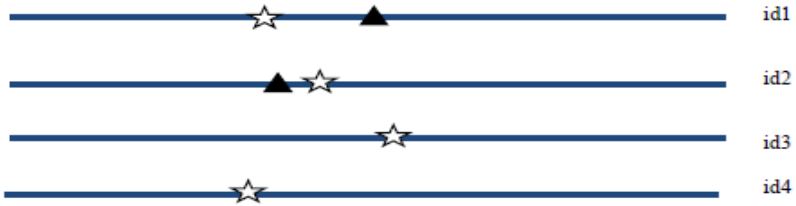
- **WHO Global Vaccine Safety Initiative:** http://www.who.int/vaccine_safety/en/
- **FDA:** Guidance for Industry Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment http://www.fda.gov/cder/guidance/index.htm

- **ADVANCE** consortium looking at vaccine benefit risk http://www.advance-vaccines.eu/

- **SCCS Website:** http://statistics.open.ac.uk/sccs Created by Heather Whitaker – to be updated in the next year or so…
- **Tutorial paper:** Whitaker et al., *Statist. Med.* 2006, 25: 1768 – 1797
- **Useful overview of case-only methods:** Farrington, Vaccine 2005, 2064-70. Control without separate controls:…

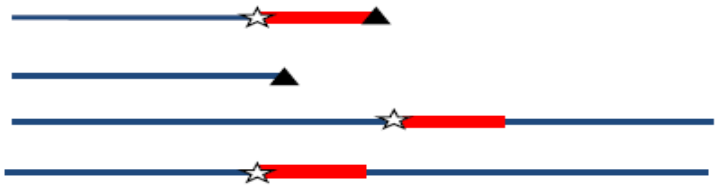
Comparing designs

The exposure and event history for four individuals



Blue line is 200 days person follow-up time; star is vaccination time and triangle event time.

Cohort



Rate of events in 30 day post vaccination risk period (red) compared to non-risk period (blue), follow-up stops at an event (if non recurrent). Poisson regression or survival analysis can be used.

Matched case-control

Cases are matched to non-cases (for example id 1 to 3 and id 2 to 4) and the odds of vaccination in the 30 days prior to the case event time (orange) compared using conditional logistic regression.

Case-crossover

Just using cases (id 1 & 2) the odds of vaccination in 30 days prior to the event time (orange) is compared to the previous 30 day period (green) using conditional logistic regression.

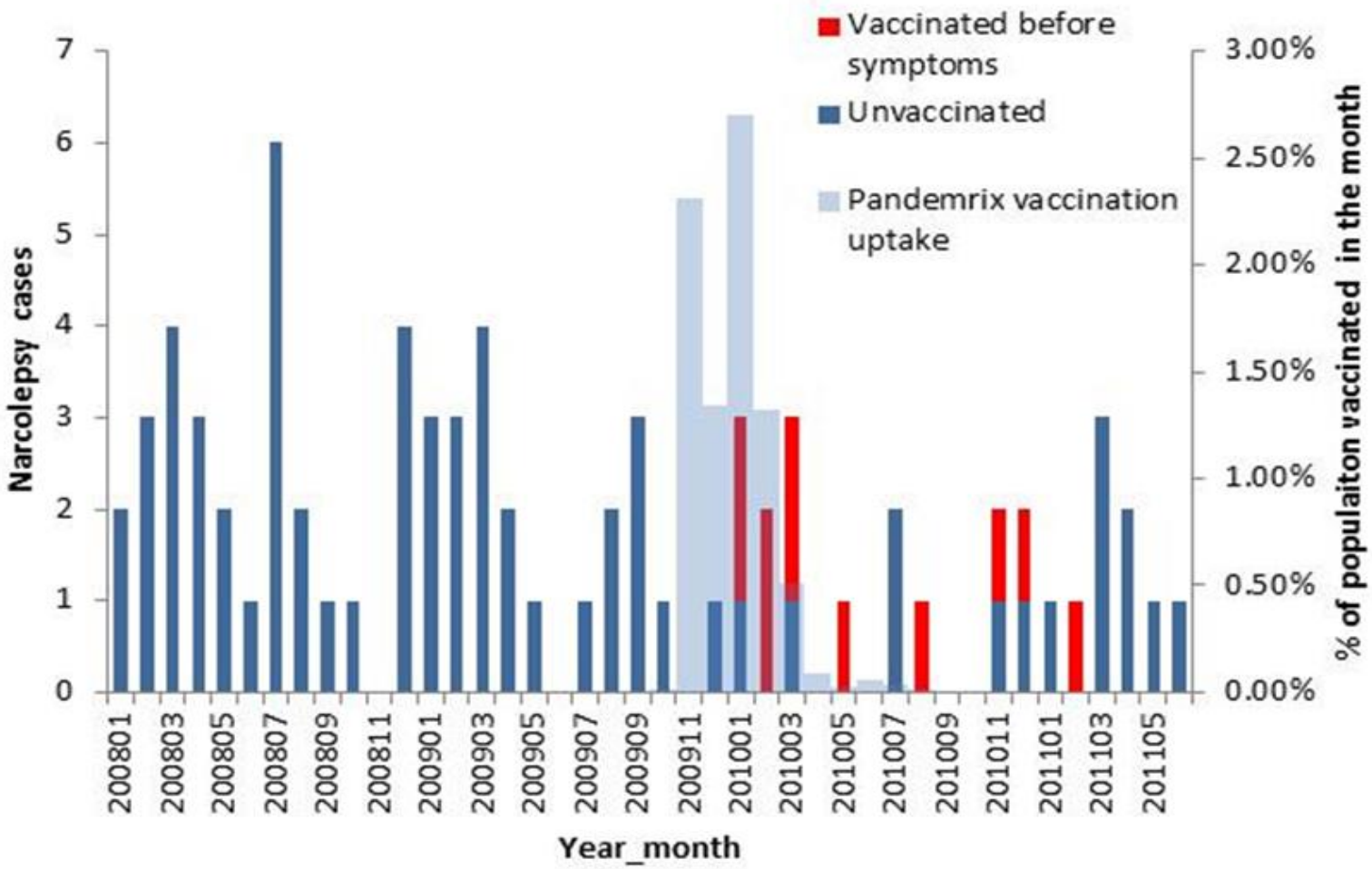
SCCS

Just using cases (id 1 & 2) event rate 30 days post vaccination (red) compared to non-risk period (blue) using conditional Poisson regression.

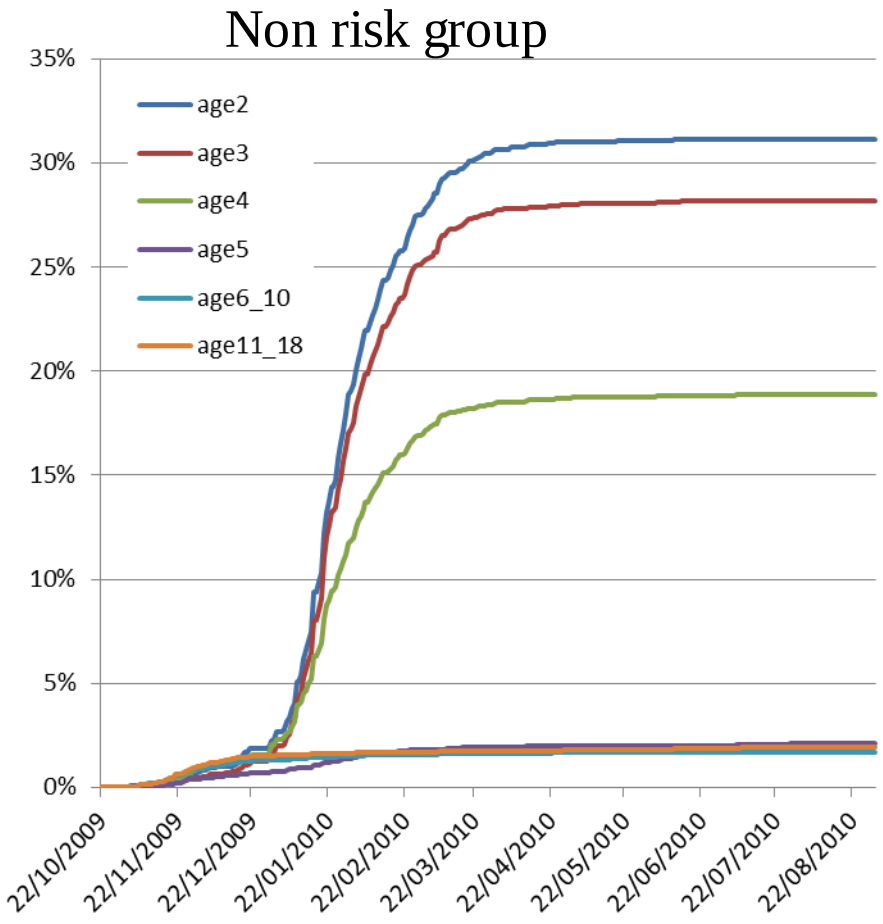
Pandemrix H1n1 2009 vaccine and narcolepsy in England (Miller et al, Lancet, 2013)

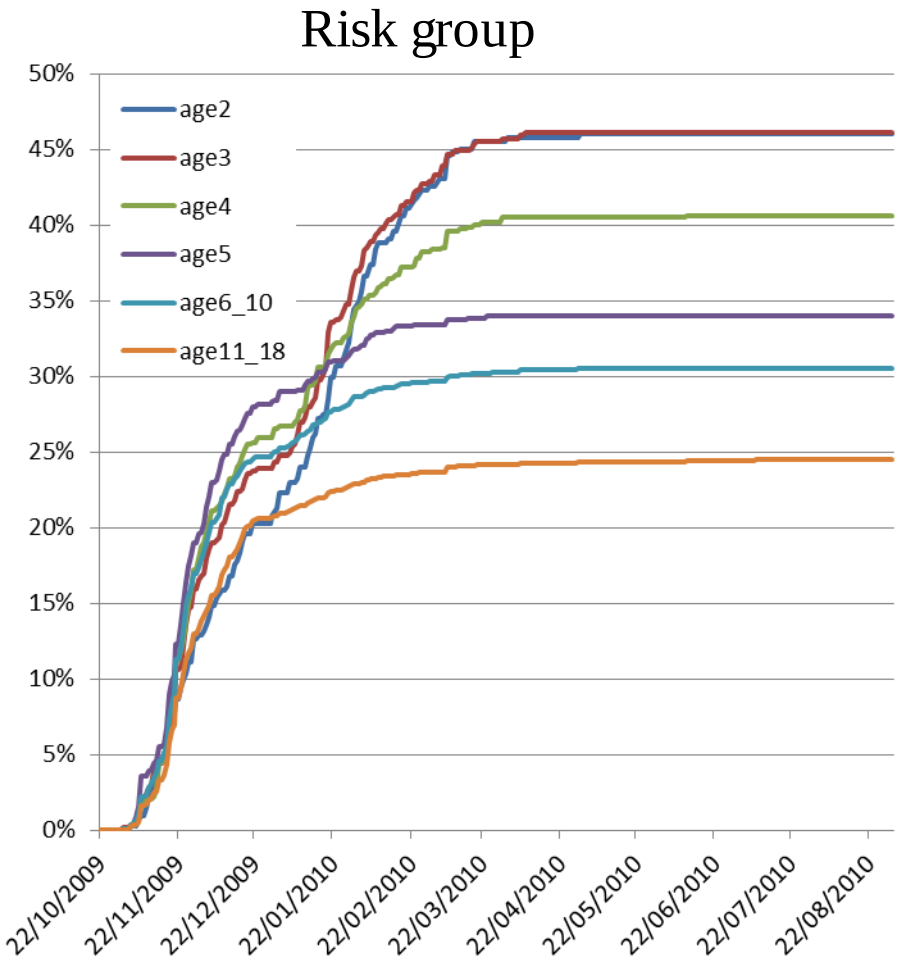
- Cases data obtained on children aged 4-18 from sleep clinics. Onset 2008-2011, diagnosed by mid 2011.
- Vaccination history from GPs
- Design
  - Case-coverage design comparing proportion of cases vaccinated to age, period matched population data from 100 GP practices.
  - Analysis by logistic regression with an “offset” in the model for the log-odds of the matched population coverage.

Cases by onset date and vaccination status



Coverage data for pandemic vaccine from primary care databases in England





Results

- Case Coverage
  - Of 17 cases in the post vaccine period 10 were vaccinated (matched coverage about 16%)
  - OR 14.4, 95% CI (4.3-48.5)