



Epidemiological designs for vaccine safety assessment: methods and pitfalls

Nick Andrews, Statistics Unit, Health
Protection Services, Health Protection
Agency, UK



Outline

- Introduction
- Defining the question
- Data sources
- Design issues
- Statistical methods and pitfalls (with example of MMR and autism)

Introduction

- Clinical trials may not identify rare adverse events
- Vaccine safety signals or issues may arise from a number of sources
 - Pharmacovigilance (UK yellow card)
 - Clinical trials (e.g. one or two events seen but not significant).
 - Biological mechanism
 - Events seen with other vaccines
 - Ad-hoc reports
 - Data mining
- Post-licensure surveillance of safety is essential
- Use of routine data sources along with appropriate statistical methods can provide an efficient way to investigate signals.
- However there are pitfalls

Defining the question

- It is important to define the safety question as precisely as possible, without being too restrictive. This will effect the possible design.
- Key factors are:
 - Exposure (e.g. specific manufacturer)
 - Case definition (how specific to be?)
 - Risk period (any time, <6 weeks...)
 - Size of effect that is important
 - The population of interest
- It may be necessary to specify sensitivity analyses where the question is not specific – but too many may mean false positives.

Example – OPV and Intussusceptions (Andrews et al EJE 2001)

- Looked at 3 risk periods (0-13,14-27,28-41 days) after each of three doses (9 periods) and also overall.
- 14-27 days post dose 3 had $RI = 2.15$ 95% CI (1.25-3.69). No other period had a raised RI
- Multiple testing.
- Repeated the study using two more data sets. $RI = 1.03$ (0.64-1.67) for this period

Data sources (case ascertainment)

- How can you identify cases in an unbiased way? What is the comparator (control)?
- How are vaccination data obtained?
- Routine data sources:
 - Immunisation registers
 - Hospital
 - General practice (physician) databases
 - Health Maintenance / Insurance
 - Specialist networks
 - Disease registers
 - Longitudinal databases

Issues to consider with a data source

- Case definition & validation
- Size
- Patient follow-up
- Data completeness / quality
- Linkage to immunisation data
- Availability of confounding variables
- Possible biases
- Population covered

Design Issues (all methods)

- Three major areas:
- Bias in case and exposure ascertainment
- Important confounders
- Case definition specificity

Bias in case and exposure ascertainment

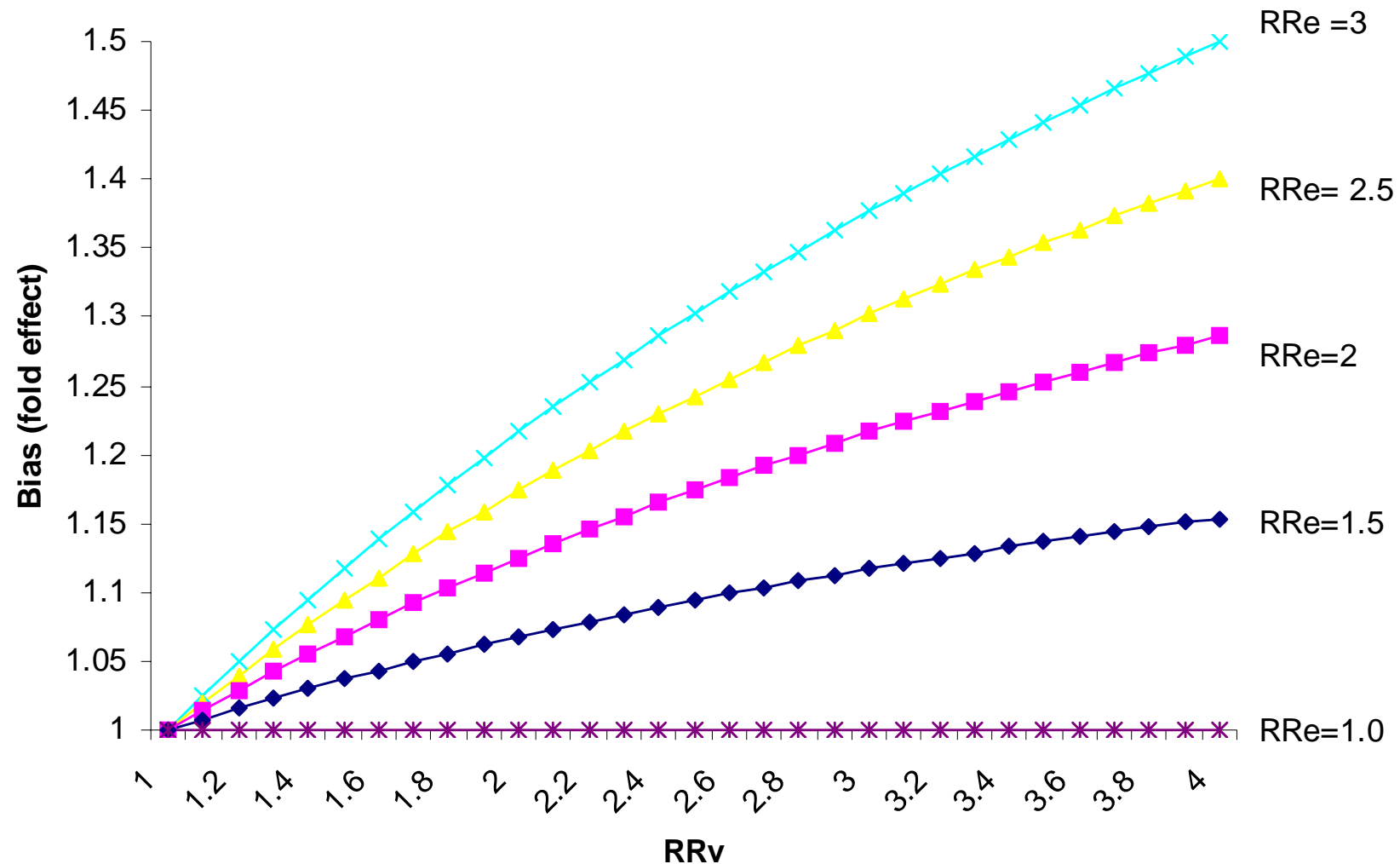
- Eg. Media scare or keen specialist
- Vaccinated cases more likely to be reported than unvaccinated cases.
- Vaccine histories sought more carefully in cases than non-cases.
- Patient or parental recall of vaccine history more likely in cases.
- Ideally use databases or insure complete reporting.
- Use vaccine registries.

Important confounders

- Don't over complicate the question by collecting too much information.
- List possible confounders and estimate how important they might be
 - Depends on possible strength of association with vaccine and event and how common the confounder is.

Relative bias on vaccine risk according to RR of event (RRe) and of vaccination (RRv) in unmeasured confounder (using formulae in Lin et al Biometrics 1998)

[For 10% population vaccinated and 20% population having confounder]



Example DTP and SIDS (from Fine and Chen 1992, AJE)

- Studies generally found SIDS less likely in those vaccinated – particularly in the short interval post vaccination.
- However most likely confounders would tend to lead to under estimates (socio-economic, young mother, mother smoking). Studies did try to take these into account.
- Also the healthy vaccinee effect would lead to an under-estimate due to delayed vaccination.
- Lack of an association difficult to interpret.

Case definition specificity

- Lack of specificity will reduce RR estimates
- E.g. True RR=2 and 50% specific case definition gives observed RR= 1.5.
- Note however that attributable risk estimate is unaffected.
- If specificity is non-differential by vaccination status then this is more serious (may not just reduce RR).

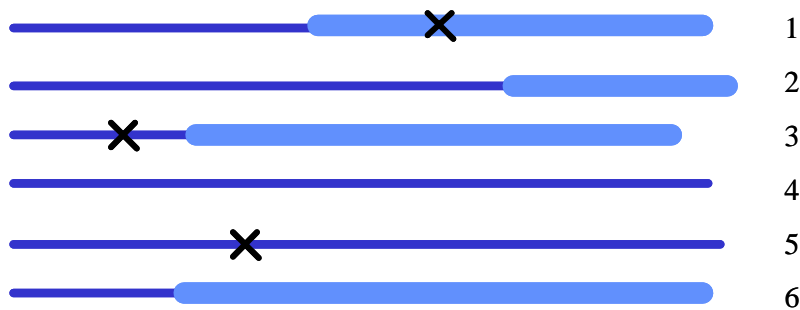
Other design Issues

- Independence of events within individuals
- Study power
- Most appropriate statistical method(s) for analysis
- Statistical analysis plan

Methods

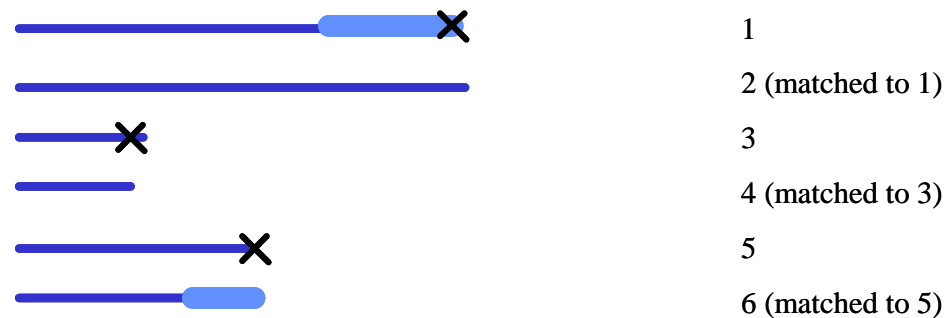
- Cohort (historical)
- Case-control
- Case-only: self controlled case series (SCCS)

Cohort



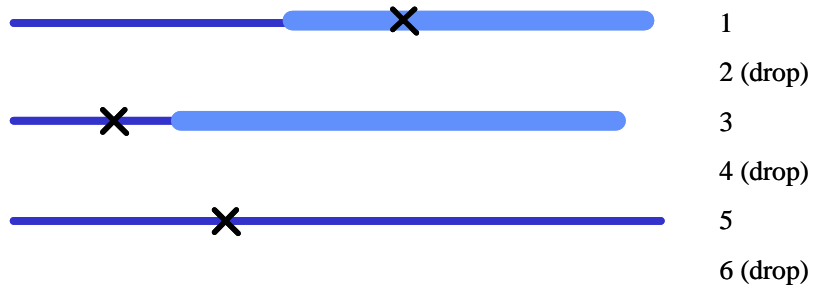
Poisson regression

Case Control

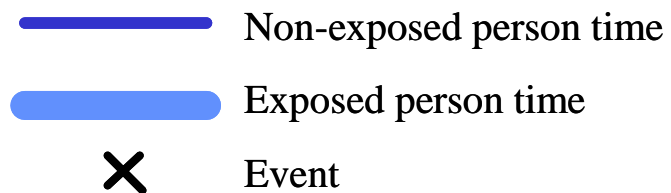


Conditional logistic regression

SCCS



Conditional Poisson regression



Historical cohort design - pitfalls

- Uncontrolled individual level confounding - cannot collect additional data on the cohort.
- Very large databases – may cause issues with speed of analysis (e.g. GPRD: Thiomersal and Developmental problems).
- Cannot easily validate data (e.g. vaccination history) on all cases and non-cases.
- **Key advantages:** Direct estimates of absolute and attributable risk, bias of case ascertainment less likely.

Example: Cohort Study

Influenza and Asthma - Kramarz et al 2000

- Vaccine Safety Datalink study
- Population: 1 to 6 year olds from 4 HMOs in three influenza seasons (retrospective)
- Risk period: 2 weeks after vaccination
- Adjustment for sex, age, HMO, season, asthma severity, preventive care schemes.

Cohort v SCCS: Influenza & Asthma

Year	RawRI	cohort RI	SCCS RI
93/94	2.51	1.00 (0.60 -1.56)	0.58 (0.36-0.95)
94/95	2.22	1.09 (0.67-1.62)	0.74 (0.47-1.17)
95/96	3.29	1.39 (1.08-1.77)	0.98 (0.76- 1.27)

- Difference explained by the more complete adjustment for asthma severity in the SCCS study

Example MMR & autism (Madsen et al, NEJM 2002)

- Retrospective cohort of children born 1991-1998.
- Danish civil registration number used to set up cohort by linking various databases with data on vaccination, autism and some possible confounding variables.
- Record review on 40 cases. Date of symptom onset not available.
- Adjustment for age, sex, period, socioeconomic status, mothers education, gestational age and birth weight.
- 738 cases
- RR = 0.92, 95% CI (0.68-1.24) for autistic disorder
- RR = 0.83, 95% CI (0.65-1.07) for other autistic spectrums

Case-control design pitfalls

- Control selection (easier in nested study)
- Uncontrolled individual level confounding
- **Key advantages:** only need information up to the event date (don't need to define person time), more detailed data could be collected.

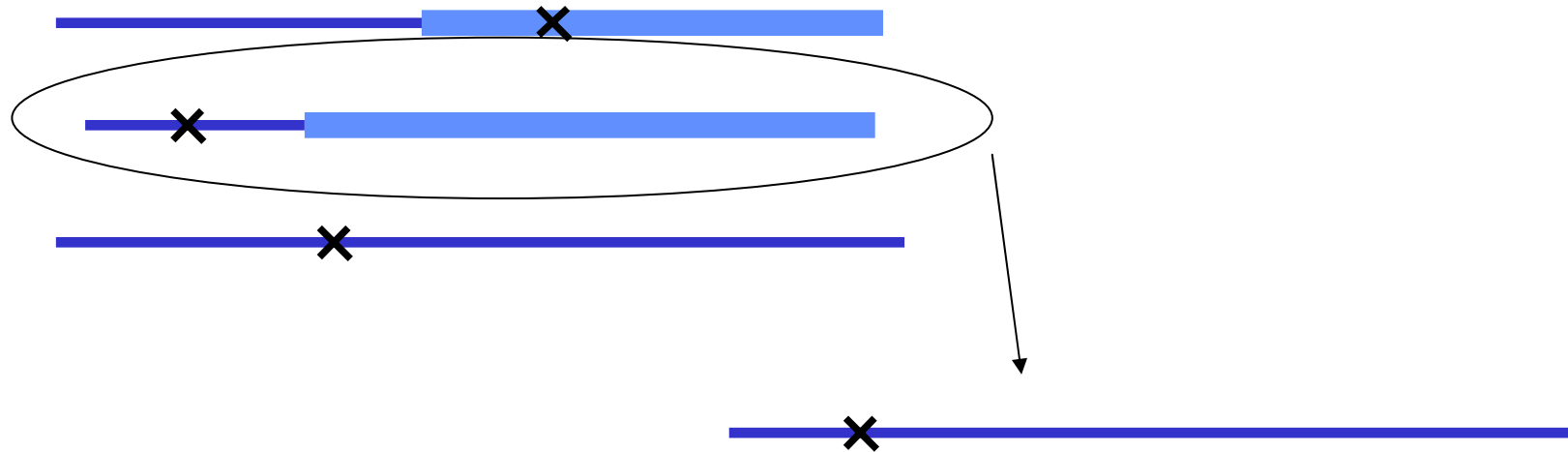
Example MMR & autism (Smeeth et al, Lancet 2004)

- Nested, matched case-control study
- UK General Practice Research database 1987-2001.
- Cases identified using clinical codes for pervasive developmental disorders. Vaccination history also in records.
- 5 Controls per case matched on year of birth, sex and General Practice.
- Other confounding variables were consulting frequency, length of time registered.
- Case records obtained for validation on 318 /1294 cases
- Risk was vaccination any time before diagnosis.
- OR 0.86, 95% CI (0.68-1.09) for pervasive developmental disorder
- OR 0.88, 95% CI (0.67-1.15) for autism

SCCS Pitfalls

- Cannot use for long post vaccination risk if exposure is at a single point in time / age and time or age is a time-varying confounder.
- The exposure should not depend on the event (special methods)
- Follow-up time should not depend on the event (special methods)
- Events must be captured throughout the follow-up period in an unbiased way
- Key advantages individual level confounding adjustment implicit, only need cases and power often similar to a cohort

Event dependent Exposure



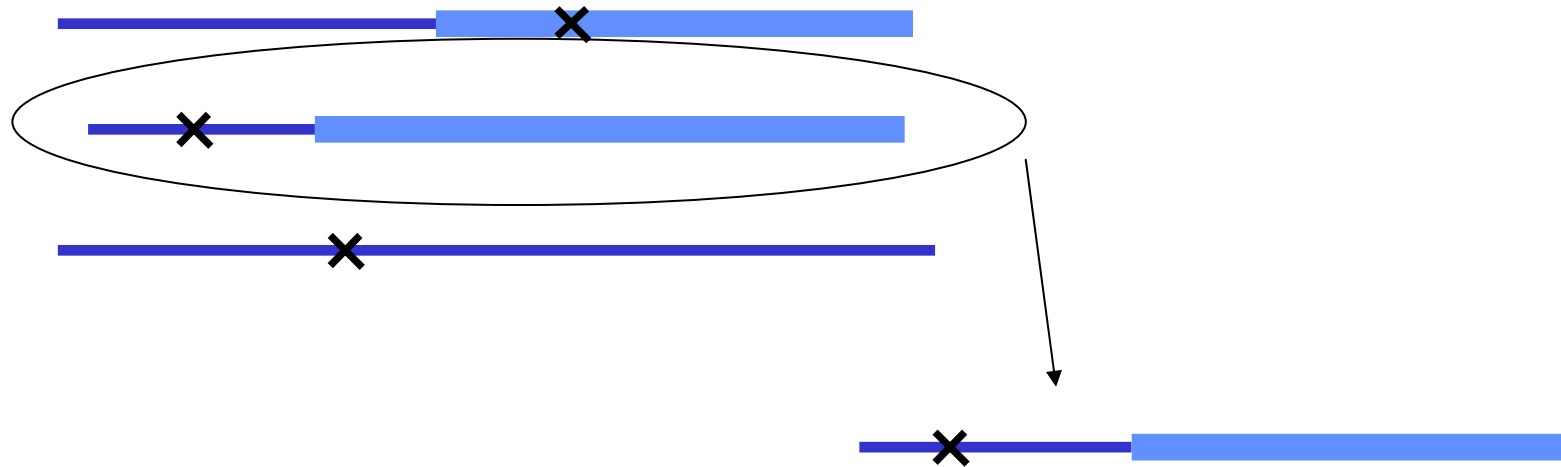
Solutions

Just use follow-up time from the point of exposure (drop unvaccinated cases or cases prior to vaccine – loss of power)

Use pseudolikelihood method which estimates risk using person time after vaccination (step1) but then also uses other person time to estimate effects of other time varying covariates (step2). – more power.

If event dependent exposure cannot look at risk at any time post vaccination

Event delays exposure



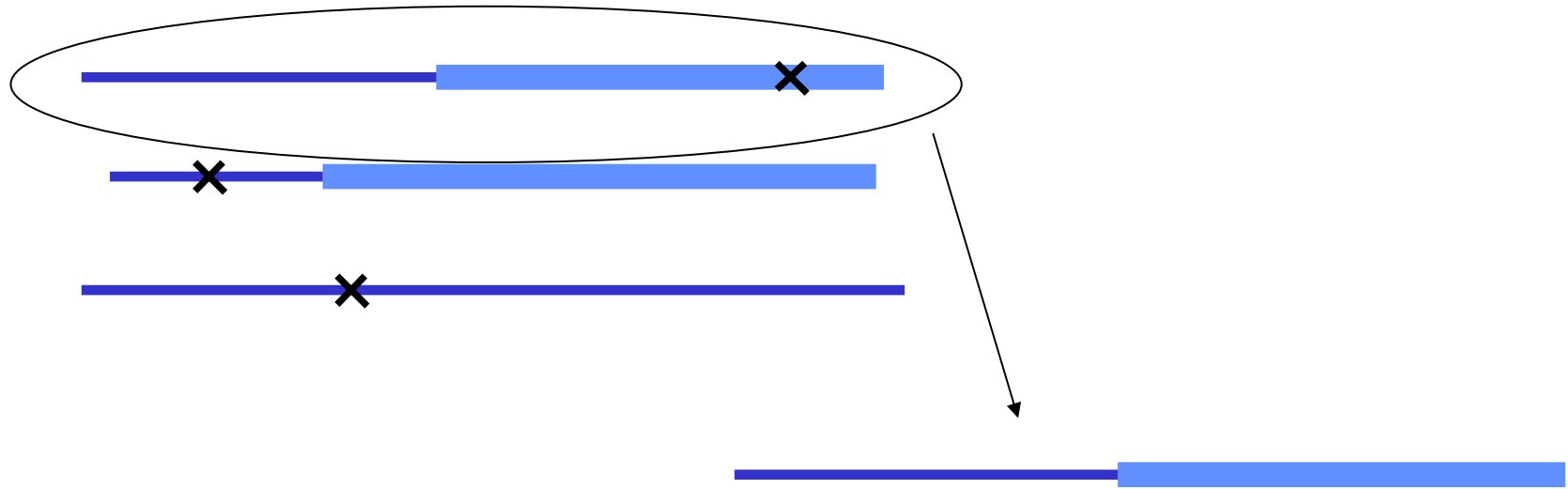
Solution

Remove pre-vaccination 'low' from background by setting this as a separate risk period.



e.g. OPV- intussusception RI was about 0.15 for the 2 weeks pre-vaccination

Events not captured near the end of “follow-up”



Solutions

Censor follow-up to period events should be captured

Adjust for period in the analysis (OK if non-differential)

Example: MMR & autism (Taylor et al 1999, Farrington et al 2001)

- Cases born since 1979 identified from special needs / disability registers and special schools
- All cases checked using case notes
- Immunisation data obtained independently from a child-health immunisation database
- adjustment for age
- 357 cases obtained (105 with regression)
- Various post vaccination risk periods

Period	RI (95% CI)
12m	0.94 (0.60-1.47)
24m	1.09 (0.79-1.52)
5yrs	1.24 (0.67-2.27)
ever	1.06 (0.49-2.30)



Conclusions

- Key issues for all designs are case and exposure ascertainment, confounding and case-definition specificity.
- Various designs have pitfalls to avoid – the most important apply to all, some subtle ones for SCCS.
- The control for individual level confounding and the fact only cases are needed in the SCCS method makes it particularly suitable for collaborative studies.



Acknowledgements

- Prof Liz Miller, HPA
- Julia Stowe, HPA
- Prof Paddy Farrington, Open University
- Prof Brent Taylor, Royal Free – University College London