Potential pitfalls in disproportionality analysis

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UMC Pharmacovigilance Course Module IIA. May 11, 2011.

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My background

- Head of Research, Uppsala Monitoring Centre.
- Adjoint Associate Professor, Stockholm University
- Academic qualifications:
  - PhD Mathematical Statistics, Stockholm University, 2007
  - M.Sc. Engineering Physics, Chalmers University of Technology, 2002
- Worked for the WHO Collaborating Centre since 2002

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Presentation outline

- Recap of disproportionality analysis
- Potential pitfalls
  - Confounding
  - Masking
  - Innocent bystander biases
  - Duplication
- Use of sophisticated computational methods

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Acknowledgments

- The examples presented draw on various research projects by past and present colleagues at the UMC
- See list of references for further reading

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Individual Case Safety Reports

- Reports of **suspected** adverse drug reactions in real world clinical practice
- Based on voluntary submission
  - Physicians
  - Nurses
  - Pharmacists
  - Patients
- Anecdotal in nature
- Of varying quality

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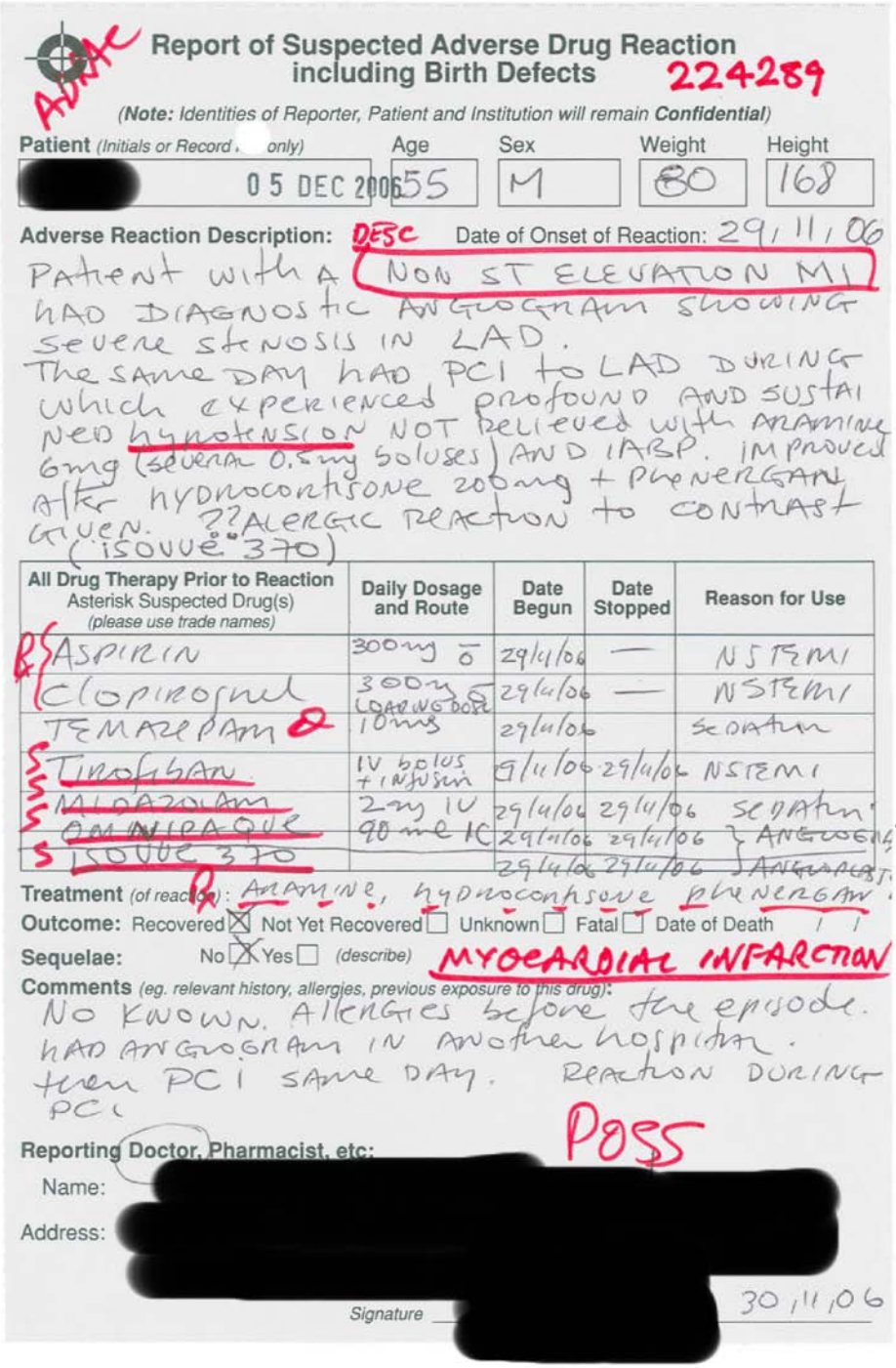

Report of Suspected Adverse Drug Reaction including Birth Defects 224289

(Note: Identities of Reporter, Patient and Institution will remain Confidential)

Patient (Initials or Record only)	Age	Sex	Weight	Height
[redacted] 05 DEC 2006	55	M	80	168

Adverse Reaction Description: DESC Date of Onset of Reaction: 29/11/06

PATIENT WITH A NON ST ELEVATION MI HAD DIAGNOSTIC ANGIOGRAM SHOWING SEVERE STENOSIS IN LAD. THE SAME DAY HAD PCI to LAD DURING WHICH EXPERIENCED PROFOUND AND SUSTAINED HYPOTENSION NOT BELIEVED WITH ARAMINE 6mg (SEVERAL 0.5mg BOLUSES) AND IABP. IMPROVED AFTER HYDROCORTISONE 200mg + PHENERGAN GIVEN. ??ALLERGIC REACTION to CONTRAST (ISOVUE 370)

All Drug Therapy Prior to Reaction Asterisk Suspected Drug(s) (please use trade names)	Daily Dosage and Route	Date Begun	Date Stopped	Reason for Use
ASPIRIN	300mg O	29/11/06	—	NSTEMI
CLOPIDOGREL	300mg LOADING DOSE	29/11/06	—	NSTEMI
TEMAZEPAM	10mg	29/11/06		SEDATION
TIROFIBAN	IV BOLUS + INFUSION	29/11/06	29/11/06	NSTEMI
MIDAZOLAM	2mg IV	29/11/06	29/11/06	SEDATION
OMNIPAQUE	90ml IC	29/11/06	29/11/06	ANGIOGRAM
ISOVUE 370		29/11/06	29/11/06	ANGIOGRAM

Treatment (of reaction): ARAMINE, HYDROCORTISONE PHENERGAN

Outcome: Recovered ☒ Not Yet Recovered ☐ Unknown ☐ Fatal ☐ Date of Death / /

Sequelae: No ☒ Yes ☐ (describe) MYOCARDIAL INFARCTION

Comments (eg. relevant history, allergies, previous exposure to this drug): NO KNOWN ALLERGIES before the episode. HAD ANGIOGRAM IN ANOTHER HOSPITAL. THEN PCI SAME DAY. REACTION DURING PCI.

POSS

Reporting Doctor, Pharmacist, etc:

Name: [redacted]

Address: [redacted]

Signature [redacted] 30/11/06

Authentic report

Courtesy of the Adverse Drug Reactions Unit at the Therapeutic Goods Administration of Australia

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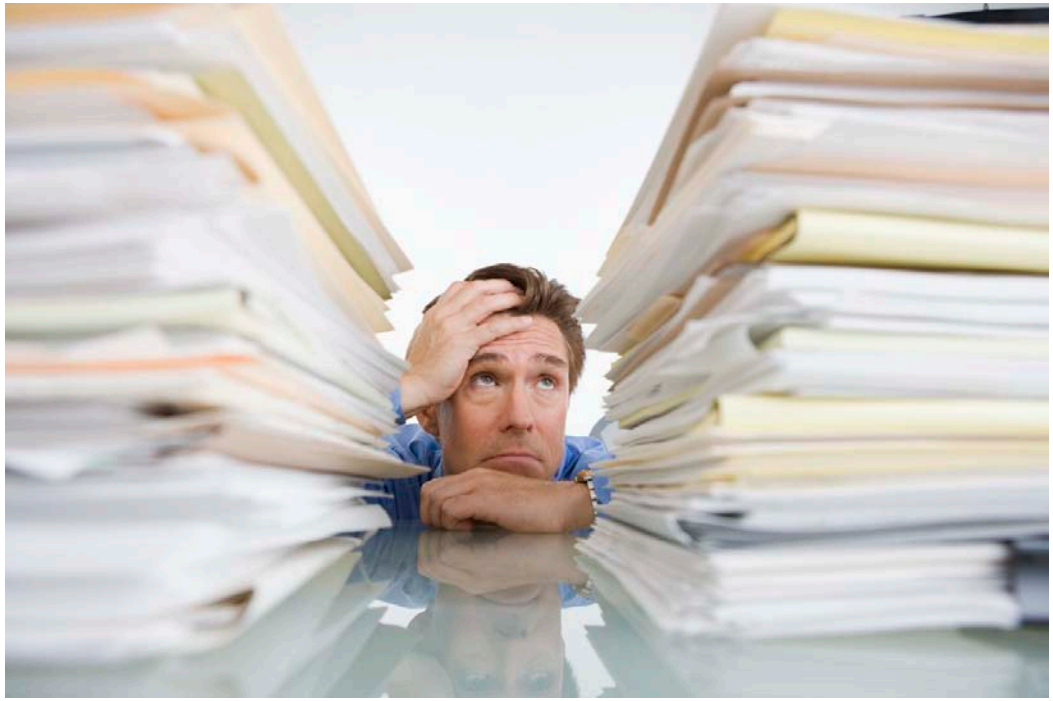
Large scale screening

- Six million reports and half a million added annually
- Nearly one million co-reported drug-ADR pairs



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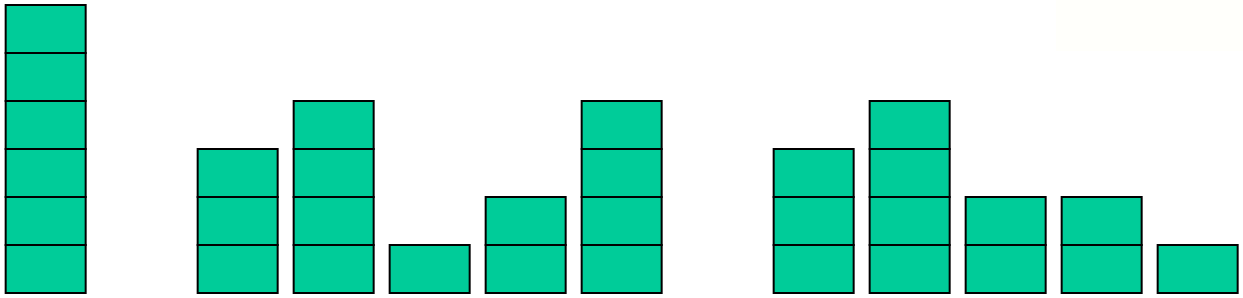
Absolute reporting rates

- Each column represents a drug
- The height of each column represents the number of reports on an ADR of interest for that drug



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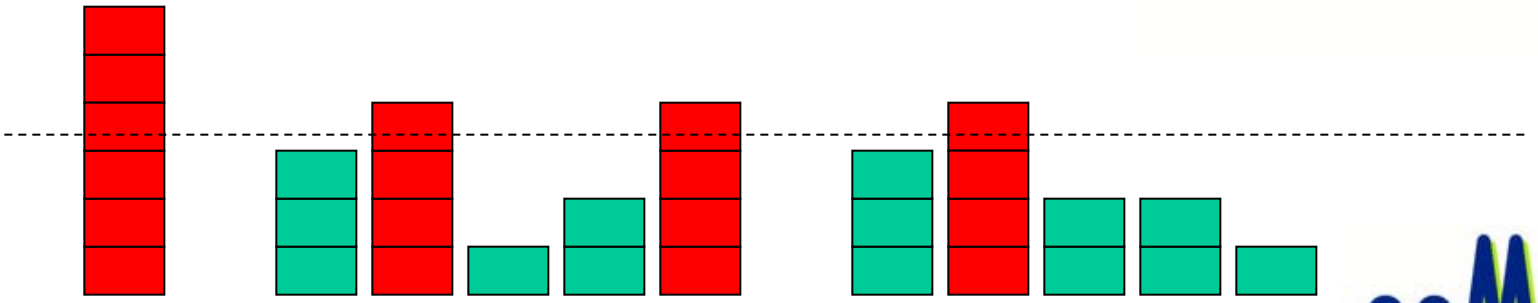
Absolute reporting rates

- Excessively reported in absolute terms (here, more than 3 reports)



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Interpretation of absolute reporting rates

- 4 reports can mean different things
  - 4 reports of rash (common event) for paracetamol (common drug) would typically not be a major concern
  - 4 reports of acute renal failure (rare event) for dronedarone (new drug) may be!
- Challenge: no reliable information on
  - Number of exposed patients
  - Background occurrence of adverse event

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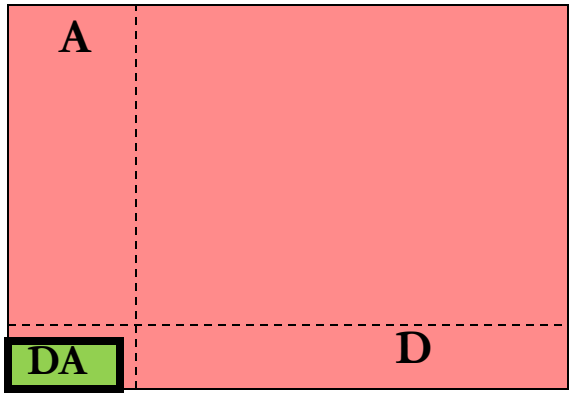
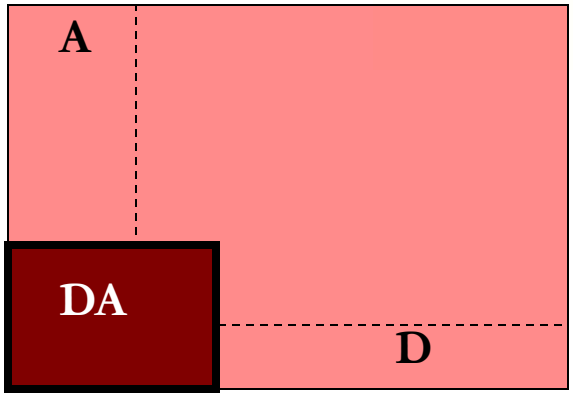
Basic disproportionality analysis

- Contrast the observed number of reports on ADR A for Drug D to an expected number based on
  - The overall reporting rate of ADR A in the database
  - The total number of reports on Drug D





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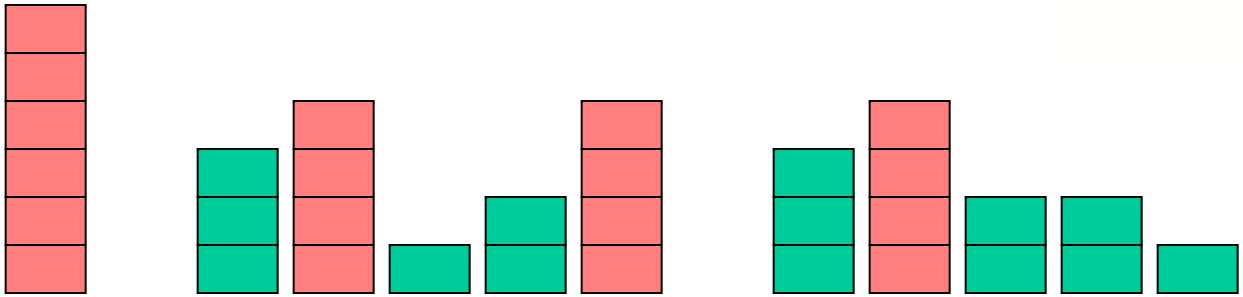
Relative reporting rates



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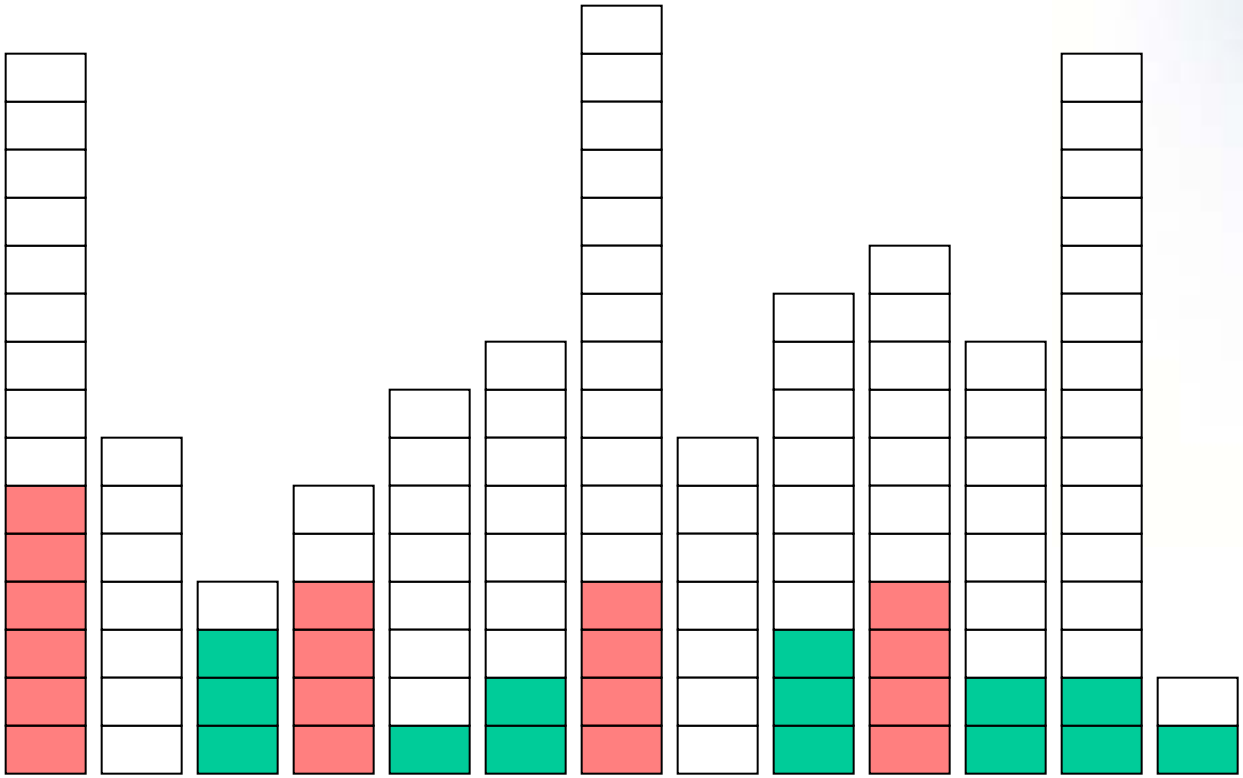
Relative reporting rates



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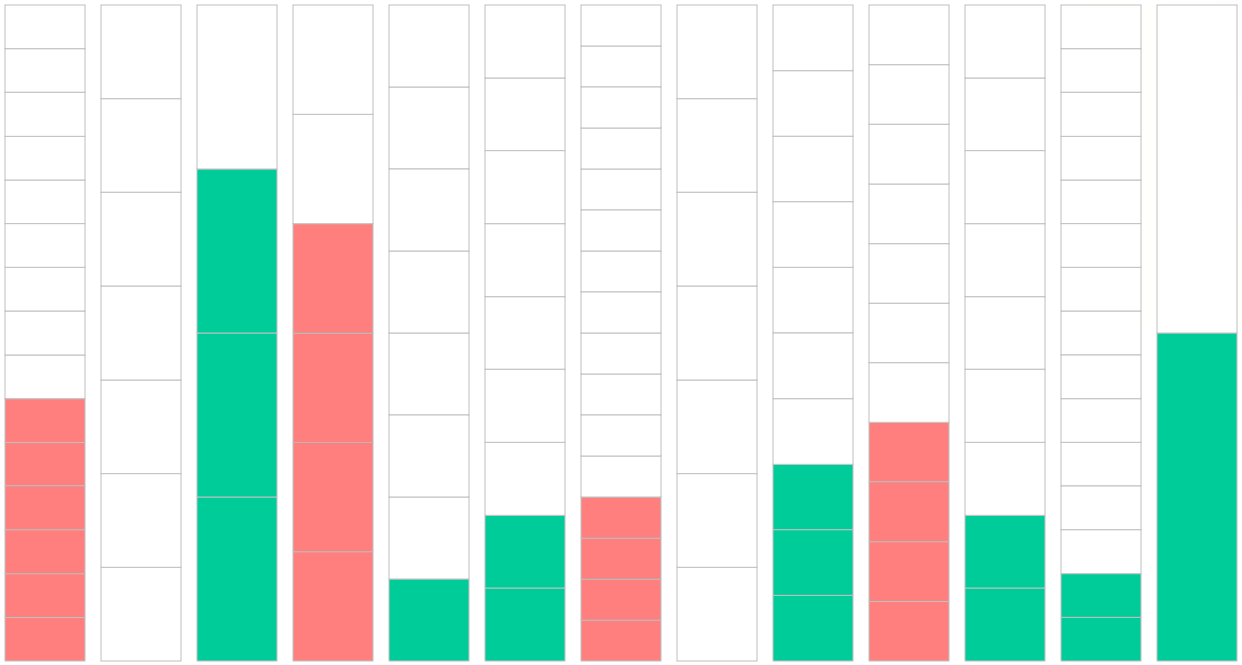
Relative reporting rates

- Account for total number of reports on the drugs
- Measure relative strength of association



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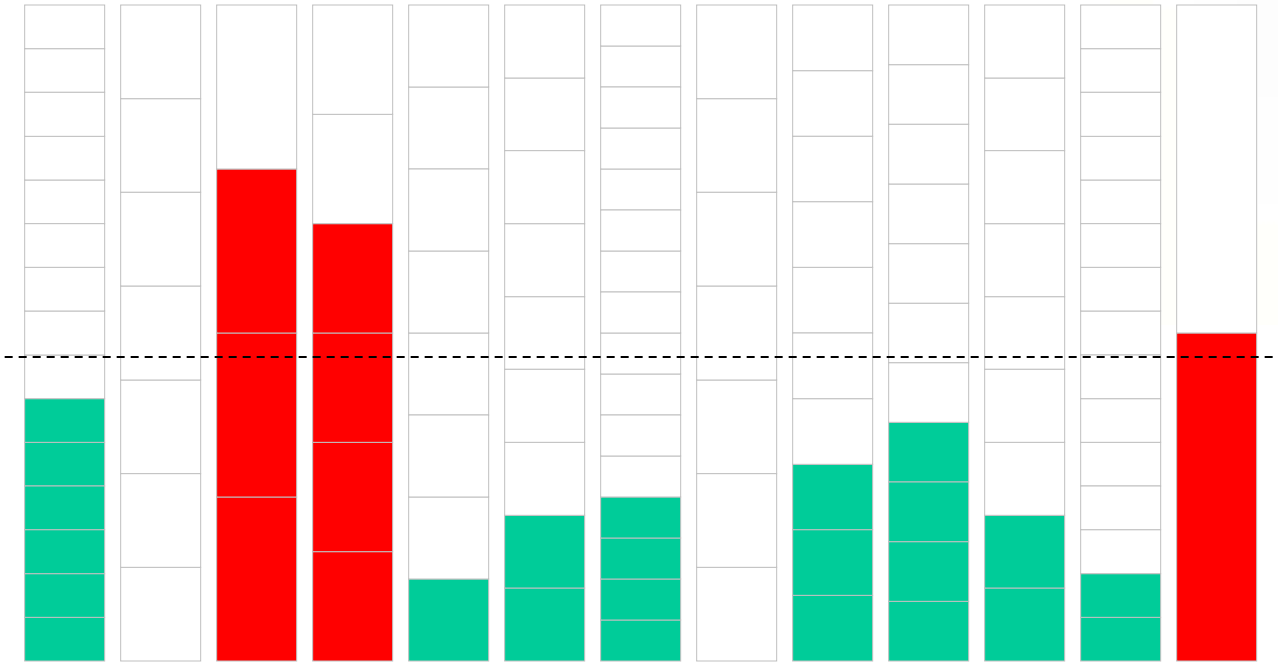
Relative reporting rates

- Excessively reported in relative terms
- Beware of random variability!



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Disproportionality paradigm

- DIS-PROPORTIONAL-ITY
  - Not the same ...
    - ... proportion (of reports on the ADR)

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Basic contingency table

	ADR Y	**Not ADR Y**	
Drug X	$n_{xy}=a$	b	f(x)=(a+b)/(a+b+c+d)
Not Drug X	c	d	
	f(y)=(a+c)/(a+b+c+d)		N=a+b+c+d

Total number of reports in the database

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Disproportionality measures

- Simple OE ratio: $\frac{f(x,y)}{f(x)f(y)} = \frac{f(y|x)}{f(y)}$
- Proportional reporting ratio (PRR): $\frac{f(y|x)}{f(y|\neg x)}$
- Reporting odds ratio (ROR):

$$\frac{odds(y|x)}{odds(y|\neg x)} = \frac{f(y|x) \,/\, (1-f(y|x))}{f(y|\neg x) \,/\, (1-f(y|\neg x))}$$

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Disproportionality measures

- OE, PRR, ROR can be re-expressed as ratios of the observed count *a* to different expected counts:

- For OE: $$Exp = \frac{(a+b)(a+c)}{(a+b+c+d)}$$

- For PRR: $$Exp = \frac{(a+b)(c)}{(c+d)}$$

- For ROR: $$Exp = \frac{bc}{d}$$

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Norén et al
Stat Meth Med Res, 2011

Simple shrinkage

- Modified observed-to-expected ratio: $\frac{Obs + 1/2}{Exp + 1/2}$
- +1/2 pulls ratio towards 1 and protects against chance findings when Exp is near 0
- Information Component (IC) is logarithm of above formula for OE on previous slide
- Logarithm -> Positive values correspond to excess number of reports and vice versa

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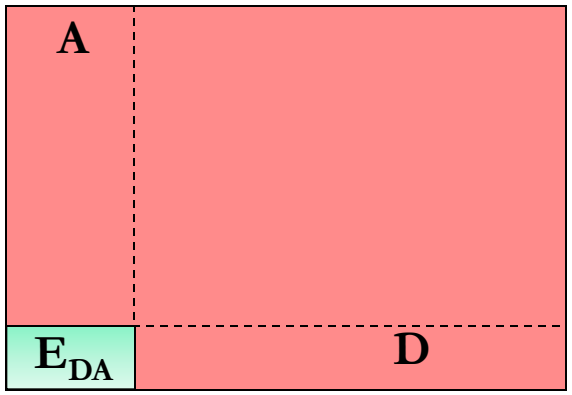
Choice of baseline model

All models are wrong – but some are useful

- G. E. P. Box



How useful is this model?

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Poliovirus vaccine & growth retarded

- Example from Jakobsson, 2008

Observed	Expected	IC	IC_{025}
17	7.0	1.21	0.45

- Positive IC value and lower 95% bound
- Unexpectedly many reports?

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Poliovirus vaccine & growth retarded

- Each age group analysed separately
  (excluding age groups with observed and expected ≈ 0)

Ages	Observed	Expected	IC	IC_{025}
<1 y	14	23.2	-0.71	-1.57
1–4 y	2	5.1	-1.16	-3.74
5–14 y	0	10.4	-4.44	-14.43
Unknown	1	0.2	0.01	-2.78

- Less reports than expected in all age groups when considered separately!

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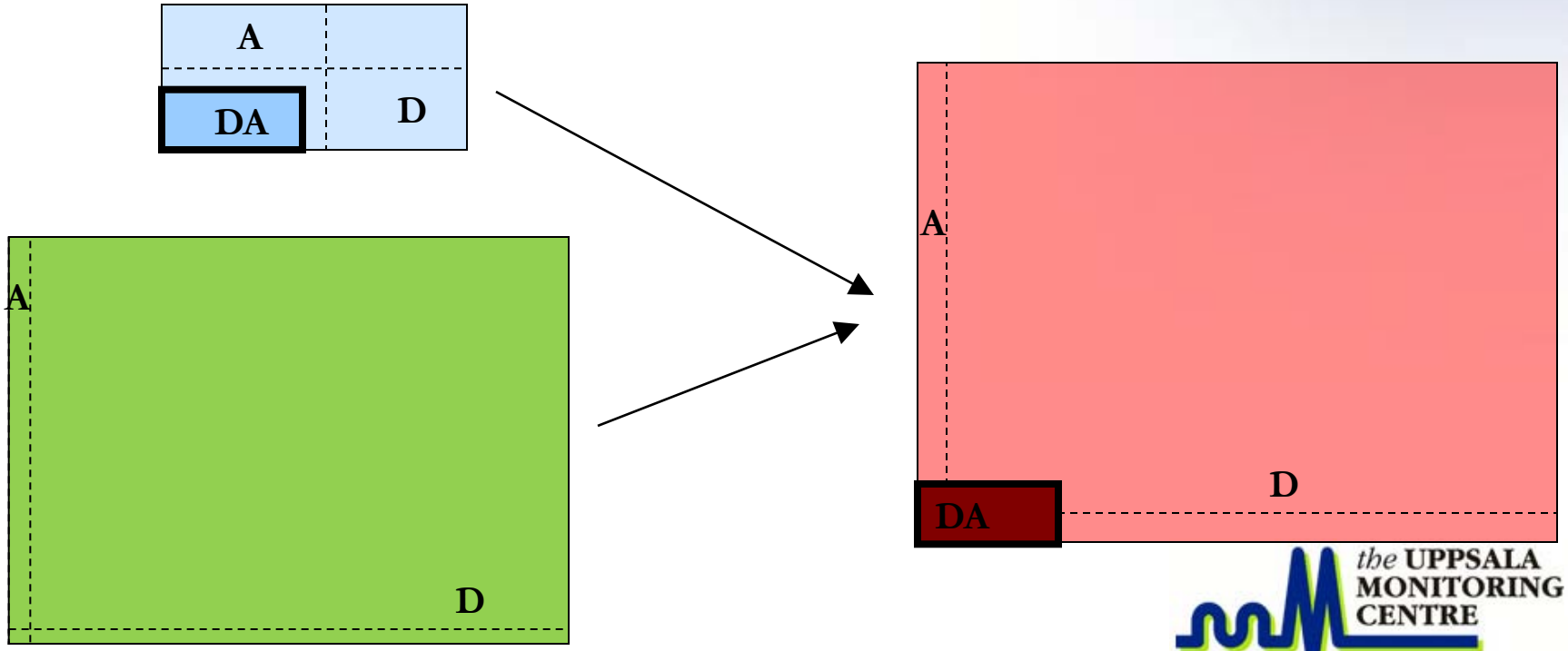
Confounding

- Explanation



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Poliovirus vaccine & myalgia

- Another example from Jakobsson, 2008

Observed	Expected	IC	IC_{025}
360	625.4	-0.80	-0.95

- Negative IC value and upper 95% bound (not shown)
- Nothing to worry about!?

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Poliovirus vaccine & myalgia

Ages	Observed	Expected	IC	IC_{025}
<1	39	22.0	0.81	0.32
1–4	140	38.1	1.87	1.62
5–14	124	46.3	1.41	1.15
15–24	14	3.0	2.05	1.20
25–44	17	4.1	1.92	1.15
45–64	14	2.5	2.25	1.40
65–74	3	0.5	1.86	-0.19
Unknown	9	15.1	-0.71	-1.81

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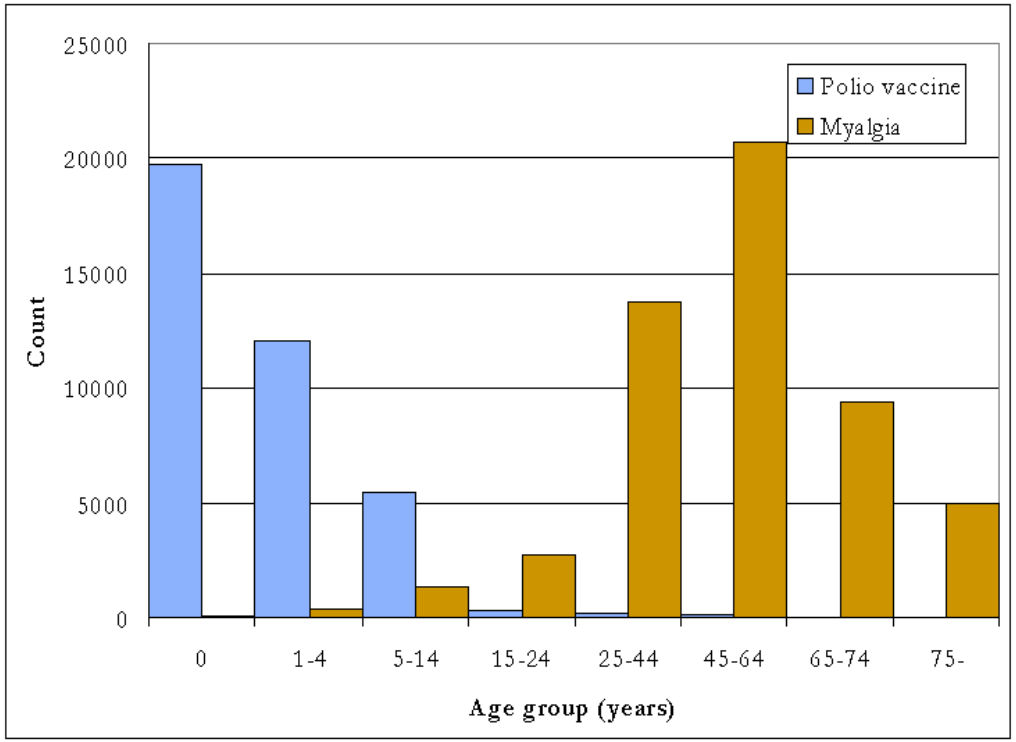
Poliovirus vaccine & myalgia



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Masking

- The comparison to an overall reporting rate for the ADR is fundamental to disproportionality analysis
  - For example, 5.7% of all reports in VigiBase list rash
- The idea is that for most drugs the reported adverse events are
  - Coincidental
  - Due to other drugs
  - Due to the underlying disease
- And thus represent some form of ’background’ reporting rate

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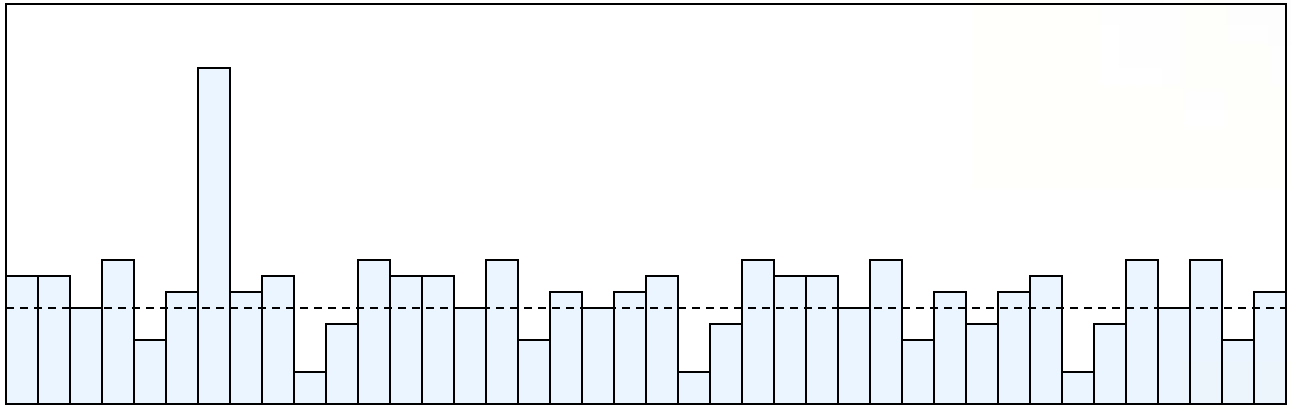
Ideal reporting model

- Most drugs scattered around background rate
- Some with excessive rates and some with lower rates
- Overall reporting rate is a weighted average of the individual reporting rates
  - Weighted by total number of reports



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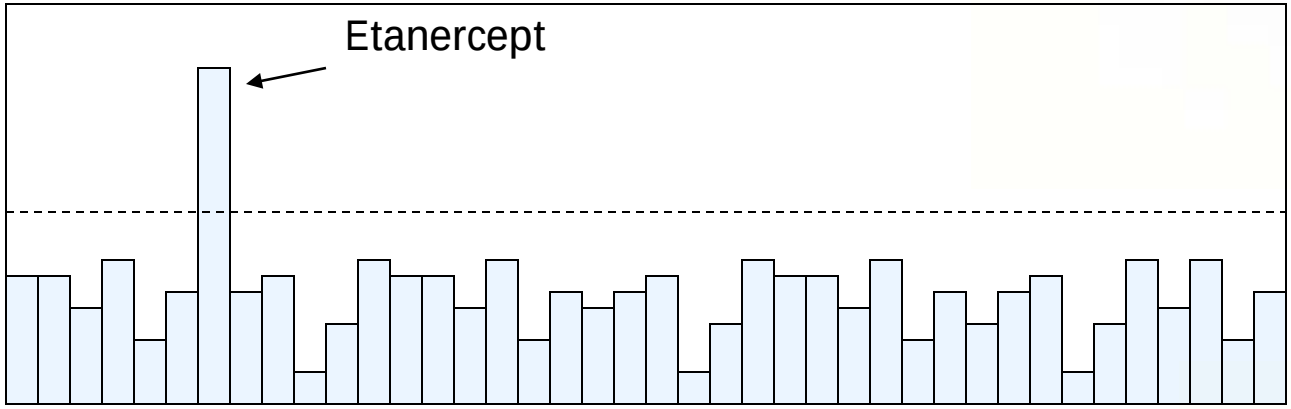
Masking

- If there is excessive reporting for a common drug, the overall rate will be inflated
- -> other associations may be hidden



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Venlafaxine – Rhabdomyolysis

- Example from Caster et al. 2008
- Apparently lower-than-expected reporting of rhabdomyolysis for venlafaxine

Observed	Expected	IC	IC_{025}
48	58.3	-0.28	-0.73

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Venlafaxine – Rhabdomyolysis

- Masking?
  - A large proportion of the reports on rhabdomyolysis are for statins
  - The statins have excessive reporting rates of rhabdomyolysis
- Consider an overall reporting rate for rhabdomyolysis excluding statin reports:

Observed	Expected	IC	IC_{025}
45	15.5	1.51	1.05

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Montelukast - Photosensitivity

Observed	Expected	IC	IC_{025}
19	29.5	-0.62	-1.35

- No quantitative association!
  - Stratification by country of origin, time of reporting, patient age, and/or patient gender does not change this
  - Nor does shrinkage regression to eliminate masking and confounding by co-reported drugs

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Montelukast - Photosensitivity

- From Tengstrand et al. (2009)
- What there is
  - Geographic spread: Australia, Austria, Canada, Germany, France, UK, Netherlands, US
  - 3 positive dechallenge interventions
  - 2 positive rechallenge interventions
  - On 18/19 reports, Montelukast is solely suspected

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Quality of reports

- All reports are equal – but some reports are *more equal* than others ☺
- The most important discrepancy between methods for automated screening and the clinical review of ADR reports:
  - In clinical review, report quality is fundamental
  - In automated screening, all reports are treated equally
  - Incredible room for improvement!

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Steering clear of the pitfalls

- Distortion from age, geography, time, …
  - Stratification – adjusted as well as subgroup analyses (Hopstadius et al 2008)
  - Computational implementation must be done with care!
- Masking
  - Shrinkage regression – computationally sophisticated option (Caster et al 2010)
  - Simple unmasking (work in progress at UMC)
- Absence of quantitative associations
  - Computerized methods to detect strong case series (work in progress at UMC)

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Summary

- Disproportionality analysis is a valuable **supplement** to manual clinical review
- Don’t over-interpret summary statistics!
- More sophisticated analysis methods can help!

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References

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