Knowledge finding for globally important ADR signals

I. Ralph Edwards

WHO Collaborating Centre for
International Drug Monitoring

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Presentation outline

- What do we do?
  - Patient Safety
- The Global Programme
  - The WHO database
  - Data mining (knowledge discovery)
  - Pattern recognition
- Knowledge discovery in health care data

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Why are we here?

We gave the world drug safety: the WHO Drug Monitoring Programme

Education, service, support

Repository of global ADR reports
for ADR signal detection

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We gave the world drug safety: the WHO Drug Monitoring Programme

- Started in 1968 to prevent drug disasters
  - by pooling data from 10 countries with existing spontaneous reporting systems
- Scientific and technical operations moved to Uppsala, Sweden in 1978
  - The WHO Collaborating Centre for International Drug Monitoring (Uppsala Monitoring Centre, UMC) was set up specifically for this purpose
- Vigibase is the data repository
  - Holds ICSRs data from 1968 to date
  - Is managed by the UMC
  - Database now contains about 4 million ICSRs

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Flow of reports

- Report originator sends ICSR to their National Centre
  - in most countries, the National Centre is part of the regulatory authority
  - in some countries, e.g. a hospital may be designated as the National Centre
  - some countries also have regional centres as an intermediary step
- National Centre reports to the UMC

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Individual Case Safety Reports (ICSRs)

- Each report is a concern, communicating a negative outcome in an individual patient's treatment
  - They reflect facts, biases, prejudices misdiagnoses, impressions
  - They also tell us about true, rare events as well as common
    - Unusual drug interactions, unusual phenotypes, new drugs, unusual disease effect

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Data access – to whom

- National Centres (NCs)
  - receive all regular data output from UMC
  - have access to Vigisearch web interface
  - can request database searches made by UMC
- Other stakeholders
  - can request database searches made by UMC
    - service available to any inquirer with a legitimate interest in pharmacovigilance data
    - guidelines for interpretation should be adhered to
    - set out in 'Caveat' document

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Strengths

- Continuous data collection
- Low cost
- Whole populations covered (at least in theory)
- >3,800,000 individual case safety reports
- Now 81 countries representing all continents
- Possibility to make country comparisons and analyse differences between countries/regions
- International panel of experts for clinical review

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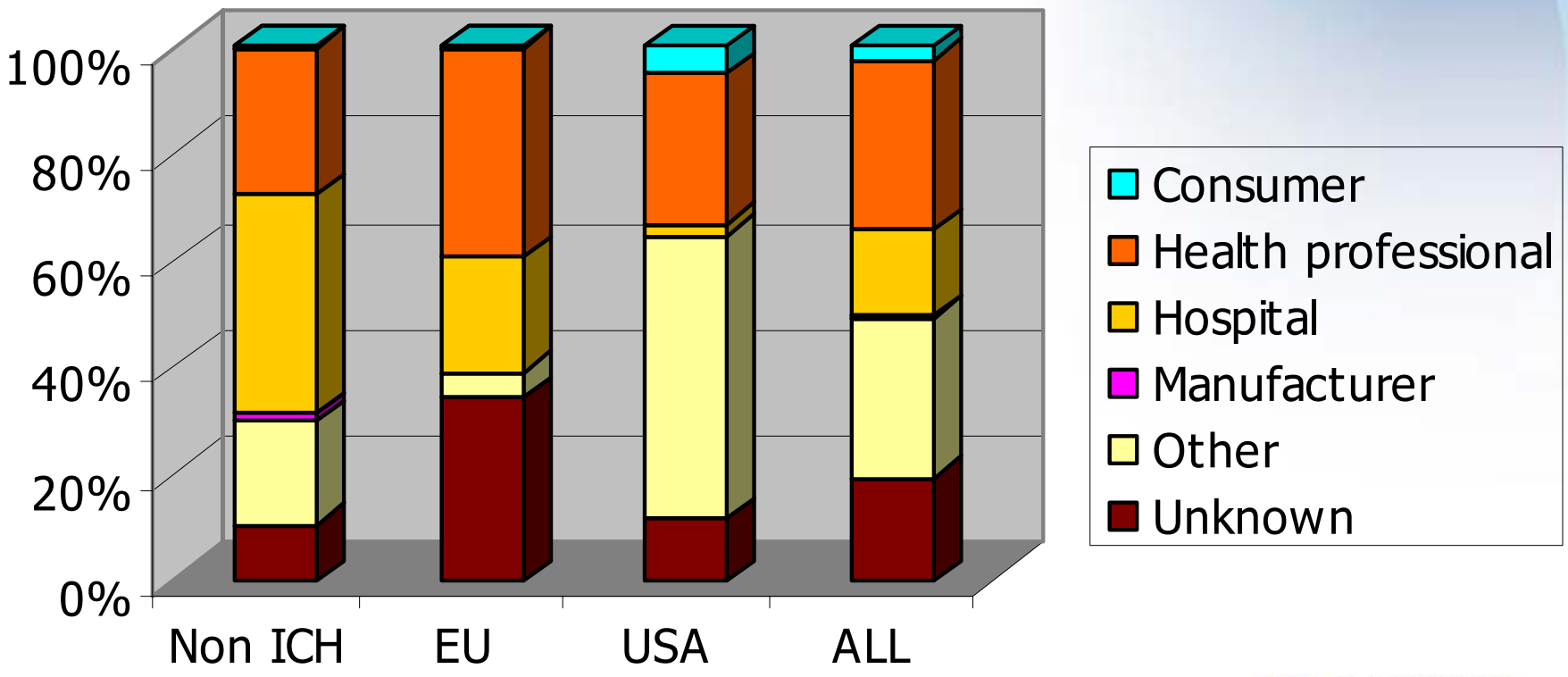
Reporter categories

Data from 1968 to date



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Top 15 contributors

Data from
2000 - 2005

Country	# Reports
USA	**953,919**
UK	**116,105**
Canada	**65,103**
Germany	**63,532**
Australia	**59,499**
Thailand	**55,560**
Netherlands	**44,676**
Spain	**39,441**
France	**39,256**
New Zealand	**17,380**
Sweden	**16,193**
Italy	**11,777**
Switzerland	**11,031**
Ireland	**10,110**
Cuba	**9,194**

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Top 15 contributors

Country	# Reps/mill. inhab.	# Reports
New Zealand	717.8	17,380
USA	537.6	953,919
Australia	493.6	59,499
Netherlands	453.8	44,676
Ireland	419.6	10,110
Canada	330.8	65,103
UK	320.2	116,105
Sweden	299.8	16,193
Denmark	249.0	8,117
Switzerland	245.5	11,031
Norway	178.3	4,915
Spain	162.9	39,441
Finland	158.5	4,968
Thailand	141.5	55,560
Cuba	135.0	9,194

Data from 2000 - 2005

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Most reported reactions

NAUSEA	G-I	17,532
RASH	SKIN	16,451
HEADACHE	CNS	12,847
DIZZINESS	CNS	12,707
VOMITING	G-I	11,802
DYSPNOEA	RESP	11,619
MEDICINE INEFFECTIVE	GENERAL	11,529
FEVER	GENERAL	10,818
PRURITUS	SKIN	10,581
ABDOMINAL PAIN	G-I	9,193
DIARRHOEA	G-I	8,651
FATIGUE	GENERAL	8,374
MYALGIA	MUSC-SKEL	7,869
URTICARIA	SKIN	7,810
ASTHENIA	GENERAL	7,767
SOMNOLENCE	PSYCHIATR	7,654
MEDICATION ERROR	EVENTS	7,635

Data from 2005

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Most reported drugs

Pharmaceutical product	# Reports	ATC class	First entry
Ethinylestradiol/Norelgestromin	10,434	SEX HORMONES	2002
Rofecoxib	9,375	NSAIDs	1998
Teriparatide	8,804	CALCIUM HOMEOSTASIS	1990
Paroxetine	7,698	PSYCHOANALEPTICS	1987
Adalimumab	7,655	IMMUNOSUPPRESSANTS	2003
Oxycodone	6,958	ANALGESICS	*)
Bupropion	6,939	OTHER CNS DRUGS	1991
Atomoxetine	6,725	PSYCHOANALEPTICS	2003
Interferon	6,474	IMMUNOSTIMULANTS	*)
Medroxyprogesterone	5,679	SEX HORMONES	*)
Clozapine	5,026	PSYCHOLEPTICS	*)
Medroxyprogesterone acetate/ Estrogens conjugated	4,945	SEX HORMONES	2004
Estrogens conjugated	4,909	SEX HORMONES	*)

Data from 2005

*) Drug first entered before 1985

Source: WHO Drug Dictionary

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Drug fatalities

Non ICH countries	#	%
Clozapine	476	7.8
Warfarin	214	11.9
Rofecoxib	97	3.6
Celecoxib	95	1.8
Acetylsalic. acid	90	3.6
Olanzapine	87	5.3
Heparin	84	11.4
Methotrexate	77	8.4
Bupropion	72	2.0
Rivastigmine	70	7.7

ICH countries	#	%
Thalidomide	1,794	18.6
Clozapine	1,608	10.8
Fentanyl	1,481	20.6
Oxycodone	1,168	12.1
Gemcitabine	1,118	17.9
Paclitaxel	777	9.1
Paracetamol	760	9.0
DPT vaccine	758	2.6
Warfarin	757	6.7
Tamoxifen	682	23.9

Data from 2000 – 2006:1

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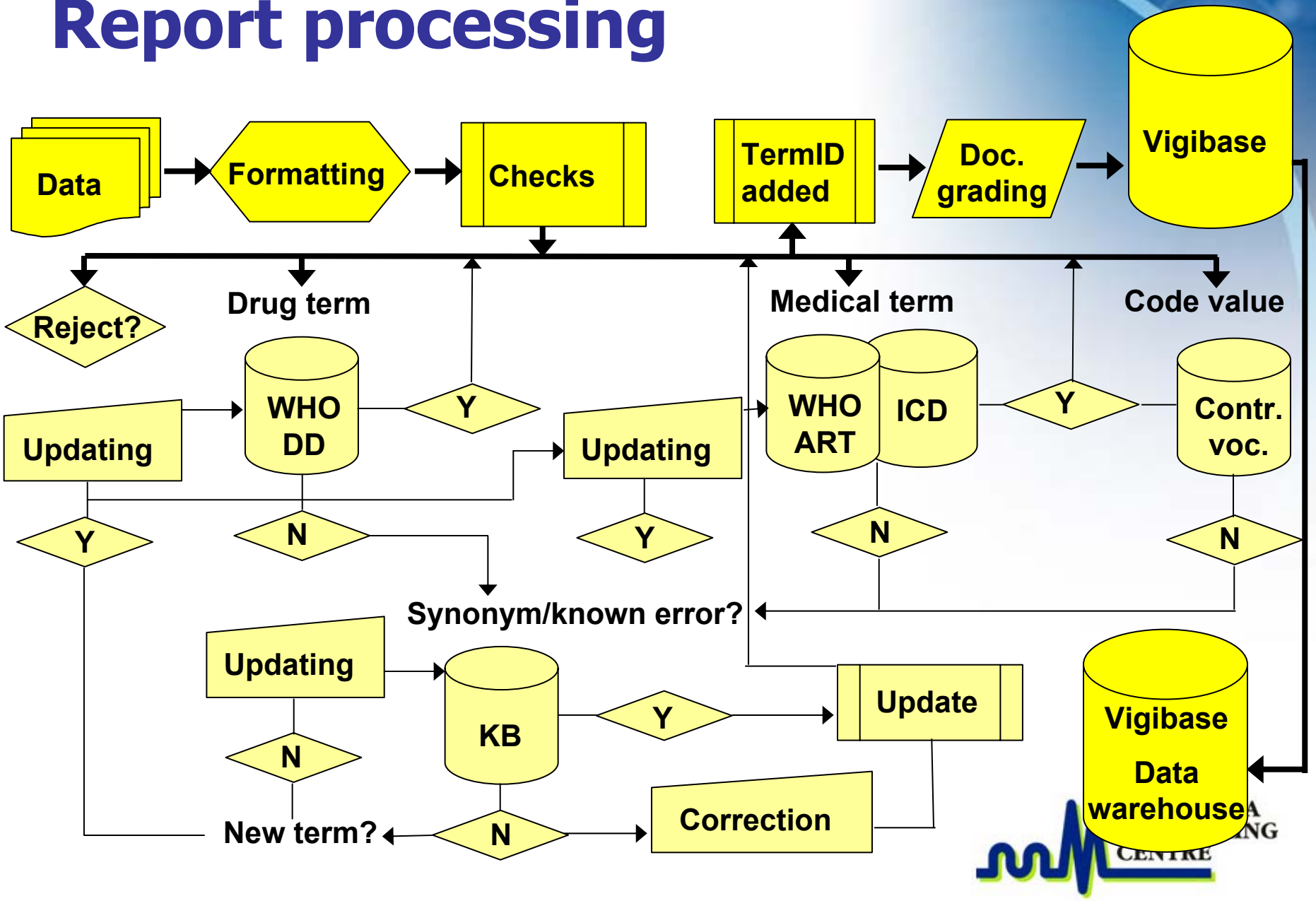
Report processing



Do we have a problem here?

- Large numbers of drugs
- HUGE numbers of ADRs

- How to link ADRs with genome
  - This is being attempted!

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Knowledge discovery

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Knowledge discovery

- Why?
  - Too much data, not enough information!
  - quantitative methods for signal detection
- What?
  - methods overview
- How?
  - used on the WHO database
  - Health care data

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Quantitative signal detection

Different approaches

- Several methods for analysis of large amounts of ICSRs
- Use different 'measures of disproportionality'
- But all aim to detect the unexpectedly frequently reported
  - relative to a background of other reports

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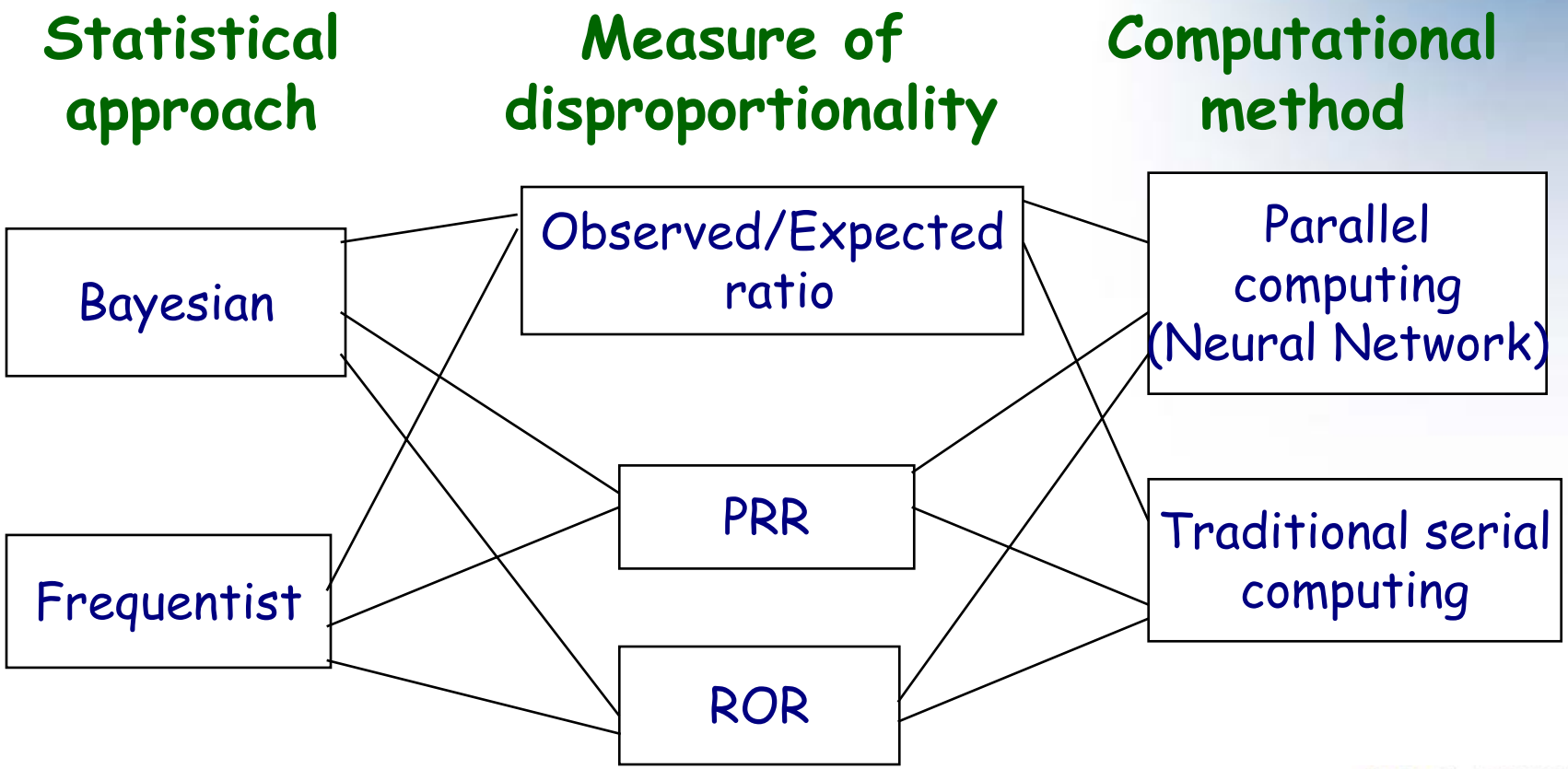
Quantitative signal detection



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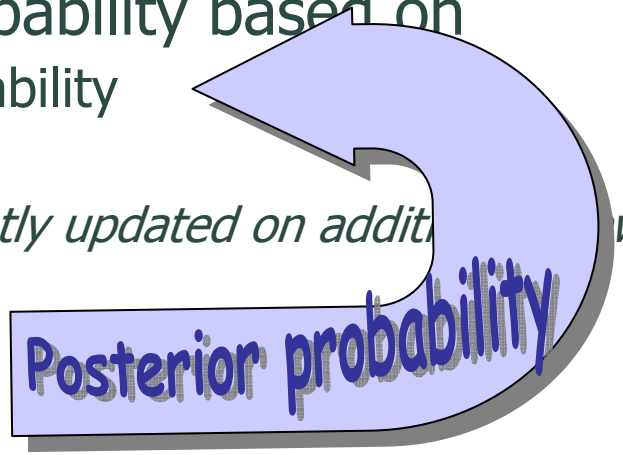
Bayesian methods

- An alternative statistical approach
- Derived from Bayes' Law
- Uses 'probability' to express subjective 'degree of belief' in a specific outcome
- Current probability based on
  - prior probability
  - new data
    - *constantly updated on addit w data*



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You are going to Sweden in winter

The weather forecast:

50% chance of cloudy and snowing upon arrival

Is it going to be like this?

... or like this?

Bayesian statistics

Applied to ADR data

- Prior probability
  - Drug-ADR combination (weakly) assumed unrelated
- Data: Reporting to the WHO ICSRs database
- Posterior probability
  - Drug-ADR combination related?
    - Given Prior, and Reporting to the database

⇒ Without including prior knowledge we are over-sensitive to data 'false' signals

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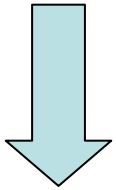
BCPNN method

Used by the UMC on WHO database

Bayesian statistics

A neural network implementation



Bayesian Confidence Propagation Neural Network (BCPNN)

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An automated signalling process

The start

- 1995 - Pilot study using a data mining approach
  - Developments together with Royal Institute of Technology, Stockholm
- Implemented as a Bayesian Confidence Propagation Neural Network (BCPNN)
- 1996 - Validation and testing
- 1998 - Routine quarterly production

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BCPNN method

What is the Information Component (IC)?

- The measure of disproportionality
- IC = $\log_2$ (posterior/prior probability)
- Is zero (0) when variables are independent
- Is > 0 when a combination occurs more often than expected
- Use within BCPNN allows us to have useful dampening property
  - When there are few reports

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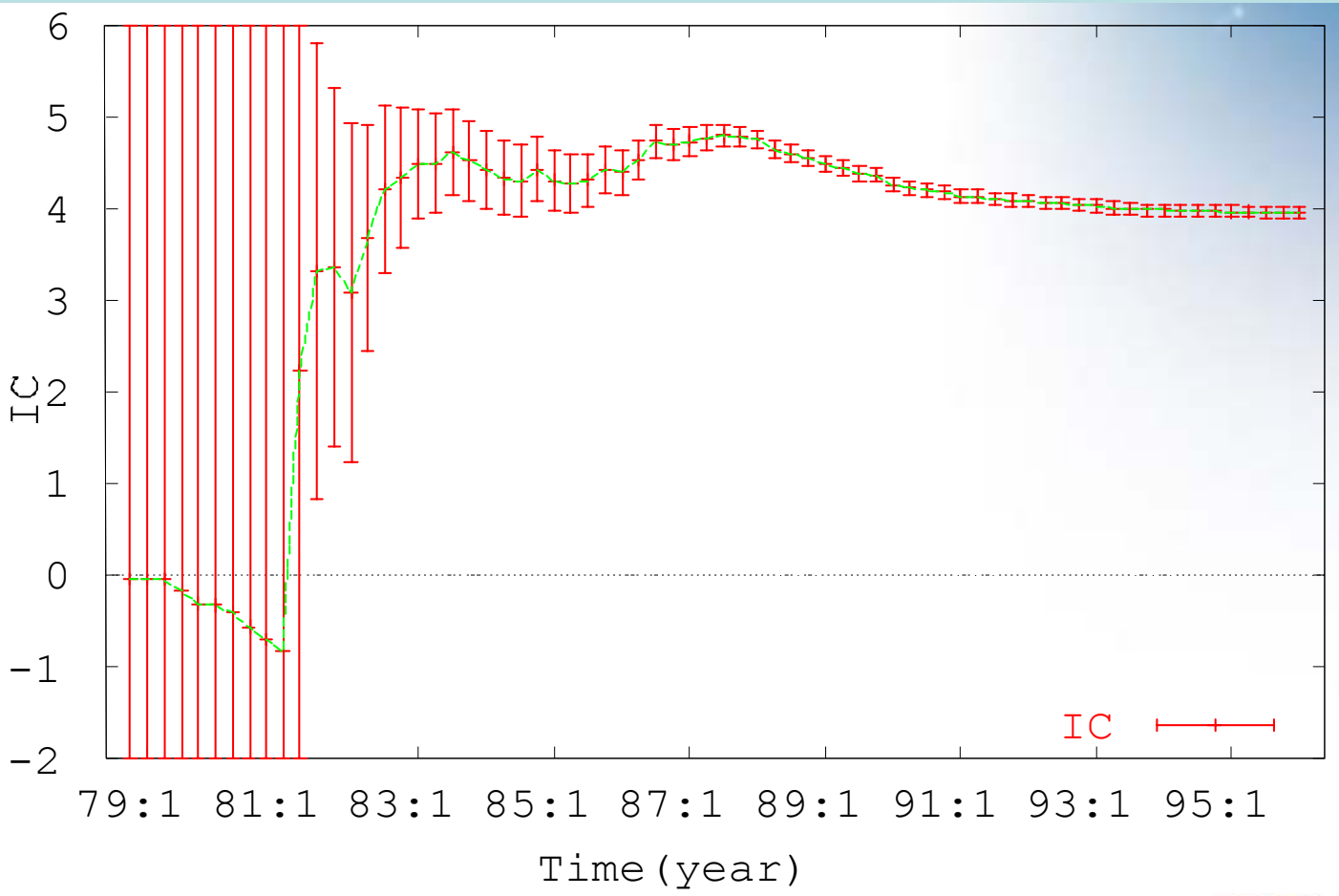
IC development over time

Example captopril - coughing



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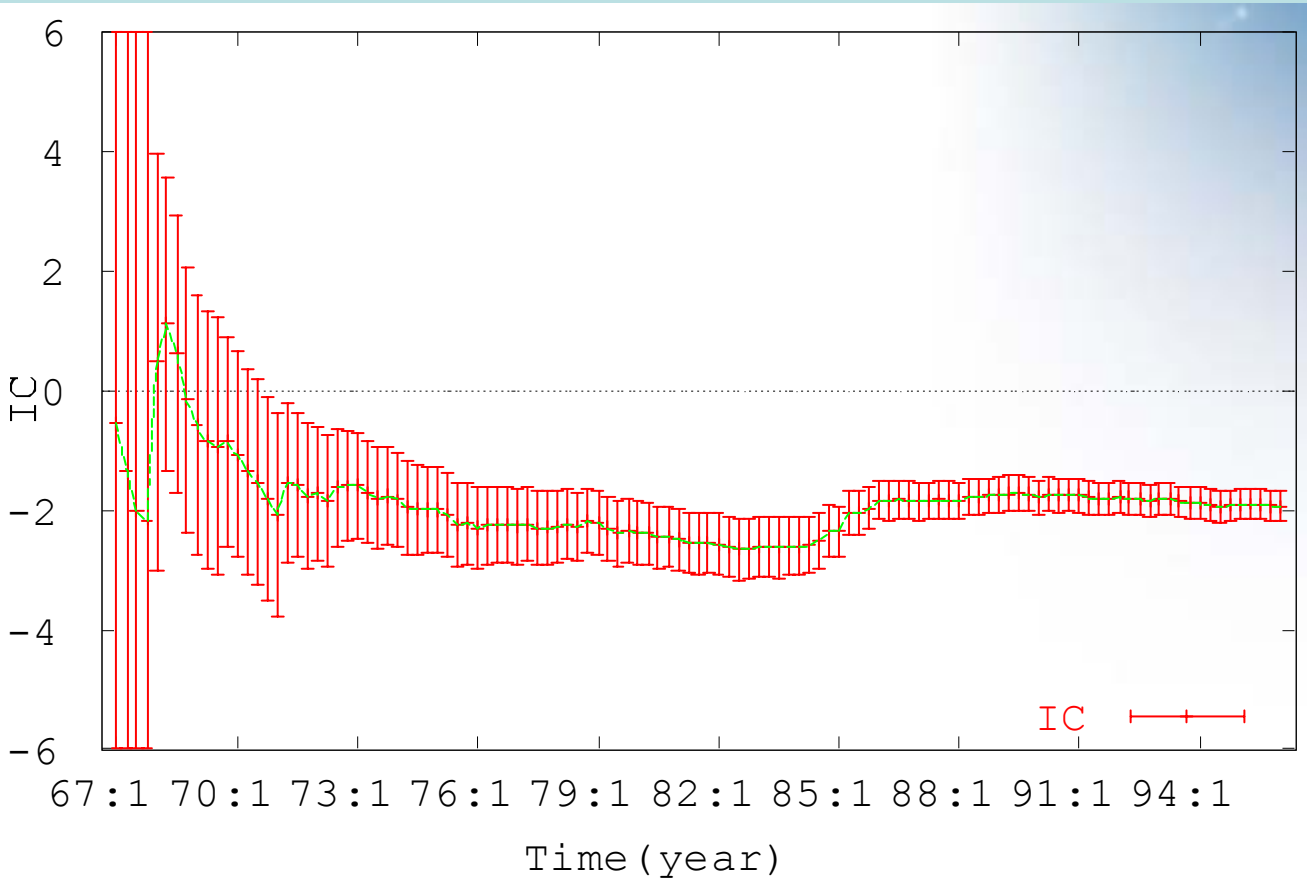
IC development over time

Example digoxin - rash



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BCPNN validation

Retrospective predictive value test

	Signal	Non-signal	Total
+ Associations	42	53	95
- Associations	2	11	13

Signal: Not listed in Martindale (MD) '93 but listed in MD- or PDR '00

Non-signal: Listed in MD '93 or not listed in MD-or PDR '00

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Method comparison

- All measures similar
  - Certainly when large number of cases
  - All based on unexpectedness relative to the rest of the data set
- Difference is in the implementation within process

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Our routine operation

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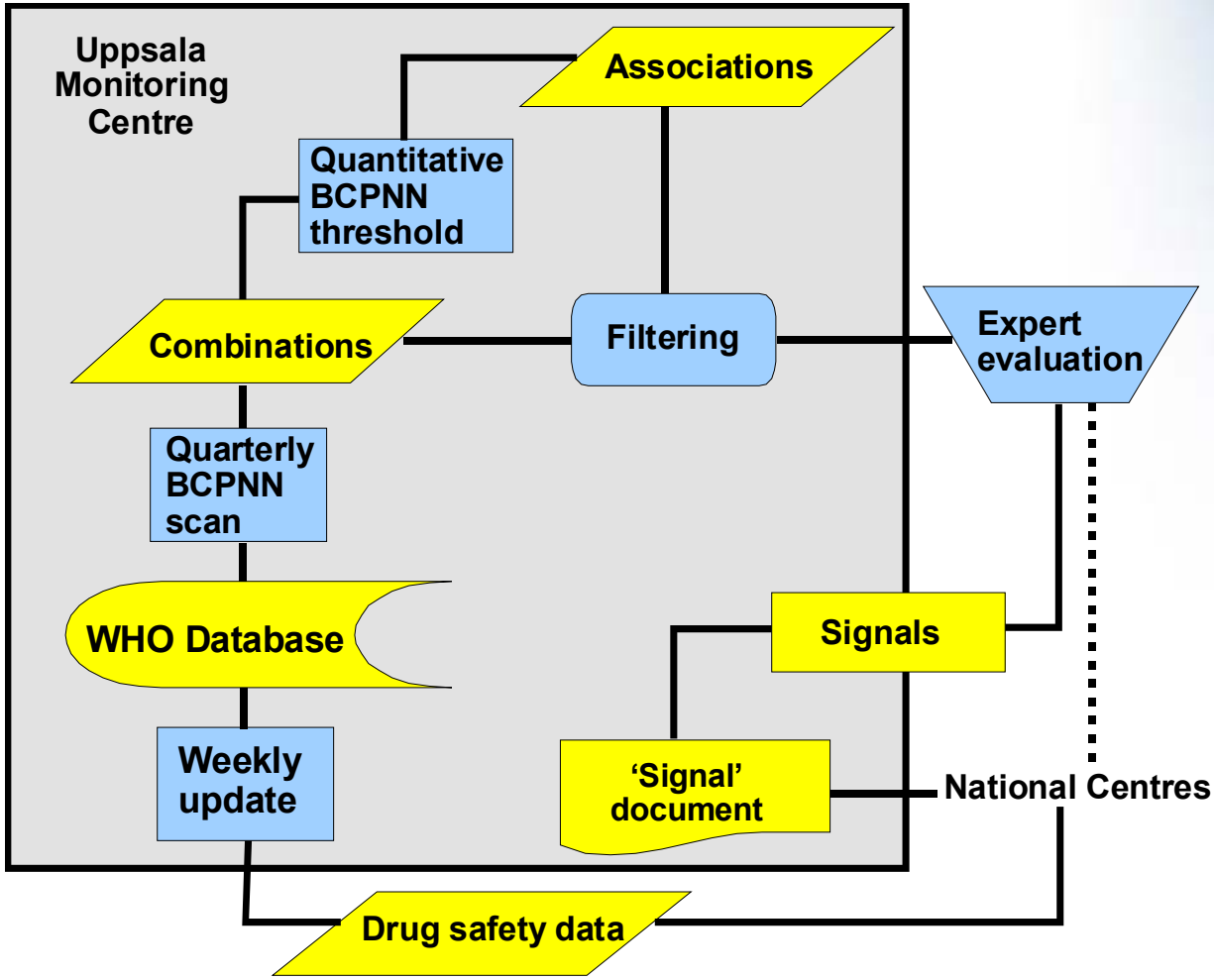
UMC signalling procedure



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Combinations

- IC values for every drug-ADR
  - Using BCPNN (Bayesian Confidence Propagation Neural Network)
  - also IC based on data from previous quarter
- Quantitative filtering for clinical review (IC-2SD newly>0)
- Other filtering
  - Strength of case series information
    - Eg Number of fatalities, rechallenge reports
  - Literature check, year of drug entry into database etc

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Combinations database - example

	Drug name	ADR name	IC	Old IC	IC-2std	Old IC-2std	Ndrug to
1	ABACAVIR	AGITATION	0.42	-0.45	-1.66	-3.37	
2	ABACAVIR	ANAPHYLACTIC SHOCK	0.67	-0.25	-1.40	-3.17	
3	ABACAVIR	ANAPHYLACTOID REACTION	0.36	-0.51	-1.72	-3.43	
4	ABACAVIR	ANXIETY	0.55	-0.35	-1.53	-3.27	
5	ABACAVIR	BRONCHOSPASM	0.41	-0.47	-1.67	-3.39	
6	ABACAVIR	CIRCULATORY FAILURE	1.64	1.31	0.15	-0.42	
7	ABACAVIR	COORDINATION ABNORMAL	0.89	-0.09	-1.19	-3.01	
8	ABACAVIR	COUGHING	0.31	-0.54	-1.77	-3.46	
9	ABACAVIR	DEPRESSION	1.02	0.56	-0.69	-1.53	
10	ABACAVIR	DYSPNOEA	-0.18	-0.97	-2.26	-3.89	

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Examples of WHO signals generated by data mining

- Topiramate and glaucoma
  - Spring 2001
- Antipsychotics and myocarditis
  - Spring 2001
- Olanzapine and granulocytopenia
  - Spring 1998

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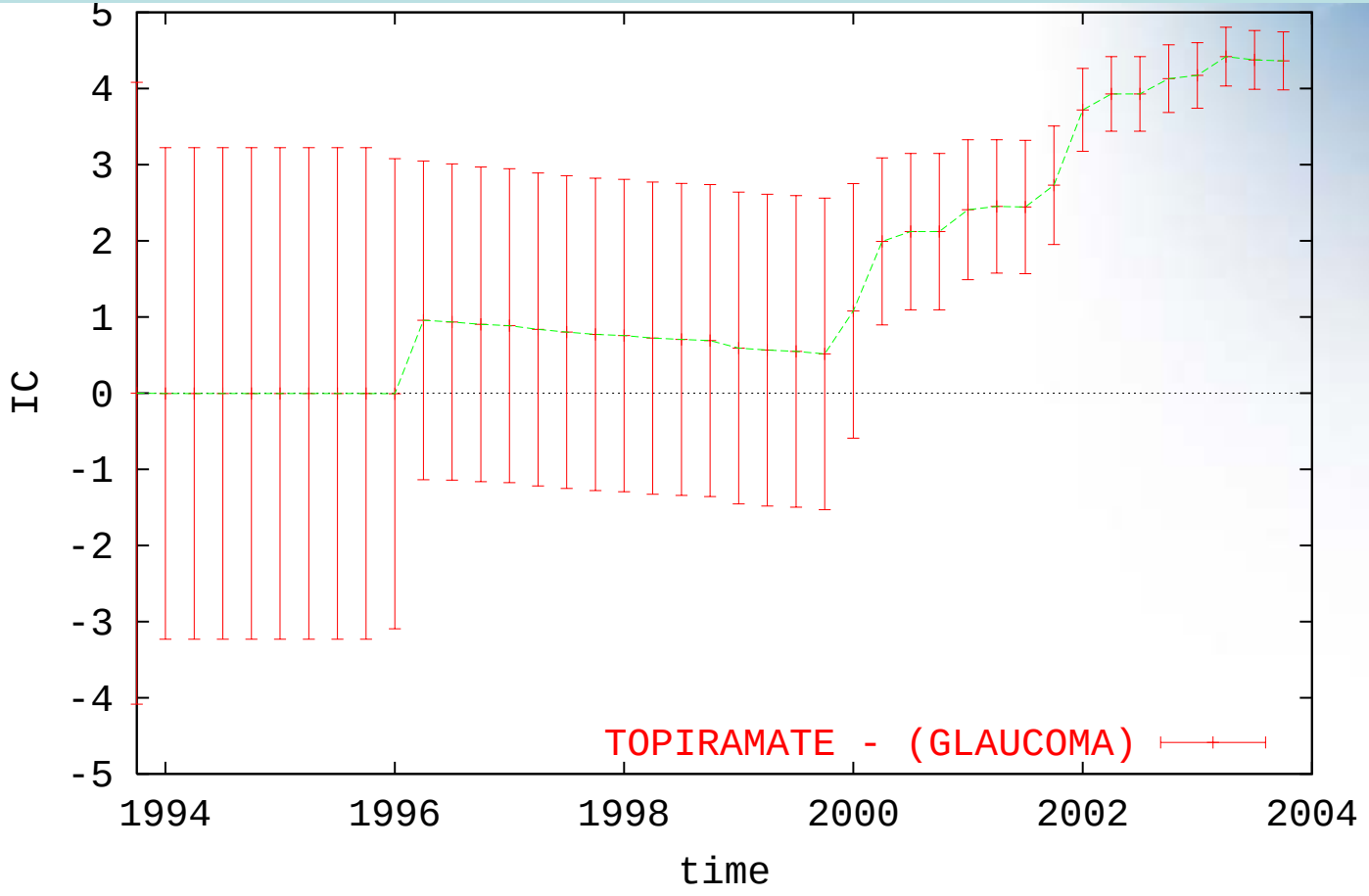
BCPNN timescan

Topiramate - glaucoma



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Topiramate glaucoma

- Combination highlighted quantitatively second quarter 2000
- WHO signal spring 2001
- FDA labelling warning 2004

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RESTRICTED

WHO Collaborating Centre for International Drug Monitoring

SIGNAL

Analyses of Adverse Reaction Reports in the WHO Database · April 2004

WHO Collaborating Centre
for International Drug Monitoring
Stora Torget 3, SE753 20 Uppsala, Sweden
Tel +46 18 65 60 60, Fax +46 18 65 60 80
E-mail: info@who-umc.org

Signals in this issue

Follow-up

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Refining signals

Group effects

- Detect specific drug- specific ADR signal
  - IC [Drug -ADR]
- Examine relation between group and same ADR
  - Group selection made on ATC
  - IC [(ATC group - Drug) - ADR]
- Compare and contrast

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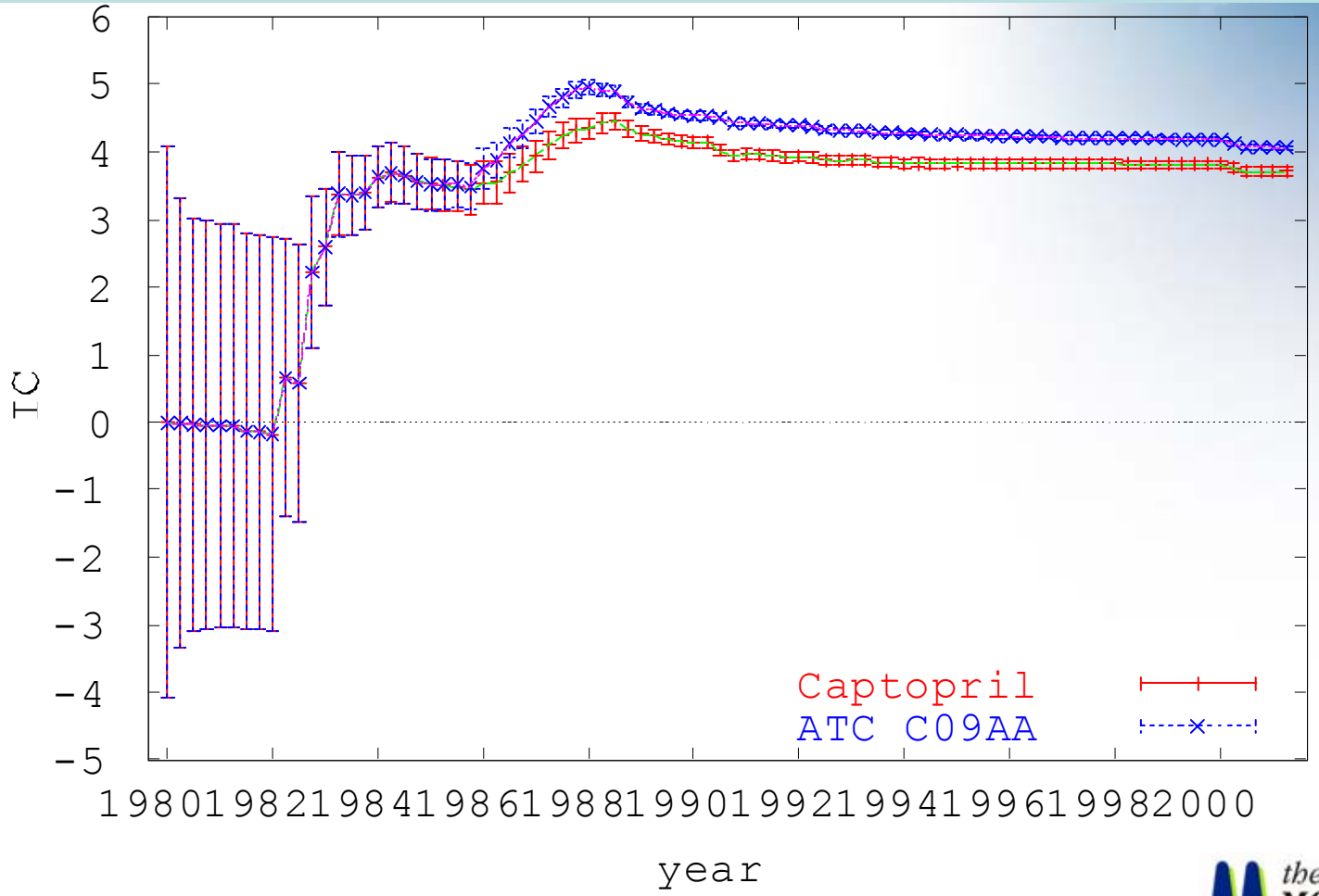
BCPNN timescan

Captopril vs all other ACE inhibitors



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Stratum specific effects

- Rather than comparison to background of whole database compare to a more restricted background
  - Eg IC (Vaccines) to background of paediatric-only ADRs
- Useful for detecting stratum specific effects (and confounders)

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Coxibs

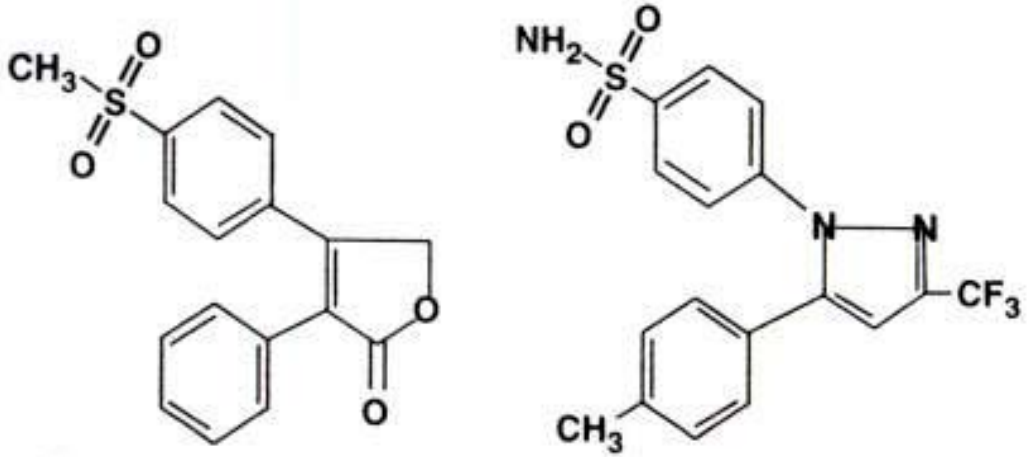

Figure 1. Chemical structures of rofecoxib and celecoxib

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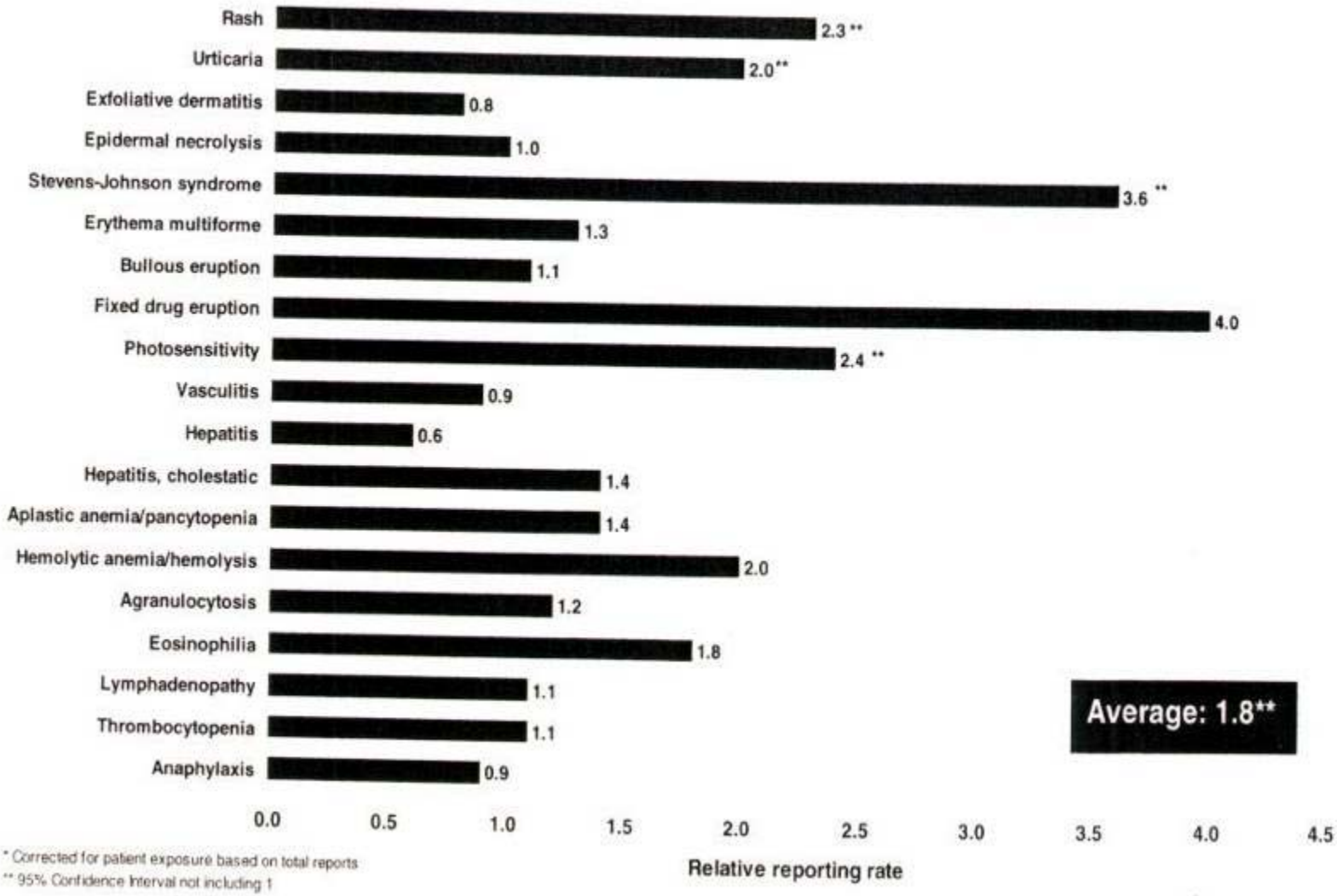
Coxibs

Sulphonamide relative reporting rates



Complex patterns in data

- 'Syndromes' of ADRs partially reported
- Risk groupings
  - E.g. Patients of a certain age, gender, concomitant disease

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Haloperidol pattern

- The highlighted ADRs were:
  - NMS, hypertonia, fever, tremor, confusion, creatine phosphokinase increased, agitation, coma, convulsions, tachycardia, stupor, hypertension, sweating increased, **dysphagia**, leukocytosis, urinary incontinence, apnoea
- All symptoms associated with NMS in standard literature sources
  - not dysphagia: but published case reports exist

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Haloperidol pattern

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- All symptoms associated with NMS in standard literature sources
  - not dysphagia: but published case reports exist

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Fluoxetine and Paroxetine

Pattern comparison

- 20 ADRs were in both paroxetine and fluoxetine pattern
  - Paroxetine pattern had 28 ADRs, fluoxetine had 26 ADRs
  - Extra paroxetine ADRs:
    - Hypoaesthesia, paraesthesia, vertigo, emotional lability, flushing, vision abnormal, concentration impaired, muscle weakness
  - Extra fluoxetine ADRs:
    - Tachycardia, Abdominal pain, weight decrease, dyspnoea, chest pain, rigors

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Amitriptyline pattern

- 16 ADRs included in pattern
- ADRs included that were neither seen with paroxetine nor fluoxetine:
  - Hallucination, Hypertonia, Speech disorder

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Summary

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WHO database

- Strengths
  - Database size (nearly 4 million cases, 200+ fields)
  - Number of new reports (about 60,000 quarterly)
  - International coverage since 1968
    - Reporting of all marketed drugs from 74 countries
- Weaknesses
  - Missing data
  - Under-reporting
  - No denominator
  - 'Noise'
  - Duplication of reports
  - Delayed reporting

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WHO database

- BUT few alternatives to spontaneous reporting for the detection of:
    - Rare unpredictable ADRs
    - Interactions
    - High risk patient groups

  (Although not yet especially effective for the latter…
- Other large data sets have similar strengths and weaknesses

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Summary

- IC analysis developed specifically for signal detection on WHO database
  - A quantitative tool for highlighted unexpected combinations of clinical review
  - Clinical judgement more important than IC
  - Bayesian implementation causes dampening of IC at low values, this is deliberate
- Similar methods in use on other databases
- Methods are not perfect, nor is any other!

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Summary of analysis of ICSRs

- The BCPNN is a tool developed to enhance rather than replace signal detection procedures in the WHO database
  - It has been in routine use in the initial highlighting of associations for **clinical review** since 1999
  - And now is used as a tool for
    - further analyses of potential signals
    - and detection of complex dependencies in the data

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- Data mining tools were developed to enhance rather than replace signal detection procedures in large databases of ICSRs

  - They have been in routine use in the initial highlighting of associations for **clinical review** since 1999
  - And now are used as successful tools for
    - further analyses of potential signals
    - and detection of complex dependencies in the data
  - They are methods for hypothesis generation
    - NOT hypothesis testing on WHO data

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The Future

With careful classification, it will be possible download data on ADRs, drug chemical structures and human genomics and to find hitherto unsuspected patterns and relationships.

Our problem will be how to interpret them!

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"We must serve patients"

Only patients can tell us if we are doing a good job!

Consumer groups

Patient groups

Health care industry & researchers

Device industry

Pharma ⟷ WHO ⟷ Regulators

UMC

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Some references

Bate, A. The Use of a Bayesian Confidence Propagation Neural Network in Pharmacovigilance: Umeå University, 2003.

Bate, A., Lindquist M., Edwards I.R., et al. A Bayesian neural network method for adverse drug reaction signal generation. *Eur J Clin Pharmacol* 1998;**54**(4)**:**315-21.

Bate, A., Lindquist M., Edwards I.R., Orre R. A data mining approach for signal detection and analysis. *Drug Saf* 2002a;**25**(6)**:**393-7.

Bate, A., Orre R., Lindquist M., Edwards I.R. Pattern recognition using a recurrent neural network and its application to the WHO database. *Pharmacoepidemiol Drug Saf* 2001b;**10**(S1)**:**S163 (abstract).

Edwards, I.R., Fucik H. Impact and Credibility of the WHO Adverse Reaction Signals. *Drug Inf J* 1996;**30**(2)**:**461-464.

Edwards, I.R., Lindquist M., Wiholm B.E., Napke E. Quality criteria for early signals of possible adverse drug reactions. *Lancet* 1990;**336**(8708)**:**156-8.

Fucik, H., Backlund, A., Farah, M. Building a Computerized Herbal Substance Register for Implementation and Use in the World Health Organisation International Drug Monitoring Programme. *Drug Inf J* 2002;**36:**839-854.

Lindquist, M. The WHO Programme for International Drug Monitoring: The Present and Future. In: Mitchard, M., ed. Electronic Communication Technologies. Buffalo: Interpharm Press Inc., 1998: 527-549.

Lindquist, M. Seeing and Observing in International Pharmacovigilance - Achievements and Prospects in Worldwide Drug Safety: University of Nijmegen, 2003.

Lindquist, M., Edwards I.R., Bate A., Fucik H., Nunes A.M., Ståhl M. From Association to Alert - a revised approach to International Signal Analysis. *Pharmacoepidemiol Drug Saf* 1999;**8:**S15-S25.

Lindquist, M., Stahl M., Bate A., Edwards I.R., Meyboom R.H. A retrospective evaluation of a data mining approach to aid finding new adverse drug reaction signals in the WHO international database. *Drug Saf* 2000;**23**(6)**:**533-42.

Lindquist, M. Data quality management in pharmacovigilance. *Drug Saf* 2004 (in press).

Ståhl, M., Edwards I.R., Bowring G., Kiuru A., Lindquist M. Assessing the Impact of Drug Safety Signals from the WHO Database Presented in 'SIGNAL': Results from a Questionnaire of National Pharmacovigilance Centres. *Drug Saf* 2003;**26**(10)**:**721-7.

Ståhl, M., Lindquist, M., Edwards, I.R., Brown, E.G. Introducing Triage Logic as a New Strategy for the Detection of Signals in the WHO Drug Monitoring Database. *Drug Saf* 2003;**26**(10)**:**721-7.

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