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Nederlands Bijwerkingen Centrum
Netherlands Pharmacovigilance Centre

Pharmacovigilance

What can be learned from drug safety ?

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Netherlands Pharmacovigilance Centre Lareb

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Heijermanslezing, 14 december 2007

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Outline of the presentation

- What is pharmacovigilance?
- Causality assessment
- Who should report?
- International co-operation
- Final remarks

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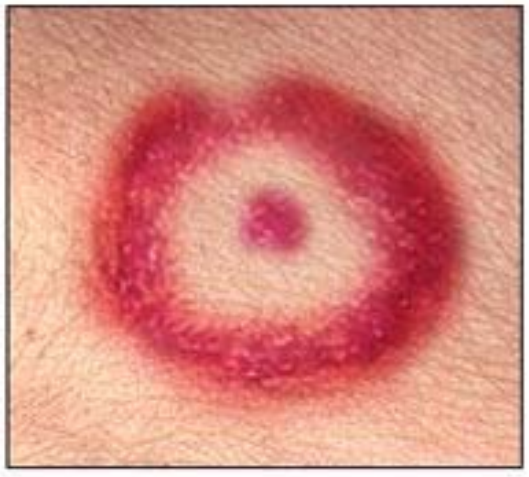
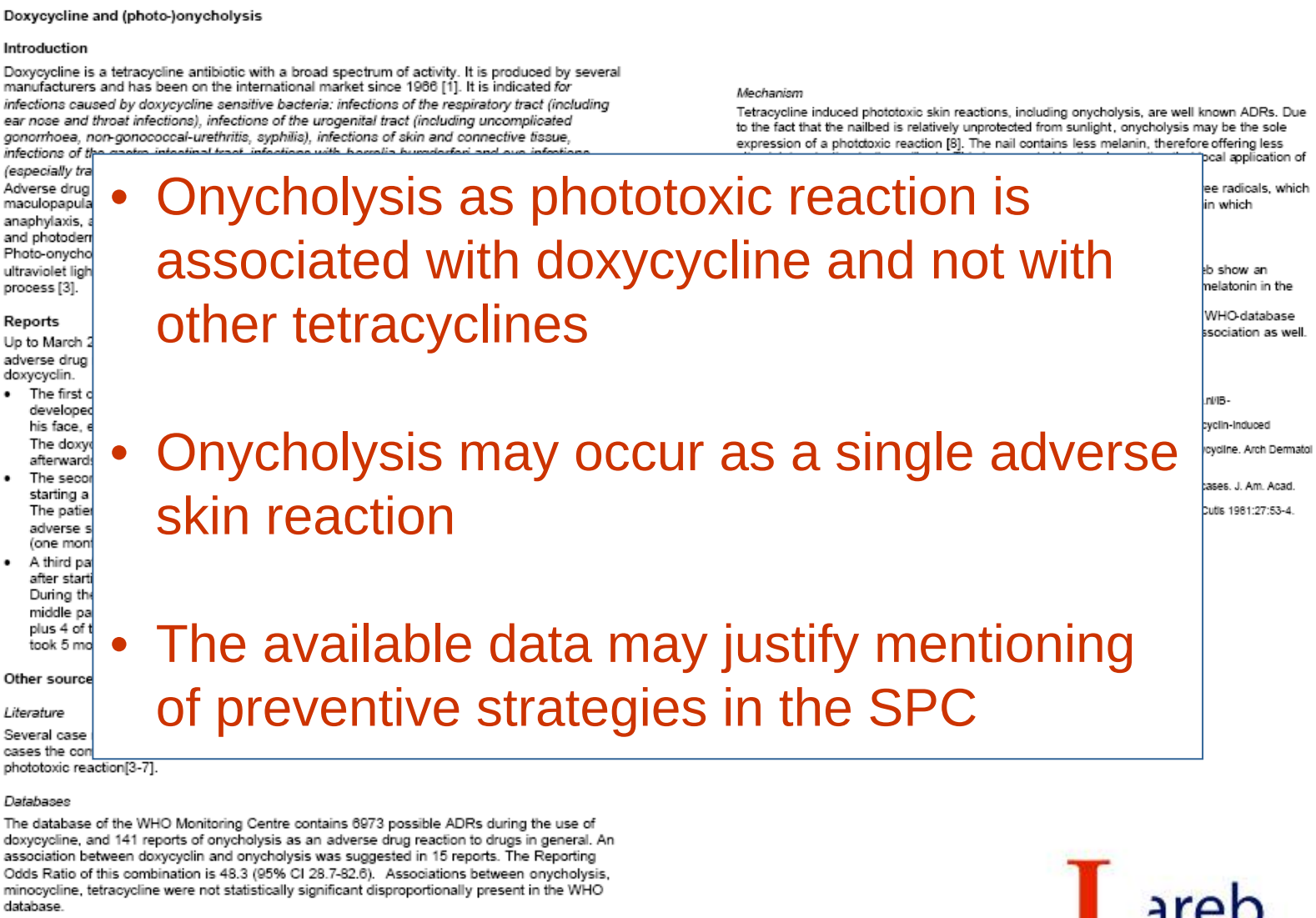
A report Lareb received

- Female, 58
- Doxycycline as prophylaxis to prevent Lyme disease
- 1 dd 200 mg, 15 days



Report to Medicines Evaluation Board



Doxycycline and (photo-)onycholysis

Introduction

Doxycycline is a tetracycline antibiotic with a broad spectrum of activity. It is produced by several manufacturers and has been on the international market since 1966 [1]. It is indicated *for infections caused by doxycycline sensitive bacteria: infections of the respiratory tract (including ear nose and throat infections), infections of the urogenital tract (including uncomplicated gonorrhoea, non-gonococcal-urethritis, syphilis), infections of skin and connective tissue, infections of the gastro-intestinal tract, infections with borrelia burgdorferi and eye infections (especially tra*

Adverse drug
maculopapula
anaphylaxis, a
and photoderm
Photo-onycho
ultraviolet ligh
process [3].

Reports

Up to March 2
adverse drug
doxycyclin.

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Other source

Literature

Several case
cases the con
phototoxic reaction[3-7].

Databases

The database of the WHO Monitoring Centre contains 6973 possible ADRs during the use of doxycycline, and 141 reports of onycholysis as an adverse drug reaction to drugs in general. An association between doxycyclin and onycholysis was suggested in 15 reports. The Reporting Odds Ratio of this combination is 48.3 (95% CI 28.7-82.6). Associations between onycholysis, minocycline, tetracycline were not statistically significant disproportionally present in the WHO database.

Mechanism

Tetracycline induced phototoxic skin reactions, including onycholysis, are well known ADRs. Due to the fact that the nailbed is relatively unprotected from sunlight, onycholysis may be the sole expression of a phototoxic reaction [8]. The nail contains less melanin, therefore offering less

pcal application of

ee radicals, which
in which

b show an
melatonin in the

WHO-database
ssociation as well.

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cyclin-Induced

oycline. Arch Dermatol

ases. J. Am. Acad.

Cutis 1981;27:53-4.

- Onycholysis as phototoxic reaction is associated with doxycycline and not with other tetracyclines
- Onycholysis may occur as a single adverse skin reaction
- The available data may justify mentioning of preventive strategies in the SPC

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DRUG POINTS

Photo-onycholysis associated with the use of doxycycline

Anneke Passier, Astri Smits-van Herwaarden, Eugène van Puijenbroek

The Netherlands Pharmacovigilance Centre Lareb received five reports concerning photo-onycholysis associated with the use of doxycycline (table). All five patients used 200 mg of doxycycline a day for the prophylactic treatment of Lyme disease after tick bite. In all cases the affected nails had been exposed to the sun during the summer. All patients showed (partial) recovery after several months. To our knowledge, no other factors (either specific physical disorders or concomitant drug use) were responsible for the onycholysis in these patients.

Although the association between doxycyline and onycholysis has been sparsely reported,[1-3] the circumstances of the patients we report differ from those described elsewhere. All five patients used doxycycline exclusively for the prophylactic treatment of Lyme disease; we did not find any studies that suggested a possible connection between Lyme disease and onycholysis.

The mechanism of this phototoxic reaction is not fully understood. The nail bed is relatively unprotected from sunlight and contains less melanin (implicating less ultraviolet protection) than other skin sites. Onycholysis may, therefore, be the sole expression of a [illegible] injury to mitochondria, the preferential intracellular site of localisation of doxycycline.[5]

Borrelia burgdorferi—which causes Lyme disease—is becoming a more common coinfecting pathogen, and doctors are developing an increased knowledge and awareness concerning the potential risks of tick bites. Due to these developments, more high dosages of doxycycline may be prescribed more often. Considering the relatively good health of the patients using doxycycline for the given indication, exposure to sunlight is the likely cause of onycholysis. These patients should avoid exposure of their nails to the sun shortly after using doxycycline.

Funding: None.

Competing interests: None declared.

1 Yong CK, Prendiville J, Peacock DL, Wong LT, Davidson AG. An unusual presentation of doxycycline-induced photosensitivity. *Pediatrics* 2000;106:E13.
2 Cavens TR. Onycholysis of the thumbs probably due to a phototoxic reaction from doxycycline. *Cutis* 1981;27:53-4.
3 Frank SB, Cohen HJ, Minkin W. Photo-onycholysis due to tetracycline hydrochloride and doxycycline. *Arch Dermatol* 1971;103:520-1.

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BMJ 2004;329:265

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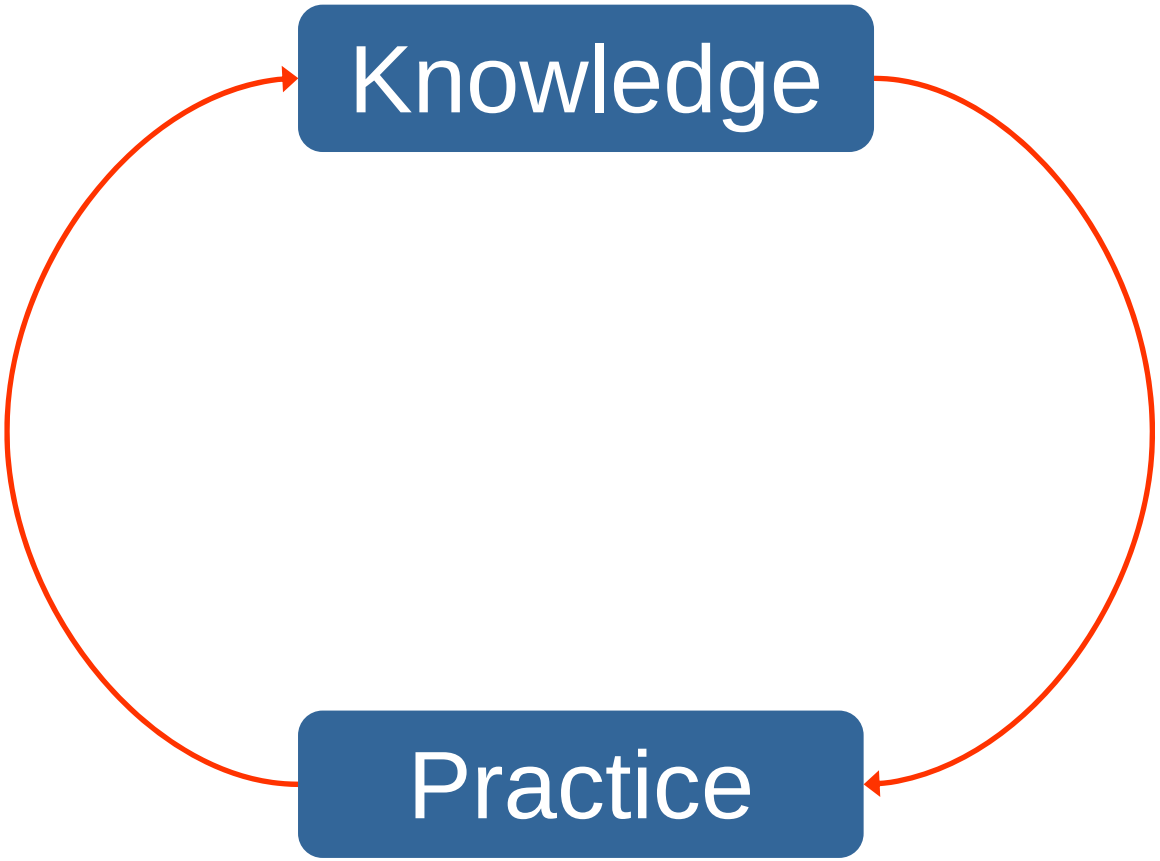
Circle of practice and knowledge



What is pharmacovigilance?

WHO:

‘The *science* and *activities* relating to the detection, assessment, understanding and prevention of adverse drug effects or any other drug related problem’

The Importance of Pharmacovigilance, WHO 2002

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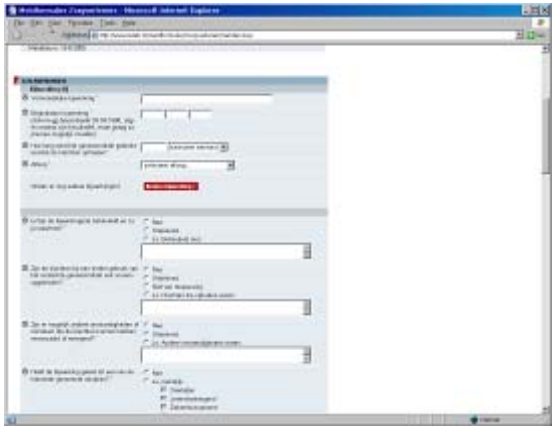
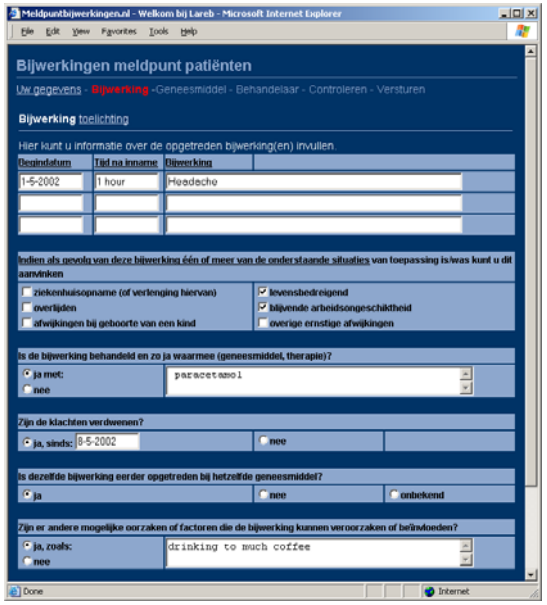
Receipt of reports

- Paper forms
- Website healthcare professionals
- Website patient reporting





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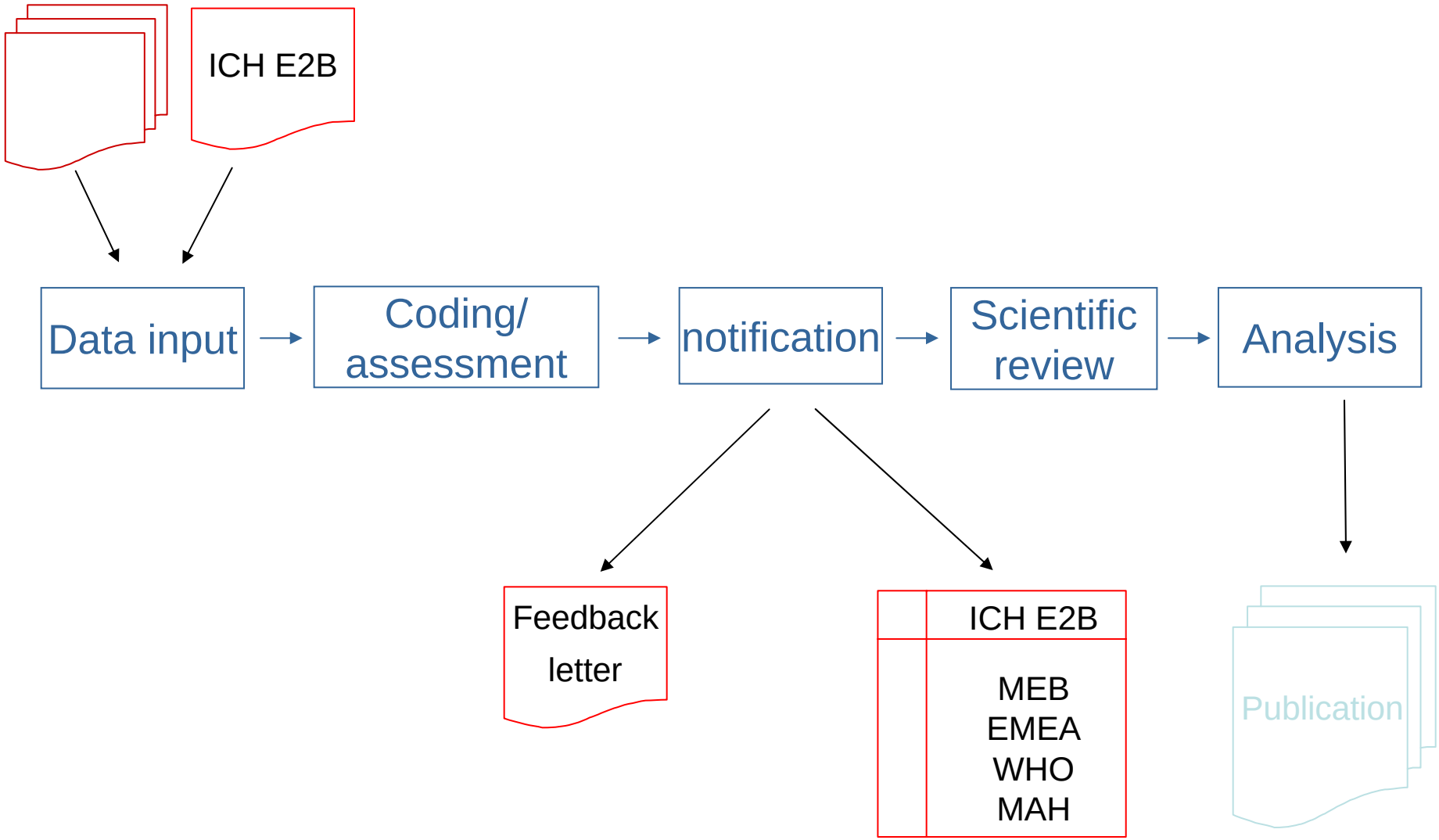
Processing of ADRs



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Causality assessment

- Background information / Mechanism
- Involvement of co-factors

  indication, risk-factors and concomitantly used medication

- Time-course

  period of latency; dechallenge or rechallenge

Reported before?

- Safety report overview
  - Detail
  - Line-listing
- Literature
- WHO-database

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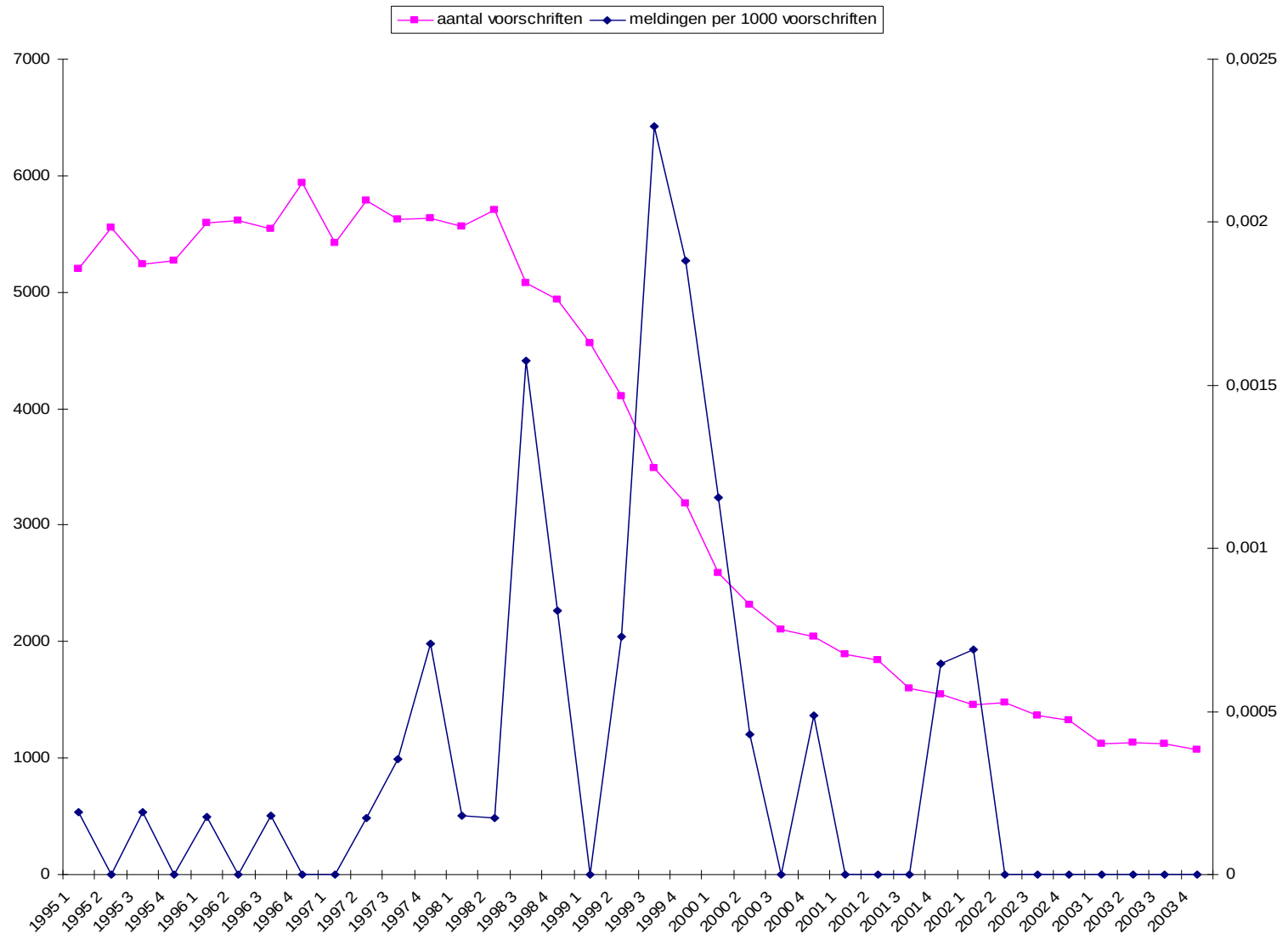
Vigabatrin

relation between reports and prescriptions



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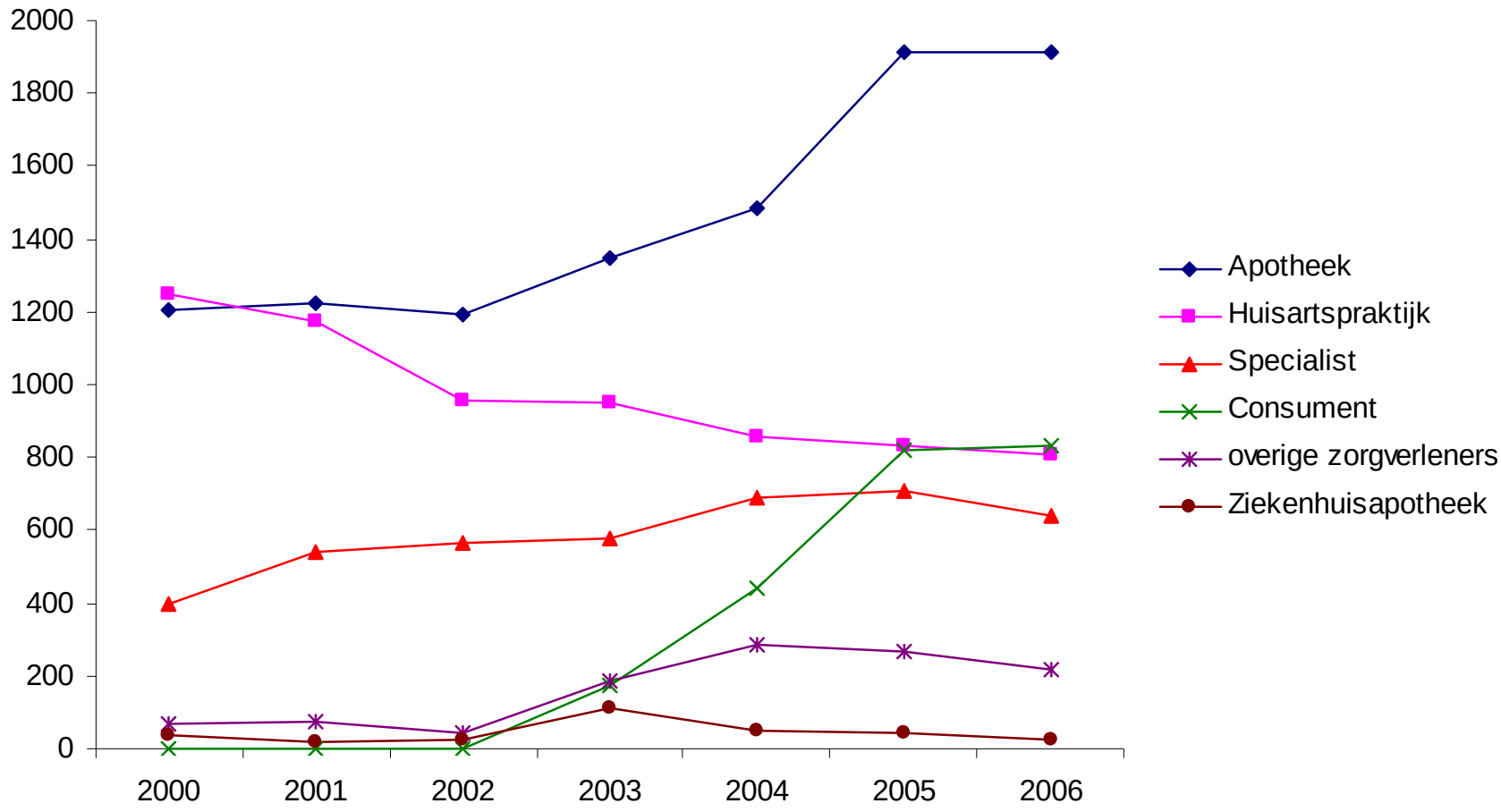
Source of reports



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Serious reports

Percentage of serious reports:

- Patients 21.3%
- Physicians 33.7%
- Pharmacists 9.2%

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Patient reports: advantages

- Patients often provide more detailed information
- Information on actual drug use, also on OTC
- ADR is reported without a medical filter
- Patients frequently report on psychofarmaca

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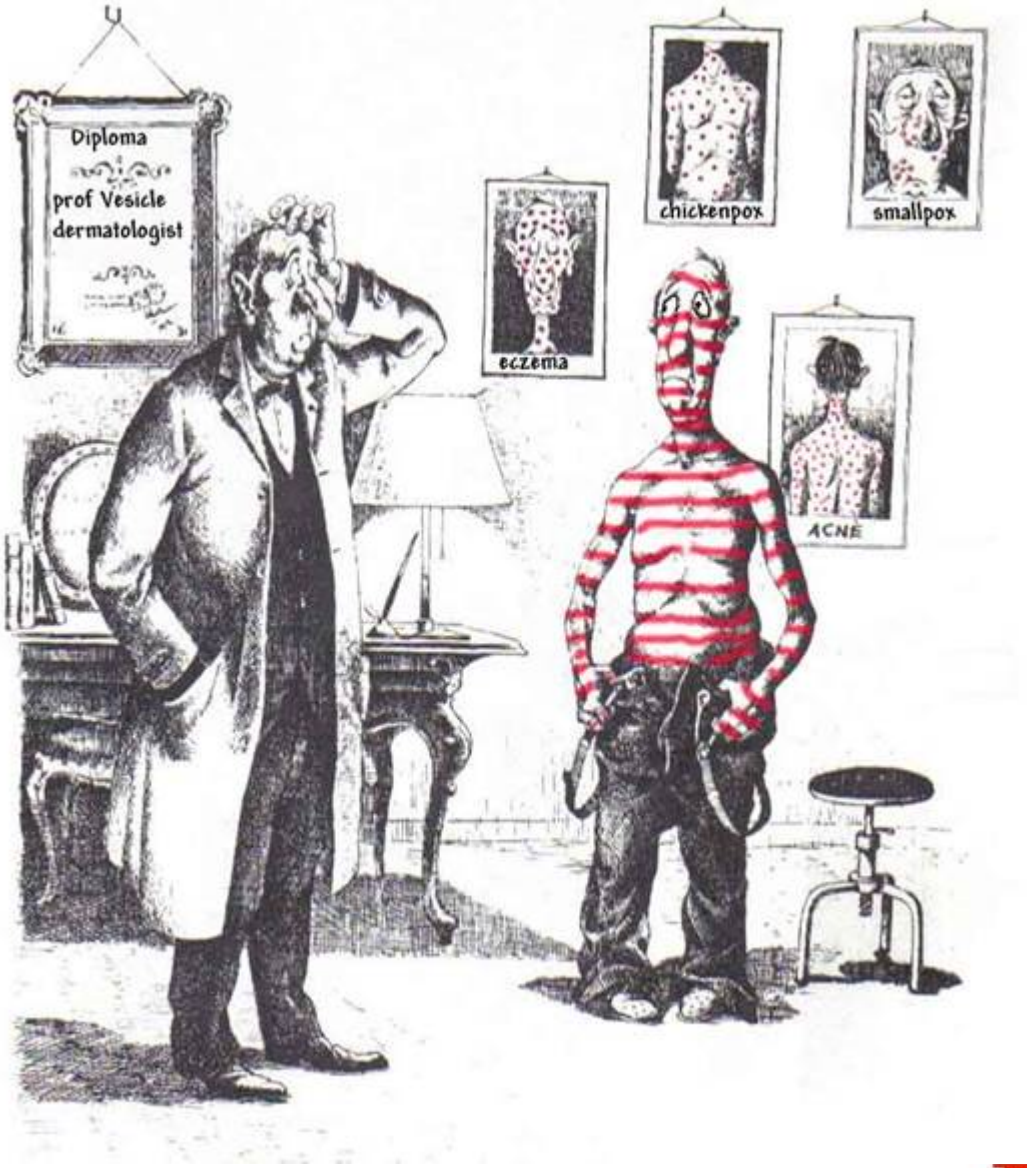
Diploma
prof Vesicle
dermatologist
eczema
chickenpox
smallpox
ACNE

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Louis Pasteur:

‘Chance favours only the prepared mind…’

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Je gaat het pas zien als je het doorhebt
Over Cruijff en leiderschap
Pieter Winsemius
BALANS

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1957 - 2007

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THALIDOMIDE AND CONGENITAL ABNORMALITIES

SIR,—Congenital abnormalities are present in approximately 1·5% of babies. In recent months I have observed that the incidence of multiple severe abnormalities in babies delivered of women who were given the drug thalidomide (' Distaval ') during pregnancy, as an antiemetic or as a sedative, to be almost 20%.

These abnormalities are present in structures developed from mesenchyme—i.e., the bones and musculature of the gut. Bony development seems to be affected in a very striking manner, resulting in polydactyly, syndactyly, and failure of development of long bones (abnormally short femora and radii).

Have any of your readers seen similar abnormalities in babies delivered of women who have taken this drug during pregnancy?

Hurstville, New South Wales. W. G. MCBRIDE.

*** In our issue of Dec. 2 we included a statement from the Distillers Company (Biochemicals) Ltd. referring to " reports from two overseas sources possibly associating thalidomide (' Distaval ') with harmful effects on the fœtus in early pregnancy ". Pending further investigation, the company decided to withdraw from the market all its preparations containing thalidomide.—ED.L.

W.G. McBride, *The Lancet 1961 dec 16: 1358*

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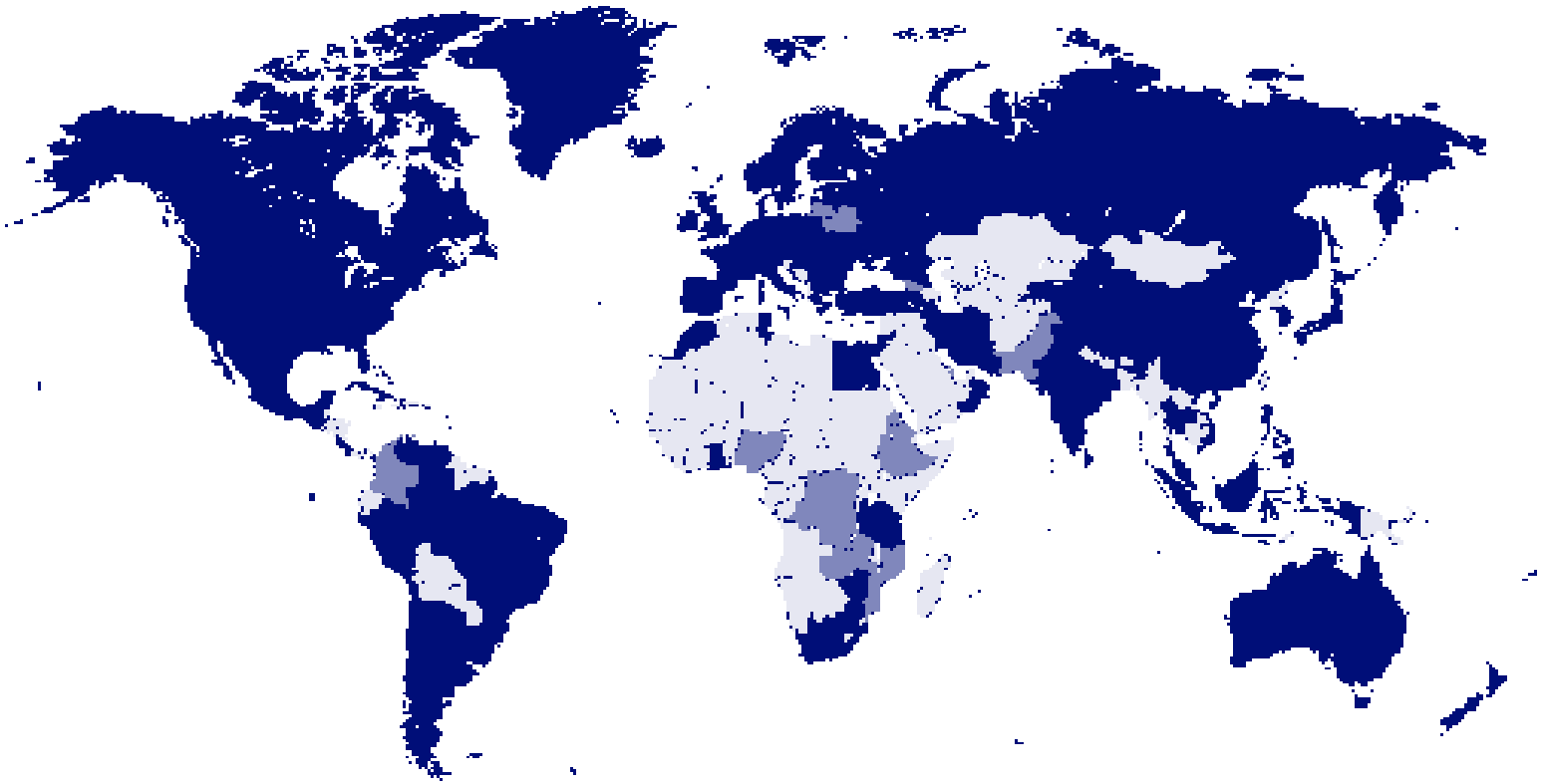
Countries participating in WHO Drug Monitoring Programme



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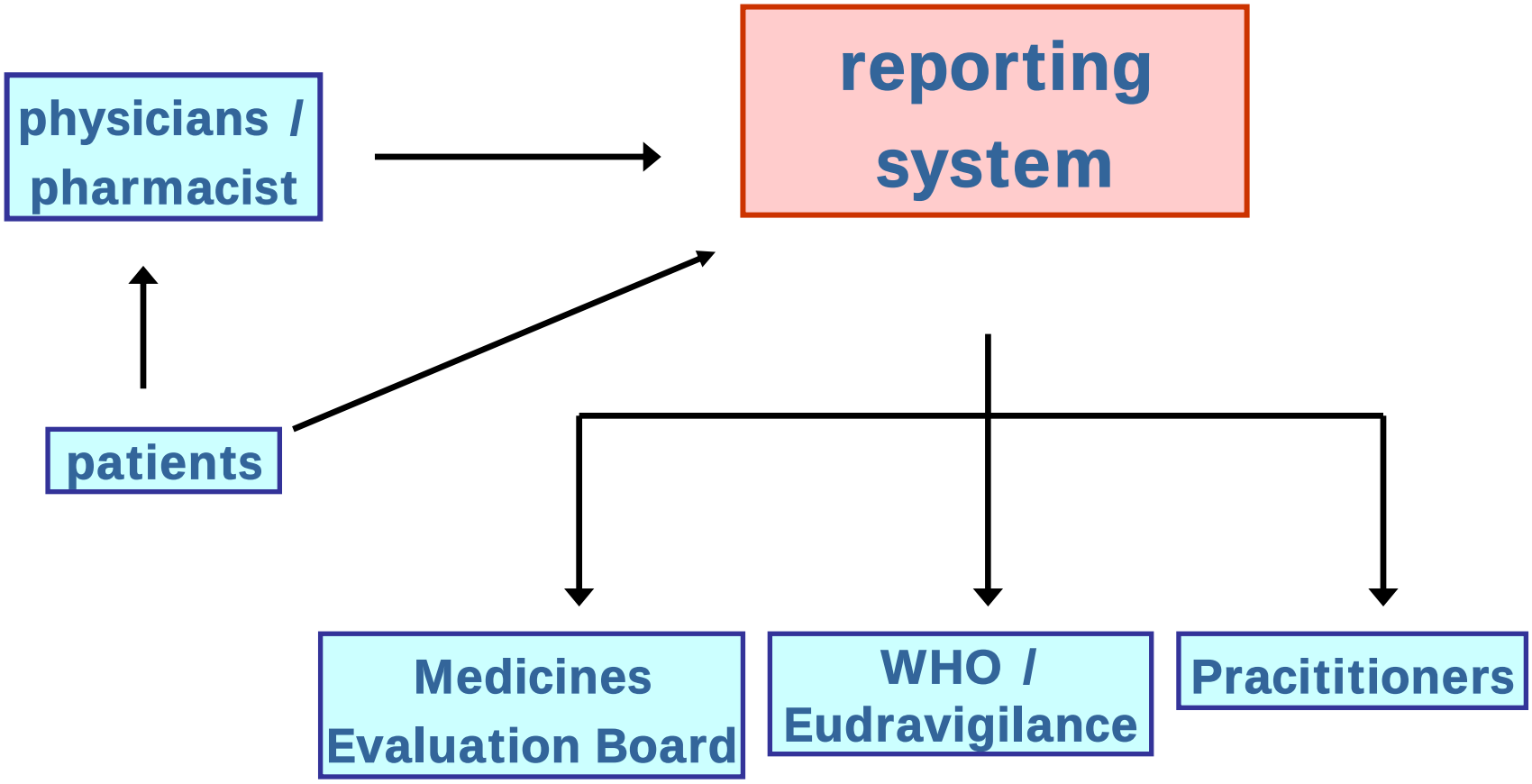
Role of Lareb



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Goals of ADR reporting

1. *Signal detection*: finding new signals

2. *Awareness* of physicians and pharmacists:
   - prevention of ADRs
   - recognition of ADRS

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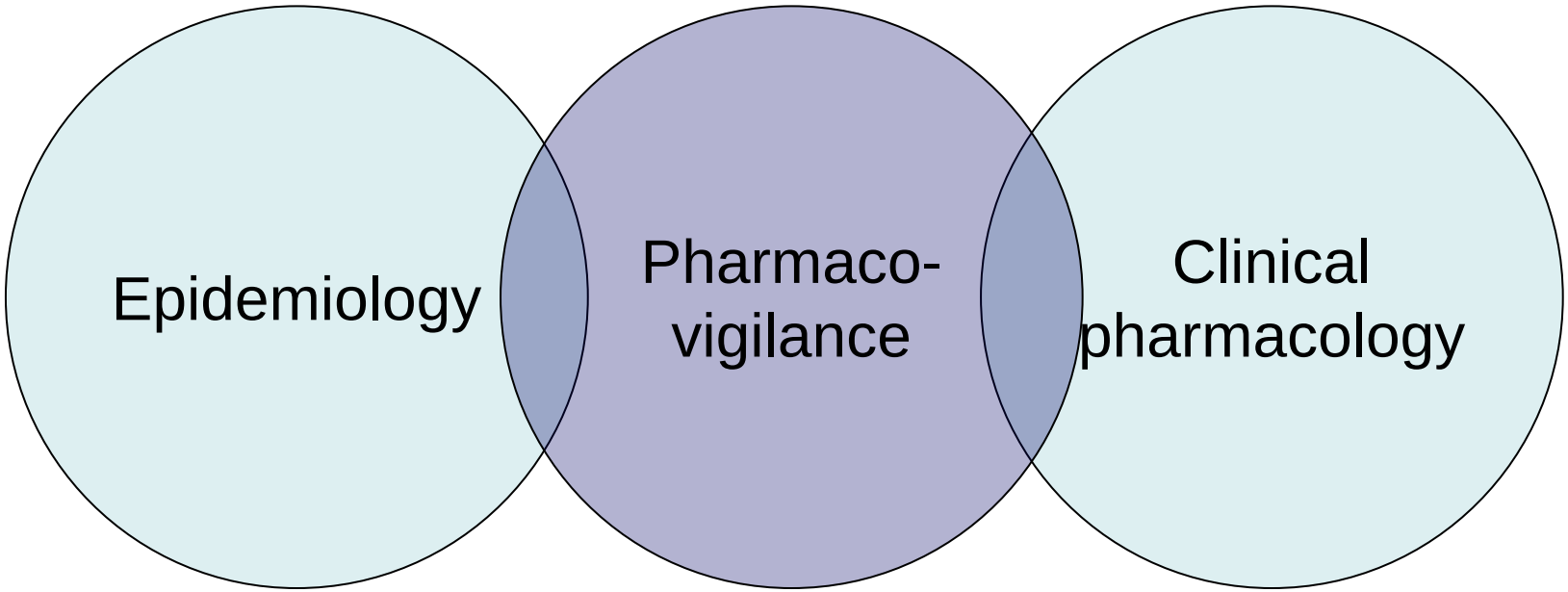
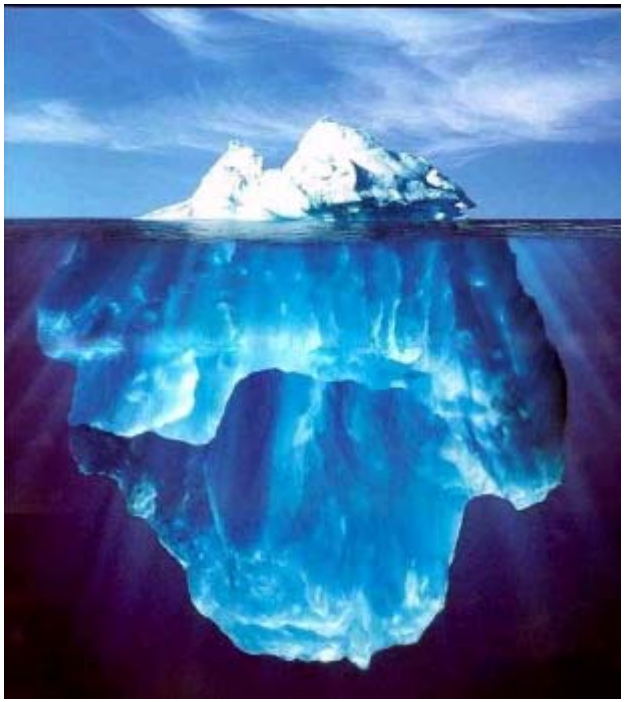
Position of pharmacovigilance

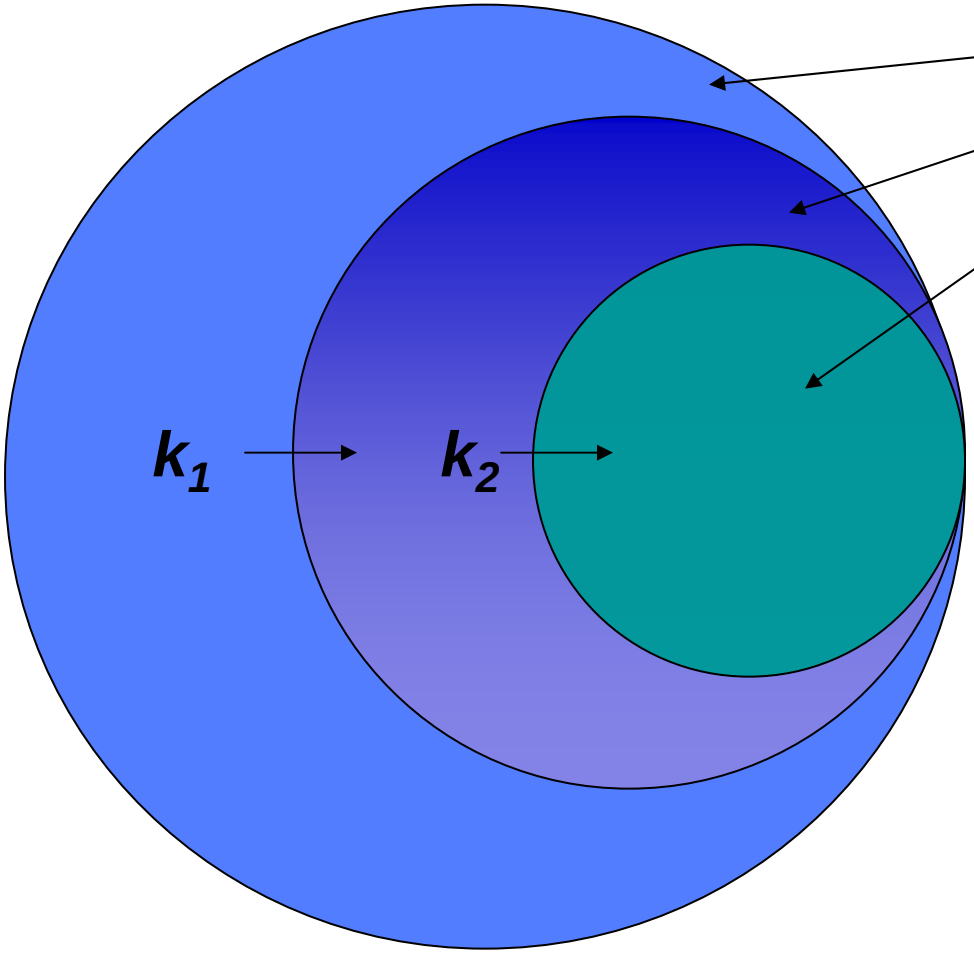


The tip of the iceberg



underreporting

Statistical signal detection



Drug using population

ADR experiencing population

ADR reported population

k_1 incidence ratio

k_2 reporting ratio

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The value of cases

Table 44.1. Drug safety issues and their evidence.

Drug	Safety Concern	Key evidence	Regulatory action
Trovofloxacin	Hepatotoxicity	Spontaneous ADRs	Withdrawn
Tolcapone	Hepatotoxicity	Spontaneous ADRs	Suspended
Cisapride	QT prolongation cardiac arrhythmias	Spontaneous ADRs	Patient registration – licences subsequently cancelled
Bupropion	Seizures drug interactions	Spontaneous ADRs	Posology change warnings
Cerivastatin	Rhabdomyolysis	Spontaneous ADRs	Withdrawn
Hormone replacement therapy	CVS risk and cancer long term	Epidemiological studies	Warnings and restriction of indication
SSRIs	Suicidal behaviour in children	Clinical trials	Warnings accompanied by clinical guidance
COX IIs	CVS risk	Clinical trials	Warnings and clinical guidance
Topical macrolide immunosuppressants	Risk of cancer	Spontaneous reports	Restriction of use risk management plan

J.Raine in ‘Pharmacovigilance’, 2007

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UK/USA: 11 withdrawals 1999-2001

- 8/11 (73%): evidence from spontaneous reports
- Four times: only spontaneous reports
- Two times: randomised study

Similarities and differences

Case by case

- Value of the individual report
- Frame of reference: experience of reporter and assessor
- Signal refers to the selected cases

Statistical signal detection

- All reports are equal
- Frame of reference: (part of) dataset
- Signal also refers to other reports in the dataset

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VOELEN DAT AAN HUN WATER

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medicines, drugs or coffee ?

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