




40 years of medicine safety monitoring – *looking back*

A.C van Grootheest MD PhD
Director Netherlands Pharmacovigilance Centre Lareb
Professor of Pharmacovigilance University of Groningen

World Health Organization

WHO Programme for International Drug Monitoring

1968 – 2008

- Some history
- Some background
- Some evaluation

What happened last half century?

1950	cure	pharmacology
1960	tolerance	toxicology
1970	efficacy	clinical pharmacology
1980	safety	pharmacovigilance
1990	costs	pharmacoeconomics
2000	risk/ public health	pharmacoepidemiology
2010?	genomics	pharmacogenomics

Moride, ISPE 2008




1952



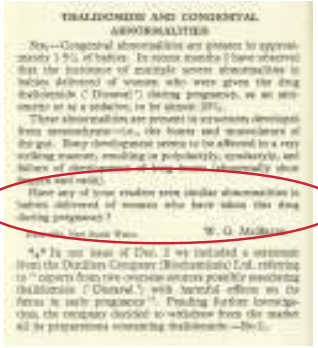

2007

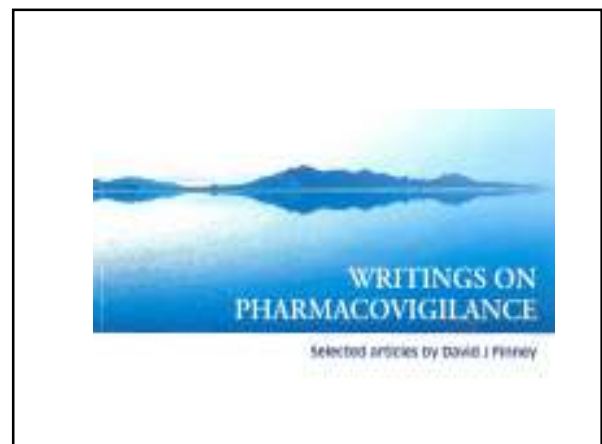
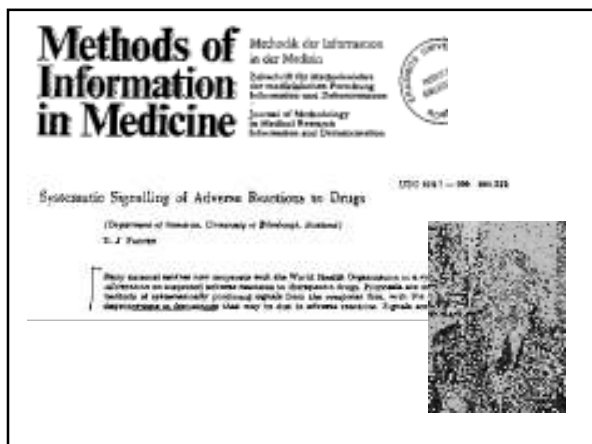
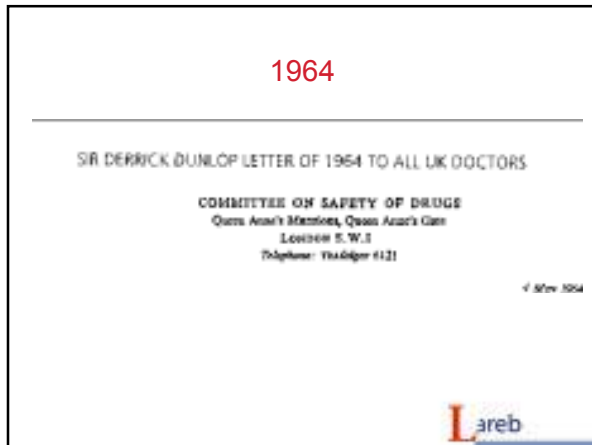
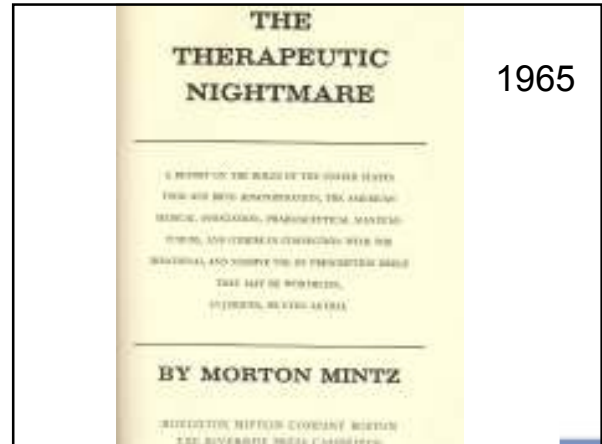
1957 - 1961




Thalidomide disaster

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



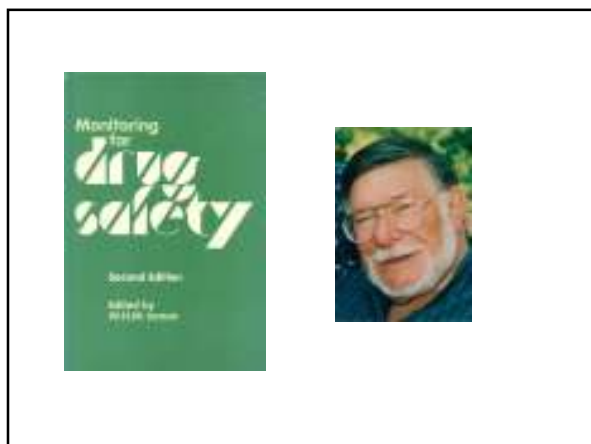
How did the programme start?

- 1969 WHO Report
- 1970 Official start in Geneva
- 1972 Technical Report No.498
- 1974 First National Centres Meeting
- 1978 Programme moved to Uppsala
Sten Olsson, Cecilia Biriell



Founding countries

- USA
- Denmark
- Australia
- Canada
- Germany
- Great Britain
- Netherlands
- New Zealand
- Sweden
- Ireland



Many more names....

- Ed Napke - 'pigeon hole system'
- Bruce Royal – first director of the programme
- Åke Lijestränd – Sweden
- Ron Meyboom – pioneer from the beginning



The word *Pharmacovigilance*

Being vigilant regarding drugs

Started in France in the regional centres

Internationally introduced around 1980
by prof. René Royer

Definition by WHO in 2002: *science and activities*



R.H.B. Meyboom

'Regarding the detection of adverse drug reactions, experience learns us that Spontaneous Reporting Systems can not be replaced by any other method yet'

Ned Tijdschr Geneesk 1986



The value of spontaneous reports

Table 44.1 Drug safety issues and their evidence

Drug	Safety Concern	Evidence	Regulatory action
Ticofloxacin Sibapone Cisapride	Hepatotoxicity Hepatotoxicity QT prolongation cardiac arrhythmias	Spontaneous ADRs Spontaneous ADRs Spontaneous ADRs	Withdrawn Suspended Patient registration – finally subsequently cautioned
Etoposide	Seizures (drug interactions)	Spontaneous ADRs	Package change warning
Levodopa Homocysteine implantation therapy	Myocarditis CNS risk and cancer lung cancer	Spontaneous ADRs Epidemiological studies	Withdrawn Warnings and restrictions of indication
999s	Sexual behaviour in children	Clinical trials	Warning accompanied by clinical guidance
COX-2s	CVD risk	Clinical trials	Warnings and clinical guidance
Topical minoxidil (anti-hypertensives)	Risk of cancer	Spontaneous reports	Restrictions of use with management plan

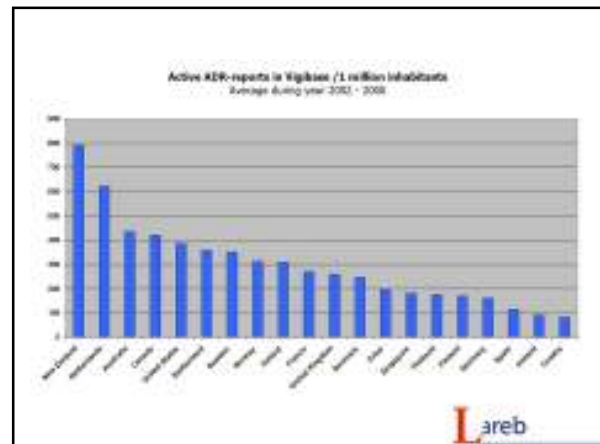
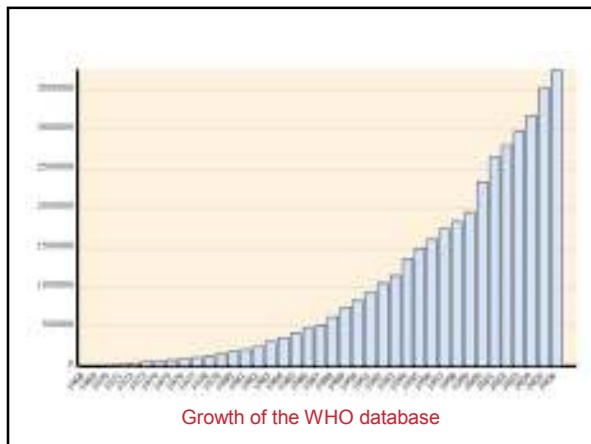
J.Raine in 'Pharmacovigilance', 2007



SRS *did* find the rofecoxib signal within the first year of marketing

Groups outside the current pharmacovigilance community are seeking and getting money for 'new' ideas, but many of those 'new ideas' can often be found by searching the literature from the 1960s and 70s. We have also been trying to develop those ideas over the years: there has been no shortage of good ideas, only resources. This interest in new approaches is understandable in one way because our continuing use of the cheapest globally useful method for safety monitoring 'spontaneous reporting' is regarded as a 'failure': we 'missed' the Vioxx problem. But I must remind sceptics yet again that the signal on Vioxx and myocardial infarction was found using ICSR (individual case safety report) data, and prominently reported by the Netherlands centre (Lareb) at a WHO National Centres Meeting (Tunis, October, 2000) only 6 months after the launch of Vioxx. In my view, any reason for 'failures' over Vioxx, or most other product withdrawals, has always been lack of resources in following up signals.

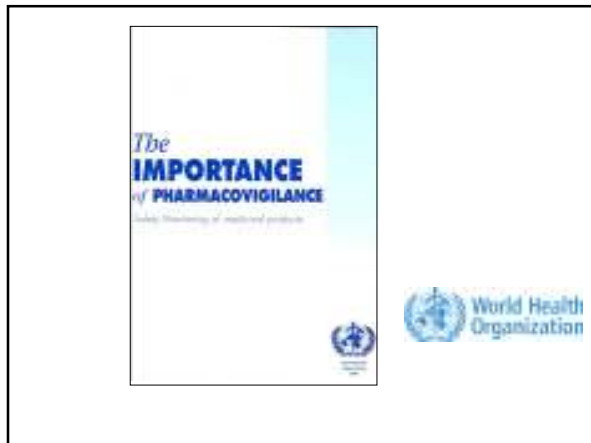
Ralph Edwards, Uppsala Reports, April 2008



Important achievements

- Definition and standards

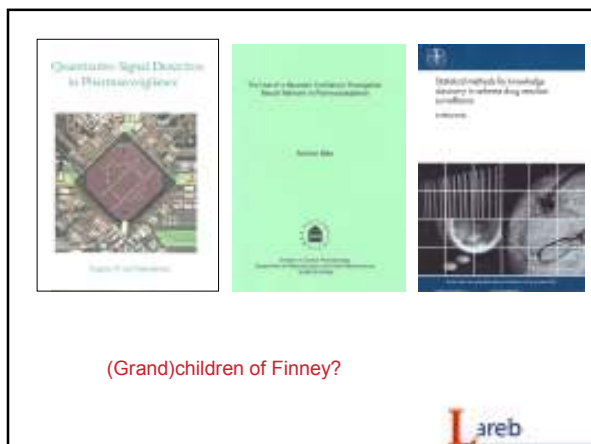
Lareb



Important achievements

- Definitions and standards
- Use of statistical approaches in signal detection

Lareb



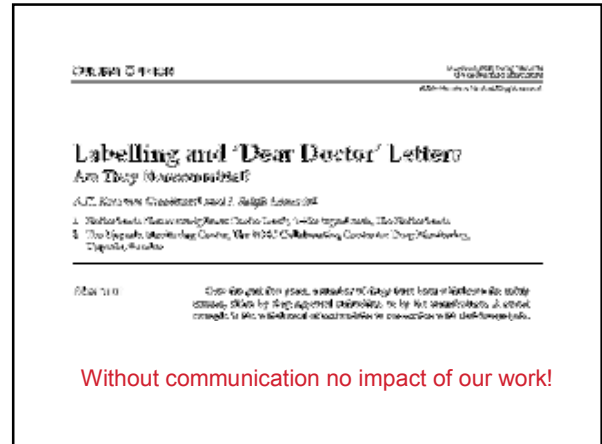
Important achievements

- Definitions and standards
- Use of statistical approaches in signal detection
- Emphasis on communication and transparency

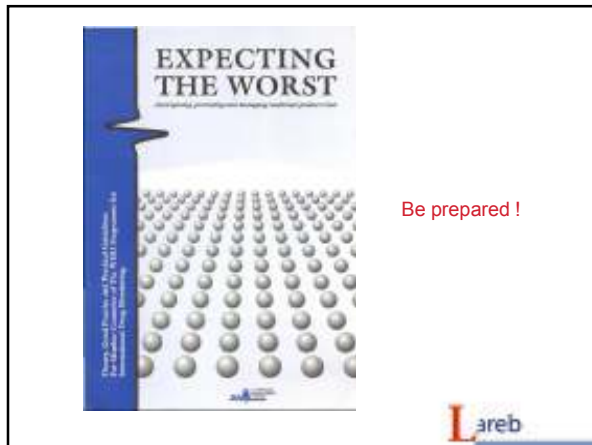
Lareb



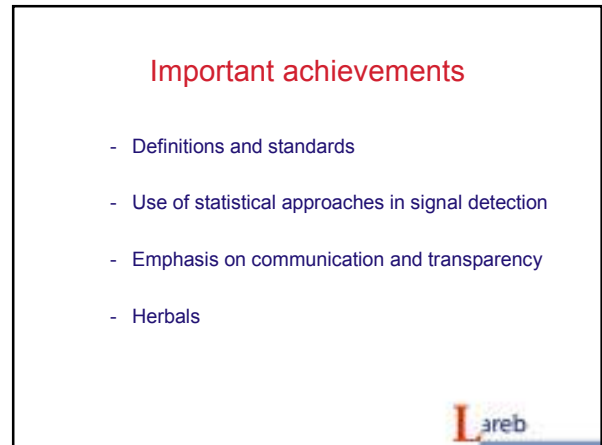
1997



Without communication no impact of our work!

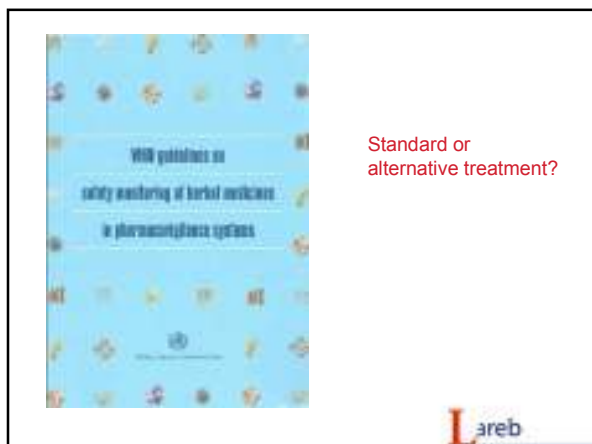


Be prepared !

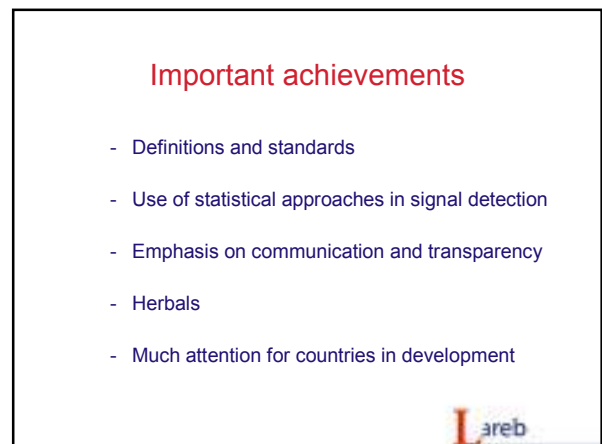


Important achievements

- Definitions and standards
- Use of statistical approaches in signal detection
- Emphasis on communication and transparency
- Herbals



Standard or alternative treatment?



Important achievements

- Definitions and standards
- Use of statistical approaches in signal detection
- Emphasis on communication and transparency
- Herbals
- Much attention for countries in development

Countries participating in WHO Drug Monitoring Programme



1968 - 2008

Much seems to be the same...



STUDIES ON THE EPIDEMIOLOGY OF ADVERSE DRUG REACTIONS

III. Reactions in Patients on a General Medical Service¹

LARRY G. SEIDL, GEORGE F. THORNTON, JAY W. WHITE,
and LEONARD E. CLAPP²

Department of Medicine, The Johns Hopkins University School of Medicine and Hospital
Received for publication April 22, 1966

Adverse reactions to drugs have always been with us, although they have assumed increasing importance during the past 25 years (1). New, potent, or intensely life-saving drugs have been introduced, but all of these drugs may produce adverse reactions.

Seidl, 1966: 5% of hospitalisations



Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients

Mina Pirmohamed, Sally Jones, Sharm Malik, Chris Green, Andrew K Scott, Thomas J Willey, Keith Farrer, E Kevin Park, Alanist M Breckenridge

Abstract

Objective: To describe the current burden of adverse drug reactions (ADRs) through a prospective analysis of all admissions to hospital.
Design: Prospective observational study.
Setting: Two large general hospitals in Merseyside.

also conducted in individual units such as the care of the elderly.¹² The largest UK study was based on retrospective review of case notes,¹³ and given the possible underreporting of ADRs in medical case notes, it probably underestimated the impact. Of the two prominent UK studies, our current study is a more methodical admission unit¹⁴ study similar but local

Department of Pharmacology and Therapeutics, University of Liverpool, Liverpool, UK (Pirmohamed, Jones, Malik, Green, Scott, Willey, Farrer, Park, Breckenridge).

Pirmohamed, 2004: 5% of hospitalisations



1953



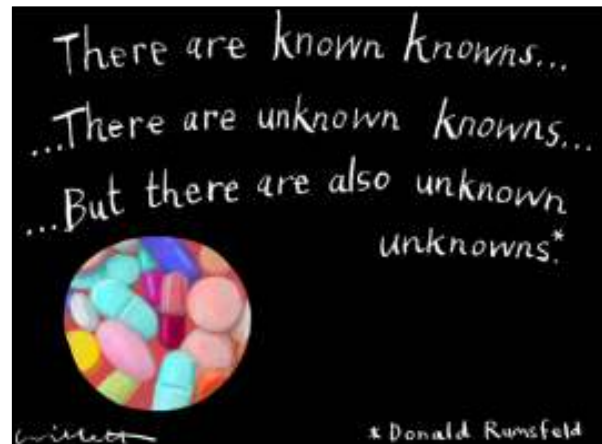
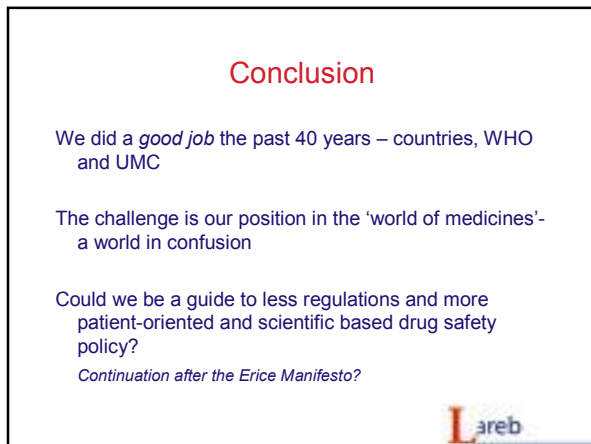
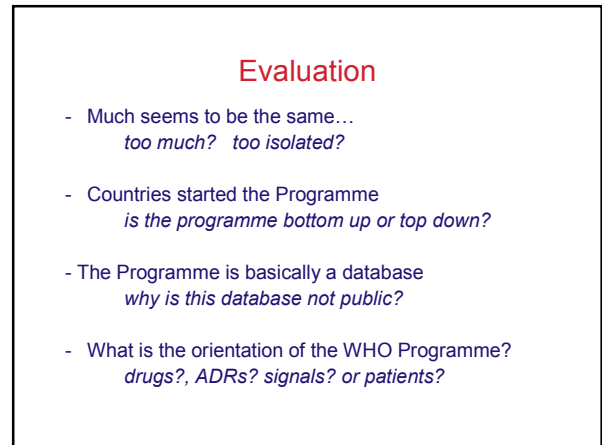
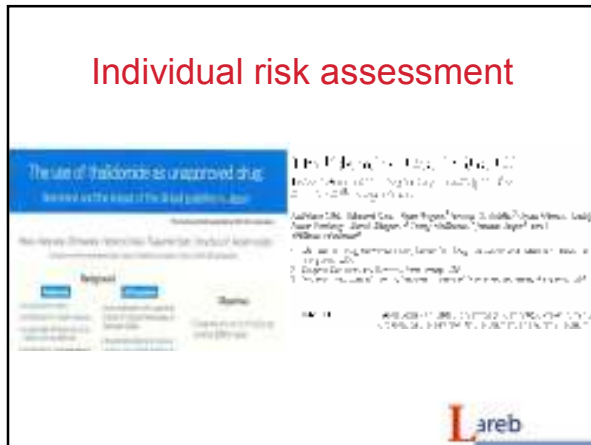
1960



2002



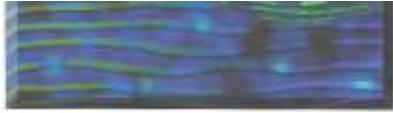
2006





World Health
Organization

WHO Programme for International Drug Monitoring



A Network for Safety

*Placing the optimal balance of risk
to benefit for medicinal drugs worldwide*

