

ISPE 2011 Mid-Year Meeting

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Introduction to Pharmacoepidemiology

Pharmacovigilance

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What we are discussing today

- The burden of iatrogenic diseases,
- The fundamentals of pharmacovigilance,
- Some problems open in pharmacovigilance
- Some proposals

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The problem of safety

Drug-induced adverse events

An increasing social and economical problem

The use of polypharmacy is increasing

There was a time when polypharmacy was considered to be a bad thing in older patients.

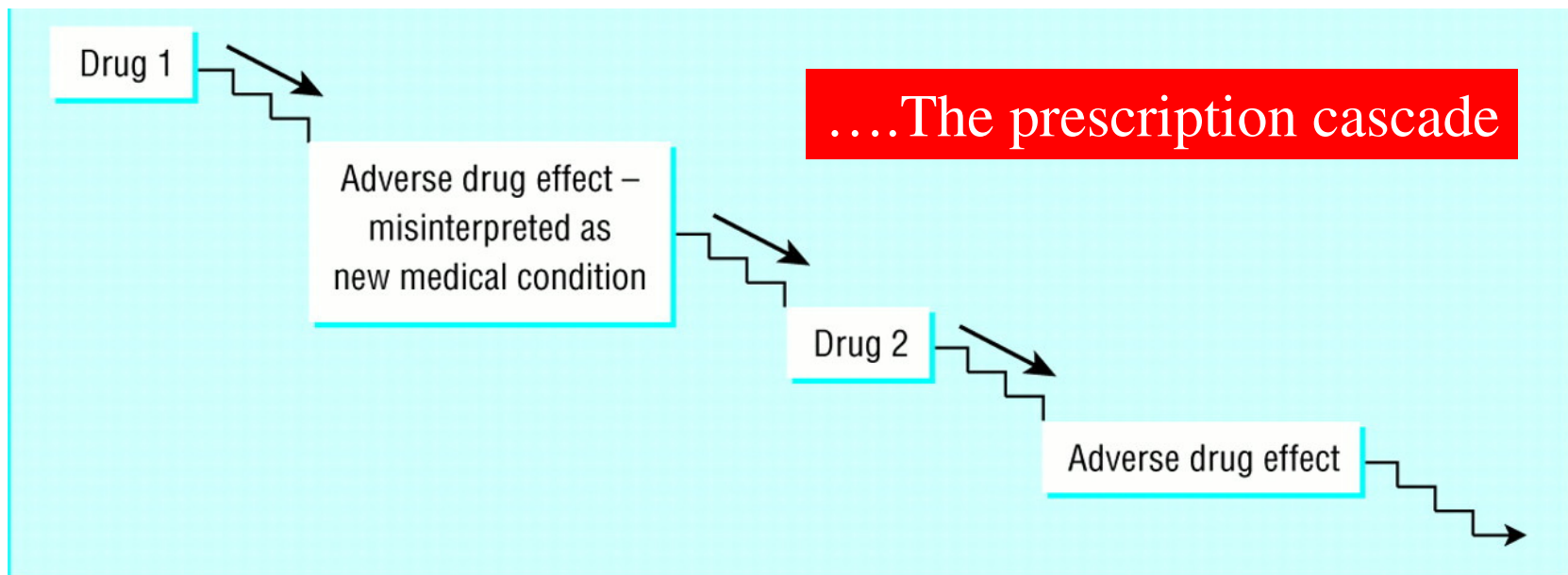
Chutka et al. Mayo Clin Proc 2004; 79:122-39

It is well known that use of larger number of drugs is associated with an increased likelihood of inappropriate prescribing and adverse drug events.

Goulding MR et al, Arch Intern Med 2004; 164:305-12; Field et al. Arch Intern Med 2001; 161:1629-34.

An adverse drug event undiagnosed

causes the use of a second drug to be treated



Rochon, P. A et al. BMJ 1997;315:1096-1099

Antibacterials and the risk of arrhythmia

Corrao G. et al. Generating signals of drug-adverse effects from prescription databases and application to the risk of arrhythmias associated with antibacterials. Pharmacoepidemiol Drug Saf 2005; 14:31-40

NNH for arrhythmias

**379 persons treated with erythromycin,
1322 with clarithromycin,
641 with ciprofloxacin
809 with levofloxacin.**

Antibacterials and the risk of arrhythmia

Corrao G. et al. Generating signals of drug-adverse effects from prescription databases and application to the risk of arrhythmias associated with antibacterials. Pharmacoepidemiol Drug Saf 2005; 14:31-40

“This explains why a not irrelevant portion of new prescriptions of antiarrhythmics (almost 6% according to our data) is attributable to the use of the four considered antibacterials”.

A prescribing cascade involving cholinesterase inhibitors and anticholinergic drugs

Gill SS et al. Arch Intern Med 2005; 165:808-13

“Older adults with dementia who were dispensed cholinesterase inhibitors have an increased risk of subsequently receiving an anticholinergic drug”.

4.5% vs 3.1% (P<.001)

Adjusted HR = 1.55 (1.39-1.72; 95%CI)

The problem of safety: old drugs

Prescribing is becoming increasingly difficult and the inherent risks of adverse reactions and interactions have increased.

*A prescription for better prescribing.
Aronson JK, Henderson G, Webb DJ, Rawlins MD
BMJ 2006; 333:459-60*

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Definition of pharmacovigilance

The science and the monitoring processes of drug safety, of the activities to reduce the risk and increase the benefits of the medicines

European Medicine Agency (EMA)

Pharmacovigilance: *Definitions*

- Pharmacovigilance is a clinic science with the aim of surveillance, reporting and evaluation of adverse effects of medicines used in medical treatments
- The main source of information comes from spontaneous reporting of ADRs
- Pharmacovigilance includes the dissemination of this informations and the regulatory measures taken, to prevent more ADRs, to assure the safety of medicinal products and to assure a better profile risk/benefit of drugs.

➤ *WHO, 1964*

Adverse Drug Reaction (ADR) Definition

“a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological functions”

(WHO, 1972)

New definition

“a response to a medicinal product that is noxious and unintended”

(Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010)

Adverse Drug Reaction (ADR) Seriousness

An adverse reaction which results in

- Death
- Life-threatening
- Hospitalisation or prolongation of existing hospitalisation
- Persistent or significant disability
- Congenital anomaly/birth defect

Article 1(12) of Directive 2001/83/EC

Main aims of pharmacovigilance

- To identify the unknown ADRs and calculate their incidence;
- To have more and better information on known ADRs, and to calculate the incidence of serious and non serious ones;
- To evaluate the risk-benefit balance of a drug in comparison with other drugs, for the same indication or for other kinds of treatment;
- To communicate adequately the risk and to improve the clinical practice.



So, the PhV may improve the appropriate use of drugs

Clinical relevance

ADR is a differential diagnosis not simple

- Aspecific: clinical picture very similar with different drugs and non pharmacologic causes (e.g. headache)
- Polymorfous: the same drug can cause different ADRs, on different organ classes (e.g. NSAIDs)
- Individual Susceptibility: gender , age, physiologic alterations, esogen factors (drug interactions, food, medicinal herbs) concomitant diseases, genetic causes
- Etiology, fisiopathology and frequence of many ADRs are still unknown.

Social Relevance

ADRs as cause of hospitalisation and death

- 5-10% of patients treated with drugs develop an ADR (*Moore et al. BJCP 1998*)
- more than 10% of hospitalisation are cause of ADRs: 11.5% in Norway, 13% in France, 16% in U.S. (*WHO, 2002*)
- In U.S. in 1994 106,000 deaths were calculated (95% CI 76,000-137,000) caused by ADRs (*Lazarou et al., JAMA 1998*)
- In Europe EMA estimates 197,000 deaths per year from ADRs (5th most common cause of death in hospital) (*P Arlett, ENCePP, 18.11.2010*)
- In Sweden fatal ADRS account for 3% of total deaths (7th cause of death)

Economic Relevance

- The ADRs direct costs vary between 30 and 130 billion USD per year, more than those originated by diabetes (*Shu et al. Ann. Pharm. 2000*)
- A French study evaluates the cost of an ADR which causes admission in hospital as 11,357 € per hospital bed per year (*Lagnaoui et al. EJCP 2000*)
- In Lombardy, on the basis of Mereafaps study, the costs for ADRs in hospital account for 22 Million € (3,66 million € for preventable ADRs) (*Vighi G et al, personal data, 2010*)

Adverse drug reactions in Germany: direct costs of internal medicine hospitalizations.

Rottenkolber D, et al for the Net of Regional Pharmacovigilance Centers.
Pharmacoepidemiol Drug Saf. 2011 Mar 8.

RESULTS: The incidence of hospitalization due to at least 'possible' serious outpatient ADRs was estimated to be approximately 3.25%. Mean age of the 1834 patients was 71.0 years (SD 14.7). Most frequent ADRs were gastrointestinal hemorrhage (n=336) and drug-induced hypoglycemia (n=270). Average inpatient length-of-stay was 9.3 days (SD 7.1).

Average treatment costs of a single ADR were estimated to be approximately € 2250.

The total costs sum to € 434 million per year for Germany.

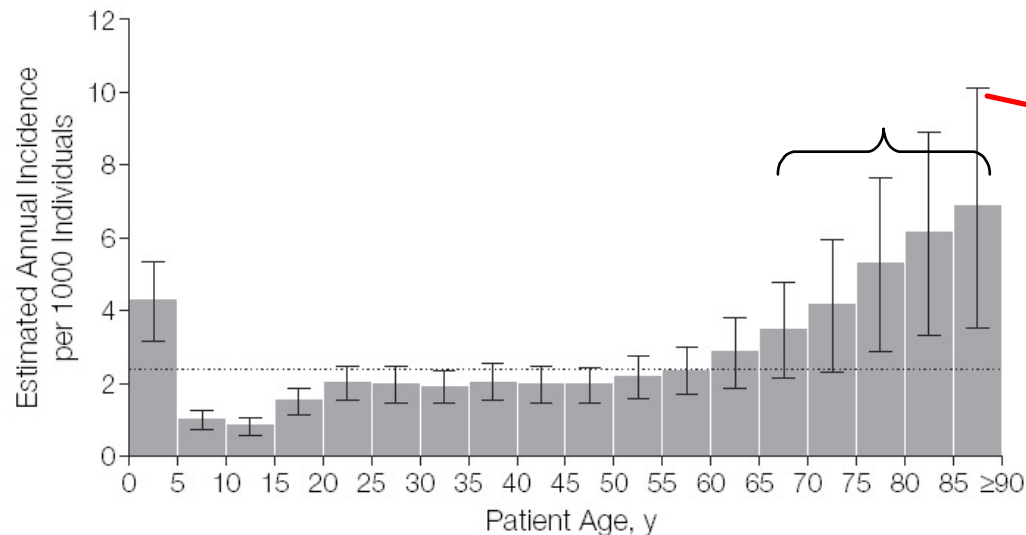
Considering the proportion of preventable cases (20.1%), this equals a saving potential of €87 million per year.

CONCLUSIONS: Preventing ADRs is advisable in order to realize significant nationwide savings potential. Our cost estimates provide a reliable benchmark as they were calculated based on an intensified ADR surveillance and an accurate person-related cost application.

Budnitz DS et al.
National Surveillance of Emergency Department
Visits for Outpatient Adverse Drug Events
JAMA, 296:1858-66; 2006

warfarin, insulin and digoxin, with
low therapeutic index and high risk
of toxicity are cause of 1/3 of
ADRs in patients > 65 years old:

Figure. Estimated Annual Incidence of Adverse Drug Events Treated in US Emergency Departments



The estimated annual population rate of adverse drug events (dotted line) is 2.4 per 1000 (95% confidence interval, 1.7-3.0). Error bars represent 95% confidence intervals. Data are from the 2004-2005 National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance project.

“Preventable” ADRs as cause of hospitalisation

Sistematic review on 43.380 cases (RL Howard et al. BJCP 2006)

How many ADRs as cause of hospitalisation are preventable?

Mean 3,7% (range:1,4-15,4%)

Which are the drugs involved?

4 groups of drugs cause more than 50% of ADRs:
antiplatelets, diuretics, NSAIDs, anticoagulants

12 groups (4 groups + opioid analgesics, beta-blockers, ACE-inhibitors, antidiabetics, positive inotropes, corticosteroids, antidepressants, Ca-antagonists) account for >80%

Which are the causes of inappropriateness?

Prescription
indication failed
(30,6%)

Monitoring
Therapy clinic monitoring failed(22,2%)

Adherence
Treatment adherence failed
(33,3%)

The signal detection

- One of the most important function of spontaneous reporting is to generate signals.
- The spontaneous reports can be examined singularly, to validate the case, and statistically, to generate possible signals.

SIGNAL: WHO definition



World Health Organization

“Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously.

Usually more than one report is required to generate a signal, depending on the seriousness of the event and the quality of the information”

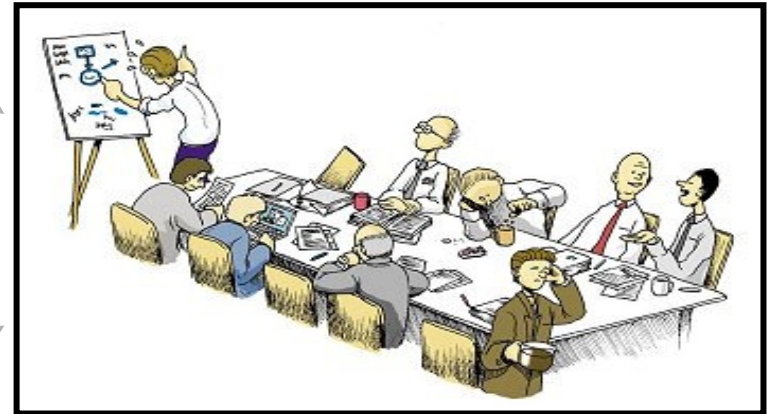
Signal Detection Activity

- 2 approaches:

Validation meeting

Statistic
approach

Clinical
approach



The Proportional Reporting Ratio (PRR)

The proportion of reports for a specific suspected adverse events for a drug compared with the proportion for the same suspected adverse reaction for all other drugs.

The reporting database may have the following structure:

	Drug 1	Drug 2	Drug 3	Drug 4	Drug 5	Drug 6	Drug 7	...	Drug N
Event 1	n11	n12	n13	n14	n15	n16	n17	...	n1N
Event 2	n21	n22	n23	n24	n25	n26	n27	...	n2N
Event 3	n31	n32	n3N
Event 4	n41	n42	n4N
Event 5	n51	n52	n5N
Event 6	n61	n62	n6N
...
Event P	nP1	nP2	nP3	nP4	nP5	nP6	nP7	...	nPN

Disproportional Analysis

$$\text{PRR} = \frac{a/(a+b)}{c/(c+d)}$$

	Event (R)	All other events	Total
Medicinal Product (P)	a	b	a + b
All other medicinal products	c	d	d + d
Total	a + c	b + d	n= a+b+c+d

Signal Detection Activity

PRR Statistic

PRR PRR = 1: no reporting difference
 PRR > 1: there is a difference

95% confidence interval:

$$S = (1/a + 1/b - 1/(a+b) - 1/(c+d))0.5$$

$$\text{Lower bound} = \text{PRR} / \exp(1.96S)$$

$$\text{Upper bound} = \text{PRR} \times \exp(1.96S)$$

PRR threshold in EudraVigilance for a potential signal

$$\text{PRR} \geq 2$$

Lower bound of the 95% Confidence Interval of PRR ≥ 1

Chisquare statistic

$$\chi^2 = \frac{(ad-bc)^2(a+b+c+d)}{[(a+b)(c+d)(a+c)(b+d)]}$$

Clinical Evaluation:

- Biological plausibility
- Dechallenge/Rechallenge
- Time to Onset (TTO) = temporal association
- Confounders: co-suspected drugs, concomitant drugs
- Underlying disease

Causal Relationship Assessment

- **Very likely/Certain:** plausible TTO, with no alternative explanations
- **Probable:** reasonable TTO, unlikely attribute to alternative explanations
- **Possible:** reasonable TTO but it could also be attributed to alternative explanation
- **Unlikely:** improbable TTO also attribute to underlying disease and concomitant drugs
- **Unrelated:** incompatible TTO and confounded by underlying disease and concomitant drugs
- **Unassessable:** insufficient information

A proactive approach to pharmacovigilance

- In the last ten years regulators tried not only to identify early the pharmacovigilance problems, but also to have a proactive approach, starting from the safety data of the registration studies.
- This approach is obtained with Risk Management Plans.

Risk management system:

- “...set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicinal products, and the assessment of the effectiveness of those interventions.”
- A Risk Management Plan is a mechanism by which such a risk management system can be presented to Competent Authorities.

Risk management system:

“... The aim of a risk management system is to ensure that the benefits of a particular medicine exceed the risks by the greatest achievable margin for the individual patient and for the target population as a whole.

This can be done either by increasing the benefits or by reducing the risks but, by its definition, risk management focuses upon the risk reduction approach.

The EU-RMP is mandatory for any new marketed drug but it can be asked to MAH when new safety issues arises for already marketed drugs..”

Risk minimisation plan:

“The risk minimisation plan details the risk minimisation activities which will be taken to reduce the risks associated with an individual safety concern.

When a risk minimisation plan is provided within an EU-RMP, the risk minimisation plan should include both routine and additional risk minimisation activities.”

Often pharmacovigilance is an activity not linked with health professionals and with clinical practice

- Usually the presence in the regulatory Agencies of clinician is marginal.
- Often the Authority decisions are not well understood by professionals
- In our experience in Lombardy we tried to involve clinicians in the pharmacovigilance activities.

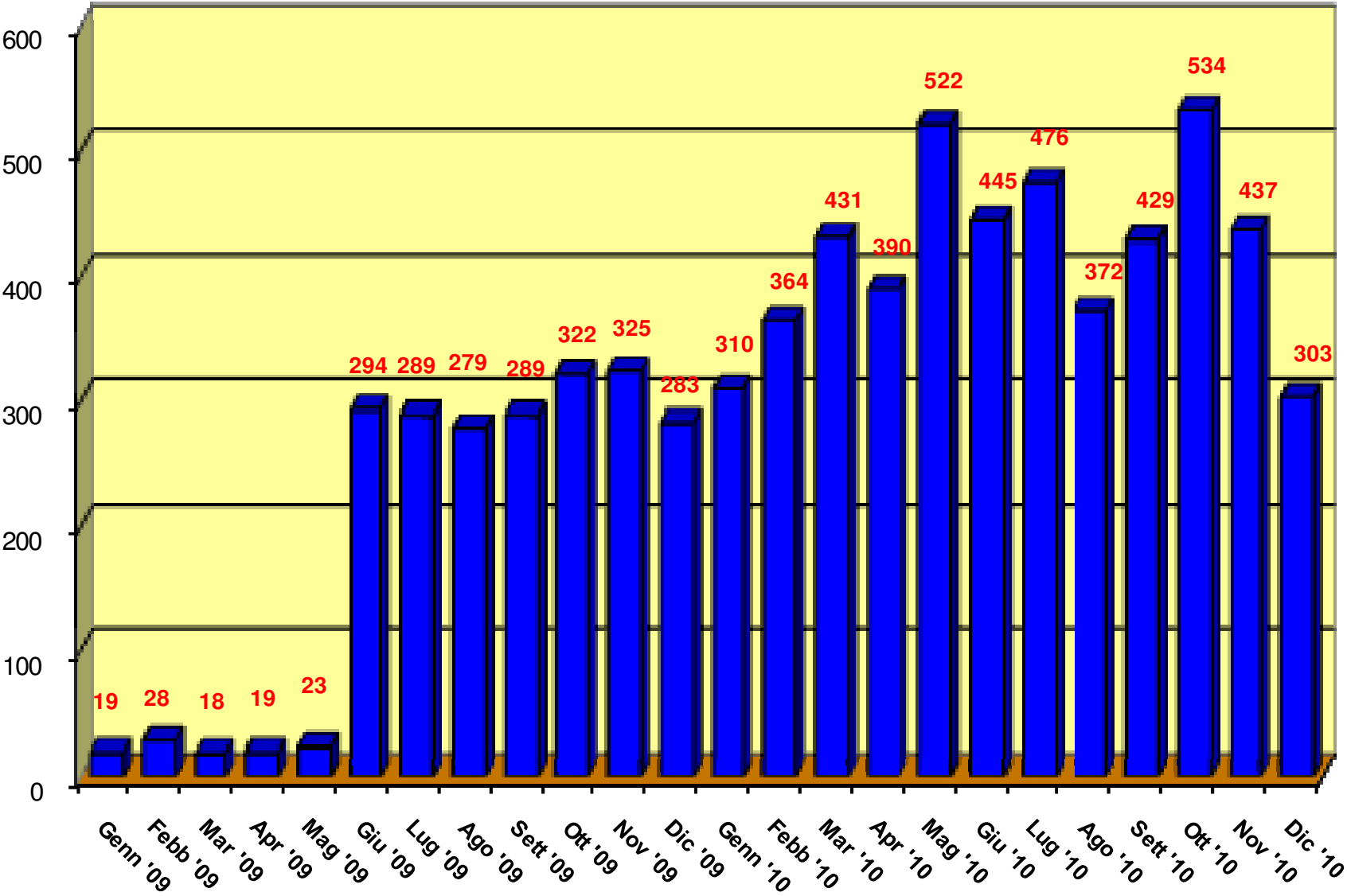
The effects of the pharmacovigilance on the clinical practice

- In Lombardy we tried to link pharmacovigilance and clinicians with projects in which they are directly involved.
- The projects have been successful, and the most important result was not only the increase in the reporting but the impact on the clinical practice.

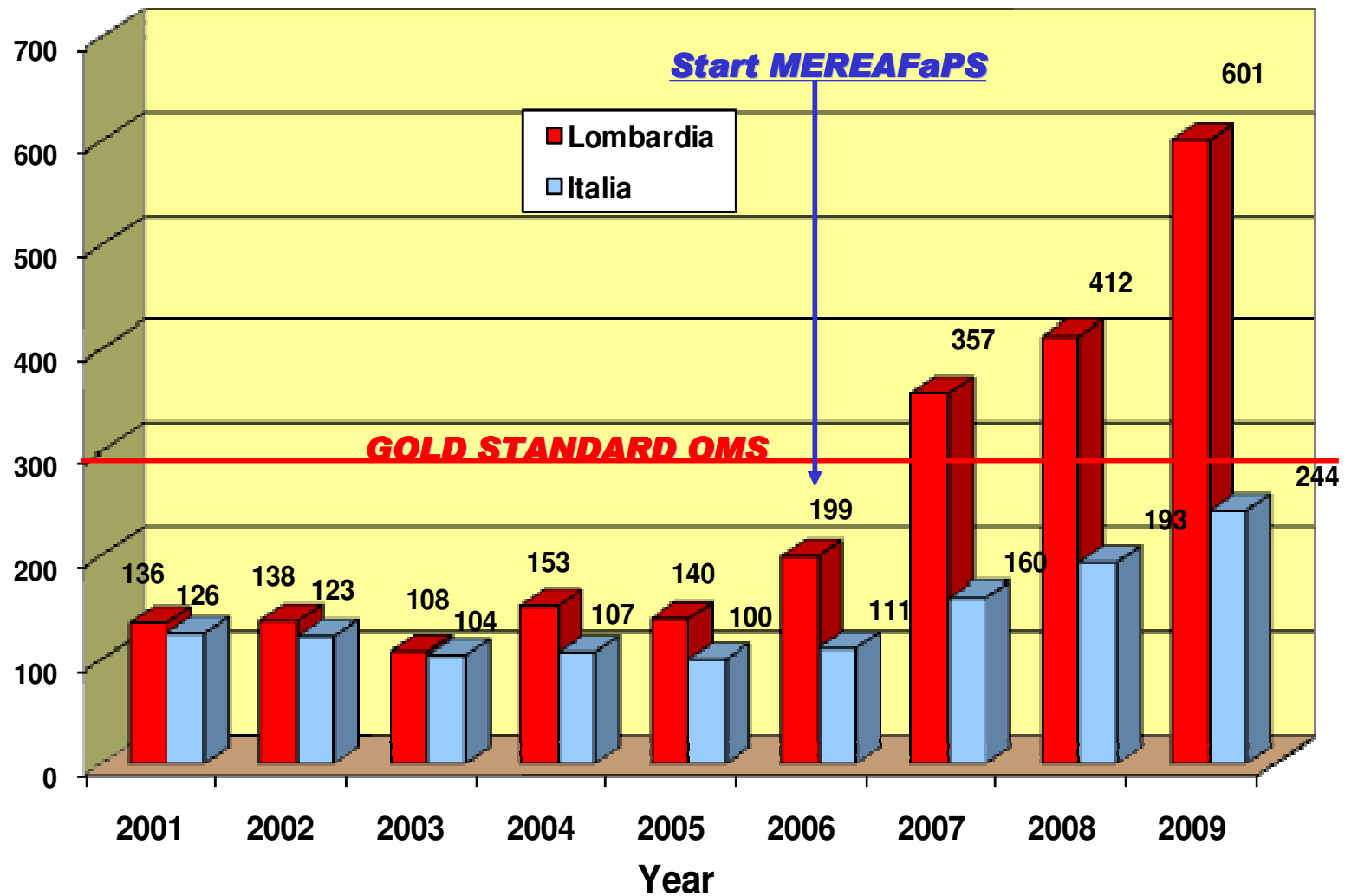
The Mereafaps project

- A project to identify the ADRs in Emergency Depts, initially on 8 hospitals, and now on 33 ED of Lombardy + 5 Italian Regions.
- The results of the first years have been excellent.
- We are planning the possibility to maintain permanently this project, with a monitor for each hospital who surveys ED and other medical wards.

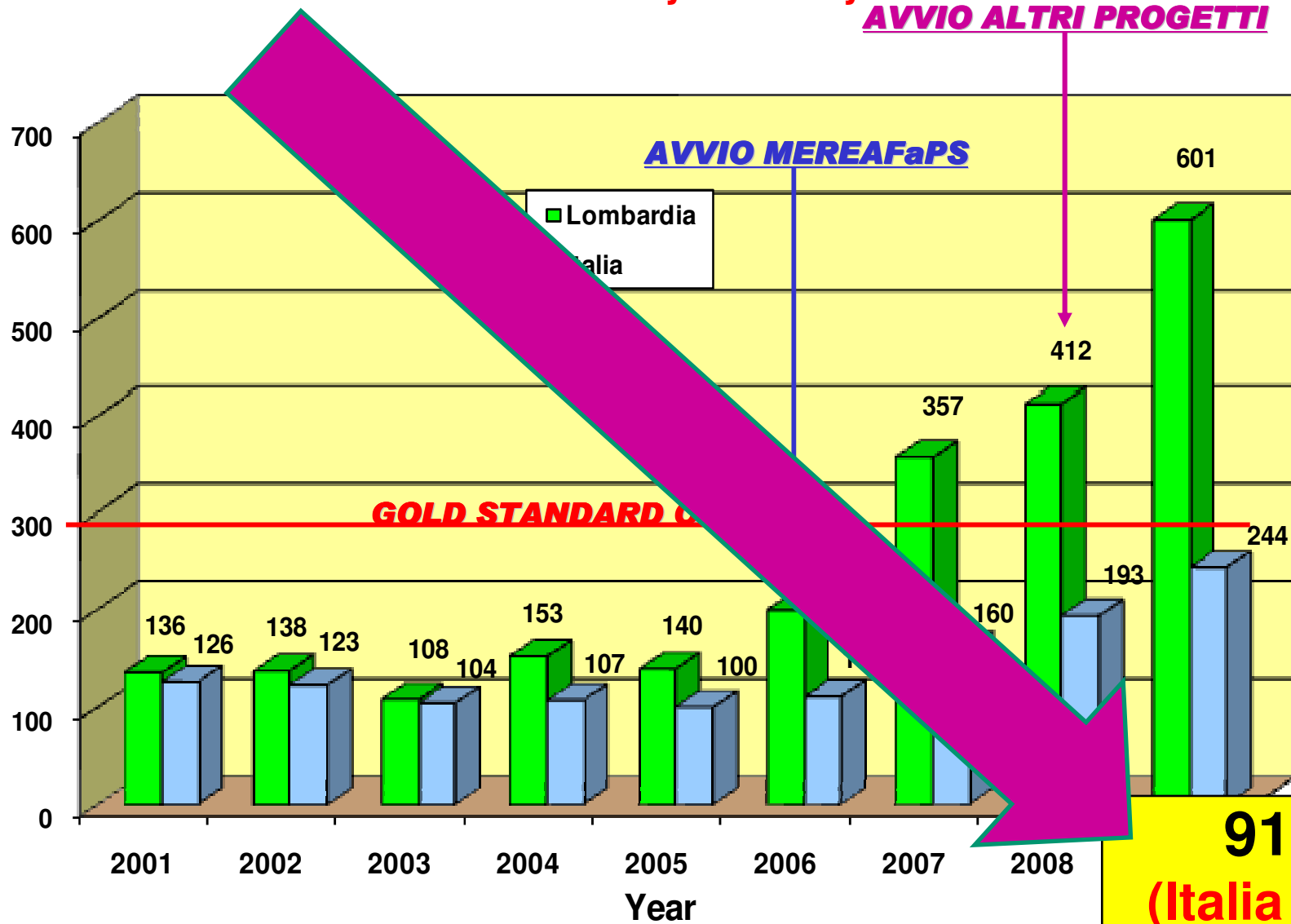
Reports per month (January 2009- December 2010) total: 7491



Reporting rate per million inhabitants/year: comparison between Lombardy and Italy



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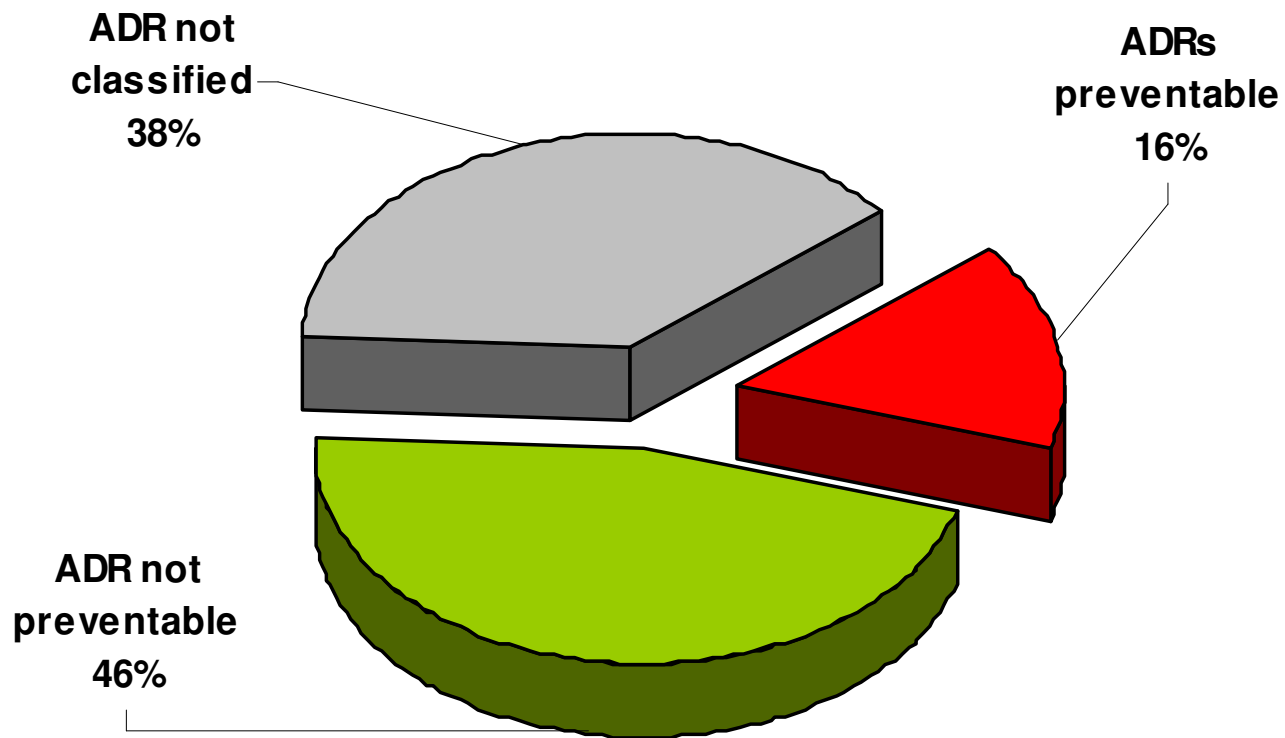


915
(Italia 332)
ANNO 2010

Lombardia	140	199	357	412
anno	2005	2006	2007	2008

Pharmacovigilance Projects

New MEREAFaPS



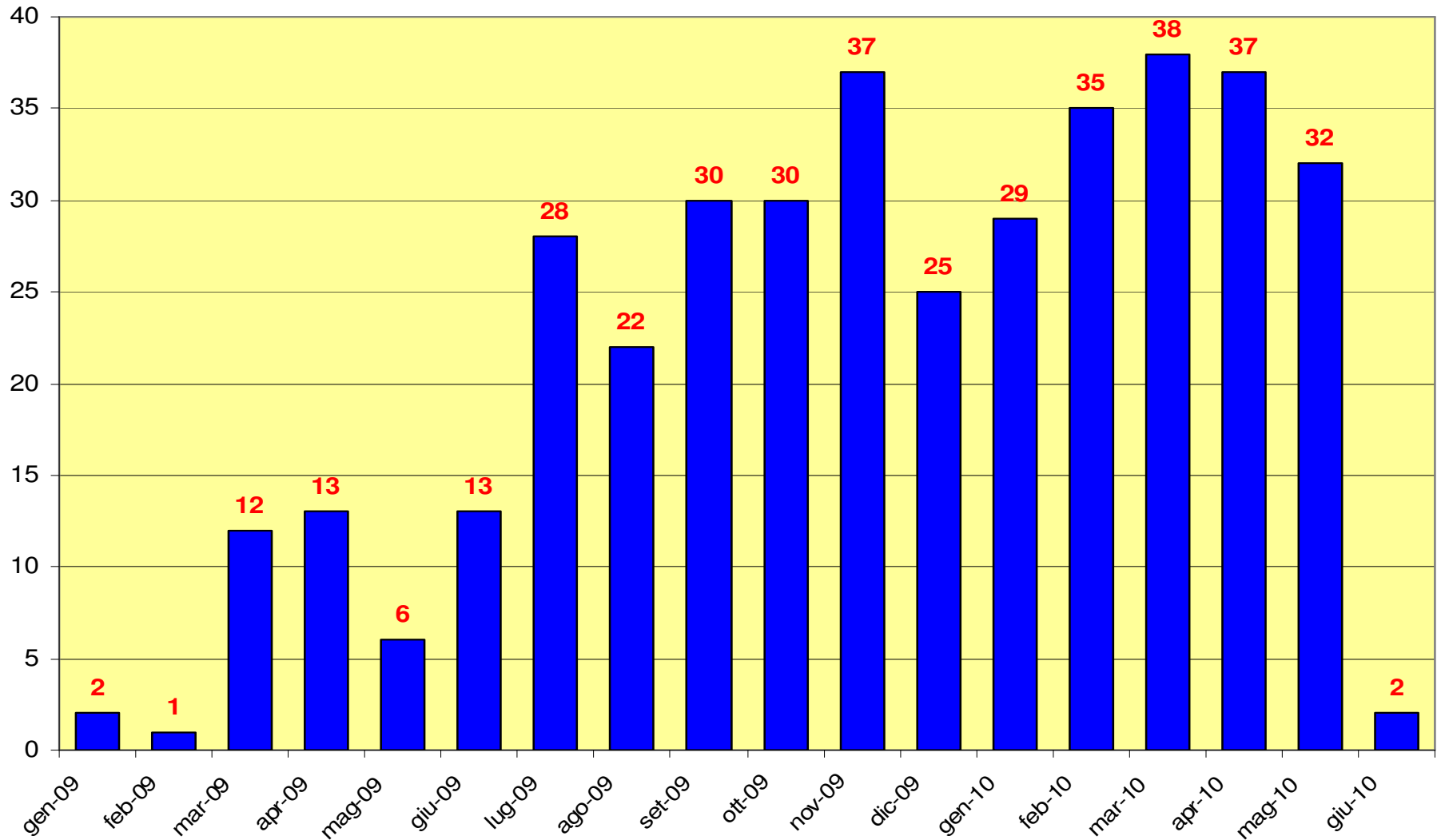
The Farmaonco Project

- A project to report the ADRs in several ward of Oncology.
- The aim of the project, beyond the reporting, is to give better information on the safety of drugs used in oncology.
- “Once we had just a treatment for each cancer –said our oncologists- now we have more possibility and is very important to know the safety profile of any medicine”.

Pharmacovigilance Projects



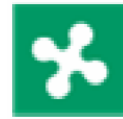
FARMAONCO: reports per month (tot. 392)



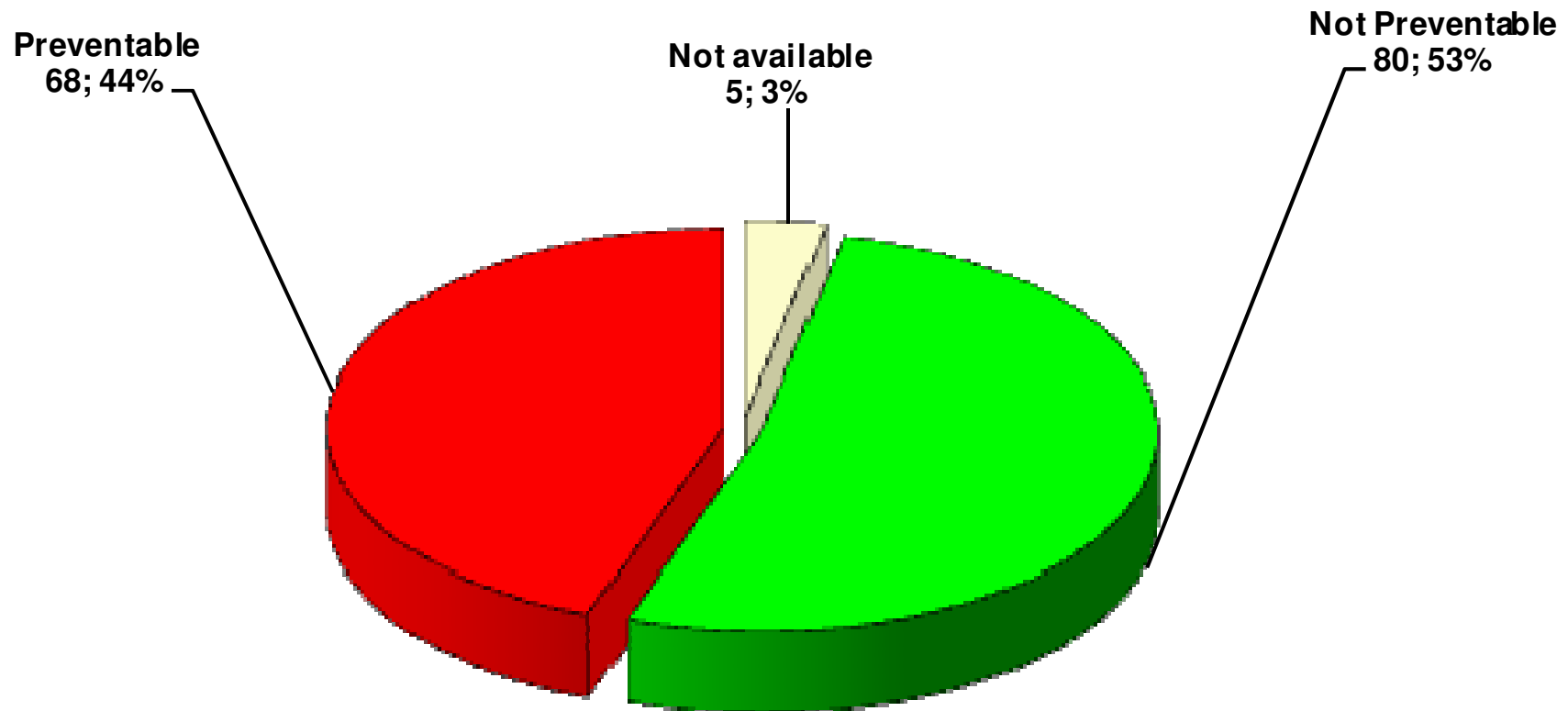
The Farmicav Project

- A project to recognize the ADRs identified in three Poison Control Centres of Lombardy.
- Apart from ADRs and from the evaluation of preventability, many cases of medication errors have been collected, which were useful for regulatory measures for Italian Agency (Paracetamol, Tantum Rosa).

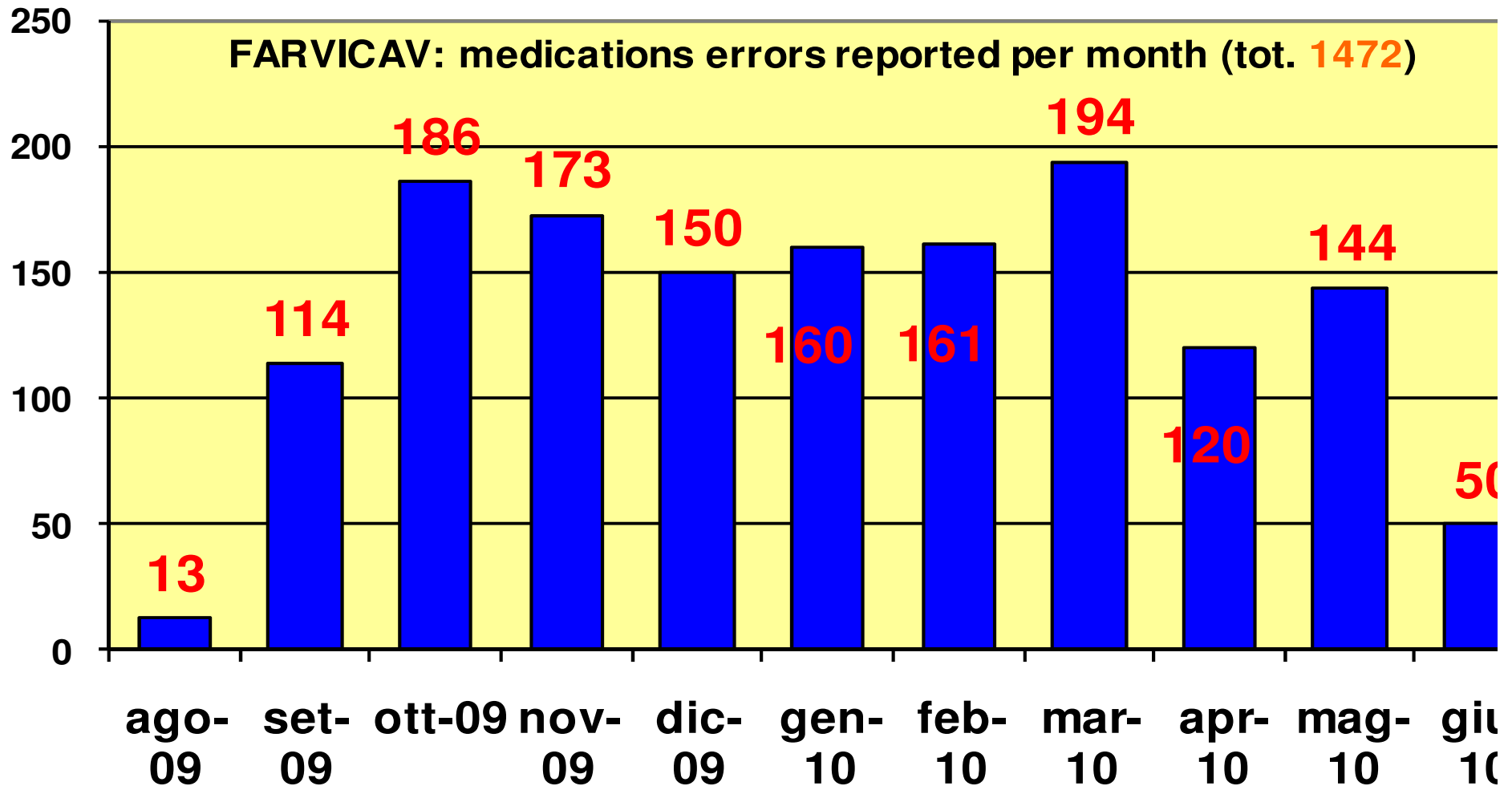
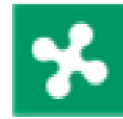
Pharmacovigilance Projects



FARVICA: preventable reactions



Pharmacovigilance Projects



The Meap project

- A project of pediatric ADRs reporting, initially in pediatric wards, now with family pediatricians .
- Hospital pediatricians and family pediatricians have periodic meeting to discuss the cases reported.
- Some publications originated from this activity

A Case of Atrial Fibrillation Induced by Inhaled Fluticasone Propionate

A. Oteri, A. Bussolini, M. Sacchi, E. Clementi, GV Zuccotti
and Sonia Radice

Pediatrics, 2010

Paroxetine and neonatal withdrawal syndrome

L. Pogliani, L. Schneider, D. Dilillo, F. Penagini and GV
Zuccotti

BMJ Case Reports 2010

MEAP Project

(Monitoraggio Eventi Avversi in Pediatria)

290 reports

14 hospitals since March 2009

68 Family Pediatricians :

- Asl Monza since July 2009
- ASL Lecco since September 2009
- ASL Milano since March 2010

The React project

- A project to identify serious dermatologic ADRs in clinical wards, especially cases of Steven-Johnson syndrome and Lyell syndrome.
- As these patients are treated in different wards (Internal Medicine, Dermatology, Intensive Care Unit, Burn Units) it is very important to establish a common approach to the patient.

Pharmacovigilance Projects



REACT project: risk evaluation of serious dermatologic adverse events attributable to medications.

- A diagnostic protocol for the definition diagnosis and treatment of Lyell syndrome and Steven Johnson syndrome was prepared and accepted.

The different pharmacovigilance projects in Lombardy: what do they have in common?

- A network of physicians linked with pharmacovigilance officers (more than 300 doctors).
- An intensive training program (globally 86 meetings in less than two years)
- A specific application web based for each project for ADRs reporting with statistic elaborations in real time.

The key of a good result

We hope to have obtained:

“...a progressive involvement of reporters in a permanent pharmacovigilance network with fast return of results”
as WHO suggests.

The key element is to have realized that the reporters often belong to a clinical network and we had to start from these networks

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The last arrived: the “Mediator affaire” (benfluorex, Servier)

- The French Agency was accused for the management of this problem.
- The Director, Jean Marimbert, resigned, and many members of the pharmacovigilance staff could do the same.
- Benfluorex was registered in Europe in the 90's with the indication “to induce a weight loss in patients with tipe 2 diabetes”.
- An association between this drug and the insurgence of cardiac valvulopathies was demonstrated.

Mediator, the consequences on the public health

- Over the last thirty years, approximately from 500 to 1,000 patients who took Mediator have died, and further 3,500 people have been hospitalized.

Why this event could happen at the French Agency, one of the most organized and big of Europe (more than 1,000 employees, with more than 100 involved in pharmacovigilance)?

- Why the ascertainment of the possible association between valvulopaties and Mediator took more than ten years?

The “Mediator affaire”: timetable (1)

- September 1998. Three French physicians write to the French Agency, asking why the restrictions imposed for the anphetamines use do not apply to Mediator.
- December 1998. The “Comité Technique de Pharmacovigilance” “is afraid for the possibility of insurgence of valvulopaties associated with the use of Mediator”.
- February 2001. Servier proposes an RCT protocol, 12 months long, to the French Agency: the protocol was judged negatively and a new version was required.
- Finally, after many changes, the protocol was approved in 2004-2005.

The “Mediator affaire”: timetable (1)

- Servier spontaneously withdraws the drug in Italy and in Spain (respectively in 2003 and in 2004). The drug remains on the market in Europe only in France and Portugal.
- January 2006: first patients are enrolled.
- January 2009. Study data collection is finished.
- May 2009. Efficacy data are ready. Ultrasound cardiac data are ready in Summer 2009.
- September 2009. The study results are presented to the French Agency.
- November 2009. On the basis of the data presented, Mediator is withdrawn.

Is the Mediator affaire an isolated case?

- Unfortunately, some cases in pharmacovigilance are similar to that of Mediator:
- **Sibutramine**: a trial was committed by EMA in 2002, the trial begun in January 2003, completed in November 2009 and published in September 2010 (the drug was suspended in January 2010).
- **Rosiglitazone**: EMA commitment in July 2000, the study was published in June 2009, the drug suspended in September 2010.
- “Safety questions can be answered only by large, long term studies. Manufacturers have every interest in prolonging the time between beginning a trial and the final result, during which they carry on earning income”.

Garattini S, Bertelè V, BMJ 9 October 2010, 781

Lack of information

“There is a total break in responsibility between regulators and industry, which provide information on medicines and make them available, and those who prescribe medicines.

In several studies, about half of serious adverse reactions have been said to be “avoidable”. This suggest a serious defect.”

Edwards IR, The future of Pharmacovigilance: a personal view.

Eur J Clin Pharmacol 2008; 64:173-81

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Considerations (1)

- A problem remained unsolved, even after the new European legislation, is the asymmetry between Companies and citizens: the voice of customers (and independent researchers) is faint, compared with the continue and massive presence of industry.
- Taking regulatory measures, EMA and national Agencies have to cope with objections and documents prepared by experts and loyers of industries, who often succeed at least to delay some restrictive decision.

Considerations (2)

- This delay allows the companies to maintain the incomes for more time, but may have a cost on public health.
- The agencies (national and European) must stop to behave as **referee**, to become **agents** of citizens, and act in behalf of them.

So that:

- It is better to obtain an appropriate prescription than to adopt restrictive measures. The Agencies duty is therefore to inform completely and timely citizens and physicians about everything which concerns the drug safety.

Considerations (3)

- The safety question to answer should be: How necessary is this drug for patients, is there a better alternative in terms of efficacy, safety and costs?
- If there is not an interest for citizens, it is not ethic to accept any risk.
- If these rules would have been followed, many failures of pharmacovigilance could have been avoided.