



L'Integrità della Ricerca Biomedica  
nell'era dell'Evidence-based Health Care

**GIMBE**<sup>®</sup>

*Gruppo Italiano per la Medicina Basata sulle Evidenze*

Evidence-Based Medicine Italian Group

*Bologna, 23 novembre 2001*

**Istituti Ortopedici Rizzoli**

# La frode scientifica nella ricerca clinica

Antonino Cartabellotta

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**GIMBE**<sup>®</sup> - Gruppo Italiano per la Medicina Basata sulle Evidenze

# La frode scientifica nella ricerca clinica

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- 1. Esempi di frode**
2. Tassonomia della frode
3. Conseguenze della frode
4. Prevenzione della frode

# Esempi di frode

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## **Publicazione di dati “fabbricati”**

1. JA, a senior Consultant Physician, pleaded guilty for conducting a sham trial of a calcium-channel antagonist: he had forged consent forms for 17 pts who were never given the drug, and invented EchoCG and MR imaging of the patients.

*BMJ 1997;315:205*

## **Publicazione di dati “gonfiati”**

2. Two clinical scientists distorted their research results. They reported a larger n° of patients and a longer follow up than what could be reconstructed from independent registers.

*Lancet 1999;354:57-61*

# Esempi di frode

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**Pubblicazione di review apparentemente imparziali, orientate a promuovere un farmaco (scrive un “ghost writer” dell’industria e firma un esperto indipendente)**

3. An American Information Company offered a Nordic expert the authorship of a completed review paper recommending a certain drug. The Company aimed to give the impression that the review was impartial

*Lancet 1999; 354: 57-61*

# Esempi di frode

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## Publicazione ripetuta dei dati di un singolo RCT, in articoli firmati da Autori diversi

4. A single RCT of risperidone was reported “not transparently” in 6 different publications with different Authorship

*Lancet 1996;347:1024*

5. Nine RCTs of ondansetron were published a total of 23 times. There were 4 pairs of almost identical reports with completely different authors

*BMJ 1997;315:635*

# Esempi di frode

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## **Plagio: pubblicazione di dati altrui**

6. The Author of a paper discovered that his paper had been plagiarised. Later on, more than 20 papers were found to be plagiarised by the same person, who was dismissed from his professorship

*Lancet 1999; 354: 57-61*

# Esempi di frode

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## Invenzione-Falsificazione di dati

7. HD, a clinician, reported that treatment with IFN, colchicine and benzathine penicillin was useful in Behcet disease. The Investigational Committee of the University found that:
- the no. of pts had been inflated;
  - contrary to statements in the paper, neither ethics committee approval nor written informed consent had been obtained;
  - HD had forged the signatures of alleged co-authors, who denied their participation

*Lancet 2000; 356: 1292 & 1351*

# Esempi di frode

## Invenzione-Falsificazione di dati

8. AKB, a consultant surgeon was suspended for 1 year by the GMC for publishing a deliberately falsified an article about NSAID-induced damage in rats.

There was a 6-7 years of delay for the case to get to the GMC, due to the effort of the University of Mr AKB to cover the affair.

Recently, the research supervisor of the Department of AKB was “asked to refrain from teaching, supervising and examining students, until he has taken a course in research supervision”

*Gut 1990;31:358*

*BMJ 2000; 321:1429*

*Lancet 2001;357:780*



# Esempi di frode

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## Publication bias

- I trials con risultati negativi hanno minori probabilità di essere pubblicati rispetto a quelli con risultati positivi.
- Il publication bias determina una distorsione in senso “ottimistico” dei risultati dei trials che si manifesta nelle meta-analisi con stime esagerate dell’effetto terapeutico, o, meno frequentemente, con risultati falsamente positivi.

*Chalmers I*

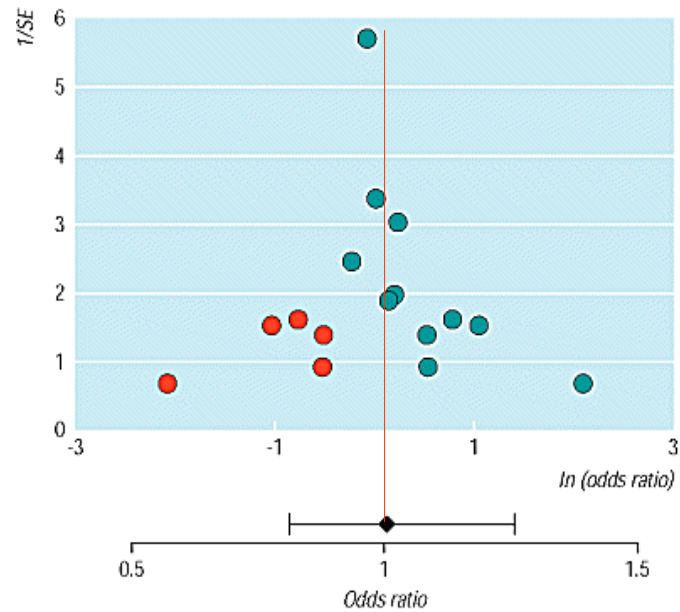
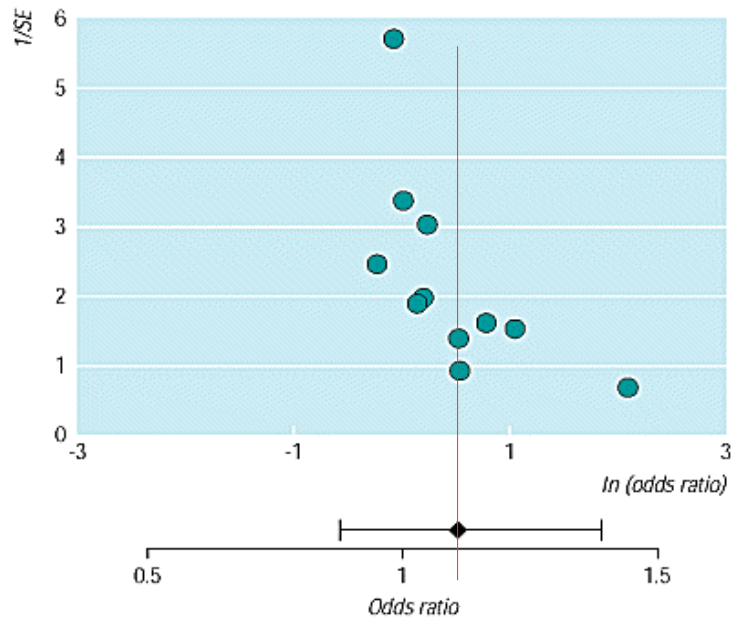
**Underreporting research  
is scientific misconduct**

JAMA 1990;263:1405-1408

*Sutton AJ, Duval SJ, Tweedie RL, Abrams KR, Jones DR*

# **Empirical assessment of effect of publication bias on meta-analyses**

*BMJ 2000;320:1574-7*



Sutton AJ, et al. BMJ 2000

# Esempi di frode

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## Publication bias: dimensioni del fenomeno

- Possibile sino al 50% delle meta-analisi pubblicate
- Molto probabile (“strongly indicated”) nel 20% dei casi
- In grado di determinare una modifica dei risultati in meno del 10% dei casi

*Sutton AJ, et al. BMJ 2000*

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# Tassonomia della frode

<b>BEHAVIOUR</b>	<b>RCP 1991</b>	<b>MRC</b>	<b>US</b>	<b>Denmark 1992</b>	<b>Finland 1994</b>	<b>Norway 1994</b>	<b>Sweden 1997</b>
<b>Inventing a case</b>	Yes	Yes	Yes	Yes	Yes	Yes	Yes
<b>Failing to get consent from an ethics committee</b>	No	Yes	Yes	No	Yes	Yes	?
<b>Publication of <i>post hoc</i> analyses without declaration that they were <i>post hoc</i></b>	?	Yes	?	?	?	?	?
<b>Gift authorship</b>	?	Yes	?	Yes	?	?	?
<b>Not disclosing a conflict of interest</b>	?	?	?	?	?	?	?
<b>Not publishing completed research</b>	No	?	?	No	No	No	No

# Serious research misconduct



- Fabrication: invention of data or cases
- Falsification: wilful distortion of data
- Plagiarism: copying of ideas, data or words without attribution
- Failing to get consent from an ethics committee for research
- Not admitting that some data are missing
- Ignoring outliers without declaring it
- Not including data on side effects in a clinical trial
- Conducting research in humans without informed consent or without justifying why consent was not obtained from an ethics committee
- Publication of post hoc analyses without declaration that they were post hoc
- Gift authorship
- Not attributing other authors
- Redundant publication
- Not disclosing a conflict of interest
- Not attempting to publish completed research
- Failure to do an adequate search of existing research before beginning new research

# Minor research misconduct

*COPE Report 2000 (modified)*



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# Conseguenze della frode

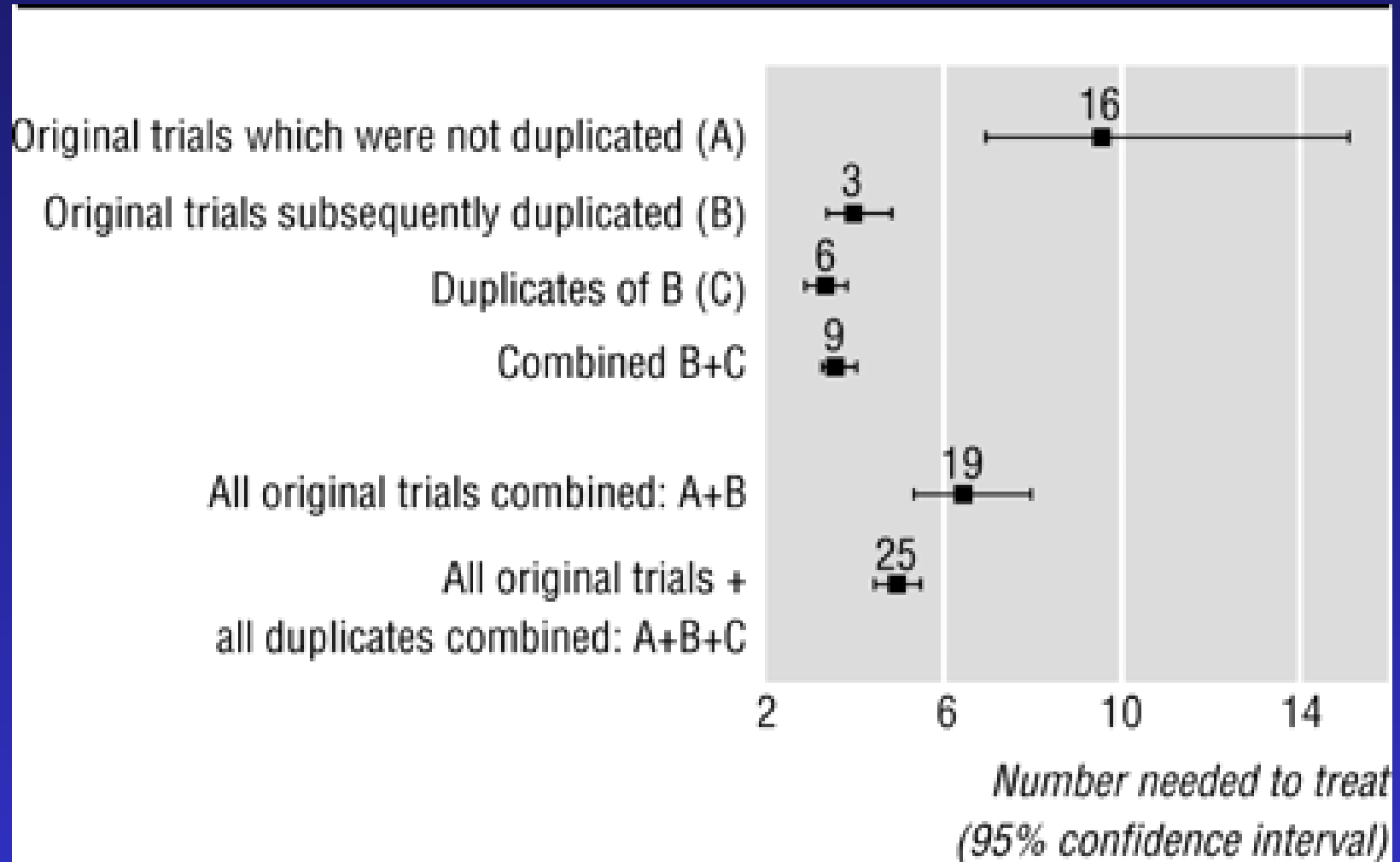
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- Sperimentazioni cliniche “fabbricate” o “gonfiate”
- Rassegne elaborate dall’industria e firmate da esperti
- Pubblicazione ripetuta, non dichiarata, di RCTs con risultati positivi
- Mancata pubblicazione di RCTs negativi (publication bias)



**Sovrastima dell’efficacia terapeutica**

Number needed to treat to prevent vomiting up to the 24th postoperative hour with intravenous ondansetron 4 mg compared with placebo. The numbers above the symbols are the numbers of reports.



*Stelfox HT, Chua G, O'Rourke K, Detsky AS.*

# **Conflict of interest in the debate over calcium-channel antagonists**

*N Engl J Med 1998; 338: 101-6*

**TABLE 3. AUTHORS WITH FINANCIAL RELATIONSHIPS WITH PHARMACEUTICAL MANUFACTURERS.**

<b>MANUFACTURER</b>	<b>SUPPORTIVE AUTHORS (N=24)</b>	<b>NEUTRAL AUTHORS (N=15)</b>	<b>CRITICAL AUTHORS (N=30)</b>	<b>CHI-SQUARE FOR LINEAR TREND</b>	<b>P VALUE FOR TREND</b>
	no. of authors (%)				
Manufacturer of calcium-channel antagonist	23 (96)	9 (60)	11 (37)	22.02	<0.001
Manufacturer of competing product	21 (88)	8 (53)	11 (37)	14.84	<0.001
Any manufacturer	24 (100)	10 (67)	13 (43)	22.68	<0.001

*Stelfox HT, et al. N Engl J Med 1998*

# Conseguenze della frode

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- Pubblicazione di dati copiati da lavori pubblicati da altri
- Falsificazione
- Invenzione-falsificazione di dati sperimentali



**Promozione di carriere professionali,  
in particolare accademiche**

# La frode scientifica nella ricerca clinica

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# Prevenzione della frode scientifica

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## 1. Nella fase del disegno della sperimentazione

- Comitati Etici
- Osservatorio Nazionale delle sperimentazioni cliniche
- Registri di RCTs

## 2. Durante il corso della sperimentazione

- Organismi di monitoraggio e controllo (eligibilità dei soggetti, applicazione dei trattamenti, end points, etc)

## 3. Dopo la pubblicazione

- “Retraction”, pubblicata dalla stessa rivista



# Organismi di monitoraggio e controllo

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## 1. Ad hoc organizations

- USA: Office of Research Integrity (ORI)
- UK: Committee on Publication Ethics (COPE)
- National Committees on Scientific Dishonesty in the Nordic Countries
- Italia: Osservatorio Nazionale sulle Sperimentazioni Cliniche (Ministero della Salute)

## 2. Organismi interni delle Istituzioni di ricerca

- Comitati etici, *clinical trial units*

## 2. Industria Farmaceutica

- Organismi per il monitoraggio dei propri RCTs

*Nylenna M, Andersen D, Dahlquist G, Sarvas M, Aakvaag A, on behalf  
National Committees on Scientific Dishonesty in the Nordic Countries*

# **Handling of scientific dishonesty in the Nordic countries**

*Lancet 1999;354:57-61*



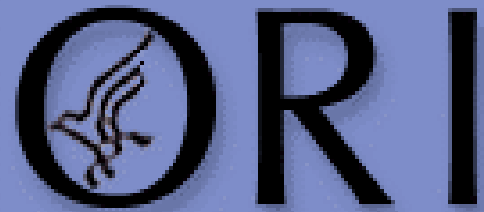
**Committee on Publication Ethics**  
**The Cope Report 2000**



[www.publicationethics.org.uk](http://www.publicationethics.org.uk)

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Office of Research Integrity

U.S. Department of Health & Human Services

[ori.dhhs.gov](http://ori.dhhs.gov)



*Ministero della Sanità*

Dipartimento per la Valutazione dei Medicinali e la Farmacovigilanza  
Ufficio Sperimentazione Clinica



## Osservatorio sulla Sperimentazione Clinica



[oss-sper-clin.sanita.it](http://oss-sper-clin.sanita.it)

# Registri di RCTs

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*Horton R, Smith R.*

**Time to register randomised trials**  
**The case for registering all**  
**clinical trials is now unanswerable**

*BMJ 1999;319:865–6*

*Lancet 1999;354:1138-9*

# Registri di RCTs

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## ***m*RCT**

*meta*Register of Controlled Trials

## **ISRCTN**

International Standard Randomised  
Controlled Trial Number



# Retraction of publication

- Dichiarazione di "misconduct" e pertanto di non validità di studi già pubblicati

*" The retraction [of a fraudulent work published by a journal], so labeled, should appear in a prominent section of the journal, be listed in the contents page, and include in its heading the title of the original article"*

*International Committee of Medical Journal Editors.  
Retraction of research findings.  
Ann Intern Med 1988*

# Retraction: Interferon alfa-2b. . . in Behçet's disease

*Lancet 2000;356:1292*

See page 1351

On Feb 19, 2000, *The Lancet* published an article by Haluk Demiroglu and colleagues reporting the results of a randomised trial of interferon alfa-2b, colchicine, and benzathine penicillin among patients with Behçet's disease.<sup>1</sup> In a letter in today's *Lancet*, the Dean of Hacettepe University Medical School, Prof Iskender Sayek, informs us that, according to the findings of an "Investigational Committee", and contrary to statements made in the published paper, there was no ethics committee approval for the study and written informed consent was not obtained from participating patients. The corresponding author, Dr Demiroglu, admits to these fabrications.

The journal was alerted to problems with this paper by letters, also published in our Correspondence columns today, from alleged co-authors Bora Eldem, Semra Dunder, and Osman Ozcebe. They denied responsibility for the published article. The Hacettepe committee found, and Dr Demiroglu conceded, that the signatures of all authors on the submitted manuscript were forged by Dr Demiroglu himself.

Taken together, these fabrications, and the serious ethical transgressions they hide, mean that the paper by Demiroglu and colleagues must be retracted from the published record. In a letter to the journal, also published this week, Dr Demiroglu disputes the grounds for this retraction. But I am satisfied that his admissions justify the decision to retract. False statements about patients' consent and ethics committee approval cannot be mitigated by pointing to the importance of the study question or its final result. In short, the end cannot justify the means.

Finally, there is remaining uncertainty about the validity of the reported data. Professor Sayek notes that "the investigational committee believed that some fabrication and falsification might have taken place". Dr Demiroglu denies this allegation. The Higher Educational Council of the University met on Sept 27 to consider this matter further but could not reach a final conclusion. Further investigations are in progress.

Hacettepe University deserves credit for moving to resolve this matter quickly, carefully, and openly.

*Richard Horton*

*The Lancet*, London WC1X 8RR, UK

1 Demiroglu H, Ozcebe OI, Barista I, Dunder S, Eldem B. Interferon alfa-2b, colchicine, and benzathine penicillin versus colchicine and benzathine penicillin in Behçet's disease: a randomised trial. *Lancet* 2000; 355: 605-09

# Retraction of publication

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## La "retraction" è tempestiva?

- L'intervallo medio intercorso fra la pubblicazione dell'articolo e la sua "retraction" nei 25 casi registrati dall'ORI è stato di 83 mesi

*Parrish DM. Acad Med 1999.*

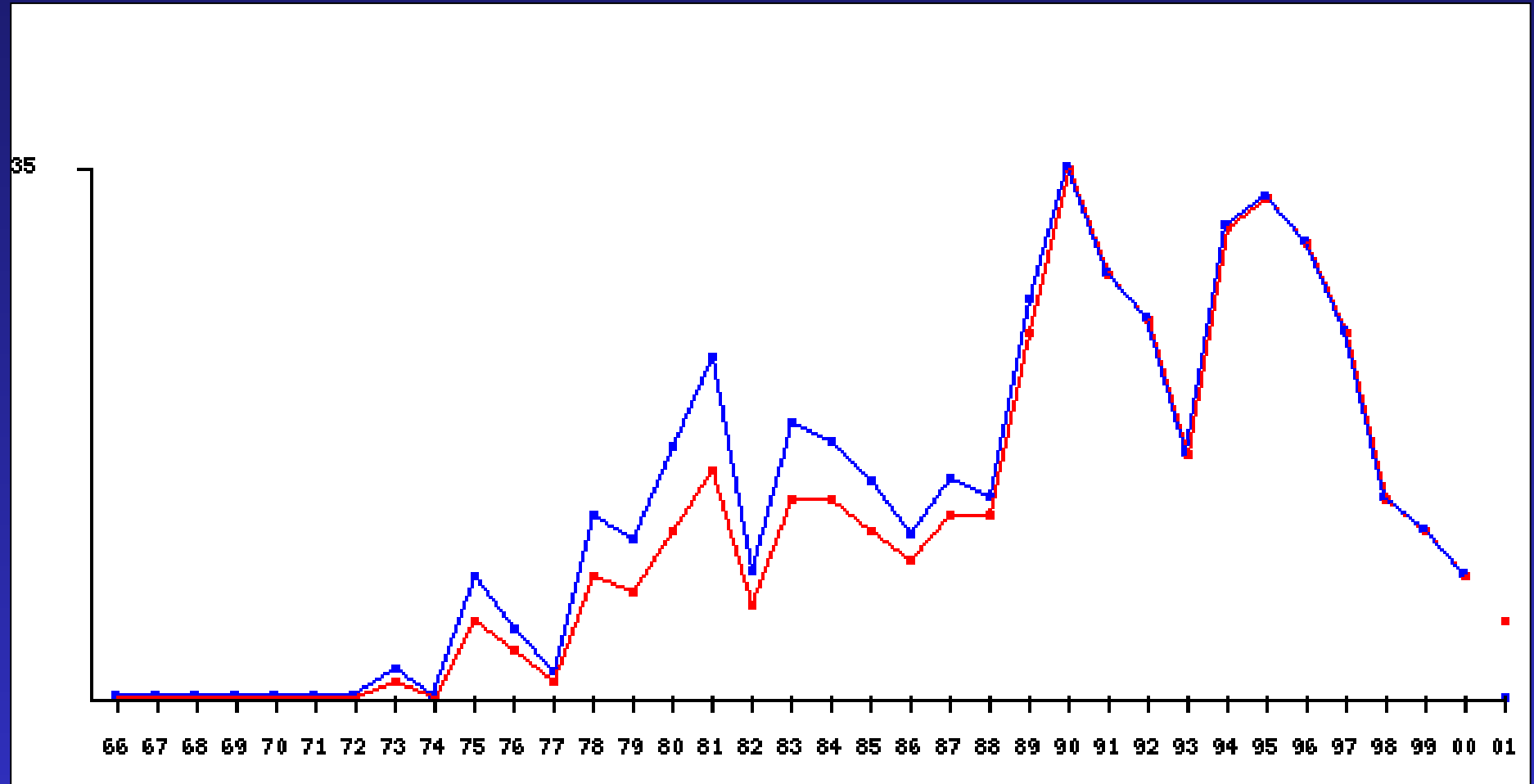
## La "retraction" è efficace?

- Dopo retraction, le citazioni degli articoli affetti da "misconduct" si riducono del 35% circa, ma non si azzerano

*JAMA 1990*

- Qual è l'entità del fenomeno "retraction"?

# Retracted publication: MEDLINE 1966-2001



# Conclusioni

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- Esistono in letteratura numerosi esempi di frode che vanno dalla completa invenzione di uno studio, alla sua parziale falsificazione, al "gonfiamento" dei dati, alla duplicata pubblicazione dei risultati di un singolo RCT, alla mancata pubblicazione dei RCTs negativi
- La prevenzione e la correzione della "misconduct" richiedono la collaborazione tra ricercatori, sanità pubblica, industria ed editori.

# RINGRAZIAMENTI

Si ringrazia il Prof. Luigi Pagliaro dell'Università degli Studi di Palermo per il materiale fornito ed i preziosi suggerimenti