Adverse Events Following Immunisation

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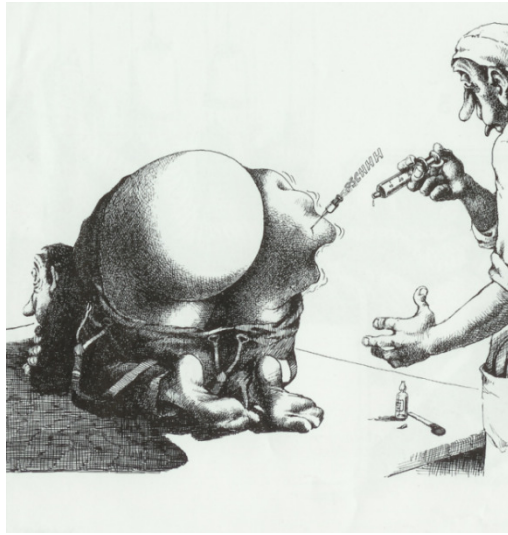
Galway

Nov. 30th, 2016



Definitions

- **Adverse Event (AE)**

  .. untoward medical occurrence…during treatment with a pharmaceutical product but which **does not necessarily have a causal relationship** with this treatment

- **Adverse (Drug) Reaction (ADR, AR)**

  Response to a drug which is noxious and unintended

R.E.G.R.E.T.

"**R**eactions and **E**ffects of **G**ardasil **R**esulting in **E**xtreme **T**rauma"

Set up by parents of girls who have developed serious health problems after entering secondary school. “These parents are certain that the HPV vaccine (Gardasil) is the cause of their daughters' otherwise unexplained illness.”

One is entitled to one’s beliefs and feelings, but not to one’s own science

Personal belief is subjective; scientific evidence is objective

No vaccine is 100% safe
No vaccine is 100% effective

Frequency of Reactions

- Very common…….. >10%
- Common……..1-10%
- Uncommon……1/100-1/1,000
- Rare……..1/1,000-1/10,000
- Very rare……<1/10,000

Known Adverse Reactions

More Common (>1 in 100)	Less Common (<1/100)
• Redness • Swelling, nodule • Pain • Fever, irritability, loss of appetite •nausea, D+V	• Encephalitis • Paralysis • Arthritis • Allergic reaction • Thrombocytopoenia • Febrile seizure • Fainting • Narcolepsy • Death

What is “Less Common”?

Frequency of known injury*	**What else is this common?**
1/1,000 to 1/100,000 – Fainting or collapse – Febrile seizure – Thrombocytopoenia	Having quadruplets
1/100,000 to 1/1,000,000 – Serious allergic reaction – Arthritis	Getting struck by lightning
> 1 in a million – Encephalitis – Paralysis – Death	Winning the lottery

*highest rate for any childhood vaccine

Presenting Risk Information

Up to 3 children out of 10,000 will experience a serious reaction

This vaccine is very safe - 9,997 children out of 10,000 will experience no significant adverse reaction

What Causes AEFIs?

Vaccine – inherent properties, over-attenuated live vaccine, instability, mixing interferences, strain variation

Programme, administration – storage, site, mixing

Injection reaction – anxiety, pain

Unknown – cause cannot be determined

Timing of Vaccine Reactions

- **Inactivated vaccines**: generally within 48hrs

- **Live vaccines**: according to time for organism to replicate

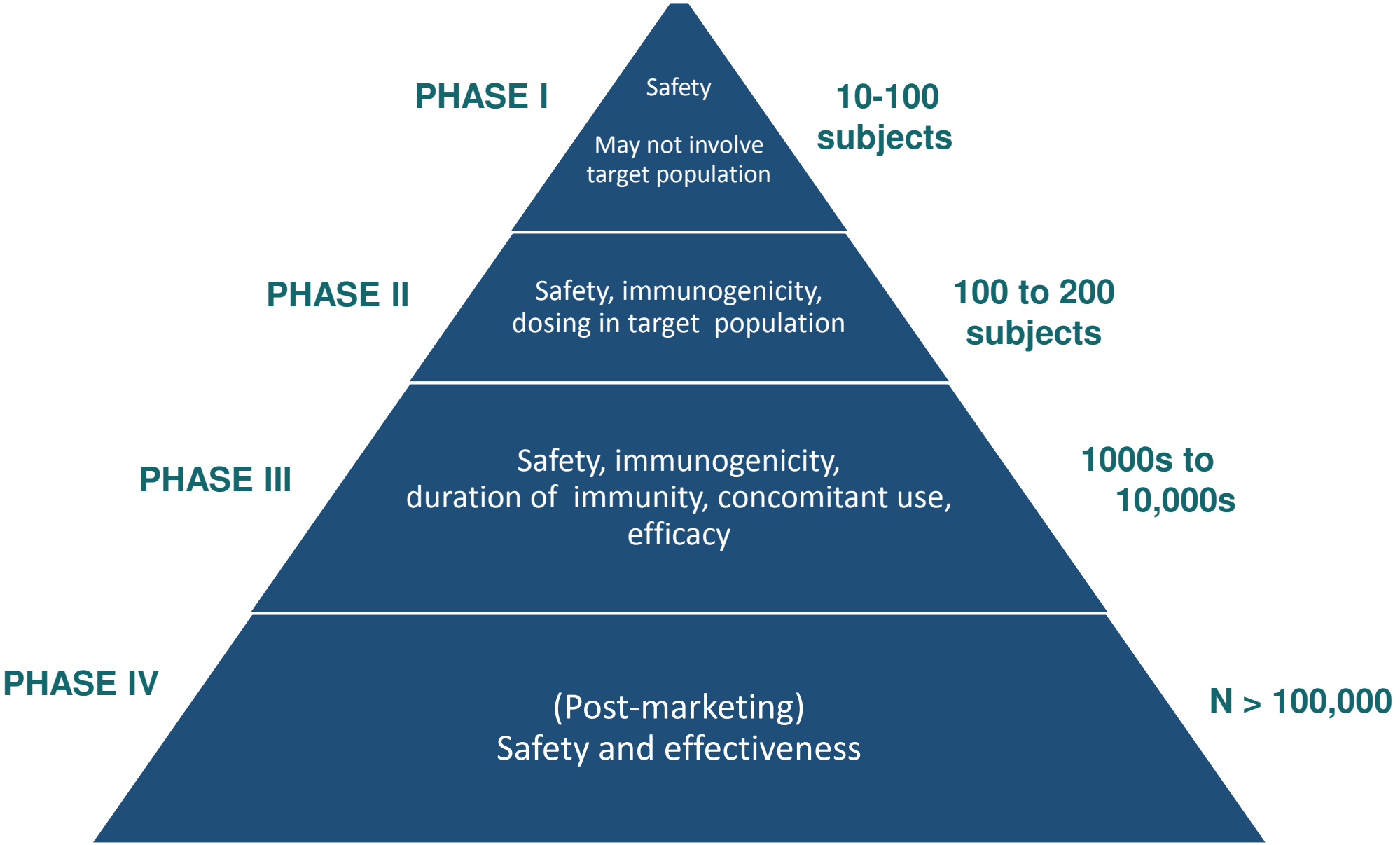
MMR: - mini-measles 6-11 days (SSPE years)

- rubella 2nd week

- mumps 3 to 6 weeks

BCG: days - 12 months +

Vaccine Safety Studies



Benefit-risk Balance

Medicines tested in trials (selected, relatively few subjects), but

used in patients who differ from trial subjects

(age, additional diseases, other medicines)

Pharmacovigilance (PhV)

Detection, assessment, understanding, prevention of ARs

Objectives : - preventing harm

- promoting safe, effective use

Why Pharmacovigilance?

- No vaccine is 100% safe

  Rare events require huge numbers to detect

- Risk / benefit balance changes over time
  - as incidence falls-e.g. VAPP with oral polio vaccine
  - as society becomes more critical

Why Pharmacovigilance?

- Identify previously unrecognized ADRs, new, frequent and/or severe
- Identify subgroups of patients at particular risk of ARs
- Continue surveillance to ensure benefits/harms balance remains acceptable

Why Pharmacovigilance?

- Detect clinically important drug–drug, drug–food interactions
- Communicate appropriate information to HCPs
- Confirm or refute of false-positive signals that arise

Pharmacovigilance by Pharma Companies

- Legal obligations (PSUR, SUSAR)
- Authorities may request further investigations
- Authorities may update SmPC
- Authorities may implement safety measures

HPRA Suspected Adverse Reaction Reports 2015

Total: 2,810

Source (%):

Pharma:	67*
Consumer:	8
Pharmacist:	8
Nurse:	4
PH Doctor:	4
GP:	4
Hospital doctor:	3
Other:	2

*Sent to Pharma by HCP, consumers

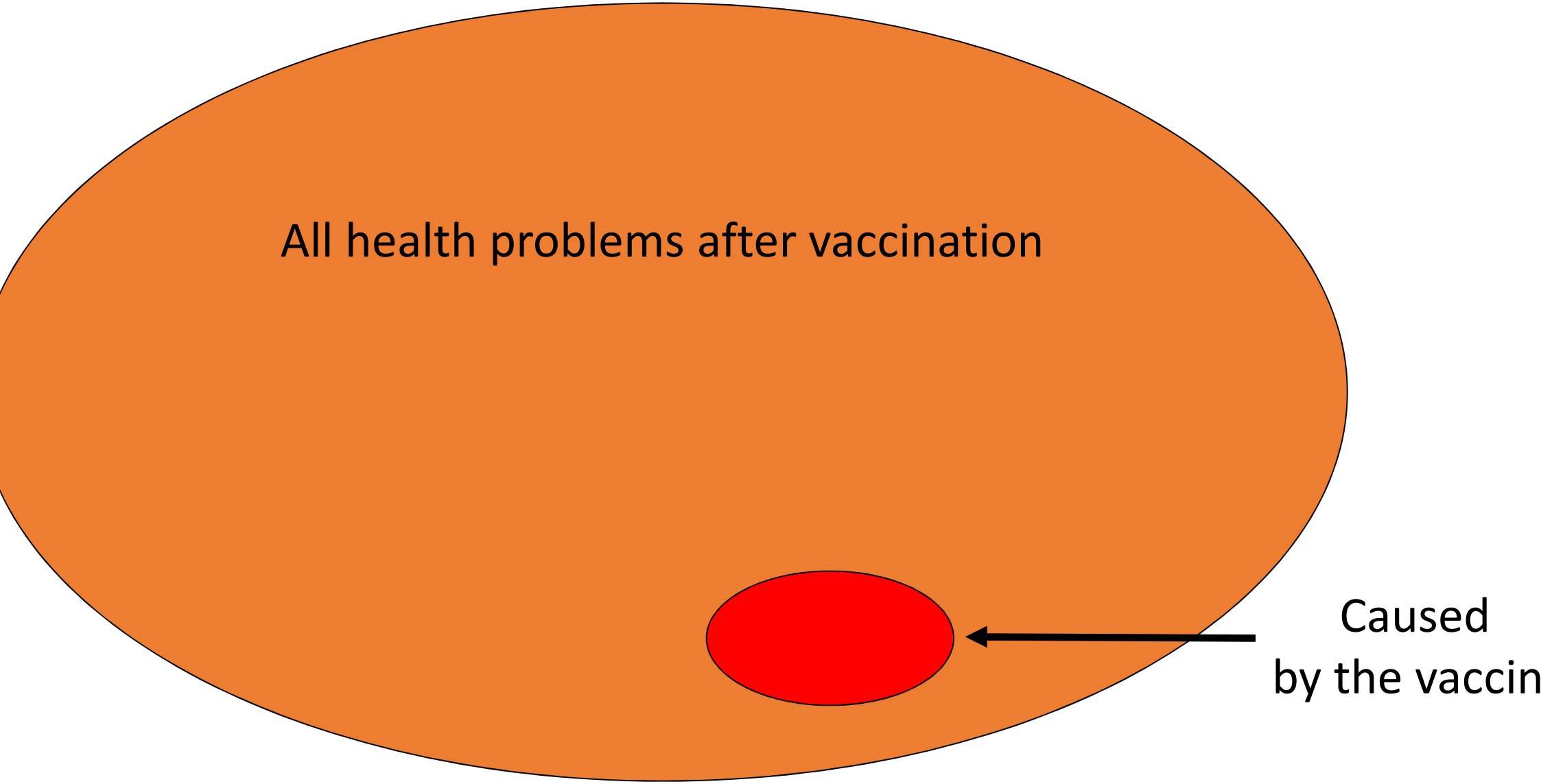
Reporting Suspected ARs

- Follow the links to reporting options on **www.hpra.ie**
  - Download report form, complete manually and ‘freepost’
  - Use the ‘Yellow card’, also freepost
  - Phone HPRA Pharmacovigilance section (01-6764971)

What HPRA does with Reports

- Individual case reports are followed up, with feedback
- Relevant reports (i.e. serious, suspected cases) forwarded to Pharma, EMA
- Details sent to WHO international database

AEFI - Coincidence or Vaccine Injury?

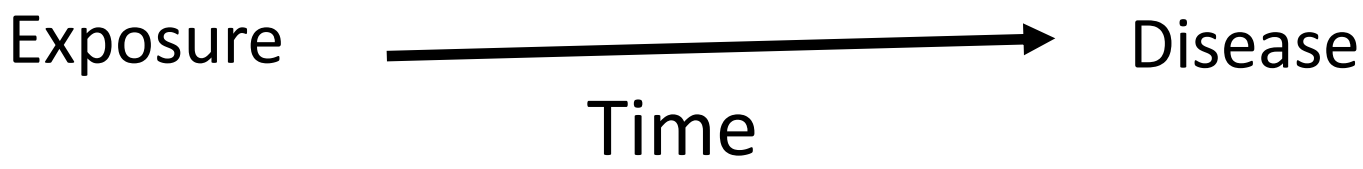


Criteria of Causality

- **Data must be strong** - substantial increase in risk compared to control population
- **Data must be consistent** across studies with different populations (gender, ethnicity, income, age).
- **Data must be specific** – e.g. lung cancer and smoking
- **Data must be temporal** – drug before effect
- **Data must possess a dose response effect –**

  more cigarettes → more cancer; more drink→ more drunk
- **Causal effect must be plausible** – carcinogens and cancer

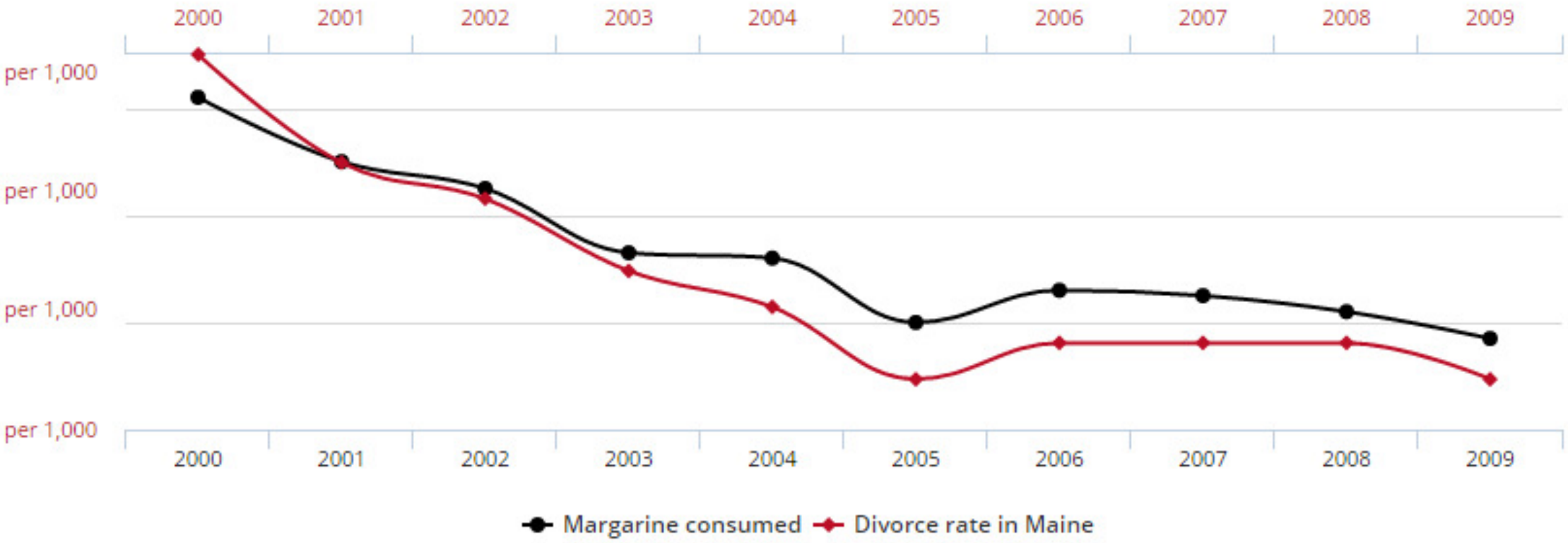
Is Sequence Consequence?



- Direct and only cause?
- One of multiple potential causes?
- Co-factor/indirect cause, trigger?
- Coincidental?

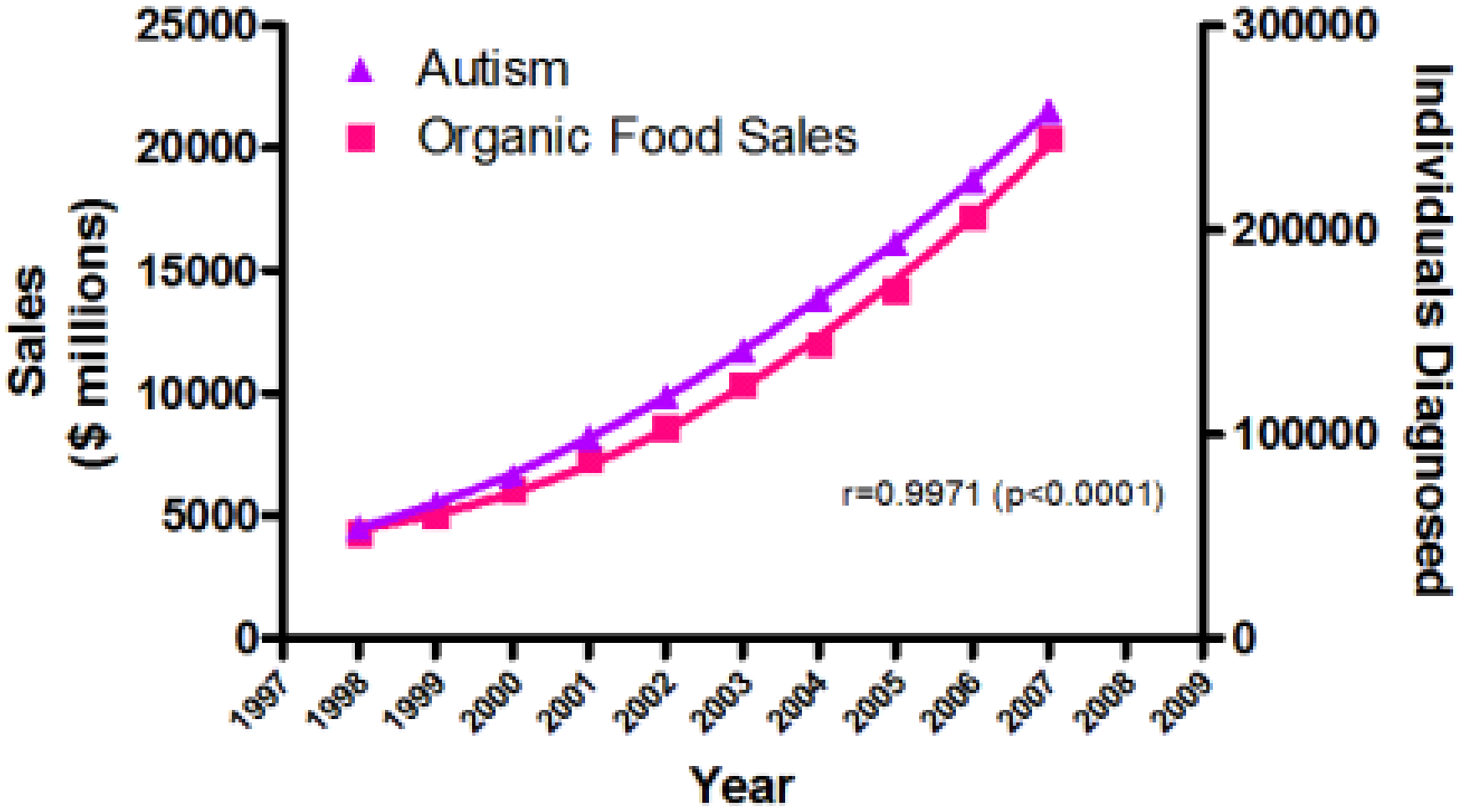
Divorce rate in Maine
correlates with
Per capita consumption of margarine

Correlation: 99.26% (r=0.992558)



es: National Vital Statistics Reports and U.S. Department of Agriculture

Organic Food Sales and Autism



Back to REGRET

Is there evidence that HPV vaccine caused the reported symptoms ?

Criteria of Causality

- **Data must be strong** - substantial increase in risk compared to control population - NO
- **Data must be consistent** across studies - NO
- **Data must be specific** - NO
- **Data must be temporal** –vaccine before symptoms - ?
- **Data must possess a dose response effect –** not applicable
- **Causal effect must be plausible** – NO

Problems with REGRET'S Beliefs

- Sampling, reporting, recall, notoriety, susceptibility biases
- No medical verification seen
- Incidence of CFS in population, in trials, after introduction of HPV vaccines

The overwhelming body of scientific evidence is that there i no causative association between HPV vaccines and POTS, CFS or CRPS

Remember…….

Incidence of HPV-related cancers

Impact of HPV vaccines

Cervical Cancer

Key facts

	Invasive	In Situ *(CIN III)*
Number of new cases per year	295	3,213
Incidence rate (cases per 100,000 per year)	12.4	126.4
Cumulative lifetime risk of diagnosis (to age 74)	1.0%	8.7%
Percentage of all invasive cancers	3.1	-
Ranking amongst most common cancers diagnosed	8th	-
Number of deaths per year	74	-
Mortality rate (deaths per 100,000 per year)	3.1	-
Cumulative lifetime risk of death (to age 74)	0.2%	-
Percentage of all cancer deaths	1.7	-
Ranking amongst most common invasive cancer deaths	15th	-
Number of people with this cancer still alive in 2013	2,977	35,175
Number alive per 100,000	128	1,517

** invasive cancers only, excluding non-melanoma skin cancer*

Impact of HPV Vaccination

Since HPV vaccine introduced in 2006:

- HPV Genital infection reduced by 64 - 85%[1]

- CIN2, 3 reduced by 75% [2]

- Cancer of vagina, vulva, anus, penis, mouth, throat

[1] US, Australia

[2] 3m. girls, Sweden, 2006-13, vaccinated <17yrs. International Journal of Cancer (2016).

Estimated Impact of no HPV Vaccination

Lifetime risk of invasive cervical cancer is 1%*

- Currently 500,000 girls <15 in Ireland; if none are vaccinated:
  - ~5,000 will develop invasive cervical cancer
  - ~1,500 will die from cervical cancer

80% uptake would prevent 2,800 cases of cancer and ~900 deaths

*National Cancer Registry 2016

The End