Post-marketing PV - Part 2: Active pharmacovigilance

Thomas Verstraeten, P95

DCVMN training on PV,

May 2017

Contents

- The principles of active PV
- Basic notions of pharmaco-epidemiology
- Post-authorization studies
- Some examples

Active PV

- No single definition
- Often used as anything to evaluate a signal
- In my opinion, anything where one tries to pro-actively detect or evaluate a safety signal
- Complements passive surveillance
  - Confirming or refuting the signals generated through passive surveillance
- Primary aim:
  - To estimate the risk of pre-specified AEFI(s) in a population exposed to a vaccine
- To evaluate if a vaccine increases the risk of a AE:
  - Determination of relative risk (RR) is required

Different steps of active PV

1. Assess the population
2. Select the outcome(s) of interest
3. Use case definitions
4. Collect data
5. Calculate and analyze incidence rates
6. Apply methodology for assessing risk
7. Report

Some definitions

- Safety signal: A report or reports of an event with an unknown causal relationship to treatment that is recognized as worthy of further exploration and continued surveillance (CIOMS VI).
- An identified risk: An untoward occurrence for which there is adequate evidence of an association with the medicinal product of interest.
- A potential risk: An untoward occurrence for which there is some basis for suspicion of an association with the medicinal product of interest but where this association has not been confirmed.
- Missing information: Information about the safety of a medicinal product which is not available at the time of submission of a particular risk management plan and which represents a limitation of the safety data with respect to predicting the safety of the product in the marketplace.
- Safety concern: An important* identified risk, important potential risk or important missing information.

*: Could have an impact on BR balance

Examples of potential sources of signals

- Spontaneous reports (incl published case reports)
- Clinical trial data
- Post-marketing (safety) studies
- Manufacturing problems/ product complaints
- External research (laboratory, clinical, non-interventional)

Recent examples of signals

- Rotavirus vaccines and intussusception
- MMR-V vaccines and febrile seizures
- Influenza vaccines and fever in children
- PCV (Porcine Circo Virus) contamination of rotavirus vaccines
- HPV vaccines and pregnancy outcomes
- Thiomersal and neurodevelopmental disorders
- Etc etc

Example: Rotarix

- Potential risks:
  - Bronchitis
  - Intussusception
  - Pneumonia deaths
- Identified risks: None
- Missing information:
  - Vaccine effectiveness
  - Strain variation
  - Genetic variability
    vaccine transmission
  - Use in preterm children
  - Use in immunocompromised children

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000639/WC500054803.pdf

Basic notions of Pharmaco-Epidemiology

Definition

Epidemiology = epi “upon” + demos “people” + logos “study”

The epidemiology is the study of the occurrence and distribution of health-related events, states and processes in specified populations, including the study of the determinants influencing such processes, and the application of this knowledge to control relevant health problems.

Porta M. A dictionary of epidemiology. 6th ed. Oxford, Oxford University Press, 2014

Epidemiology as “the basic science of public health”

Relative risk (risk ratio) - RR

- Ratio of the risk of occurrence of a disease among exposed people to that among the unexposed
- Measures the strength of the association between the exposure of interest and the outcome
- Used in cohort studies

$$RR = \frac{\text{Incidence among the exposed group}}{\text{Incidence among the unexposed group}}$$

Odds ratio - OR

- Odds= ratio of the probability of occurrence of an event to the probability of non occurrence of this event
- Eg. Odds of obtaining a six when throwing a dice

$$\frac{1/6}{5/6} = 1/5 = 0.20$$

Is rotavirus vaccination associated with development of intussusception?

TABLE 2. MATCHED ODDS RATIOS IN THE CASE–CONTROL ANALYSIS OF INTUSSUSCEPTION AFTER VACCINATION WITH RRV-TV.*

DOSE	RISK PERIOD†	NO. OF INFANTS WITH INTUSSUSCEPTION VACCINATED DURING RISK PERIOD	NO. OF CONTROLS VACCINATED DURING RISK PERIOD	UNADJUSTED ODDS RATIO (95% CI)‡	P VALUE	ADJUSTED ODDS RATIO (95% CI)§	P VALUE
	days						
All	Any day before reference date¶	67	190	1.8 (1.3–2.5)	0.001	2.2 (1.5–3.3)	<0.001
	0–2	0	19	—	0.99	—	0.99
	3–14	53	47	9.2 (5.3–16.2)	<0.001	10.6 (5.7–19.6)	<0.001
	3–7	41	22	13.7 (7.0–26.8)	<0.001	14.4 (7.0–29.6)	<0.001
	8–14	12	25	3.9 (1.6–9.2)	0.002	5.3 (2.1–13.9)	0.001
	15–21	4	24	0.9 (0.3–2.6)	0.79	1.1 (0.3–3.3)	0.91
First	0–2	0	8	—	1.00	—	1.00
	3–14	43	22	16.8 (8.3–34.3)	<0.001	21.7 (9.6–48.9)	<0.001
	3–7	35	12	27.9 (10.8–72.1)	<0.001	37.2 (12.6–110.1)	<0.001
	8–14	8	10	6.4 (2.1–19.1)	0.001	8.2 (2.4–27.6)	0.001
	15–21	2	15	0.7 (0.1–3.2)	0.63	1.1 (0.2–5.4)	0.87
Second	0–2	0	8	—	1.00	—	1.00
	3–14	9	21	3.4 (1.3–9.2)	0.02	3.3 (1.1–9.8)	0.03
	3–7	6	8	5.0 (1.4–17.3)	0.01	3.8 (1.0–14.0)	0.05
	8–14	3	13	1.5 (0.3–6.6)	0.61	1.8 (0.4–9.5)	0.47
	15–21	1	6	0.9 (0.1–8.0)	0.93	0.9 (0.1–8.6)	0.94

*CI denotes confidence interval.

Interpretation of the OR

- OR = 1 → Exposure does not affect odds of disease (=There is no risk)
- OR > 1 → Exposure associated with higher odds of disease(= Increased risk)
- OR < 1 → Exposure associated with lower odds of disease (= Reduced risk)

Infants with intussusception are 2 times more likely to have received rotavirus vaccination

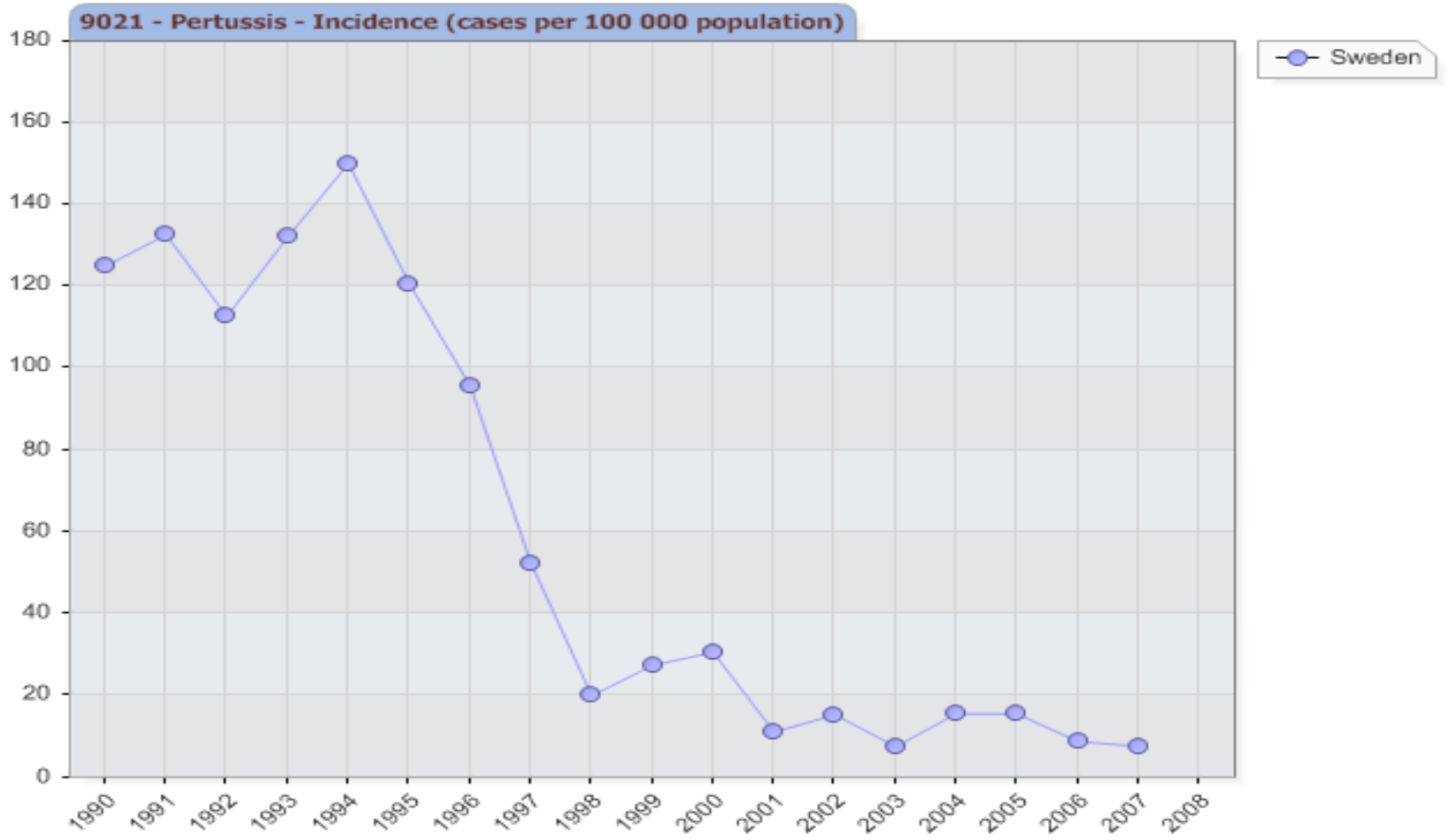
Observational studies

- Descriptive
- Analytical
  - Cross-sectional
  - Cohort
  - Case-control
  - Self-controlled case series
  - Case-cohort
  - Ecological

Descriptive studies

- Simple description of a health status of a population
- There is no attempt to analyze the links between exposure and effect
- Eg. Analysis of surveillance data

Incidence of Pertussis in Sweden, 1990 - 2007



Source: WHO-EU, 2008

Cross-sectional studies

- Used to measure the prevalence of disease
- Data collected at one particular point of time
- Relatively easy and inexpensive to conduct
- Difficult to assess causality, since it may not be possible to establish whether the exposure occurred before the outcome

Serogroup A Meningococcal Conjugate Vaccine Coverage After the First National Mass Immunization Campaign — Burkina Faso, 2011

TABLE 1. Regional and weighted national PsA-TT serogroup A meningococcal conjugate vaccine coverage — Burkina Faso, 2011

Region	Target population size	Sample size	Coverage* (%)	(95% CI)
Centre-Ouest	889,975	2,134	98.3	(96.9–99.0)
Centre-Sud	464,731	1,585	98.2	(96.2–99.2)
Centre-Est	861,630	1,676	98.2	(96.7–99.0)
Cascades	436,411	1,655	98.1	(96.2–99.1)
Nord	889,517	1,918	97.3	(95.5–98.4)
Centre-Nord	922,309	1,892	96.9	(94.8–98.2)
Hauts-Bassins	1,174,646	1,938	96.7	(93.3–98.4)
Plateau Central	514,841	2,098	96.6	(94.9–97.8)
Boucle du Mouhoun	1,094,806	1,998	96.0	(92.6–97.9)
Sud-Ouest	452,547	1,700	95.9	(91.0–98.1)
Est	976,766	1,949	94.8	(89.2–97.5)
Sahel	749,382	1,526	94.5	(91.3–96.6)
Centre	1,458,605	1,508	90.8	(85.3–94.4)
Burkina Faso	10,886,166	23,577	95.9	(95.0–96.7)

Abbreviation: CI = confidence interval.
* Receipt of vaccination was documented by a vaccination card specifically designed for this campaign, or by verbal recall.

TABLE 2. Weighted national PsA-TT serogroup A meningococcal conjugate vaccine coverage, by age and sex — Burkina Faso, 2011

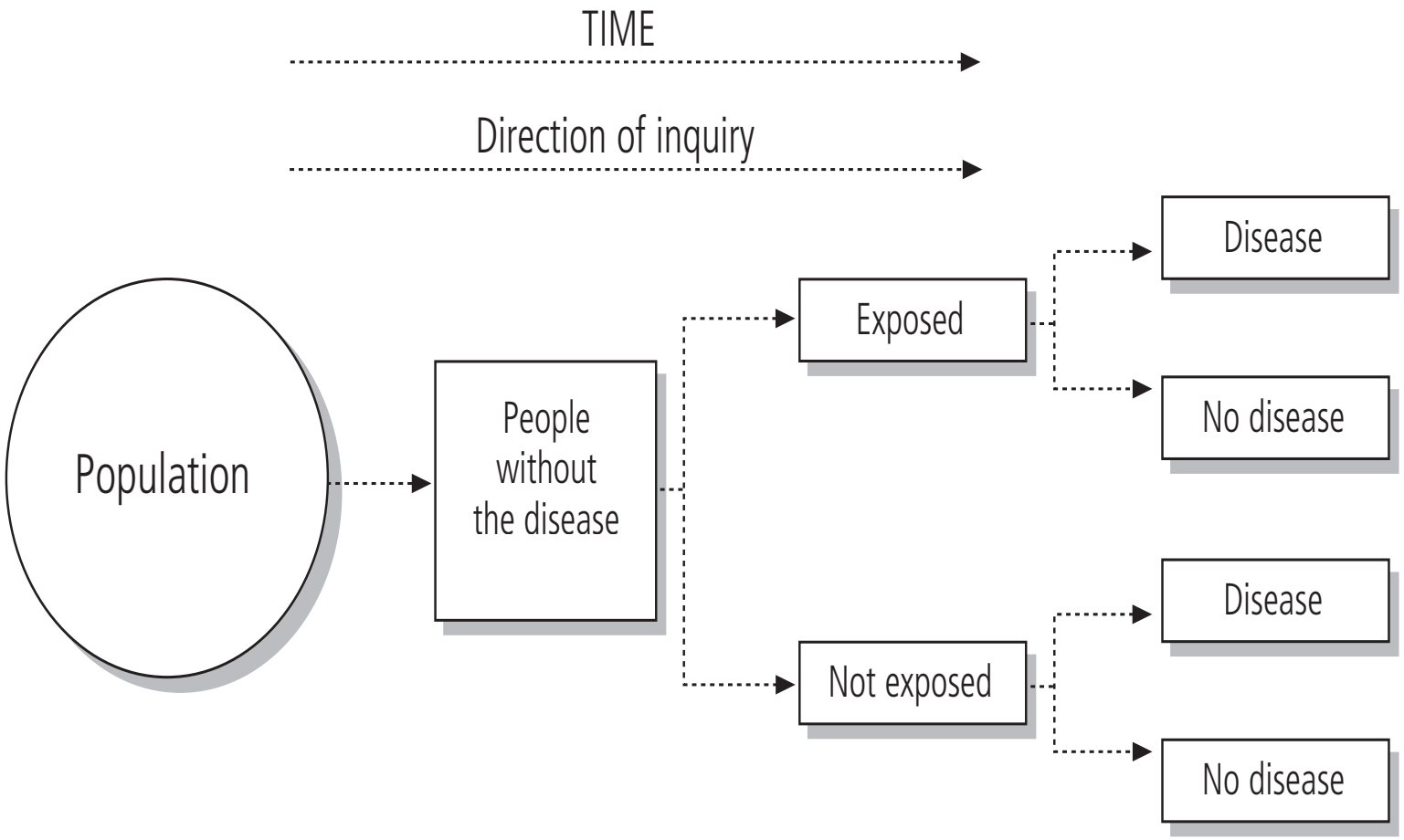
Age group (yrs)	Sex	Coverage* (%)	(95% CI)
2–5	F	97.7	(96.8–98.4)
	M	96.5	(95.0–97.5)
6–15	F	97.5	(96.6–98.2)
	M	97.3	(96.4–98.1)
16–30	F	93.6	(92.1–94.8)
	M	93.0	(91.2–94.5)

Abbreviations: F = female; M = male; CI = confidence interval.
* Receipt of vaccination was documented by a vaccination card specifically designed for this campaign, or by verbal recall.

Source: Medah et al. MMRW 2012

Cohort study

- "Gold standard" of observational studies
- Used to:
  - Measure incidence of an outcome
  - Identify associations between exposures and outcomes → RR
- They provide the best information about the causation of disease and the most direct measurement of the risk of developing disease



Source: Basic epidemiology 2nd ed. R Bonita et al. WHO 2006

AS03 Adjuvanted AH1N1 Vaccine Associated with an Abrupt Increase in the Incidence of Childhood Narcolepsy in Finland

Hanna Nohynek[1]*, Jukka Jokinen[1], Markku Partinen[2], Outi Vaarala[1], Turkka Kirjavainen[3], Jonas Sundman[1], Sari-Leena Himanen[4], Christer Hublin[5], Ilkka Julkunen[6], Päivi Olsén[7], Outi Saarenpää-Heikkilä[8], Terhi Kilpi[1]

Table 4. Main results of the cohort analysis using two follow-up periods among those born at or after 1 January 1991.

Incidence in confirmed narcolepsy cases

Follow-up period	Narcolepsy cases		Follow-up years		Relative Risk		
	Not vaccinated	Vaccinated	Not vaccinated	Vaccinated	Risk ratio	95%LCL	95%UCL
First contact: 2009-01-01 to 2010-12-31	7	57	1,069,247	762,461	11.4	5.6	27.5
First contact: 2009-01-01 to 2010-08-16[1]	7	46	986,195	510,874	12.7	6.1	30.8

[1]The date when the news on the possible association between narcolepsy and Pandemrix vaccination observed in Sweden was published in the national media in Finland.

LCL = Lower confidence limit, UCL = Upper confidence limit.

doi:10.1371/journal.pone.0033536.t004

Source: PLoS ONE 2012

Cohort studies

Advantages

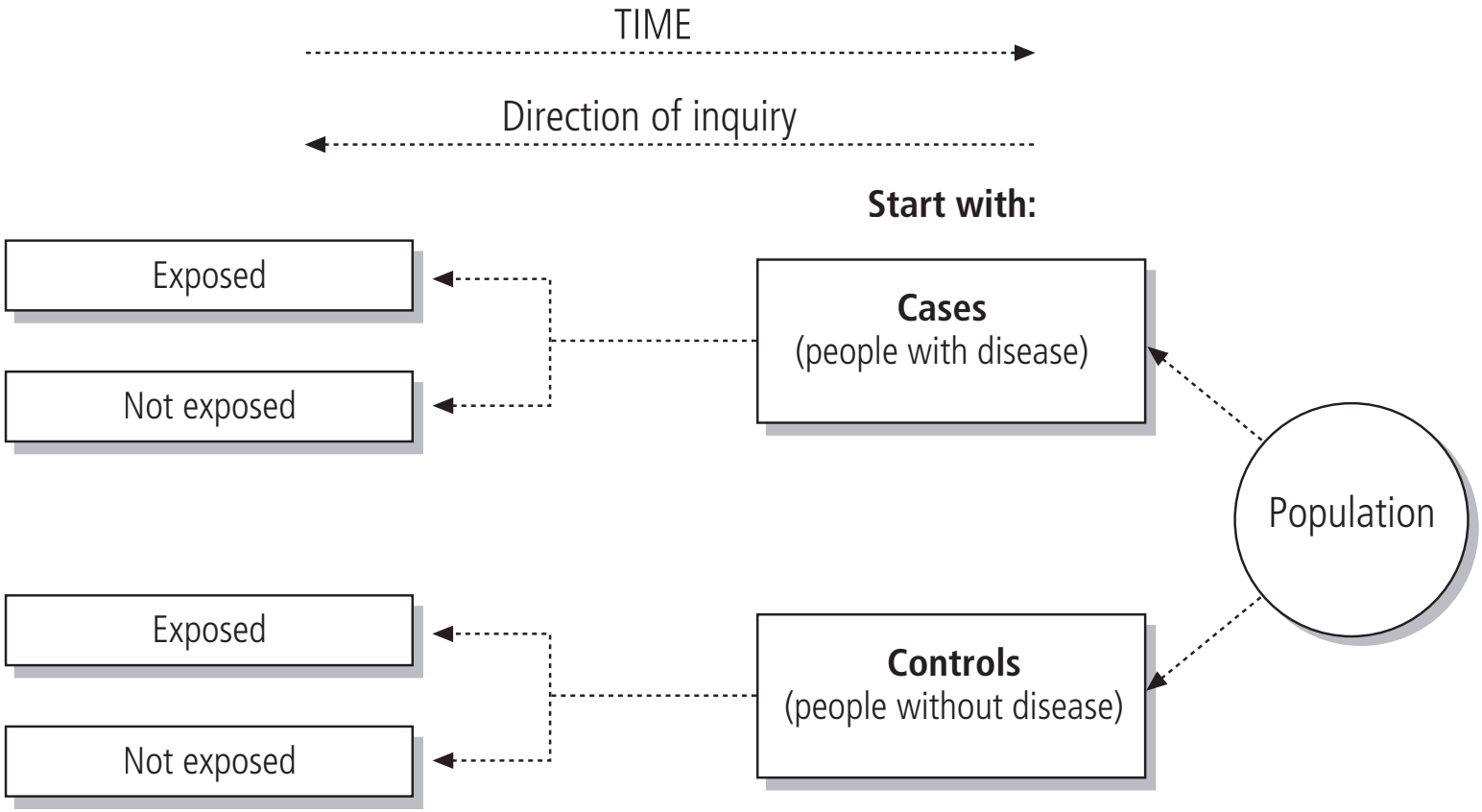
- Different outcomes for the same exposure can be investigated
- Temporal relationship exposure-outcome is clear
- Direct measurement of incidence and RR
- Best for investigation of rare exposures

Disadvantages

- Expensive and time consuming
- Not practical for investigation of rare diseases
- Investigation of long latent periods
- Loss to follow-up

Case-control

- Used to identify associations between exposures and outcomes → OR
- Compares a group of people with the outcome of interest (cases) to a group of people without the outcome (controls)



Source: Basic epidemiology 2nd ed. R Bonita et al. WHO 2006

INTUSSUSCEPTION AMONG INFANTS GIVEN AN ORAL ROTAVIRUS VACCINE

TRUDY V. MURPHY, M.D., PAUL M. GARGIULLO, PH.D., MEHRAN S. MASSOUDI, PH.D., M.P.H., DAVID B. NELSON, B.S., AISHA O. JUMAAN, PH.D., M.P.H., CATHERINE A. OKORO, M.S., LYNN R. ZANARDI, M.D., M.P.H., SABEENA SETIA, M.P.H., ELIZABETH FAIR, M.P.H., CHARLES W. LEBARON, M.D., MELINDA WHARTON, M.D., M.P.H., AND JOHN R. LIVINGOOD, M.D., FOR THE ROTAVIRUS INTUSSUSCEPTION INVESTIGATION TEAM*

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	15–21	1	6	0.9 (0.1–8.0)	0.93	0.9 (0.1–8.6)	0.94

*CI denotes confidence interval.

Source: NEJM 2001

Influenza vaccine effectiveness estimates in Europe in a season with three influenza type/subtypes circulating: the I-MOVE multicentre case–control study, influenza season 2012/13

E Kissling (e.kissling@epiconcept.fr)[1,2], M Valenciano[1,2], U Buchholz[3], A Larrauri[4], J M Cohen[5], B Nunes[6], J Rogalska[7,8], D Pitigoi[9,10], I Paradowska-Stankiewicz[11], A Reuss[3], S Jiménez-Jorge[4], I Daviaud[5], R Guiomar[6], J O'Donnell[7], G Necula[9], M Głuchowska[11], A Moren[1]

Table 3a

Pooled crude and adjusted seasonal vaccine effectiveness against laboratory-confirmed influenza by influenza type/subtype, overall and among target groups for vaccination, I-MOVE multicentre case–control study in seven European Union study sites to measure 2012/13 influenza vaccine effectiveness, ISO week 43 in 2012–ISO week 18 in 2013, influenza season 2012/13

Analysis scenarios, population included	Influenza B VE (95%CI)	Influenza A(H1N1)pdm09 VE (95%CI)	Influenza A(H3N2) VE (95%CI)
Primary analysis			
All age groups[a]			
N (cases/vaccinated; controls/vaccinated)	4,344 (1,860/92; 2,484/236)	3,196 (978/44; 2,218/214)	3,012 (672/46; 2,340/212)
Crude (study site as fixed effect)	46.5 (30.9 to 58.6)	56.1 (38.6 to 68.7)	22.5 (-8.6 to 44.7)
Adj. for onset week	50.2 (35.4 to 61.6)	57.5 (40.2 to 69.8)	29.1 (-0.5 to 50.0)
Adj. for sex	46.6 (31.0 to 58.7)	56.2 (38.7 to 68.7)	22.4 (-8.7 to 44.6)
Adj. for chronic condition	43.2 (25.9 to 56.5)	54.0 (34.9 to 67.5)	17.4 (-17.2 to 41.8)
Adj. for age	45.7 (28.3 to 59.0)	50.3 (28.9 to 65.2)	38.6 (11.1 to 57.5)
Adj. for onset week, age	50.1 (33.8 to 62.5)	51.9 (30.9 to 66.6)	45.7 (20.5 to 63.0)
Adj. for onset week, sex	50.3 (35.5 to 61.7)	57.6 (40.4 to 69.9)	29.0 (-0.6 to 49.9)
Adj. for onset week, chronic condition, age, sex	49.3 (32.4 to 62.0)	50.4 (28.4 to 65.6)	42.2 (14.9 to 60.7)

Source: Eurosurveilllance 2014

Case-control studies

Advantages

- Different exposures for the same outcome can be investigated
- Best for investigation of rare outcomes
- Cheaper and faster than cohort studies
- Investigation of long latent periods

Disadvantages

- Temporal relationship exposure-outcome is less clear
- No direct measurement of incidence and RR
- Not suitable for rare exposures
- More prone to bias (selection and recall)

Other designs

- Self-controlled case series (Cases act as their own control)
- Case-cohort: mix of cases and a control cohort
- Ecological studies: trends over time

Declining Genital Warts in Young Women in England Associated With HPV 16/18 Vaccination: An Ecological Study

Rebecca Howell-Jones,[1] Kate Soldan,[1] Sally Wetten,[1] David Mesher,[1] Tim Williams,[2] O. Noel Gill,[1] and Gwenda Hughes[1]

Exposure = HPV vaccination
Outcome = Genital warts

Groups defined by age and HPV vaccination status

Table 1. Incidence Rate Ratios of Genital Warts Diagnoses in Females in Vaccinated Compared With Unvaccinated Female Cohorts, by Age, Adjusted for Chlamydia Diagnoses Rates

	IRR (95% CI) of GW					
	England-level Analysis			PCT-level Analysis[b]		
Age, y	n	IRR (95% CI)	Adjusted[a] IRR (95% CI)	n	IRR[b] (95% CI)	Adjusted[c] IRR (95% CI)
15	1731/1 212 679	0.83 (.73, .95)	0.84 (.74, .95)	1344/994 464	0.84 (.74, .97)	0.81 (.71, .93)
16	4792/1 247 308	0.81 (.73, .89)	0.84 (.77, .91)	3703/1 022 137	0.87 (.75, 1.01)	0.89 (.77, 1.03)
17	9233/1 278 085	0.69 (.62, .76)	0.78 (.71, .86)	7157/1 046 426	0.74 (.60, .90)	0.76 (.62, .92)
18	12 586/1 314 995	0.73 (.65, .83)	0.89 (.79, 1.00)	9781/1 075 034	0.75 (.58, .97)	0.77 (.60, .99)
19	14 684/1 344 061	0.97 (.86, 1.09)	1.10 (1.00, 1.21)	11 367/1 094 272	0.86 (.65, 1.13)	0.87 (.67, 1.15)
20	13 860/1 358 690	0.90 (.74, 1.10)	0.99 (.86, 1.14)	10 652/1 102 375	0.95 (.64, 1.40)	0.96 (.65, 1.40)

Source: JID 2013

Potential errors in epidemiological studies

- Random error
- Systematic error (bias)
- Confounding
- Validity

Random error

- The value of the sample measurement diverges, due to chance alone, from that of the true population value
- Causes inaccurate measures of association
- 3 major sources
  - Individual biological variation
  - Sampling error
  - Measurement error
- Can never be completely eliminated

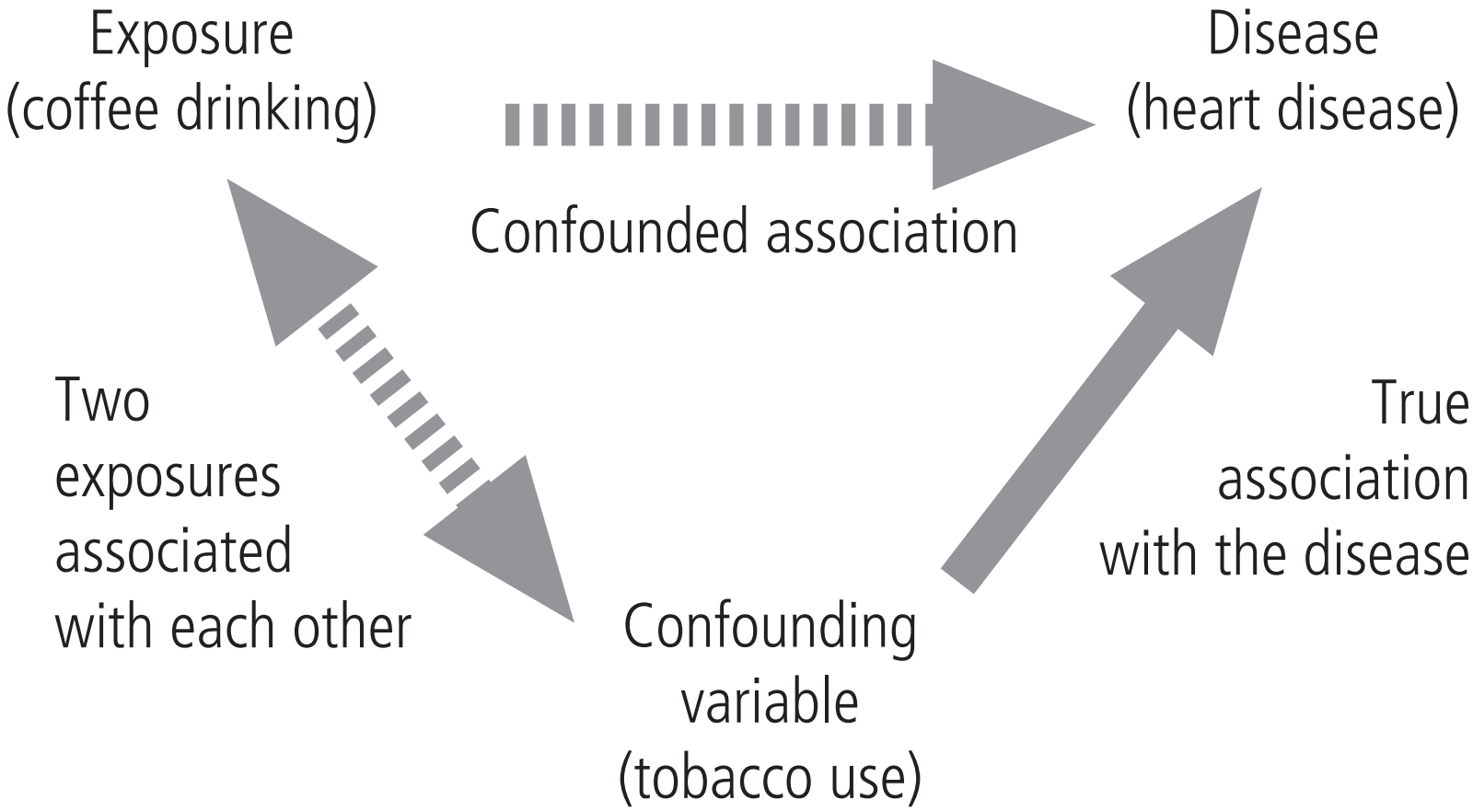
Systematic error (Bias)

- Error that results in an incorrect estimate of association between exposure and outcome
- 2 categories:
  - Selection bias
  - Information (or measurement or classification) bias

Confounding

- An exposure in the study population is associated with both the exposure under study and the outcome
- May create the appearance of a cause-effect that does not exist (Crude RR/OR is wrong)
- Common confounders:
  - Age
  - Gender
  - Social class

Confounding



Source: Basic epidemiology 2nd ed. R.Bonita et al. WHO 2006

Confounding by indication

- Flu vaccination in the elderly
  - Elderly at higher risk of developing flu are more likely to be vaccinated → underestimation of vaccine effectiveness against severe flu (= confounding by severity)

- Childhood vaccinations
  - Sick children tend not to receive vaccination → underestimation of the adverse event rate in the early post-immunization period (= healthy vaccinee effect)

Statistical significance

- Many tests regarding differences between means or proportions

- Help to establish if the observed difference is **real**

  →if it is not due to the **chance alone**

Significance testing – practicalities : H0 rejected using reported p value

p = probability that our result (for example a difference between proportions or a RR) or more extreme values could be observed under the null hypothesis

Small *p* values = low degree of compatibility between H_0 and the observed data:
→you reject H_0 and the test is significant.

Large *p* values = high degree of compatibility between H_0 and the observed data:
→you don't reject H_0, the test is not significant

We can never reduce to zero the probability that our result was not observed by chance alone

Levels of significance – practicalities :

We need of a cut-off !

0.01 0.05 0.10

p value > 0.05 = H_0 non rejected (non significant)

p value ≤ 0.05 = H_0 rejected (significant)

Confidence interval - CI

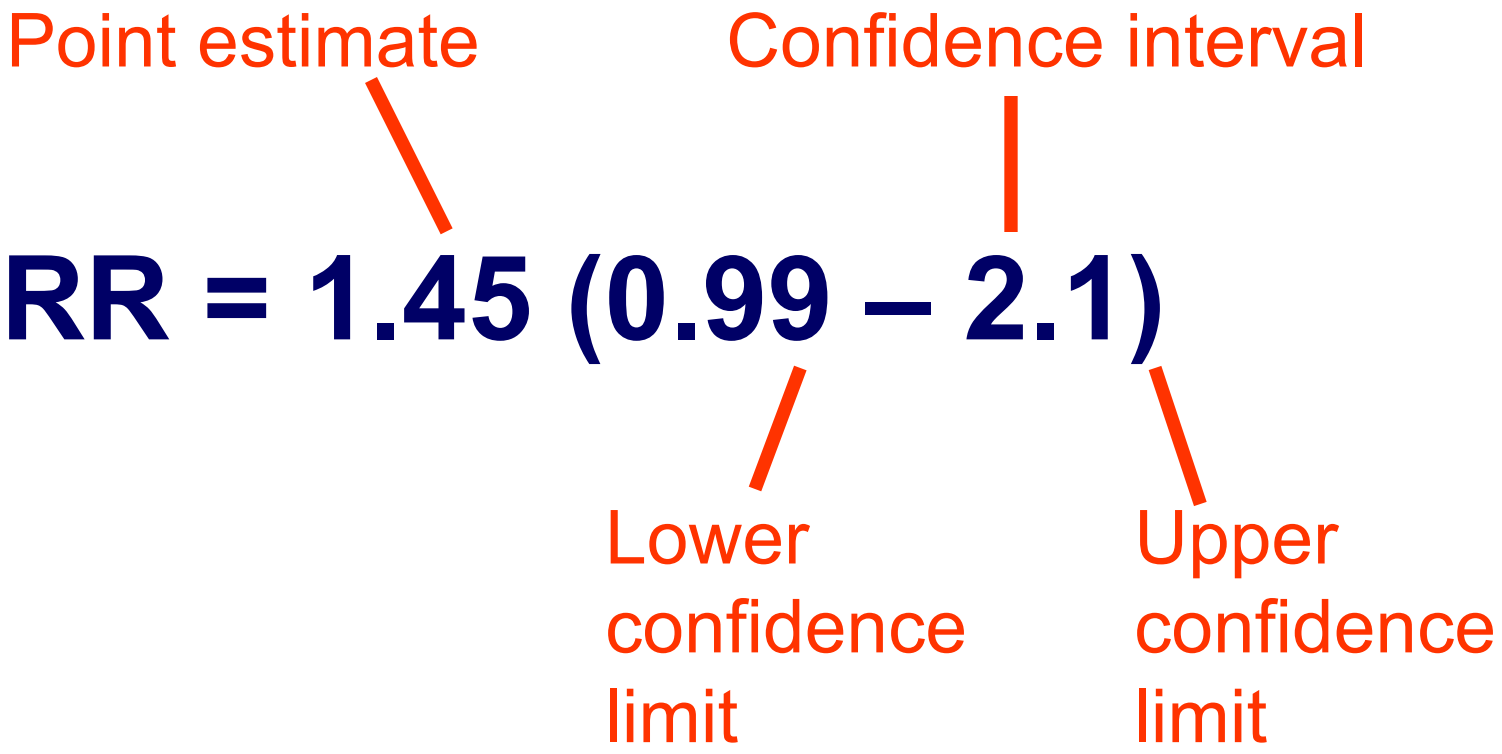
- **Text book definition of CI:**

  If the data collection and analysis could be replicated many times, the CI should include within it the TRUE value of the measure 95% of the time

➢ **Frequently used interpretation:**

The 95% CI is the range of values around point estimate within which we are 95% sure that the TRUE value of the measure lies

CI terminology

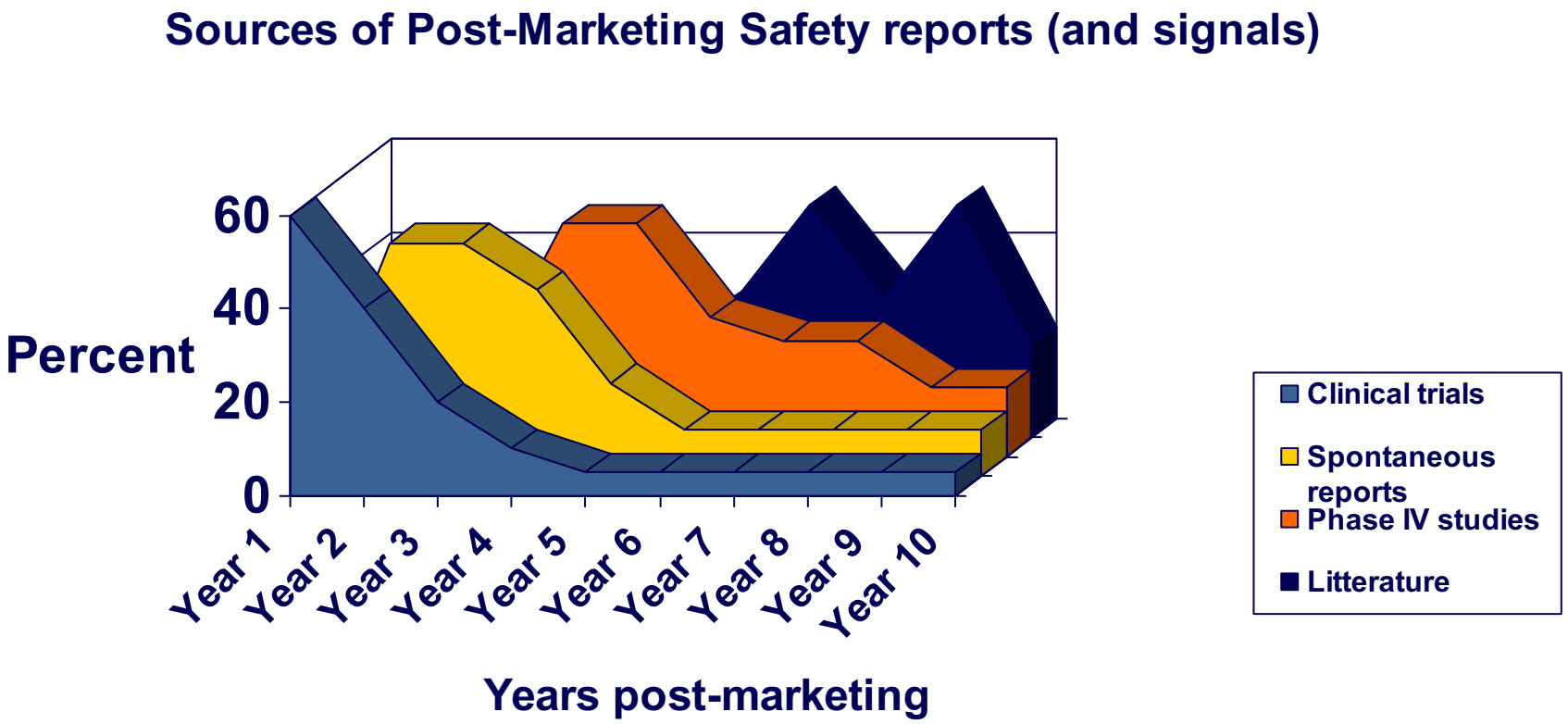


PASS studies

- Post Authorisation Safety Studies: A post-authorisation study should be classified as a PASS when the study includes any of the following objectives:
  - to quantify potential or identified risks, e.g. to characterise the incidence rate, estimate the rate ratio or rate difference in comparison to a non-exposed population or a population exposed to another drug or class of drugs, and investigate risk factors and effect modifiers;
  - to evaluate risks of a medicinal product used in patient populations for which safety information is limited or missing (e.g. pregnant women, specific age groups, patients with renal or hepatic impairment);
  - to provide evidence about the absence of risks;
  - to assess patterns of drug utilisation that add knowledge on the safety of the medicinal product (e.g. indication, dosage, co-medication, medication errors);
  - to measure the effectiveness of a risk minimisation activity.

- ≠ Post Authorisation Effectiveness Study (PAES)

Some examples



World Vaccine Congress
Lyon, October 8, 2009

Case study LVV: Rotarix

- Question for any vaccine:
  - Vaccine effectiveness
  - Impact on disease epidemiology
  - Co-administration studies
- Question for any live viral vaccine:
  - Genetic stability of vaccine virus
  - Vaccine virus transmission
- Question for any Rotavirus vaccine
  - Intussusception
  - Impact on RV serotype distribution
- Rotarix specific question:

  Populations not fully investigated in completed clinical trials:
  - Preterm infants
  - Immunocompromised infants

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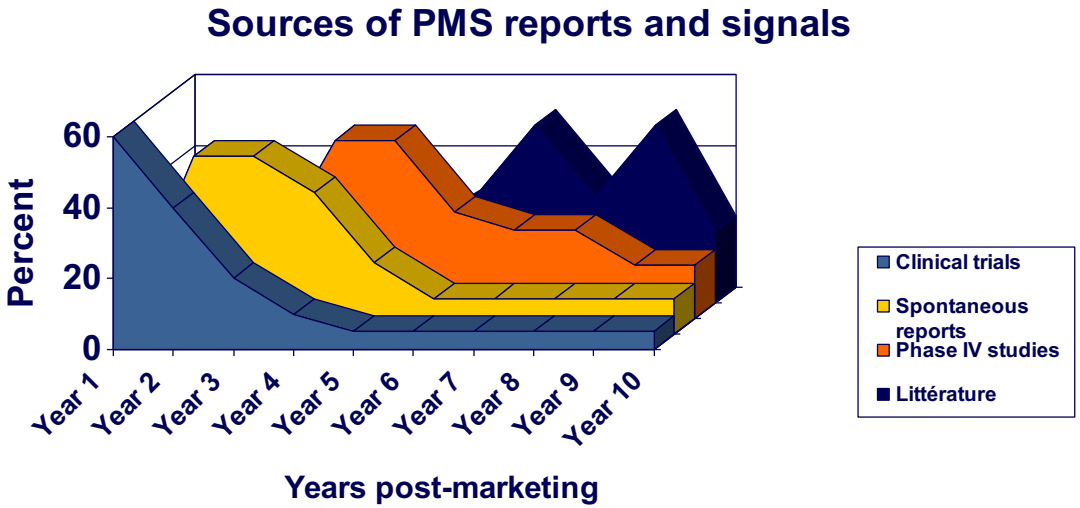
PMS experience Rotarix



Clinical data:

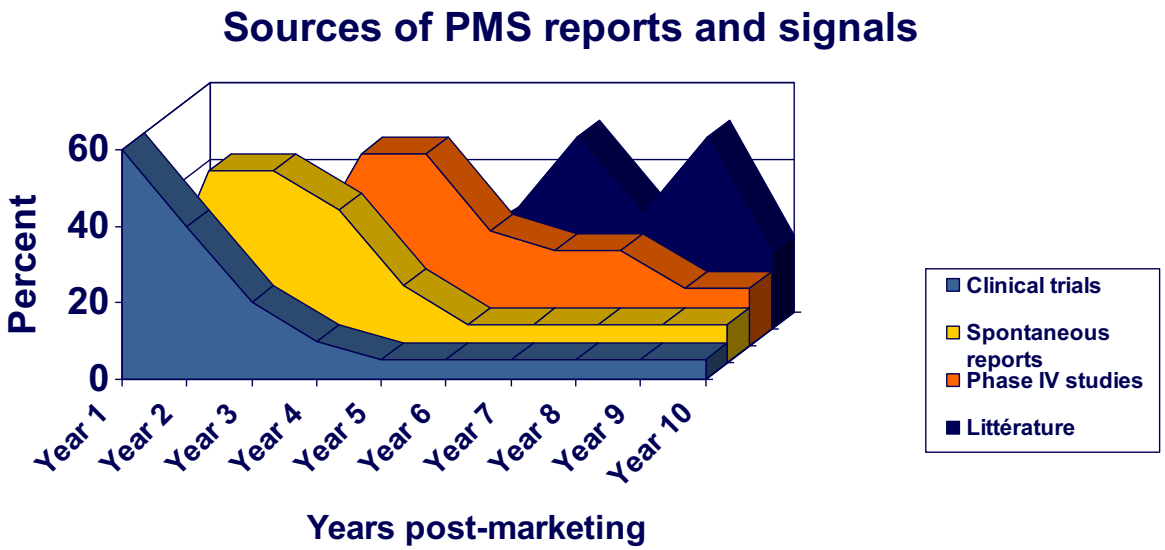
Efficacy in Africa

Studies in preterm infants and HIV +

Transmission (twins study)

Repeated meta-analysis of clinical trials: no imbalance for fatal pneumonias, balanced distribution Kawasaki

PMS experience Rotarix



Spontaneous Reports:

Intussusception

Lack of efficacy

Maladministration

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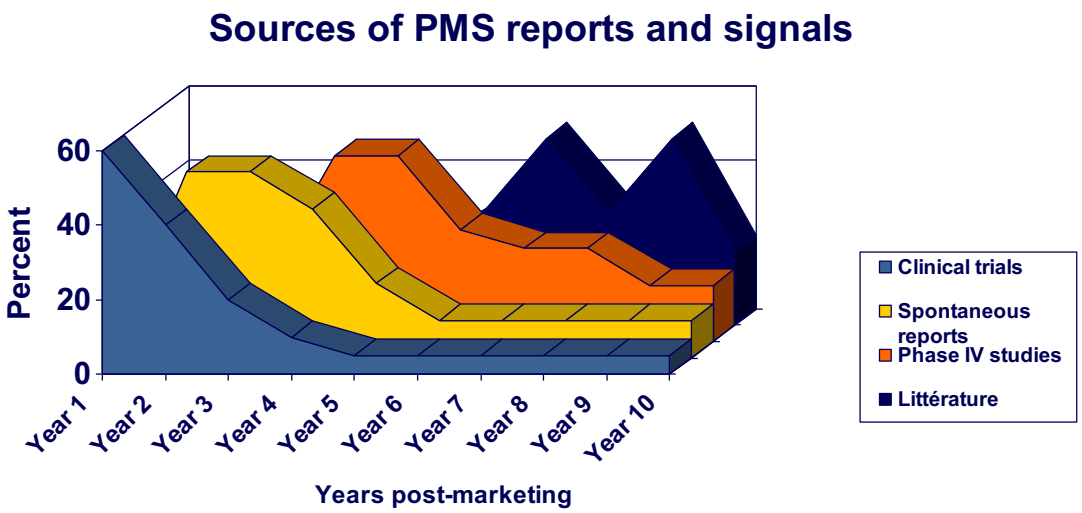
Lyon, October 8, 2009

PMS experience Rotarix



Phase IV studies:

Vaccine Effectiveness & impact studies

Intussusception

Serotype replacement

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Case study novel adjuvanted vaccine: Cervarix

- Question for <u>any vaccine</u>:
  - Vaccine effectiveness
  - Impact on disease epidemiology
  - Co-administration studies
- Question for <u>any novel adjuvanted vaccine</u>:
  - Auto-immune disorders
- Question for <u>any HPV vaccine</u>
  - Pregnancy outcomes
  - Impact on HPV serotype distribution, screening practices
- <u>Cervarix specific</u> question:

  Populations not fully investigated in completed clinical trials:
  - Immunocompromised women

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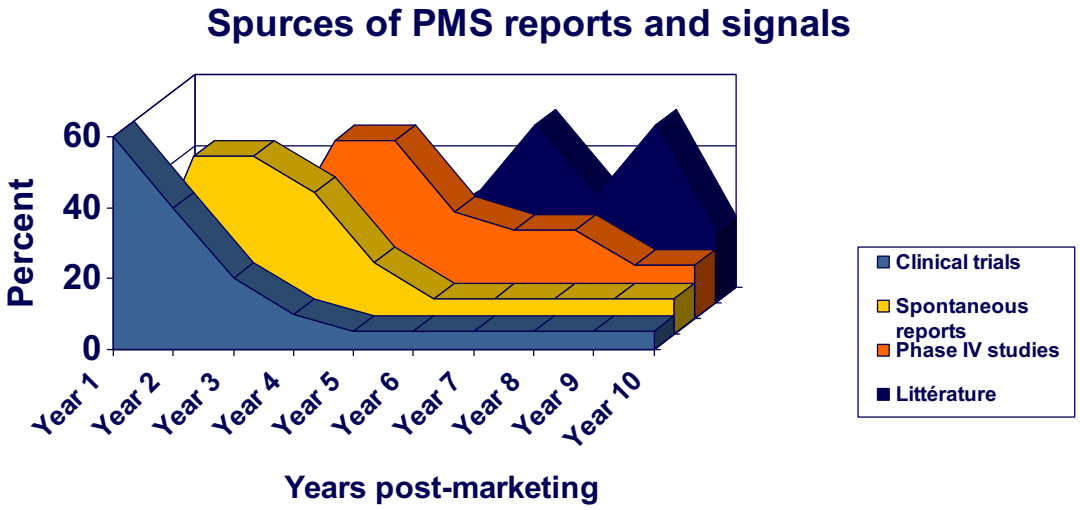
PMS experience Cervarix



Clinical data:

Efficacy/immunogenecity in ‘elder women’

Studies in HIV +

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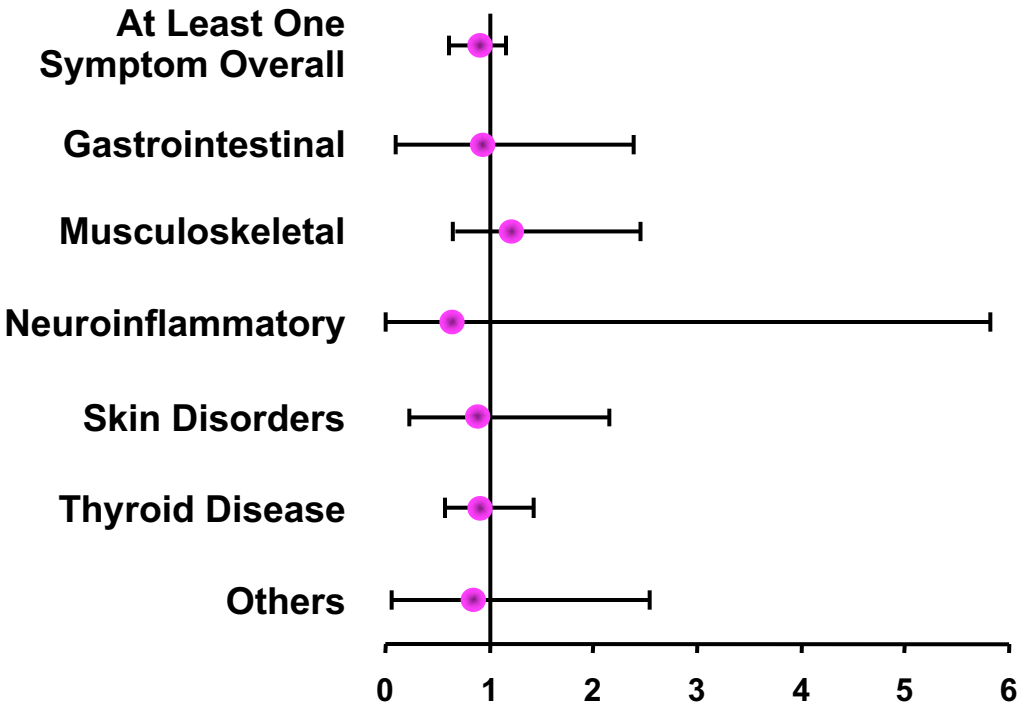
Repeated meta-analysis of clinical trials: no imbalance for Auto-Immune Diseases

Events of Potential Autoimmune Origin: Meta-Analysis of All HPV Vaccine Trials

Relative Risk (AS04 vs non-AS04) with 95% CI*



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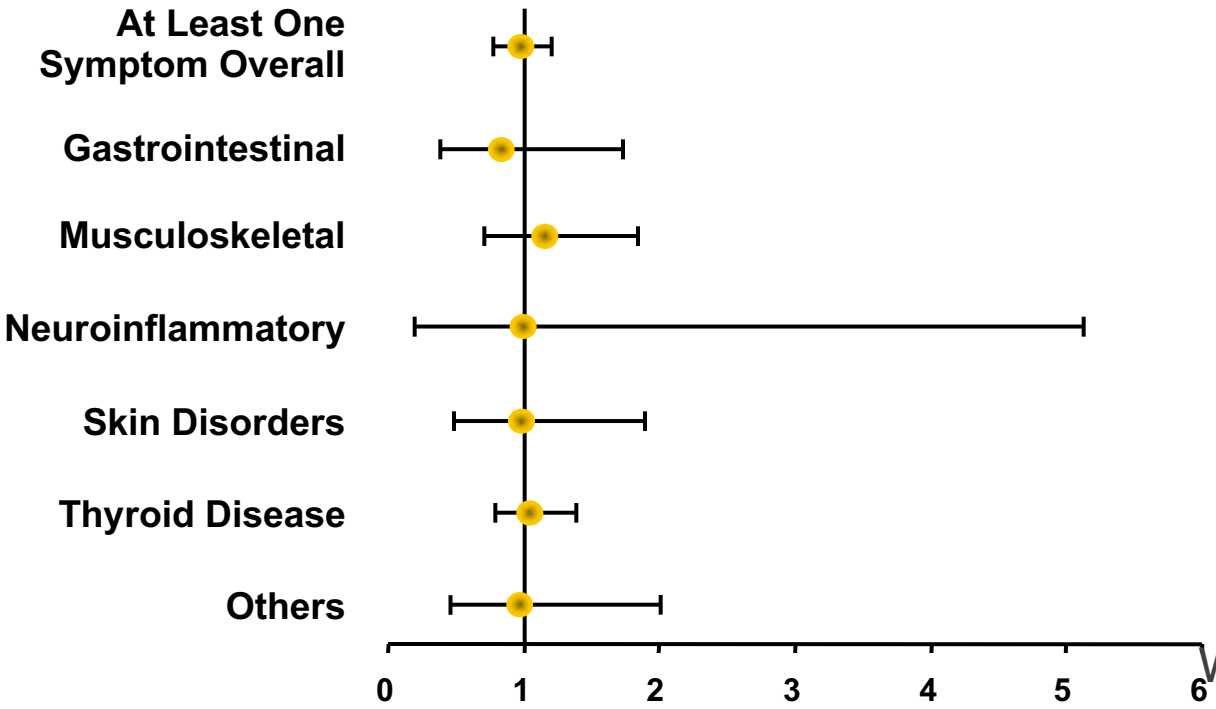
* 95% CI = 95% confidence interval for relative risk (Exact Stratified Conditional to total number of cases)

DLP: Jun 30, 2007; Verstraeten, *Vaccine,* 2008

Relative Risk (AS04 vs non-AS04) with 95% CI*



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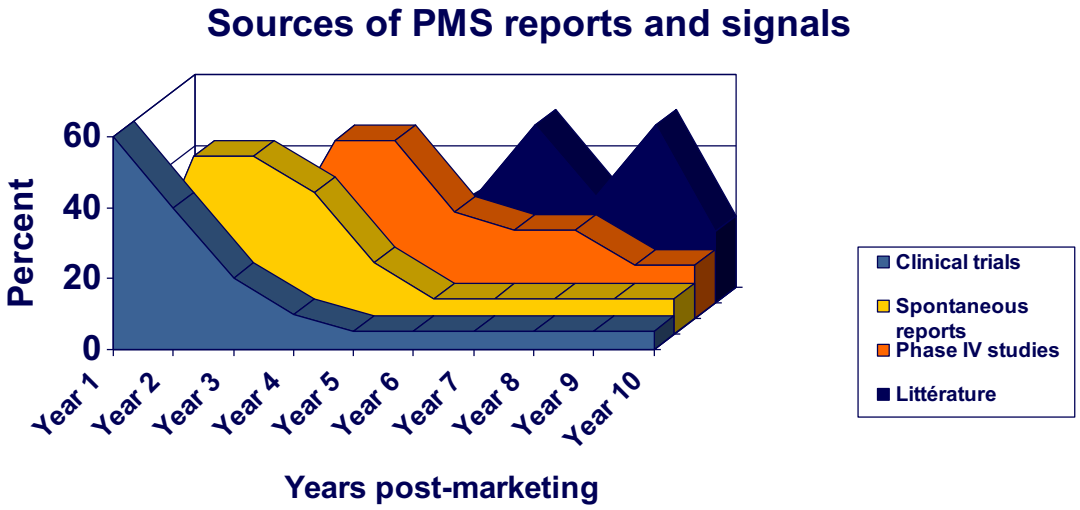
* 95% CI = 95% confidence interval for relative risk (Exact Stratified Conditional to total number of cases)

* AS04-containing vaccines: HPV, HSV and adjuvanted Hepatitis B

DLP: Jun 30, 2007; Verstraeten, *Vaccine*, 2008

PMS experience Cervarix



Spontaneous Reports:

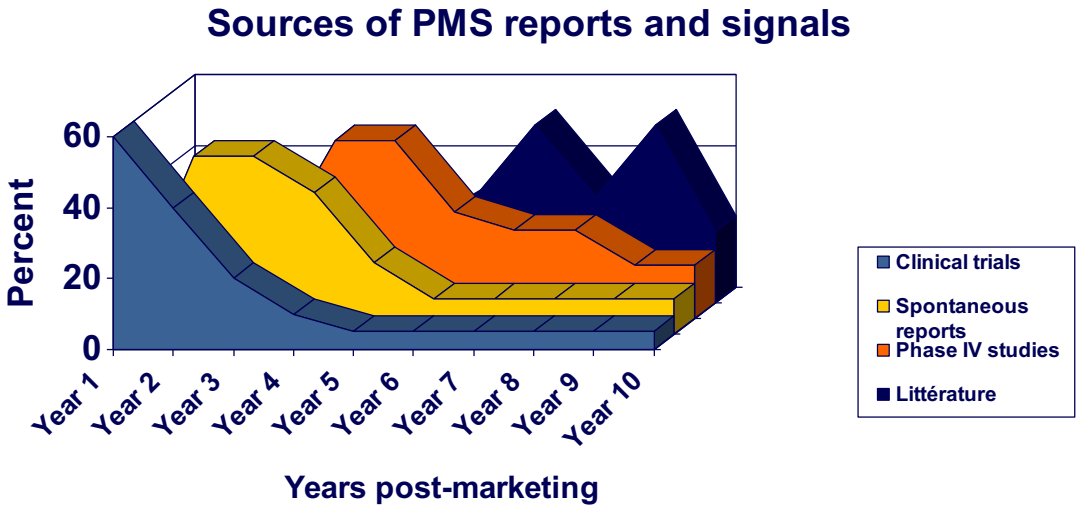
Anaphylaxis

Pregnancy outcomes

Fatal events

Auto-immune disorders

PMS experience Cervarix



Phase IV studies:

Vaccine Effectiveness & impact study

PASS - AIDs

Pregnancy outcomes

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Case study mock-up vaccine: Pandemrix (H1N1 flu vaccine)

- **H1N1 Risk Management Plan (RMP)**
  - Based on EMEA guidelines for the format and content of core Risk Management Plans (cRMP) for influenza vaccines intended for use in pre-pandemic and pandemic settings (EMEA/359381/2009)
  - H1N1 safety supported by non-clinical and clinical trials conducted with H5N1 vaccines
    - H1N1 and H5N1 strains derived and processed the same way
    - no differences in antigen manufacturing process
    - No differences in overall formulation (HA + ASO3 adjuvant)

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Adverse Events of Special Interest (AESIs)

- Adverse Events of Interest (AESIs) identified by CHMP (EMEA/ 359381/2009) for close monitoring following administration of H1N1 pandemic vaccines
  - Anaphylaxis
  - Bell's palsy
  - Convulsions
  - Demyelinating disorders
  - Encephalitis
  - Guillain-Barré syndrome
  - Neuritis
  - Vasculitis
  - Vaccination failure

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