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

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.


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

\[
\frac{1/6}{5/6} = \frac{1}{5} = 0.20
\]
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.**

<table>
<thead>
<tr>
<th>Dose</th>
<th>Risk Period†</th>
<th>No. of Infants with Intussusception Vaccinated during Risk Period</th>
<th>No. of Controls Vaccinated during Risk Period</th>
<th>Unadjusted Odds Ratio (95% CI)†</th>
<th>P Value</th>
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<td>190</td>
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<td>0.001</td>
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<td>&lt;0.001</td>
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<tr>
<td></td>
<td>0–2</td>
<td>0</td>
<td>19</td>
<td>9.2 (5.3–16.2)</td>
<td>&lt;0.001</td>
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<td>3.3 (1.1–9.8)</td>
<td>0.03</td>
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<td>21</td>
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<td>0.93</td>
<td>0.9 (0.1–8.6)</td>
<td>0.94</td>
</tr>
</tbody>
</table>

*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

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

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

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

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

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 \( \rightarrow RR \)
• They provide the best information about the causation of disease and the most direct measurement of the risk of developing disease
Disease refer to different points in time, cohort studies are longitudinal, like case-control studies. Cohort studies have been called prospective studies, but this terminology is confusing and should be avoided. As mentioned previously, the term "prospective" refers to the timing of data collection and not to the relationship between exposure and effect. Thus there can be both prospective and retrospective cohort studies. Cohort studies provide the best information about the causation of disease and the most direct measurement of the risk of developing disease. Although conceptually simple, cohort studies are major undertakings and may require long periods of follow-up since disease may occur a long time after exposure. For example, the induction period for leukaemia or thyroid cancer caused by radiation (i.e. the time required for the specific cause to produce an outcome) is many years and it is necessary to follow up study participants for a long time. Many exposures investigated are long-term in nature and accurate information about them requires data collection over long periods. However, in the case of tobacco use, many people have relatively stable habits and information about past and current exposure can be collected at the time the cohort is defined. In situations with sudden acute exposures, the cause-effect relationship for acute effects may be obvious, but cohort studies are also used to investigate late or chronic effects.

Box 3.3. Late effects of poisoning: Bhopal

An example of measuring effects over a long time period is the catastrophic poisoning of residents around a pesticide factory in Bhopal, India, in 1984. An intermediate chemical in the production process, methyl isocyanate, leaked from a tank and the fumes drifted into surrounding residential areas, exposing half a million people to the gas. 20,000 people died as a result of this exposure. In addition, 120,000 people still suffer pollution. The acute effects were easily studied with a cross-sectional design. More subtle chronic effects and those developing only after a long latency period are still being studied using cohort study designs.

Figure 3.6. Design of a cohort study

Source: Basic epidemiology 2nd ed, R Bonita et al, WHO 2006
Table 4. Main results of the cohort analysis using two follow-up periods among those born at or after 1 January 1991.

<table>
<thead>
<tr>
<th>Follow-up period</th>
<th>Narcolepsy cases</th>
<th>Follow-up years</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not vaccinated</td>
<td>Vaccinated</td>
<td>Not vaccinated</td>
</tr>
<tr>
<td>First contact:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2009-01-01 to 2010-12-31</td>
<td>7</td>
<td>57</td>
<td>1,069,247</td>
</tr>
<tr>
<td>First contact:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2009-01-01 to 2010-08-16</td>
<td>7</td>
<td>46</td>
<td>986,195</td>
</tr>
</tbody>
</table>

1The 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 $\rightarrow$ OR
• Compares a group of people with the outcome of interest (cases) to a group of people without the outcome (controls)
Case-control studies are longitudinal, in contrast to cross-sectional studies. Case-control studies have been called retrospective studies since the investigator is looking backward from the disease to a possible cause. This can be confusing because the terms retrospective and prospective are also used to describe the timing of data collection in relation to the current date. In this sense a case-control study may be either retrospective, when all the data deal with the past, or prospective, in which data collection continues with the passage of time.

**Figure 3.5. Design of a case-control study**

Direction of inquiry

TIME

Start with:

- **Exposed**
- **Not exposed**

Cases
(people with disease)

Controls
(people without disease)

Population

Selection of cases and controls

A case-control study begins with the selection of cases; these cases should represent all the cases in a specified population group. Cases are selected on the basis of disease, not exposure. Controls are people without the disease. A critical and challenging aspect of population-based case control studies is finding a cost-effective way to identify and enroll control subjects. The most difficult task is to select controls so as to sample the exposure prevalence in the population that generated the cases. Furthermore, the choice of controls and cases must not be influenced by exposure status, which should be determined in the same manner for both. It is not necessary for cases and controls to be all-inclusive; in fact they can be restricted to any specified subgroup, such as elderly people, males or females.

The controls should represent people who would have been designated study cases if they had developed the disease. Ideally, case-control studies use new (incident) cases to avoid the difficulty of separating factors related to causation and survival (or recovery), although studies have often been conducted using prevalence data (for example, case-control studies of congenital malformations). Case control studies can estimate relative risk of disease, but they cannot determine the absolute incidence of disease.

Exposure

An important aspect of case-control studies is the determination of the start and duration of exposure for cases and controls. In the case-control design, the exposure status of the cases is usually determined after the development of the disease.

**Source:** Basic epidemiology, 2nd ed. R Bonita et al. WHO 2006
INTUSSUSCEPTION AMONG INFANTS GIVEN AN ORAL ROTAVIRUS VACCINE


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

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<th>Dose</th>
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<td>0</td>
<td>19</td>
<td>—</td>
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*CI denotes confidence interval.
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


**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

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

Source: Eurosurveillance 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 Hughes1

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

<table>
<thead>
<tr>
<th>Age, y</th>
<th>England-level Analysis</th>
<th>England-level Analysis</th>
<th>PCT-level Analysis</th>
<th>PCT-level Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>IRR (95% CI)</td>
<td>Adjusteda IRR (95% CI)</td>
<td>n</td>
</tr>
<tr>
<td>15</td>
<td>1731/1 212 679</td>
<td>0.83 (.73, .95)</td>
<td>0.84 (.74, .95)</td>
<td>1344/994 464</td>
</tr>
<tr>
<td>16</td>
<td>4792/1 247 308</td>
<td>0.81 (.73, .89)</td>
<td>0.84 (.77, .91)</td>
<td>3703/1 022 137</td>
</tr>
<tr>
<td>17</td>
<td>9233/1 278 085</td>
<td>0.69 (.62, .76)</td>
<td>0.78 (.71, .86)</td>
<td>7157/1 046 426</td>
</tr>
<tr>
<td>18</td>
<td>12 586/1 314 995</td>
<td>0.73 (.65, .83)</td>
<td>0.89 (.79, 1.00)</td>
<td>9781/1 075 034</td>
</tr>
<tr>
<td>19</td>
<td>14 684/1 344 061</td>
<td>0.97 (.86, 1.09)</td>
<td>1.10 (1.00, 1.21)</td>
<td>11 367/1 094 272</td>
</tr>
<tr>
<td>20</td>
<td>13 860/1 358 690</td>
<td>0.90 (.74, 1.10)</td>
<td>0.99 (.86, 1.14)</td>
<td>10 652/1 102 375</td>
</tr>
</tbody>
</table>

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
A double-blind study means that neither the investigators, nor the participants, know how the latter are classified.

Confounding is another major issue in epidemiological studies. In a study of the association between exposure to a cause (or risk factor) and the occurrence of disease, confounding can occur when another exposure exists in the study population and is associated both with the disease and the exposure being studied. A problem arises if this extraneous factor – itself a determinant or risk factor for the health outcome – is unequally distributed between the exposure subgroups. Confounding occurs when the effects of two exposures (risk factors) have not been separated and the analysis concludes that the effect is due to one variable rather than the other. To be a confounding factor, two conditions must be met (Figure 3.10).

Figure 3.10. Confounding: relationship between coffee drinking (exposure), heart disease (outcome), and a third variable (tobacco use)

Two exposures associated with each other

Confounding variable (tobacco use)

Confounded association

Disease (heart disease)

Exposure (coffee drinking)

Confounding arises because non-random distribution of risk factors in the source population also occurs in the study population thus providing misleading estimates of effect (see Box 3.7). In this sense, it might appear to be a bias, but in fact it does not result from systematic error in research design.

Age and social class are often confounders in epidemiological studies. An association between high blood pressure and coronary heart disease may in truth represent concomitant changes in the two variables that occur with increasing age; the potential confounding effect of age has to be considered, and when this is done it is seen that high blood pressure indeed increases the risk of coronary heart disease.

In the example in Figure 3.10, confounding may be the explanation for the relationship demonstrated between coffee drinking and the risk of coronary heart disease, since it is known that coffee consumption is associated with tobacco use: people who drink coffee are more likely to smoke than people who do not drink coffee.
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

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

Small \( p \) values = low degree of compatibility between \( H_0 \) and the observed data:
\[ \rightarrow \text{you reject } H_0 \text{ and the test is significant.} \]

Large \( p \) values = high degree of compatibility between \( H_0 \) and the observed data:
\[ \rightarrow \text{you don’t reject } H_0, \text{ the test is not significant} \]

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 = H₀ non rejected (non significant)
p value ≤ 0.05 = H₀ 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

Point estimate

Confidence interval

RR = 1.45 (0.99 – 2.1)

Lower confidence limit

Upper confidence limit
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

Sources of Post-Marketing Safety reports (and signals)

Years post-marketing

Percent

- Clinical trials
- Spontaneous reports
- Phase IV studies
- Literature

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
PMS experience Rotarix

Sources of PMS reports and signals

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

Sources of PMS reports and signals

Years post-marketing

Percent

Clinical trials
Spontaneous reports
Phase IV studies
Littérature

Spontaneous Reports:
Intussusception
Lack of efficacy
Maladministration

World Vaccine Congress
Lyon, October 8, 2009
PMS experience Rotarix

Sources of PMS reports and signals

Phase IV studies:
Vaccine Effectiveness & impact studies
Intussusception
Serotype replacement

World Vaccine Congress Lyon, October 8, 2009
Case study novel adjuvanted vaccine: Cervarix

- Question for any vaccine:
  - Vaccine effectiveness
  - Impact on disease epidemiology
  - Co-administration studies
- Question for any novel adjuvanted vaccine:
  - Auto-immune disorders
- Question for any HPV vaccine
  - Pregnancy outcomes
  - Impact on HPV serotype distribution, screening practices
- Cervarix specific question:
  - Populations not fully investigated in completed clinical trials:
    - Immunocompromised women

World Vaccine Congress
Lyon, October 8, 2009
Clinical data:

Efficacy/immunogenicity in ‘elder women’

Studies in HIV +

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

World Vaccine Congress Lyon, October 8, 2009
Events of Potential Autoimmune Origin: Meta-Analysis of All HPV Vaccine Trials

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

- At Least One Symptom Overall
- Gastrointestinal
- Musculoskeletal
- Neuroinflammatory
- Skin Disorders
- Thyroid Disease
- Others

* 95% CI = 95% confidence interval for relative risk (Exact Stratified Conditional to total number of cases)
Relative Risk (AS04 vs non-AS04) with 95% CI*

At Least One Symptom Overall
Gastrointestinal
Musculoskeletal
Neuroinflammatory
Skin Disorders
Thyroid Disease
Others

World Vaccine Congress Lyon, October 8, 2009

* 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
PMS experience Cervarix

Sources of PMS reports and signals

Spontaneous Reports:
Anaphylaxis
Pregnancy outcomes
Fatal events
Auto-immune disorders

World Vaccine Congress Lyon, October 8, 2009
PMS experience Cervarix

Sources of PMS reports and signals

Phase IV studies:
- Vaccine Effectiveness & impact study
- PASS - AIDs
- Pregnancy outcomes

World Vaccine Congress Lyon, October 8, 2009
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)

World Vaccine Congress
Lyon, October 8, 2009
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
  - Neuritis
  - Vaccination failure

World Vaccine Congress Lyon, October 8, 2009