P95

TURNING DATA INTO EVIDENCE

PASS studies, Vaccine effectiveness, impact studies and Benefit-Risk assessment (post-authorisation)

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Module content

- Post-authorization observational studies
- PASS study designs for vaccines
- Vaccine Effectiveness study designs
- Benefit-risk Evaluation
- Independent Expert Committees and decision-making

Post-authorisation observational studies

Why post-authorisation studies?

To **complement vaccine trials**

- To assess vaccine performance in real-life (while trials are run under 'ideal conditions', often very selective on participant inclusion)
- To assess vaccine performance in specific subpopulations typically excluded from trials
- To assess protection against rare endpoints (for which sample size of the clinical trials is typically too small)
- To assess long-term protection (for which the duration of the clinical trials is too short)

To study **vaccine programmatic choices**

- To evaluate vaccine schedules

To study impact of vaccination at **population level,** particularly important when assessing the vaccine benefits

- Indirect effects of vaccination (~herd immunity)

Post-authorization studies

Pre-licensing	Post-authorization, observational studies
Safety Efficacy	Safety Effectiveness, impact
Primary data collection: controlled data collection for the purpose of the study	Primary data collection or secondary use of existing data (medical records, claims)
Randomized, blind, controlled clinical trials (Phase 3)	Mostly observational studies, different study designs (cohort, case-control, case only)
Randomization to vaccine and control arm	Exposure allocation by routine medical practice: prone to bias and confounding
Idealized conditions: limited generalizability	Real-life use
Resource intensive, expensive: typically limiting sample size	Depending on design, less resource intensive, expense: larger sample sizes possible
Simple interpretation of causality	Careful interpretation needed

Data sources

Primary data collection - data source was specifically created to answer a research question

- Control over the information to be collected, but typically expensive and hence limited in sample size
- Example: prospective cohort study

Secondary use of existing data- data that was originally collected for other purposes than the research question

- No control over the data to be collected, more errors in the data, but typically lots of information on many subjects ("quantity over quality"), provides the necessary sample size to study rare events

- Examples: medical records at primary care, hospital data (also called Electronic Health Record data, EHR), claims data

Common study designs

Cohort design:

- Vaccinated subjects are followed over time starting from vaccination and compared to unvaccinated subjects that have been followed over time as well
- not suited to study rare events, takes time in case of primary data collection

Case-control design:

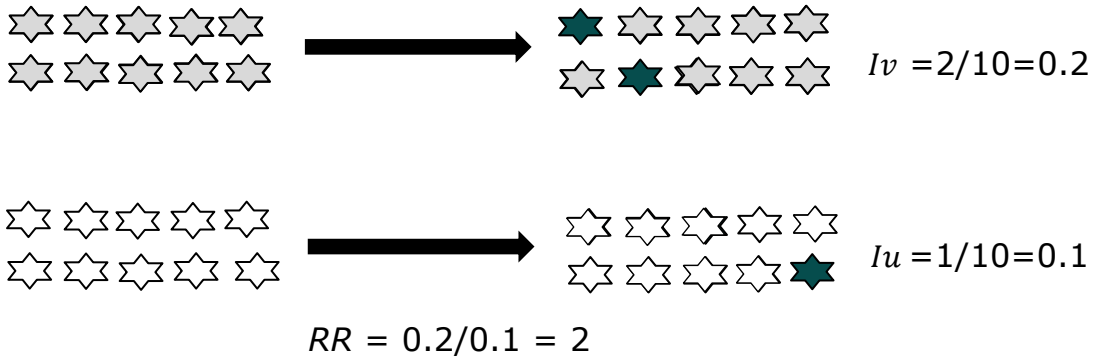
- Subjects with the outcome of interest ('cases') are identified and their vaccine exposure is retrospectively assessed. The same is done for subjects without the outcome of interest ('controls'). Comparing the exposure in 'cases' to that in 'controls' allows to measure the strength of the vaccine-outcome association
- Suited to study rare events

Other designs:

- Self-controlled case series, self-controlled risk interval
- Case-coverage design
- Test-negative case-control design
- …

Cohort design (1/2)

Two-arm cohort design



Cohort design (2/2)

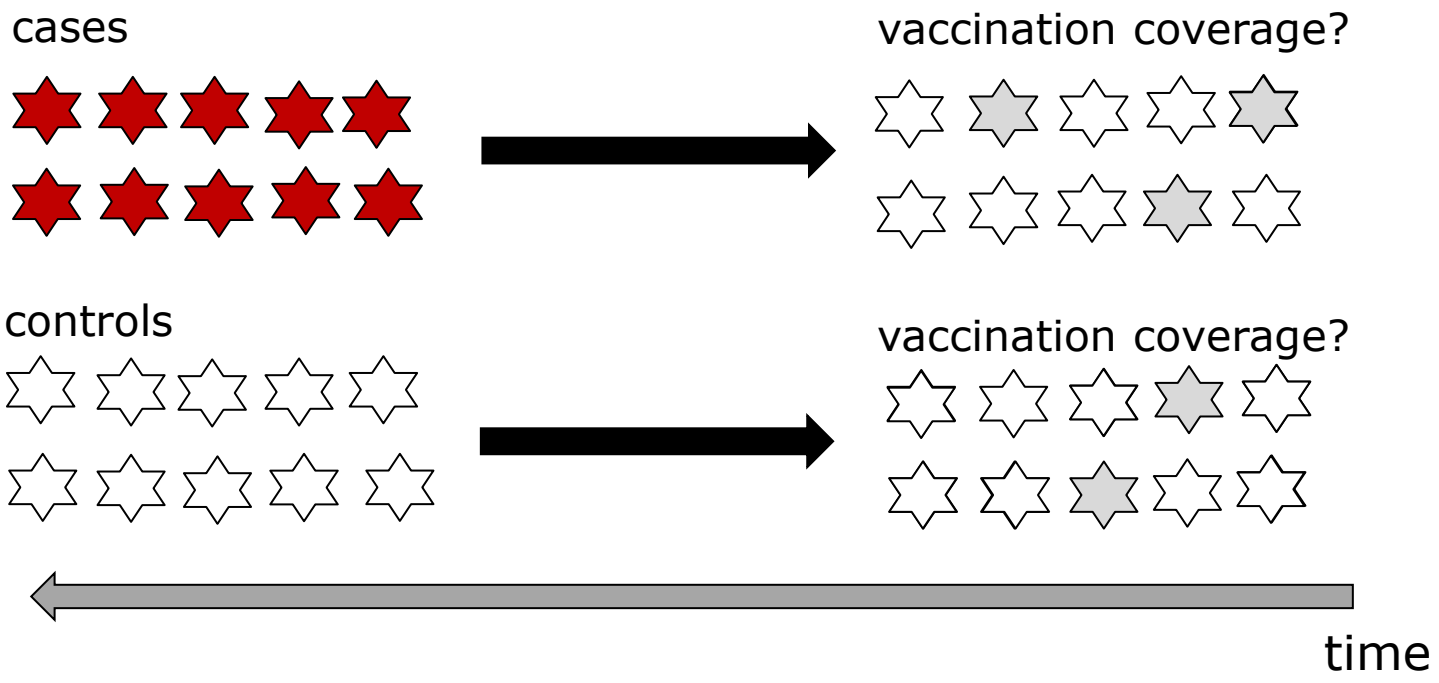
Advantages:

- Easy to explain (follows natural 'time' direction)
- Easy to collect all information on exposure (for primary data collection)
- Can be used to study multiple outcomes
- Can be used to obtain 'absolute' risk estimates
- Can include nested studies

Disadvantages:

- Potential for missing study outcomes
- Potential for bias due to differences in healthcare seeking behavior
- Might be time and resource consuming (for primary data collection)
- Insufficient to study rare outcomes (for primary data collection)
- Long time to results (for primary data collection)

Case-control design (1/2)



Odds ratio (OR) = odds of vaccination in cases/odds of vaccination in controls
with odds = probability of vaccinated/probability of unvaccinated

OR = (0.3/0.7)/(0.2/0.8) = 1.7

Case-control design (2/2)

Advantages:

- Can be used to study rare outcomes
- Fast to results (also for primary data collection)
- Less resource intensive
- Less sample size required

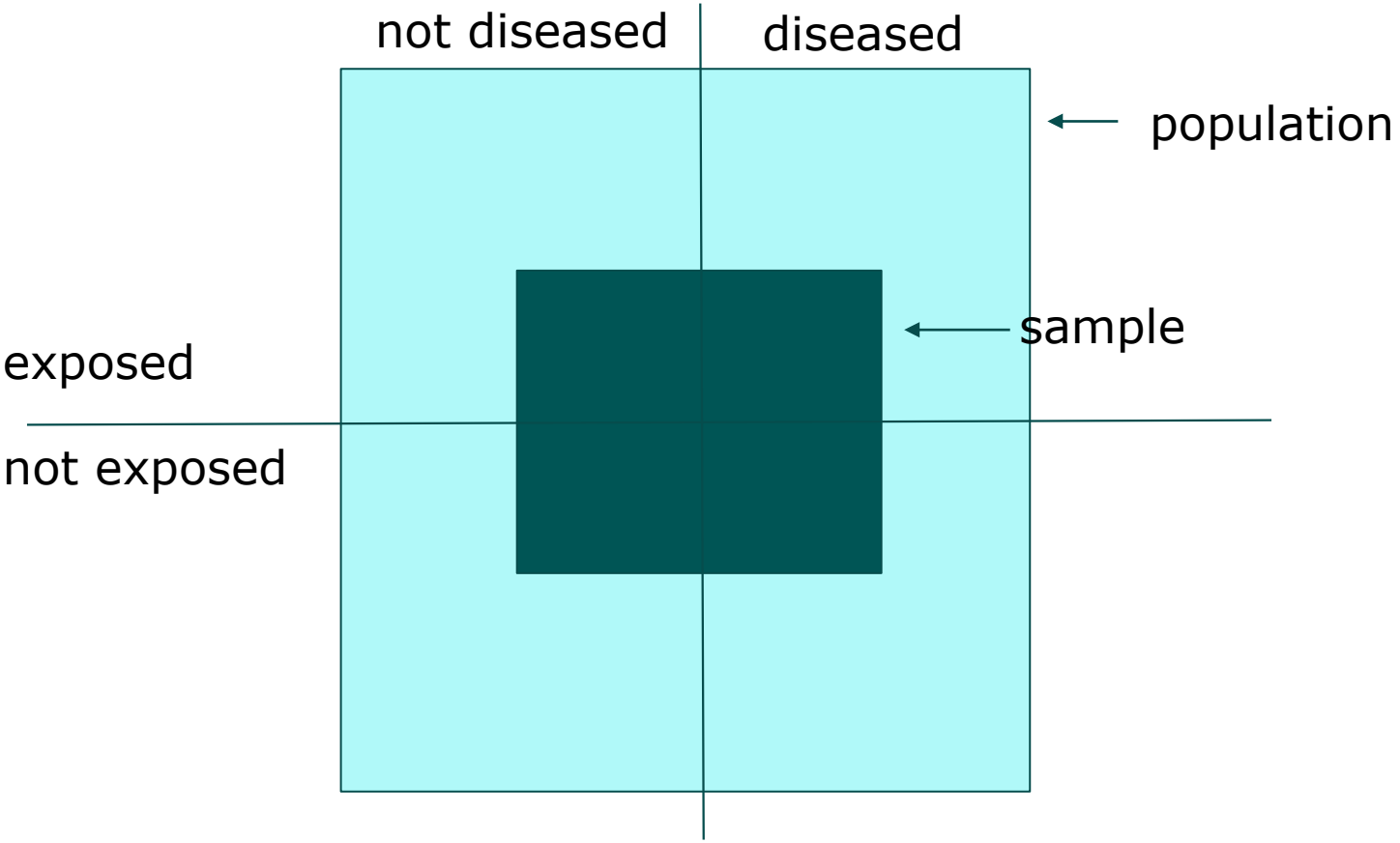
Disadvantages:

- Difficult to explain (does not follow natural 'time' direction)
- Potential for errors in vaccination exposure ascertainment
- Cannot be used to obtain absolute risk estimates
- Selection of controls not always easy

Sources of bias and confounding

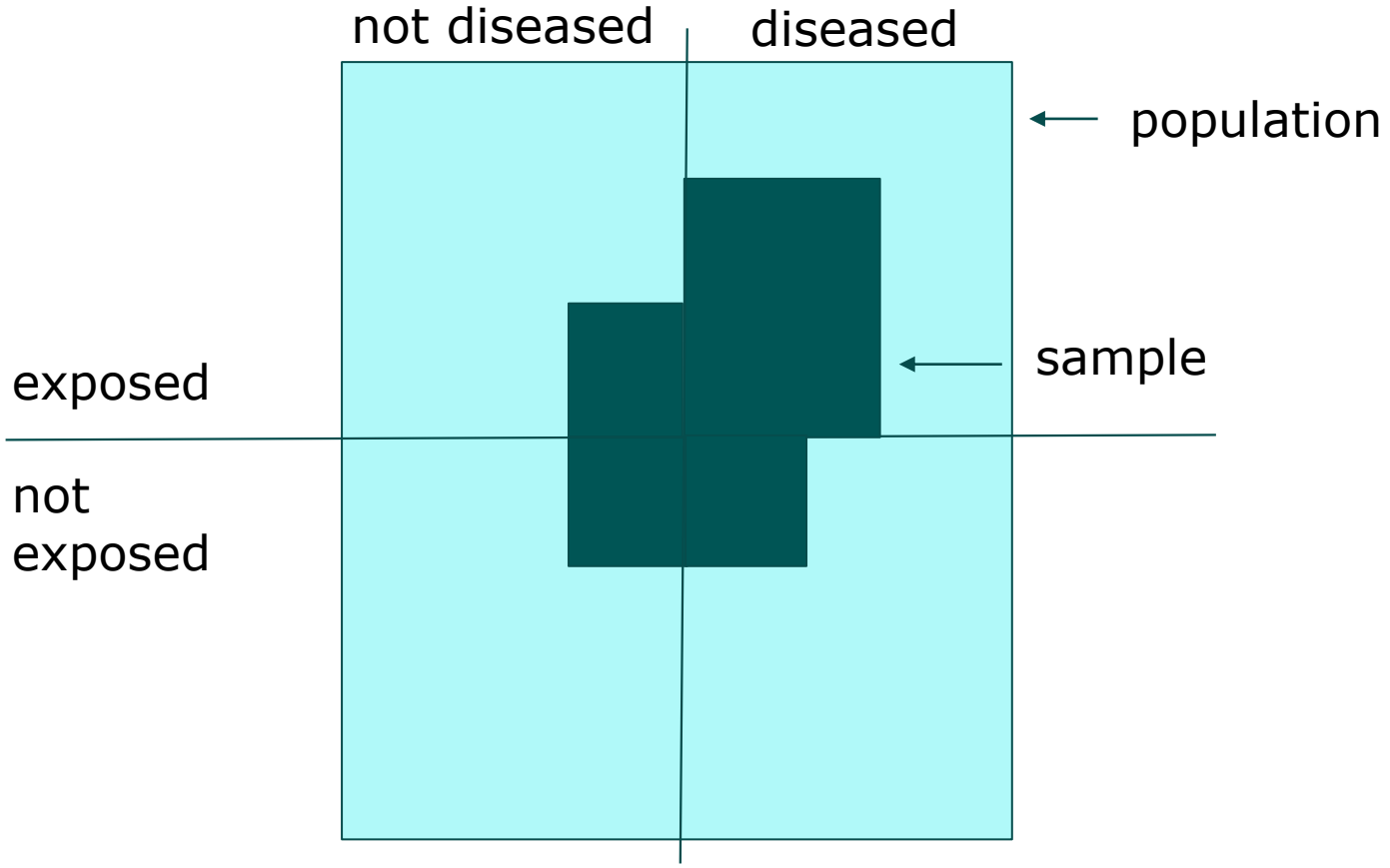
- **Selection bias**: arises from systematic differences in selecting and following study groups
- **Disease misclassification**: diseased subjects wrongly classified as non-diseased and vice versa
- **Exposure misclassification**: vaccinated subjects wrongly classified as unvaccinated and vice versa
- **Confounding**: variable that is independently related to both the vaccination status and the risk of disease

Selection bias (1/2)



Random sample: every subject within the population has the same probability of getting sampled

Selection bias (2/2)



Differences in **sampling probabilities** – some subjects are more likely to be selected than others

Misclassification

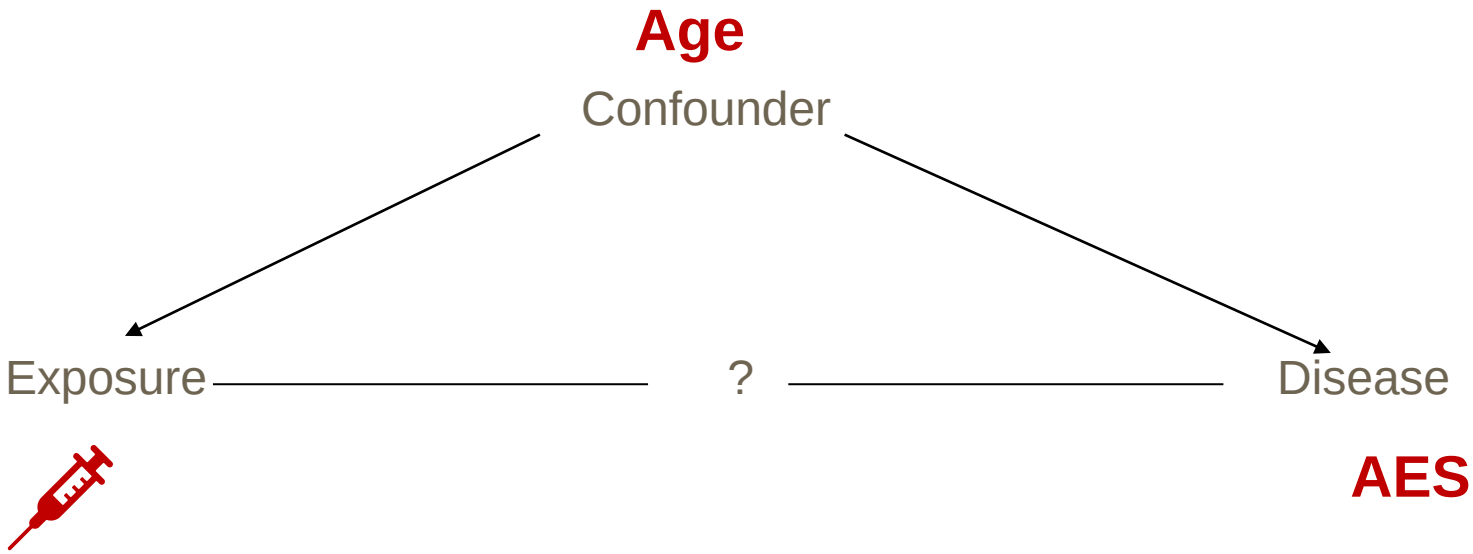
Misclassification of outcome, exposure and covariates, also called information bias

Differential misclassification means that the amount of outcome (exposure) misclassification depends on the exposure (outcome) status

If outcome misclassification is differential, the epidemiological estimate can be **biased upward or downward**

Validation studies (comparing the measurement of interest to a 'gold standard') can be performed to quantify the amount of misclassification

Confounding



The confounder is associated both with the exposure/vaccination status and the disease, but it is not an intermediate step in the casual pathway between exposure and the disease.

Certain confounders vary over time, others are time-invariant

Post-authorization safety studies (PASS) for vaccines

PASS for vaccines

- Post-authorization safety studies (PASS) for signal validation/confirmation
- PASS can either be clinical trials or non-interventional studies/observational studies
- Observational studies: exposure is not randomized (unlike in clinical trials) and the assessment of the exposure-outcome association is more complicated
- Bias and confounding are possible

Common vaccine safety study designs

Cohort design:

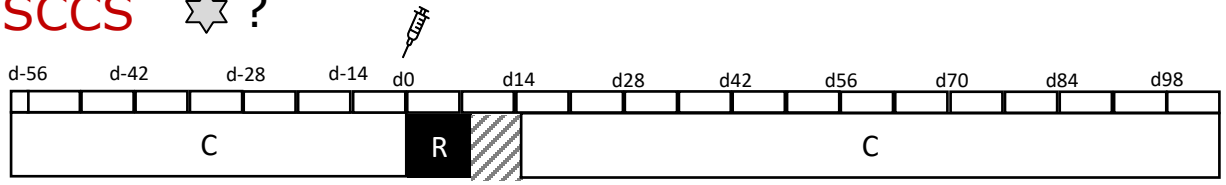
Case-control design:

Self-controlled designs:

- Only includes cases
- Subjects act as their own comparison, comparing the occurrence of events within the 'risk window' after vaccination to a control period
- Not sensitive to time-invariant confounding
- Control for time-variant confounding possible (e.g age, calendar time)
- Different types of self-controlled designs
  - Self-controlled case series (SCCS)
  - Self-controlled risk interval (SCRI)
  - Case-cross over (CCO)

Self-controlled designs (1/2)

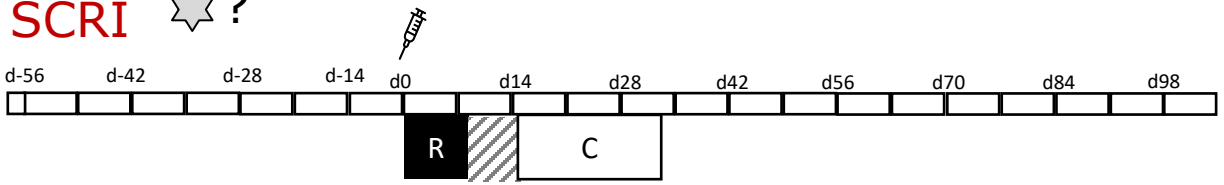
SCCS ✸ ?



Time at vaccination determines risk window

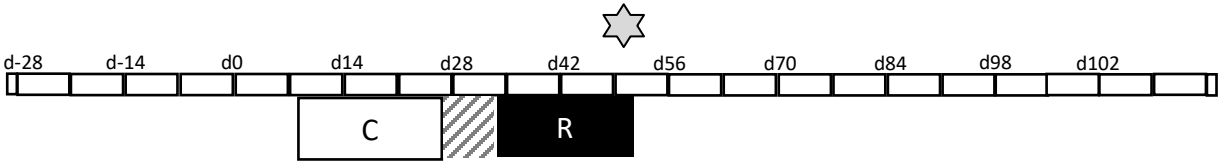
When did event happen wrt vaccination date?

SCRI ✸ ?



Simplified version of SCCS

CCO 💉 ?



Time at event determines risk window

When did vaccination happen wrt event date?

Self-controlled designs (2/2)

Advantages:

- Adjusts for time-invariant confounders
- Can be used to study rare outcomes
- More statistically efficient than cohort/case-control study
- **Can be used when vaccines are universally used!** (>90% coverage, lack of appropriate control group)
- **Not sensitive to exposure misclassification**

Disadvantages:

- Requires knowledge of post-vaccination risk window
- Only works for AESI with acute onset

Selection study design

Study design selected in function of:

- **AESI incidence**: common disease or rare disease?
- Presence of a **risk window:** e.g. vaccine-induced anaphylaxis is expected to occur within a few days after vaccination
- Presence of **comparator group**: is there an unvaccinated group comparable to the vaccinated group apart?
- **Concern of exposure misclassification**
- **Confounders**: concerns about confounding? E.g. patients from high risk groups are more likely to be prioritized for vaccination
- **Speed to results**: E.g., in case of a health crisis, fast evidence is required
- **Data availability, financial resources**

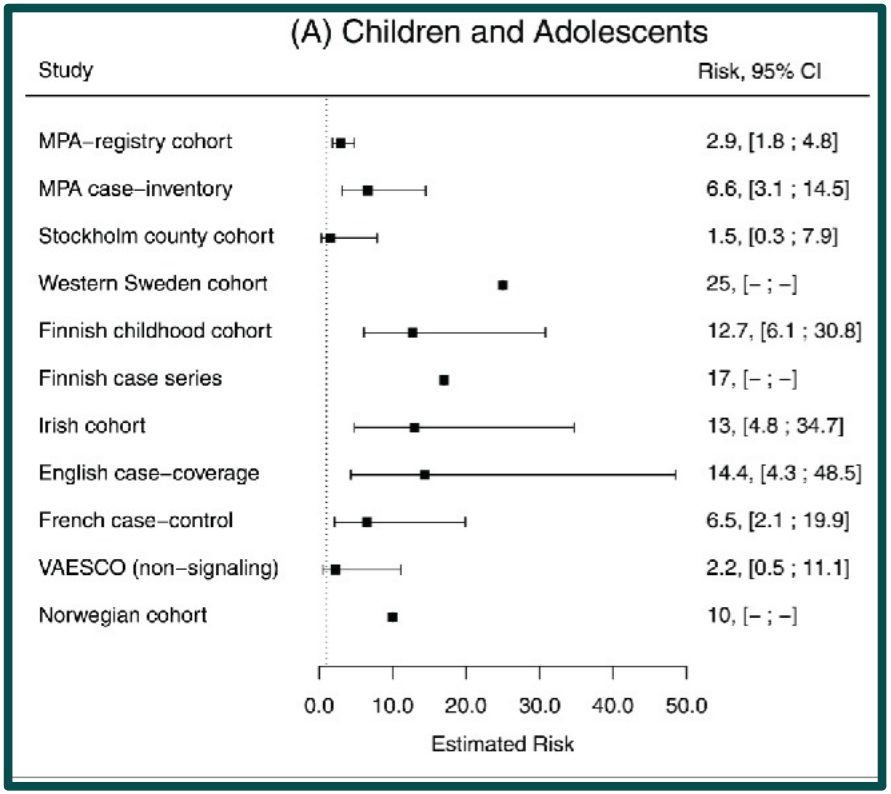
Added value of using different <u>suitable</u> designs to study same vaccine-outcome pair

Pandemrix™ and narcolepsy: A critical appraisal of the observational studies

Thomas Verstraeten[1,*], Catherine Cohet[2], Gaël Dos Santos[3], Germano LC Ferreira[1,2], Kaatje Bollaerts[1], Vincent Bauchau[2], and Vivek Shinde[4]

[1]P95 Pharmacovigilance and Epidemiology Services; Leuven, Belgium; [2]GSK Vaccines; Wavre, Belgium; [3]Business & Decision Life Sciences (contractor for GSK Vaccines); Brussels, Belgium; [4]GSK Vaccines; King of Prussia, PA USA

A link between *Pandemrix™* (AS03-adjuvanted H1N1 pandemic influenza vaccine, GSK Vaccines, Belgium) and narcolepsy was first suspected in 2010 in Sweden and Finland following a number of reports in children and adolescents. Initial scepticism about the



PASS for vaccines

- PASS can either be clinical trials or non-interventional studies/observational studies
- Observational studies: exposure is not randomized (unlike in clinical trials) and the assessment of the exposure-outcome association is more complicated
- Bias and confounding are possible

Vaccine effectiveness and impact studies

Vaccine effectiveness/impact

- Different outcomes: vaccines prevent against infection, disease, severe disease, death, transmission
- Different vaccine effects: vaccines/vaccination programmes provide protection to vaccinated subjects , unvaccinated subjects, entire populations
- Different observational study designs: choice of design based on outcome and vaccine effect of interest

Study outcomes (1/3)

Protection against **disease**

- Different levels of disease **severity** (mild, moderate, severe disease, hospitalization, mortality)
- Typically, vaccines have a higher effectiveness against more severe disease

Protection against **infection**

- Especially important for diseases with pre-symptomatic and asymptomatic transmission
- Contributes to herd immunity

Study outcomes (2/3)

Protection against **infectiousness**

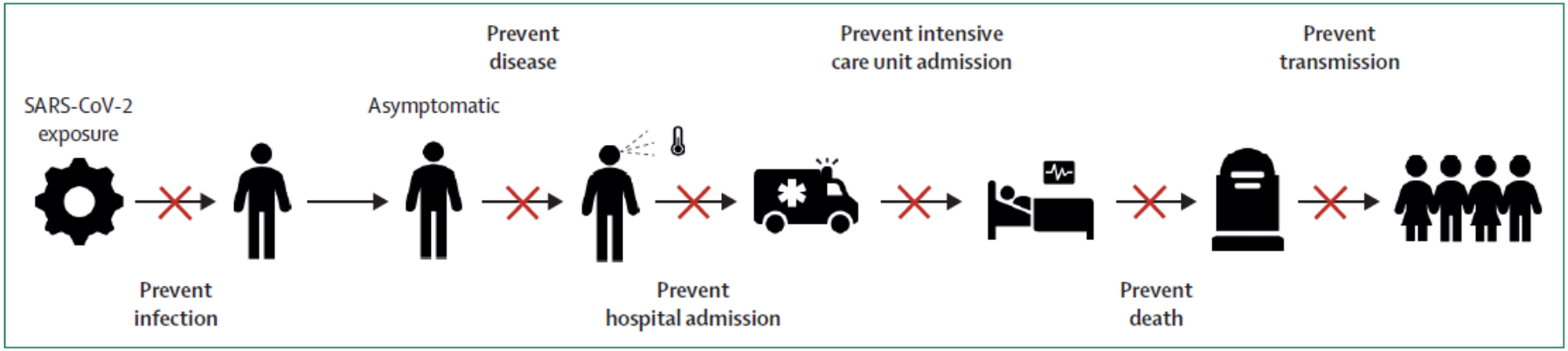
- ~ Reduced duration of infectiousness, reduced pathogen shedding
- Contributes to herd immunity

Protection against **transmission**

- Combines protection against infection and infectiousness
- Effect at population-level

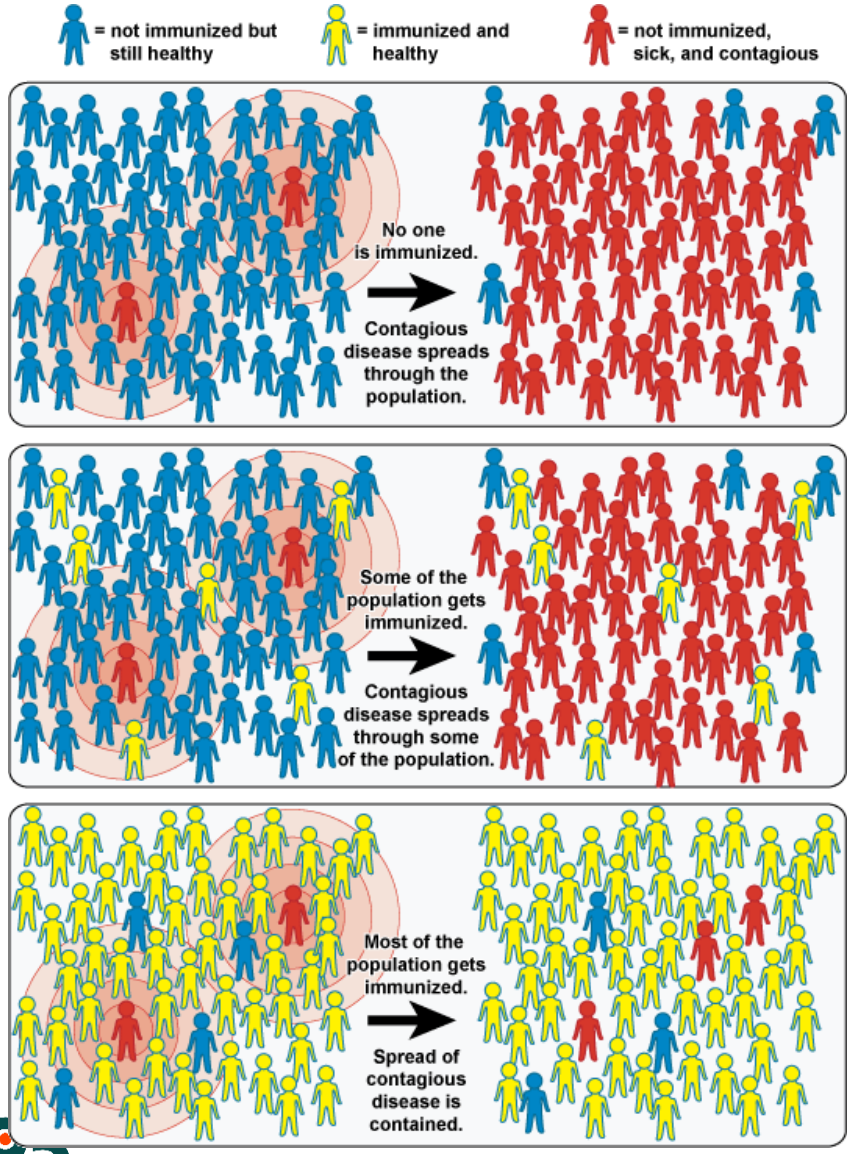
Study outcomes (3/3)

Potential outcomes of COVID-19 vaccine benefit studies



From: *Hodgson S. H. et al, Lancet ID 2021,* What defines an efficacious COVID-19 vaccine? A review of the challenges assessing the clinical efficacy of vaccines against SARS-CoV-2

Measurements of vaccine benefit (1/4)



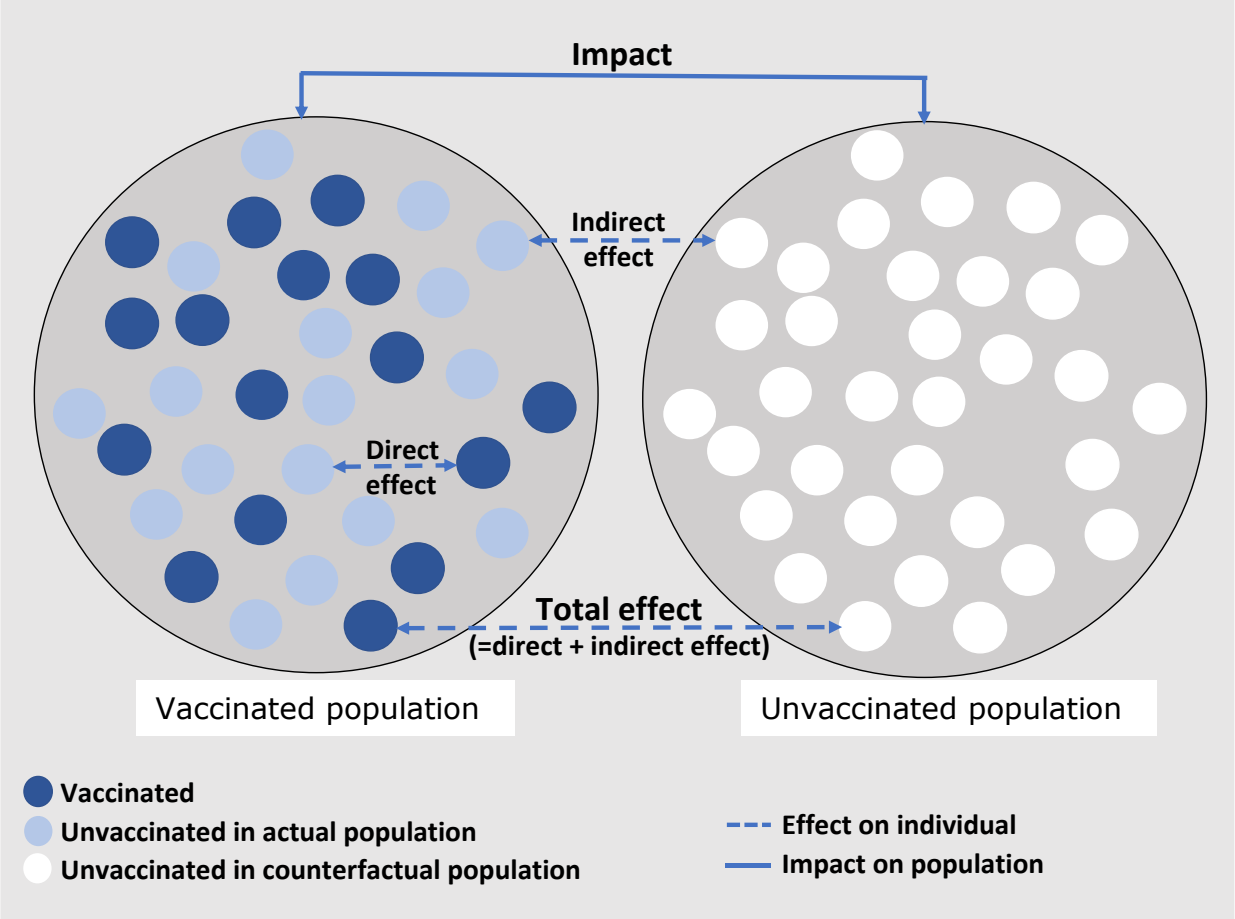
Not only vaccinated subjects are protected

When a critical portion of a community is immunized against a contagious disease, most members of the community are protected against that disease. This is known as "community (or 'herd') immunity." The principle of community immunity applies to control of a variety of contagious diseases, including influenza, measles, mumps, rotavirus, and pneumococcal disease. The top box depicts a community in which no one is immunized and an outbreak occurs. In the middle box, some of the population is immunized but not enough to confer community immunity. In the bottom box, a critical portion of the population is immunized, protecting most community members. Credit: NIAID

Measurements of vaccine benefit (2/4)

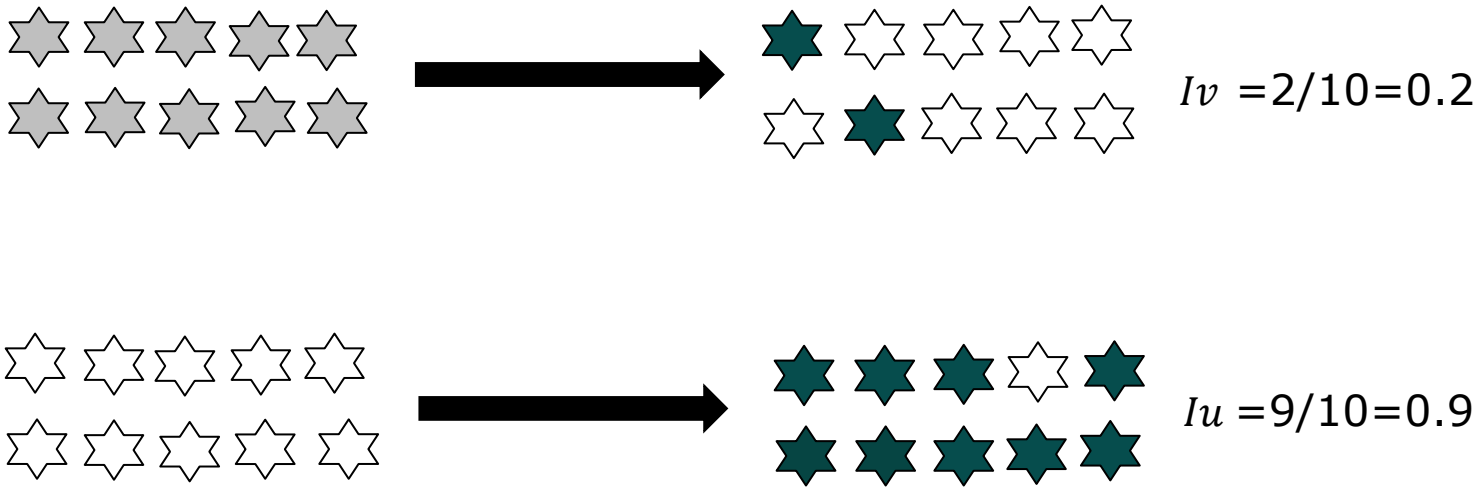
- **Efficacy**: direct protection to a vaccinated individual as estimated from a clinical trial
- **Effectiveness** (direct effect): direct protection to a vaccinated individual as estimated under real-life conditions
- **Impact**: population level effect of a vaccination programme, expressed as the proportionate reduction in disease burden comparing the (partially) vaccinated population to the unvaccinated population.
- **Indirect effect** (herd protection, herd immunity): indirect effect of vaccination due to reduced disease transmission

Measurements of vaccine benefit (3/4)



Measurements of vaccine benefit (4/4)

Vaccine effectiveness: worked-out example



VE=[1- 0.2/0.9] x 100% = 78%

Common vaccine effectiveness/impact study designs

Cohort design

- Mostly to study VE against infection and mild disease

Case-control design:

- Mostly to study VE against medically attended disease (primary care, hospitalization)
- Different possibilities for controls: test-negatives, other hospital controls

Household study:

- To study VE against infectiousness and transmission
- Cohort studies following-up households and documenting who infects who within the household

Ecological study design:

- To study population-level impact of vaccination programmes
- 'before-and-after' comparisons (simply comparing frequency of disease before and after vaccine introduction)
- Interrupted time-series (to account for disease trends pre-vaccination)

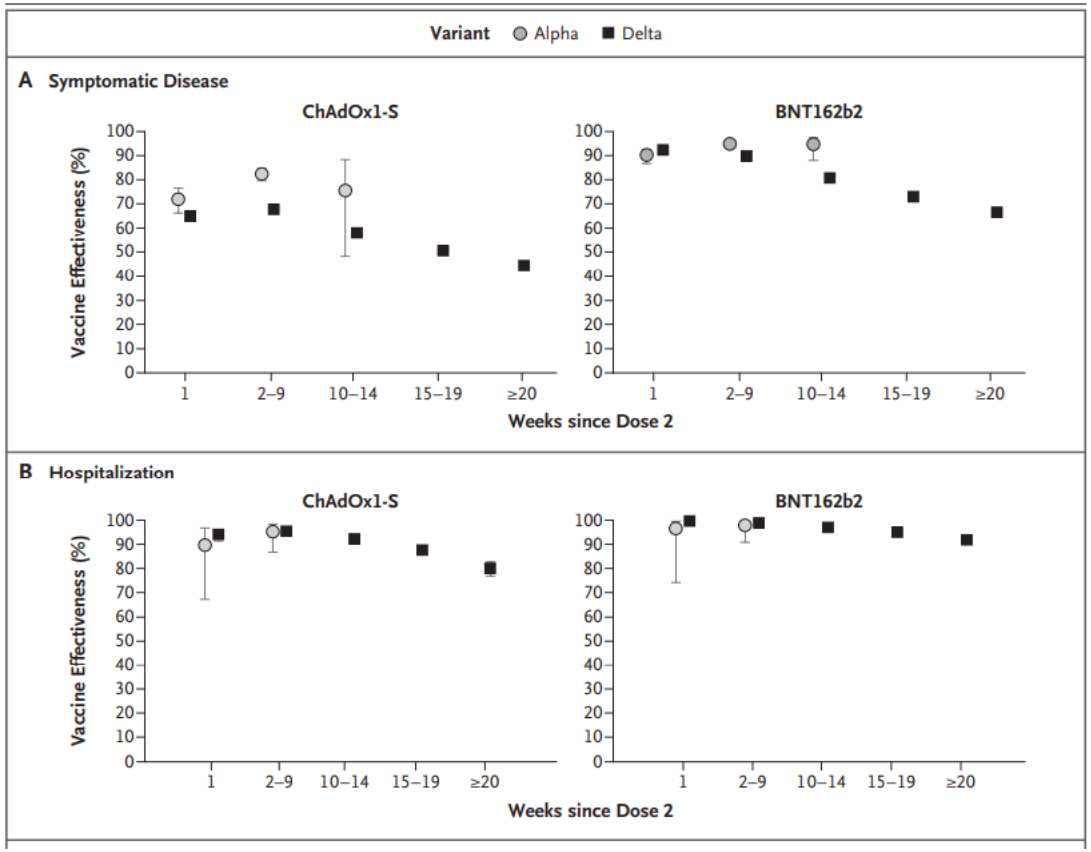
Test-negative control study: duration of protection by COVID-19 vaccines

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Duration of Protection against Mild and Severe Disease by Covid-19 Vaccines

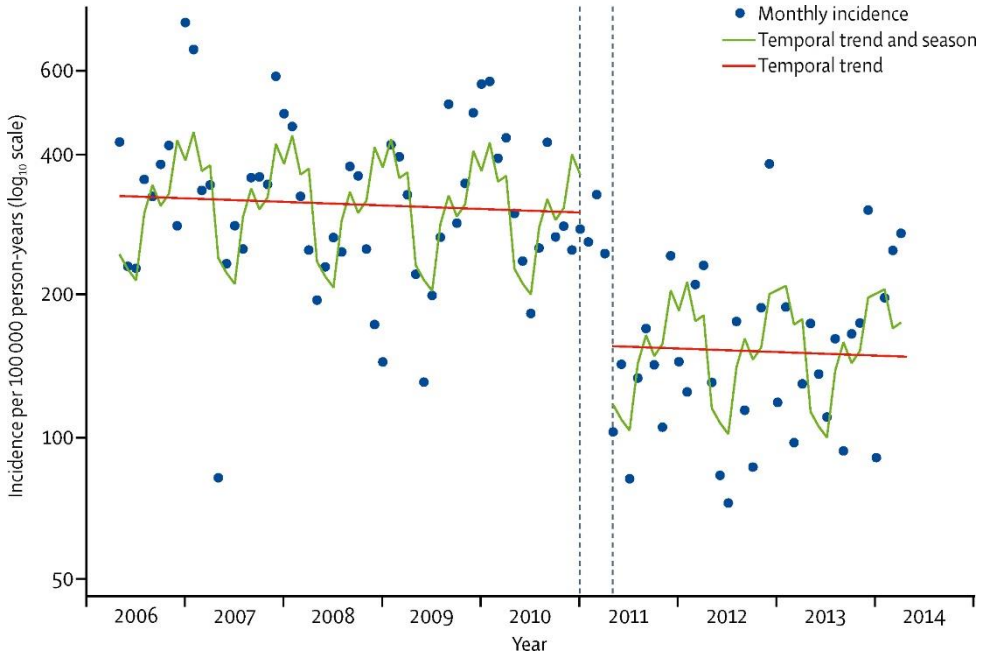
Nick Andrews, Ph.D., Elise Tessier, M.Sc., Julia Stowe, Ph.D.,



- Higher effectiveness against severe disease compared to mild disease
- Waning effectiveness by time since vaccination

Ecological study

- Focuses on the comparison of groups, rather than individuals
- Useful for short-term immunization campaigns with rapid and large vaccine uptake
- E.g. *Effect of 10-valent pneumococcal conjugate vaccine on the incidence of radiologically-confirmed pneumonia in Kenyan children (Silaba Lancet Global Health, 2019)*



Benefit-risk evaluation

Hepatitis B vaccination in France and Italy

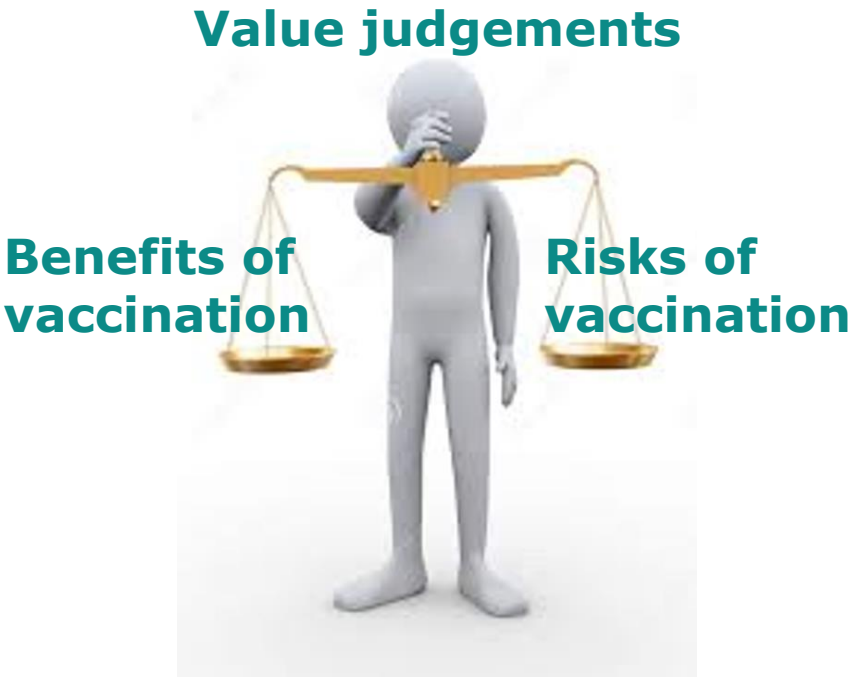
Since the early 1990s, several cases of **multiple sclerosis (MS)** were reported in **France** among people who had received **hepatitis B vaccine.** Because of this and the growing public concern, the Health Ministry of France decided **to suspend the school-based hepatitis B vaccination campaign**. The decision was based on spontaneous reports of MS cases in hepatitis B vaccinees, a pilot case-control study and two case-control studies. The studies all showed odds ratios suggesting an increased risk though the individual odds ratios were not statistically significant (pilot study: 1.7, 95% CI: 0.5-6.3; French case-control study: 1.4. 95% CI: 0.4-4.5, and UK case-control study: 1.4, 95% CI: 0.8-2.4). The overall evidence was assessed as indicating a true causal relationship between hepatitis B vaccination and MS. The decision was taken to suspend the hepatitis B vaccination campaign despite an endorsement of the efficacy of the vaccine by the French Government. This decision was strongly criticized by the WHO for the potentially negative consequences on the acceptance and vaccination uptake of hepatitis B and other vaccines (Jefferson and Traversa 2002).

At the same time, modifications to the hepatitis B vaccination policy in **Italy** were under discussion. To support decision making, a simulation study was carried out for Italy assuming that there was a true causal association between hepatitis B vaccination and MS. The **study showed that vaccinating 100,000 adolescents would incur 0.7 cases of MS but also prevent 1,099 cases of hepatitis B**, including 58 cases with chronic progression. The Italian **government decided not to change the vaccination strategy** adopted in Italy (Jefferson and Traversa 2002).

Benefit-risk evaluation

Benefit-risk (BR) evaluation is about balancing the favourable effects (benefits) of vaccines/vaccination programmes against its unfavourable effects (risks) in a structured way

BR involves accurate measurement of the benefits and risks and the value judgements about the relative importance of these



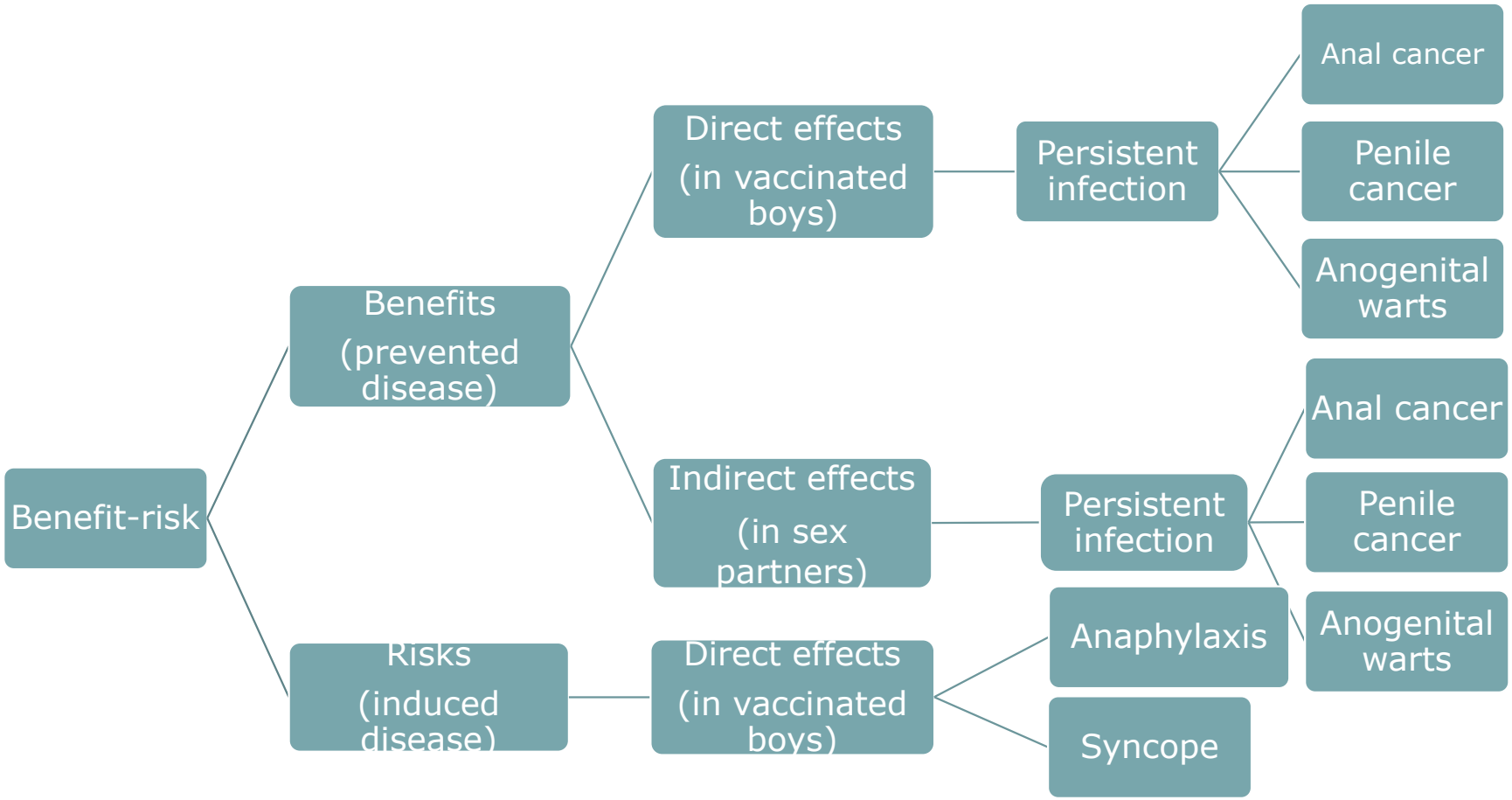
Benefit-risk assessment frameworks

- All BR assessments should start with clearly framing the BR question
- To structure the assessment and make sure all elements important to the assessment are considered, BR assesment frameworks can be used
- Benefit Risk Action Team (BRAT) and PrOACT-URL are frequently used in regulatory science
- Both frameworks are similar

PrOACT-URL framework: 8 steps

1. **Problem**: Establish the decision context (disease epidemiology, unmet medical need, vaccine product, vaccination schedule, target population)
2. **Objectives**: Describe the objectives (new vaccine introduction, changes to the vaccination schedule) and identify the relevant benefit and risk criteria. Relevant benefit and risk criteria often summarized in **outcome tree**.
3. **Alternatives**: Identify relevant alternatives (no vaccination, alternative vaccine, alternative schedule) to which the intervention of interest will be compared.
4. **Consequences**: Describe how the intervention of interest and its alternative(s) perform on the different benefit and risk criteria
5. **Trade offs**: Assess the balance between benefits and risks, often based on qualitative medical judgement. Sometimes a quantitative approach is taken by eliciting preferences from relevant groups (doctors, patients, parents) using standardized methodology.
6. **Uncertainty**: Describe the uncertainty of the performance of the intervention of interest and its alternative(s)
7. **Risk tolerance**: Assess the tolerance to risks, generally lower for vaccines given to healthy people/young children.
8. **Linked decisions**: Consider the consistency of this decision with similar past decisions.

Outcome tree



HPV vaccination in boys (showing benefits in boys only)

Benefit-risk ratio of rotavirus vaccination in Latin America

Effect of rotavirus vaccination programme as compared with no vaccination programme on deaths and hospitalizations associated with diarrhoea and intussusception in Mexico

	Without vaccination programme	With vaccination programme	Number of events averted or caused	Benefit-Risk Ratio
Deaths				
Rotavirus diarrhoea	923	260	663 averted	331.5
Intussusception	61	63	2 caused	
Hospitalizations				
Rotavirus diarrhoea	16,086	4,535	11,551 averted	281.7
intussusception	1,215	1,256	41 caused	

Patel, M. M., et al. 2011. 'Intussusception risk and health benefits of rotavirus vaccination in Mexico and Brazil', *N Engl J Med*, 364: 2283-92.

BR ratio comparing events of the same type: 'deaths' to 'deaths' and 'hospitalizations' to 'hospitalizations'

Benefit-risk difference of rotavirus vaccination in Japan

Benefit-risk of rotavirus vaccination in a birth cohort of 1 million Japanese children followed for 5 years post-vaccination

	Benefits Prevented RVGE	**Risks** Excess IS	**BR difference** Prevented RVGE minus excess IS
Hospitalisations	17,925 (11,715–23,276)	50 (7.2–237)	17,855 (11,643–23,213)
Deaths	6.3 (4.1–8.2)	0.017 (0.0020–0.097)	6.3 (4.1–8.2)

Ledent, E. et all. 2016. 'Post-Marketing Benefit-Risk Assessment of Rotavirus Vaccination in Japan: A Simulation and Modelling Analysis', *Drug Saf*, 39: 219-30.

BR difference comparing events of the same type: 'deaths' to 'deaths' and 'hospitalizations' to 'hospitalizations'

Benefit-risk methodology

- BR ratios and BR differences are both used
- Assessing BR involving a single benefit and single risk or comparing events of the same type are relatively straightforward
- BR assessment is more complex when several benefit and risk outcomes of varying severity are to be considered
- In this case, population health metrices or preference elicitation techniques can be used
  - Health metrices: disability-adjusted life years (DALYs) or quality-adjusted life years (QALYs)
  - Preference elicitation: e.g. time trade off, MCDA swing weighting, discrete choice experiments

Benefits and risks of HPV vaccination based on QALYs, Japan

Benefit-risk of the HPV vaccine in terms of QALY change

Benefits	**QALY gain/100,000 persons**
Cervical cancer	98.17
Cervical cancer-related death	605.55
CIN 3	14.45
Genital warts	30.83
Total benefit	749.00
Risks	**QALY loss/100,000 persons**
Acute reactions	0.07
Chronic reactions without assistance needs	5.83
Chronic reactions with assistance needs	5.82
Total risk	11.71
Risk-benefit ratio in QALY change	**0.0156**

Kitano, T. 2020. 'Stopping the HPV vaccine crisis in Japan: Quantifying the benefits and risks of HPV vaccination in quality-adjusted life-years for appropriate decision-making', *J Infect Chemother*, 26: 225-30.

BR ratio in QALY change comparing several benefit and risk outcomes of varying severity

Benefits and risks of HPV vaccination based on QALYs, Japan

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BR ratio in QALY change comparing several benefit and risk outcomes of varying severity

EXPERT REVIEWS

Quantitative benefit–risk assessment by MCDA of the quadrivalent HPV vaccine for preventing anal cancer in males

Expert Rev. Vaccines Early online, 1–10 (2015)

Lydie Marcelon[1], Thomas Verstraeten[1,2]*, Geraldine Dominiak-Felden[1] and François Simondon[1]

[1]*Epidemiology Department, Sanofi Pasteur MSD, Lyon Cedex 07, France*
[2]*Epidemiology and Pharmacovigilance Consulting and Services, P95, Leuven, Belgium*
**Author for correspondence: Epidemiology and Pharmacovigilance Consulting and Services, P95, Leuven*

Objectives: To quantify the benefit–risk (BR) balance of the quadrivalent human papillomavirus (qHPV) vaccine for use in males, including anal cancer prevention, by using the multi-criteria decision analysis (MCDA).
Methods: Value tree and an effect table were compiled using relevant qHPV vaccine efficacy/safety data. An expert panel validated the final model inputs.
Results: On a scale of 0–100, the MCDA qHPV vaccine score (66) was superior to the no vaccination score (46), indicating a more favorable BR balance for the qHPV vaccine. Significant changes in weight of individual outcomes were needed to change BR balance in sensitivity analyses. The qHPV vaccine maintained a better BR profile in all alternative models.
Conclusions: MCDA can be used to transparently evaluate BR balance of vaccines. The qHPV vaccine had a favorable BR balance in males. Including anal cancer as a new indication further improves the BR profile of the qHPV vaccine.

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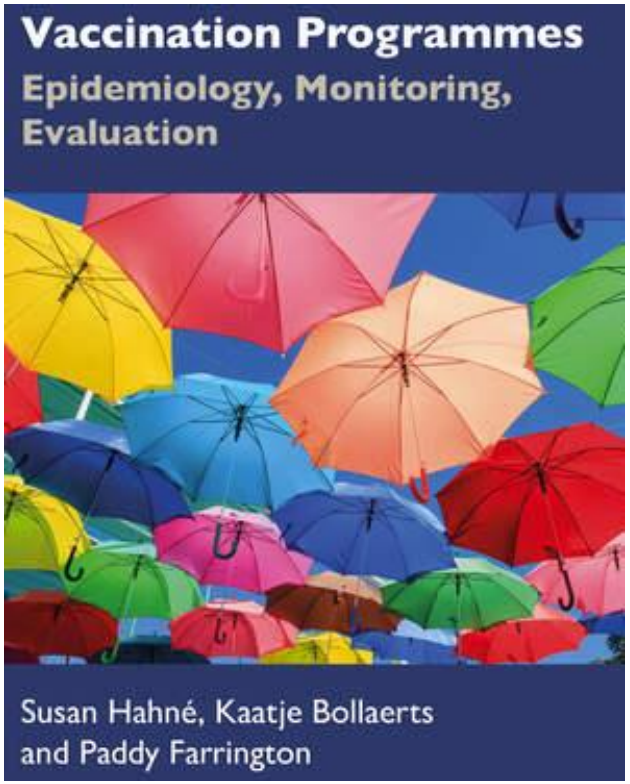
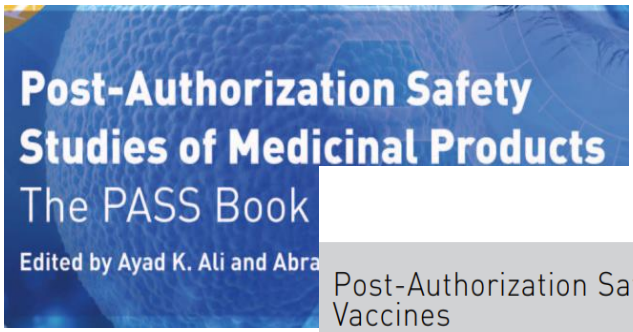
Some further reading





CHAPTER 7.3

Post-Authorization Safety Studies for Vaccines

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- Special Methodological Consideration Issues in Pharmacoepidemiology Studies of Vaccine Safety – Robert.T.Chen – *Pharmacoepidemiology*, Third Edition, 2000
- Control without separate controls: evaluation of vaccine safety using case-only methods – Farrington, CP *Vaccine* 2004: 22; 2064-2070
- Andrews NJ. Statistical assessment of the association between vaccination and rare adverse events post-licensure *Vaccine*. 2001 Oct 15;20 Suppl 1:S49-53
- Comparison of epidemiologic methods for active surveillance of vaccine safety. McClure DL, et al *Vaccine.* 2008 Jun 19;26(26):3341-5

Thank you!

Muchas gracias !

Questions & Answers session (in Spanish)