Lessons from pitfalls experienced in the registration process

Luc Hessel, MD

Consultant in Vaccinology

Chair , Clinical Development Team, TBVI (www.tbvi.eu)

*General Secretary, the **I**nitiative against **D**iarrheal and **E**nteric **D**iseases (www.idea-initiative.info)*

15th Advanced Vaccinology Course, Les Pensières, 14 May 2014

Main pitfalls experienced in vaccine registrations

1. **Addressing methodological approaches in clinical development (pre-licensure)**
   - Using immunological correlates of protection as primary endpoints
   - Assessing equivalence in combined / multivalent / concomitantly administered vaccines
   - Choosing relevant efficacy endpoints
   - Understanding the numbers
   - Safety as a primary endpoint
2. **Anticipating post-licensure activities**
   - Designing a risk management plan
   - Other post-licensure commitments

1.1. Using immunological correlates of clinical protection as primary endpoints

For vaccines [antigens] for which the protective antibody level is established, immunogenicity studies may be more suitable in establishing efficacy *(CPMP EWP/463/97)*

- **Based on immunological correlates of protection (biomarkers)**
  - **Ideally absolute correlates (D, T, HBV, Hib, Polio …)**
  - **Expressed as seroprotection (seroconversion) rates**
- **Relevant for assessing the efficacy of**
  - ***Improved existing vaccines*** , e.g. conjugates, adjuvanted
  - ***Combined vaccines*** **made of vaccine components similar to licensed vaccines** proven to be efficacious in previous efficacy trials
  - ***When large-scale field efficacy studies are not feasible*** (low incidence, outbreak situations)
  - ***Bridging studies***
  - ***Lot consistency studies ...***

1.1. Using immunological correlates of clinical protection as primary endpoints: main issues

- Choice of the protective level (post-primary, post-boo
- Seroprotective levels *vs.* GMTs
- Immunological testing
  - assay sensitivity: RIA vs EIA
  - neutralisation or bactericid
  - characterisation of i ses: class & subclass of immunoglob ity (e.g. avidity)
- Induct iological memory (priming), antibody
- ial impact of pre-existing antibodies
- Role of cellular / mucosal immunity

Prospectively defined and agreed upon endpoints and statistical approach

1.2. Combination / multivalent / concomitantly administered vaccines: synergy or interference ?

Monovalent vaccines

Combination vaccines

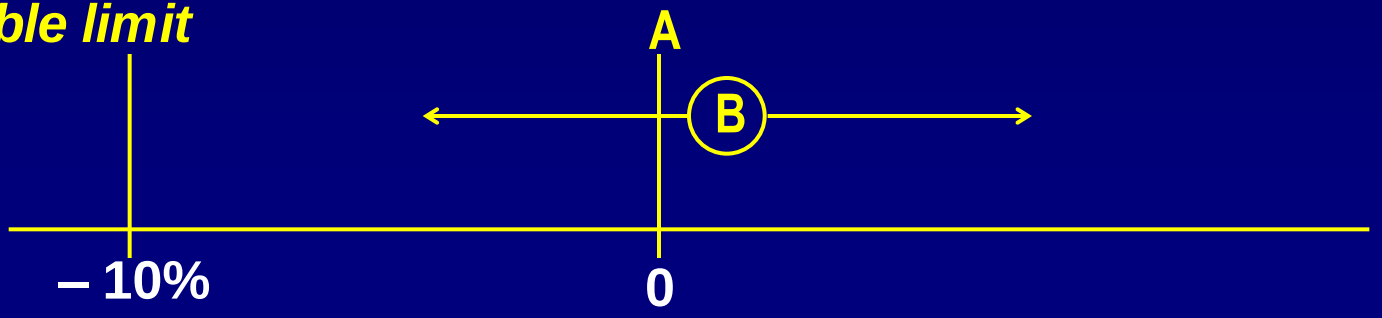
Synergy: DT & DTwP

1.2. Combination / multivalent / concomitantly administered vaccines: synergy or interference ?

Interference: thiomersal and polio, $Al(OH)_3$ & Hib, conjugate carriers

1.2. *Equivalence* in combined / multivalent /concomitantly administered vaccines

- **When given combined, efficacy** (immunogenicity) **against each antigen should not be lower than « current standard »**
  - **i.e. endpoint is *not inferior** to that of the reference regimen by more than a clinically relevant « δ » difference**
  - **If hypothesis based on SCR:**
    - **H_0: seroconversion rate (A-B) ≤ -10%**
    - **H_1: seroconversion rate (A-B) > -10%**
  - **shows that *the lower limit of the 95% CI of the difference in seroconversion rates (A-B) is above 10% of the predifined clinically acceptable limit***



* Proving equality is not possible

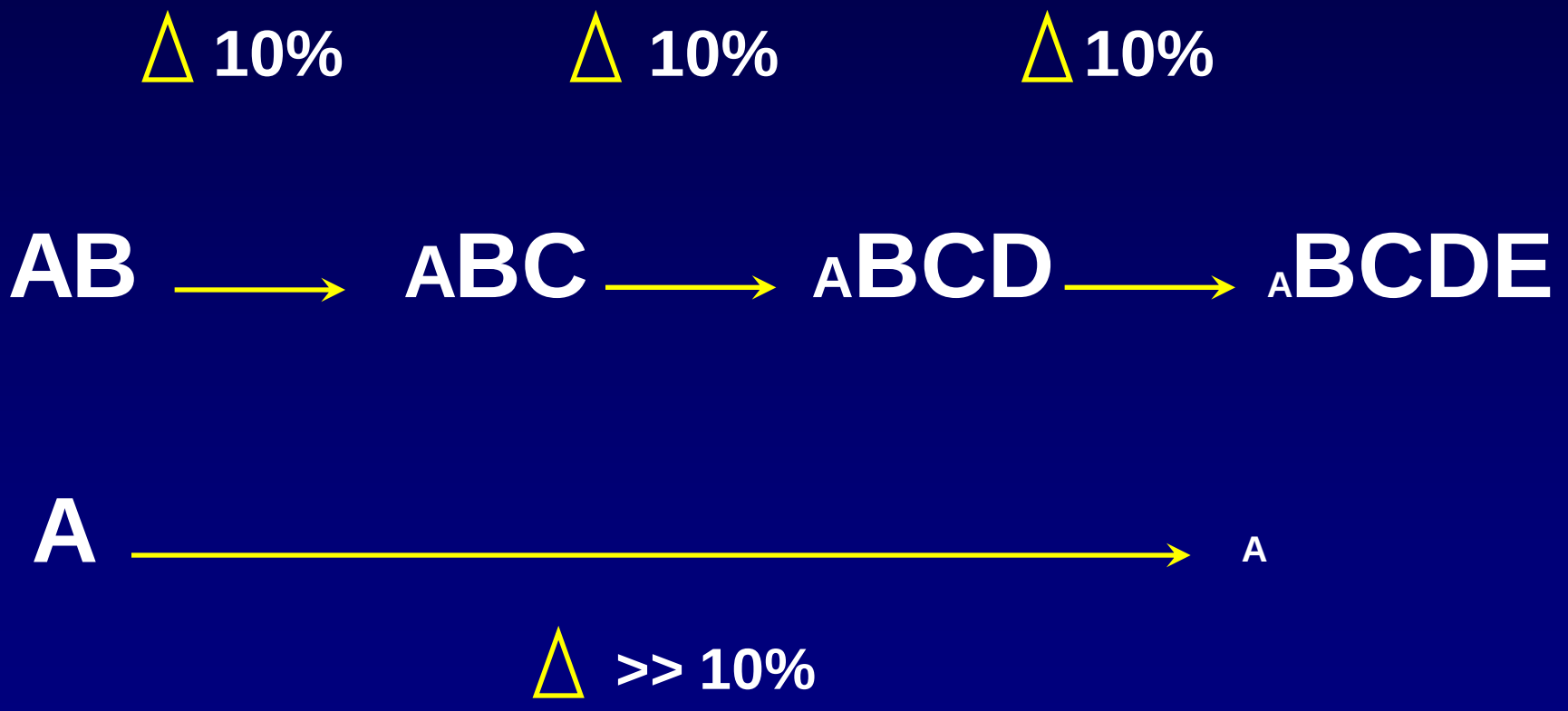
1.2. Pitfalls in non-inferiority approach: Methodology

- **What should be the reference endpoint ?**
  - Seroprotection: +++ if established (D, T, IPV, Hib, HB)
  - Seroconversion: what does it means for some antigens?
  - Define the appropriate level (primary vs. booster)
  - GMT / GMC: limited value *vs* RCDC*
- **How to set « δ »**
  - δ can often be set about 10% points, but will need to be smaller for very high protection rates (CPMP/EWP/463/97)
- **Impact on sample size**
- **What is the most appropriate control ?**
  - Monovalent vs already licensed combined vaccines: <u>impact of incremental interferences</u>

A clinical issue, not a statistical one

* Reverse Cumulative Distribution Curve

1.2. Combination vaccines: Impact of incremental interferences



1.2. Pitfalls in non-inferiority approach: Analysis / Interpretation

- **Rule out clinical differences based on immunological data: *i.e. clinical relevance of statistically significant immunological differences*** (e.g. Hib)

- ***Avoid disqualifying vaccines*** (combo / concomitant administration) ***because they do not meet narrow statistical significance***

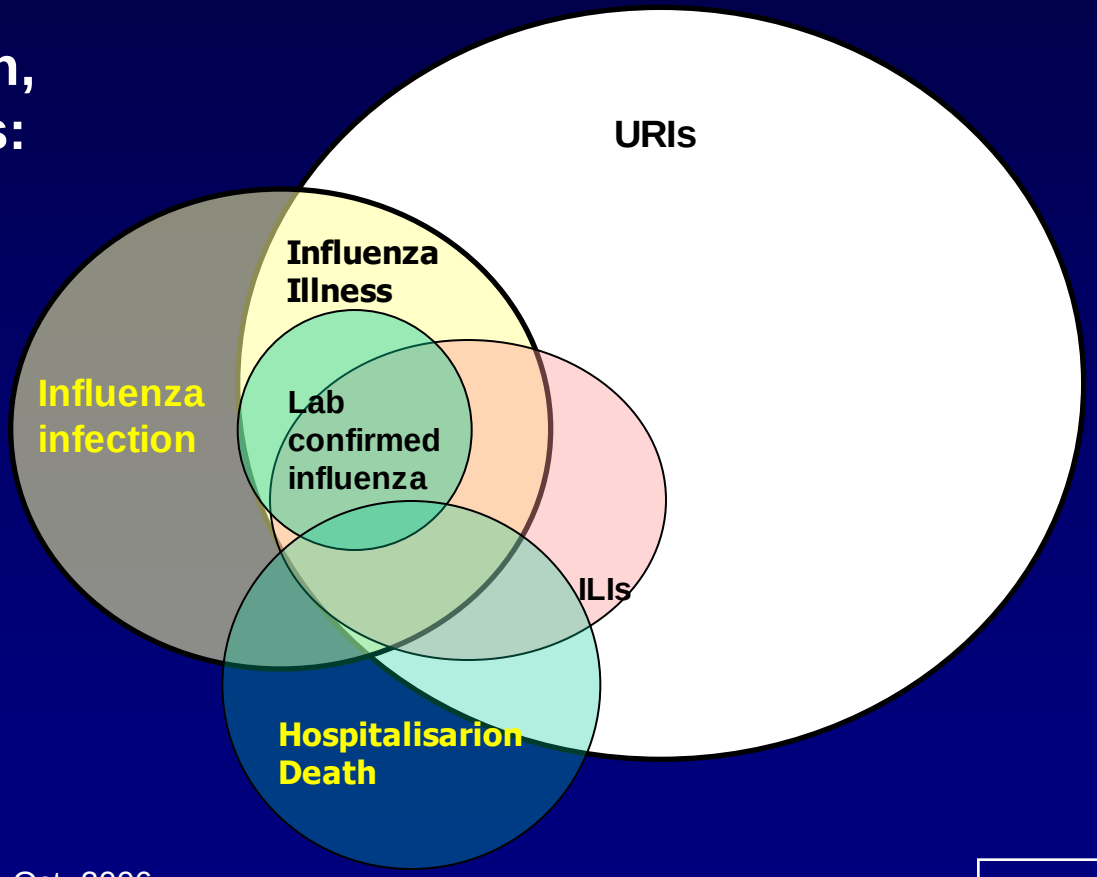
1.3. Choosing relevant efficacy endpoints

- The expected benefit of some new vaccines is not only to reduce the incidence of a well-defined infection/disease but to have an ***impact on disease complications or outcomes***
  - **Rotavirus**: severe cases, hospitalisation, family disruption
  - **Zoster**: severity, post-herpetic neuralgia, social disruption
  - **Influenza**: hospitalisation, mortality, societal impact

- Need for ***clinical*** **surrogates** of protection when expected benefit is delayed
  - **HPV:** infection, pre-cancerous lesions *vs.* cervical cancer

1.3. Choosing relevant efficacy endpoints: influenza vaccines*

Influenza Infection, Illness & outomes: Case Definitions



URI: upper respiratory tract illness

ILI: influenza-like illness

Courtesy K. L. Nichol, IVW Vienna, Oct. 2006

* See also pneumococcal infections

1.3. Choosing relevant efficacy endpoints: influenza vaccines

Impact of case definitions on Vaccine efficacy

(Hypothetical influenza season with 10 cases of influenza [illegible] and with a vaccine that will prevent 80% of influen[illegible]

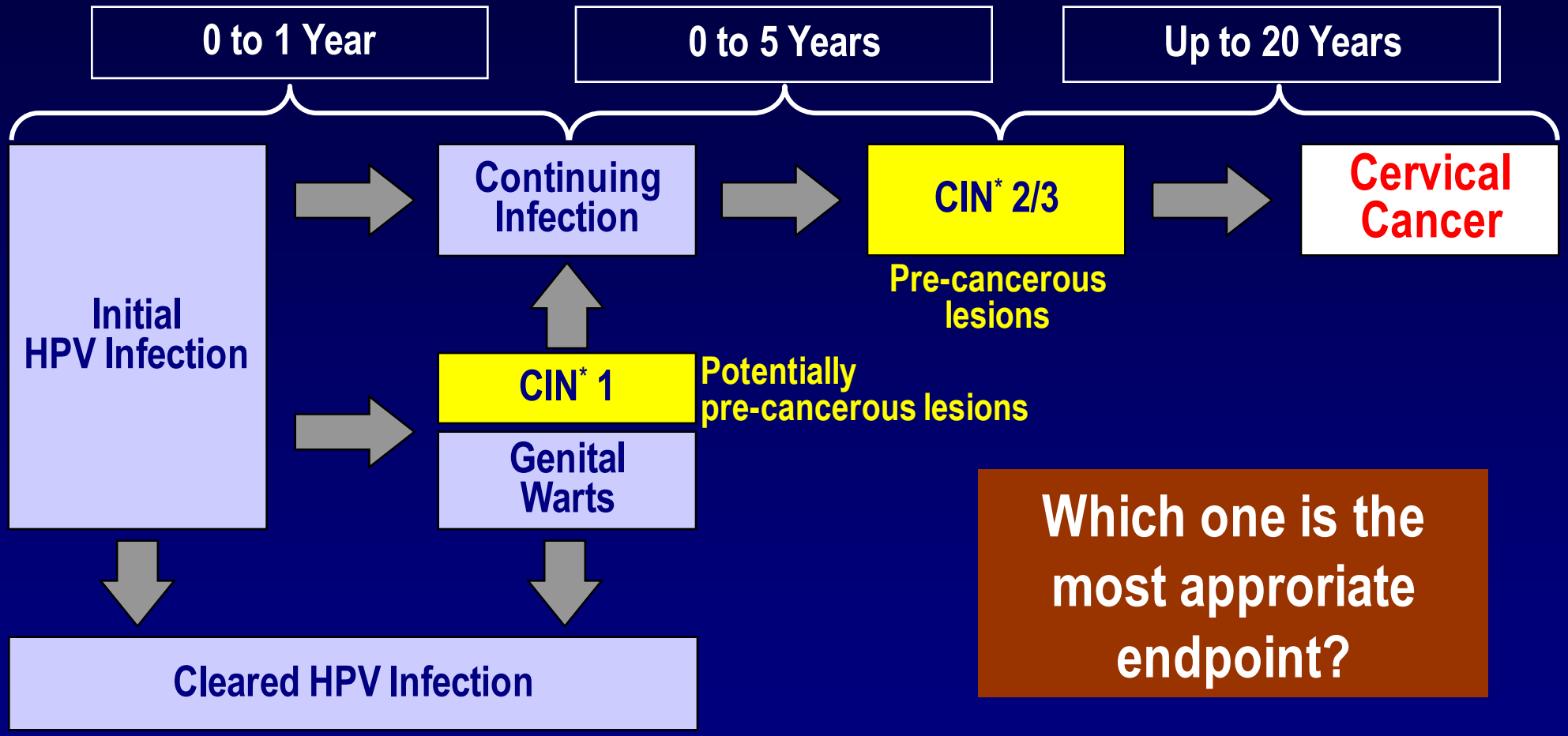
Case Definition	# of flu cases included	# non-flu cases incl[illegible]	# [illegible]cination	VE (% reduction)
Culture + ILI	5		4	80%
Clinical [illegible]		8	6.4	40%
[illegible]RI	9	27	7.2	20%

We should always expect that VE will be lower when more sensitive but non-specific clinical case definitions are used. It is a matter of arithmetic

Courtesy K. L. Nichol, IVW Vienna, Oct. 2006

1.3. Choosing clinically relevant efficacy endpoints:

Case study: HPV vaccine: How to know if a vaccine will prevent cancer since cancer is an unethical endpoint for clinical studies?



Which one is the most approriate endpoint?

* Cervical Intraepithelial Neoplasia

Adapted from Franco EL, Harper DM. Vaccine. 2005

1.3. Choosing clinically relevant efficacy endpoints:
HPV vaccines: recommended efficacy endpoints*

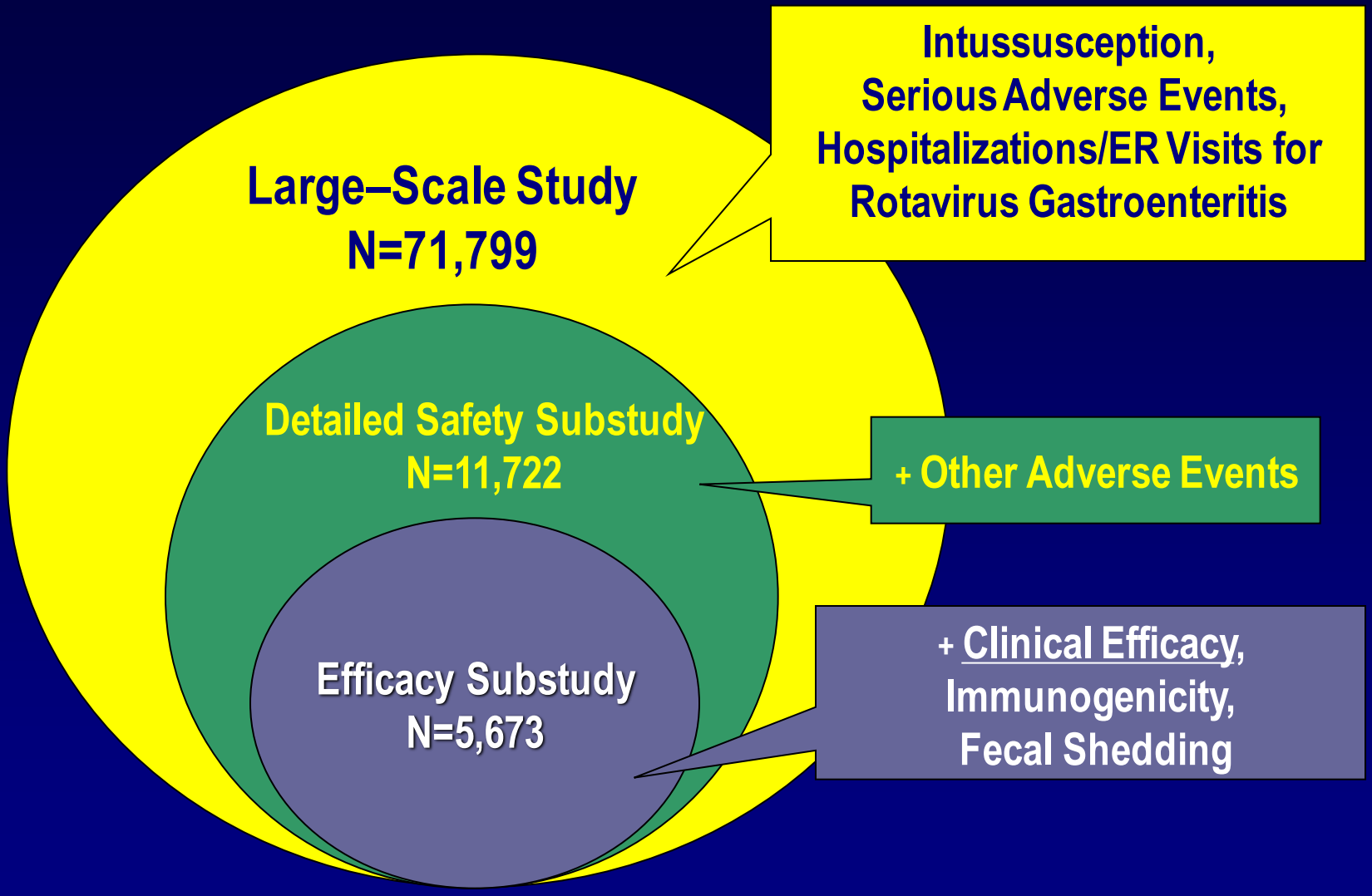
Criteria	HPV Infection	Potentially Pre-cancerous lesions (CIN* 1)	Actual Pre-cancerous lesions (CIN* 2/3)
Obligate precursor for cervical cancer	Yes	No	Yes[1,2]
Prompts treatment	No	Sometimes	Yes
Reduction leads to cervical cancer reduction	To be demonstrated (< 1% progress towards cancer[3])	To be demonstrated (< 1% progress towards cancer[4])	Yes (>14-22% progress towards cancer[4])
			Regulatory & Public Health Approval**

•CIN = Cervical intraepithelial neoplasia
•** Enpoint recommended by FDA and WHO

1.Pagliusi S, Aguado, T. Vaccine 2004; 23:569–578. 2. Wacholder S. J Natl Cancer Inst Monogr. 2003;(31):125-30. 3. Ostor AG. Int J Gynecol Pathol. 1993;12:186–192. 4. Wright T et al. Am J Obstet Gynecol 2003;189:295-304.

* See also cross protection

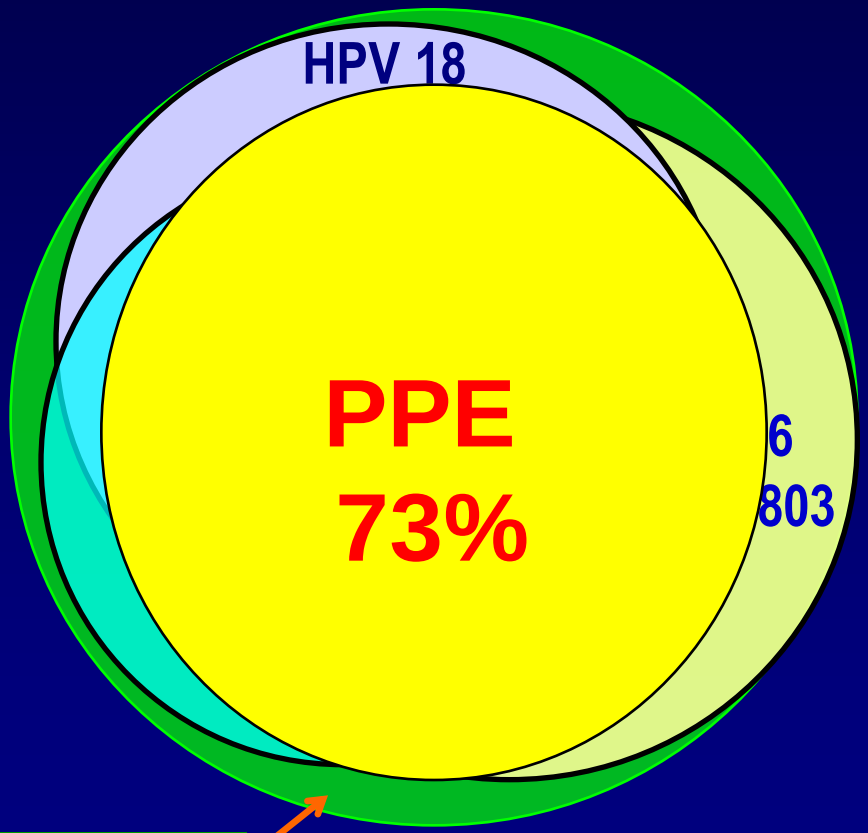
1.4. Understanding the numbers: Case study: rotavirus vaccine database (RotaTeq)



Vesikari et al., 2006

1.4. Understanding the Numbers
Case study: HPV vaccine database (Gardasil)

Per Protocol Efficacy population

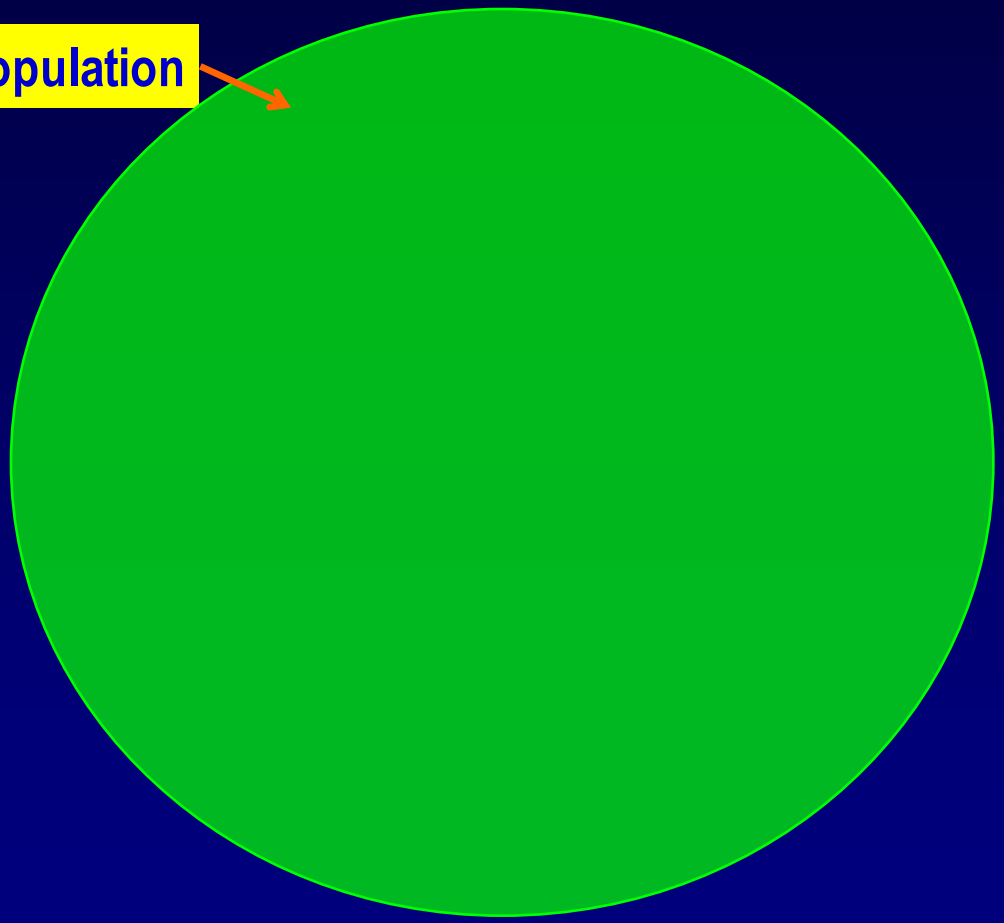


Criteria

- All women PCR – at baseline for the vaccine strain
- Who received 3 doses
- PCR – at month 7
- No protocol deviation
- Case counting starting at month 7.

Measure the absolute efficacy of the vaccine against vaccine types

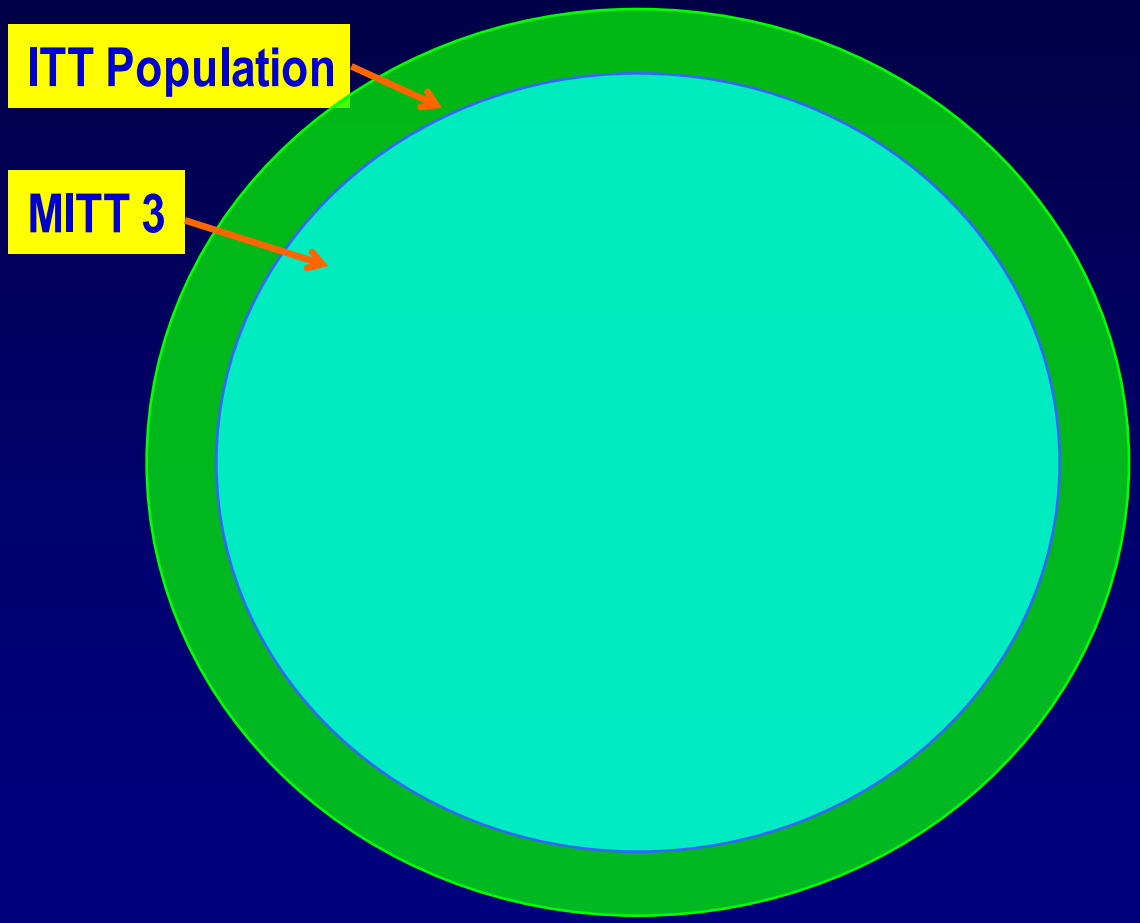
1.4. Understanding the Numbers
Case study: HPV vaccine database (Gardasil)



ITT: - All women recruited in CT
N= 20,845

ITT = Intent to Treat

1.4. Understanding the Numbers
Case study: Gardasil (HPV vaccine) database

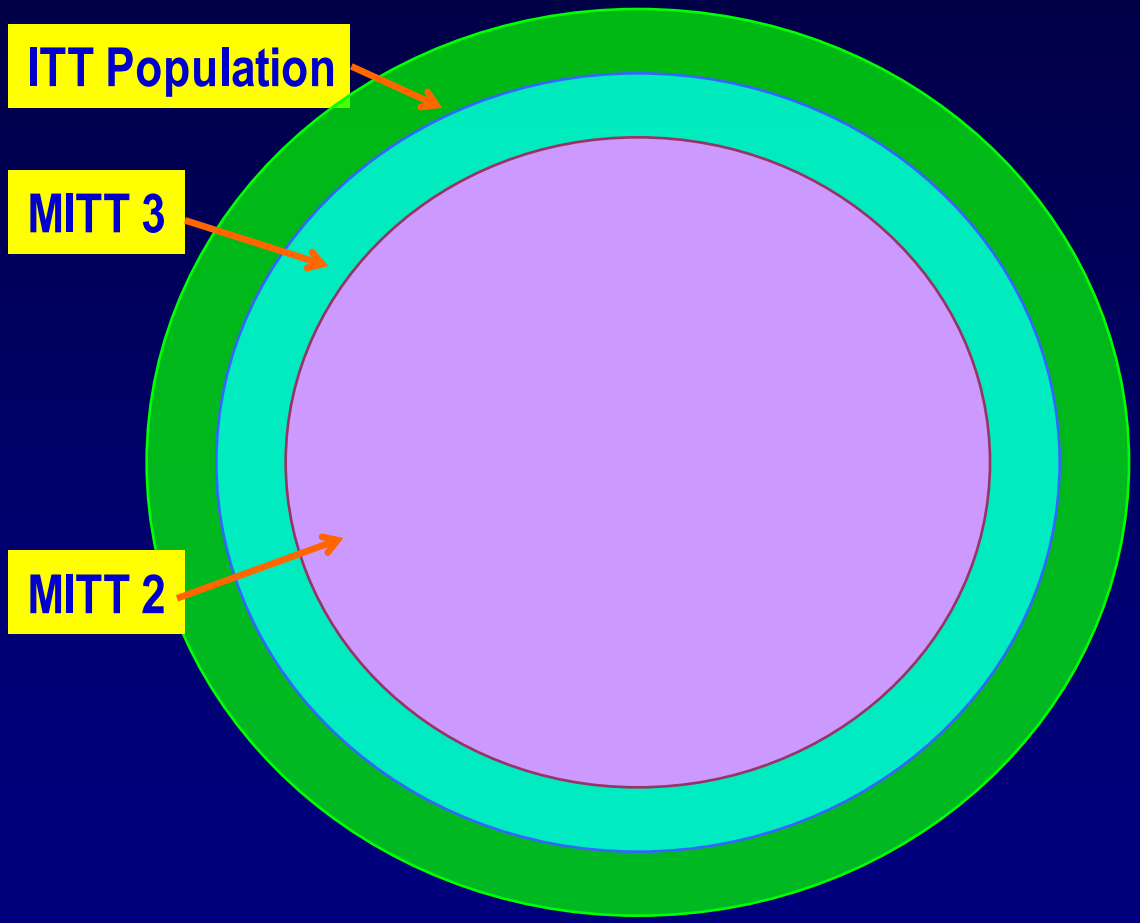


ITT: - All women recruited in CT
N= 20,845

MITT3: - All women recruited in CT
- Received at least one dose
~ 18,000

ITT = Intent to Treat
MITT = Modified ITT

1.4. Understanding the Numbers
Case study: Gardasil (HPV vaccine) database



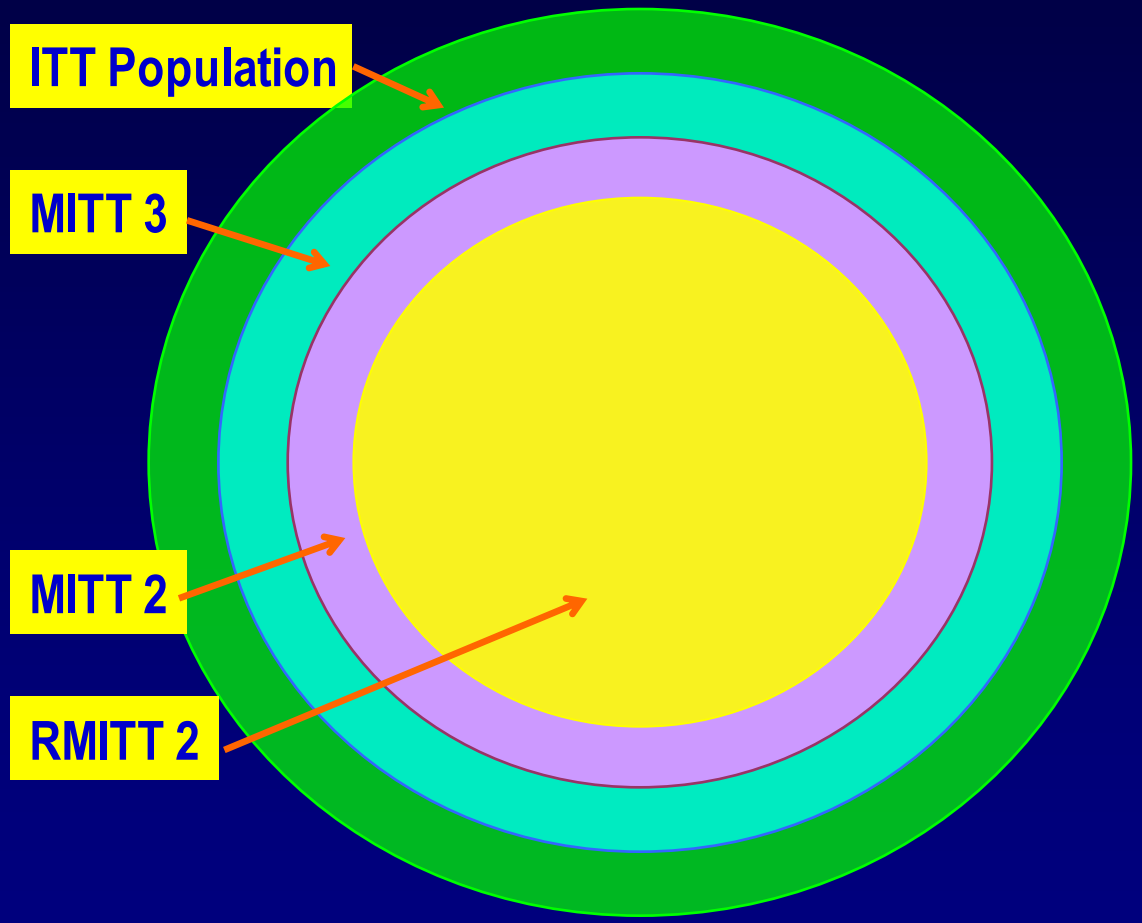
ITT: - All women recruited in CT
N= 20,845

MITT3: - All women recruited in CT
- Received at least one dose
~ 18,000

MITT2: - Women naive to HPV type for specific analysis at baseline
- Received at least one dose
~ 17,500

ITT = Intent to Treat
MITT = Modified ITT

1.4. Understanding the Numbers
Case study: Gardasil (HPV vaccine) database



ITT: - All women recruited in CT
N= 20,845

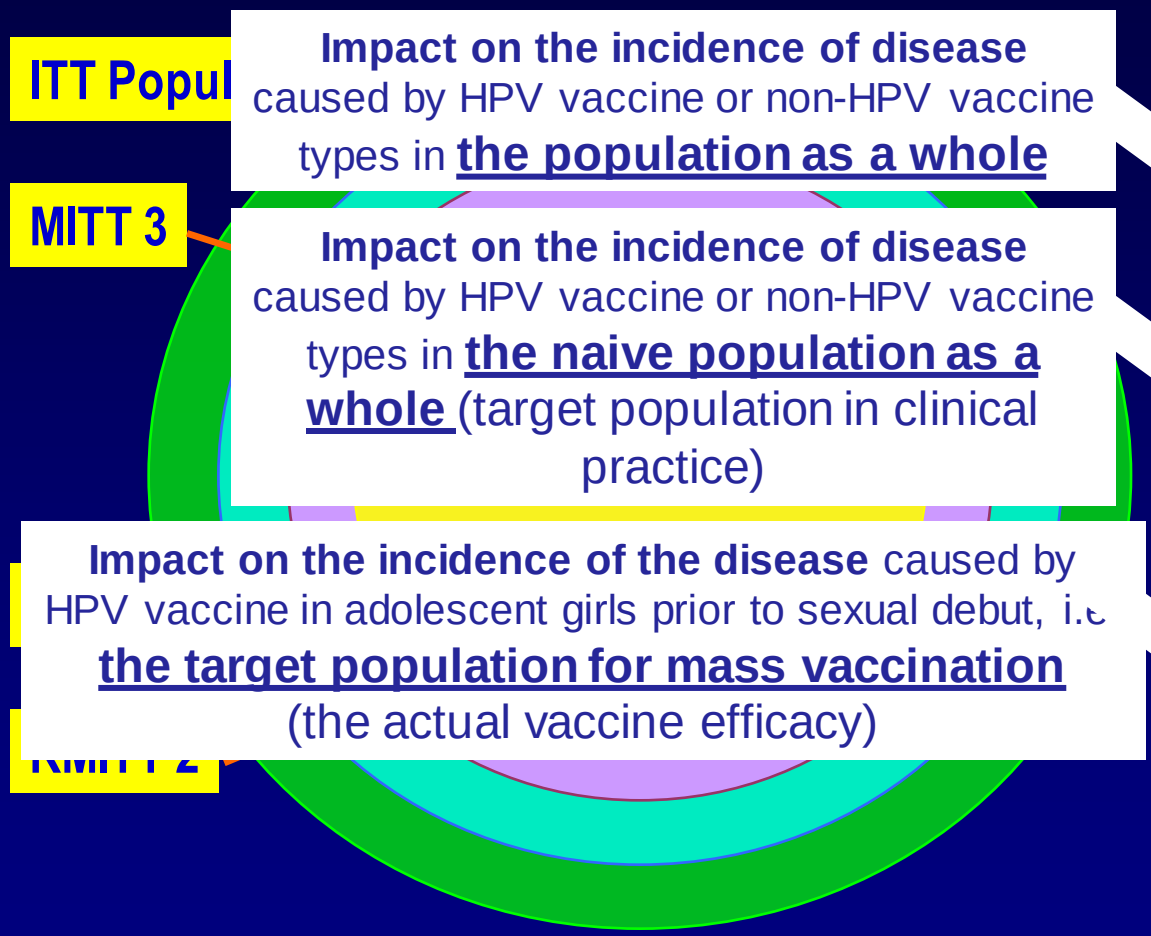
MITT3: - All women recruited in CT
- Received at least one dose
~ 18,000

MITT2: - Women naive to HPV type for specific analysis at baseline
- Received at least one dose
~ 17,500

RMITT2: - Women naive to 14 types at baseline
- Received at least one dose
~ 10,000

ITT = Intent to Treat
MITT = Modified ITT
RMITT = Restricted MITT

1.4. Understanding the Numbers
HPV vaccine: what does each population represent ?



Impact on the incidence of disease caused by HPV vaccine or non-HPV vaccine types in **the population as a whole**

Impact on the incidence of disease caused by HPV vaccine or non-HPV vaccine types in **the naive population as a whole** (target population in clinical practice)

Impact on the incidence of the disease caused by HPV vaccine in adolescent girls prior to sexual debut, i.e **the target population for mass vaccination** (the actual vaccine efficacy)

ITT: - All women recruited in CT
N= 20,845

MITT3: - All women recruited in CT
- Received at least one dose
≥ 18

Critical to understand and measure the effectiveness / impact (inc. HE / HTA) of vaccination policies

RMITT2: - All women recruited in CT
at baseline
- Received at least one dose
~ 10,000

ITT = Intent to Treat
MITT = Modified ITT
RMITT = Restricted MITT

Main pitfalls experienced in recent vaccine registrations

1. Addressing methodological approaches
   - Using immunological correlates of clinical protection as primary endpoints
   - Assessing equivalence in combined / concomitantly administered vaccines
   - Choosing relevant efficacy endpoints
   - Understanding the numbers
2. Anticipating post-licensure activities
   - Designing a risk management plan (RMP)
   - Other post-licensure commitments (FUM)

2.2. European Risk Management System

*"A set of pharmacovigilance **activities** and **interventions** designed to identify, characterise, **prevent or minimise risk** relating to medicinal products, and the assessment of the **effectiveness of those interventions**"*

Two key elements:

1. **The pharmacovigilance plan**
2. **The risk minimisation strategy**

2.1. Pharmacovigilance plan

- **Definition**: a plan proposing collection of data relevant to the safety profile of a medical product once it is marketed and aiming to demonstrate safety as well as identifying harm
- **Objective:** on the basis of pre-licensure experience, anticipate PV activities to be conducted after licensure
- **Three parts:**
  1. Situation analysis (specifications)
  2. Pharmacovigilance plan
  3. Methodology (design and conduct) of post-approval safety studies

Used as discussion document pre-approval between industry and regulators

2.1. Risk Minimisation strategy

Objectif: to reduce risk to individual patients and populations

Level 1: SPC and labelling (package insert)

Level 2: risk education programmes

- education / communication to health-care professionals (training, CME) and the public
- pre- and post authorisation

Level 3: distribution control, including prescription, dispensing, registries and consent

Level 4: protocols and guidelines

- Concomitant administration
- Travellers
- Risk groups …

2.2. Other post-licensure commitments

- As a condition for licensure, RA may ask the manufacturers for PMS commitments in the form of additional large-scale studies

- In 2014, no vaccine registration without post-licensing commitments / follow-up measures (FUM)

2.2. Objectives of post-licensure commitments

1. **To document SAFETY**
   - Rare, uncommon, distant AEs; events with no causal relationship
   - Specific populations (HPV and pregnancy registries)
   - Clinical trials or observational studies ?
2. **To document vaccine EFFECTIVENESS**
   - Pertussis, rota, HPV, influenza
   - Duration of protection / need for boosters
   - **Clinical significance of interference in immune responses:** e.g. Hib Validation of serological assays (Men C conjugates)
3. **To assess the IMPACT of the introduction of new vaccines**
   - Change in strain characteristics, e.g. pertussis
   - Change in clinical and microbiological epidemiology (serotype replacement)
   - Concomitant administration with other licensed vaccines
   - Actual public health impact of vaccination policies : Health Technology Assessment (HTA)

Respective responsibilities of the manufacturers and health authorities ?

Lessons learnt and impact on future vaccine developments

1. ***A solid scientific basis is critical for success:***

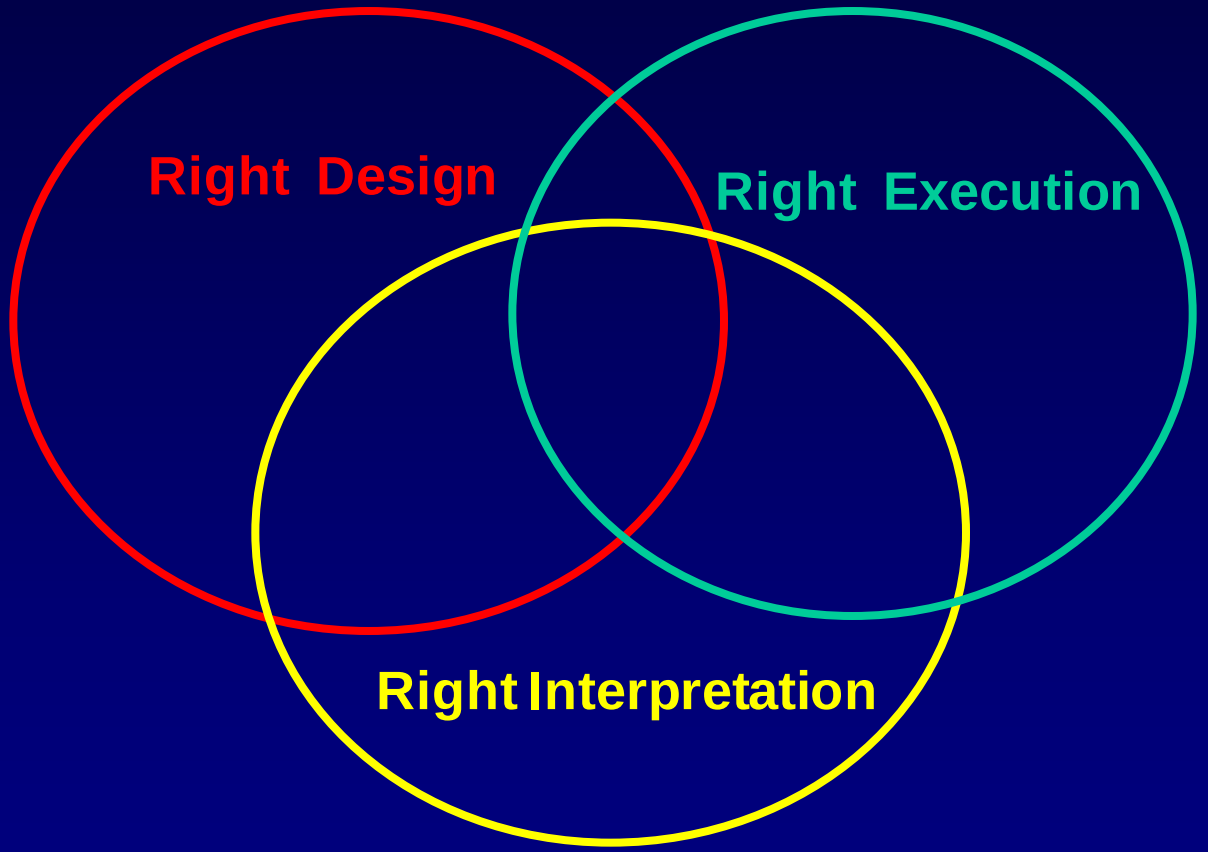
   - **Scientific foundation, e.g. immunological rationale**
   - **Bridge from basis research to pre-clinical then clinical development (safety, efficacy)**
   - **Epidemiology studies** (burden of disease, surveillance, HE) **are critical for guiding the vaccine development process, and anticipating post-licensure commitments**

Lessons learnt and impact on future vaccine developments

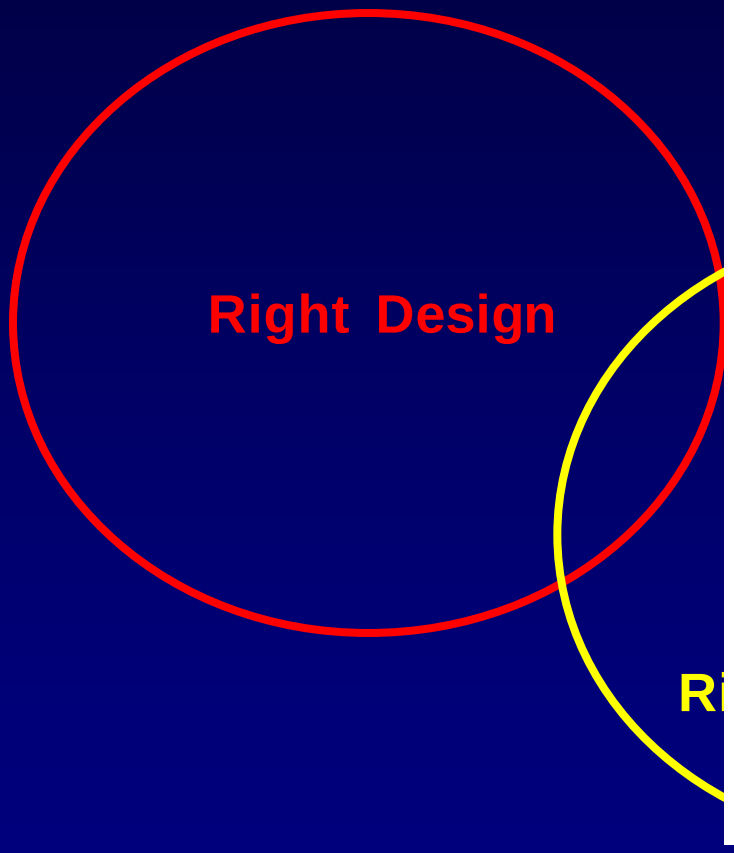
2. ***Design the right <u>Target Product Profile</u> (TPP) to anticipate the development process and ensure the relevance of efficacy and safety data:***

   - **Supported by a relevant Clinical Development Plan (CDP)**
   - **For optimal SmPC and speedy registration process**
   - **To anticipate (scientific) questions and misleading interpretations**
   - **For a swift introduction in vaccination programmes and a fast and compelling public health impact**

What you need for a successful CDP



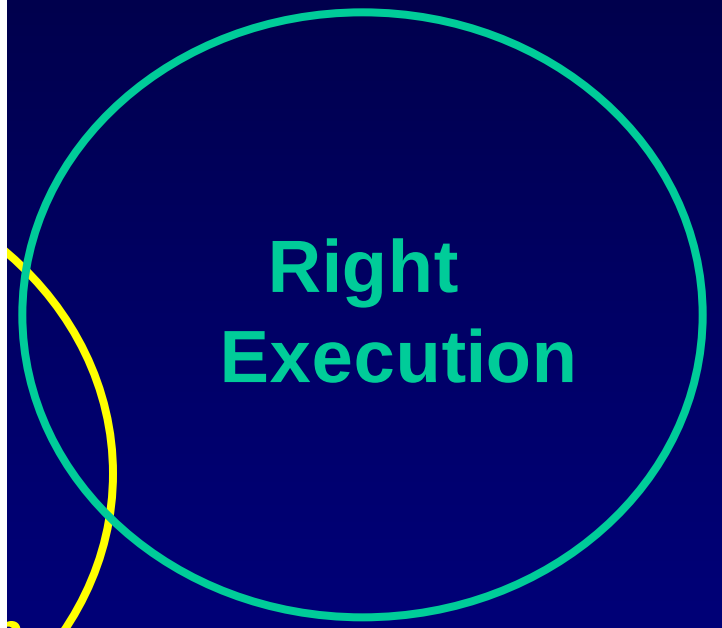
What you need for a successful CDP



- **CDP designed to answer in a logical and chronological *well-defined questions*** (appropriate indication, population & immunisation schedules)
- **Include *surveillance systems* to detect a variety of outcomes** (e.g. rare AEs or epidemiological changes)**, as part of large prelicensure or anticipated for postlicensure evaluation**
- ***Risk management and post-licensure studies*:** monitoring public health impact and population safety

What you need for a successful CDP

- **Recruitment**
- **Monitoring**
- **Data collection and quality control**
- **Data analysis** (both biology and statistics)
- **Handling of test vaccines and serum samples**
- **…**



What you need for a successful CDP

- *A priori* establishment of relevant clinical and statistical hypotheses
- Importance of « champions » and scientific independent committees / DSMB

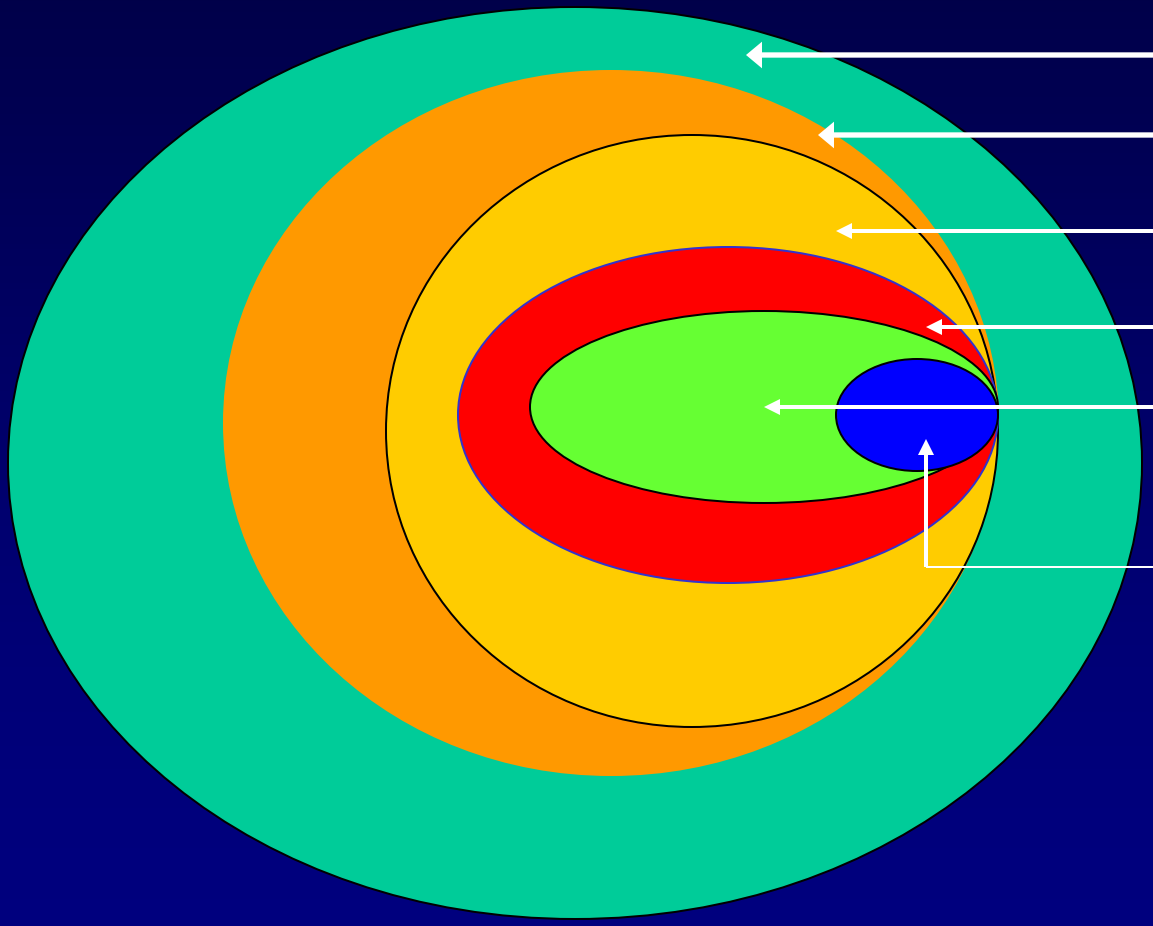
Conclusions

- **Pre-licensure trials need to be carefully designed**
- **The post-licensure environment is becoming almost as *complex* as the pre-licensure environment**

If we want these pitfalls not to become traps, a dialogue with RA experts during development should be established upfront to identify ways to address vaccine specificities in the registration file

Back-up slides

1.3. Choosing relevant efficacy endpoints: Pneumococcal infections & illness case definitions



WHO Clinical criteria

Modified WHO criteria

Any X-ray abnormality

Alveolar consolidation

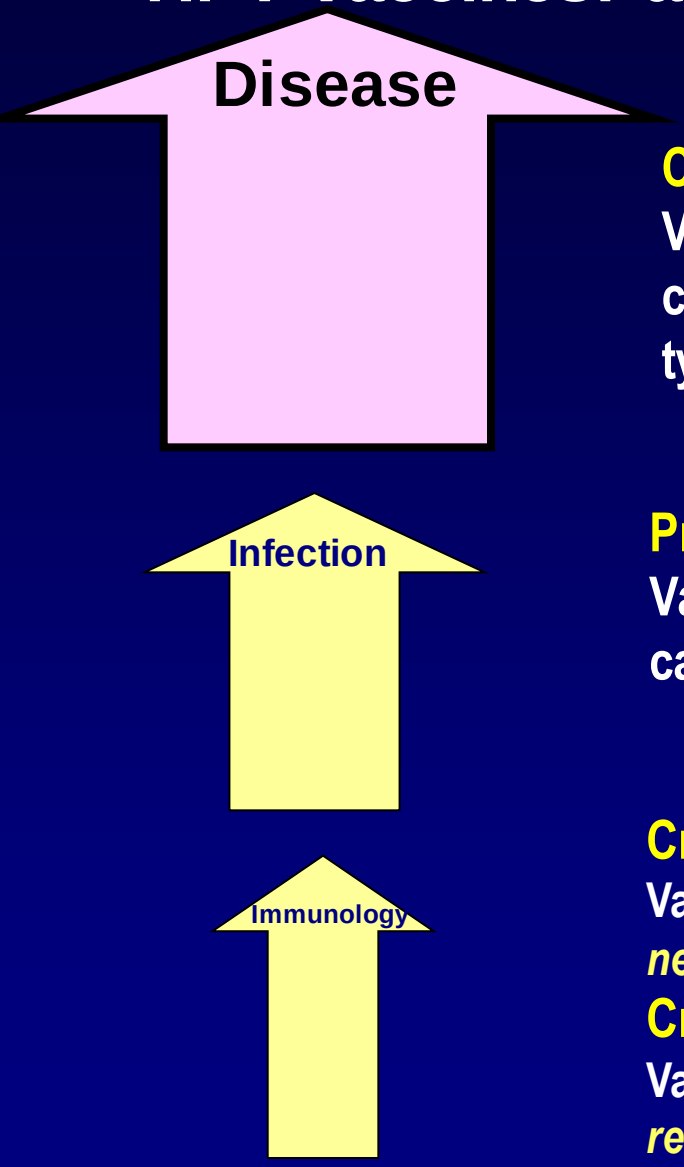
Lung aspirate culture

Blood culture

Sensitivity

Specificity

1.3. Choosing clinically relevant efficacy endpoints:
HPV vaccines: approaches to evaluate cross protection



Cross protection against clinical diseases

Vaccination with a given HPV type produces specific antibodies that can provide protection from clinical diseases caused by other HPV types

Protection against infection caused by other types

Vaccination with a given HPV type produces specific antibodies that can provide protection from infection caused by other HPV types

Cross neutralisation

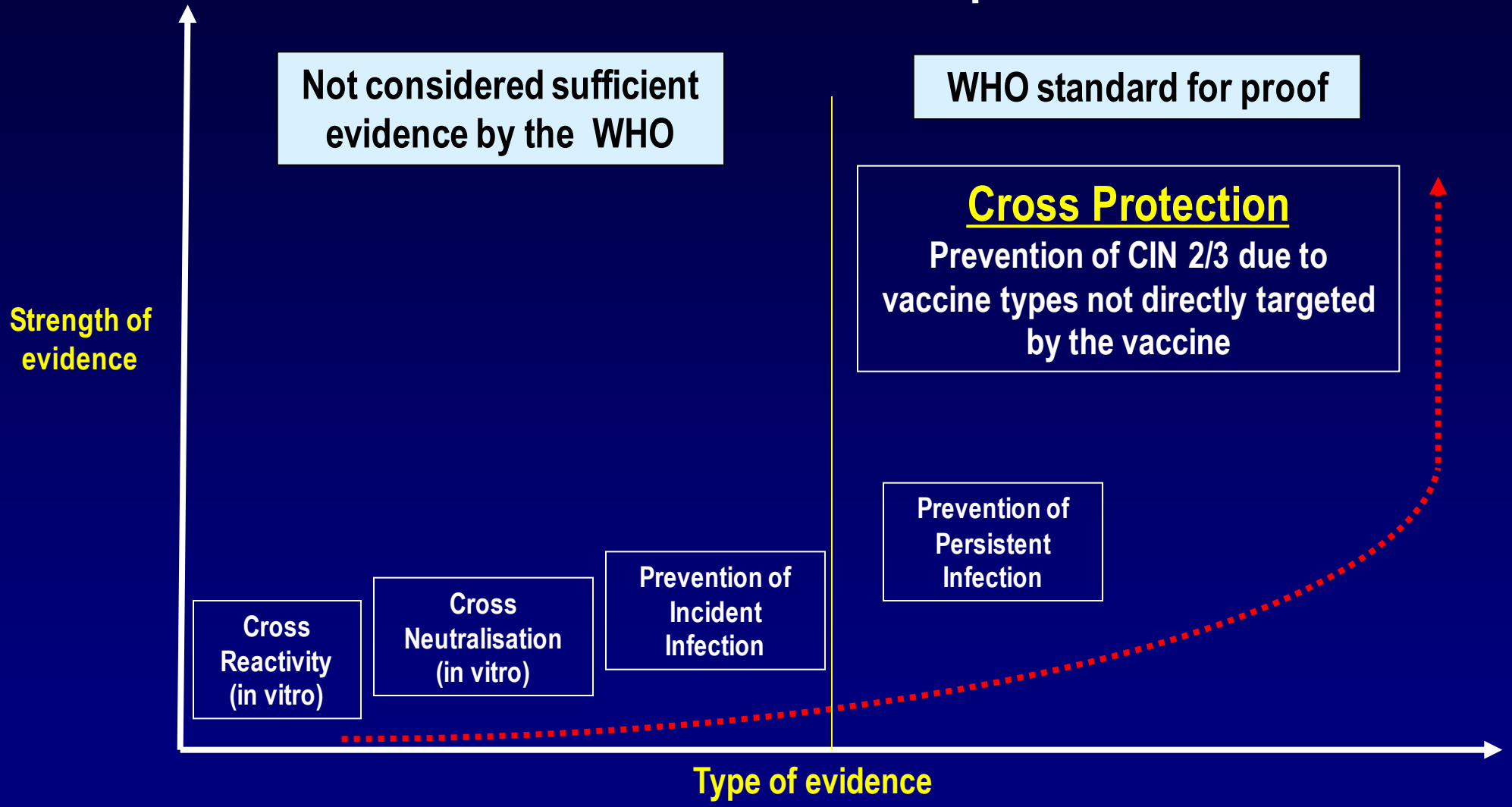
Vaccination with a given HPV type produces type-specific antibodies that can *neutralise* the infectious potential of other HPV types

Cross reactivity

Vaccination with a given HPV type produces type-specific antibodies that can *react* with other HPV types

1.3. Choosing clinically relevant efficacy endpoints:

HPV vaccines: what is the best standard for proof of Cross Protection ?



The concept of Risk Management: a paradigm change

From Surveillance to Action

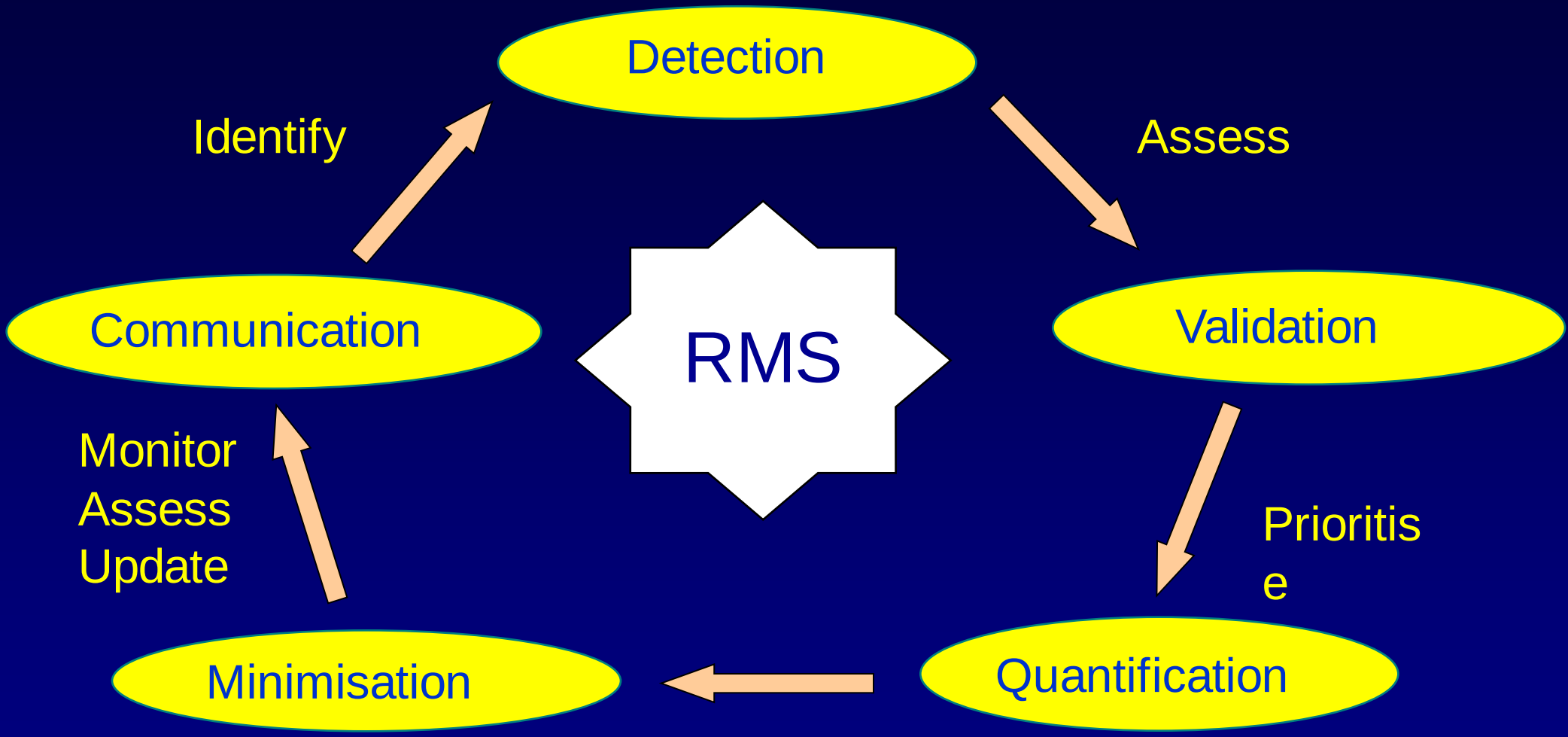
From

- **Reactive (meet regulations)**
- **Risk detection (spontaneous reporting)**
- **New drug application « safety and efficacy » (clinical trial data)**
- **Product safety**

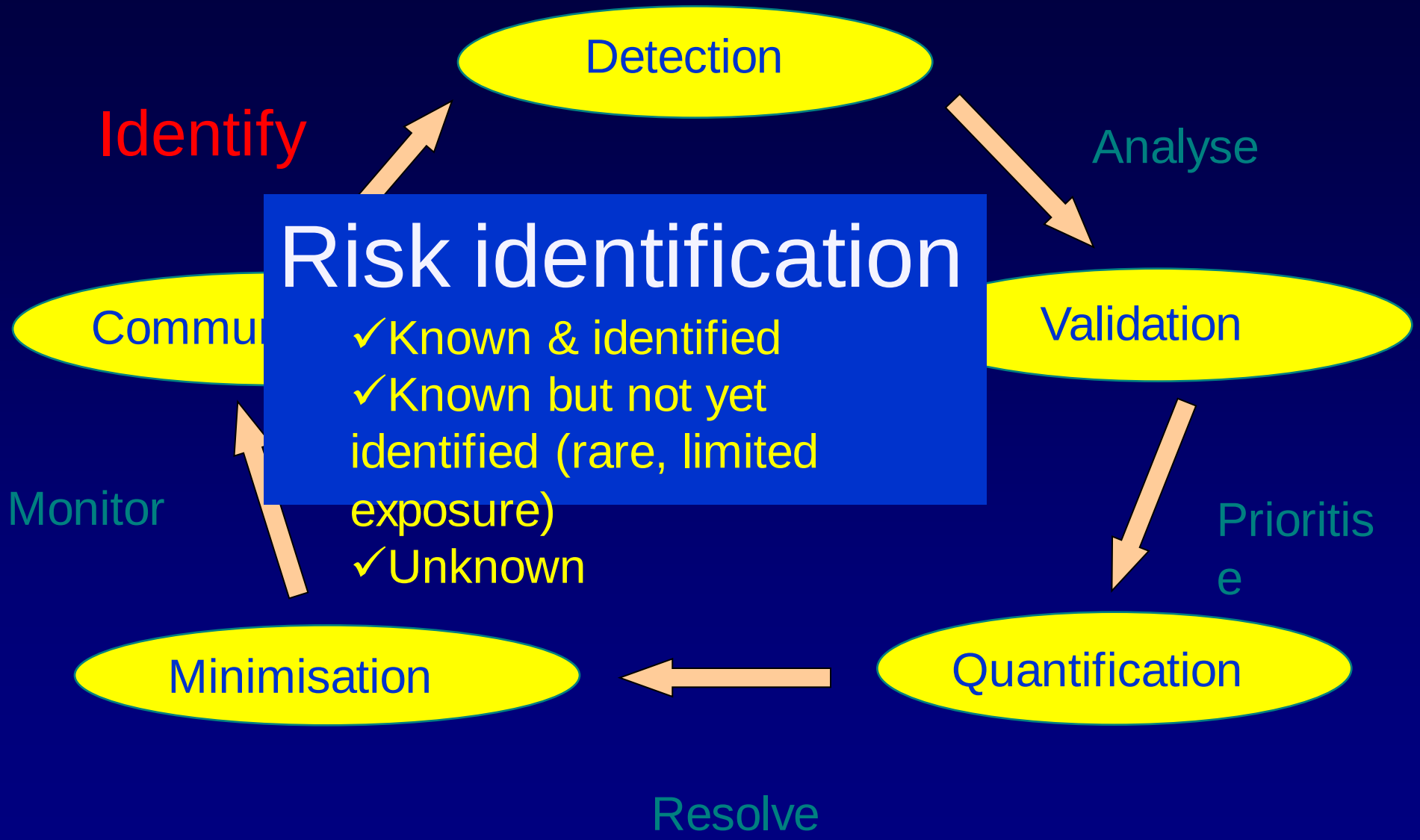
To

- Proactive (anticipate)
- Risk prevention (global management)
- Optimal use and prevention of adverse events (population data)
- **Patient safety**

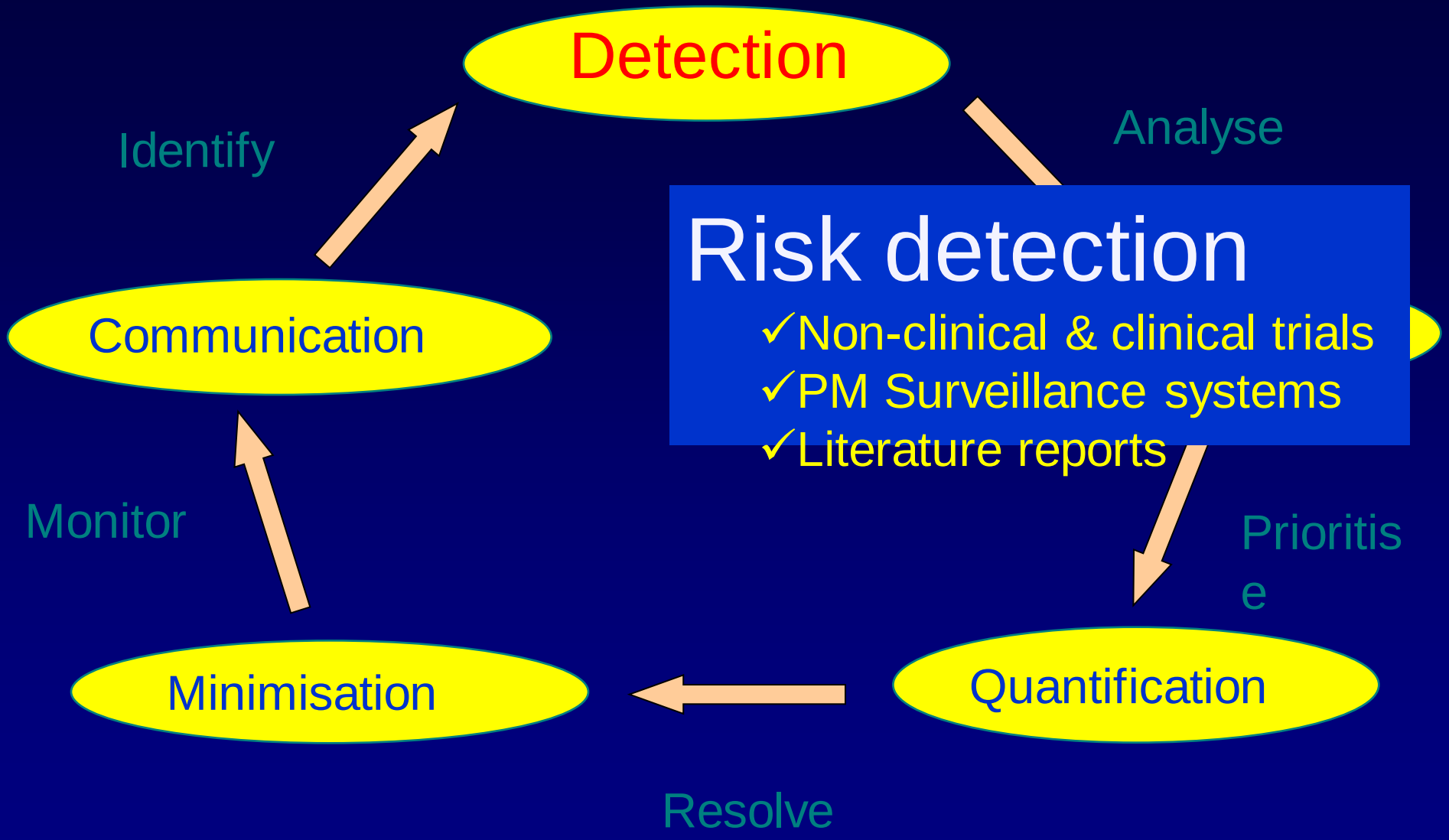
Risk Management Strategy: objectives and actions



Components of risk management strategy



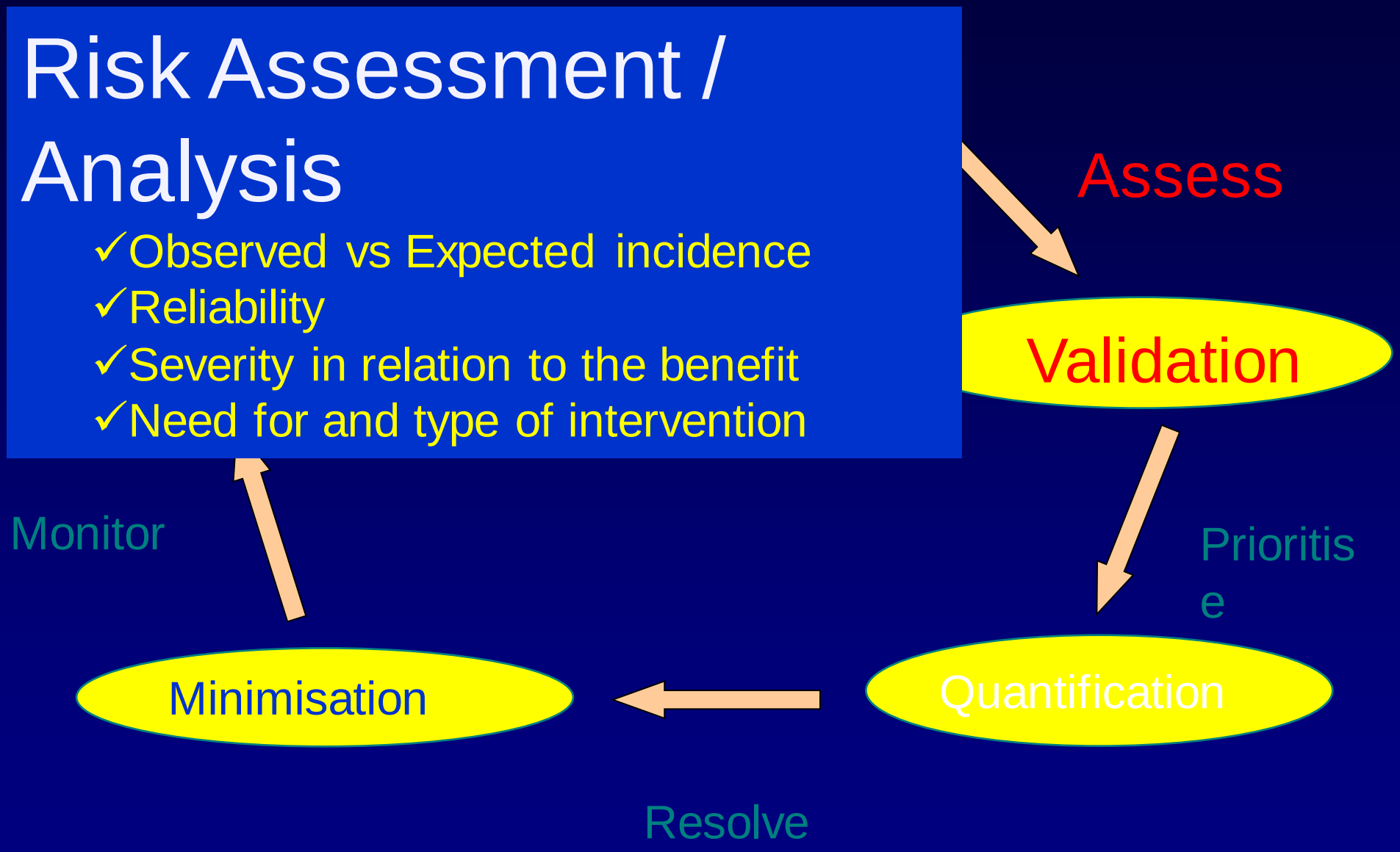
Components of risk management strategy



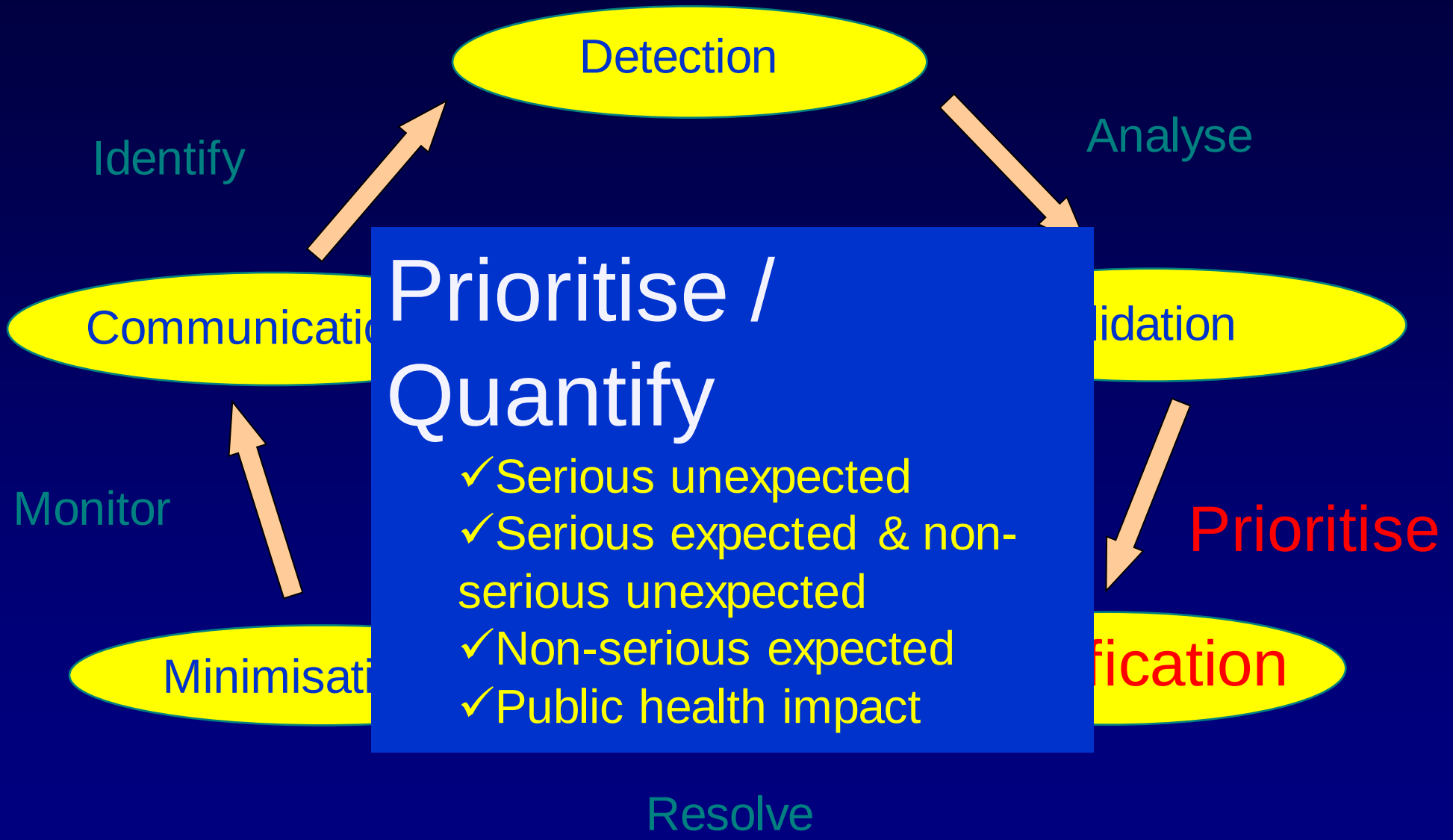
Components of risk management strategy

Risk Assessment / Analysis

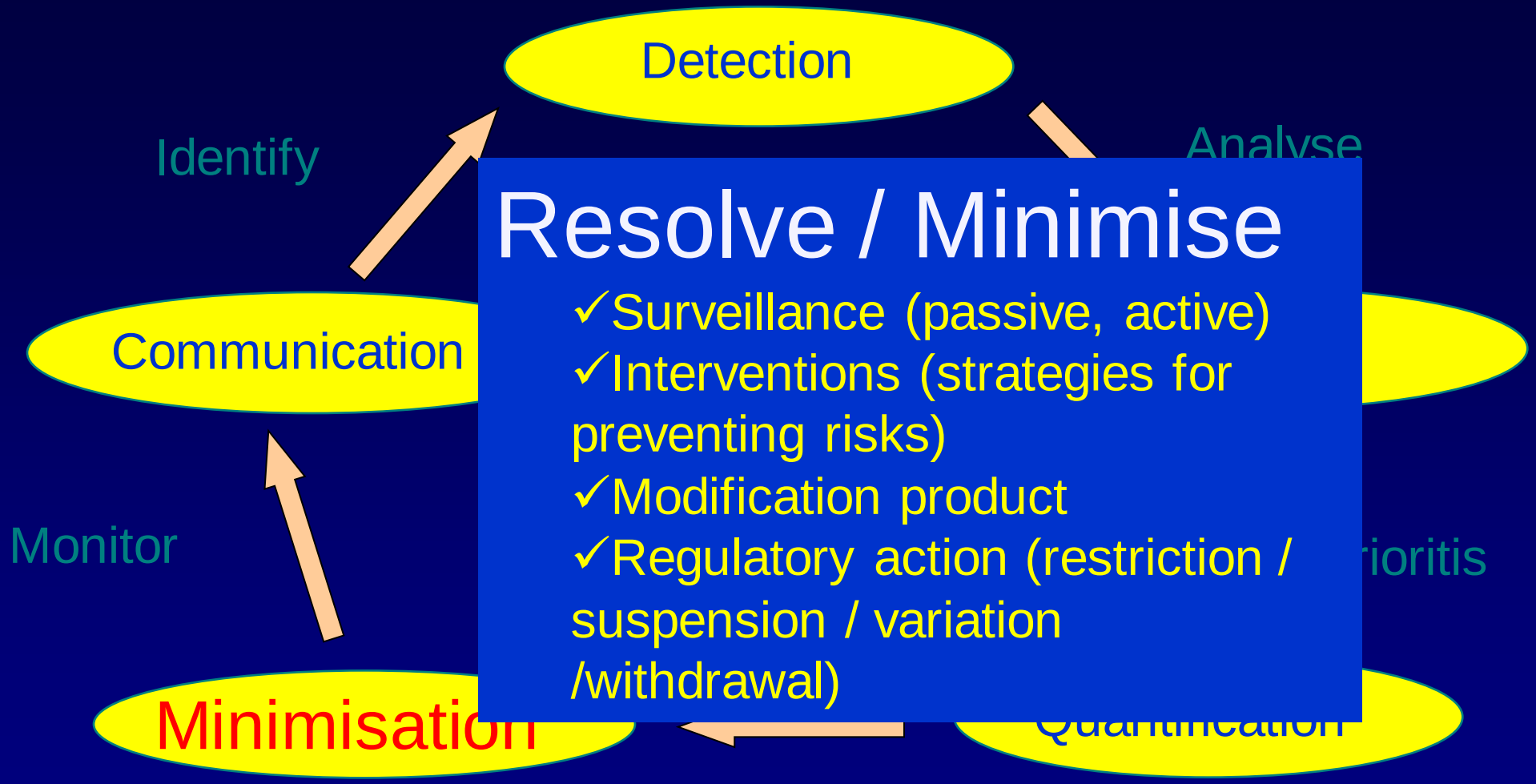
- ✓Observed vs Expected incidence
- ✓Reliability
- ✓Severity in relation to the benefit
- ✓Need for and type of intervention



Components of risk management strategy

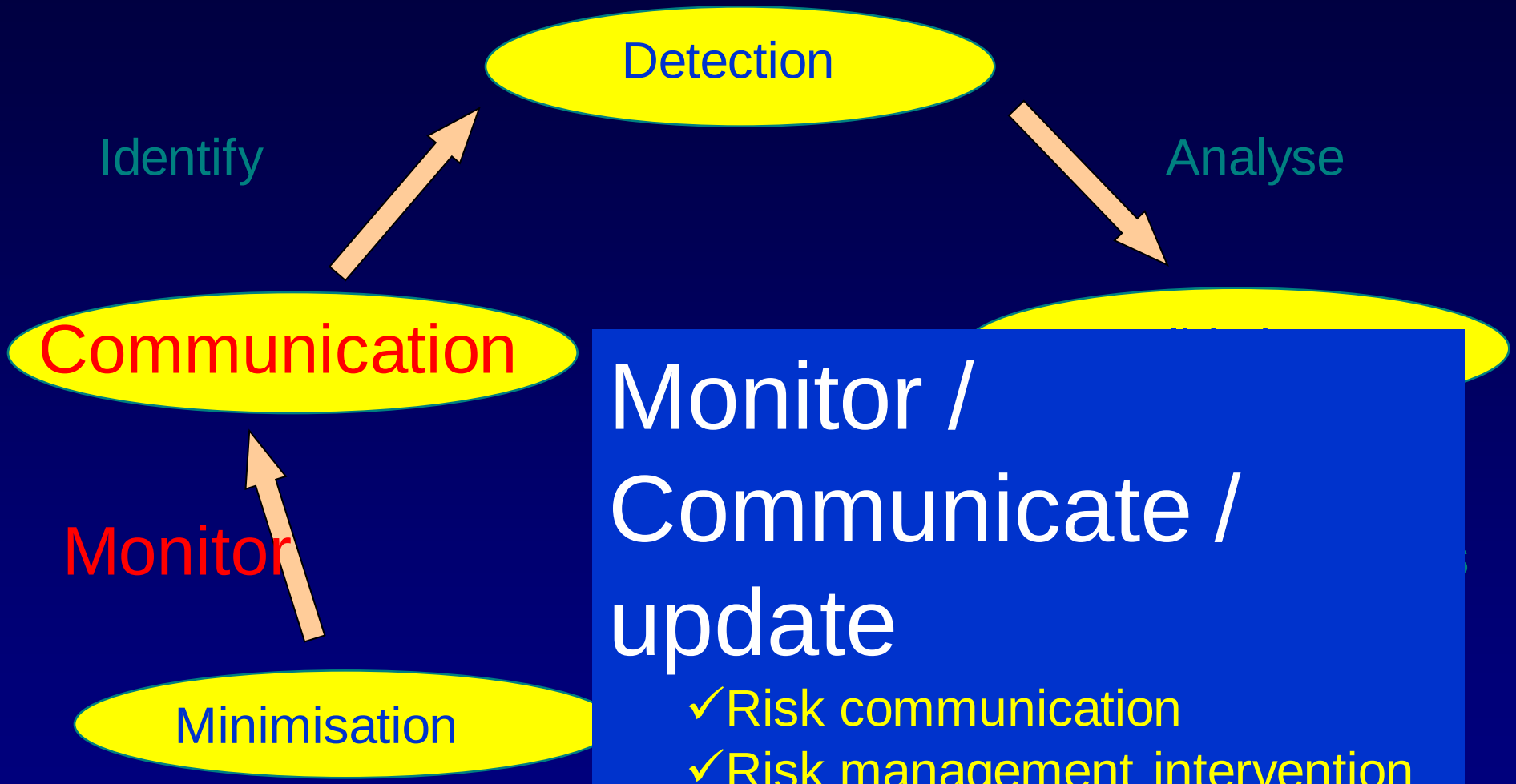


Components of risk management strategy



Resolve

Components of risk management strategy



Monitor / Communicate / update

- ✓Risk communication
- ✓Risk management intervention
- ✓Evaluating impact of RMS
- ✓Audit