Hanuman and the mountain of herbs; Mysore painting

# "Requirements for new trials to examine off-target effects of vaccination"

Workshop on: "Off-target (heterologous/non-specific) effects of vaccination"

Les Pensieres Jun 8-10, 2015

**PEM Fine**

London School of Hygiene and Tropical Medicine

"Requirements for new trials to examine off-target effects of vaccination"

# Why trials ?

## … because evidence for NSEs is

**contentious …**

**largely from observational studies …**

mainly from one small place ….. in Guinea Bissau ….

data problems (vaccine histories, follow-up….)

…. and there are obvious comparability issues

those who receive vaccines are different in many ways from those who do not receive vaccines ….

**difficult to translate into policy ….**

# What (kind of) trials ?

- **Confirmatory** (to test an hypothesis)
- **Explanatory** (to explain a mechanism)
- **Estimatory** (to assess magnitude of an effect)
- **Pragmatic** (to evaluate a policy schedule)

# Confirmatory trials ….

**Simplest: but which hypotheses are priority ?**

- BCG and bladder cancer…

- Measles and morbidity / mortality
- BCG " " "
- DTP " " "
- Order " " "
- Killed vs live " " "

- Sex differences " " "
- Vitamin A " " "
- …. ?

# Confirmatory trials ….

**Simplest: but which hypoth… are**

- BCG and bladde…
- Measles and …
- BCG "
- DTP
- Order
- Killed vs live "
- Sex differences
- Vitamin A
- …. ?

**How to prioritise ?**
--Select hypothesis with greatest observational evidence…. ?

*or*
-- hypothesis with most "serious" (detrimental ?) implications ?

# Confirmatory trials ….

**Simplest: but whic theses ori**

- BCG and B
- Measles
- BCG
- DTP
- Order "
- Killed vs live

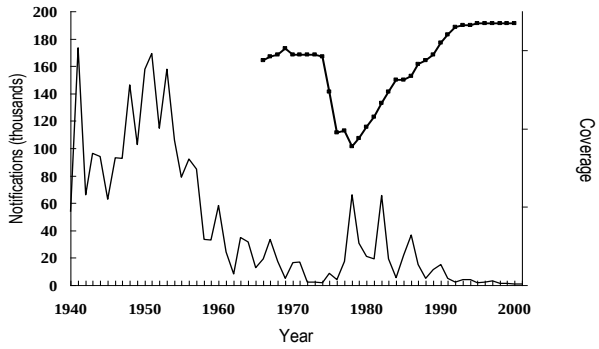
- Sex differences
- Vitamin A
- …. ?

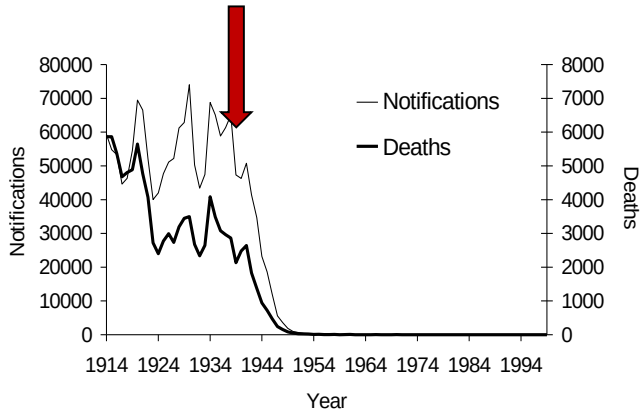
Note complexity of interpreting any "non-specific" "detrimental" effect – eg of DTP….

How to assess against obvious beneficial specific effects – eg in protecting against pertussis…

# DTP impact

## UK data

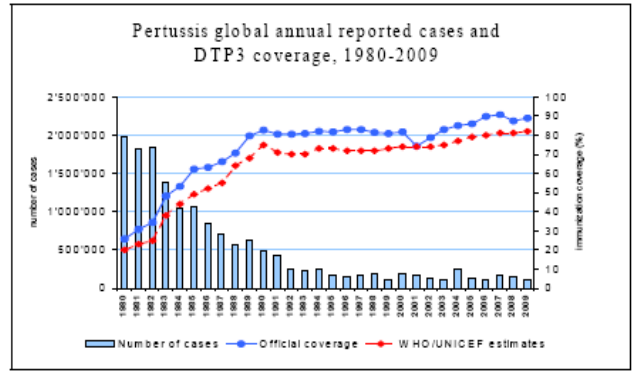


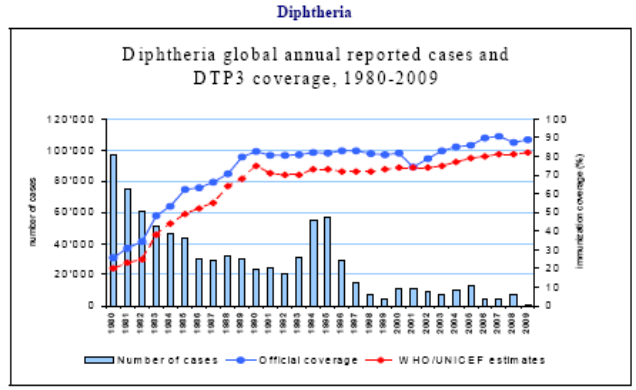

Beware the comments that "DTP increases all cause mortality" !

## Global data

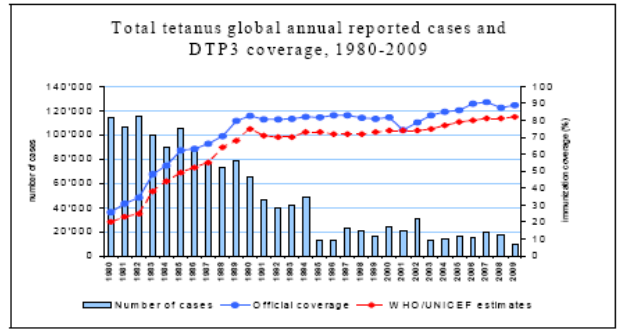
### Pertussis




### Diphtheria




### Tetanus



# Explanatory trials

In terms of immunological mechanism

or

In terms of outcome (eg causes of morbidity mortality…)

Major implications for sample collection and technical laboratory support (immunological, diagnostic ….)

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**These are linked** - knowledge of clinical outcomes may suggest immunological mechanisms – and *vice versa*….

# Explanatory trials

In terms of immunological mechanism

**To inform vaccine development**

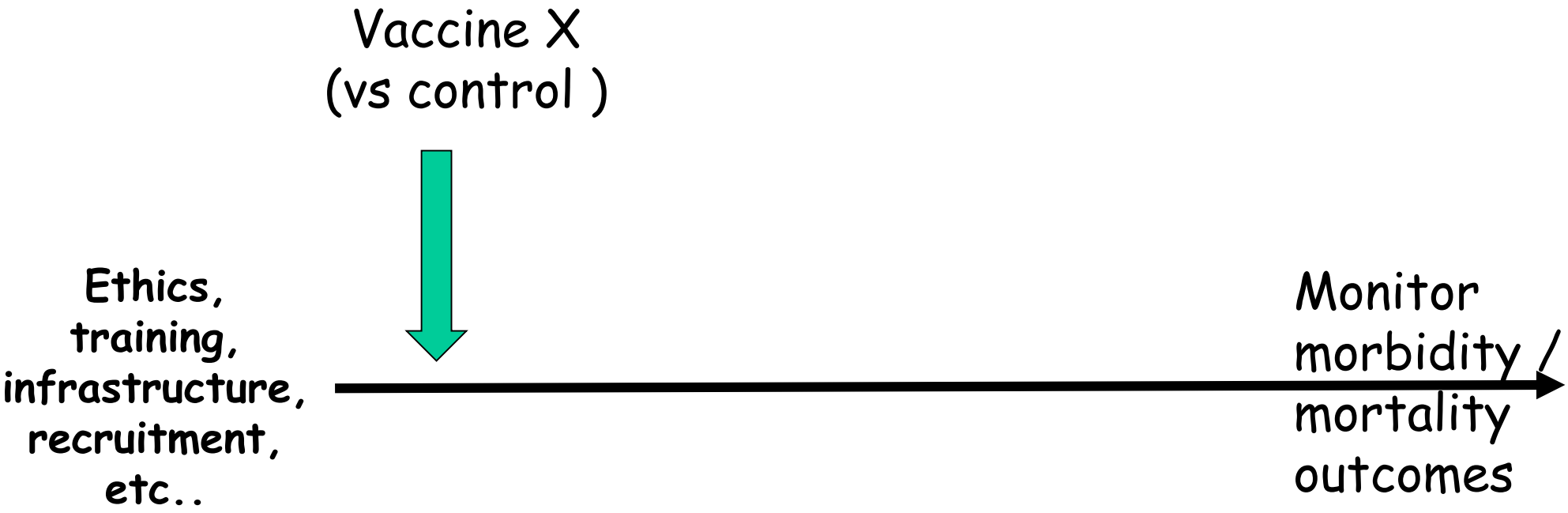
or

In terms of outcome (eg causes of morbidity mortality…)

Major implications for sample collection and technical laboratory support (immunological, diagnostic ….)

**These are linked** - knowledge of clinical outcomes may suggest immunological mechanisms – and *vice versa*….

# A basic explanatory trial design



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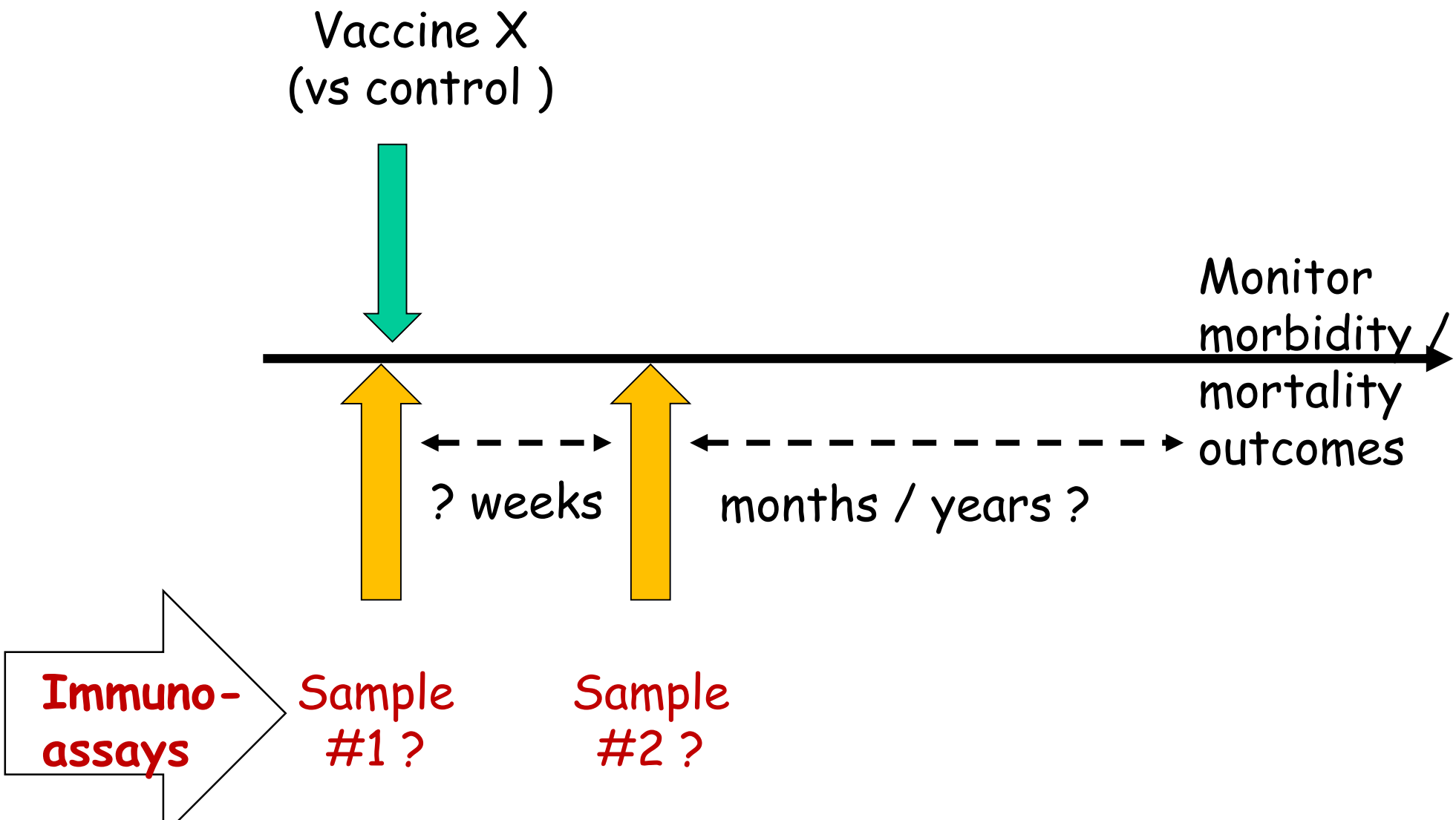

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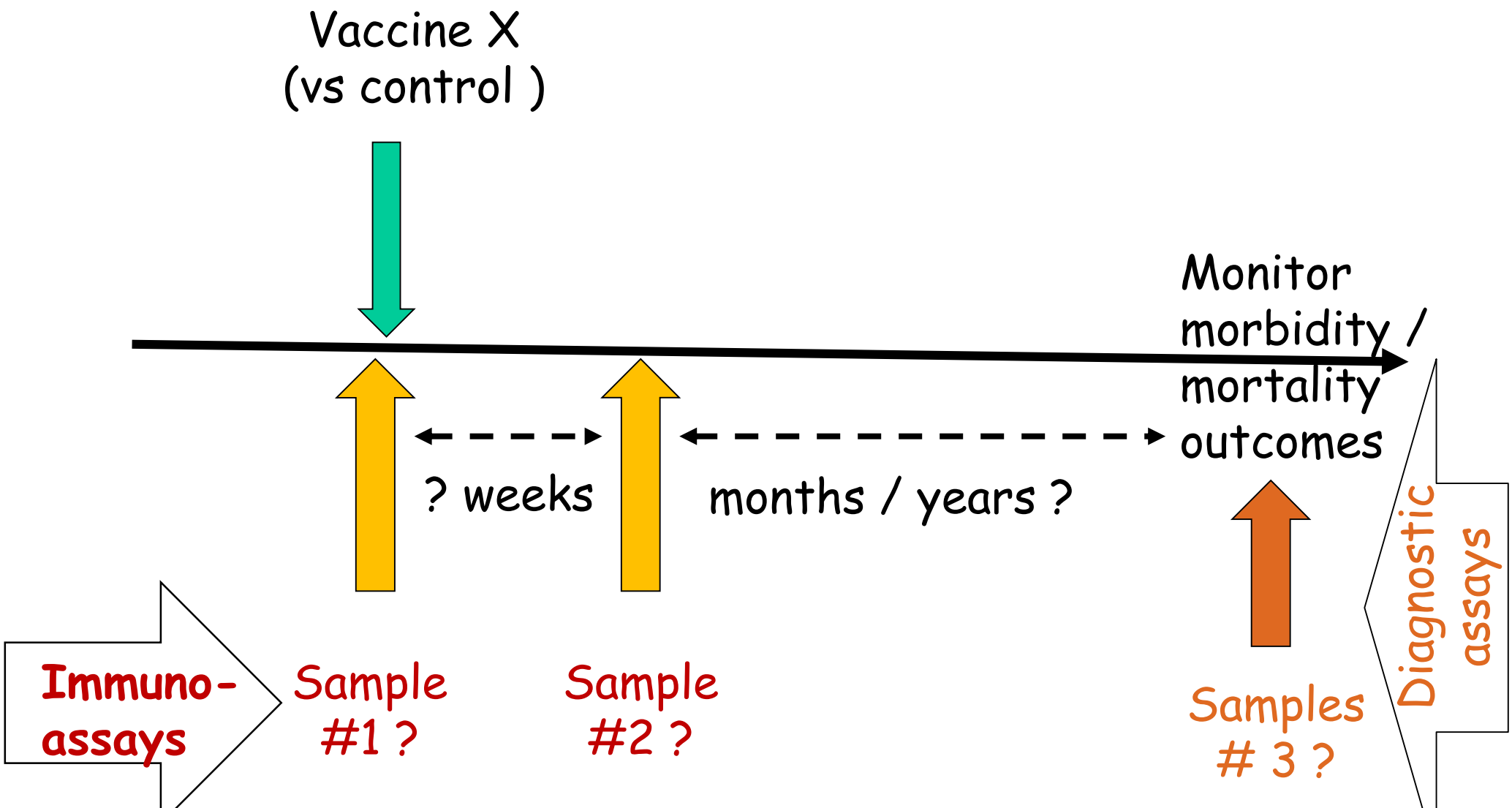

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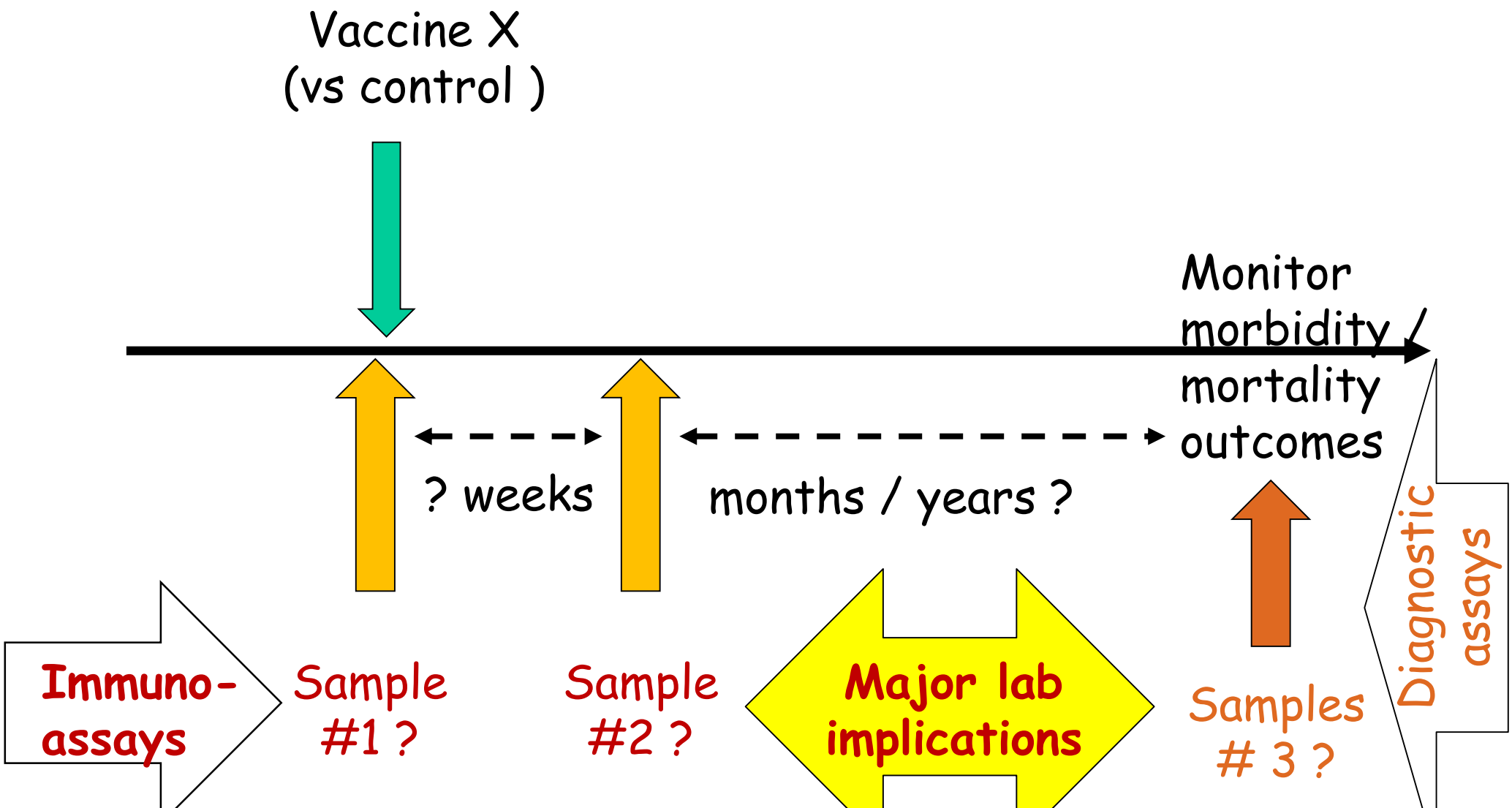
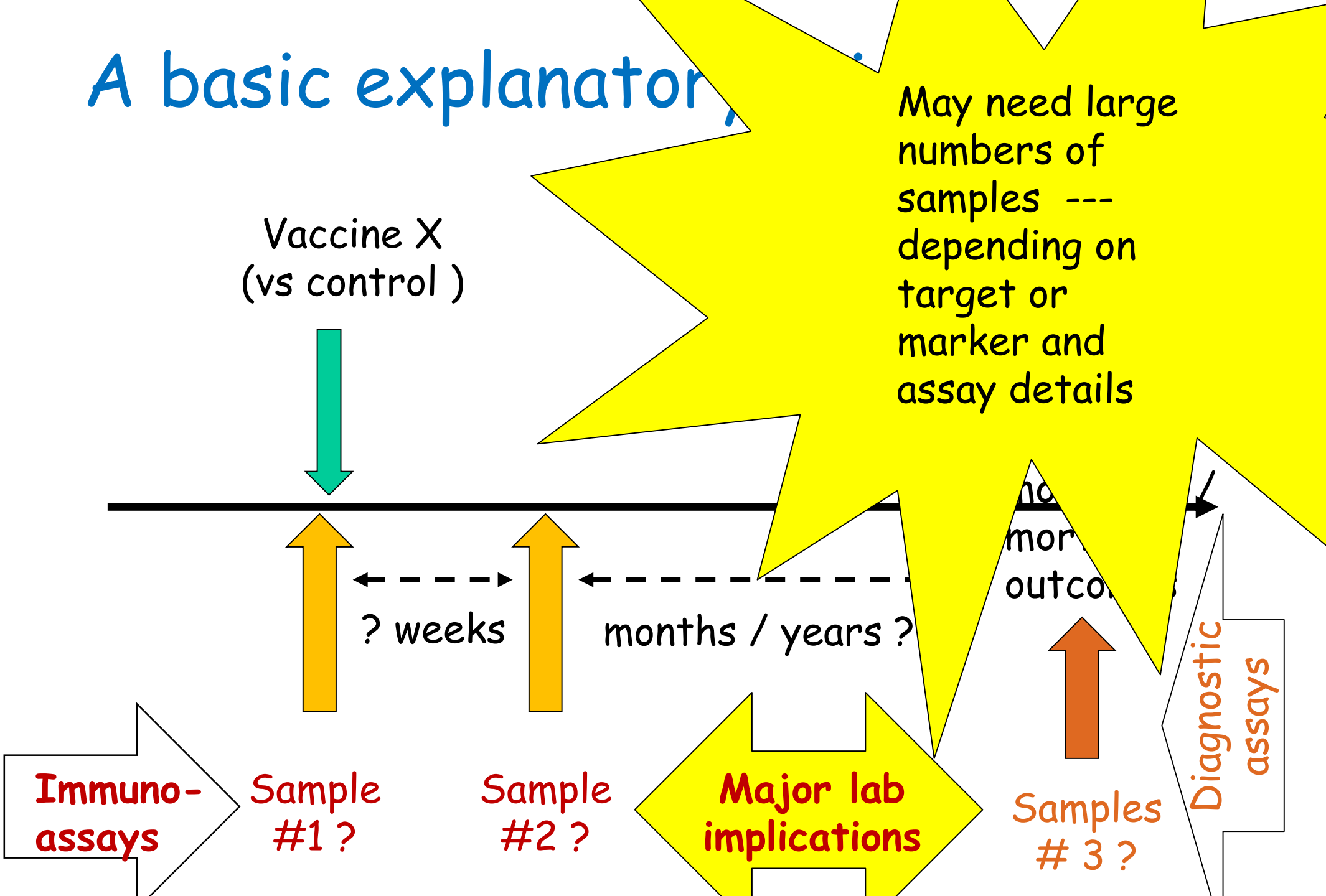
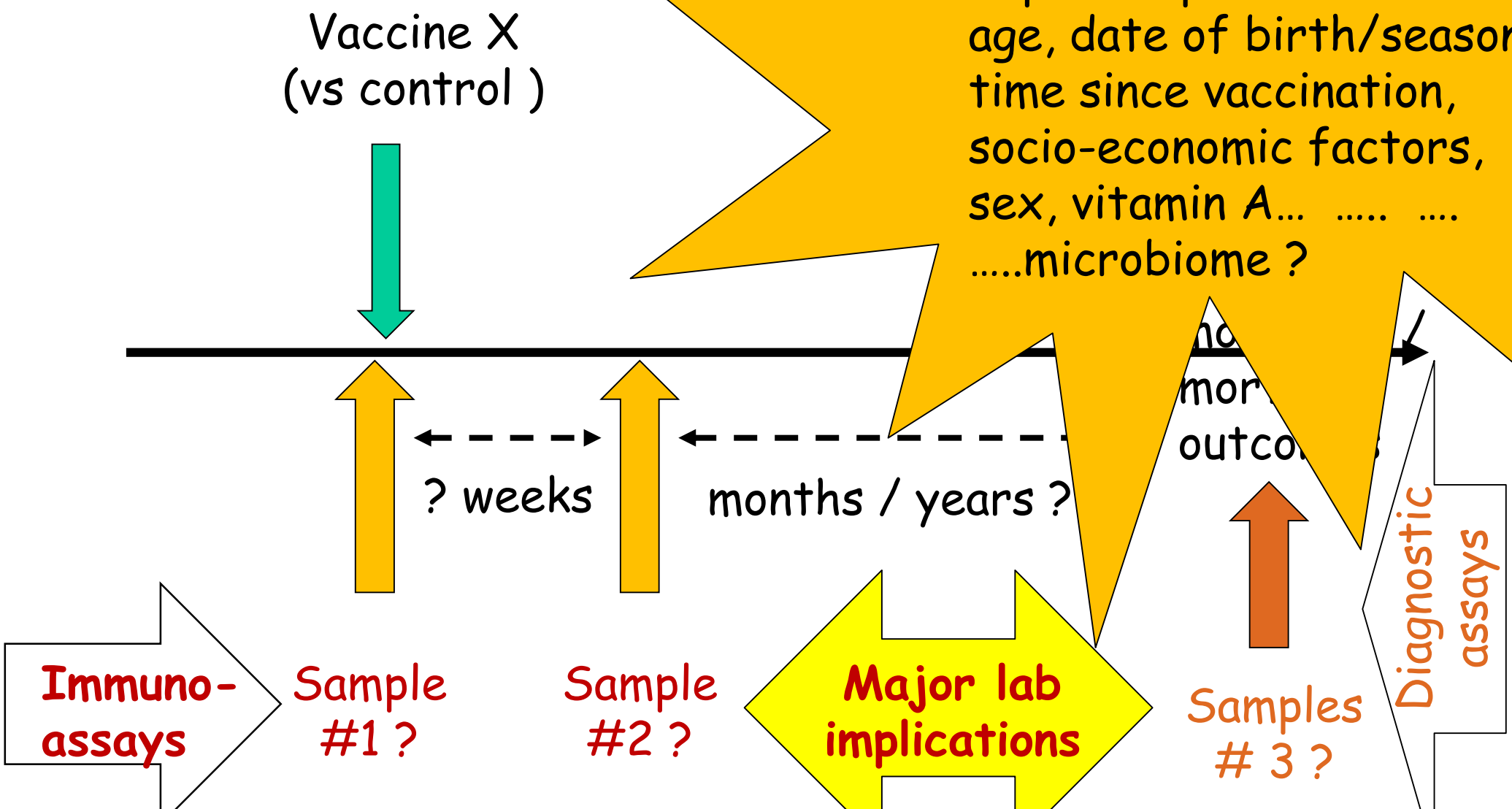


# A basic explanatory ...



# A basic explanator

**Also need info on:**
prior immune status,
exposure post vaccination,
age, date of birth/season,
time since vaccination,
socio-economic factors,
sex, vitamin A… ….. ….
…..microbiome ?



# Estimatory trials

**Major implication for sample size….**

- As function of
  - background risk of morbidity / mortality
  - ….and expected effect size.
  - **and what about duration of effect …. ?**

# Estimatory trials

**Major implication for sample size….**

- As function of
  - background risk of morbidity / mortality
  - ….and expected effect size.
  - **and what about duration of effect …. ?**
- Need at least two similar trials in ecologically different settings to reveal heterogeneity

Because any "non-target" effects likely to be a function of background variety and magnitude of infection exposures….

# The heterogeneity headache
## (eg differences between populations)

1) To what extent is this to be expected ?

   function of

   -- background patterns of infection exposures

   -- "local" causes of morbidity and mortality

   -- genetics ?

2) Implications for study design

   multisite studies with identical protocols ?

3) Implications for policy

   population specific vaccination regimens ? (Ouch !)

# Pragmatic trials – for policy

**Need to consider full schedule implications**

- Current schedules and their rationale
- Logistics, convenience, cost, sustainability ….
- All the other vaccines
- Local disease / mortality risks by age
- And the heterogeneity issue ….

# Basic EPI schedule (since 1970s)
# Purposefully simple

| | Birth (or "first contact") | 6 weeks | 10 weeks | 14 weeks | 9 months |
|---|---|---|---|---|---|
| **BCG** | ✓ | | | | |
| **DTP** | | ✓ | ✓ | ✓ | |
| **Polio (OPV)** | | ✓ | ✓ | ✓ | |
| **Measles** | | | | | ✓ |

# "EPI schedule" – today

## more antigens

## *and considerable variation between countries*

| Eg **Mali** | Birth (or "first contact") | 6 weeks | 10 weeks | 14 weeks | 9 months | |
|---|---|---|---|---|---|---|
| **BCG** | ✓ | | | | | |
| **DTPHibHBV** | | ✓ | ✓ | ✓ | | |
| **Polio (OPV)** | ✓ | ✓ | ✓ | ✓ | | |
| **PCV** | | ✓ | ✓ | ✓ | | |
| **Rota** | | ✓ | ✓ | (✓) | | |
| **IPV** | | | | ✓ | | |
| **Measles** | | | | | | ✓ |
| **YF** | | | | | | ✓ |
| **Vit A** | | | | | 6 mo | 12mo |

# "EPI schedule" – today

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| **Polio (OPV)** | √ | √ | √ | √ | | |
| **PCV** | | √ | √ | √ | | |
| **Rota** | | √ | √ | (√) | | |
| **IPV** | | | | √ | | |
| **Measles** | | | | | √ | |
| **YF** | | | | | √ | |
| **Vit A** | | | | | 6 mo | 12mo |

Also:
Meningococcus
MMR

Malaria … ?

# "EPI schedule" – today

## more antigens

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| **DTPHibHBV** | | √ | √ | √ | |
| **Polio (OPV)** | √ | √ | √ | √ | |
| **PCV** | | √ | √ | √ | |
| **Rota** | | √ | √ | (√) | |
| **IPV** | | | | √ | |
| **Measles** | | | | | √ |
| **YF** | | | | | √ |
| **Vit A** | | | | | 6 mo 12mo |

Also:
Meningococcus
MMR

Malaria … ?

?

# Example of a current schedule (England and Wales, 2014)

| Vaccine | Birth ("high risk") | 2 months | 3 months | 4 months | 12-13 months | 2 – 17 yers | 3-4 years | 12-13 years (girls) | 13-18 years |
|---|---|---|---|---|---|---|---|---|---|
| BCG | √ | | | | | | | | |
| DTaP | | √ | √ | √ | | | √ | | |
| IPV | | √ | √ | √ | | | √ | | √ |
| Hib | | √ | √ | √ | √ | | | | |
| PCV | | √ | | √ | √ | | | | |
| Rota | | √ | √ | | | | | | |
| MenC | | | √ | | √ | | | | √ |
| MMR | | | | | √ | | √ | | |
| Flu | | | | | | √ | | | |
| HPV | | | | | | | | √ | |
| Td | | | | | | | | | √ |

BCG = bacillus Calmette Guerin
DTaP = diphtheria, tetanus, acellular pertussis
IPV = Inactivated (killed) polio (trivalent)
Hib = Haemophilus influenza B
PCV = Pneumococcal conjugate

Rota = Rotavirus
MenC = Meningococcus type C
MMR = measles, mumps, rubella
Flu = influenza
HPV = Human papilloma virus
Td = Tetanus and diphtheria toxoids

# Typical DTP schedules - by income and region

| Income level | WHO region | DTP visits | | | | | | Typical vaccine |
|---|---|---|---|---|---|---|---|---|
| | | 1p | 2p | 3p | Boost ~1yr | Boost ~5yrs | Boost ~15yrs | |
| Low / Middle | Africa<br>South East Asia<br>Western Pacific | 6w | 10w | 14w | - | - | - | DT**wP**HibHepB |
| | Eastern Europe | 2m | 3m | 4m | 18m | - | - | |
| | Eastern Mediterranean<br>Latin America | 2m | 4m | 6m | 18m | ~5yrs | - | |
| High | North America<br>Western Europe<br>Western Pacific | 2m | 4m | 6m | 12m -18m | ~5yrs | 15yrs (few) | DT**aP**HibIPV |

# Key requirements (for trials - and the entire subject)

Need for specificity
about the non-specificity

Inclusion of all-cause
morbidity and mortality

Implications - good diagnostic facilities and large numbers .....
expensive.....
major and difficult priority issues ....

# Intervention opportunities

New vaccine versus placebo

| | |
|---|---|
| Vaccine X versus nil | (eg BCG in Denmark) |
| | (eg early versus delayed BCG) |
| | (eg early measles … till 9 months |
| Comparison of vaccines | (eg acellular P versus whole cell P) |
| Comparison of timing / order | (eg DTP3 before / after MSL) |
| | (eg BCG before / after DTP1) |
| | other schedule variants |