

Monitoring Vaccine Safety & Effectiveness

Edward Parker

Learning objectives

- Explain why **post-licensure monitoring** is essential following randomised trials
- Describe key methods for:
 - vaccine **safety** surveillance (pharmacovigilance)
 - vaccine **effectiveness** evaluation
- Understand potential sources of bias and uncertainty in observational data
- Interpret risk–benefit trade-offs in vaccination programmes
- Consider **best practice** on communication related to vaccine safety

Structure

- **Lecture: Monitoring vaccine safety & effectiveness** – 75 minutes
- **Break:** 15 minutes
- **Practical:** Policy simulation – 90 minutes

First principles

Vaccines differ from most other medicines

Given to people who are (usually) healthy

→ lower tolerance for harms

Used to prevent future conditions

→ benefit may never be directly experienced

→ public perceptions of benefits may be low

Given to large numbers of people

→ increased volume of adverse event reports

→ very rare adverse events are inevitable (whether causal/coincidental)

→ difficult to establish control groups for real-world studies

Risk/benefit balance is dynamic

→ if the disease disappears, so do the benefits

Don't just benefit the recipients

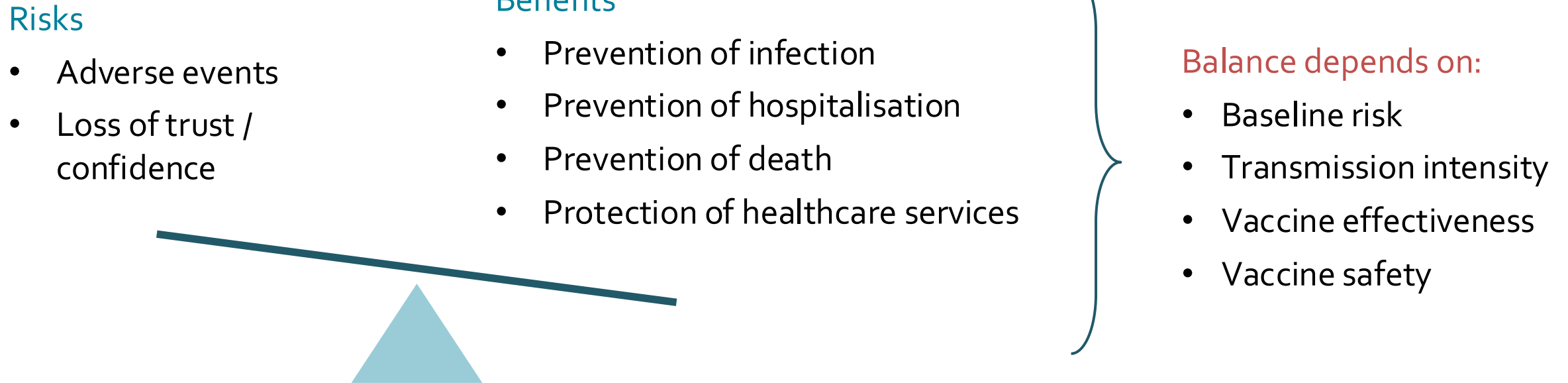
→ wider population may benefit indirectly

→ drops in uptake issues can impact society through disease resurgence

Other treatments

- Given to people who are ill
- Used to treat existing conditions
- Individual benefit often immediate
- Higher tolerance for harms may be acceptable

Balancing risks and benefits



Vaccine policy is not about determining whether a vaccine is "safe" or "unsafe"

It is about determining whether the **benefits outweigh the risks** in a **particular population and context** (and whether obtaining these benefits is achievable and cost effective)

What is known (and unknown) after clinical trials?

Phases of vaccine development

Pre-clinical

Careful testing in lab and in animal models

Phase I

Testing in 10–100 healthy volunteers

- Is the vaccine safe?
- What is the optimal dose?



Phases of vaccine development

Pre-clinical

Careful testing in lab and in animal models

Phase I

Testing in 10–100 healthy volunteers

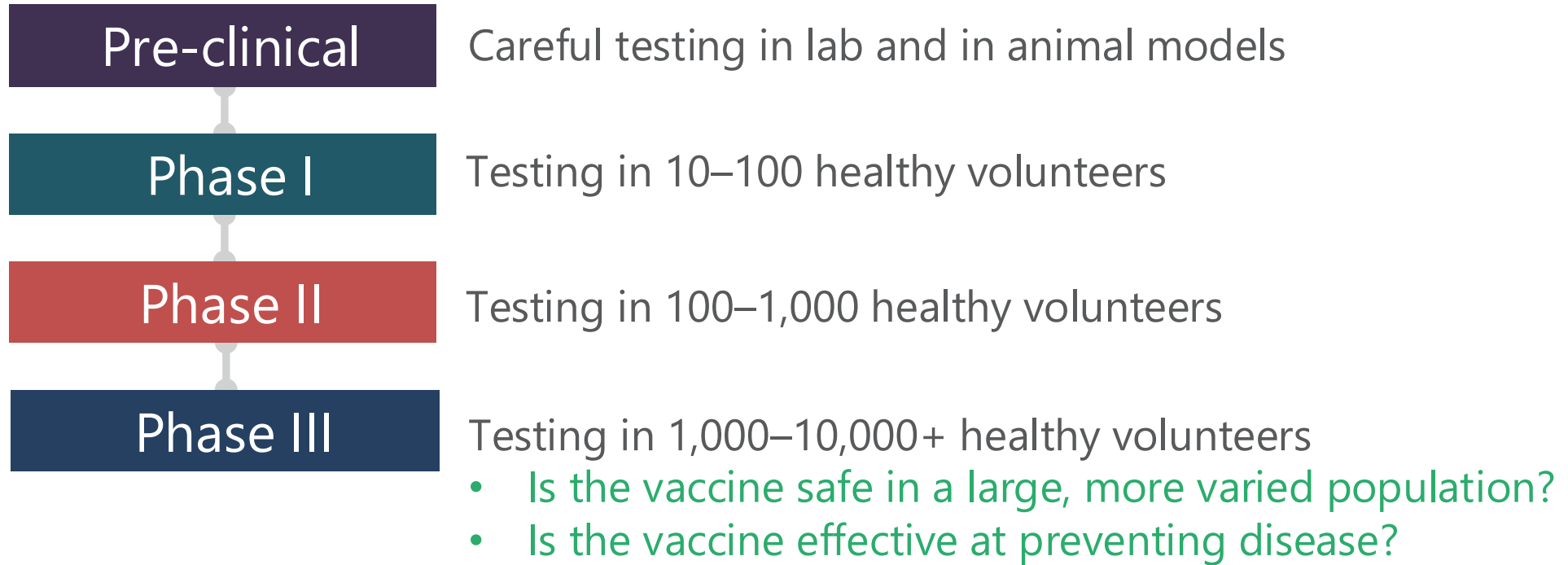
Phase II

Testing in 100–1,000 healthy volunteers

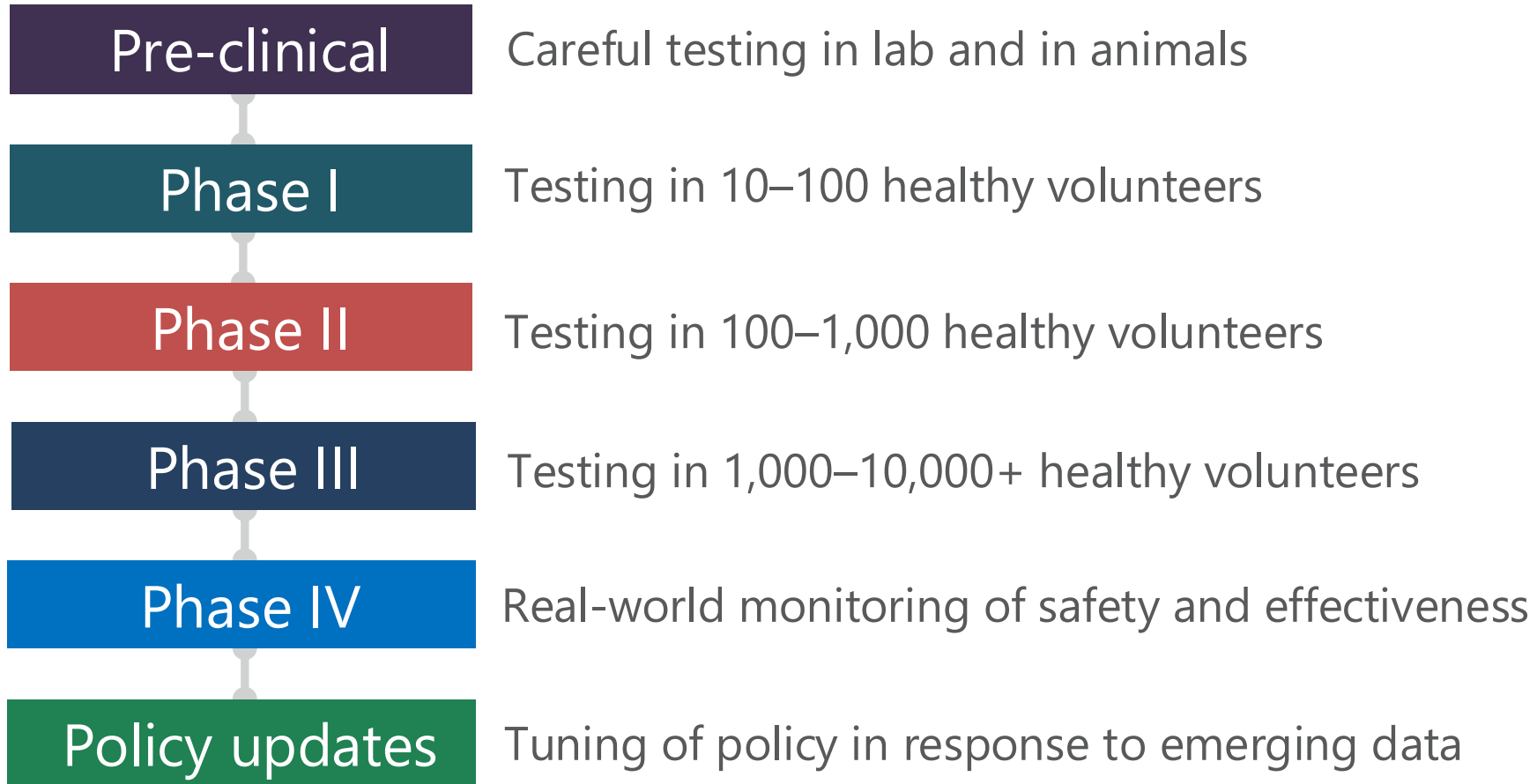
- Is the vaccine safe?
- Does the vaccine induce a strong immune response?



Phases of vaccine development



Phases of vaccine development



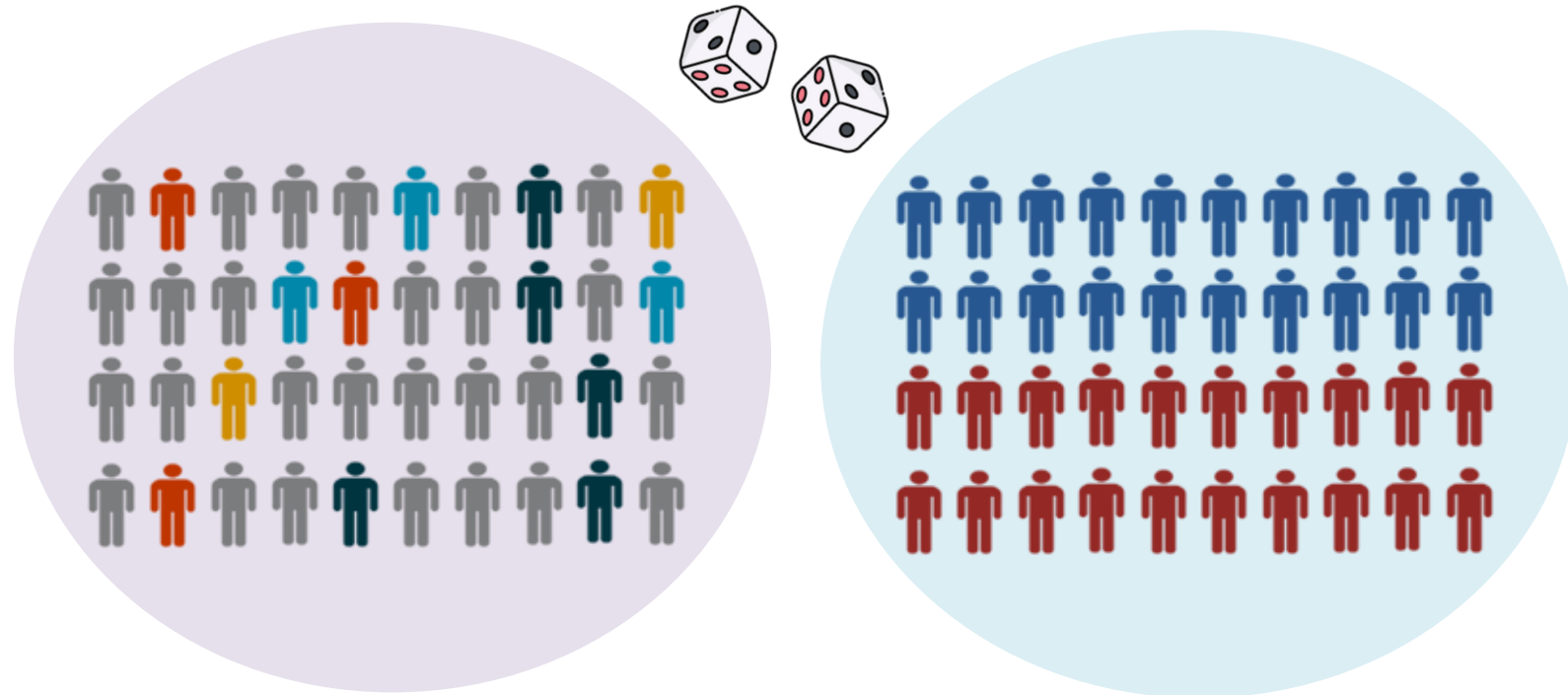
Strengths of randomised controlled trials

Randomisation

- Ensures vaccine and control groups are similar with respect to health status, behaviour, and healthcare access

Blinding

- Trial participants and researchers are not aware of which individuals received the intervention or control, **minimising bias**



Information provided by clinical trials

Immunogenicity



Antibody and cellular responses

Efficacy



Protection (usually against mild outcomes)

Safety



Common adverse events

Benefit-risk



Based on trial population, epidemiological context, and available follow-up

Questions that remain after clinical trials

Are any rare adverse events caused by the vaccine?

How well does the vaccine work...

... in routine care?

... over longer-term timeframe (beyond a few months)?

... against severe outcomes too rare to be seen in trial populations?

... in different population subgroups (including those excluded from trials)?

... against emerging variants?

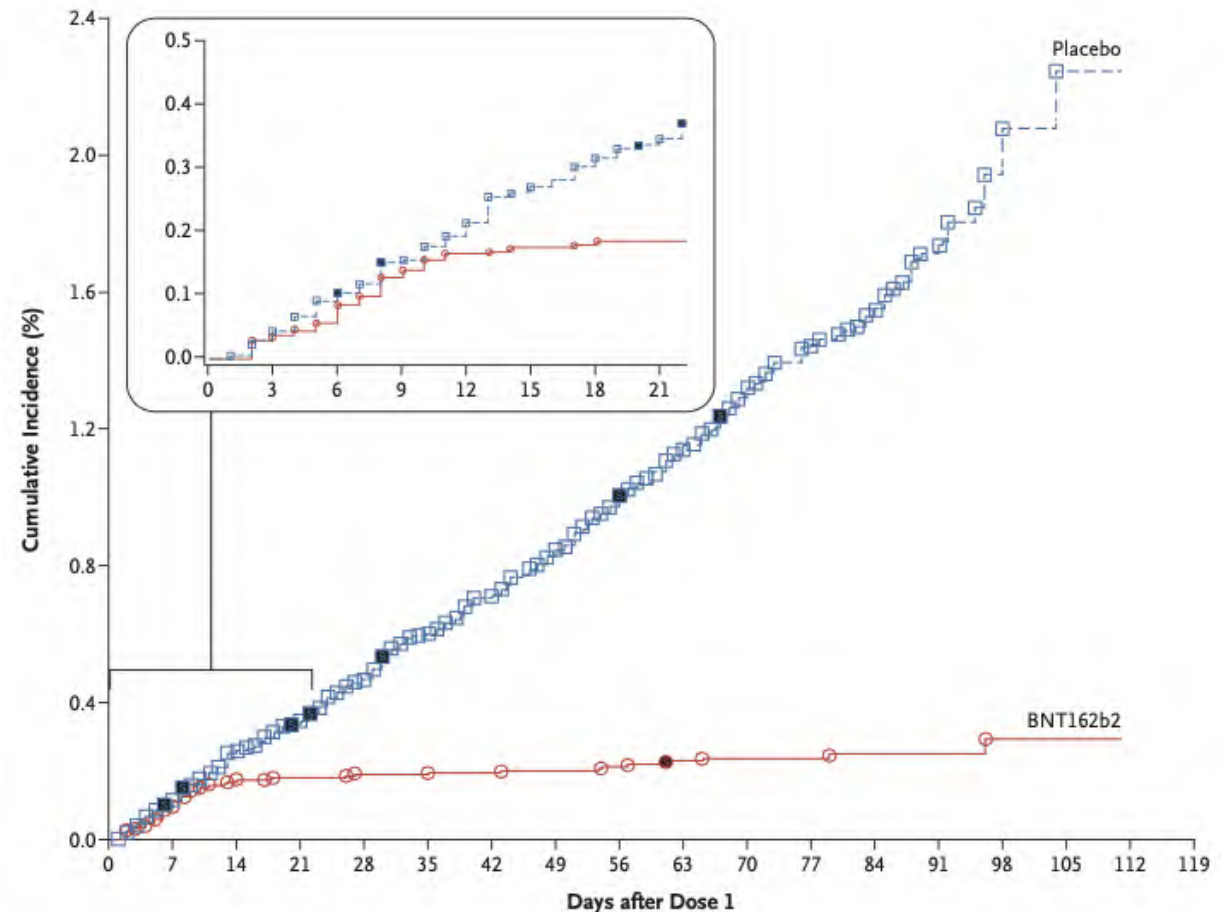
We can only start to explore these after vaccines are rolled out

Pfizer-BioNTech's BNT16b2 phase 3 trial

Design

- Multinational, placebo-controlled study
- 43,548 participants
 - 21,720 vaccine
 - 21,728 placebo
- 2 doses administered 21 days apart

Cumulative incidence of COVID-19 by study arm

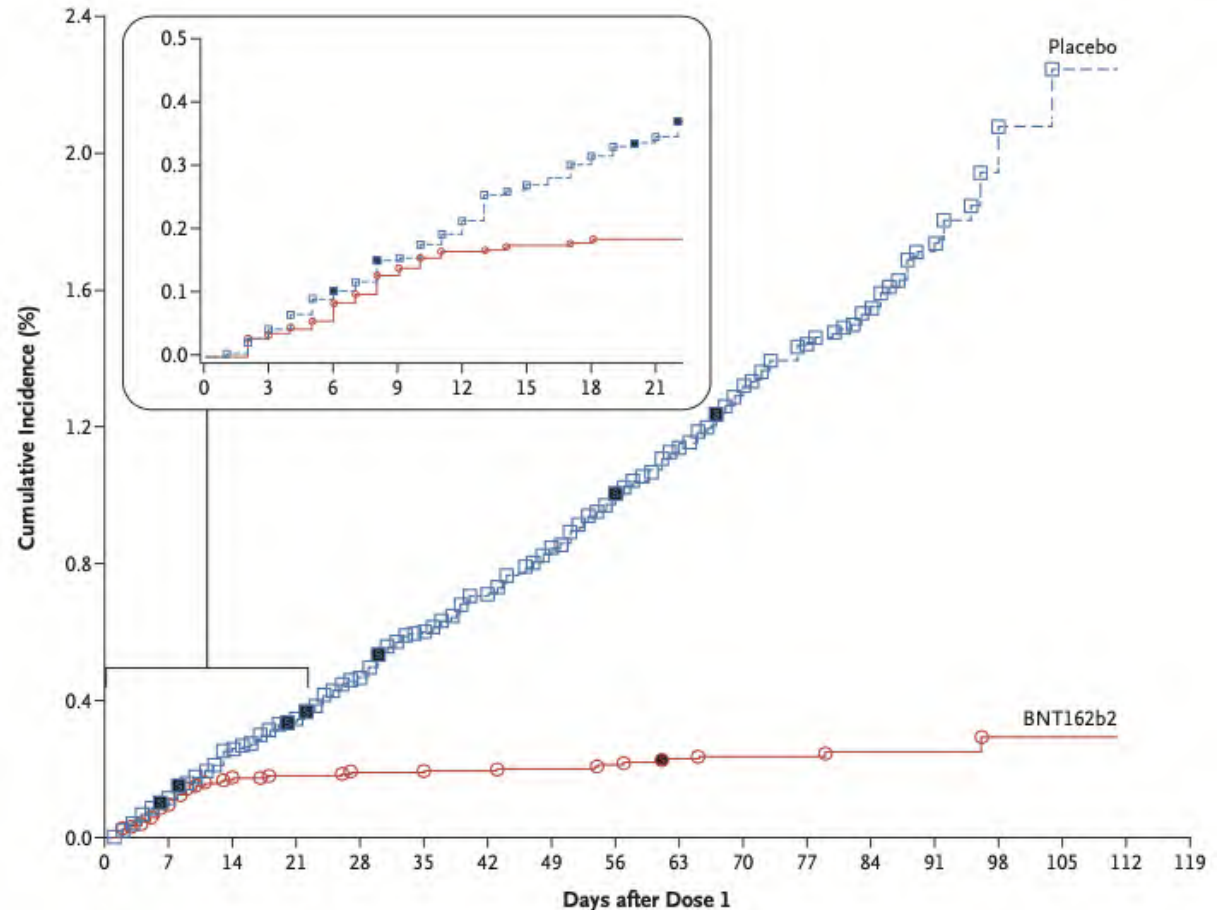


Pfizer-BioNTech's BNT16b2 phase 3 trial

Efficacy

- 95.0% efficacy (95% CI 90.0–97.9%) against symptomatic COVID-19
 - 8 cases in vaccine group
 - 162 cases in placebo group
- Consistent protection across subgroups (age, ethnicity, comorbidities)
- 10 cases of severe COVID-19 (9 in placebo group)

Cumulative incidence of COVID-19 by study arm



Pfizer-BioNTech's BNT16b2 phase 3 trial

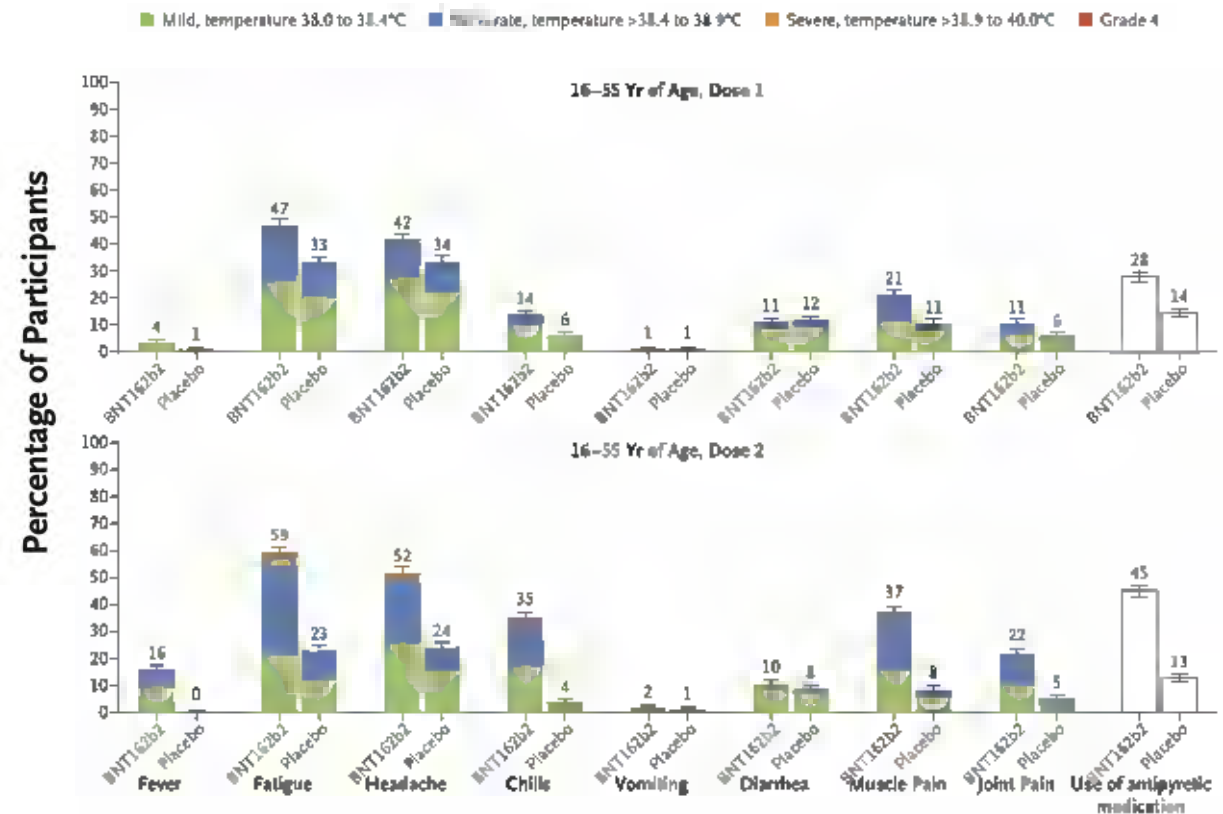
Safety

- No major safety concerns
- Local and systemic reactogenicity more common in vaccine group than placebo group (mostly mild to moderate)

Grading of adverse events in clinical trials

Grade	Description	Example
Grade 1	Mild	Injection-site pain, mild fatigue, headache
Grade 2	Moderate	Fever requiring medication, symptoms limiting usual activities
Grade 3	Severe	Significant symptoms preventing normal daily activities
Grade 4	Life-threatening	Intensive care admission, severe anaphylaxis
Grade 5	Death	Fatal adverse event

Systemic adverse events and medication use after doses 1 and 2



Pfizer-BioNTech's BNT16b2 phase 3 trial

BBC news headline, 09 November 2020

Important caveats

- Median follow-up after second dose of **~2 months**
- Primary efficacy based on mild endpoint
- ~60% of population <55 years of age
- Exclusion of individuals with high-risk comorbidities (e.g. immunosuppression)

NEWS

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Health

Covid vaccine: First 'milestone' vaccine offers 90% protection

9 November 2020 6116 Comments

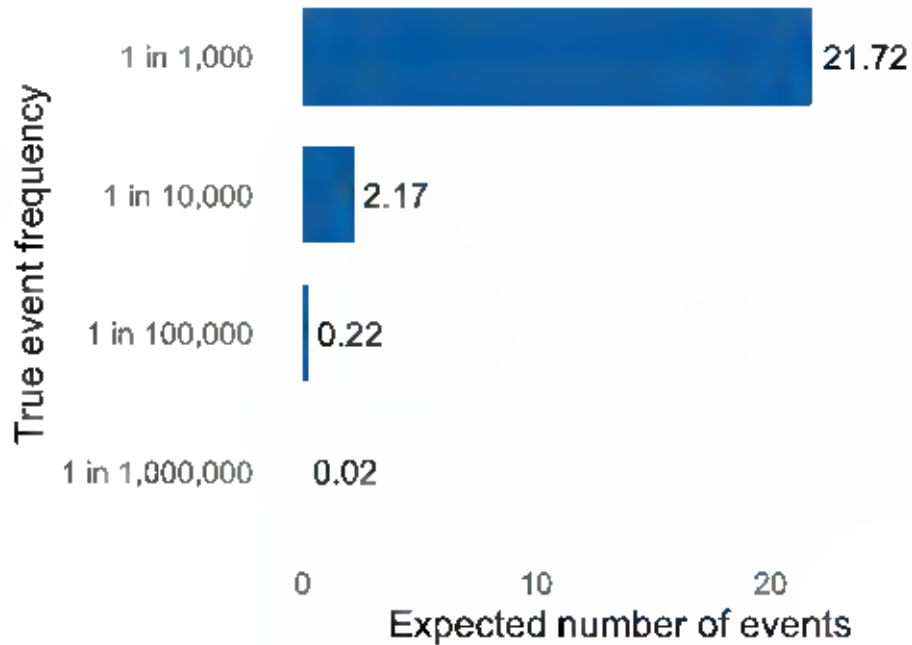
Coronavirus



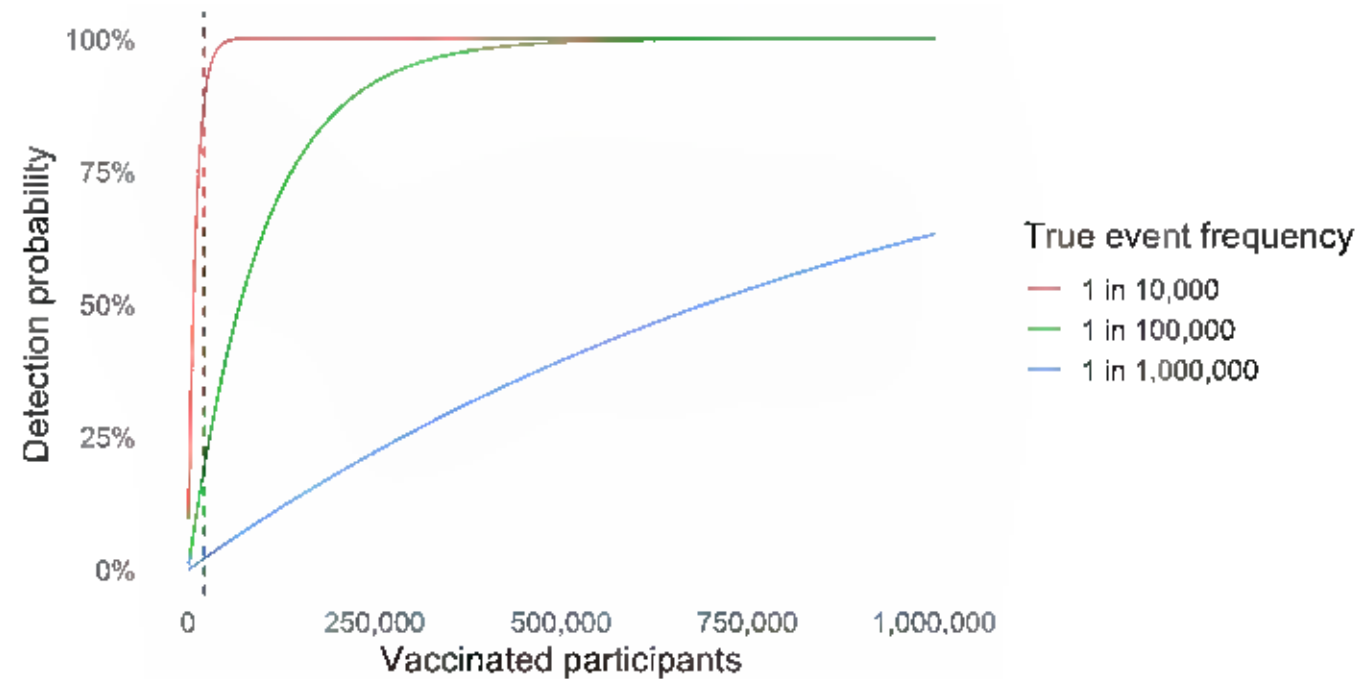
GETTY IMAGES

The challenge of rare adverse events

Expected vaccine-related adverse events among 21,720 vaccine recipients



Chance of detecting at least 1 adverse event with increasing study size (dotted line indicates 21,720)



Absence of evidence $\neq$ evidence of absence

A trial with 21,720 vaccinated participants would usually observe zero events occurring at a rate of 1 per 100,000 doses

The rule of 3

If no adverse events are observed in a clinical trial...

...the 95% confidence interval will exclude a risk of

$$\frac{3}{N}$$

...where N is the number of vaccinated individuals

Example

- A vaccine trial includes 30,000 vaccinated individuals
- If there are no cases of a given adverse event, the trial can reasonably only rule out risks larger than **1 in 10,000**

Questions

Vaccine safety monitoring

Imagine the following...

A winter booster campaign in the UK vaccinates **2 million adults aged ≥ 65 years** over its first weekend.

Over the following week, reports emerge of...

- strokes,
- heart attacks,
- pulmonary embolisms, and
- deaths

... among recently vaccinated individuals.

How concerned should we be?

We would expect **~1,800 deaths** per week in people ≥ 65 years
(12–13 million people, 0.8–1.0 deaths per 1000 per week)

Core objectives of post-licensure safety monitoring

- **Detect** potential safety concerns as early as possible
- **Quantify** the risk of suspected adverse events
- **Determine** whether observed associations are likely to be causal
- **Identify** population groups at increased risk
- **Inform** vaccine policy and clinical recommendations
- **Support** public confidence through transparent communication

Key terminology

Pharmacovigilance

The science and activities involved in detecting, evaluating, and preventing adverse events related to medicines and vaccines

Adverse Event Following Immunisation (AEFI)

Any untoward medical occurrence after a vaccination (causal or coincidental)

Adverse Event of Special Interest (AESI)

A pre-specified adverse event considered biologically plausible or of particular concern (e.g. myocarditis, Guillain-Barré syndrome)

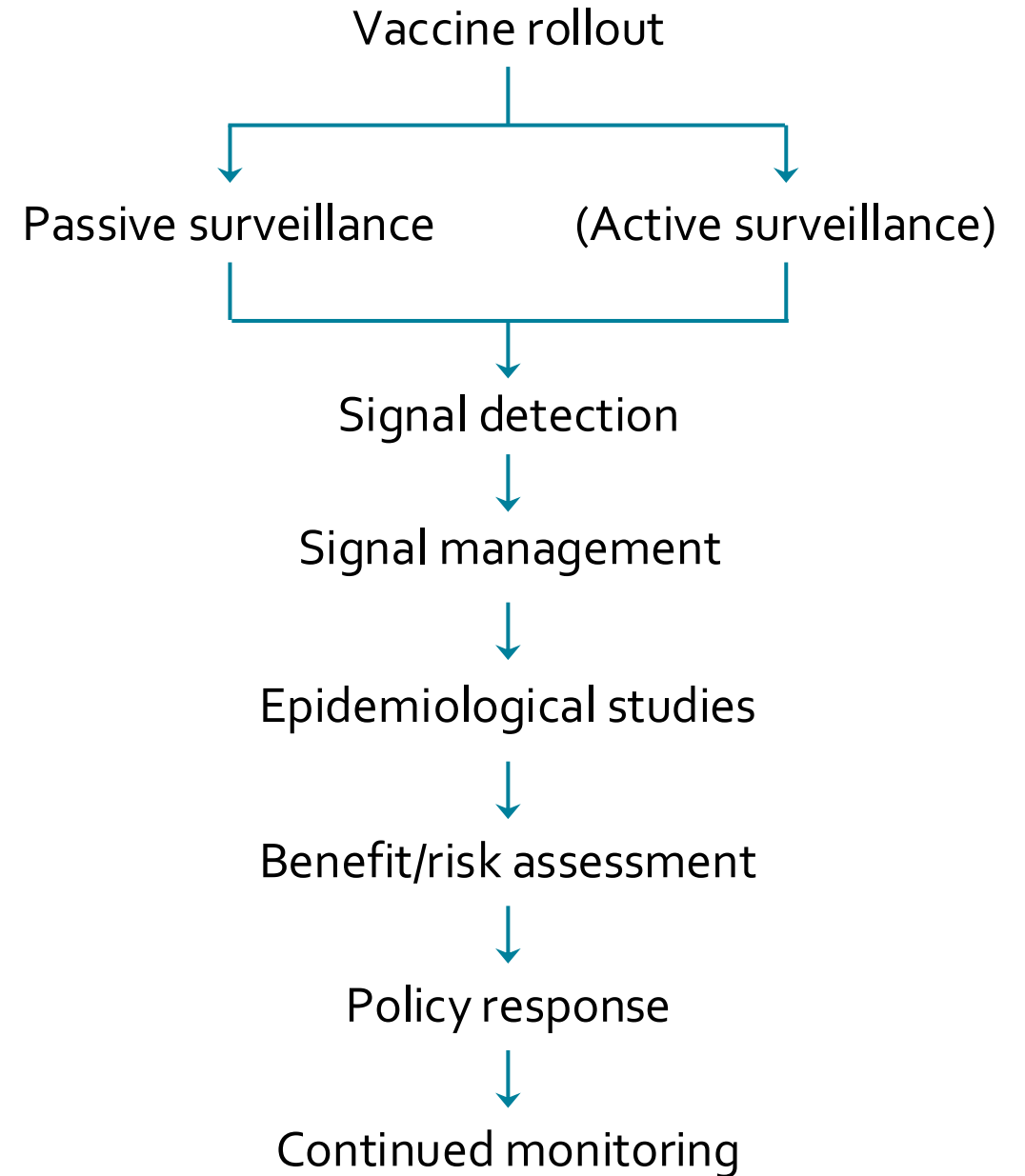
Safety signal

A pattern of observations suggesting a new potentially causal association between a vaccine and an adverse event that requires further assessment

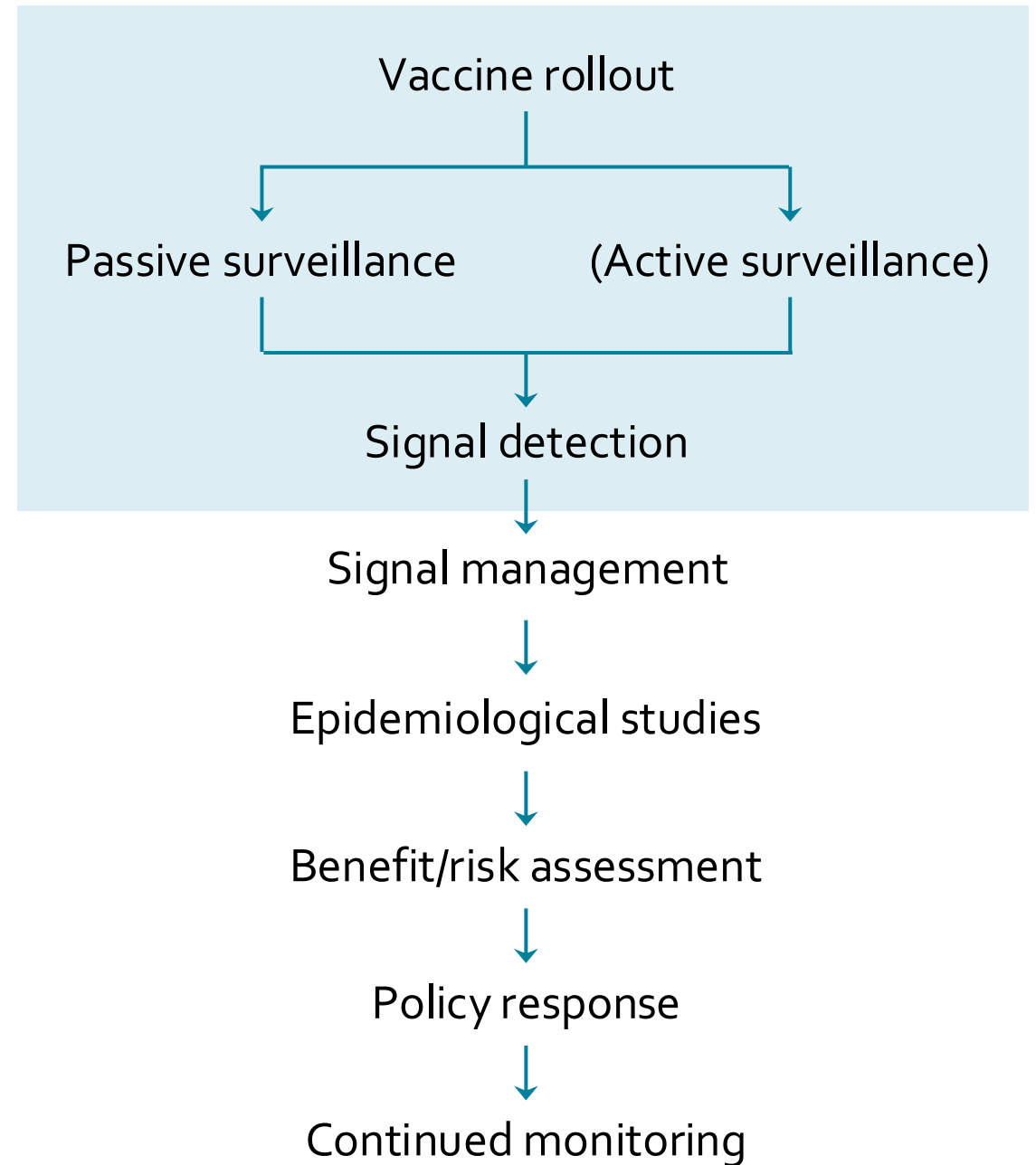
Signal detection

The process of identifying unusual patterns of adverse events that require further investigation

The pharmacovigilance cycle



The pharmacovigilance cycle



Passive surveillance – data collection

What it involves

Spontaneous reporting of suspected adverse events following vaccination by healthcare professionals, members of the public, and vaccine manufacturers (required by regulators)

Information typically collected

- Individual characteristics: age, sex, medical history
- Vaccine information: product, dose number, date
- Adverse event: diagnosis/symptoms, date of onset, severity

Examples

- Yellow Card (UK)
- Vaccine Adverse Event Reporting System (USA)
- EudraVigilance (European Union)

Passive surveillance – signal detection

Qualitative approaches

Evaluate:

- Clinical presentation and severity
- Timing relative to vaccination
- Biological plausibility
- Similarities across cases / clusters

Resource intensive, particularly in context of large campaigns

Quantitative approaches

Evaluate:

- Case numbers and distribution to detect statistical signals – has a pre-defined threshold been reached?
- Examples:
 - Disproportionality analysis
 - Observed vs Expected

Greater potential for automation, but false positives may occur

Both should ideally be carried out in parallel

Disproportionality analysis

- Is a particular vaccine–event combination reported more frequently than expected within the reporting database?
- Further investigation if pre-defined threshold is reached

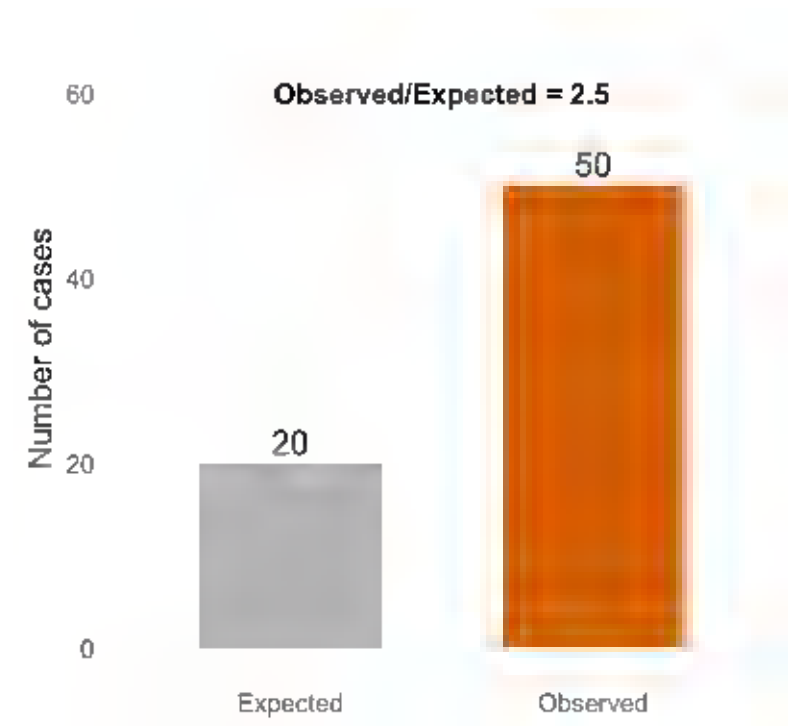
	Reports for event of interest	Reports for all other events	Total
Vaccine of interest	A	B	A + B
All other vaccines	C	D	C + D
Total	A + C	B + D	A + B + C + D

Observed vs expected analysis

Summary

- Compare the number of observed events after vaccination with the number expected based on background rates
 - Observed: obtained from passive surveillance databases (or active surveillance / health records)
 - Expected: population incidence and knowledge of number of doses given
- Requires assumptions of under-reporting rate in passive surveillance data
- Often requires stratification (by age, sex, ethnicity)
- May be used for pre-defined AEsIs or to evaluate signals from other sources

Hypothetical calculation of observed/expected ratio



Passive surveillance – strengths / limitations detection

Strengths	Limitations
• Rapid reporting / analysis • Broad population coverage • Can identify unexpected signals for further evaluation	• Under-reporting • Reporting rates may be influenced by media attention • Variable reliability / completeness of reports • No unvaccinated comparators • Cannot confirm (or refute) causality • Many signals are false positives

Active surveillance

Background

- Proactive monitoring that addresses some of the limitations and biases of passive surveillance methods
- Typically look at subset of AEsIs in subset of populations

Primary data

- Data collected specifically for safety monitoring
- Enrollment and active follow-up of cohort ('cohort event monitoring')
 - e.g. MHRA Yellow Card Vaccine Monitor administering questionnaires to volunteers enrolled after vaccination)
- Hospital-based active reporting
 - e.g. IMPACT system in Canada involving trained nurses across network of paediatric hospitals)



Active surveillance

Background

- Proactive monitoring that addresses some of the limitations and biases of passive surveillance methods
- Typically look at subset of AEs in subset of populations

Secondary data

- Continuous monitoring embedded in routinely collected electronic health records
 - e.g. MHRA 'Rapid Cycle Analysis' for COVID-19 involving weekly monitoring of AEs using Clinical Practice Research Datalink (CPRD)

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2016; 25: 225–237
Published online 28 January 2016 in Wiley Online Library (wileyonlinelibrary.com) DOI 10.1002/pds.3966

REVIEW

Near real-time vaccine safety surveillance using electronic health records—a systematic review of the application of statistical methods[†]

Andreia Leite^{1*}, Nick J. Andrews² and Sara L. Thomas¹

¹*Faculty of Epidemiology and Population Health, London School of Hygiene & Tropical Medicine, London, UK*

²*Statistics, Modelling and Economics Department, Public Health England, London, UK*

Signal assessment – is the signal credible?

- Biological plausibility
- Consistency across countries and data sources

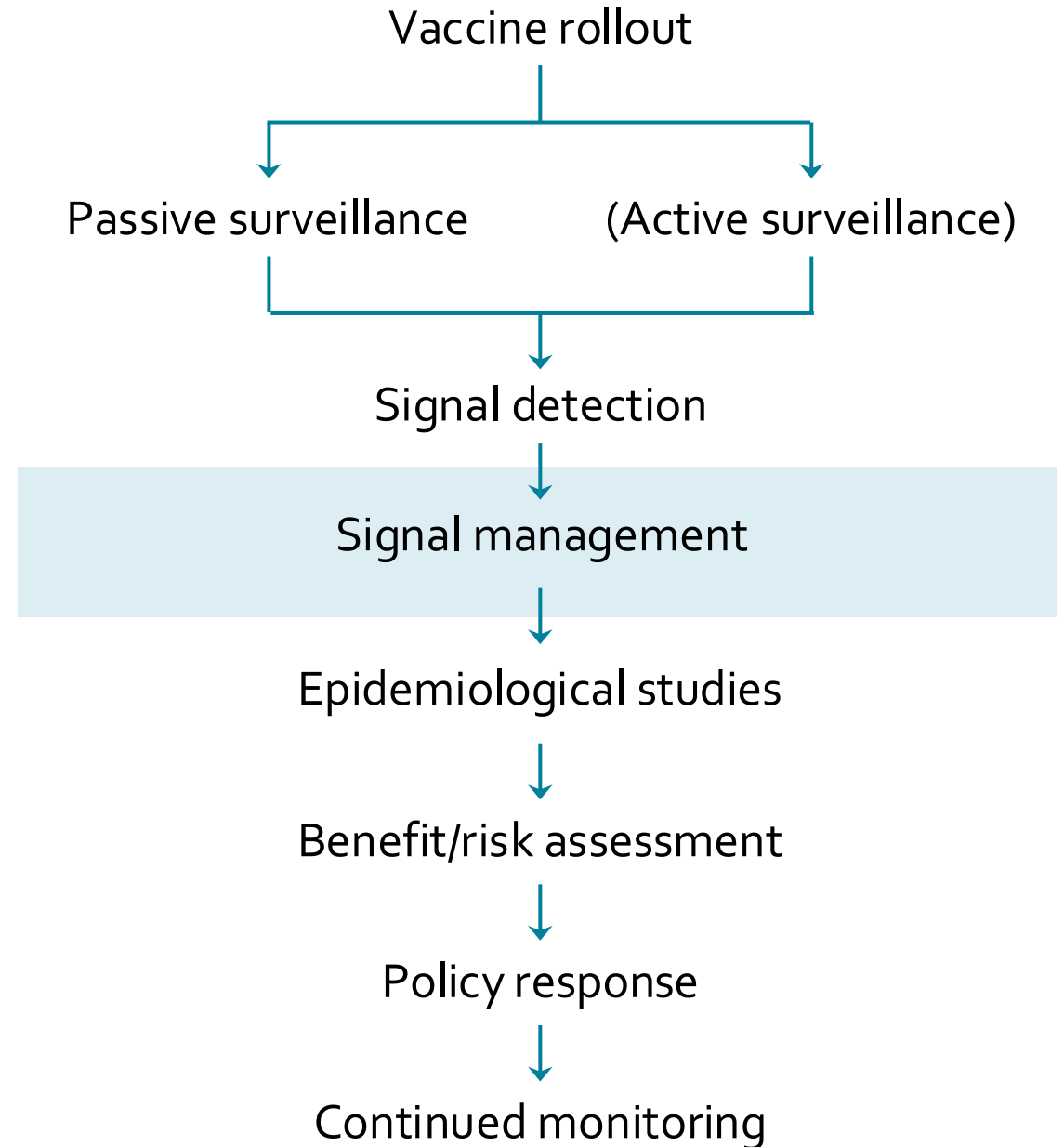
Signal prioritisation – how important is it?

- Severity of outcome
- Frequency of outcome
- Public health impact
- Potential implications for confidence in vaccination

Signal refinement – what exactly are we investigating?

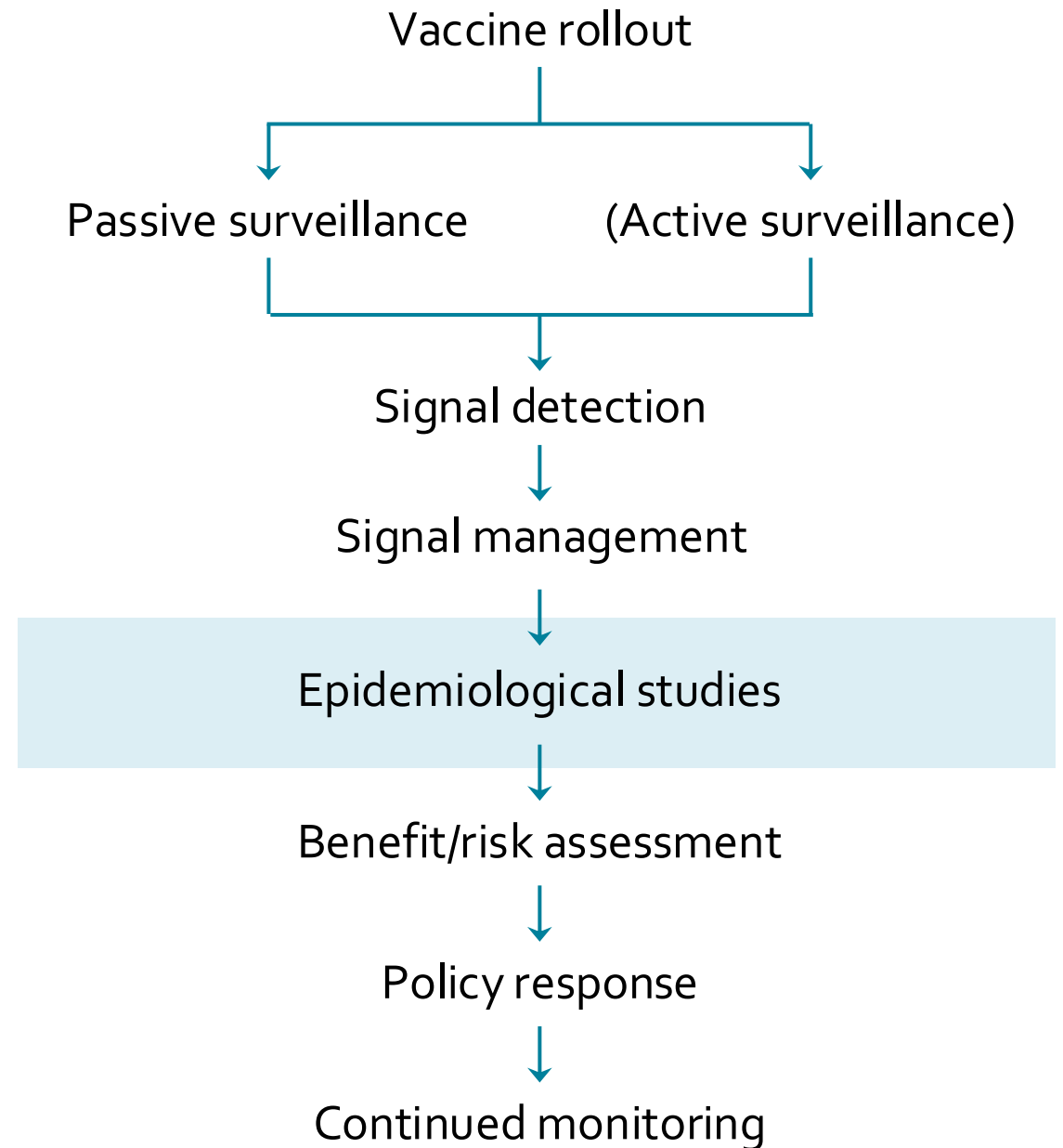
- Case definitions
- Risk windows
- Population groups affected
- Vaccine products involved

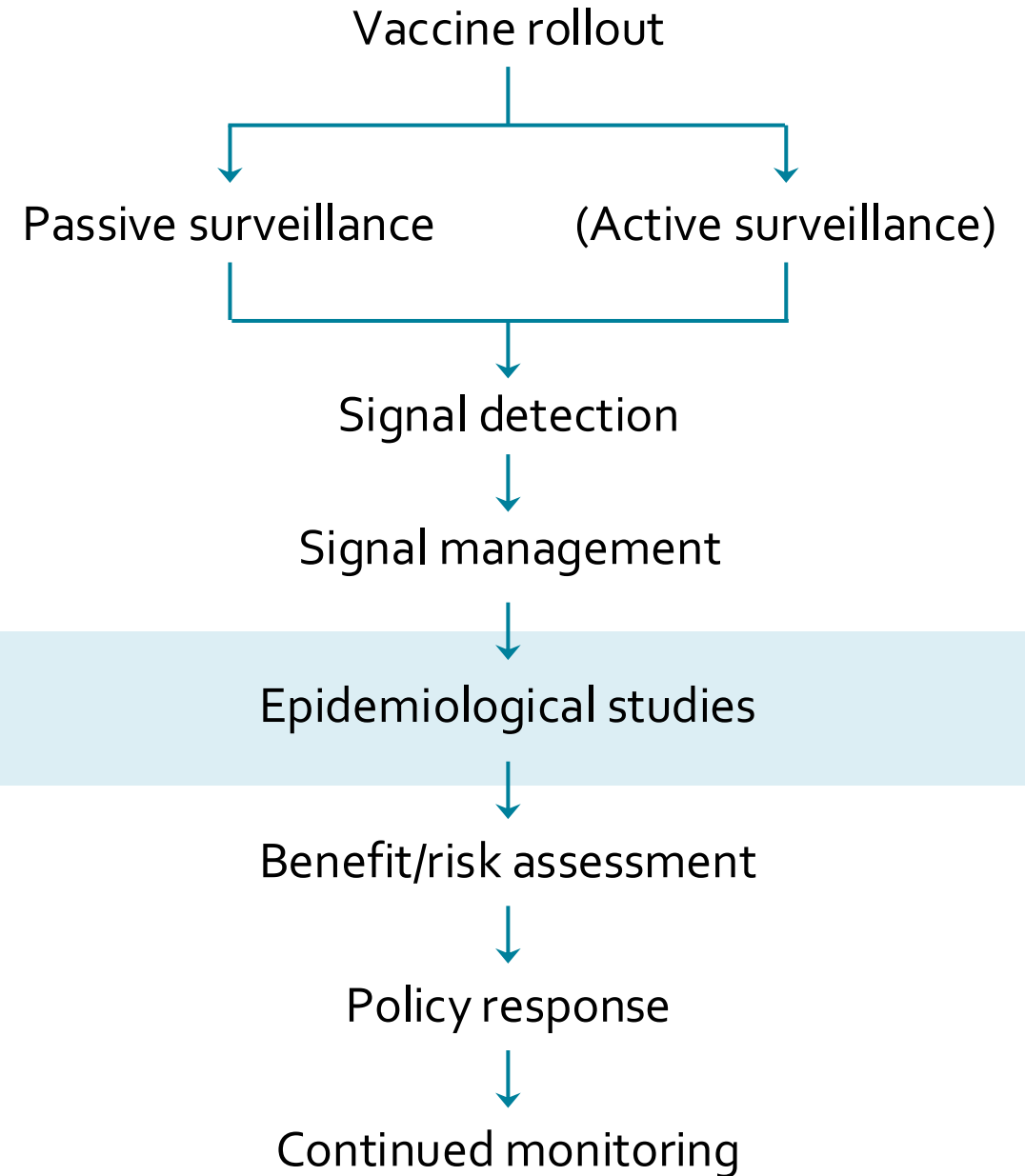
→ Refined signal suitable for epidemiological evaluation



Key questions

- Is risk actually increased?
- Is timing biologically plausible?
- How large is the increase in risk?
- Which population groups are affected?
- How does risk compare with the benefits?





Not all studies begin with safety signals

- MMR ~ autism
- COVID-19 vaccines ~ fertility

Common study designs

Cohort studies

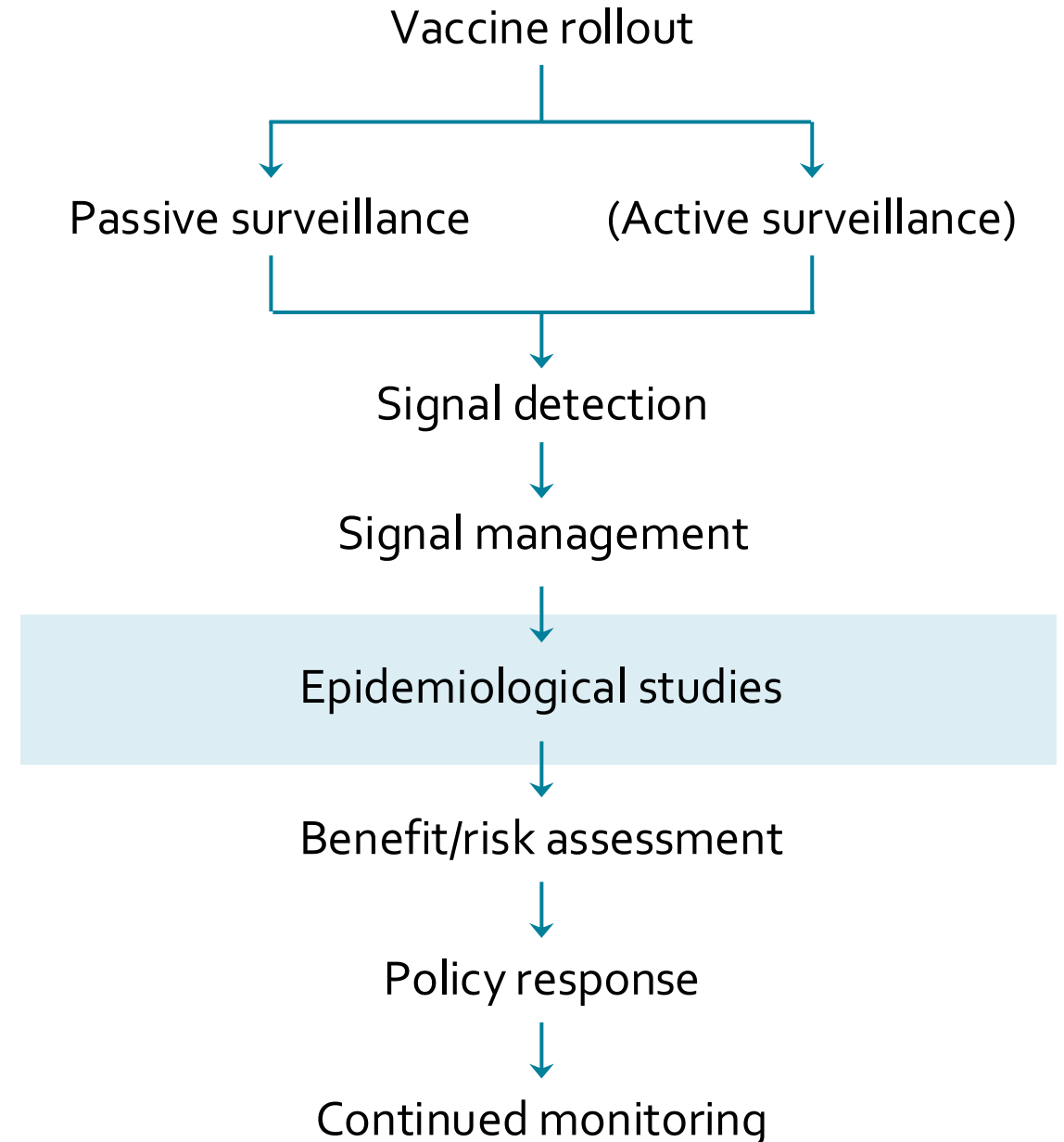
- Is the event more common in vaccinated individuals compared to unvaccinated individuals?
- Direct estimation of incidence and relative risk

Case-control studies

- Was recent vaccination more common among individuals with an event (cases) vs those without (controls)?
- Efficient for rare outcomes

Self-controlled case series

- Is the event more likely to occur shortly after vaccination than at other times?
- Efficient for rare events and controls for confounding by design



Self-controlled case series (SCCS)

Why is SCCS a key study design for vaccine safety research

- Individuals act as their own controls – comparison is across time periods rather than across individuals (**when not if**)
- Controls for key confounders by design:
 - Sex
 - Ethnicity
 - Socio-economic status
 - Long-term health conditions
- Efficient for rare adverse events



Example: rotavirus vaccination and intussusception in Australia

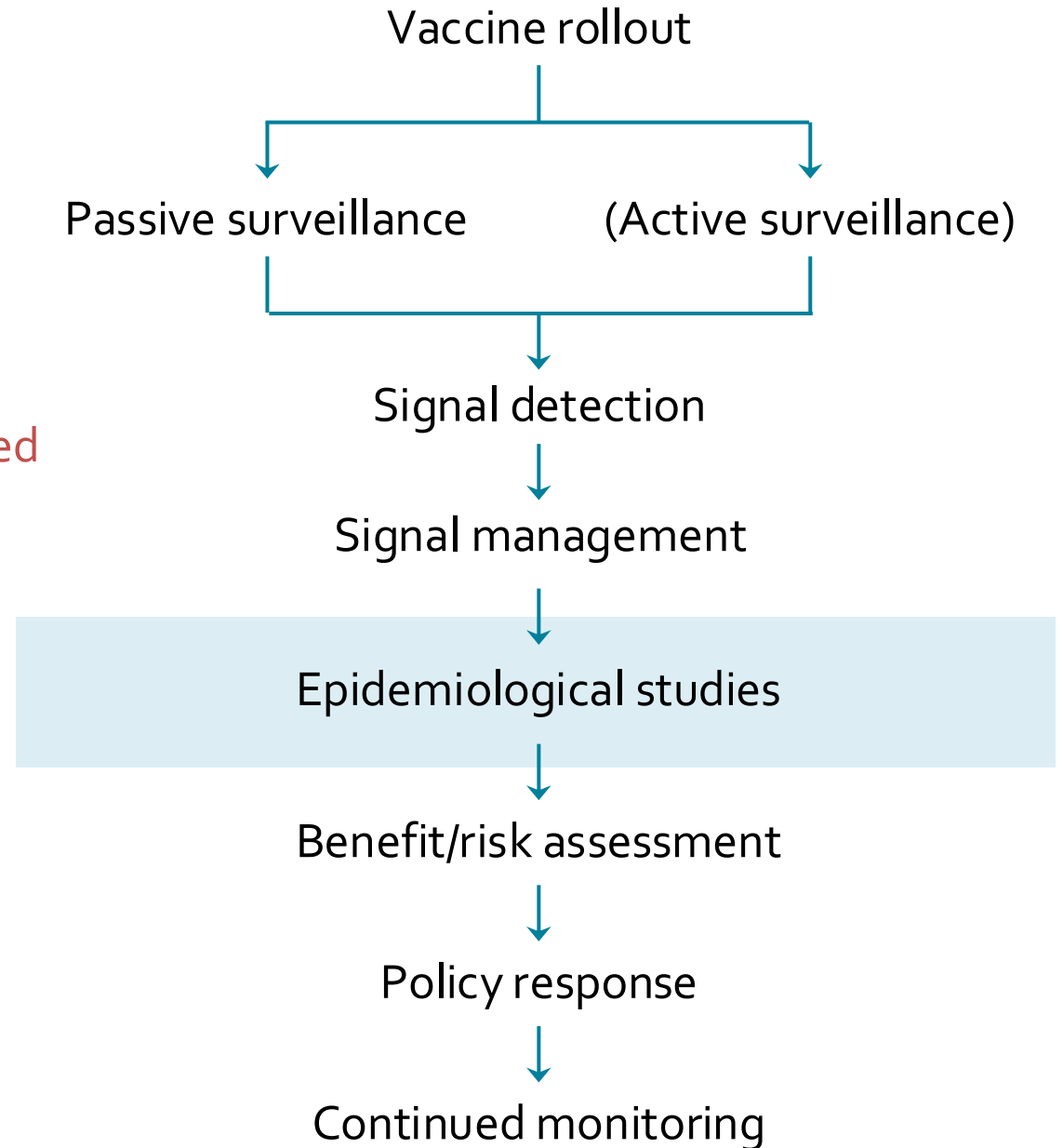
- 306 confirmed cases who received Rotarix or RotaTeq
- Increased risk during first week after vaccination (1–2 additional cases per 100,000 vaccinees), particularly for first dose
- Benefits substantially outweigh risks

From association to causation

Possible → Plausible → Probable → Likely → Established

Based on totality of evidence considering:

- Strength of association
- Consistency across studies
- Timing of events relative to vaccination
- Biological plausibility
- Alternative explanations (bias, confounding, chance)



Global vaccine pharmacovigilance

National regulators

- Review individual reports from safety surveillance
- Assess potential safety signals
- Investigate events of concern

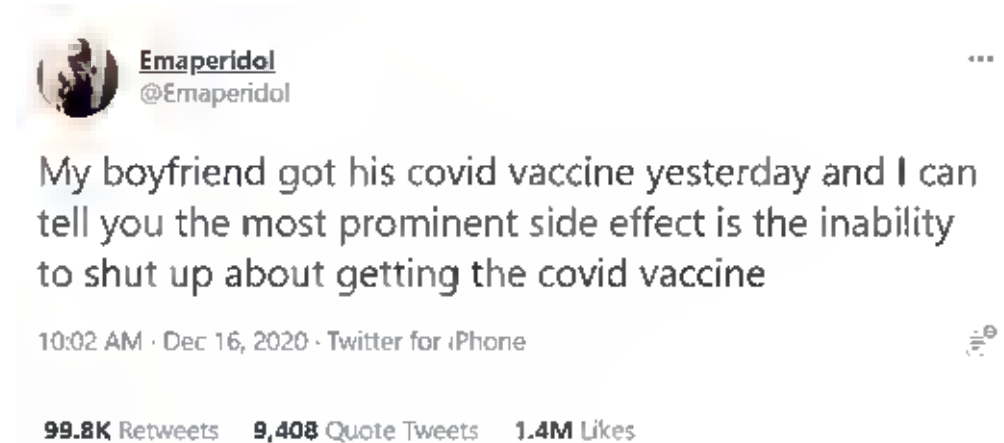
WHO Programme for International Drug Monitoring

- Coordinated by the Uppsala Monitoring Centre (UMC) in Sweden
- >160 countries and territories contribute reports to [VigiBase](#) database
- The UMC:
 - Aggregates reports from participating countries
 - Identifies unusual vaccine–event combinations
 - May detect rare events that are not visible in a single country
 - Shares emerging safety signals with national authorities



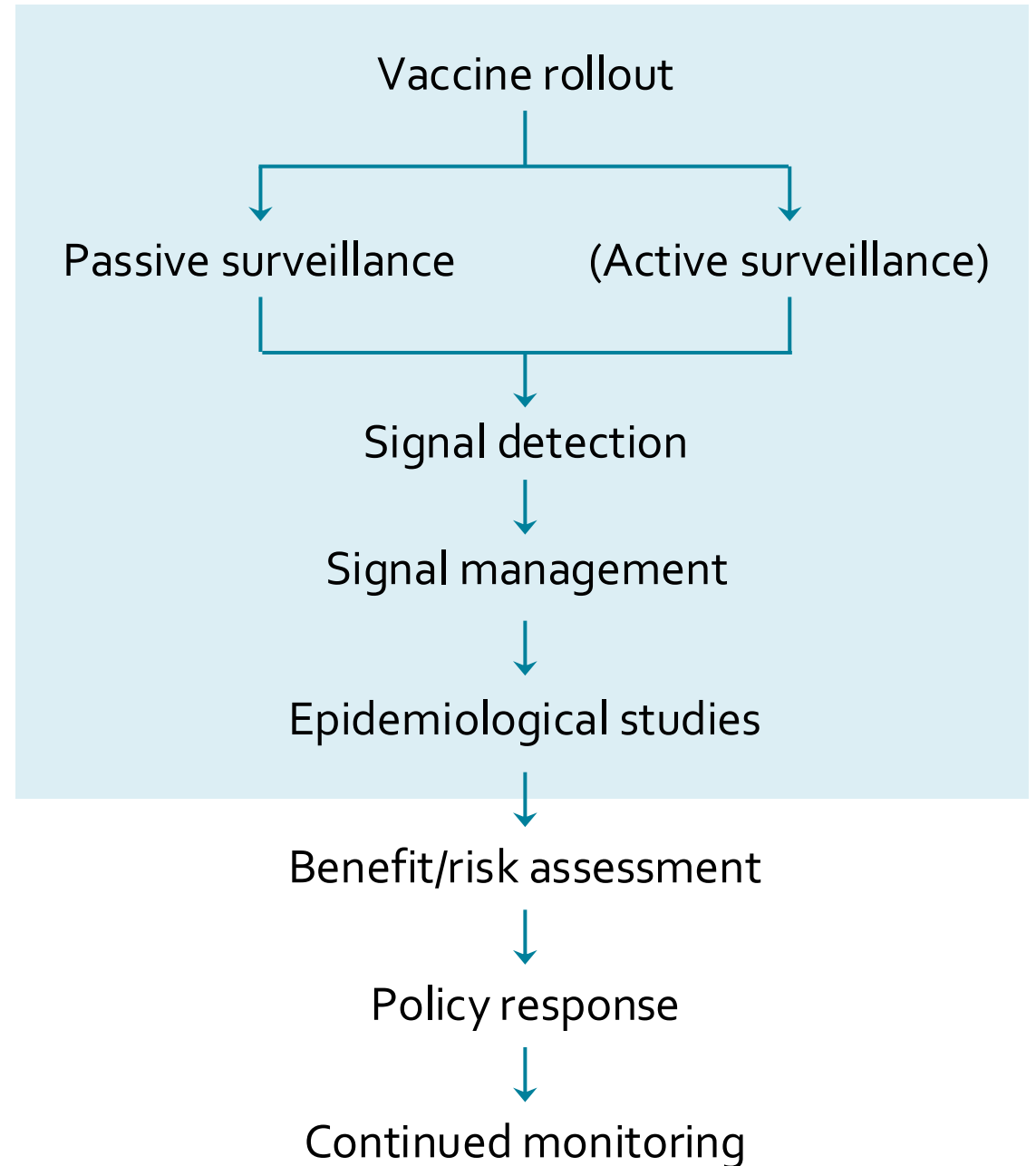
Vaccine safety monitoring vs public concerns

Commonly investigated in pharmacovigilance	Topics of online rumours
• Anaphylaxis • Myocarditis • Intussusception • Guillain-Barré syndrome • Thrombosis • Death	• "Toxins" • "Changes in DNA" • "Immune system damage" • Chronic fatigue or "brain fog" • Vaccines will give you COVID



Take-home messages

- Safety signals are common
- Most signals are not confirmed
- Multiple data sources and approaches are needed
- Epidemiological studies quantify risk



Questions

Vaccine effectiveness in the real world

Why might effectiveness differ from efficacy in RCTs?

- **Older and more diverse populations** (including groups excluded from trials)
- Different healthcare-seeking behaviour and healthcare access
- Important outcomes (e.g. hospitalisation and mortality) often too rare to be studied in trials
- Emergence of new variants
- Vaccine rollout decisions (e.g. dose interval) may differ from approach used in trials

Terminology shift! Vaccine efficacy is measured in trials; vaccine effectiveness is measured after rollout.

Measuring vaccine effectiveness

Vaccine effectiveness (VE) is the **percentage reduction** in the risk of a specified outcome among vaccinated individuals compared with individuals who are not vaccinated **over a defined time period**

Examples of outcomes

- Infection
- Symptomatic disease
- Hospitalisation
- Death

Calculation of VE

$$VE = 1 - (\text{Relative measure}) \times 100$$

- Relative risk, relative rate, or odds ratio depending on the study type
- Key confounders should be accounted for by design and/or adjustment

Example

- Hospitalisation risk of 10% in unvaccinated vs 2% in vaccinated during matched cohort study
- $$VE = (1 - 2/10) \times 100 = 80\%$$
- Vaccination was associated with an 80% reduction in the risk of hospitalisation

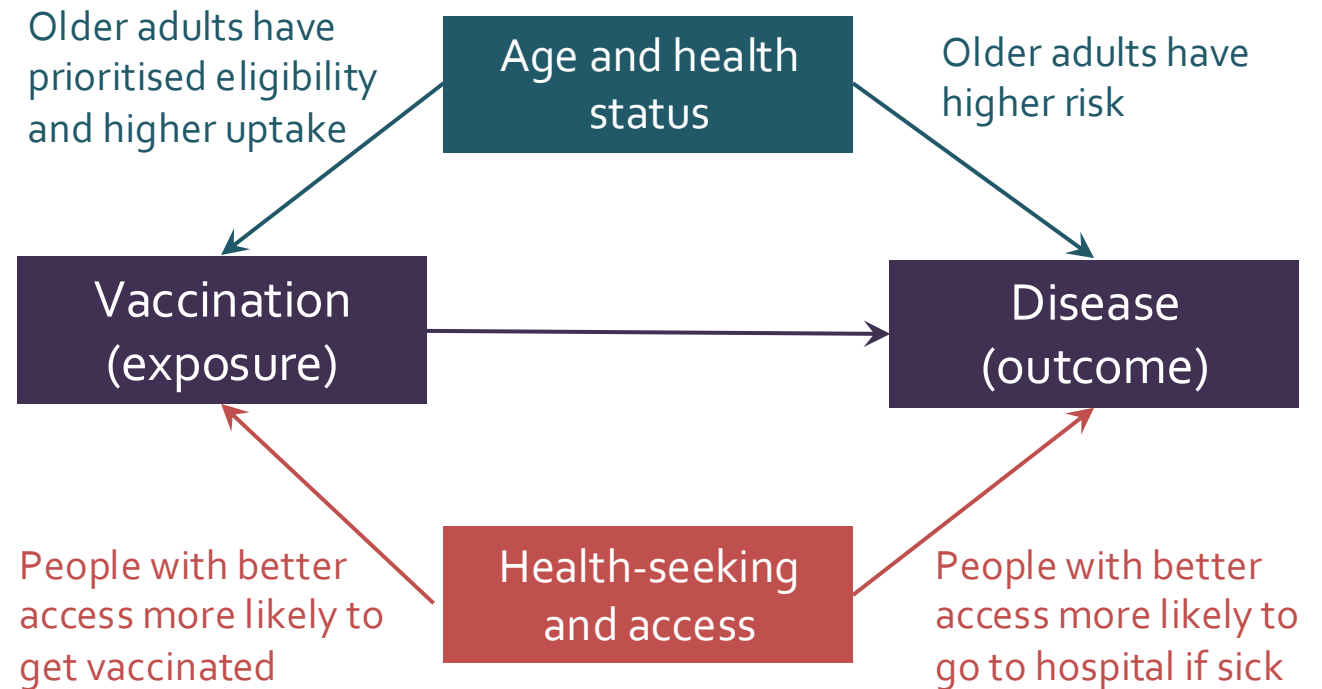
Confounding

Vaccinated and unvaccinated people differ by

- Age
- Health status
- Health-seeking behaviour
- Exposure risk
- Access to healthcare

Confounding

Differences in outcomes may reflect differences between people rather than effect of vaccine



Other challenges for effectiveness evaluation

Challenge	Example	Potential impact on VE estimates
Selection bias	Study population is not representative of the target group you want to learn about	VE may be over- or under-estimated
Information bias	Missing vaccination records, diagnostic misclassification	VE may be over- or under-estimated, or study may be underpowered
Healthy vaccinee effect	Health-conscious individuals more likely to be vaccinated	VE may appear higher than reality
Waning immunity	VE decreases over time since vaccination	Early VE may be under-estimated
Variants	Omicron replaces Delta	Changes in VE may reflect viral evolution rather than vaccine failure

Cohort studies

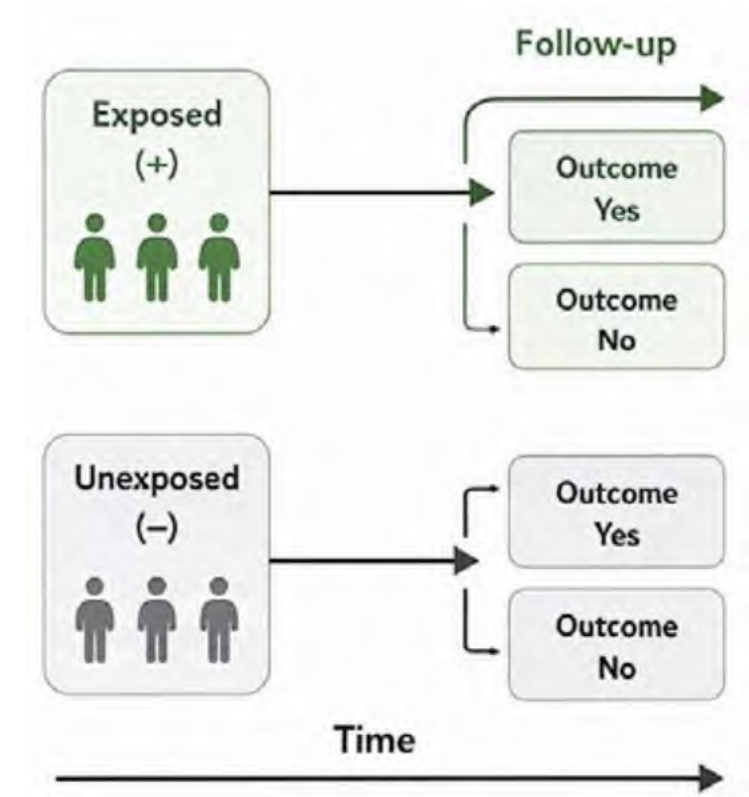
Core idea

Follow vaccinated and unvaccinated individuals over time and compare outcomes

Approaches to address confounding

- Matching
- Multivariate adjustment
- Stratification or restriction of the study population
- Emulation of target trials (eligibility, follow-up, analysis)

Strengths	Limitations
• Direct estimation of incidence • Multiple outcomes can be studied	• Residual confounding • Healthy vaccinee effect • Large datasets needed



BNT162b2 in Israel – target trial emulation

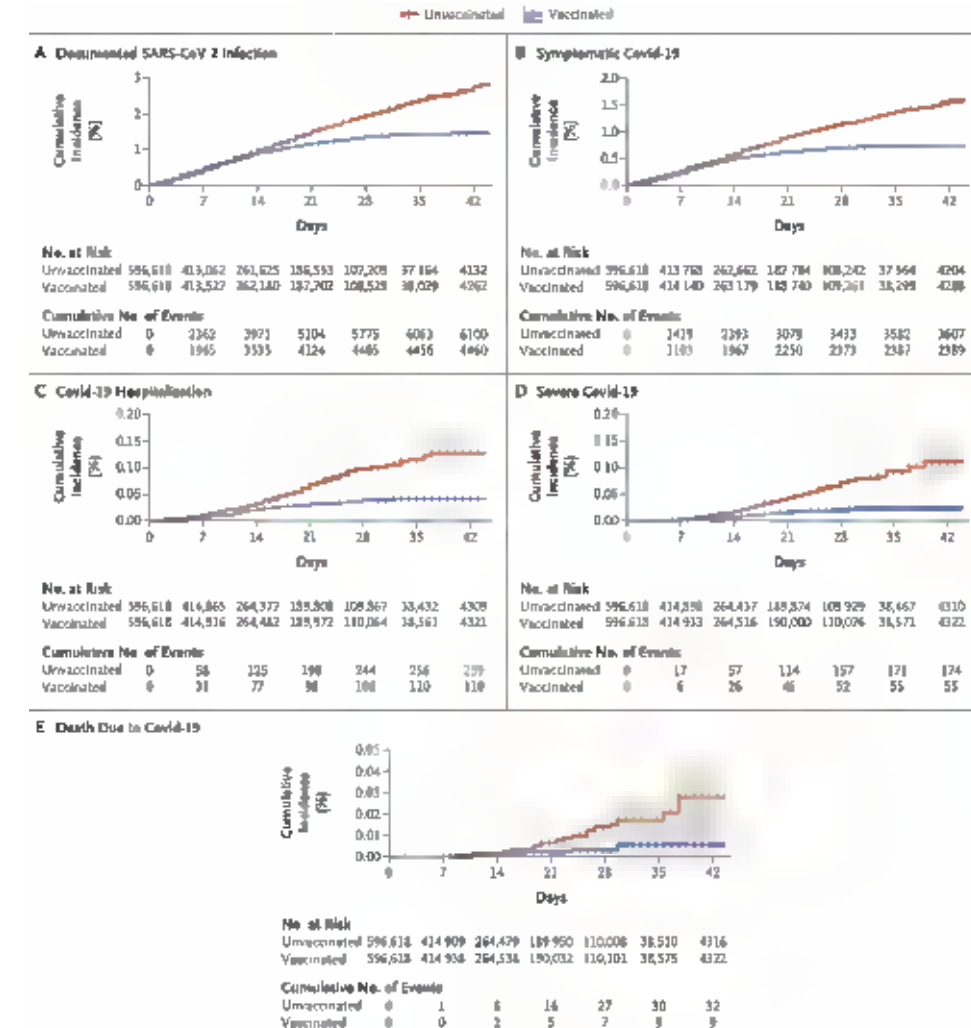
Summary

- National healthcare database
- Vaccinated individuals matched to unvaccinated controls
- Careful alignment of eligibility, follow-up and censoring to mimic trial
- Outcomes: symptomatic infection, hospitalisation and death
- 596,618 included in study population
- Mean of 15 days of follow-up (IQR 5–25 days)

Estimated vaccine effectiveness (1 – risk ratio) and 95% CI:

	Infection	COVID-19	Hosp.	Severe	Death
D1 + 14–20	46 (40–51)	57 (50–63)	74 (56–86)	62 (39–80)	72 (19–100)
D1 + 21–27	60 (53–66)	66 (57–73)	78 (61–91)	80 *59–94)	84 (44–100)
D2 + ≥7	92 (88–95)	94 (87–98)	87 (55–100)	92 (75–100)	N/A

D1, dose 1; D2, dose 2



BNT162b2 in Israel – target trial emulation

Summary

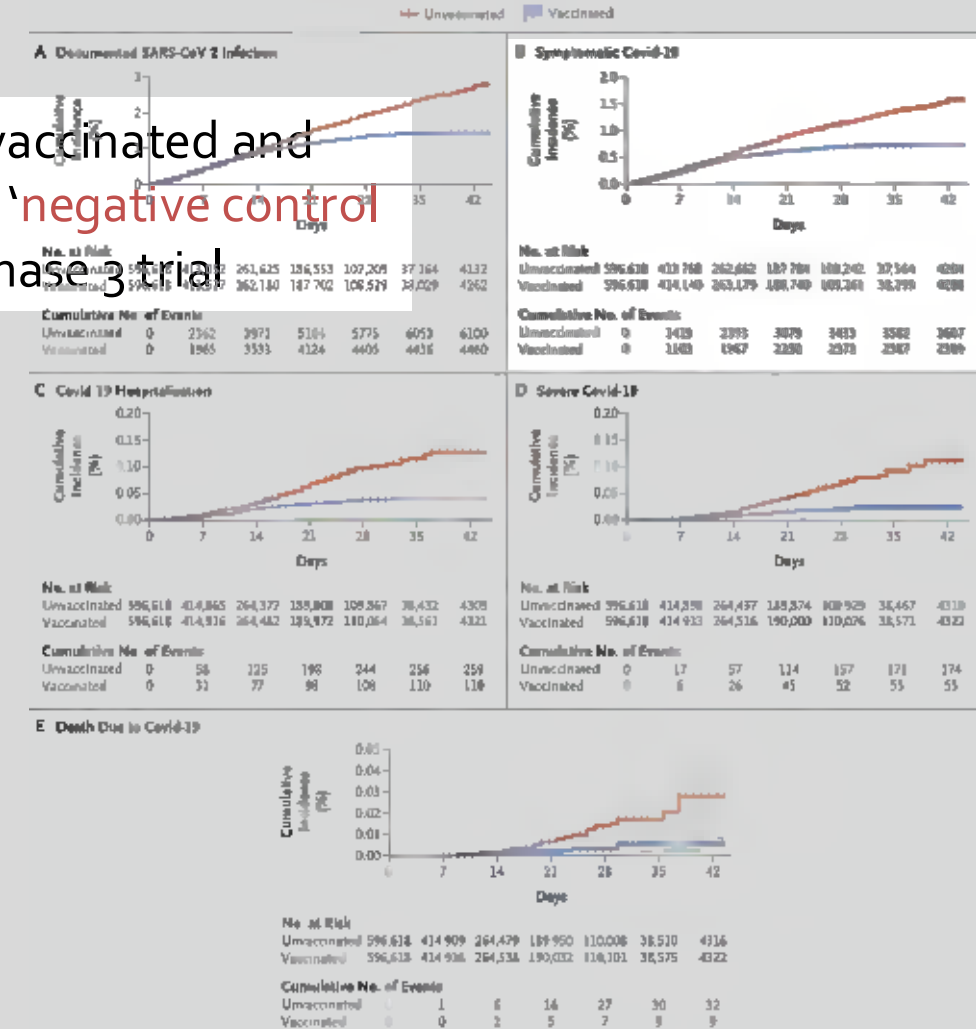
- National healthcare database
- Vaccinated individuals matched to unvaccinated during 10-day 'negative control period' – similar to phase 3 trial
- Careful alignment of eligibility, follow-up
- Outcomes: symptomatic infection, hospitalisation and death
- 596,618 included in study population
- Mean of 15 days of follow-up (IQR 5–25 days)

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D1, dose 1; D2, dose 2

No separation between vaccinated and unvaccinated during 10-day 'negative control period' – similar to phase 3 trial



BNT162b2 in Israel – target trial emulation

Summary

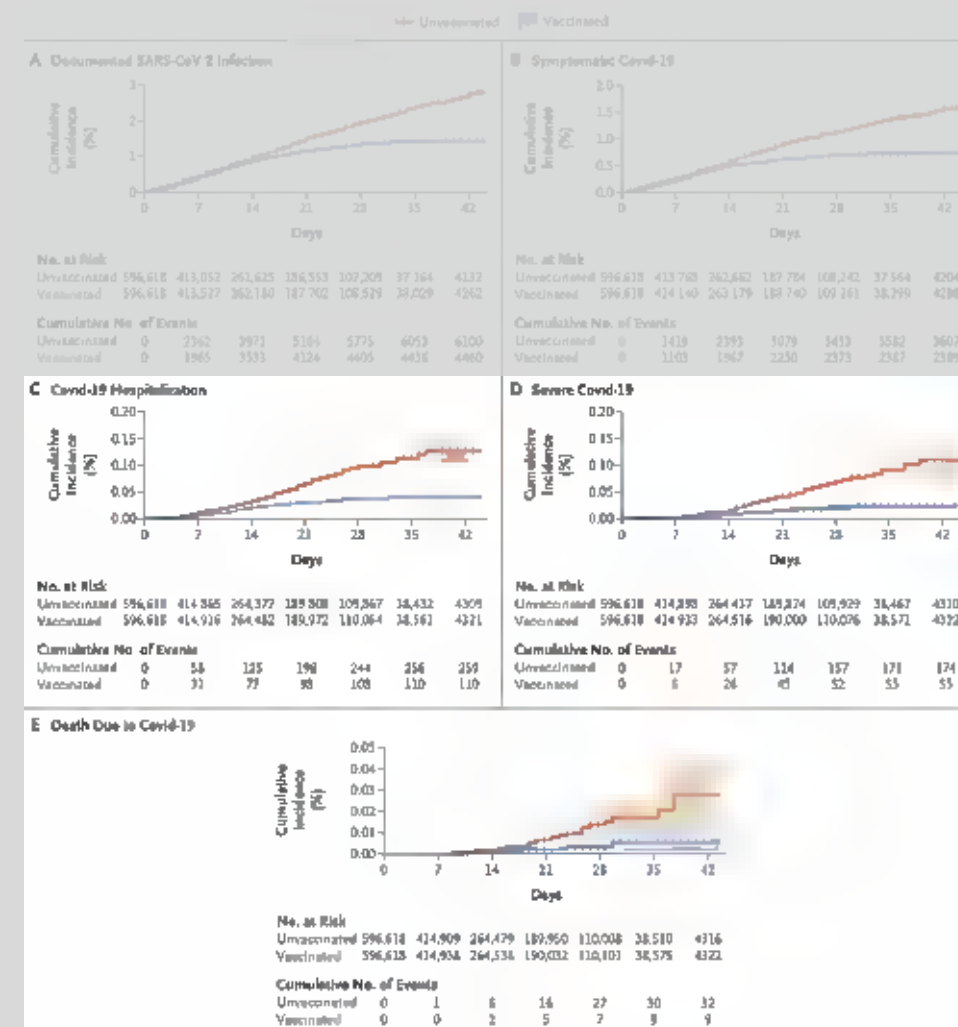
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Estimated vaccine

Large enough population to offer robust VE estimates for **severe outcomes**

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Case-control studies

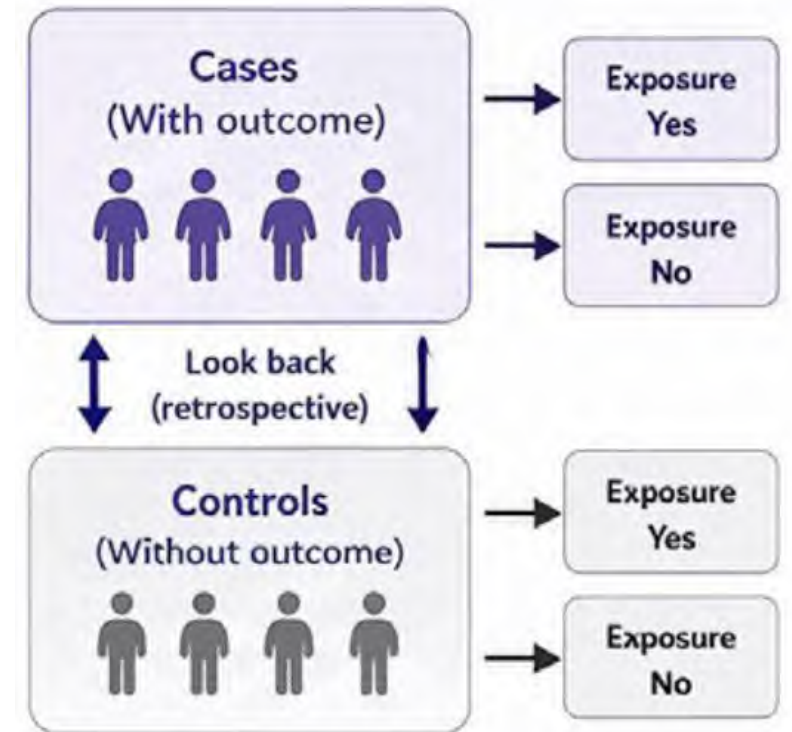
Core idea

Compare vaccination history among cases (with disease) and controls (without disease)

Approaches to address confounding

- Matching
- Multivariate adjustment
- Stratification or restriction of the study population

Strengths	Limitations
• Efficient for rare outcomes • Requires fewer participants • Relatively inexpensive	• Control selection • Exposure misclassification (e.g. recall bias) • Residual confounding



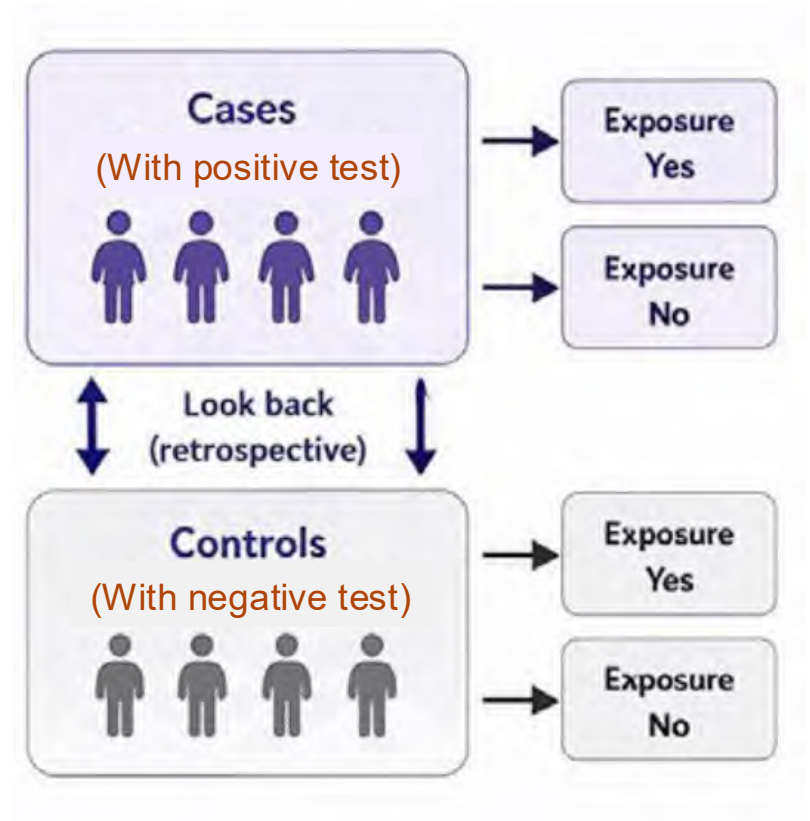
Test-negative case control studies

Core idea

- Case control study nested within patients seeking care with compatible symptoms
- Compare vaccination among test-positive vs test-negative

Strength

- Reduces confounding by healthcare seeking and access by design



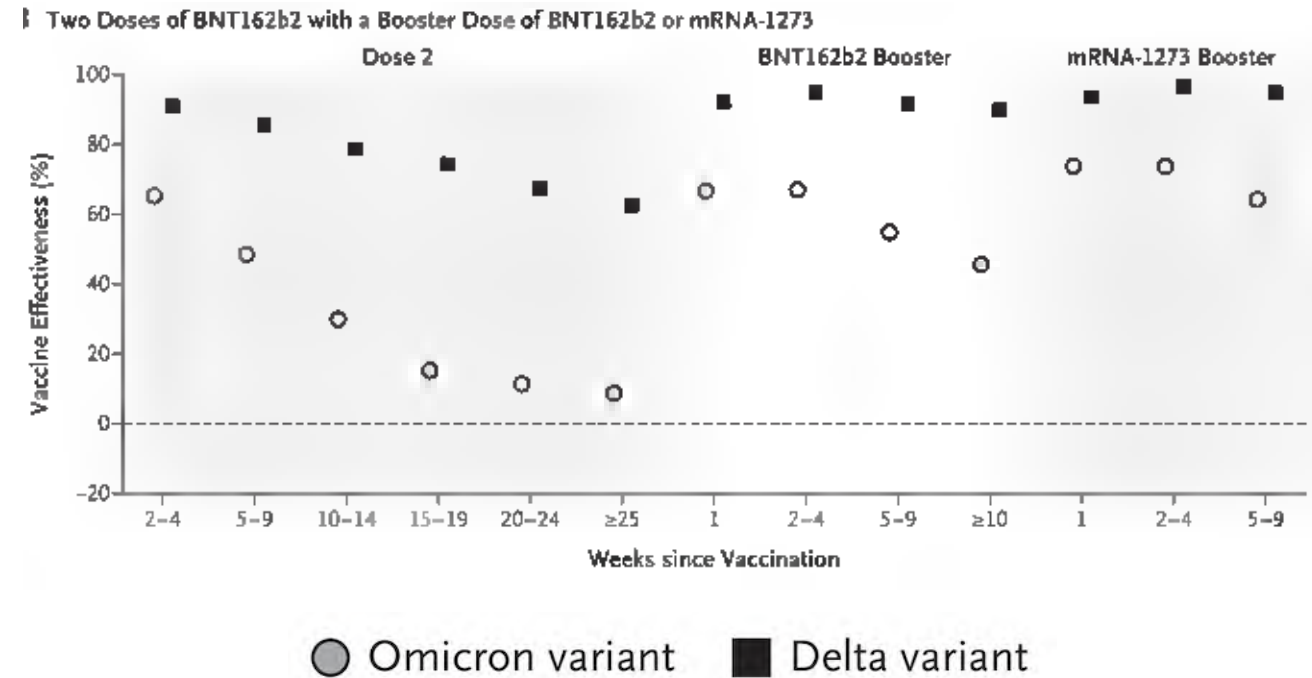
COVID-19 VE in England – waning + boosting

Summary

- Symptomatic individuals undergoing PCR testing
 - Cases: Delta-positive or Omicron-positive
 - Controls: test-negative individuals

Key findings

- Substantial waning over time
- Lower protection against Omicron
- Substantial increase in protection after booster



Other study designs

Outbreak investigation

- Cohort studies during outbreaks in schools, care homes, and other institutions
- Small population size but often high incidence

Screening / case-population method

- VE inferred from coverage in cases and coverage in population from which cases occurred
- Rapid, inexpensive, but limited potential for confounder control

Household studies

- Secondary attack rate from index cases
- VE against transmission (status of index case)
- VE against infection (status of contacts)

Before/after studies

- Incidence before vs after vaccine introduction
- Can compare against modelled counterfactual without vaccination

Take-home messages – safety and effectiveness monitoring

Safety surveillance	Effectiveness evaluation	Shared challenges
• Detects safety signals • Assesses potential causality • Involves passive/active surveillance and observational studies	• Measures protection in routine care, over time, and against new variants • Extends evidence beyond trials • Involves observational studies	• Bias • Confounding • Changing epidemiological contexts



If we can estimate both the benefits and the risks of vaccination, how should these be integrated when making policy decisions?

Questions

Benefit-risk assessment

Integrating evidence on...

Vaccine effectiveness



Vaccine safety



Disease burden



Population context



Core question: do the benefits of vaccination outweigh the risks?

What enters a benefit-risk assessment?

Evidence inputs



Vaccine effectiveness



Vaccine safety



Disease burden



Population context

Benefits

- Infections prevented
- Hospitalisations prevented
- Deaths prevented
- Healthcare demand avoided
- Indirect protection

Risks

- Adverse events
- Long-term disability
- Mortality
- Public confidence impacts

Special considerations

Vaccines may reduce transmission

In the (ideal) scenario of elimination or eradication, risks will naturally outweigh benefits at individual level, but sustained high uptake is needed

Individual vs public health perspectives

Vaccines may be *indicated* to give direct protection to a recipient, but public health benefits of vaccination may be through reduced spread to vulnerable contacts

Secondary benefits

Vaccines may be *indicated* for secondary benefits (e.g. maternal vaccination for neonatal protection)

Regulatory vs policy decisions

Regulatory context

- Can this vaccine be used?
- Decisions made by regulators such as MHRA, FDA, etc
- Informed by clinical trials, pharmacovigilance, and real-world studies
- Considers benefit-risk for authorised indications of a **product**
- Emphasis on **benefit-risk balance for individual vaccinees**

Policy context

- How should this vaccine be used?
- Decisions made by advisory groups such as JCVI, ACIP, NITAGs, etc
- Informed by multiple evidence streams and contextual factors
- Considers direct and indirect benefits (including to society)
- Considers **relative benefit-risk of all available vaccines**

Benefit-risk varies... across populations

Consider a rare adverse event occurring at 1 per 100,000 doses

Would the benefit-risk balance be the same for...

- a healthy 20-year-old
- a frail 85-year-old
- an individual with severe chronic disease

Both risks and benefits of vaccination may differ substantially

Benefit-risk varies... over time

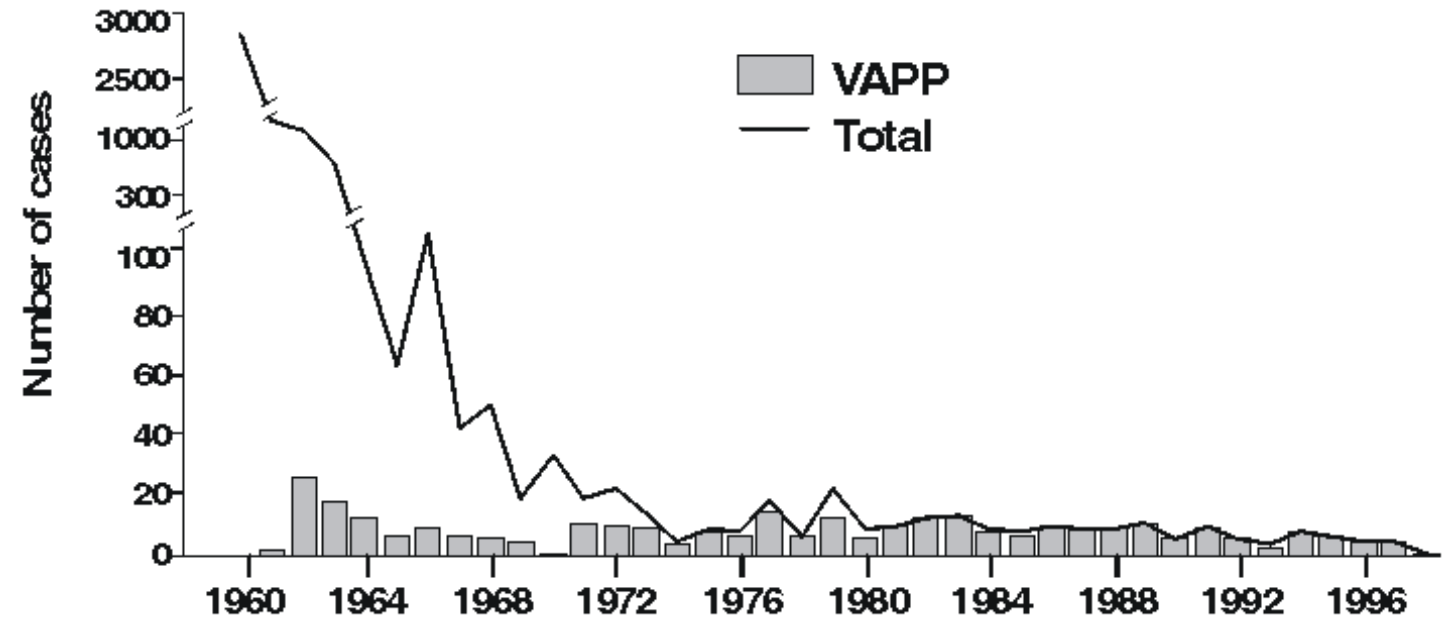
Vaccine-associated paralytic poliomyelitis (VAPP)

- Occurs in ~1 in 1-2 million children vaccinated with oral poliovirus vaccine (OPV)
- Not seen for inactivated poliovirus vaccine (IPV)

Polio in the USA

- Pre-1997: OPV-only schedule
- 1979: last locally acquired wild poliovirus case
- 1997: schedule of IPV followed by OPV
- 1999: switch to IPV-only schedule

Contribution of VAPP to overall polio burden in the USA



Decisions depend on context

- What is the current or anticipated disease burden?
- How many individuals have been vaccinated or exposed to disease?
- Are there any competing considerations (e.g. health system capacity)?
- Are there any alternative vaccines available?

Case study – rotavirus and intussusception

Background

- Rotavirus is a major cause of severe gastroenteritis in infants and young children

First licensed vaccine

- RotaShield (Wyeth) licensed in the USA in 1998 – live oral tetravalent rotavirus vaccine
- ~10,000 vaccine recipients across vaccine trials before licensure – no major safety concerns
- Near-complete protection against severe disease and hospitalisation in trials

What happened next?

- Reports of intussusception emerged during post-licensure safety surveillance – rare but potentially serious bowel obstruction in infants
 - 1–2 excess cases per 10,000 vaccinated infants
- CDC recommends suspension of use in July 1999

Case study – rotavirus and intussusception

Would next-generation vaccines fare better?

- RotaTeq (Merck) and Rotarix (GSK) authorised in USA in 2006 and 2008, respectively
- Phase III studies involved 60,000+ infants
- Efficacy against severe rotavirus gastroenteritis >95% in high-income settings
- No significant increase in intussusception detected in clinical trials

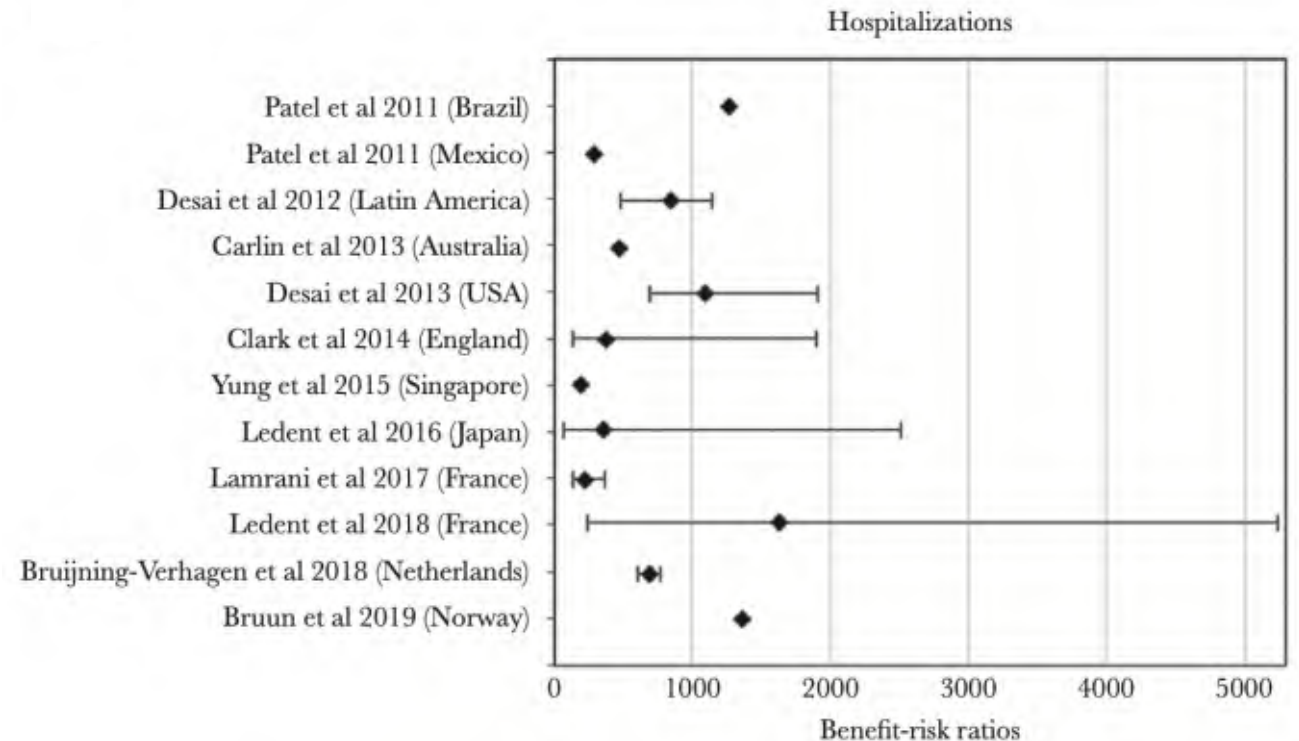
What happened next?

- Post-licensure monitoring involving passive surveillance, SCCS, and cohort studies
- Small increase in intussusception risk remained detectable
 - 1–6 excess cases per 100,000 vaccinated infants (estimates vary by setting)

Case study – rotavirus and intussusception

Context-specific benefit-risk calculations

- Highly favourable benefit-risk profile in models incorporating different estimates of coverage, IS risk, VE, and rotavirus incidence
- Benefit-risk ratios ranged from 190 to 1624 rotavirus-related hospitalisations prevented for every additional vaccine-related intussusception-related hospitalisation



Questions

Communicating risks and benefits

Why communication matters

- Safety signals can generate public concern
- Misunderstandings can undermine confidence and uptake
- Poor communication can reduce trust
- Reduced uptake can increase disease burden

6 basic principles of vaccine safety communication

1. Communicate clearly using plain language
2. Communicate what is known and unknown
3. Communicate benefits and potential risks objectively
4. Be empathic
5. Communicate what you are doing and why
6. Give tangible advice on what people should do

What to say (and what to avoid)

Avoid	Consider
"The vaccine is safe"	"The vaccine is very safe. Most people get good protection. A small number – between 3 and 12 in a 100,000 – may have a more serious reaction"
"There is no risk of severe reactions"	"We haven't detected an increased risk of severe reactions, but we are continuing to monitor this carefully"

Take-home messages

(1) Post-licensure monitoring is essential

- Clinical trials cannot answer all questions about long-term effectiveness or rare adverse events
- Pharmacovigilance identifies and evaluates potential safety signals
- Effectiveness studies evaluate protection under real-world conditions

(2) Evidence evolves

- Benefit-risk assessments are dynamic – risks may change as safety signals emerge, benefits may change as disease burden and immunity evolve
- Policy is context dependent

(3) Communication matters

- Be clear, be compassionate, acknowledge uncertainty, communicate both benefits and risks

Questions