Public Health England

Protecting and improving the nation's health

Approaches to study vaccine impact post-licensure, both vaccine effectiveness and safety

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Many countries and organizations are working on plans

- WHO - VE and Safety protocols, safety code lists
- ECDC – Coordination - pulling together plans
- Global Networks – e.g.Global Vaccine data link
- European Networks – VE and Safety protocols
- Brighton Collaboration – case definitions (SPEAC)
- Regulators (EMA, FDA) – VAC4EU (background rates)
- Manufacturers – required to have phase 4 studies.

Key areas of post-implementation surveillance

- Coverage
- Epidemiology
- Effectiveness
- Impact
- Safety
- Sero-surveillance
- Modelling

Before thinking about effectiveness and safety its essential to know how you will capture vaccination data.

- Immunisation registry
- Vaccination cards
- Questionnaires when patients present with illness
- Health records (e.g. GP)

Should be as timely as possible.

Next consider data sources and methods

- For the populations being targeted consider how to identify cases (disease or safety outcomes) in an unbiased way, a comparator group (if necessary), exposure history and confounding variables.

- Based on the above decide on the best design

Vaccine Effectiveness Outcomes

- Symptomatic disease
- Infection (PCR/seroconversion)
- Hospitalisation
- Mortality
- Transmission

Vaccine Effectiveness data sources for cases

- Laboratory confirmed (e.g. PCR positive) cases reported by laboratories to national databases.
- General Practice records
- Sentinel surveillance swabbing schemes by General Practices
- Hospital records / reporting e.g. SARI or ICU reporting
- Defined cohorts followed up with regular testing – e.g. Health Care Workers, Care home residents and staff
- Detailed follow-up of cases/ families of cases to assess infectivity (CT number) and transmission risk by vaccination status.
- Outbreak investigations

Vaccine Effectiveness methods

- Randomised
  - If more than one vaccine available is randomisation possible at point of delivery or as cluster randomisation?

- Observational with data linkage / enhanced follow-up
  - Test-negative case control
  - Case control with population or hospital controls
  - Cohort
  - Screening method (Case-coverage)
  - Ecological

Stratification and confounding

- Duration of protection
- Sub groups – e.g. specific health conditions, ethnicity, ages, those with and without past infection

- Likely confounders (related to vaccination and outcomes)
  - Age, period, region, health conditions, health care usage, past infection, influenza vaccination (if using test negative controls).

Examples of planned studies (UK)

RAPID results

- We have added a vaccination question to the test request form for the community testing – we can rapidly compare vaccination status in those testing positive with those testing negative (TNCC design).
- We can use rapidly available population uptake along with vaccination status of lab confirmed cases (hospital and community cases) for VE by the screening method.

GP based

- GP cohorts include the Royal College of General Practitioners' cohort and the clinical practice research datalink (CPRD). Can do cohort analysis and nested TNCC.

Examples of planned studies (UK)

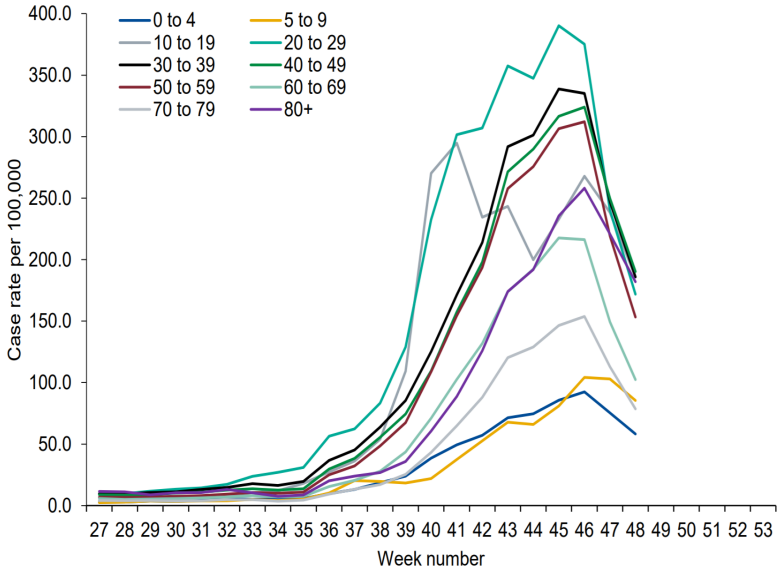
- SIREN study – prospective cohort study of 100,000 healthcare workers
- Aim to determine whether SARS2 antibody associated with reduced risk of reinfection.
- Can be used to assess VE against infection as there is regular testing (PCR and blood) for asymptomatic infection

- Transmission study
- Recruit Vaccinated and Unvaccinated cases – follow-up household contacts with PCR testing and antibody testing.

Using surveillance for Impact

- Impact on broad range of existing population level surveillance indicators
- Direct/indirect effect of the vaccine
- This is an ecological assessment so interpretation more challenging.
- Comparison of confirmed cases in target groups before to after vaccine introduction relative to changes seen in non-targeted groups
- If there is variability in the timing of vaccination within target groups (e.g. care homes) this may also allow assessment of impact.

Figure 4: Weekly laboratory confirmed COVID-19 case rates per 100,000, tested under Pillar 1 and Pillar 2, by age group



Some methodological issues

How appropriate are test negative controls – requires reasonable sensitivity and good specificity?

Sample Size – this is helped if VE really is 90% +

Might there be behavioural modification in those vaccinated?

What if very specific populations are targeted (e.g. hospitalised patients)?

Vaccine Safety

- Common and less serious events identified in trials
- Of most interest are rare and serious adverse events

- Three main components

- SIGNAL DETECTION
- SIGNAL STRENGTHENING
- SIGNAL EVALUATION (hypothesis testing)

Vaccine Safety Assessment components

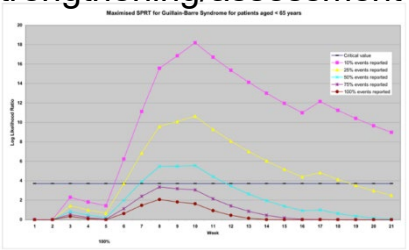
Vaccine Trials
reactogenicity

Licensure

Pharmacovigilance
(passive/active):
hypothesis generation,
RAPID

Individual
causality
assessmen
t

Signal
Strengthening/assessment



Epidemiological
studies
(hypothesis
testing)

Priority?

Plausibility, other data/methods,
experts, other risks, interval
from vaccine,….

Signal detection

Signal Detection –

Passive surveillance – vaccine pharmacovigilance. E.g. disproportionality analysis

Active surveillance –

Database - comparing observed rates to back ground rates

- comparing rates in specific post vaccine windows

Cohort event monitoring – active follow-up of a cohort e.g. using a phone app, or careful monitoring all admissions to a hospital

Sequential testing is usually done so statistical methods to allow for this should be used. Sequential probability ratio test (SPRT)

Active surveillance is usually for a predefined set of events.

MANY SIGNALS ARISE UNEXPECTEDLY FROM OTHER SOURCES – good to have a network to talk to one another.

Signal strengthening

Rapid Assessment

- Causality assessment tools to investigate cases (WHO tools)
- Is the signal seen in other countries using the same vaccine?
- Ecological studies looking at rates before – after vaccination e.g. using hospital of GP data
- Comparison of rates by vaccine manufacturer within similar target groups.
- Assessment of timing of events and rapid Observed vs Expected analyses if not on the pre-specified list.
- Input from specialists on plausibility and likely risk windows to inform hypothesis testing

Signal Evaluation – data sources and methods for well designed studies

- GP data - best for events presenting at GPs where coding has reasonable specificity. Cohort/Case-control/Self controlled case series methods
- Hospital data – linked to immunisation register or vaccination history obtained by linkage to or contacting GPs. Self controlled case-series, case-coverage methods
- Specialist registers – some events (e.g. narcolepsy) require careful ascertainment and validation of cases from registers through hospital visits and use of expert panels.
- Code validation – where GP/Hospital codes are used validation of a subset or all cases through case-note ascertainment/ prescription data often needed.

Self Controlled Case-Series

- Ideal for rare events where a risk period can be defined
- Only requires cases (must be an unbiased set)
- Compare the event rate in the vaccine risk window to rate in person time outside the risk window.
- Deals with individual level confounding
- Still need to adjust for time varying confounders (e.g. age, period)

Some methodological issues

- Targeting vaccination at individuals at hospital or other special populations
- The Pandemic itself has changed many baselines for observed v expected
- Different vaccines given to different populations
- Separate data sources to identify and test hypotheses

Questions ?

Also thanks to various people I have spoken to about VE and Safety

Including…

PHE: Jamie Lopez, Julia Stowe, Mary Ramsay, Liz Miller, Heather Whitaker, Charlotte Gower.

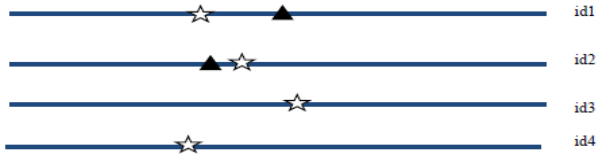
P95: Kaat Bollaerts

Global Vaccine Datanet: Steve Black and others

BACK UP SLIDES

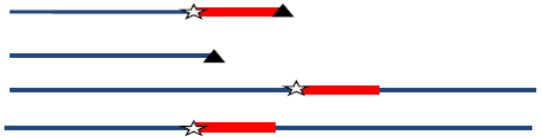
Comparing designs

The exposure and event history for four individuals



Blue line is 200 days person follow-up time; star is vaccination time and triangle event time.

Cohort



Rate of events in 30 day post vaccination risk period (red) compared to non-risk period (blue), follow-up stops at an event (if non recurrent). Poisson regression or survival analysis can be used.

Matched case-control

Cases are matched to non-cases (for example id 1 to 3 and id 2 to 4) and the odds of vaccination in the 30 days prior to the case event time (orange) compared using conditional logistic regression.

Case-crossover

Just using cases (id 1 & 2) the odds of vaccination in 30 days prior to the event time (orange) is compared to the previous 30 day period (green) using conditional logistic regression.

SCCS

Just using cases (id 1 & 2) event rate 30 days post vaccination (red) compared to non-risk period (blue) using conditional Poisson regression.