COVID-19 VE among hospitalised SARI patients

Expert meeting
Epiconcept
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Background

COVID-19 VE among hospitalised SARI patients

- Some European countries established severe acute respiratory illness (SARI) surveillance during the COVID-19 pandemic
- This protocol focuses on *existing SARI surveillance systems* to measure VE
- SARI surveillance can be/has been adapted to include SARS-CoV-2
- SARI VE protocol developed for the I-MOVE-COVID-19 network*
  - basis for WHO/Euro SARI VE guidance document adapted for LMICs
  - same protocol as starting point for ECDC-funded sites?

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European Union

Objectives

- **Primary objective**

  To measure overall and **product-specific** vaccine effectiveness (VE) against laboratory-confirmed SARS-CoV-2 infection among hospitalised SARI patients
  - for each site individually and pooled across all participating sites

- **Secondary objectives (pooled ➡ multicentre study)**

  1. To measure VE in hospitalised SARI patients against PCR+ SARS-CoV-2 by
     - sex, age group
     - risk group (e.g. specific chronic conditions)
     - vaccination target groups
     - vaccine dose (one vs two), where applicable
     - time since vaccination, between doses and regularly over calendar time

Objectives

- **Secondary objectives**

  2. To measure VE in hospitalised SARI patients against
     - clade/genetic variant if feasible
     - more severe outcomes (ICU admission, invasive ventilation, in-hospital mortality)

  3. To identify the role of potential factors that may modify VE
     - chronic conditions
     - influenza vaccination
     - statins or other long-term medications
     - severity (oxygen support/intubation/assisted ventilation, ICU, in-hospital death)
     - setting (e.g. long-term care facilities)

Objectives: WHO/Euro guidance document

- **Same as for I-MOVE-COVID-19 protocol, except**
  - no pooling
  - includes non-pharmaceutical interventions as risk exposure variables
    - mask use
    - hand hygiene
    - social distancing
    - pandemic perception

Methods

- Hospital-based, test-negative, case–control design
- Study population

  Individuals hospitalised with SARI symptoms
  in participating hospital
  with no vaccine contra-indication

  Initially: those belonging to vaccination target group(s)

Methods

- Possible SARI case definition*

  a hospitalised person with **at least one** of the following symptoms:

  cough, fever, shortness of breath, **or** sudden onset of anosmia, ageusia or dysgeusia

- If possible all SARI patients should be tested for SARS-CoV-2 **within 48 hrs** of admission

- Confirmed case

  PCR test positive within 48 hrs of admission **or** ≤ 14 days prior to hospital admission

- Control

  PCR test negative within 48 hrs of admission **and** within 14 days prior to admission (if tested)

Note: SARI patients may optionally be recruited with onset up to 14 days prior to admission, as these can be excluded from primary analyses, but will be included in sensitivity analyses.

*ECDC possible COVID-19 case definition: https://www.ecdc.europa.eu/en/covid-19/surveillance/case-definition

Methods: WHO/Euro guidance document

- **All the same as I-MOVE-COVID-19 protocol except**
  - WHO/Euro guidance only offers WHO case definition
    - a hospitalised person with acute respiratory infection, with

      a history of fever or measured fever of ≥ 38 C°

      and cough

    - with symptom onset within the last 10 days

  Where a minimum of 24 hours in-hospital is required to be considered hospitalised

  - I-MOVE offers both case definitions
  - WHO/Euro: VE covered under SARI surveillance ➡ consent inherent
  - guidance document includes draft proposed questionnaire
    - I-MOVE provides list of minimum variables

WHO SARI case definition: https://apps.who.int/iris/bitstream/handle/10665/333912/WHO-2019-nCoV-Surveillance_Case_Definition-2020.1-eng.pdf?sequence=1&isAllowed=y

Methods

- Exposure: vaccination
  - depends on the vaccine (# doses; # days since vaccination)
  - vaccine product

  importance of good quality data collection: date of vaccination, brand, batch

- Outcome
  - RT-PCR
  - laboratory-confirmed SARS-CoV-2 in patients hospitalised with SARI symptoms
    - if possible, by genetic variant

Sample size estimations (crude analysis)

- Assumptions/criteria
  - case to control ratio 1:1
  - vaccine coverage 80% in source population*
  - OR between 0.1 and 0.5

Precision to lower CI boundary	Controls/ case	Detectable OR	Vaccine coverage in source population/ controls	Number of cases	Number of controls	VE	CI
0.1	1	0.1	0.8	89	89	90	80-95
0.1	1	0.2	0.8	241	241	80	70-87
0.1	1	0.3	0.8	477	477	70	60-78
0.1	1	0.4	0.8	808	808	60	50-68
0.1	1	0.5	0.8	1242	1242	50	40-58

*For VC 30–50%: sample size is higher for the lower VE estimates and slightly lower for the 50–60% VE estimates.

Effect modifiers / confounding factors

- Demographic (age, sex, ethnic group)
- Pre-existing chronic conditions
- Clinical (medications, severity of underlying condition)
- Smoking status
- Previous vaccination
  - influenza, pneumococcal vaccines
- Previous SARS-CoV-2 infection
- Antivirals prior to swabbing
- Functional impairment/frailty

Effect modifiers / confounding factors

- Socioeconomic status/deprivation
- Time from onset to hospitalisation
  - test-negatives: late presenters?
  - more severe disease: late presenters?
- Risk-taking behaviour/exposure
  - no social distancing, no/inappropriate mask use, vaccine-averse
- Setting
  - long-term care facilities

Exclusions

- Refusal; cannot communicate/give consent
- Vaccine contraindications
- Cannot be swabbed (septum deviation/obstruction, etc.)
- History of hospitalisation: previous 14 days to admission
  - easy to collect?

- Onset to hospitalisation delays: to be addressed in sensitivity analyses
  - I-MOVE-COVID-19 surveillance data show 89% hospitalised ≤ 14 days
    - 0–4 days: 39%
    - 5–9 days: 33%
    - 10+ days: 22%
    - In-hospital onset: 5%

Exclusions/stratifications in sensitivity analyses

- Varying delay (in days) for exclusion, between
  - onset and admission
  - onset and swab
  - vaccination and onset
- Positive to seasonal coronavirus (other respiratory viruses?)
- Nosocomial exposure
  - # days in hospital: >8 days for suspected; > 14 days for confirmed?
- Those who received antivirals within xx days of swabbing
- Extreme frailty
- Controls with suggestive CT, or positive within 3 months before admission

Potential biases: TND controls

- Is this a good control group?
  - represent VC in the population giving rise to SARI-positive cases in target group(s)?
  - PCR sensitivity decreases over time
    - if severe cases hospitalised later: misclassified as controls if test-negative?
  - CDC: non-SARI hospital patients as second control group
- Controls more likely to have indication for COVID-19 vaccine
  - minimise by collecting data on chronic conditions (for adjustment)
- Previous infection (symptomatic/asymptomatic) among controls
  - what if previous infection was unknown/unconfirmed?
    - "probable" prior infection (dry cough, fever, anosmia, close contact)?
  - sensitivity analyses: range of scenarios ⟶ to obtain effect on VE
- Effect of vaccine on other respiratory viruses (adenovirus, etc.)?

Potential biases/challenges

- High-risk groups: more likely to be vaccinated (and hospitalised with SARI)
  - initially will be the focus (but target groups may differ by country?)
  - stratify by target groups
- "Extreme frailty": less likely to be vaccinated
  - sensitivity analyses: excluding those who are extremely frail
- Influenza-positive cases: less likely to have been vaccinated?
  - co-infections ➡ more severe COVID-19 disease
  - sensitivity analyses: excluding influenza-positive cases
- Hospital sites becoming dedicated COVID-19 hospitals
  - only cases; no controls

Other potential issues

- Medications for chronic conditions
  - statins, ACE inhibitors, etc. : included as optional
- Occupation, SES, deprivation: optional
- Risk-takers (less likely to be vaccinated; more likely to be exposed?)
  - how to account for this bias (no such questions included)?
    - sensitivity analyses using plausible values ⟹ obtain effect on VE
    - sub-studies on mask use, efforts to social distance, pandemic perception

Discussion

- Issues with the test-negative design
  - representative controls?
  - PCR sensitivity lower over time: misclassification of cases as controls?
    - standardisation of PCR?
    - adjustment for test performance?
  - second control group (disease-free: ER, hospital, community*)?
- How to minimise biases?
  - previous COVID-19, co-infection with influenza
  - co-morbid conditions (medication?)
  - risk-takers
  - frailty, severity
  - time between onset and admission
  - setting
- Have we missed anything?

*Patel et al., Postlicensure evaluation of COVID-19 vaccines, JAMA 2020; 324(19):1939-1940