COVID 19 Vaccine effectiveness studies
Updated guidance on study design and bias

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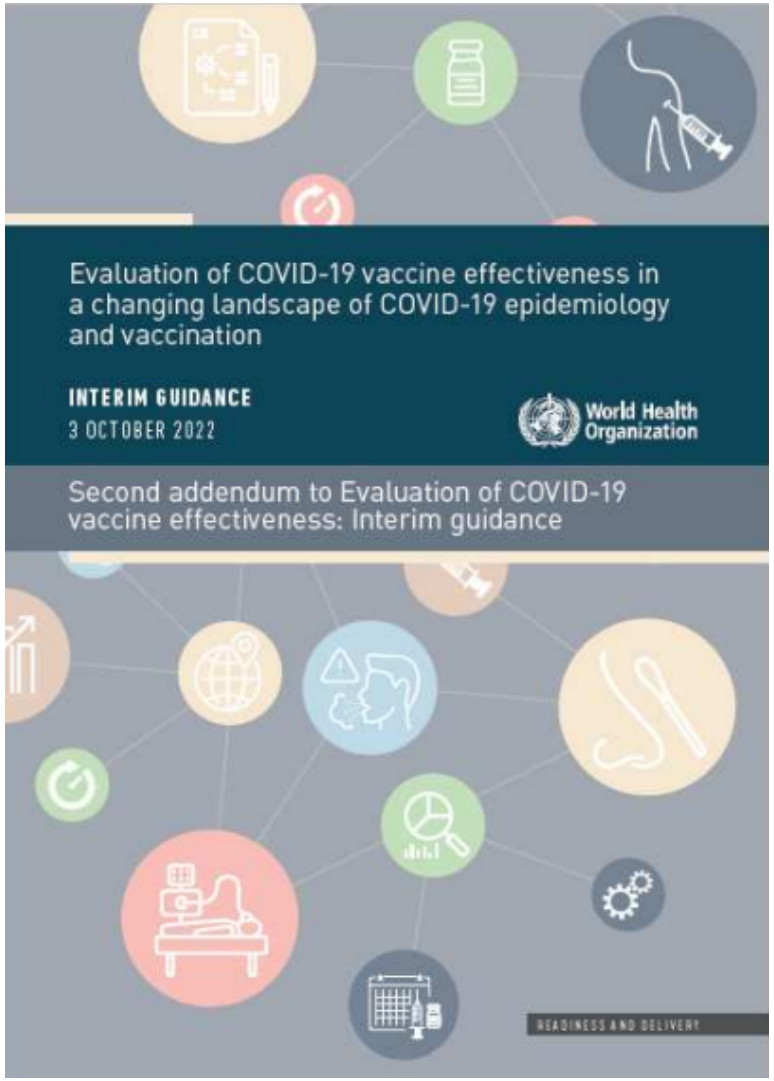
WHO EMRO COVID-19 Vaccine Effectiveness Study;
Status Update and Important Considerations
17 and 24 November 2022

World Health Organization
REGIONAL OFFICE FOR THE Eastern Mediterranean
HEALTH FOR ALL BY ALL a call for solidarity and action

Global guidance from WHO

- March and July 2021: Global guidance and 1st addendum on conducting COVID-19 VE studies
- October 2022: 2nd addendum
  - Lessons learnt from >2000 studies that have highlighted several methodological concerns
  - Waning VE is prominent
  - Omicron causing immune evasion
  - High vaccination rate in some settings
    - unvaccinated dissimilar to vaccinated ➡ Bias
  - Complex vaccination landscape:
    - multiple vaccines used at different periods
    - targeting specific groups of individuals
    - heterologous schemes for primary series and booster vaccines
  - Hybrid immunity common in many settings makes interpretation of VE evaluations more challenging



Overview

- Covid-19 Vaccine Effectiveness studies (VE): Updates from HQ (Daniel Feikin presentation)
  - Hybrid immunity
  - Variant specific VE estimates
  - Absolute and Relative VE of 2nd booster dose

- This presentation
  - Study design
    - Case selection
    - Outcome comparison group selection (controls)
    - Vaccine comparison group
      - Relative VE
      - The first week after vaccine dose
      - Using other time periods after vaccination
  - Bias
    - Negative VE
    - Changes in testing practices
    - Test negative controls positive for influenza
    - Duration of protection

Study design

Study design/ Case selection – outcome definition

- Severe disease definition in the context of Omicron in VE evaluations
  - Hospitalization with SARS-CoV-2 infection (+/- symptoms) = commonly used proxy for severe disease

  But
  - Criteria for hospitalization varied across place and time
  - Omicron = attenuated intrinsic severity + high prevalence of infection ➡
    - Frequent hospital admissions among people with incidental Omicron infection unrelated with reason for admission
    - Frequent hospital admissions among people with infection-induced exacerbation of chronic medical conditions
  - Misclassifications of the severe outcome due to Omicron ➡
    - Underestimation of VE against hospitalized Omicron cases
  - Suggestions
    - Use of more specific case definition for severe respiratory COVID 19 infection
      - Indicators of respiratory distress = O_2 requirement, ICU admission, mechanical ventilation
    - Duration of hospitalization > 2 days or more in the case definition
    - VE against progression from Omicron infection to hospitalization or severe respiratory disease

⚡ Change in case definition makes historical comparison difficult – small sample size because severe cases are rare

Study design / Outcome comparison group selection (controls)

- Assuming persons without a positive test result are negative
  - Omicron = high incidence of infection including asymptomatic
    - Control = tested negative at one point in time or never tested negative
    - Misclassification in VE evaluations
  - Suggestions
    - Routine testing in order to avoid misclassification in cohort study (issue mostly for database studies)
    - TND: exclusion of all persons with a recent history of infection (<90 days prior to enrollment) + participants tested at enrollment

- Control selection for VE evaluations of severe diseases among hospitalized cases
  - Controls = test-negative hospitalized cases (TND)
  - High COVID 19 incidence
    - Few persons with COVID 19 symptoms are tested negative ➡ few controls
    - Lower negative predictive value of lab test ➡ false negative and misclassification bias
  - Suggestions
    - Controls = Test negative persons from the general population (TND) when testing is done prior to decision to hospitalize and cases and controls rise from the same source pop

Study design/ Vaccine comparison group

- Vaccinated comparison group for VE of boosters doses

  - Absolute VE (aVE) = $\frac{\text{risk among vaccinated}}{\text{risk among unvaccinated}}$ X 100

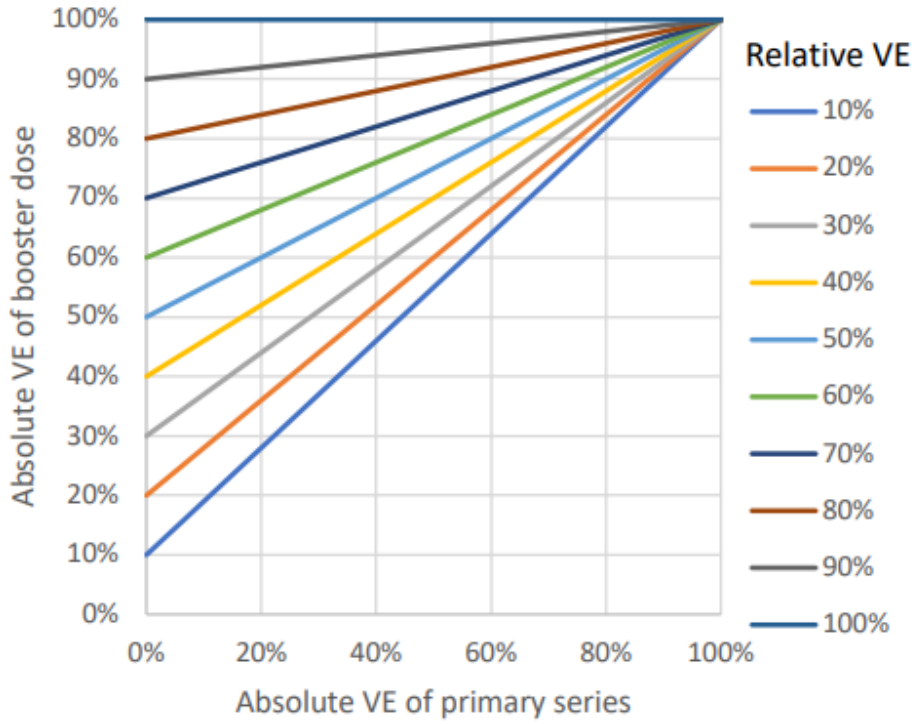
But

  - High vaccine coverage in many settings → Unvaccinated individuals quite different from vaccinated individuals
    - SARS COV 2 exposure and/or disease risk
  - Suggestions
    - Vaccine comparison group for VE of booster doses (1st or 2nd booster dose)
    - Relative VE = compare different level of vaccine doses (e.g. 1st booster compared to primary series or second booster dose compared to first booster dose)
- When we use vaccinated comparison group, it is important to select:
  - Comparable group in terms of age and risk profile
  - Only persons who are eligible for the vaccination being evaluated (1st or 2nd booster dose)
    - Higher risk of exposure (HCW) or higher risk of severe disease (elderly)
- Comparison to time frames post vaccination
  - Comparison of persons during the same period of time to account for circulating variant
    - Stratification by time period
    - Adjustment by calendar time
  - Interpretation of VE estimates: time since administration of the last dose should be considered (waning)
    - Compare 1st booster dose to primary series in the period 6-9 months after primary series (due to waning)

Study design/ Vaccine comparison group/ Relative VE

- Relative VE (rVE) provides a way to quantify additional preventive benefit of a booster dose vs a primary series
- rVE= $\frac{\text{aVE booster} - \text{aVE primary serie}}{1 - \text{aVE primary series}}$ X 100
- Low aVE primary series
  - aVE booster dose = rVE booster dose
  - If aVE primary series = 0% (x axis) and rVE of the booster dose = 50% (light Blue line) then aVE of the booster dose = 50%
- High aVE primary series
  - rVE of the booster dose vary quite dramatically
  - Compare to incremental gain of the aVE who is small
  - If aVE primary series = 90% (x axis) and rVE of the booster dose = 50% (light Blue line) then aVE of the booster dose = 95%

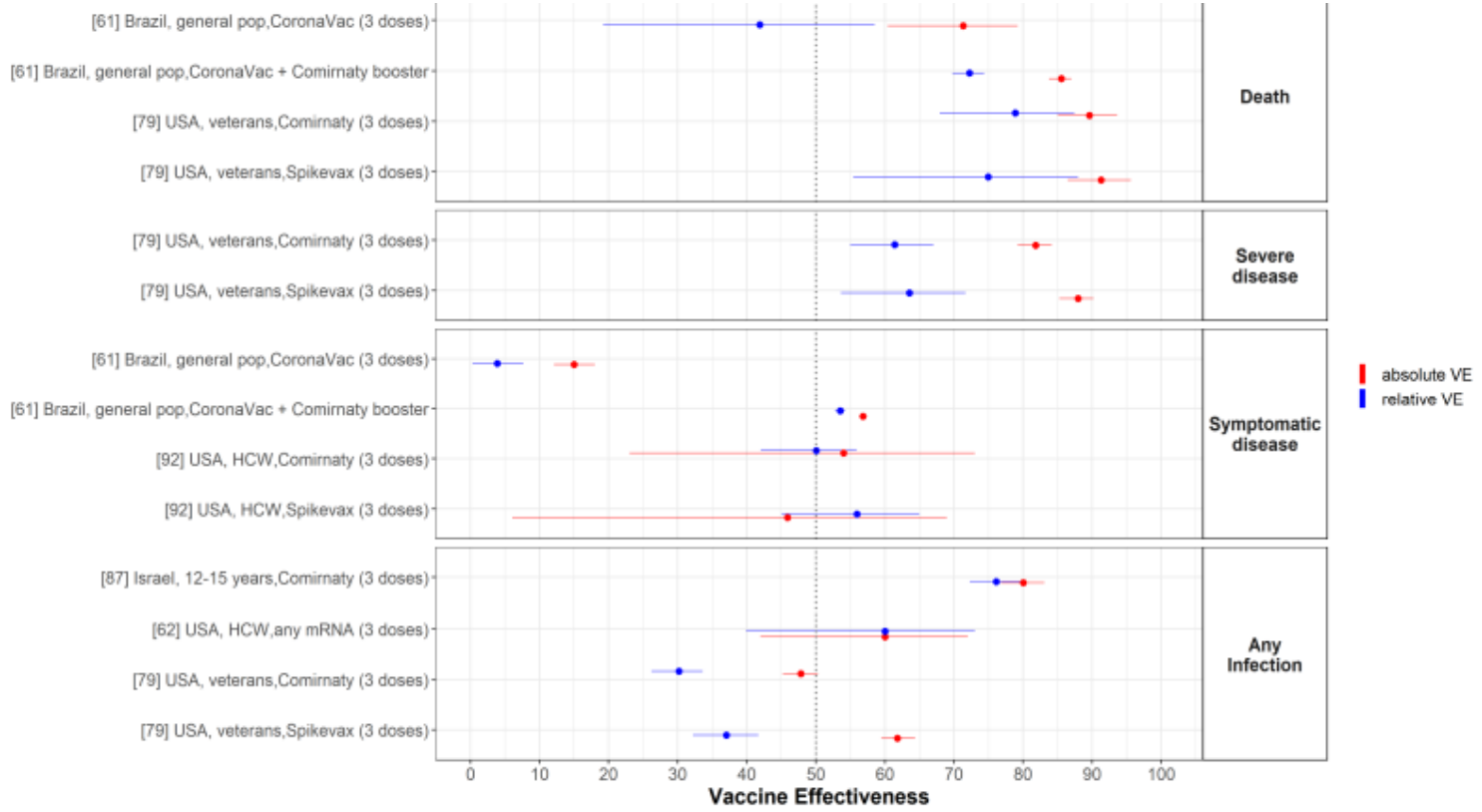
Relative VE/ Relation between Absolute VE to relative VE



Study design/ Vaccine comparison group/ Relative VE

- The true aVE of the booster dose should always be higher than the rVE
- The rVE of a dose must be interpreted with this understanding
  - comparison group has potentially some residual protection from the vaccine.
- Interpreting the rVE requires knowing
  - the population and vaccine being evaluated
  - the timing of the last dose
  - the clinical outcome
  - epidemiologic situation, including the circulating SARS-CoV-2 variants
- aVE of the primary series from one study is context and time-specific
  - cannot be used to calculate the aVE of a booster dose in another study
- rVE of a given vaccine cannot be compared across studies
  - rVE is dependent on aVE
  - averted events can vary widely from study to study
- If possible investigators should report
  - rVE and aVE of the dose being evaluated (even suspected bias in aVE)
  - Absolute risk reduction in cases averted per denominator pop
- Communication challenges in communicating relative vaccine effectiveness
  - This study demonstrated a rVE of 50%
    - There was 50% of reduction in the risk of Omicron symptomatic disease
    - among those who received a booster dose of vaccine X, a median of y DAYS ago
    - compared to those who received the primary series of vaccine X, a median of X DAYS ago.

Absolute and relative VE of the first booster dose against Omicron



- rVE is lower or equal to the aVE of the booster dose
  - persons in the comparison group potentially have some vaccine-induced immunity
- aVE of the booster dose
  - cannot be calculated from the rVE alone and need to be provided by the investigators
  - rVE and the aVE of the primary series at the same time in the same population is necessary

[a] Labels on y-axis indicate: [reference number], country, population, vaccine. Reference numbers refer to study numbers in Table 2 of the *COVID-19 Vaccine Effectiveness Results Summary Table* found at https://view-hub.org/resources.

Study design/ Vaccine comparison group/ The 1st week after vaccine dose

- Comparison of risk among those at least two weeks post-vaccination to those in the first week after vaccination.
- Not expected impact of the vaccine in the first week (immune system responding to a vaccine dose)
- Issue: reduced risk observed in the first few days after vaccination
  - During COVID-19 vaccination roll-out, many countries advised persons to defer vaccination if they were feeling ill
  - Persons recently infected selectively excluded from vaccination but likely have been diagnosed in the week when they were originally scheduled for vaccination → Deferral bias/healthy vaccinee bias
- Persons vaccinated with a first or a second booster more similar to those with primary series or first booster dose/ unvaccinated
  - minimizing confounding due to behavioral differences between vaccinated and unvaccinated persons.
  - first week after the 1st booster dose = comparison group
  - Use day 3-7 or day 4-6 after vaccination as the comparison group, excluding persons in the first three days after vaccination.

Study design/ Vaccine comparison group/Using other time periods after vaccination

- Waning VE against Omicron infection and symptomatic disease for the primary series within a few months after vaccination
- Presence of waning immunity against infection and symptomatic disease can be used
  - to minimize the bias of comparing vaccinated persons to the increasingly different unvaccinated persons
- rVE evaluation against infection comparing vaccinated persons with persons vaccinated further in the past
  - results in the rVE approaching the aVE.
- rVE evaluation against infection comparing persons with their last dose of the primary series >180 day ago to persons who received their booster dose.
  - If the effectiveness of the primary series is near zero by six months post vaccination ⇒ rVE for the booster dose close to the aVE for the primary series + booster dose
  - Time frame of >180 days need to be adjusted to the context
- rVE evaluation against infection comparing persons with a booster dose to those vaccinated with the primary series 5-9 months and >9 months ago
  - rVE of a booster dose against infection restricted to those vaccinated with the primary series 5-9 months ago was 36.4%
  - 46.5% when restricted to those who received their primary series >9 months prior
  - Due to residual protection from the primary series in the 5–9-month period
- rVE evaluation against severe disease using comparison with other time periods after vaccination is not recommended
  - due to the generally slower waning of protection against severe disease with time since vaccination.

- Thank you for your attention