Important considerations in the statistical analysis of COVID-19 vaccine effectiveness studies & interpretation of results for immunization policy-making

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Content

I. Considerations in statistical analysis of CVE studies

II. Considerations for combined VE estimates

III. Considerations in the interpretation of results for policy-making

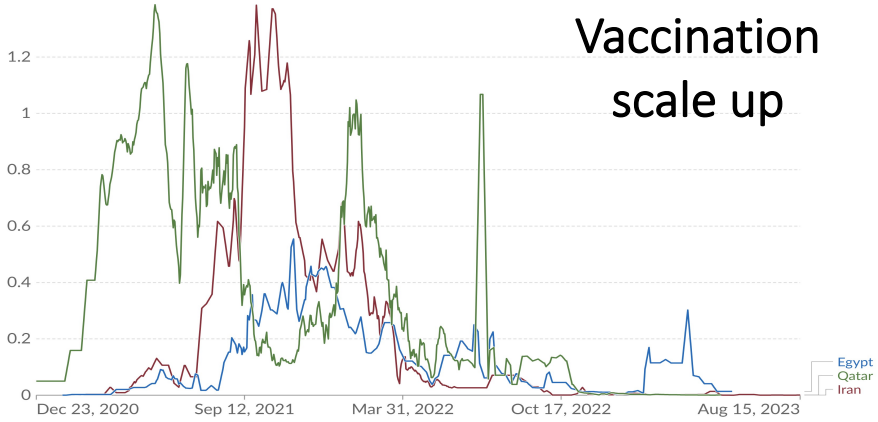
COVID-19 Vaccine Effectiveness (CVE) studies

- **constantly evolving COVID-19 situation** and epidemiology (i.e. emerging variants, varying vaccination strategies) that varies by country
- policy recommendations need to be regularly updated and **rely on evidence from CVE studies**

- CVE studies **provide real-time data** on the effectiveness of COVID-19 vaccines (primary series and booster doses)
- estimation of magnitude and duration of protection in the population
- effectiveness against circulating variants of concern (VOC)

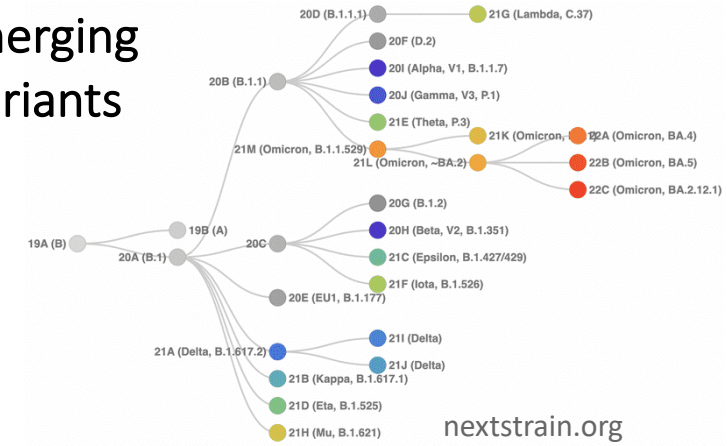
- observational studies are **prone to bias and confounding**
- careful study design and analysis plans can minimize biased results

Vaccination scale up



https://ourworldindata.org/covid-vaccinations

Emerging variants



nextstrain.org

Factors to consider in planning and analysis of study

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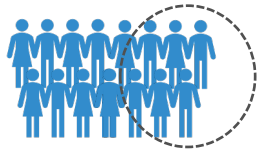
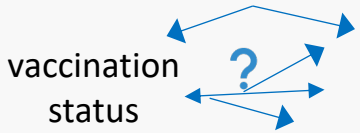
Study design & planning

Sample size & selection



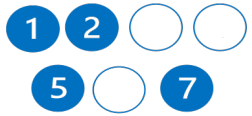
Bias



- No correction for low sample size (or bias) during analysis possible!
- Need for careful study design, clear definition of inclusion & exclusion criteria

Data collection & analysis

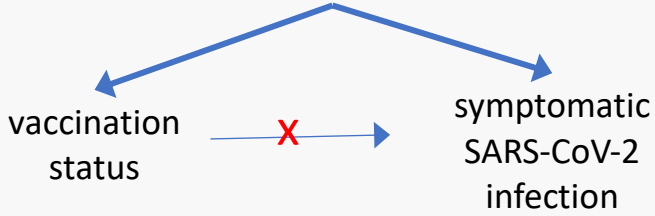
Missing values



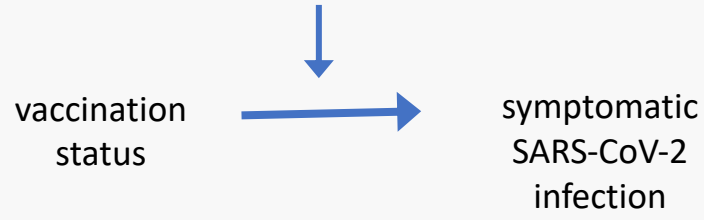
Lost to follow up
(cohort only)

- Adjustment possible but can be 'tricky' to avoid introducing bias (NB: complete case analysis can also introduce bias!)

Confounder



Effect modifier



- Can be accounted for in multivariable or stratified analysis (for known observed confounders)

Two common CVE designs are cohort and TND

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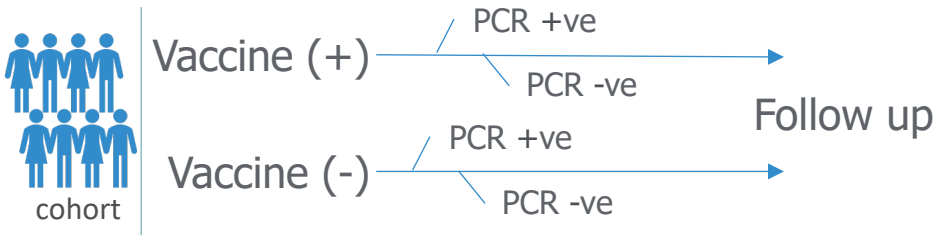
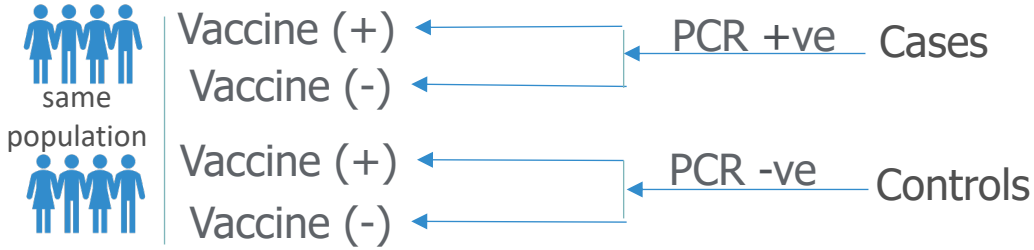
Cohort study (i.e., in health care worker)



- Provides disease burden measures (incidence among vaccinated and unvaccinated persons)
- Use for specific cohorts easy to follow up
- Nested TND design may be conducted
- ~12 months
- VE = 1 – hazard ratio (HR)
- VE = 1 – rate ratio (RR)

Test-Negative case control design (i.e. in SARI patients)



- Leverages an existing surveillance platform, such as Severe Acute Respiratory Infection (SARI)
- Includes cases and controls from the same source populations
- Vaccination status assessed prior to knowing the test result
- Recommended design L/MICs, requires less resources than a cohort study
- ~> 6 months
- VE = 1 - odds ratio

Specific considerations of cohort and TND studies

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Cohort study (i.e., in health care worker)

- Censoring and lost to follow-up, (adherence to follow-up protocols)
- Studies may lack power if vaccine coverage is very high among HWs
- Clustering by health facility to be accounted for in analysis
- Variation in exposure by HW unit, with or without patient-facing role

Test-Negative case control design (i.e. in SARI patients)

- Misclassification of cases and controls most relevant bias
- Avoiding health care seeking bias
- Reduced selection bias (if SARI case definition is adhered to)
- Controls who tested positive for influenza might need to be excluded
- Adjustment by calendar time required in analysis
- Analysis of secondary outcomes, i.e. using conditional logistic regression

Adapted from WHO guidance documents for HW cohort and TND SARI studies

Potential confounders to adjust for in CVE studies

Common confounders:

Person-related
- Age
- Sex
- Comorbidities
- Health care worker
- Health care worker department (if HW cohort)
- Personal protective behavior

Study-related
- Region, study site, hospital
- Calendar time,
- Time of specimen collection

Other possible confounders:
Smoking status, Pregnancy, …

Characteristics	PCR test positive, cases (n = 19,500)	PCR test negative, controls (n = 22,585)	P-value
Age group (years)			<0.001
0-9 years	563 (2.9%)	448 (2.0%)	
10-19 years	239 (1.2%)	4%)	
20-29 years	1026 (5.3%)	.4%)	
30-39 years	2800 (14.4%)	.4%)	
40-49 years	3495 (17.9%)	.5%)	
50-59 years	4115 (21.1%)	.0%)	
60-69 years	3857 (19.8%)	3%)	
≤70 years	3404 (17.5%)	928 (4.1%)	
Gender			<0.001
Male	8613 (44.2%)	11,290 (50.0%)	
Female	10,886 (55.8%)	11,295 (50.0%)	
Health care workers			<0.001
No	19,348 (99.2%)	21,524 (95.3%)	
Yes	151 (0.8%)	1061(4.7%)	
History of PCR positive			0.923
No	19,377 (99.4%)	22,442 (99.4%)	
Yes	122 (0.6%)	143 (0.6%)	
(table truncated)			

Heidarzadeh et al 2022, CVE case control study Iran (Int. Journal Inf. Diseases)

Example of confounders with effect on VE

(Unadjusted vs adjusted VE estimates)

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VE of AstraZeneca against **temporary admission** in the general population (circulating variants were alpha and Delta)

Vaccination status	Cases N (%)	Controls N (%)	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)	Adjusted vaccine effectiveness (95% CI)
Unvaccinated	1881(0.94)	15676 (0.92)	Reference	Reference	Reference
Single dose, <21 days	34 (0.01)	61 (0.003)	2.14 (1.49-3.08)	1.67 (1.15- 2.41)	-
Single dose, ≥21 days	64 (0.03)	676 (0.03)	0.79 (0.61-1.02)	0.47 (0.36- 0.62)	0.53 (0.38-0.64)
Two doses, within 1-30 days	9 (0.004)	201 (0.01)	0.44 (0.22-0.86)	0.22 (0.11-0.44)	0.78 (0.56-0.89)
Two doses, within 31-60 days	1 (0.0005)	105 (0.006)	0.09 (0.01-0.71)	0.03 (0.005- 0.25)	0.97 (0.75-0.995)
Two doses, within 61-90 days	0	54 (0.003)	1	1	-
Two doses, within 91-120 days	2 (0.001)	89 (0.005)	0.24 (0.06-0.98)	0.07 (0.01-0.31)	0.93 (0.69-0.99)
Two doses, within 121-150 days	0	79 (0.004)	1	1	-
Two doses, ≥ 151 days	0	11 (0.0006)	1	1	-
Third dose	0	11 (0.0006)	1	1	-

Heidarzadeh et al 2022, CVE case control study Iran (Int. Journal Inf. Diseases)

Adjusted for: Age group, sex, week sampling polymerase chain reaction (PCR). Health care workers, History of PCR positive

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Example of confounders with negligible effect on VE

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COVID-19 Vaccination Status	Total Person Time (Days)	Number of PCR Positives	Incidence Rate per 100,000 Person-Days	Unadjusted Vaccine Effectiveness % (95% CI) *	Adjusted Vaccine Effectiveness % (95% CI) **
Unvaccinated	90,367	114	126.2	Reference	Reference
Partially vaccinated					
≥28 days after receiving ChAdOx1 first dose only ***	159,423	87	54.6	75.5 (67.6–81.5)	75.4 (67.2–81.6)
≥14 days after receiving BNT162b2 first dose through receipt of second dose	7196	2	27.8	91.6 (65.9–97.9)	91.4 (65.1–97.9)
Fully vaccinated					
≥14 days after BNT162b2 second dose	90,015	12	13.3	95.1 (90.6–97.4)	94.5 (89.4–97.2)

Alali et al 2021, retrospective HW cohort study Kuwait (Healthcare (Basel))

* Vaccine effectiveness was estimated using a Cox proportional hazards model accounting for time-varying immunization status in STATA statistical software ver. 16.1 (Stata Corp., College Station, TX, USA). ** Hazard ratio is adjusted for age, sex, and nationality. *** Participants received first dose of ChAdOx1 but had not received second dose by the end of the study period. PCR: polymerase chain reaction; CI: confidence interval.

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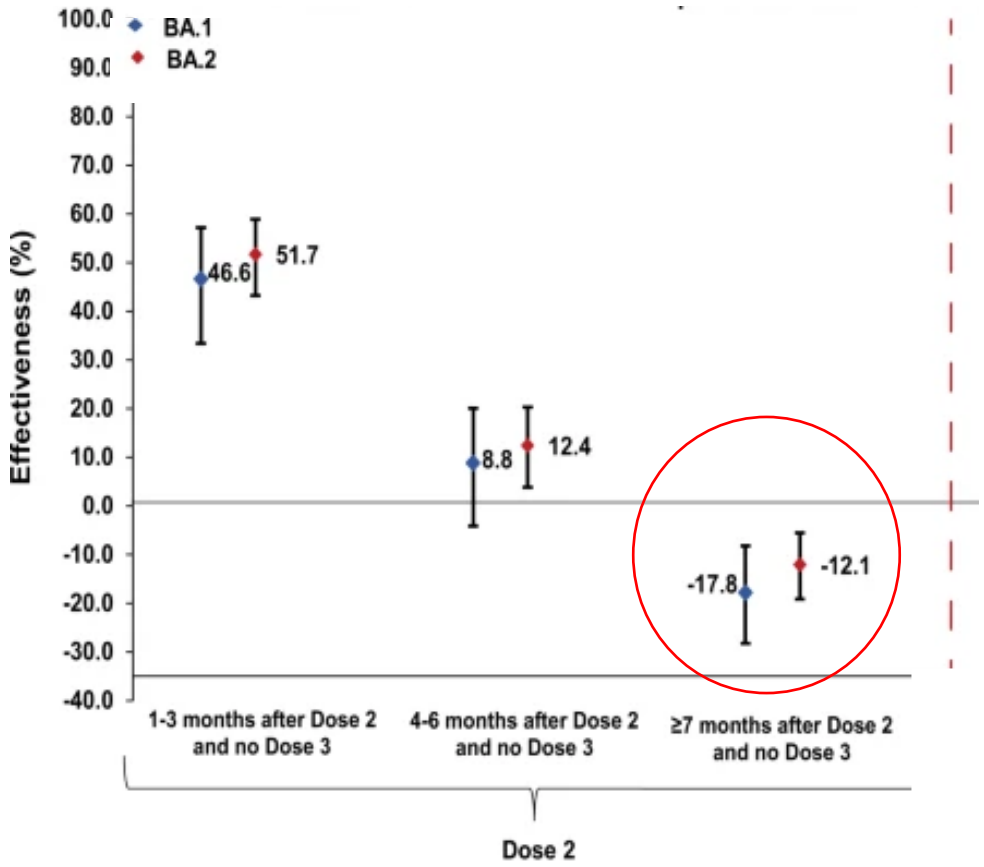
Example negative VEs

Effectiveness of BNT162b2 against symptomatic BA.1 and BA.2 Omicron infections



Chemaitelly et al. 2022. TND Qatar. (Nature Communications)

Possible explanations:

- True effect…not impossible but unlikely
- Residual confounding
  (potential differences between the cohort that received 2nd dose and cohort that did not receive a 2nd dose)
  - "vaccinated persons having a higher social contact rate or adhering less to safety measures than unvaccinated persons"
- Differential outcome misclassification
  (cohort that did not receive the 2nd dose could have been less frequently tested if ill)
- Depletion of susceptibles bias
  (the use of discrete-time hazards conditioned on survival at least 6 months after vaccination could have resulted in selection bias was due to depletion of susceptibles from the cohort that did not receive the 2nd dose)

Barda, N., 2023 (The Lancet Infectious Diseases)

Potential biases that can affect CVE estimates

Bias	Methods to minimize biases
Selection bias	Inclusion and exclusion criteria, follow up with refusals
Collider bias (TND)	Limit to severe patients; limit to older adults
Recall/ascertainment bias	Use vaccination records where available instead of reported vaccinations
Diagnostic bias	Test all persons or a systematic random sample meeting protocol-specified case definitions
Misclassification of the exposure	Exclude outcomes occurring in periods of ambiguous vaccine effect, e.g. 2 weeks after first dose from primary analysis
Misclassification of outcome (TND)	Exclude TND controls with COVID-19-specific symptoms (reduce false negatives) Use clinical case definition for enrolment (reduce false positives)
Prior infection	Perform sensitivity analysis excluding those with prior SARS-CoV-2 infection by history or lab confirmed
Spurious immunity	Do VE study soon after vaccine introduction; anchoring in time

Table adapted from WHO guidelines

Prior infection & differential depletion of susceptibles

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Prior infection

- Previous infection may alter the effect of vaccines
- Previous infection may also affect exposure and outcome in individuals (i.e. more/less likely to be vaccinated, more/less likely to be exposed and less likely to be infected again)
- Status and date of previous infection in study participants might not always be known and different definitions based on ascertainment/diagnostic exist (e.g. laboratory-confirmed by rRT-PCR or rapid test, epidemiologically linked, or clinical)

Differential depletion of susceptibles

- Infected people in the population will be for some time at lower risk of reinfection and disease
- Infected people are more likely to be unvaccinated than vaccinated, and difference increases over time

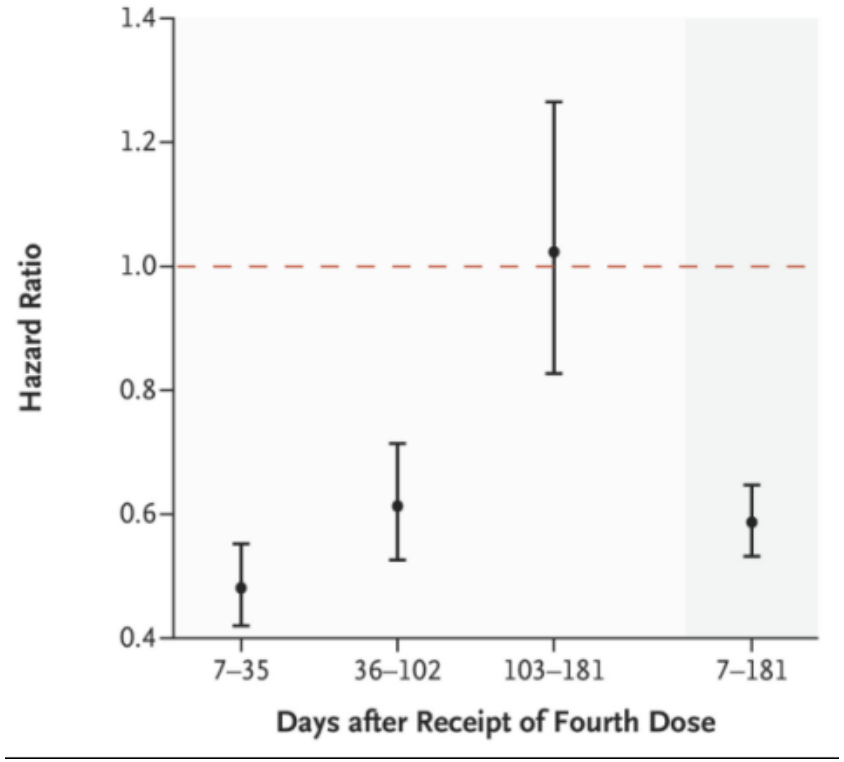
➢ VE may appear to wane more quickly over time than, hence less effective as in reality

- To minimize bias the model needs to be adjusted for history of prior infection
- The influence of the bias is affected by the predominant variant circulating

WHO. 2021. Evaluation of COVID-19 vaccine effectiveness

Waning immunity

"Not a bias but a biological course to estimate"

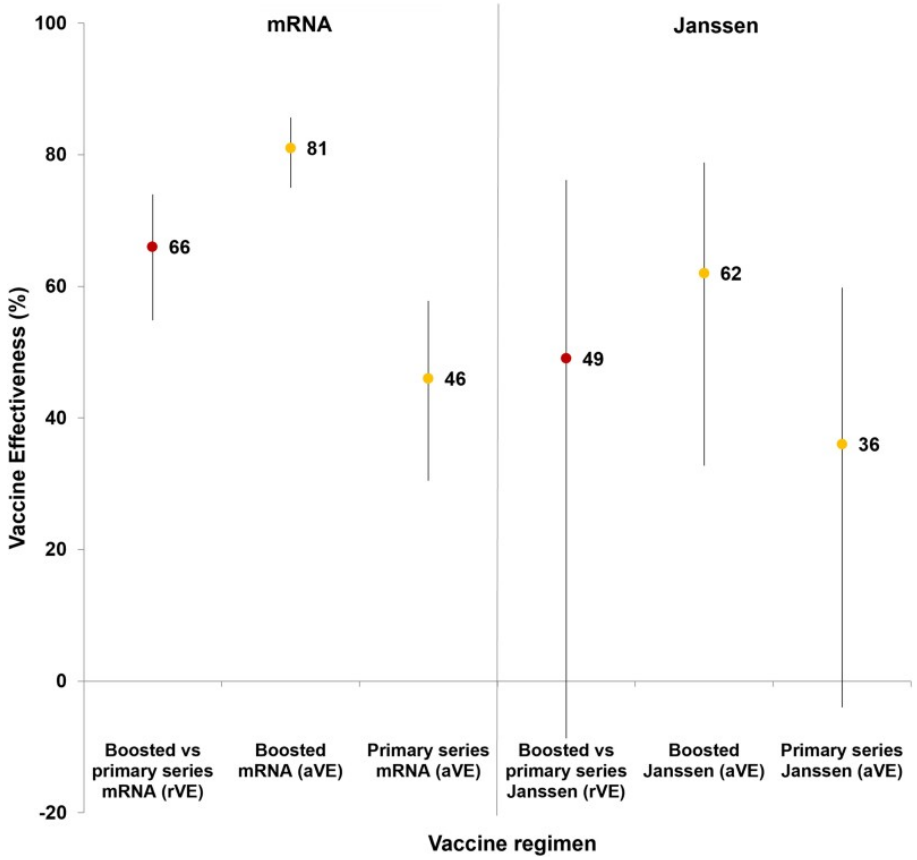


Courtesy: Noam Barda MD, PhD

- Looking at the entire period masks differences in the effectiveness over time
- Modeling discrete periods introduces potential selection bias (requires individuals to remain unexposed until a specific period)
- Review individuals included vs. excluded in each discrete period to gauge severity of selection bias
- No "gold standard" exists and careful interpretation is required

Figure and text adapted from Noam Barda MD, PhD, WHO Global Consultation for Vaccine Effectiveness Studies 14 September, 2023

Absolute vs relative VE



Absolute and relative vaccine effectiveness (rVE) against hospitalization (point estimates [95% confidence intervals]) for mRNA and Janssen vaccine primary series plus first booster dose and primary series alone, December 2021–April 2022

absolute VE (aVE): comparing frequency in outcome in vaccinated versus unvaccinated groups

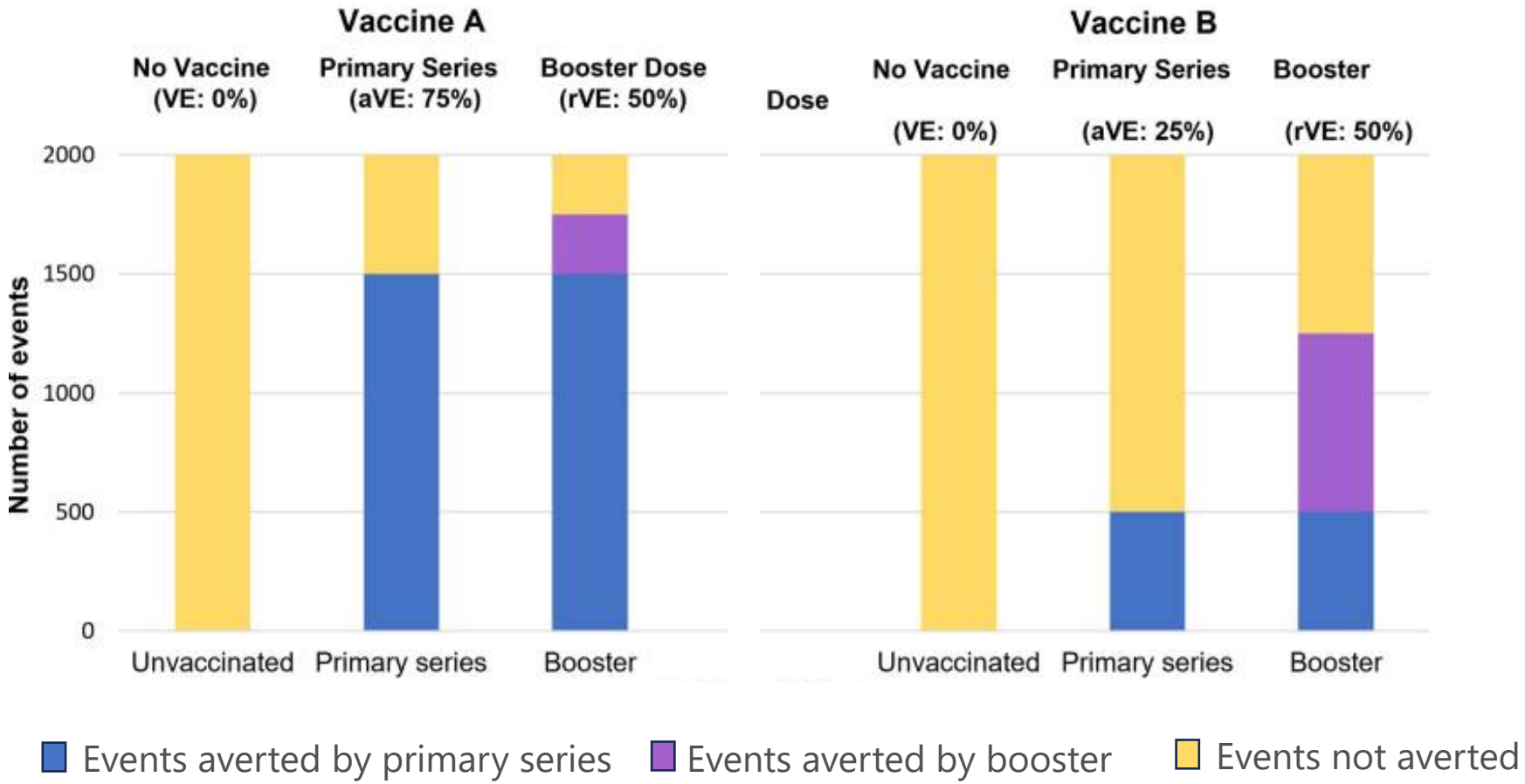
relative VE (rVE): comparing frequency in outcome in vaccinated with additional dose(s) versus vaccinated with primary series only

relative VE:

- Proportion of residual disease remaining after the primary series that is prevented by additional vaccine dose(s)
- Useful to describe incremental benefit
- Limited use when comparing across studies, or when aVE varies for the comparator vaccine
- Future studies may be able to only look at rVEs , while aVE remains more robust indicator

Lewis et al. Open Forum Infect Dis. 2022 Dec 31;10(1):ofac698.

Absolute vs relative VE, illustrative example



Lewis et al. Open Forum Infect Dis. 2022 Dec 31;10(1):ofac698.

Different outcome measures of interest for VE evaluations

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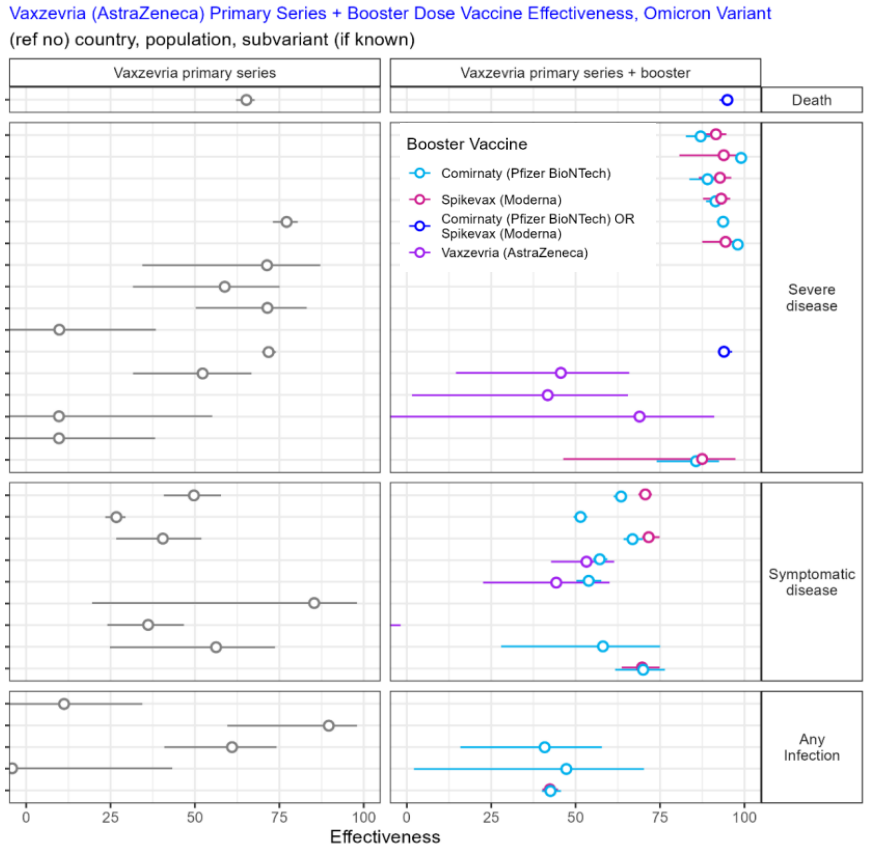
VEs of interest for different outcomes

- **Mortality**
  - Difficult to distinguish COVID-19 and non-COVID-19 deaths
  - In the later periods deaths might *with* SARS-CoV2 rather than *due* to SARS-CoV2
  - Relatively rare events, difficult to accumulate enough 'events' to reach statistical power
- **Severe COVID-19 disease**
  - Use of hospital and ICU admission as proxy challenging due to differential health care utilization and admission criteria over time and location
- **Symptomatic COVID-19 disease**
  - Primary outcome of most vaccine clinical trials
  - Requires consideration of health care seeking behavior
- **COVID-19 Infection and transmission**
  - VE evaluation more difficult than for disease outcomes
  - Requires testing regardless of symptoms
  - Recommended only in specific well-resourced settings

VEs varies by outcome



WHO October 2023. Results of COVID-19 Vaccine Effectiveness Studies

Summary points

- Observational studies have merits in informing policies, despite their potential flaws
- Limitations need to be clearly presented and communicated

- Study design specific biases need careful consideration for calculating and interpreting VE estimates

- Absolute VE estimates better reflect the true benefit of vaccines
- Relative VE estimates can be useful for incremental effects

- Many questions remain on booster recommendations, duration of protection among other, hence ongoing CVE studies will be needed

Content

I. Considerations in statistical analysis of CVE studies

II. Considerations for combined VE estimates

III. Considerations in the interpretation of results for policy-making

Meta-analysis

Pooled analysis

Systematic review/ evidence synthesis

Meta-analysis

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Strengths/benefit

- Provides a range of VE estimates across different settings as well as a combined summary estimate
- Strengthened evidence while “not hiding” potential meaningful variation across studies
- Allows to attach weights to single studies to reflect quality/reliability of results

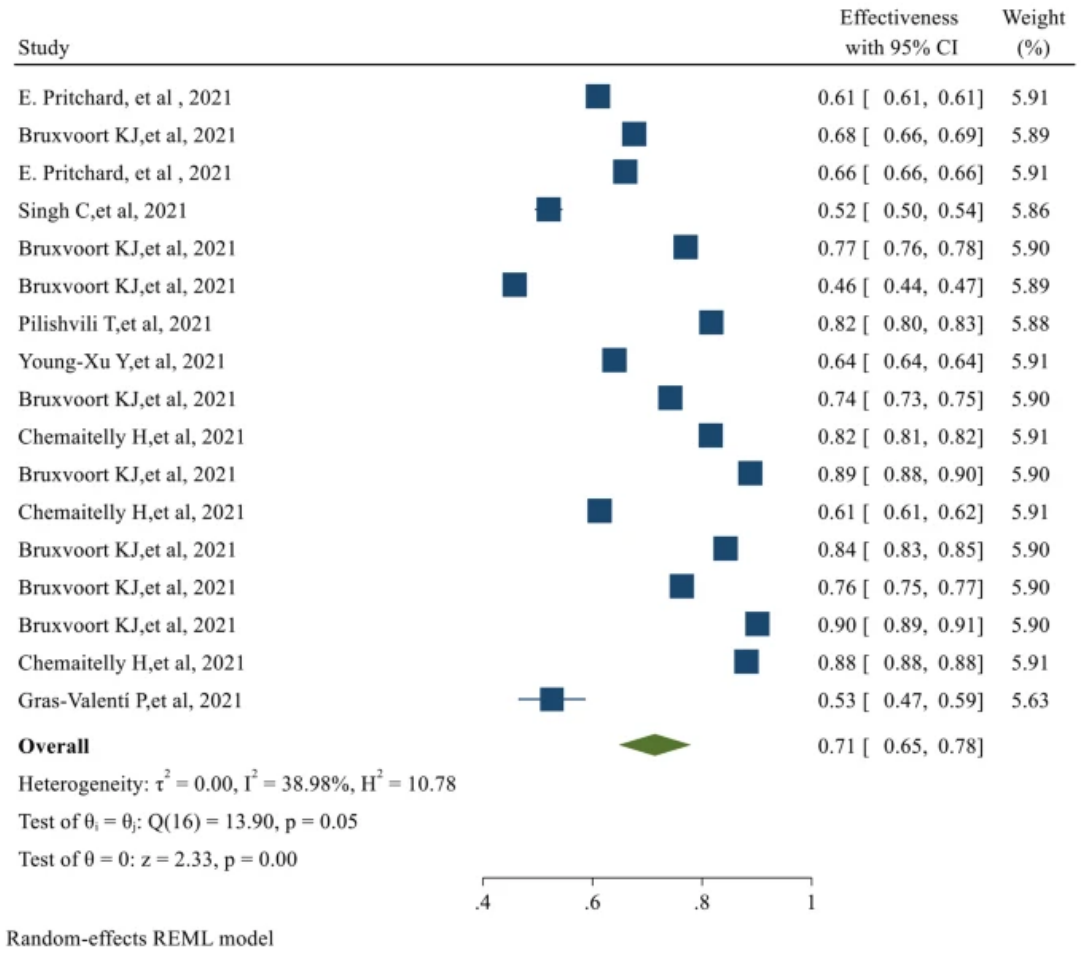
Limitations

- Prone to publication bias
- Can be misleading if studies differ in outcome or exposure definition
- Relies on reported VEs

Requirements:

- Defined inclusion criteria for studies
- Systematic review and search for published results
- Risk of bias assessment for individual studies
- Analysis skills to obtain overall estimate

Example, meta-analysis, VE against infection



Soheili M et al 2022. Annals of Clinical Microbiology and Antimicrobials.

Pooled analysis

Strengths/benefit

- Increased statistical power and more robust VE estimates/smaller CIs
- Single estimate to communicate (simpler, but looses granularity)

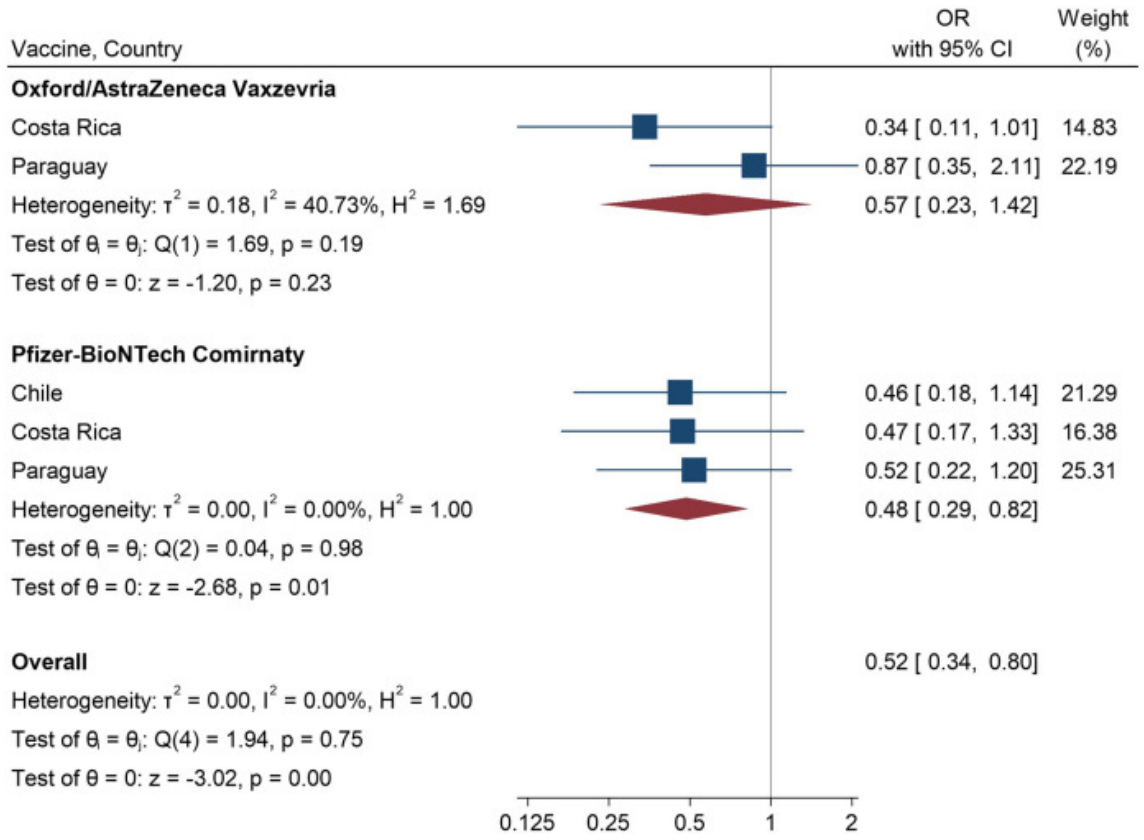
Limitations

- Can be misleading if studies have high heterogeneity in location/environment
- WHO EURO* guidelines **caution** against pooling of data if populations differ by:
  - Vaccine programs or policies
  - Health systems or care seeking behaviors
  - Overall infection risk

Requirements:

- Access to raw data
- Inclusion and exclusion criteria
- same outcome with at least similar case definition, same vaccine product, same setting, and same or sufficiently similar inclusion/exclusion criteria
- Measure of heterogeneity (Cochrane's Q and the I^2 index)

Example TND SARI PAHO region



Nogareda, et al 2023. The Lancet Regional Health

Systematic review and evidence synthesis

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Strengths/benefit

- Maintains granularity and aims to understand context and relationships
- Draw inference for specific situation and contexts

Limitations

- Does not provide a quantitative but qualitative results, not single estimate hence takes longer to communicate

Requirements:

- In-depths understanding of epidemiological situations in VE study settings and countries
- Structural framework, defined strata to compare and explain different VE estimates

Considerations for combining VE estimates for the EMR

- Time period when studies were conducted
- Study design, follow up periods
- Target population – subgroup
  - HW, total population including/excluding children, SARI
- Vaccine products used
- Differential depletion of susceptibles
  - Vaccination scale up
  - Infection waves
- Country context, vaccination coverage, preventive measures, change in testing or vaccination policies.

		Egypt	Pakistan	Iran	Jordan
Study design		HW cohort	HW cohort	TND SARI	TND SARI
Sample size		1'257	1'707	19'360	1'874
Variants		Omicron	Omicron	Delta, Omicron	Omicron
Vaccines	**Platform**				
Sinopharm	Inactivated	x	x	x	x
Sinovac	Inactivated	x	x		
Bharat	Inactivated			x	
Pfizer	mRNA	x	x		x
Moderna	mRNA		x		
AstraZeneca	Vector-based	x	x	x	x
Johnson& Johnson	Vector-based	x			
Sputnik V	Vector-based	x	x	x	x
Cansino	Vector-based		x		
Jcovden	Vector-based			x	
Sputnik light	Vector-based			x	
Other				x	

Summary points

- Motivation and objectives for combing VE estimates across studies need to be clearly defined,
  - Considerations: WHY, for which comparison group, for which period, outcome and study populations, for specific vaccines or combined by platform, which studies to pool from?
- Pooled analysis is only meaningful for data across similar studies to increase sample size and power of evidence
- If studies or study settings are heterogenous, a pooled estimate is less useful or worse, even misleading, and a meta-analysis or evidence synthesis can be more informative
- Understanding VE estimates from individual studies in respective context before using them in policy or further analysis is crucial

Content

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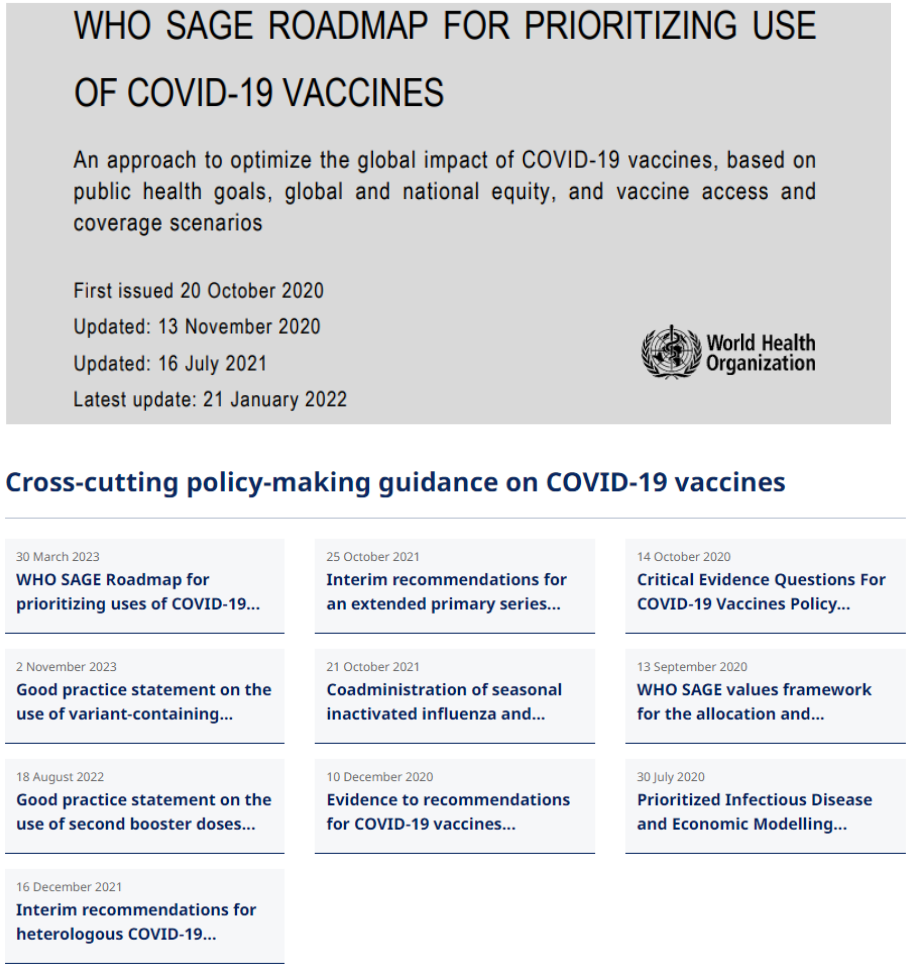
COVID-19 vaccination recommendations need to be context specific and up to date

- Policy recommendations need to be time and context-specific during an evolving pandemic.
- **Recommendations are time-limited** and mainly apply to the prevalent **epidemiological scenario**
- WHO recommendations and the WHO SAGE roadmap for prioritizing the use of COVID-19 vaccines are periodically updated based on the prevailing context.



https://www.who.int/groups/strategic-advisory-group-of-experts-on-immunization/covid-19-materials

Factors to consider when making policy recommendations

- Status of the pandemic and the existing rates of natural and vaccine-induced immunity
- Circulating variants and their immune-escape potential
- Disease control objectives
- The priority target groups and the VE of vaccines and waning of protection in these groups
- Programme feasibility and competing priorities
- Vaccine supply availability

WHO interim recommendations for the optimal use of COVID.19 vaccines (1/2)

HIGH priority-use groups		
Target population	**Vaccination of persons who have never received a COVID-19 vaccine**	**Re-vaccination of persons who have received at least one dose of COVID-19 vaccine**
Oldest adults[1] Older adults with multiple co-morbidities that put them at high-risk of severe COVID-19	Single dose [3]	6-12 months after previous dose
Older adults [2] Other adults [4] with severe obesity or a co-morbidity that puts them at higher risk of severe COVID-19	Single dose [3]	Approximately 12 months after previous dose.
MEDIUM priority-use groups		
Healthy adults [4] Children and adolescents 6 m-17 y with severe obesity or a co-morbidity that puts them at higher risk of severe COVID-19 [5]	Single dose [3]	Not routinely recommended[6]

[1] Age cut-off to be decided by countries (often 75 or 80y). 2 Age cut-off to be decided by countries (often 50 or 60 y). 3 In vaccine-naïve persons a single dose can be considered for primary vaccination since the vast majority of the population has been infected at least once. For inactivated vaccines, 2 doses are required for the primary series. 4 Age cut-off to be determined by countries (often 18-49 or 18-59 y). 5 Regulatory approval and WHO EUL may differ by product (refer to product-specific recommendations. 6 "Not routine recommended" because of low impact and cost-effectiveness.

WHO interim recommendations for the optimal use of COVID.19 vaccines (2/2)

LOW priority-use groups		
Target population	**Vaccination of persons who have never received a COVID-19 vaccine**	**Re-vaccination of persons who have received at least one dose of COVID-19 vaccine**
Healthy children and adolescents 6 mo to 17 y	If countries opt to vaccinate low priority-use groups, they should consider single dose for those > 5 y and 2 doses for those 6 mo to 5 y.[7]	Not routinely recommended[6]
Sub-populations with special considerations		
Persons > 6 mo of age with moderate to severe immunocompromising conditions	2 or 3 doses in consultation with healthcare provider	
Pregnant adults and adolescents[8]	Single dose at each pregnancy regardless of previous vaccination status; ideally in the 2nd trimester or at any opportunity	
Healthcare workers with direct patient contact	Single dose	Approximately 12 months after previous dose

6 "Not routine recommended" because of low impact and cost-effectiveness. 7 Benefit of vaccinating healthy children and adolescents is substantially lower than in older persons or compared to other routine childhood vaccinations. Countries may consider vaccination based on disease burden, cost-effectiveness and other programmatic priorities. 8. Regulatory approvals or WHO EUL for the use in pregnancy may differ by vaccine products.

How did/could VE data inform policy recommendations?

- **Protection** provided by the **index-virus vaccines and hybrid immunity** against different COVID-19 outcomes caused by the circulating virus variants.
- Rate of **waning of protection** in different target groups and the **relative effectiveness of additional doses** of vaccines.
- **Incremental protection provided by variant-adapted vaccines** against different COVID-19 outcomes in priority target groups.
- **Estimation of net benefits** of vaccination **compared to other health interventions** (comparison of the numbers needed to vaccinate (NNV) to avert one hospitalization or death).

Pooled analysis

- What do we mean by a pooled analysis?
  - Synthesis of data from different studies (descriptive)?
  - Meta-analysis with a summary estimate of vaccine effectiveness?
- What type of pooled analysis will assist with policy-making?
  - What are the relative benefits and risks of using descriptive analysis versus summary estimates of VE from meta-analysis for policy-making?
- How should data be pooled & what summary estimates of VE are required to meet this objective?
  - By region?
  - By vaccine?
  - By target group?
  - By variant of concern?
  - By phase of the pandemic?
  - Other factors?

HEALTH FOR ALL BY ALL

GLOBAL HEALTH CONSULTING

Thank you

Technical Consultation Meeting for the EM Regional COVID-19 Vaccine Effectiveness Studies

12–13 November 2023 | Cairo, Egypt

World Health Organization

REGIONAL OFFICE FOR THE Eastern Mediterranean

Biases that can affect estimates of duration of vaccine effectiveness for COVID-19 vaccines

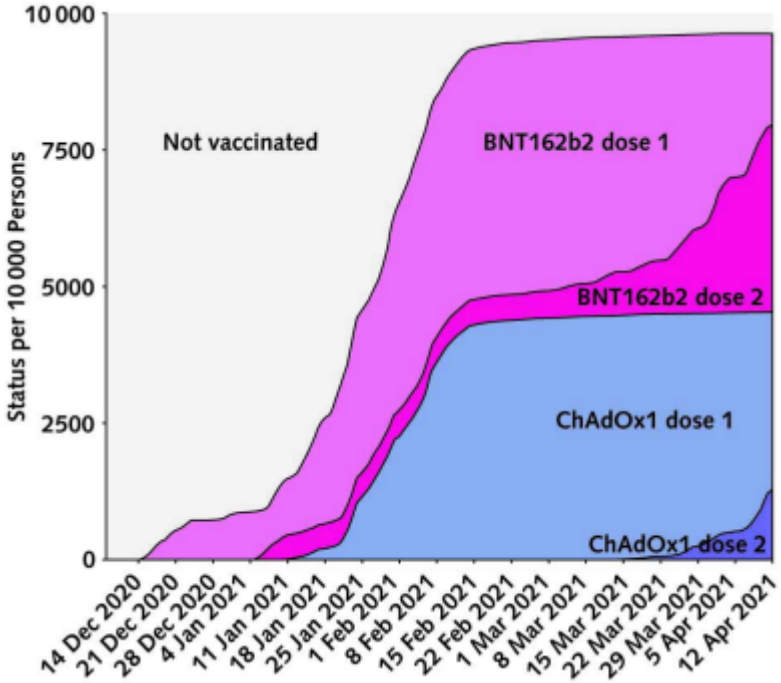
World Health Organization
REGIONAL OFFICE FOR THE Eastern Mediterranean

Bias	Examples	How to minimise bias
People who are unvaccinated have a differential risk of exposure as coverage plateaus at a high level	Demographic and ethnic high-risk groups are over-represented in unvaccinated groups	Adjust for factors if measured and consider using a vaccinated group as a comparator
Earliest vaccinated groups have sustained higher risk	Health-care workers and care home residents	Adjust for factors if measured and stratify vaccine effectiveness analysis by phase of vaccine introduction
People who are vaccinated change behaviour over time in a way that is different to those who are unvaccinated	Differential adherence to NPIs and restrictions by vaccine status (eg, Green Pass or vaccine passports)	Adjust for NPI adherence alone or with mobility (not possible if using administrative databases)
People who are vaccinated have differential testing behaviour over time relative to those who are unvaccinated	Testing differs by vaccine status (eg, Green Pass or vaccine passports), travel-related testing, and use of home testing (eg, lateral flow tests) before accessing confirmatory tests	Test-negative design adjust for testing frequency in the analysis and exclude PCR-negative tests if they shortly follow lateral flow positive tests
Infection-derived immunity increases among people who are unvaccinated	Depletion of susceptible people because of higher rates of infection in those who are unvaccinated over time; this depletion is only an issue if the additional protection of vaccine in people with past infection is greater than those not previously infected	Test (or ask about) previous infection and exclude people with infection from analysis
Misclassification of COVID-19 deaths increases with time	Older people are more likely to die of all causes with time	Verify cause of death where possible
Denominator overestimation of people who are unvaccinated over time	Emigration of people initially in the cohort study out of the catchment area	Regularly correct denominator in cohort studies
Changes in positive predictive value of a COVID-19-positive test result	When prevalence is low for the same specificity, positivity predictive value will be lower, leading to a greater misclassification bias	Use tests with high positive predictive values and use symptomatic cases
Changes in interval between doses over time	Some countries changed dosing intervals several times because of vaccine supply fluctuations	Assess whether interval affects vaccine effectiveness in sensitivity analyses and consider restricting the analysis to the dominant dosing interval

Feikin DR, et al. 2022 (The Lancet)

Limitations of observational VE studies

- Limited **generalizability**, since assumptions about study and target populations might differ
- To what extent study results can be applied to a different population than was sampled for the study is often unclear (**transportability**)
- Limited **reproducibility** or not feasible given time-varying factors and evolving pandemic over time
- Potential risk for **misinterpretations** by media and policymakers

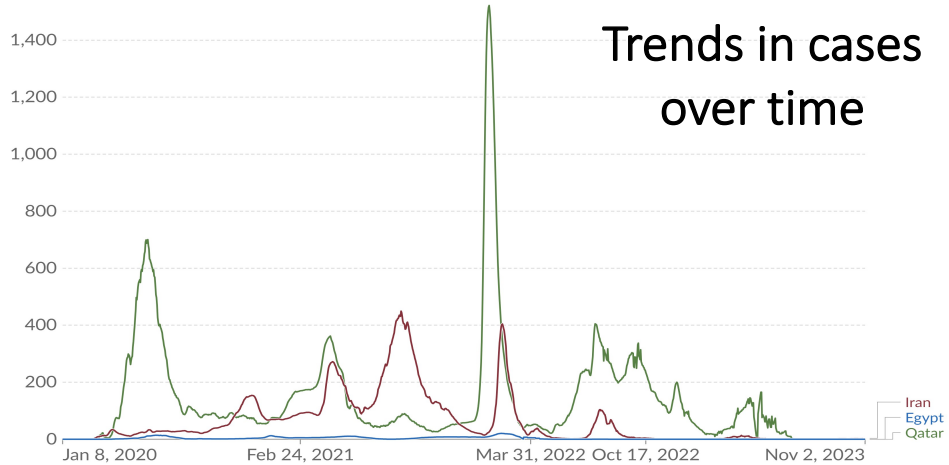


Hulme WJ, et al. 2023 (Ann Intern Med)

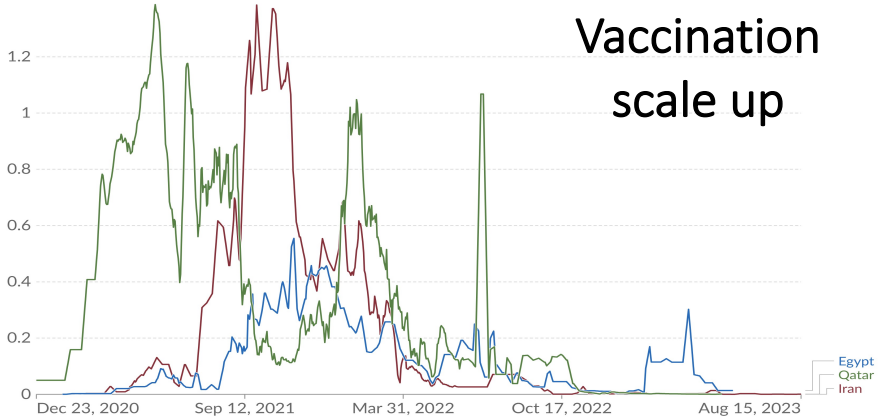
Considerations and limitations when using VE studies for policy-making

- Level of community transmission
- Infection-induced immunity, and hybrid immunity
- Mitigation policies and adherence in population
- Asymptomatic vs. symptomatic infection
- Interval between vaccination
- SARS-CoV2 Variants in circulation
- Homologous vs Heterologous schedules
- Timing and target populations of vaccines

Changing landscape of COVID-19



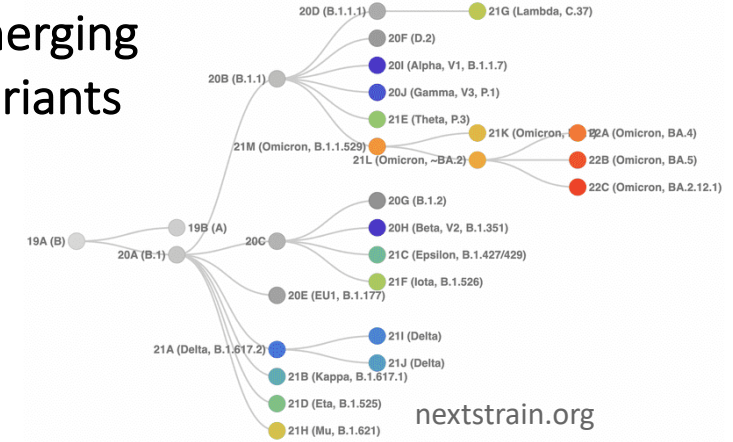
Trends in cases over time



Vaccination scale up

https://ourworldindata.org/covid-vaccinations

Emerging variants

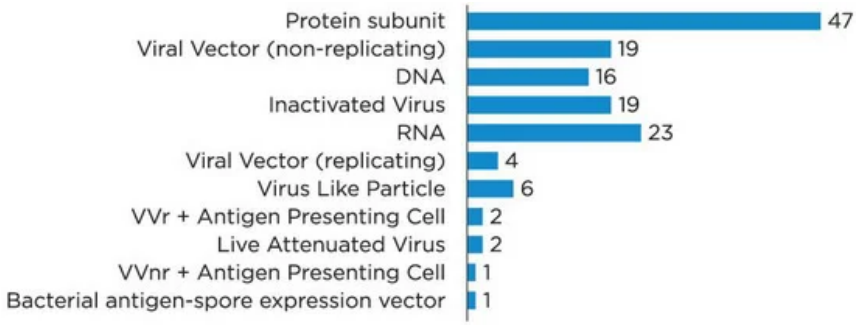


Other time-varying factors

- Change in vaccination policies
- Change in testing policies
- Scale up of home test kits
- Change in hospitalization and ICU admission criteria
- Change in care seeking behavior

Changing, complex vaccination strategies & status

Different vaccine platforms

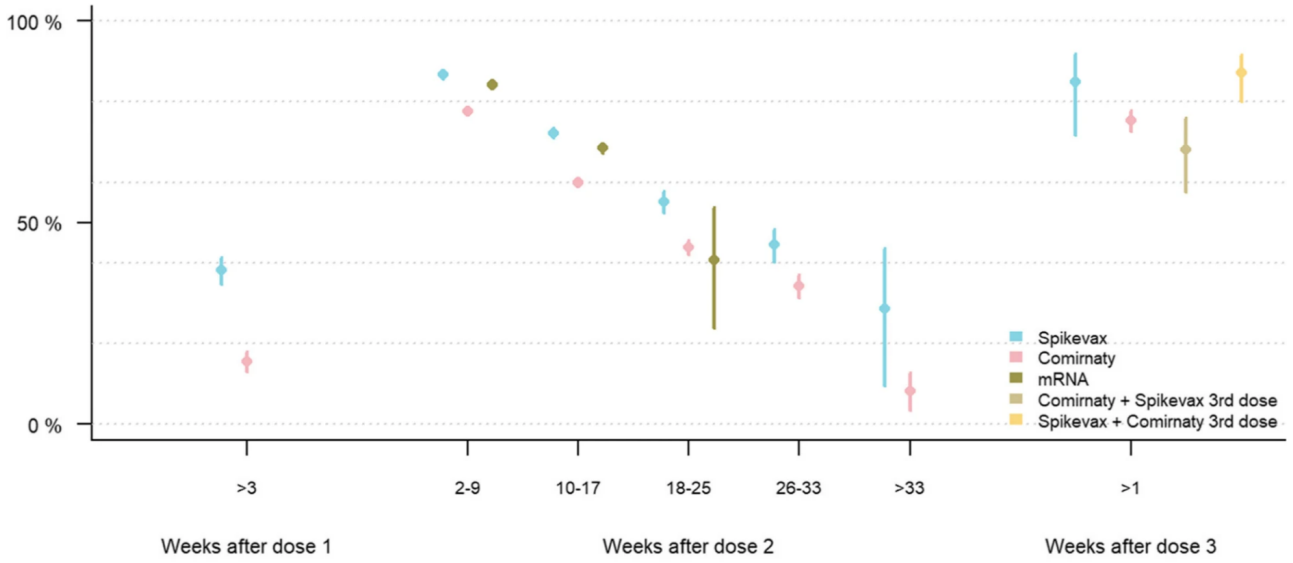


Kudlay et al Feb 2022. MDPI

Complex vaccination status

- Number of doses and dosing intervals depending on vaccine product
- Varying primary series and booster schedules
- Homologous vs. heterologous vaccination
- Different combinations of immunization and infection events, leading to complex patterns of immunity

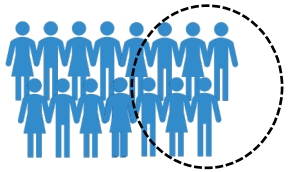
Example varying VE estimates against infection for 3 vaccine products and their combination



Starrfelt et al 2021. National cohort study Norway, BMC Medicine

Factors to consider when planning observational studies

Sample size

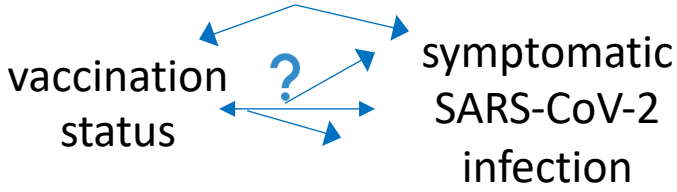


depends on:

- Expected vaccination coverage
- Expected vaccine effectiveness
- Incidence of SARS-CoV-2 in the unvaccinated study population over the follow-up time
- Desired precision

- **No correction for low sample size during analysis!**
- **In practice could be increased to account for dropout or stratification**

Bias



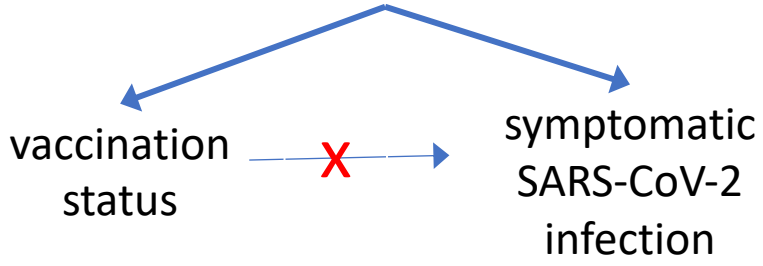
without randomization:

- Study prone to various types of bias
- Direction of bias (underestimating vs overestimating) on VE is unknown/ non-systematic
- Vaccinated persons often differ from unvaccinated persons in their disease risk, independent of vaccination

- **No correction for bias possible!**
- **Need for careful study design, clear definition of inclusion & exclusion criteria**

Factors to consider when analyzing observational studies

Confounder

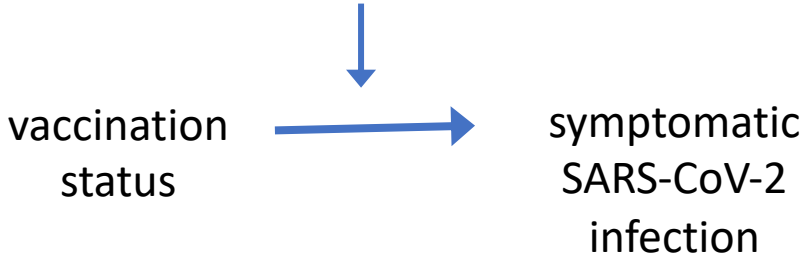


Characteristics:

- related to both COVID-19 and vaccination status
- but *not* on the causal pathway between vaccination and outcome measure

➢ **Can be accounted for in multivariable or stratified analysis**

Effect modifier



Characteristics:

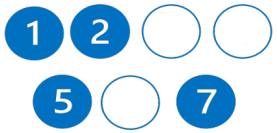
- related to both COVID-19 and vaccination status
- and on the causal pathway between vaccination and outcome measure
- -> subgroups in which VE truly differs

➢ **Can be accounted for in multivariable or stratified analysis**

Adjustments can only be done if factors were observed in the study.

Factors to consider when analyzing observational studies

Missing values



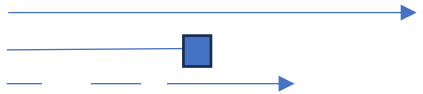
Consequences and what to do:

- Missing values can reduce sample size and power of the study and introduced selection bias if not randomly distributed

➢ **Adjustment possible but can be 'tricky' to avoid introducing bias (NB: complete case analysis can also introduce bias!)**

Lost to follow up

(cohort only)



Consequences and what to do:

- Complete – individual stops to provide information before end of study
- Partial - individual does not provide information for a while and reappears

➢ **Assumptions can be made for imputing missing follow-up, but requires careful consideration**