COVID-19 vaccine effectiveness estimation using the screening method

Operational tool for countries

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WHO is providing generic epidemiological investigations protocols for COVID-19, including vaccine effectiveness ones. Links to them are available on the WHO Unity Studies webpage

All and more resources, including guidances, on can be found on WHO COVID-19 Vaccine effectiveness and Impact webpage

Contents

Abbreviations

COVID-19	Coronavirus disease 2019
CVE	COVID-19 vaccine effectiveness
GP	General practitioner
ICD	International classification of diseases
PCV	Proportion of cases vaccinated
PPV	Proportion of the population vaccinated (vaccine coverage in the reference group)
RT-PCR	Reverse-transcription polymerase chain reaction
SARS-CoV-2	Severe acute respiratory syndrome – coronavirus 2
VE	Vaccine effectiveness
WHO	World Health Organization

1 Introduction

The global COVID-19 pandemic has led to the rapid development and global distribution of vaccines to reduce the burden of this disease. As of 20 May 2022, over 520 million confirmed cases of COVID-19 and 6.2 million deaths worldwide had been reported to WHO, and a total of 11.7 billion vaccine doses administered[1].

Given the speed and scale of COVID-19 vaccination, post-introduction studies are of capital importance to monitor the effectiveness of products in use.

WHO has advised that countries implement active surveillance for cases of SARS-CoV-2 infection to target control measures and continue to develop epidemiological insights. This includes systematic collection of case-based data, including on COVID-19 vaccination status [number of doses, date(s) of vaccination, product (s*).*

Systematic testing of patients meeting COVID-19 case definitions and collection of individual patient data (including on number of vaccine doses, date(s), COVID-19 product) can allow rapid evaluation of any COVID-19 vaccine post-licensure.

Evaluating the performance COVID-19 vaccines post-licensure is critical given the uncertainties in the context of a rapid response to an emerging pathogen. A number of factors can impact real-world vaccine effectiveness (VE), including transportation and storage conditions, how vaccines are administered, age, presence of underlying medical conditions and previous SARS-CoV-2 infection. In addition, post-licensure evaluations of pandemic vaccines will allow public health authorities to a) understand the duration of protection of vaccines and5 thus the need (and frequency) for re-vaccination, b) estimate the level of protection against severe disease and death, c) assess the relative effectiveness of different vaccine types and number of doses and d) evaluate VE for new emerging virus variants.

Current evidence suggests that COVID-19 VE may decrease over time following vaccination[2,3,4] and may be affected by circulation of different genetic variants[5], dosing intervals and subgroup characteristics. Since licensed Covid-19 vaccines (as of 10 May 2022) do not induce sterilising immunity, it is expected that vaccinated individuals may be infected with SARS-CoV-2. As vaccine coverage increases, vaccinated individuals may represent a greater proportion of detected cases. However, observed rises in case numbers among vaccinated individuals may cast doubt on the perceived effectiveness of vaccines. Generating evidence on VE is essential to communicate clear messages ani4d support vaccination campaigns

COVID-19 vaccines were evaluated in clinical trials for efficacy in preventing moderate to severe disease. By contrast, studies can enable post-licensure estimates for VE against mild disease, infection or other outcomes or interest for the real-world effect of vaccination. Effectiveness of licensed vaccines in preventing transmission should continue to be investigated and monitored.

Traditionally, VE is measured during clinical trials by calculating the attack rates of disease among vaccinated and unvaccinated persons and determining the percentage reduction of disease incidence

among vaccinated persons compared to unvaccinated persons. The screening method offers a less resource-intensive alternative for monitoring VE and may be deployed in parallel to formal VE studies and systems, or in lieu of these. The screening method is based on an observational case-cohort study design that uses two metrics to measure VE: the proportion of vaccinated among cases (or proportion of cases vaccinated (PCV) and vaccination coverage in the population[6]. Because these data may be available as part of routine data collection (e.g. surveillance systems at primary care or hospital level), this method can be rapidly implemented, providing early estimates of crude VE as part of the pandemic response[4, 7, 8].

Evaluation of COVID-19 vaccine effectiveness: Interim guidance, 17 March 2021. Section 6.4[12]

The screening method is a pseudo-ecologic design, which uses individual-level data on vaccination history from cases and vaccination coverage in the source population from which the cases came. It is an attractive method in settings where disease surveillance data are available, but where few other resources are available as it does not require ascertainment of vaccination status of non-cases. Only two data points are needed to calculate VE: the proportion of reported cases occurring in vaccinated persons, which can be calculated from surveillance data; and the vaccination coverage in the population, which may be estimated from vaccine coverage surveys or available from a national registry or administrative databases. As such, it is relatively easy to perform and inexpensive.

The screening method requires valid coverage estimates corresponding precisely to the population from which cases came. For COVID-19 vaccines, this is unlikely to be available in the first year as denominators for many of the target populations are unclear and coverage would need to be available by each targeted group. Moreover, coverage will likely be rapidly changing in the accelerated vaccine rollout phase. It can be difficult to adjust for some potential confounders using this design, given lack of individual-level data in the population. Studies using the screening method should only be undertaken in settings where vaccine coverage is stable and can be measured with high accuracy. We therefore recommend against the use of screening method designs for estimating COVID-19 VE in the early stages of vaccine rollout when vaccine coverage is rapidly changing; it could potentially be used in defined settings where coverage is more stable.

Note that the screening method was originally developed to serve as a “screening” tool to understand if the proportion of cases who have received vaccine are within the expected range, or if there is a need for more rigorous investigation. For example, if a vaccine has a true VE of 70%, at 75% coverage in the population, then it would be expected that approximately half of the COVID-19 cases would be vaccinated; at 90% VE and 90% coverage, one would also expect about half of the cases to be vaccinated (65). Therefore, the screening method serves as a useful tool to determine if the number of vaccine breakthrough cases is within the expected range.

It should be noted that the use of aggregate data for vaccine coverage in the population limits the ability to adjust for potential confounders. This method therefore is subject to more bias than VE estimates obtained from other observational studies (cohort or case control study designs) where individual level data from cases and non-cases are available. The screening method has been used to measure seasonal and pandemic influenza VE against different outcomes, in particular to provide real-time and early season VE estimates[18-22]. Studies comparing VE estimates derived from different methods suggest that the screening method can be a useful approach for real-time influenza VE[9]. These estimates, however, can also be less precise and vary considerably depending on the time period and the outcomes selected for investigation[10].

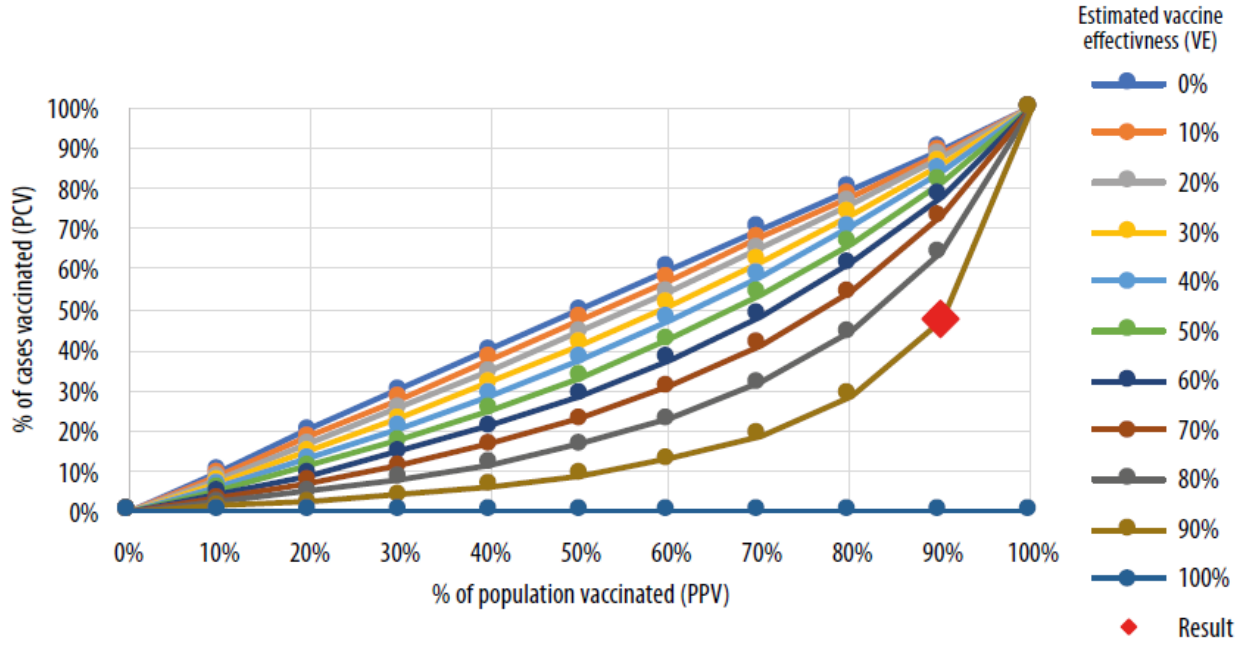

Figure 1. Screening method: relationship between % of population vaccinated (PPV), estimated vaccine effectiveness and % of cases vaccinated (PCV). Example shown in figure with red diamond is the result for vaccine with 90% estimated VE and 90% PPV. [6, 11]

When using the screening method, bias may be introduced into VE estimations if the cases and the reference group are drawn from different populations. When vaccination coverage increases over time (as is currently the case with COVID-19 vaccines), the vaccine coverage in the reference group should be measured at the time of occurrence of cases used for the proportion of cases vaccinated (PCV). If the data availability and methods are the same and assumed bias is constant over time, the screening method can identify changes in VE in different periods of time. The screening method is a simple method to implement that can provide early and real-time VE estimates, albeit with some methodological challenges for interpretation.

As for all VE studies, the study population should be restricted to vaccine target groups to reduce the presence of confounding factors

This document describes how case-based and vaccine coverage data may be used to measure VE in the vaccine-eligible population or specific groups using the screening method. The methods are aligned with WHO interim guidance[7,12].

This document outlines general principles. Country-specific guidelines and protocols for measuring COVID-19 VE using the screening method should be detailed at national levels.

COVID-19 surveillance, including that used for measuring COVID-19 vaccine effectiveness (CVE), should be conducted in accordance with the WHO guidelines on ethics in public health surveillance[12]. Formal ethical committee approvals or waivers should be obtained in accordance with national regulations. Surveillance procedures should protect the interests of patients and mitigate any foreseeable risks and harms to patients.

2 Key considerations

The screening method can be used to estimate CVE in settings where:

- **limited resources are available to conduct other type of observational studies**[12]
- **COVID-19 surveillance data are available**
- **surveillance data include valid cases´ vaccination status with a high degree of completeness**
- **data on vaccination coverage of the reference population are available and of high quality**
- **vaccination coverage is stable.**

The screening method can be used to provide early estimates of CVE as well as an early warning system to detect changes in CVE over time. Used with this goal in mind, changes in CVE estimates obtained could be used to trigger further investigation to better understand the possible factors leading to observed differences.

Before starting a study, teams should evaluate the sources of data available and their validity and completeness. Study populations and outcomes should be selected accordingly.

The interpretation of results should be made considering the population under study and the outcomes considered. If data at the general population level are not available, and a subpopulation is considered (e.g. hospital-based health workers or people attending specific health centres), the representativeness of the subpopulation should be taken into account. Selection of outcomes will also affect results, and VE measured for more severe outcomes (e.g. hospitalization, severe acute respiratory infection) is likely to be higher than VE against symptomatic infection.

In the context of different vaccines in use over time, a crude VE may be affected by product differences. To the extent possible, VE estimates should be product-specific.

3 Objectives

3.1 Primary objective

- To measure overall COVID-19 vaccine effectiveness against laboratory-confirmed symptomatic SARS-CoV-2 infection (COVID-19) in the vaccine-eligible population using the screening method.

3.2 Secondary objectives

- To estimate CVE against laboratory-confirmed symptomatic infection with SARS-CoV-2:
    - by age group
    - by sex
    - in specific risk groups (e.g. specific chronic conditions; pregnancy)
    - over time (weekly or monthly)
    - against specific SARS-CoV-2 variants
    - against hospitalization
    - by product (product-specific CVE).

Note: The feasibility of reaching the secondary objectives will depend on the information available on vaccine coverage for the reference group including, stratification variables (age group, time period, type of vaccine), information available on COVID-19 variants and the sample size.

4 Methods

4.1 Study design

- Screening method (or case coverage or case cohort design)

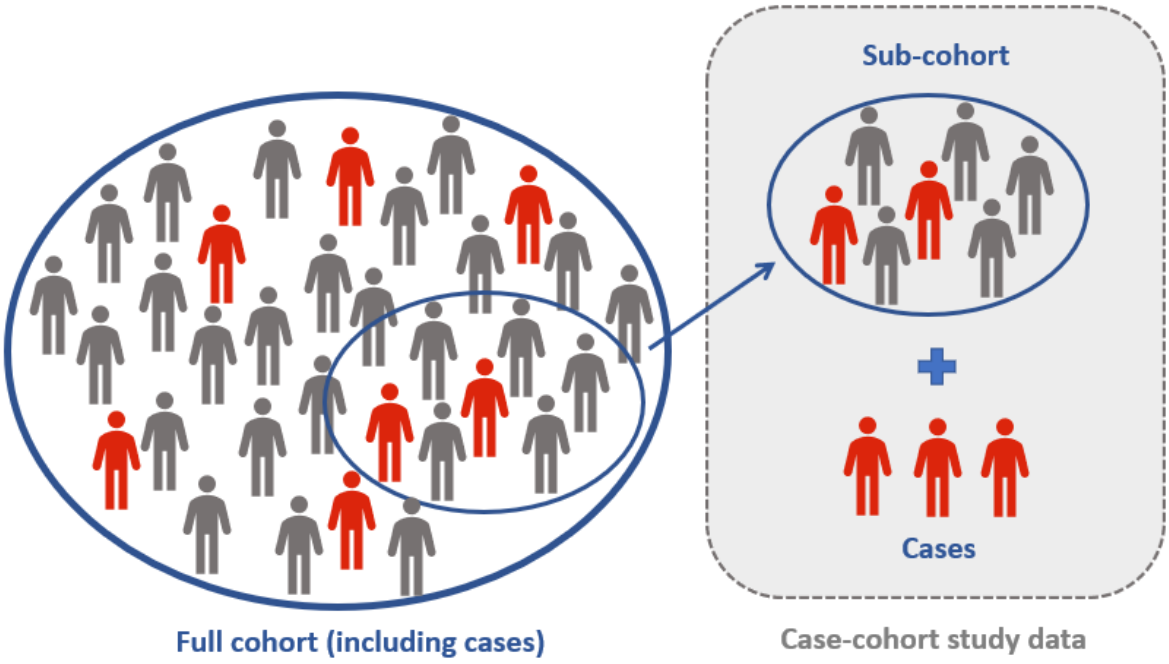

Figure 2. Schematic of a case-cohort study design. Data from a sub-cohort and data from cases arising from the same full (parent) cohort are used in a case-cohort study.

4.2 Study population

The study population can be defined to measure a specific outcome and should be as follows.:

- Individuals should be part of the target population for COVID-19 vaccination (for all outcomes).
- When hospitalization for laboratory-confirmed SARS-CoV-2 is the outcome under consideration, the study population should be residents of the catchment areas of the hospital(s) or health centre(s) participating in the study.
- When primary consultation for COVID-19-like symptoms is the outcome, the study population should be individuals belonging to the catchment population of the primary care centre.

If information at the general population level is not available, then a subset of the vaccine-eligible population can be used if:

- all cases are identified; *and*
- the denominator population is known and vaccine coverage data for the denominator population is available.

As such, the study may consider the general population or other populations such as hospital-based health workers or people attending defined health centres. The generalizability of VE results obtained from subpopulations will depend on whether the subpopulation considered is representative of the general population. For example, if only health workers are considered, VE might be different than it is in the general population, since health workers tend to be younger but also have A higher risk of exposure.

- The study team should identify and describe study populations based on feasibility.

4.3 Study period

The study period can be selected within the timeframe when SARS-CoV-2 was circulating *and* COVID-19 vaccines were available. The study team should determine and describe the study period.

4.4 Outcome(s)

Outcomes should be selected on the basis of existing surveillance for COVID-19. These may include:

- symptomatic laboratory-confirmed SARS-CoV-2 as per case definitions
- hospitalization for COVID-19
- severe acute respiratory infection (SARI), influenza-like illness (ILI) or acute respiratory infection (ARI).

➢ The study team should specify the outcomes used. It should be noted that VE may differ based on the outcome chosen (e.g. VE is expected to be lower if the outcome selected is infection than if the outcome is severe disease).

4.4.1 COVID-19 Case definitions

COVID-19 case definitions in the country of study should be used or defined by the source of data collection.

Alternatively, WHO COVID-19 case definitions may be used and can be accessed at: https://www.who.int/publications/i/item/WHO-2019-nCoV-Surveillance_Case_Definition-2020.2.

➢ The study team should specify the COVID-19 case definition used.

4.4.2 Laboratory confirmation

SARS-CoV-2 laboratory confirmation should be done according to existing testing algorithms in place to confirm cases for public health surveillance.

Specimens will be collected from COVID-19 suspect cases <10 days from symptom onset, according to the requirements of the specific study or the surveillance system.

Where VE against specific variants is considered, an appropriate method should be employed to confirm the variant (whole genome sequencing, spike gene sequencing, adapted RT-PCR method). Where less accurate or proxy methods are used (e.g. S-gene dropout or spike gene sequencing), sensitivity should be considered.

➢ The study team should specify laboratory confirmation methods.

4.5 Case identification

Potential places for cases to be identified:

- from public health surveillance records
- from primary care records or gps
- from hospital records (patients hospitalized with laboratory-confirmed SARS-CoV-2)
- from laboratory records.

➢ The study team should specify the method for case identification and data collection, which may include:
  - procedures to identify cases (e.g. use of ICD codes or systematic screening of patients with respiratory symptoms)
  - procedures for testing suspected cases of COVID-19 .

➢ The study team should specify data sources used in the study, which may include:
  - hospital records and hospitals participating in case identification (number, distribution, catchment population)
  - primary care records
  - laboratory records
  - the national disease surveillance system.

Case exclusion criteria

Cases will be excluded if:

- they are not eligible or have not had sufficient time to complete full COVID-19 vaccination
- it is not acceptable to make use of case data on the basis of ethical regulations.

Reasons for exclusion should be documented.

4.6 Vaccine coverage

4.6.1 Vaccination status definition for cases

- An individual is considered as fully vaccinated with a primary course vaccination against COVID-19 if the final dose of a one or two-dose vaccination schedule was administered ≥14 days before disease onset.
- An individual is considered as unvaccinated if they did not receive COVID-19 vaccine.
- An individual is considered as partially vaccinated if they have received only one dose of a vaccine recommended for a two-dose schedule. These individuals should be excluded from the case group and from the reference population for analysis.

In countries where booster vaccinations are in use, the study may consider booster or additional doses as part of the vaccination definitions. For example, effectiveness of a primary course

- The study team should specify vaccination definitions used in the study.

4.6.2 Ascertainment of vaccination in cases

The exposure of interest in this study will be COVID-19 vaccination history. The vaccination history should include number of doses, date(s) of administration and product names for each dose.

The vaccination status of individuals should be verified, preferably through formal sources. Vaccination can be ascertained by one of the following:

- evidence of vaccination from a vaccination registry
- report of COVID-19 vaccination in a disease surveillance system in which vaccination status is confirmed by reliable sources

  COVID-19 vaccination card/vaccination booklet
- self-report of having received a complete primary course (all doses of a licensed schedule) of COVID-19 vaccine. This method should only be used where other means of ascertainment are not feasible.

Vaccine documentation should include the type of vaccine(s) used (i.e. product), the number of doses and dates of dose administration.

- The study team should specify the precise mode of vaccine ascertainment.

4.6.3 Vaccine coverage in the reference group

Vaccine coverage can be measured using different population sub-groups (henceforth called reference groups in this document). The best reference group should be one that is representative of the vaccination coverage in the population giving rise to the cases. (For example, if cases are identified through hospital records, the vaccination coverage in the hospital catchment area should be used.)

The size of the reference group should be large (> 1000 individuals).

For the purposes of the analysis, the time for a vaccine to be protective should be accounted for. Therefore, the vaccine coverage data should be considered at time of COVID-19 onset minus 14 days (see 4.6.1 and 4.9).

For cases aggregated by month, vaccination coverage at the midpoint of the preceding month can be used. If the outcome is hospitalization or severe disease, vaccination coverage 3–4 weeks prior to hospitalization, severe disease outcome or death may be used to account for time from illness onset to these more severe outcomes.

- The study team should describe the reference group selected: source, accessibility, variables available, data validation, time of data extraction (if available).

4.6.4 Vaccination definition in the reference group

- How the term *vaccinated* is defined will depend on the data source used and the availability of date(s) of vaccination.
- Vaccination definitions should be same in the reference group as in the cases.
- Individuals will be considered as unvaccinated if they did not receive COVID-19 vaccine.

➢ The study team should specify the definition of the term vaccinated in the reference group.

4.6.5 Vaccination coverage ascertainment in the reference group

- The best method to ascertain vaccination coverage in the reference group should be determined based on the local context.

Sources may include:

➢ electronic medical records
➢ vaccination registries
➢ health insurance data
➢ vaccine distribution data (i.e., administrative data on number of doses administered)
➢ vaccination coverage surveys.

4.7 Sample size

The sample size for cases should be calculated taking into account[14]:

- expected true vaccine effectiveness
- the precision around the VE estimate (e.g. 40-60%)
- PPV: proportion of population vaccinated, or vaccination coverage expected in the reference group
- alpha error.

Number of vaccine eligible cases to achieve a 95% confidence interval width of 5% (either side of the VE estimate) for various vaccine effectiveness and PPV[11, 16]

PPV (%)	**VE (%)**					
	40	**50**	**60**	**70**	**80**	**90**
40	2841	2153	1558	1052	628	279
50	2510	1846	1292	840	480	203
60	2047	1706	1150	715	387	154
70	2060	1717	1107	652	330	120
80	2360	1967	1205	664	307	98

90	3627	3022	1742	882	361	94

Number of vaccine eligible cases to achieve a 95% confidence interval width of 10% (either side of the VE estimate) for various vaccine effectiveness and PPV

PPV (%)	**VE (%)**					
	40	50	60	70	80	90
40	744	565	410	277	166	410
50	666	492	346	226	130	55
60	646	462	314	197	108	43
70	685	474	309	185	95	35
80	832	555	346	195	93	31
90	1365	874	516	271	117	33

If the vaccination coverage is homogeneous between population subgroups in which stratified analysis is planned, the sample size needed for each sub-group will be similar (e.g. age groups, time period).

4.8 Data collected

Data on cases should be collected at central, district, hospital or primary care level depending on the setting. The data collection on vaccination coverage in the reference group will depend on the reference group used.

The study should include details on data collection methods, data entry and data transmission.

Information collected for cases:

- study identification: country, study site
- case demographics (age, sex)
- date of onset of COVID-19
- date of specimen collection (for laboratory confirmed outcomes)
- laboratory results (for laboratory confirmed outcomes, including genetic variant if available)
- COVID-19 vaccination including date(s) of vaccination and number of doses (or other way to ascertain protection)
- COVID-19 vaccine product for each dose (if the vaccine coverage data in the reference group is stratified by this information)
- information on comorbidities (if reference group vaccine coverage data is stratified by this information).

Information collected for the reference group will depend on the population and data collection method. Vaccination coverage should be obtained from a reference group that is the target group for vaccination. Where possible, the study should consider data on vaccine coverage by:

- age group and sex
- over time (e.g. by month)

- in the population with chronic conditions
- by number of vaccine doses
- by vaccine brand.

➢ The study team should detail the information collected and the data sources for cases and in the reference group.

4.9 Analysis

4.9.1 Descriptive analysis

The proportion of eligible cases should be calculated. If cases are excluded, the reasons should be described. Cases should be described by baseline characteristics, including time, period (e.g. week/month of onset or report), age group, underlying conditions, vaccination status and time since last vaccination. The vaccination coverage in the reference population should be described by baseline characteristics (e.g. age-group, time, vaccine type) and over time (e.g. by week or month).

4.9.2 Measure of effect

The VE against each of the outcomes selected (e.g. laboratory-confirmed symptomatic SARS-CoV-2 infection, hospitalization, specific variant) can be calculated two ways– first, as odds of vaccination in cases / odds of vaccination in the population, or

$$\mathrm{VE} = \frac{\mathrm{PPV}-\mathrm{PCV}}{\mathrm{PPV}\,(1-\mathrm{PCV})}$$

in which PPV is the proportion of the persons in the reference group vaccinated (vaccine coverage in the reference group that represents the same population as the cases) and PCV is the proportion of cases vaccinated.

Ninety-five percent confidence intervals can be computed using the Farrington method[14] (see Section 4.11 for more details).

Time considerations:
The time from vaccination to assumed protection should be taken into account. It is assumed that it takes two weeks (14 days) for a vaccinated person to mount a protective immune response. For this reason, the definitions for vaccine status account for 14 days following the date of last vaccination. Similarly, if the vaccine coverage data, or proportion of reference group vaccinated (PPV), is derived from vaccination campaign data, then data on proportion vaccinated should be used 14 days earlier than time for PCV.

If cases are aggregated by month, vaccination coverage (PPV) at the midpoint of the preceding month can be used. If an outcome of severe disease, hospitalization or death is used, the vaccination coverage (PPV) 21 or 28 days prior to the outcome can be used to compute VE. This approach aims to account for the time between the exposure to infection and the outcome.

Measuring effect by the number of vaccine doses

The number of doses may vary according to different vaccination schedules, and the vaccination definitions should be clear (see.4.6.). As additional doses may be administered ("booster" vaccination) in addition to licensed schedules, it may be desirable to compute VE of a primary course with booster(s).

The study team should select which definitions are used in cases and consider vaccine coverage data accordingly. If vaccine coverage is high in the population, VE may include evaluation of the impact of three doses versus two or one.

For the purpose of measuring vaccine effectiveness where a two-dose vaccine is in use, it is recommended that partially vaccinated individuals be excluded from the cases and the reference group.

4.10 Stratified analysis

Analysis should be stratified according to the availability of vaccination coverage data in the reference group by:

- age groups and sex
- product
- time:
  - weekly/monthly estimates *OR*
  - other defined time periods during which a given variant or combination of variants predominated
- underlying or chronic conditions.

These analyses should only be performed if sufficient sample size in each stratum can be reached. The study should detail the stratifications to be performed.

4.11 Adjusted analysis, Farrington method

Each case is matched to the coverage from the population that best matches that case according to key confounding variables such as age, gender, geography, chronic conditions and time period. The analysis is then performed as a logistic regression with the proportion of cases vaccinated as the dependent variable and an offset as the logit of the matched coverage[10].

$$\text{Logit [PCV]} = \text{logit[PPV]} + a + b_x X_x + \ldots b_o x$$

The results will provide a VE adjusted by the key confounding variables (i.e. $X_x, \ldots X_k$), and its 95% CI will be obtained.

Confounding variables are included in the model to test for interaction and define if there is effect modification. If effect modification is identified, then a stratified analysis should be conducted. The analysis can be done only if PCV and PPV are available by the effect modifier strata. For example, if age is an effect modifier, PCV and PPV should be available by age group.

- The study team should detail adjustments to be conducted.

4.11.1 Sensitivity analyses

Sensitivity analyses can be conducted by varying the vaccination coverage of the reference group (increasing/decreasing the estimated coverage by some percentage points), using a different definition of vaccination status or restricting the case definition (e.g. those swabbed < 3 days after symptom onset if laboratory confirmed outcome used).

If vaccination has been ascertained by means of self-report in a minority of cases, the team may perform sensitivity analyses to compare results when self-reported cases are included and the results if self-reported vaccinated cases are excluding.

- The study team should detail the sensitivity analyses to be conducted.

4.12 Data management

Summary and frequency tables and graphic displays of appropriate variables should be used to find erroneous, implausible or missing values within the cases' dataset. Data validation or checks for inconsistencies should be carried out (e.g. date of swabbing before date of onset of symptoms). Any changes to the data should be documented and stored separately from the crude database. Any recoding of data (e.g. age from date of birth) must be documented.

5 Limitations

The use of aggregate data instead of individual case data limits the ability to adjust for potential confounders due to challenges of quality and completeness. Depending on the source of data used, information from the reference group is generally minimal and the possibility to control for confounding factors is limited. Therefore, several biases have to be anticipated. Biases related to surveillance (e.g. testing strategies, missing data) can also impact results.

In addition, statistical models suggest that the screening method estimates may be more biased when VE is low[15].

- The study teams should take time to discuss limitations and possible biases of the study, depending on their specific context and sources of data.

5.1 Negative confounding

These are biases reflecting the fact that high-risk groups are more likely to be vaccinated, which can lead to underestimation of VE. Negative confounding will be minimized by stratifying by age group, chronic conditions or time period.

VE measures in the initial phases of vaccine introduction, or at low coverage, may also be susceptible to negative confounding.

To limit negative confounding, it is important to:

- estimate VE stratified by age group and chronic conditions if possible
- conduct the study when vaccination coverage is stable.

5.2 Positive confounding

These biases include the "healthy-vaccinated effect", whereby people with healthy behaviour and a good functional status are more likely to accept / request vaccination, which can lead to overestimation of the measured VE. Positive confounding is also present if very frail people are not offered vaccination. As in other study designs, without the variables used to evaluate healthy behaviour or frailty, it is not possible to control for positive confounding. If positive confounding may be present, the potential overestimation of the CVE should be taken into account in the interpretation of the results.

5.3 Representativity of the reference group in which vaccine coverage is measured

The main limitation of the screening method is that it is difficult to have a reference group representing the vaccination coverage of the source population giving rise to cases. The potential difference between the reference group and the source population should be described.

For instance, cases recruited at primary care or general practice (GP) level may represent a group of individuals seeking health care more often and thus could have a better vaccination coverage than the rest of the population. Using the vaccine coverage of a reference group not recruited at GP practices (e.g. in the general population, health survey) may lead to underestimation of VE.

If the vaccine coverage in the reference group is estimated at a specific point in time (e.g. early in the study period), and the vaccine coverage increases over time, VE may be underestimated. When vaccine coverage is rapidly changing, it may be difficult to determine vaccine coverage (PPV) accurately.

Discussion on timing of assessing PPV is further discussed in WHO's Guidance on Conducting Vaccine Effectiveness Evaluations in the Setting of New SARS-CoV-2 Variants Addendum to Evaluation of COVID-19 Vaccine Effectiveness: Interim Guidance, published in July 2021 (12).

To avoid bias related to the representativity of the reference group, study sites should identify the source of vaccination coverage representing the vaccination coverage of the population giving rise to the cases: vaccine registry for the general population, hospital databases for hospitalized cases and long-term care facility registries for cases reported by long-term care facilities.

5.4 Vaccine status ascertainment

Depending on the reference group, vaccine ascertainment may be different between the cases and the reference group. This may lead to overestimation or underestimation of VE.

Study teams should describe how vaccine ascertainment is reported in each group and how this can affect the estimates. For example, are numbers of doses reported among cases and in the reference group? Is the vaccination status of cases assessed through a vaccine registry but self-reported in the reference group?

5.5 Limitations related to the setting, case definition used, data sources, etc.

Each study setting will have specific limitations related to the study population, variables documentation, specificity of the outcome used, etc.

Study teams should evaluate and describe the potential biases present in the study and how they will

affect the results.

6 Ethics and consent

Studies must be conducted in compliance with ethical requirements for consent in place at the study setting. Traditionally, use of surveillance data does not require consent. The study team should consider national or regional regulations in place and the data under consideration to ensure appropriate consent is obtained.

6.1 Ethical considerations

Ethical requirements will vary by country. In some countries, this investigation may fall under public health surveillance (emergency response) acts and may not require ethical approval from an institutional review board. Regulations and ethical requirements should be checked in each context to ensure compliance.

6.2 Informed consent

Requirements for informed consent should be assessed in the national and local context. Where existing surveillance data are used for calculating crude CVE using the screening method, obtaining informed consent from individuals may not be feasible or required.

If informed consent is required by local regulations, the purpose of the investigation must be explained to all individuals identified for inclusion in the investigation (i.e., cases included in the study), and informed consent must be obtained from all individuals willing to participate. Consent for children under the legal age of consent must be obtained from a parent or legal guardian. All participants must be informed that participation in the investigation is voluntary and that they are free to withdraw, without justification, from the investigation at any time without consequences.

Informed consent should be designed to obtain approval to collect and use epidemiological data for the intended purpose of this investigation.

6.3 Risks and benefits for subjects

This investigation poses minimal risk to participants. The primary benefit of the study is indirect in that data collected will help improve and guide efforts to understand the extent of SARS-CoV-2 infection and may prevent further transmission of the virus.

6.4 Confidentiality

Participant confidentiality must be maintained throughout the investigation. All subjects who participate in the investigation will be assigned a study identification number by the investigation team for the

labelling of questionnaires and specimens. The link of this identification number to individuals should be maintained by the investigation team and the ministry of health (or equivalent) and must not be disclosed elsewhere.

If the data are shared by the implementing organization to WHO or any agency or institution providing support for data analysis, data shared should include only the study identification number and not any personably identifiable information.

Article 45 of the International Health Regulations (IHR) (2005) describes the "treatment of personal data". Person-identifiable data collected under the IHR should be kept confidential and processed anonymously, as required by national law. However, such data may be disclosed for assessments and management of public health risks, provided the data are processed fairly and lawfully.

6.5 Prevention of COVID-19 virus infection in investigation personnel

All personnel involved in the investigation need to be trained in standard infection prevention and control procedures as established in national or local guidelines. These procedures should include proper hand hygiene and the correct use of surgical masks, if necessary, to minimize the risk of infection transmission among research team members in close contact with individuals with COVID-19 and other participants in the investigation.

WHO technical guidance on infection prevention and control specific to COVID-19 can be found on the WHO website.

7 Additional studies

Additional studies potentially include:

- comparing results obtained with the screening method and other methods such as cohort or case control studies in the same population
- validating vaccine coverage in the reference group
- any other study that teams believe can contribute to better interpretation of study results.

8 Acknowledgements

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10 Annexes

Study-specific annexes:

- Description of the data sources including surveillance systems, testing algorithms and/or hospitals participating in the study (number, distribution, catchment population, mode of recruitment).
- Vaccine products used and target groups over time
- COVID-19 case identification
- Laboratory confirmation: mode of selection of individuals for whom a specimen is collected
- Vaccine ascertainment method used for cases
- Sample size calculation for cases
- Detailed data collection methods, data entry and data transmission
- Data validation procedures
- Vaccination coverage in the reference group: size of the reference group, data sources, VC by age group, over time
- Laboratory methods:
    - specimen collection, storage, transport
    - Tests used (PCR, culture, strain characterisation)
- Potential limitations
- Consent, study ethical procedures
    - Oral / written consent if applicable
    - Submission to ethical committee if applicable
- Human resources needed
- Additional studies if applicable