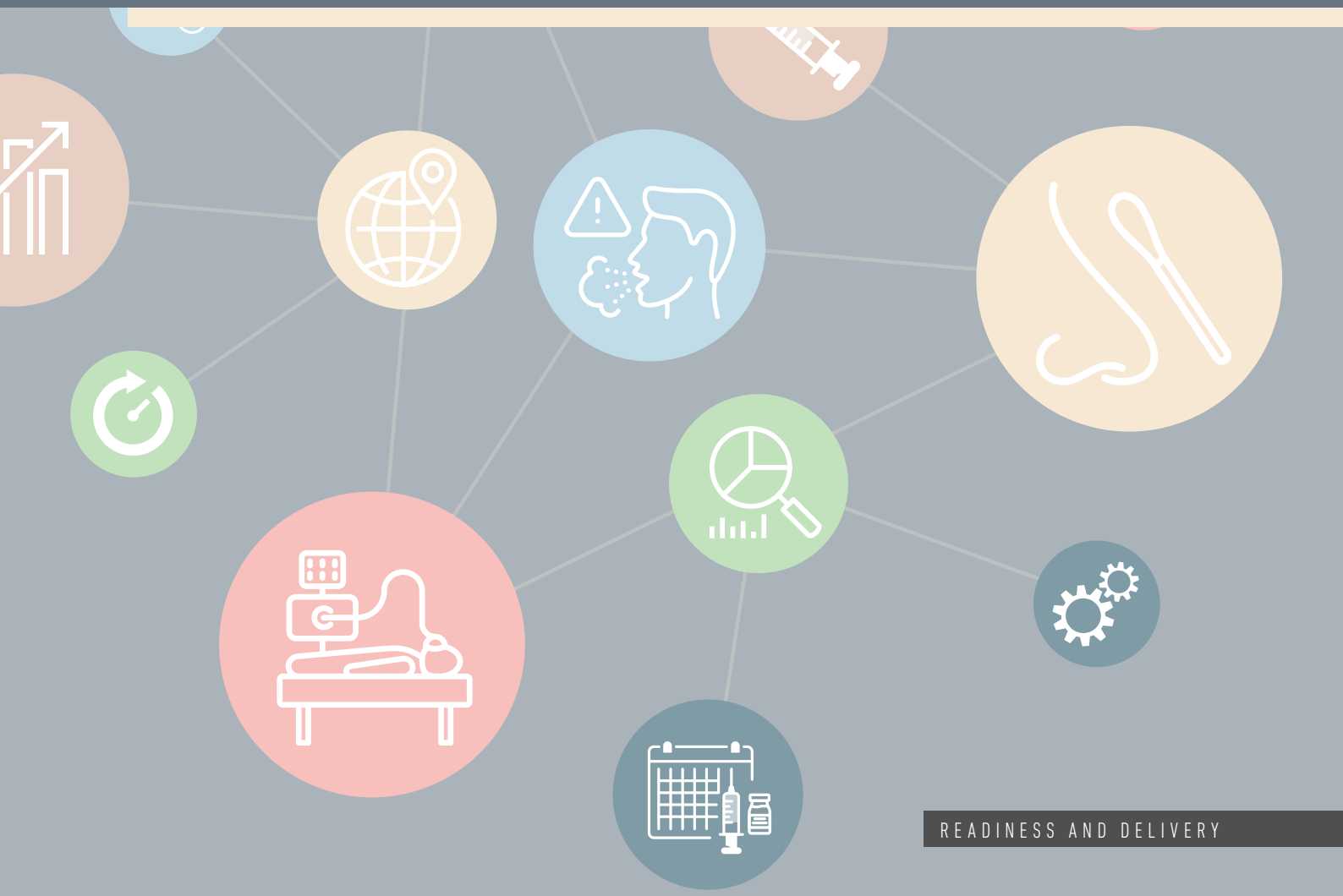
Evaluation of COVID-19 vaccine effectiveness in a changing landscape of COVID-19 epidemiology and vaccination

INTERIM GUIDANCE

3 OCTOBER 2022

World Health Organization

Second addendum to Evaluation of COVID-19 vaccine effectiveness: Interim guidance



READINESS AND DELIVERY

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WHO continues to monitor the situation closely for any changes that may affect this interim guidance. Should any factors change, WHO will issue a further update. Otherwise, this interim guidance document will expire 2 years after the date of publication.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by WHO in preference to others of a similar nature that are not mentioned.

WHO reference number: WHO/2019-nCoV/vaccine_effectiveness/VE_evaluations/2022.1

Contents

Acknowledgements

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Abbreviations

aVE	absolute vaccine effectiveness
ICD	International Classification of Diseases
NPV	Negative predictive value
PPV	Positive predictive value
rRT-PCR	Real-time reverse-transcription polymerase chain reaction
rVE	relative vaccine effectiveness
TND	Test-negative design
VE	Vaccine effectiveness
VOC	Variant of concern
WHO	World Health Organization

1. Introduction

In March 2021 the World Health Organization (WHO) made interim guidance available on best practices for undertaking vaccine effectiveness (VE) evaluations in *Evaluation of COVID-19 vaccine effectiveness: interim guidance (1)*. This was followed in July 2021 by an addendum addressing VE evaluations in the context of new variants of concern (VOC) *(2)*. That guidance still generally applies to carrying out VE evaluations. Nonetheless, in the past year, several factors have arisen that indicate the need for a second addendum to the interim guidance, namely:

1. Experience has been gained from dozens of COVID-19 VE evaluations in many different settings that have highlighted several methodological concerns that either were not addressed in the initial guidance or are in need of modification.

2. Waning VE with time since vaccination has been documented for all vaccines, particularly against SARS-CoV-2 infection and symptomatic COVID-19 disease *(3)*.

3. Since December 2021, the Omicron variant has become the predominant variant in circulation worldwide and its ability to partially evade humoral immunity has resulted in lower VE estimates for all outcomes.

4. In many countries the majority of persons in many risk groups have been vaccinated with the primary series and a growing number have received booster vaccination. This complicates the approach to comparing vaccinated to unvaccinated persons as unvaccinated persons likely are dissimilar to vaccinated persons for important characteristics (e.g. due to behavioral differences).

5. There is a complex vaccination landscape with multiple vaccines used at different periods targeting specific groups of individuals, heterologous schemes for primary series and booster vaccines, and new vaccines targeting VOCs that will soon add further complexity.

6. Lastly, more than two years into the COVID-19 pandemic with multiple waves of infection, including with the highly transmissible Omicron variant, most of the population in many countries have infection-derived immunity, and many have hybrid immunity (i.e. infection-derived plus vaccine-derived immunity). The unknown extent of infection-derived and hybrid immunity makes interpretation of VE evaluations more challenging.

All these issues present methodological challenges in the execution and interpretation of VE evaluations, which in turn can have implications for setting vaccine policy. The current policy-related questions that rely on the results of VE evaluations include: the number and timing of booster doses after receiving the primary series; whether vaccine products and schedules should be amended in the setting of high population immunity; how to optimize VE evaluations in the setting of future variants with immune evasion; and whether vaccines with antigen compositions different from the original vaccines are more or less beneficial.

This addendum addresses some of the methodological aspects of VE evaluations that have been learned during the past year, as well as those that have become relevant in the current epidemiological setting of the COVID-19 pandemic. For some of the COVID-19 vaccine methodology issues there are still insufficient data to make a recommendation, in which case different options for approaching VE evaluations are presented.

2. Study design

2.1 Case selection

2.1.1 Severe disease definition in the setting of Omicron

Various definitions of severe COVID-19 have been used in VE evaluations. Hospitalization with SARS-CoV-2 infection, with or without COVID-19 symptoms, has been the most common definition *(4)*. Hospitalization is a convenient and easily defined measure of severe disease, particularly when using electronic databases. However, criteria for hospitalization vary significantly by geographical location, between hospitals or even at different stages of a COVID-19 wave when factors such as standard of care, reimbursement structure, staffing shortages and bed capacity can affect thresholds of severity for hospital admission. Furthermore, assessing VE against Omicron severe disease using hospital admission as a measure of severe disease has become more challenging because of Omicron's attenuated intrinsic severity and the high prevalence of infection in many populations. It is likely that many hospital admissions occur among people with incidental Omicron infection unrelated to the reason for admission, or among those with infection-induced exacerbation of chronic medical conditions leading to misclassification of the outcome of severe disease due to Omicron *(5)*. The reduced VE against Omicron infection can lead to lower estimates of protection against hospitalized disease due to Omicron that might not truly reflect the vaccine-conferred protection against severe COVID-related disease.

Several approaches are proposed to better characterize vaccine protection against severe COVID-19 disease caused by the Omicron variant than using the hospitalization of Omicron-infected persons to define severe disease. Using more specific definitions for severe respiratory COVID-19 disease – such as requiring indicators of respiratory distress such as oxygen requirement, mechanical ventilation and admission to the intensive care unit– is likely to better reflect protection against severe disease and, in the case of Omicron, results in an increased VE compared to protection against hospitalization *(6, 7)*. Some studies have shown that increasing the number of days of hospitalization in the case definition to two or more is more likely to select for severe Omicron disease, which is generally associated with higher VE than that for hospital admission with COVID-19 infection *(6)*. Second, VE against progression from Omicron infection to hospitalization or severe respiratory disease might also better indicate whether vaccines are protecting against severe Omicron disease once someone is infected. For example, in the United States of America, the overall VE for two or three doses of mRNA vaccines in immunocompetent adults was 44% (95% CI 0–69) against progression to invasive mechanical ventilation or death among persons admitted with Omicron infection *(8)*. In South Africa, effectiveness of the primary series of Janssen-Ad26.COV2.S or Pfizer-BioNTech-Comirnaty vaccines against progression from infection to severe admission (defined as admission to the intensive care unit, need for mechanical ventilation, or steroids prescribed) or death was about 55% (95% CI 44–64) *(9)*. In instances where VE platforms are conducting ongoing analyses, it should be noted that changing the definition used will make comparisons to historical data challenging. Furthermore, in some settings it may be challenging to obtain the sample size required in view of the decreased severity of Omicron disease.

2.1.2 Using International Classification of Diseases (ICD) codes to define the outcome

WHO has issued ICD-10 and ICD-11 codes specific to COVID-19 *(10)*. Some studies have used these ICD codes – which are based on clinical characteristics and do not necessarily include laboratory confirmation – to define the outcome being studied rather than laboratory-verified outcomes. Several studies have been conducted to evaluate the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of these ICD codes, mostly from the pre-vaccine era, looking at their performance in a range of settings (outpatient visits, emergency department visits, and/or hospitalizations). The sensitivity of U07.1 (the code for COVID-19, virus identified) ranged from 49% to 98%, specificity ranged from 93% to 99%, PPV ranged from 78% to 99%, and NPV ranged from 95% to 100% *(11-15)*. Consequently, misclassification can result in both false-positive and false-negative study participants. One study found that the most frequent reasons for misclassification include erroneous use of this code for a history of COVID-19 (rather than the current diagnosis) or for ordering a test *(13)*. Given the variable performance of ICD codes, it is still recommended that laboratory test results are used to classify cases and controls appropriately. If investigators choose to use ICD codes to define cases without confirming laboratory results to confirm the presence of SARS-CoV-2, an analysis restricted to those persons with documented SARS-CoV-2 test results should also be conducted and presented to aid interpretation of the results.

2.2 Outcome comparison group selection ("controls")

2.2.1 Assuming persons without a positive test result are negative

Omicron led to a high incidence of infection, including an increase in the proportion of asymptomatic infections *(16)*. This can lead to a misclassification bias in those VE evaluations that assume that those who have not been tested for SARS-CoV-2 or tested negative at one point in time have remained SARS-CoV-2 negative, which has been done for some large cohort studies linking government administrative databases *(17-19)*. In a high-incidence setting, or if a VOC leads to a substantial number of asymptomatic infections, it is recommended that cohort studies evaluating VE against infection should perform routine testing in order to avoid misclassification. Studies using administrative databases should be conducted in settings where a significant amount of testing is being undertaken and recorded in a database. Test-negative design (TND) studies minimize this bias since all persons should meet an enrolment case definition, are excluded if they have a recent history of infection (usually <90 days prior to enrolment), and are tested at the time of enrolment.

2.2.2 Control selection for VE evaluations of severe disease among hospitalized cases

When assessing VE against severe disease among hospitalized cases in a TND study, the choice of a control group depends on the study population. When the capture of both test-positive and test-negative persons occurs from the same source population, particularly when testing is done prior to the decision to hospitalize, test-negative persons from the general population can be used – although, ideally, the reasons for testing should be documented and used in a sensitivity analysis. This might be preferable in periods of high COVID-19 incidence, when few persons hospitalized with COVID-19-like symptoms will test negative, yielding few eligible controls. Moreover, there is a potential risk of false negatives among hospitalized persons during waves of COVID-19 as a result of lower negative predictive value in high-incidence settings, which would lead to misclassification bias. Adjusting for risk factors for hospitalization (e.g. underlying comorbidities, age) can reduce confounding. However, in study settings where testing is done on admission to hospital, or is differential between inpatients and outpatients, it is preferable to select controls from among only test-negative hospitalized cases.

2.3 Vaccine comparison group

Most VE evaluations compare the risk of a clinical outcome among vaccinated persons to the risk among unvaccinated persons, sometimes referred to as absolute VE (aVE), as follows *(1)*:

$$aVE = 1 - \frac{risk\ among\ vaccinated}{risk\ among\ unvaccinated} \times 100\%$$

However, at this stage in the pandemic with high COVID-19 vaccine coverage in many populations, the remaining unvaccinated population is likely to be quite different from the vaccinated population in terms of SARS-CoV-2 exposure and/or disease risk, leading to bias in the aVE results. Thus, many recent booster VE studies, have used a vaccinated comparison group (e.g. vaccinated with complete primary series) in place of, or in addition to, an unvaccinated group. Investigators should choose a comparison group that is best positioned to answer the question being asked.

2.3.1 Vaccinated comparison groups for VE of booster doses

Many VE studies of COVID-19 booster vaccines have not compared booster dose recipients to unvaccinated persons but rather to persons who have received only the primary series. Moreover, for VE studies of the second booster dose, the comparator is often persons who have received only the first booster dose. When choosing a vaccinated comparison group, it is important to choose, as far as possible, a comparable group in terms of age and risk profile, and to select only persons who are eligible for the vaccination that is being evaluated (e.g. a booster dose). It is likely that those persons who first receive the booster dose are at a higher risk of virus exposure or severe disease (e.g. health workers and older persons, respectively). In addition, it is important to compare persons during the same period to account for the circulating variant; this can be done by adjusting for calendar time or stratifying by time periods when a specific VOC is predominant. In interpreting the VE estimates, the time since administration of the last vaccine dose should be considered. It is likely that more time will have elapsed since the last dose of the comparator vaccine than the most recent booster dose being evaluated. Consequently, protection derived from the comparison group may have waned.

In using a vaccinated comparison group, persons vaccinated with one brand of vaccine should not be compared to persons not vaccinated with that specific brand of vaccine. This point has become relevant because most countries are using more than one COVID-19 vaccine, and persons who are not vaccinated with one brand are likely to be a mix of unvaccinated persons and those vaccinated with another vaccine brand. Because those vaccinated with another brand of vaccine probably have some vaccine-induced protection, this would lead to artificially low VE estimates.

Perhaps the most important difference in using a vaccinated comparison group is that the VE estimate is it results in a relative VE rather than an absolute VE. The relationship between relative and absolute VEs is described in the next section.

2.3.2 Relative VE

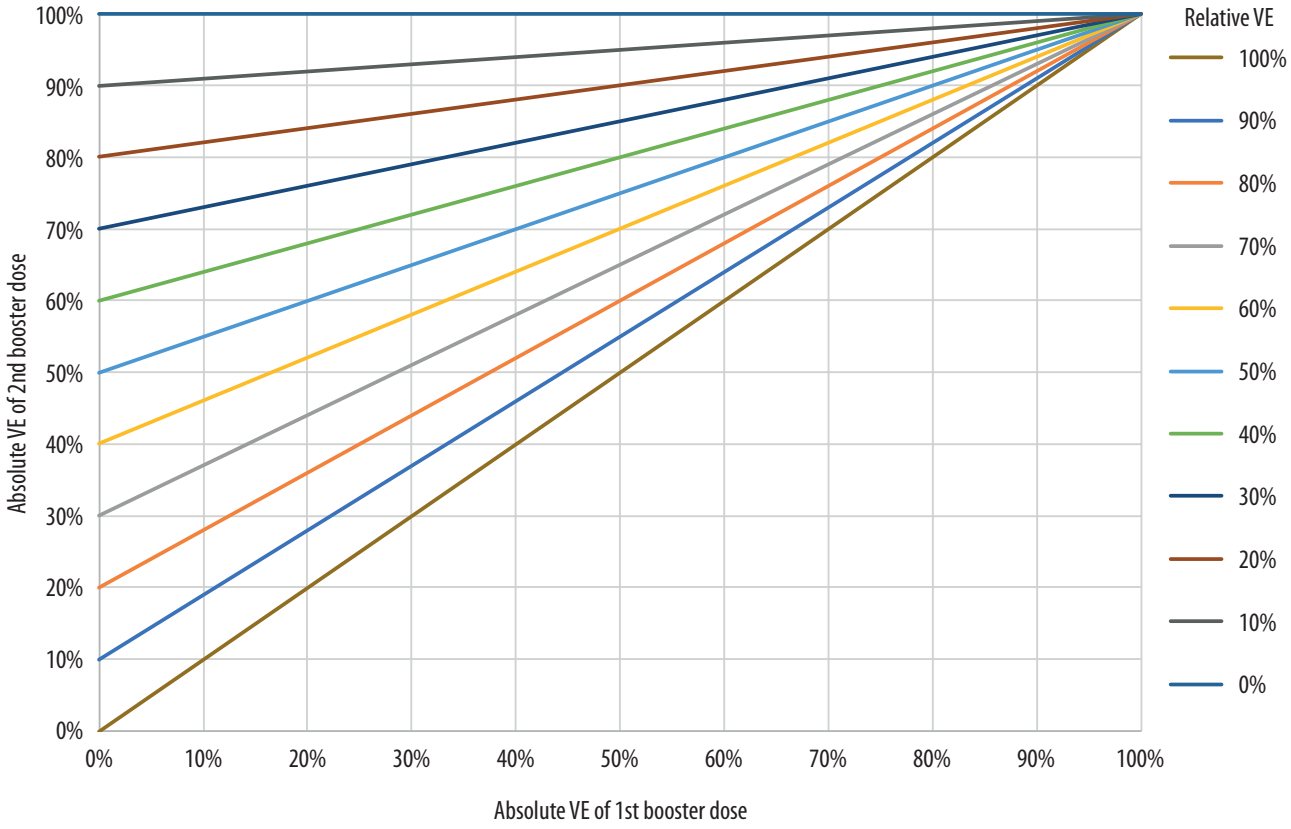
Relative VE (rVE) is derived from comparing recipients of one booster dose to recipients of the primary series, or comparing recipients of two booster doses to recipients of one booster dose or the primary series, and so on. This type of comparison has been done for other vaccines such as influenza *(20)*; for COVID-19 vaccines, rVE has been reported in studies from a few countries including Israel, Brazil, Canada and the United Kingdom *(21-24)*. rVE provides a way to quantify the additional preventive benefit of a booster dose versus a primary series (or whatever is the number of doses of vaccine being compared).

The relationship between absolute VE and relative VE can be expressed as follows (using boosted versus primary series as an example):

$$rVE = \frac{aVE_{boosted} - aVE_{primary\ series}}{1 - aVE_{primary\ series}} \times 100\%$$

and is also shown in Figure 1.

Fig. 1. Relationship between absolute vaccine effectiveness to relative vaccine effectiveness



At low aVE of the primary series, the rVE of the booster dose approximates the aVE of the booster dose. At high aVE of the primary series, the rVE of the booster dose can vary quite substantially while the incremental gain in aVE of the booster is small. For instance, if the aVE of the primary series is 90% and the rVE of the booster dose is 50%, then the aVE of the booster dose is 95%. On the one hand, the rVE of 50% appears to be a substantial increase in protection but the gain in absolute VE is only 5%. On the other hand, it means that the risk to persons who receive a booster dose is halved compared to the risk to those who have had only the primary series. Similarly, if the aVE of the primary series is 0% and the rVE of the booster dose is 50%, then the aVE of the booster dose is 50%, equating to a gain of 50% in absolute VE. The aVE of the booster dose should always be higher than the rVE (or equal to it if the aVE of the comparison group is 0%), but by how much it will be higher will depend on the aVE of the primary series which itself depends on a variety of factors. This is because persons in the comparison group may have some vaccine-induced immunity. However, in real-world VE studies, it is possible to observe an rVE that is higher than the aVE as a result of study-related issues such as confounding bias and uncertainty of estimates. It should be noted that the aVE of the booster dose cannot be calculated from the rVE alone; both the rVE and the aVE of the primary series are needed at the same time to calculate the aVE of the booster dose.

The rVE will generally depend on the interval since the completion of the comparator vaccine (e.g. primary series, first booster dose). If the interval is short, the rVE may be lower than if the interval is long because protection conferred by the vaccine declines with time. When interpreting the rVE one must bear in mind the extent of the likely residual protection from the vaccine; the higher the residual VE from the comparator vaccination, the lower the rVE is likely to be. Interpreting rVE requires knowledge of the population and vaccine being evaluated, the timing of the last dose, the clinical outcome being evaluated and the epidemiological situation – including the circulating variant(s). Because these are context- and time-specific, an aVE of the primary series from a different study and the rVE from the study in question should not be used to calculate the aVE of the booster dose. Furthermore, it is challenging to compare the rVE of a given vaccine across studies because the rVE is dependent on the aVE *(25)*.

If possible, investigators should report both the absolute and relative VE results of the dose being evaluated, even if the aVE is suspected of being biased because of residual confounding in the comparison with unvaccinated persons. Furthermore, investigators reporting rVE should report the absolute risk reduction in terms of cases averted per denominator population as achieved by the first booster dose versus primary series (or the second booster dose versus the first booster dose, etc.) to help put the added benefit in a public health context. It should be noted that absolute risk reduction depends on the level of transmission; thus, an rVE in a high-incidence period could lead to greater absolute risk reduction than the same rVE in a low-incidence period (with the same being true for aVE estimates). To aid interpretation of the results, the report's limitations section should draw attention to the challenges in generalizing the results and should provide proper contextual details. Communicating what the rVE means to the public can be challenging and a communication strategy should be developed to help avoid misinterpretation of the results (Box 1). For instance, for an rVE of 50%, the message might be that the booster dose in the setting of the Omicron variant reduces your risk of disease by 50% compared to the primary series among persons who received the vaccine X–Y months ago.

Box 1. Communicating relative vaccine effectiveness

The rVE should be reported in the context of:

- the vaccine being evaluated;
- the vaccine and number of doses with which it is being compared;
- the outcome being measured;
- the time since the last dose for both the evaluated and comparator vaccine; and
- the variant setting.

Example: This study demonstrated an rVE of 50%, meaning that there was a 50% 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 a median of X days ago.

rVE does not give the amount of disease prevented or the absolute VE compared to unvaccinated persons.

2.3.3 The first week after the vaccine dose

To avoid the potential bias of comparing vaccinees to a small unrepresentative unvaccinated group with a different risk, some investigators have compared risk among persons at least two weeks post-vaccination to those in the first week after vaccination. The rationale for this is that an impact of the vaccine is not expected to be seen in the first week because of the time it takes for the immune system to respond to a vaccine dose. However, in some studies, a reduced risk was observed in the first few days after vaccination. A likely explanation for this is that during COVID-19 vaccination roll-out many countries advised people

who were feeling ill to defer vaccination to help minimize transmission. Consequently, persons who were recently infected would have been selectively excluded from vaccination but would probably have been diagnosed in the week or so when they were originally scheduled for vaccination. This led to a deferral bias/healthy vaccinee bias that was seen in multiple studies *(26-29)*. Furthermore, Hitchings et al. outlined a theoretical framework and discussed the underlying assumptions that are needed in order to use persons vaccinated in the first week as a comparison group; they recommend against using this group as a comparison group as it relies on strong unverifiable assumptions *(30)*.

At the same time, persons who have been vaccinated with a booster dose are probably more similar to those who received the primary series than to unvaccinated persons, potentially minimizing confounding due to behavioural differences between vaccinated and unvaccinated persons. Similarly, this is likely to be the case in comparing persons receiving one or two booster doses. On the basis of this rationale, some studies have used the first week after the booster dose as the comparison group *(24, 31, 32)*. Frequently these studies have avoided the first few days after vaccination for the reasons stated above but rather use days 3–7 or days 4–6 after vaccination as the comparison group. This seems to be a reasonable approach and excluding persons in the first three days after vaccination is recommended if one chooses to use an early period after vaccination as the comparison group.

2.3.4 Using other time periods after vaccination

Within a few months after vaccination, the primary series of the current vaccines (based on the ancestral strain) has much reduced effectiveness against infection and symptomatic disease caused by the Omicron variant *(3)*. Investigators can take advantage of the presence of waning immunity against infection and symptomatic disease to minimize the bias when comparing vaccinated persons to the increasingly different unvaccinated persons. Due to this waning of immunity, an rVE evaluation comparing recently-vaccinated persons with persons vaccinated further in the past results in the rVE approaching the aVE. One could compare persons who received their last dose of the primary series over 180 days ago to persons who have received their booster dose. If the effectiveness of the primary series is near zero by six months post-vaccination, the rVE for the booster dose will be close to the aVE for the primary series plus the booster dose. This time frame of over 180 days should be adjusted according to the current data and situation. One study compared persons with a booster dose to those vaccinated with the primary series 5–9 months previously, as well as to those vaccinated more than 9 months ago. The study found that the rVE of a booster dose against infection restricted to those vaccinated with the primary series 5–9 months previously was 36.4% (33.3–39.4%), while it was 46.5% (44.1–48.7%) when restricted to those who received their primary series more than 9 months previously – presumably due to some residual protection from the primary series in the 5–9-month period which was greater than the residual protection after longer periods *(33)*. When evaluating rVE against severe disease, the comparison to a certain time period after the primary series is not recommended because of the generally slower waning of protection against severe disease with time since vaccination.

2.4 Vaccination data collection

As noted, investigators must collect vaccine-specific details such as the brand and formulation of the vaccine used and the date of administration for each dose. These data should come from reliable sources such as vaccination registries or immunization cards. Variant-containing vaccines will be available soon, potentially leading to confusion as to which vaccine a person has received. It is important that investigators collect information on the specific vaccine used, noting if it is a vaccine based on the ancestral strain, a variant, or on a combination. All analyses should treat the variant-containing vaccines as different from the vaccine based on the ancestral strain, even if produced by the same manufacturer, as it is unknown at this time – and is important to determine – whether the effectiveness is different.

3. Hybrid immunity

The infectiousness of Omicron has led to a large number of cases and a rise in hybrid immunity – i.e. immunity derived from both vaccination and infection with SARS-CoV-2. Persons with hybrid immunity are heterogenous. For instance, hybrid immunity applies to persons who were infected and then vaccinated as well as persons who were vaccinated and then infected. It includes persons receiving different numbers of vaccine doses and infected with different virus variants. Currently, many aspects of hybrid immunity are incompletely understood with respect to the protection afforded against different outcomes, against different variants, and with respect to the duration of this protection. An additional complication is that infections may be asymptomatic, and symptomatic infections may be incompletely diagnosed or recognized. Further studies of the protection afforded by hybrid immunity are important.

When considering hybrid immunity, investigators should consider the following:

- ☐ Which vaccines were used and how many doses of vaccine were given?
- ☐ When was the prior SARS-CoV-2 infection and when was the last dose of vaccine?
- ☐ What variant was the person most likely infected with?
- ☐ Was the person: a) infected before vaccination, or b) vaccinated before infection?
- ☐ How severe was the prior infection?
- ☐ Is there a difference by age group?
- ☐ How many times has the person been infected?

Investigators to date have conducted two types of analyses. Some studies have evaluated VE exclusively among persons with previous infection. This is similar to the relative VE concept described above in that it is expected that persons will have some immunity if they have previously been infected, and the question is whether vaccination (with a partial primary series, a full primary series and/or a booster dose) provides additional protection on top of that derived from infection. As with rVE studies, it is challenging to compare findings across studies; however intra-study comparisons are valuable for guiding vaccine policy. Other studies have evaluated aVE with hybrid immunity, comparing persons with hybrid immunity to unvaccinated persons without known prior infection. In this scenario, the absolute benefit of hybrid immunity can be calculated, but the benefit afforded by infection and vaccination individually cannot be identified separately; protection afforded by prior infection and vaccination among those without prior infection could be calculated separately to provide additional insight. The challenge with this type of comparison is that some persons in the comparison group might have been unknowingly infected. Ideally, persons are seronegative at the time of enrolment if the unvaccinated/no prior infection comparison group is used, especially where seroprevalence studies have identified a large amount of undiagnosed infection. If a study attempting to evaluate aVE with hybrid immunity is done in a setting with high background seroprevalence, and if persons with undiagnosed infection cannot be removed from the comparison group, then it is possible that the VE estimate more likely reflects a mixture of VE among previously infected and uninfected persons. This interpretation of the results should be discussed in any report.

Few studies have taken account of the likelihood that protection from prior infection will wane over time, as happens with vaccine-induced protection (34). Investigators should attempt to evaluate whether the time since the last vaccine dose and the time since prior infection has an impact on the results that are obtained. Additionally, a combination of the time element related to the most recent exposure should be considered. For instance, a person who was last vaccinated 12 months ago but infected 3 months ago might have more protection than a person last vaccinated 12 months ago exclusively because the last immunological exposure for the first person was more recent. Therefore, in the analysis, it is suggested also to explore the duration of protection from the last immunological exposure – either the last vaccine dose or the last infection.

3.1 Defining prior infection

WHO currently defines reinfection as a confirmed or probable COVID-19 case (in accordance with WHO's case definition), with a history of a primary confirmed or probable COVID-19 infection, with at least 90 days between the episodes *(35)*. To minimize misclassification when considering re-infections for the purpose of VE studies, persons with prior infection should be those persons with a history of SARS-CoV-2 infection confirmed by laboratory testing ¬– e.g. rRT-PCR, genomic sequencing, lateral flow testing, antibody testing (considering type of vaccine received) – at least 90 days previously. While this time frame is currently being investigated and may be decreased for surveillance purposes, the longer time frame of 90 days minimizes misclassification in a hybrid immunity VE evaluation. If a lot of genomic sequencing is being conducted, consideration could be given to including persons who are infected with two distinct lineages regardless of the time that elapsed between episodes.

Prior infection data can be obtained from a variety of sources. Possible sources include (in descending order of data from the highest level of confidence to the lowest level of confidence):

- positive rRT-PCR or lateral flow testing results documented by a reliable source (e.g. laboratory or medical practitioner);
- serological testing that is positive for nucleocapsid antibody among persons who have not received an inactivated vaccine (Note that antibodies can wane over time so this is not a perfect measure of prior infection and some amount of misclassification bias may still remain);
- patient recall of a positive rRT-PCR or lateral flow test result.

Patient recall of symptoms consistent with SARS-CoV-2 should not be considered as a history of prior infection (nor should it be considered as lack of a history of prior infection).

It is likely to be easier to identify prior infection in prospective cohort studies than in TND studies as the former offer regular documentation of test results and/or serological testing while identification of prior infection in the latter would be retrospective and it could be challenging to interpret serological results.

4. Sample size

APrevious guidance provided sample size estimates for different study designs along with the formula to calculate the sample size *(1)*. As a reminder, investigators should calculate a sample size based on the objectives of the study, taking into account the impact of adjustments and the desire for VE estimates by strata. After reviewing studies that have been proposed, further clarification is needed. Most countries are using more than one COVID-19 vaccine, and total vaccine coverage reported by an administrative area (e.g. district, province, country) is frequently reported without disaggregation by vaccine brand. However, in order to calculate sample size for a case-control study, one must consider the coverage by a specific vaccine brand (and not by the total vaccination coverage of all brands used in the population being studied). This will ensure that brand/formulation-specific estimates can be obtained. If stratified estimates are required (e.g. by age), brand/formulation-specific coverage in each stratum should be used to calculate the sample size. The use of total coverage in the calculation of the sample size will result in a study being under-powered for the brand/formulation-specific VE. Similarly, sample size calculations for booster dose regimens should consider specific combinations of vaccines if VE estimates are to be calculated for each combination.

An additional challenge is that, in the case of booster doses, both homologous (the same vaccine as primary series) and heterologous (a different vaccine) schedules are being used. Ideally, the VE for each combination of vaccines in the primary and booster series should be calculated and reported separately, and the appropriate sample size should be obtained when possible. Many studies have, however, combined different mRNA vaccines given as boosters in calculating a VE for an mRNA booster. This approach can still provide useful data – although not about individual vaccines – while decreasing the sample size required. However, combining booster doses across vaccine platforms in a VE analysis is not recommended because of the different performance of these vaccines *(4)*. Additionally, some combinations of vaccines might be used infrequently and therefore require a large sample size to obtain a robust VE estimate; in these cases, investigators can either exclude persons from the study with these less common vaccine combinations or can provide estimates with a note of caution regarding the low sample size on which these estimates are based.

5. Variant-specific estimates

Knowledge of VE estimates against different VOCs are extremely important in order to understand if a VOC is evading vaccine-induced immunity. Ideally, every participant, or a random selection of participants, infected with SARS-CoV-2 will have genomic results for calculating a variant-specific VE. However, in many settings, it is not possible to determine the variant for each participant in an observational study. Some studies have used time periods to define when a particular VOC is predominant but it is important to know the number of samples sequenced and the sampling strategy in the study setting when defining these dominant periods. Additionally, care must be taken because predominance of a VOC in the study setting does not necessarily mean that the VOC-specific VE is being estimated if other variants are still in circulation. For example, when Omicron started replacing Delta, Omicron was accounting for a majority of mild cases while Delta accounted for many severe cases *(36)*. Calculating a VE against severe disease during this time period when both variants were circulating widely was resulting in a VE against severe disease driven in large part by Delta and not by Omicron. Thus, instead of defining dominant periods on the basis of a transition from <50% to >50%, a time gap should be considered whereby cases that occur during this period of co-circulation may be: 1) excluded, or 2) analysed separately or 3) included as part of a sensitivity analysis showing the impact of including these persons. For instance, during the rapid transition from Delta to Omicron, a gap of a few weeks helped to decrease the impact of Delta on the VE estimate while still allowing investigators to provide data rapidly *(37, 38)*. If VOC screening (e.g. S-gene target failure testing or whole genome sequencing) is done on a proportion of the samples during the defined dominant period, then a sub-analysis should be attempted on those with VOC-specific information for comparison to the main study results. If these data are presented, it is important to describe the VOC screening strategy as this could affect the results.

6. Biases

Bias, especially confounding bias, remains a major limitation of observational studies. It is important that all VE evaluations account for confounding as far as is possible. While it is suggested that one should account for as many of the potential confounders (as listed in the interim guidance *(1)*) as possible – including factors such as socioeconomic status and comorbidities – evaluation of VE studies to date have shown that, at a minimum, any model should be adjusted for age, calendar time and location/study site. Time and place help to adjust for the changing vaccination coverage and local incidence and account for the circulating variant while age has been one of the major drivers of the vaccine rollout strategy. Test positivity rates could also be used.

Changes in non-pharmaceutical interventions, national policies, vaccination coverage, treatment and incidence have resulted in other concerns which are further explored below.

6.1 Negative VE

Observational studies can sometimes yield negative VE estimates. This most often occurs as a consequence of extreme levels of biases causing the observed VE to be lower than the true vaccine efficacy. That is, there are times when VE can be negative even when a vaccine provides protection. Such an apparent negative VE estimate can occur with certain types of biases, including outcome ascertainment and selection bias (related to testing) and/or differential exposure patterns (i.e. residual confounding between vaccinated and unvaccinated) are present. These factors could act independently or in concert to produce negative VE estimates.

First, differential ascertainment of the outcome (e.g. SARS-CoV-2 infection) may lead to an apparent negative VE if vaccinated persons are more likely to be tested or more likely to be eligible for testing (e.g. health-care workers undergoing routine testing for asymptomatic infection are also more likely to be vaccinated) *(39)*. This largely occurs when VE is measured using a cohort design which usually does not control for differences in test-seeking behaviours. VE calculations using a TND can correct for some of these biases (e.g. differential testing by vaccination status), but cannot correct for all types of testing biases *(1, 40, 41)*. For instance, apparent negative VE may still occur using a TND when the relative differences in testing probability between infected and uninfected vaccinated persons differ from those of their unvaccinated counterparts. Even when restricting the outcome to symptomatic infections, some testing biases can still be present (e.g. if behaviours also vary with the number or type of symptoms).

Second, SARS-CoV-2 exposure risks may be correlated with vaccination status. This means that, if vaccinated persons experience higher exposure risks and the study is not able to adjust adequately for this, then the true effect of vaccines can be underestimated and this may in some circumstances lead to apparent negative VE estimates. An example of differential exposure risks by vaccination status could be in the context of health-care workers who may be more likely to be vaccinated and more likely to be exposed to SARS-CoV-2 by the nature of their work. Another example of this residual confounding can result from policies that create differences in exposures by vaccination status. For instance, "vaccine passports" that preferentially enable vaccinated persons to participate in activities among other people (such as dining indoors at restaurants), while unvaccinated persons may not do so, can result in vaccinated persons potentially having more contacts (and hence more exposures) than unvaccinated individuals. If a study is not able to adjust adequately for this confounding, this may lead to an apparent negative

VE estimate. Recent work suggests that the influence of greater number of contacts among vaccinated persons (i.e. contact heterogeneity) affecting VE estimates depends on the timing of the epidemic *(42)*. "Contact heterogeneity" might only occur during the growth phase of an epidemic or during a wave of infection. This probably resulted in some studies reporting negative VE estimates against symptomatic infection during the early Omicron period when viral circulation may have occurred predominantly among more vaccinated groups; in several settings, the VE estimates were no longer negative when additional weeks of data were included *(38, 43-45)*.

The issues outlined above provide examples of VE estimates that may appear negative even when a vaccine is protective. This can happen when the effects of the bias are large enough to counteract the true benefits of a vaccine, so if the true benefits of the vaccine for preventing infection are already low for a given variant (e.g. as with Omicron versus Delta), the same mechanisms and extent of bias may be more likely to result in a falsely negative VE. Negative VEs were not seen against severe disease outcomes caused by Omicron, in part because the true VE was much higher.

6.2 Changes in testing practices

Differential SARS-CoV-2 testing between vaccinated and unvaccinated persons can lead to bias in studies of COVID-19 VE. This difference in testing by vaccine status could be exacerbated as testing becomes less common or targets only specific groups. There have been major changes in SARS-CoV-2 testing patterns over time for a variety of reasons, such as: variable testing availability; increased availability of home-based testing; changing requirements for travel, work, school and exiting quarantine; reduced access to free testing; testing for access to treatment; and perceptions of lower risk of severe disease with Omicron. Changes in testing could potentially affect VE estimates if there are differences by vaccination status, as have been seen in some studies *(39, 46-49)*. As the pandemic has evolved, differential testing by vaccine status might increase due to changing policies that require or recommend more testing for unvaccinated persons, as well as potential differences in perceived risk of disease based on vaccine status *(50)*. For TND studies, even in the presence of an enrolment case definition, this situation could undermine one of its underlying assumptions – that vaccinated and unvaccinated persons have similar health-care-seeking behaviour. If one group is more or less likely to present for testing, then a selection bias will be introduced. This is less likely to affect the evaluation of severe outcomes – such as admission to an intensive care unit or death – where the probability of unvaccinated and vaccinated persons being tested is unlikely to be different *(51)*. Retrospective cohort studies – especially those linking administrative databases – will raise a similar issue. Prospective cohort studies where persons are regularly monitored and tested are less likely to suffer from these challenges. Ideally, study time periods will be limited to, or stratified by, periods during which the same testing practices/policies are in place.

If persons who are vaccinated are less likely to be tested, this will result in an overestimation of the VE; if the unvaccinated are less likely to seek out care, this will lead to an underestimate of the VE *(39, 51)*. Ideally, testing rates by vaccination status should be presented and accounted for in the analysis. Investigators should collect information on the reason for testing, potentially matching or restricting cases/control selection or analysis on the basis of the reason for testing (e.g. specific clinical criteria, known high-risk exposure, routine screening) *(51)*. Analyses should adjust for calendar time to help account for changing circumstances (not only in relation to changing testing but also changes in burden of infection, changes in non-pharmaceutical interventions recommended etc.).

In addition to testing potentially varying by vaccination status, testing could also vary by whether someone has COVID-19 or another type of respiratory infection (e.g. a case or a control). However, in an influenza simulation, it was found that this selection bias had a significant impact on the VE estimate only

when persons with influenza-related acute respiratory illness were twice as likely to seek care/testing than persons seeking care/testing for non-influenza acute respiratory illness *(52)*. Thus, this is less likely to influence the results.

The original guidance recommended the use of rRT-PCR testing to define the outcome, given its superior sensitivity over lateral flow testing. Furthermore, there are data showing that rapid testing has a lower sensitivity among vaccinated compared to unvaccinated persons prior to the Omicron era *(53)*. If this also holds true for Omicron, vaccinated persons in a TND case-control study are more likely to be misclassified as controls (false negatives) resulting in an artificially elevated VE estimate. Additionally, the availability of home-based lateral flow testing has led to another potential source of bias; for instance, one study found that persons who received a booster dose were more likely to use a home-based lateral flow test *(47)*. That said, the availability of home-based rapid testing could also lead to biases as to who is choosing to take an rRT-PCR test, especially for asymptomatic persons or those with mild symptomatic disease not requiring medical care. rRT-PCR might be more common among certain populations (e.g. those requiring documentation for work or travel). The extent to which this bias could have an impact on VE results is unknown as there is minimal literature on who is using home-based rapid testing and/or obtaining an rRT-PCR test. Ideally investigators should collect data on this to inform the extent of the bias in VE studies. Furthermore, there will be differences between study settings according to the population's access to home-based testing and rRT-PCR testing. If investigators include results from home-based lateral flow tests, they should obtain information on the type of test used and present the proportion receiving each type of test by vaccination status and by outcome investigated in order to make sure they are comparable. If possible, investigators should conduct a sensitivity analysis including and excluding lateral flow tests.

6.3 Test-negative controls positive for influenza

In TND case-control COVID-19 VE studies, test-negative individuals are used as controls to estimate the true COVID-19 vaccination odds in the source population from which the cases derived (*54)*. Since the uptake of COVID-19 vaccine is likely to be correlated with the uptake of other vaccines, controls with another vaccine-preventable disease should generally be excluded. This is because, in situations of positive correlation where vaccines are protective against a disease outcome, controls with another vaccine-preventable disease are simultaneously less likely than the source population to be vaccinated for both the etiology of their illness and for COVID-19. In these situations, when controls with another vaccine-preventable disease are included in COVID-19 case-control VE studies, vaccination for the other vaccine-preventable disease, particularly influenza, can act as a confounder, and crude VE estimates might underestimate true COVID-19 VE *(55)*.

The magnitude of this bias was recently explored via simulations in COVID-19 test-negative VE studies that included controls who tested positive for influenza. Where COVID-19 vaccination coverage was higher than influenza vaccination coverage, simulations found that moderate-to-high levels of bias in VE estimates could occur when true COVID-19 VE was less than 90% and influenza controls represented more than 25% of the control population. Bias generally increases with a higher proportion of influenza controls and a stronger relationship between the uptake of vaccines. If the prevalence of influenza among test-negative controls was <25%, confounding of the COVID-19 VE was low *(55)*.

In situations where a higher proportion of influenza controls are included in the TND and a strong relationship exists between the uptake of vaccines against COVID-19 and influenza, bias in COVID-19 VE estimates is greater where true COVID-19 VE is low and true influenza VE is high. For instance, given a true influenza VE of 60% and a true COVID-19 VE of 40%, COVID-19 VE would be estimated as only 30% from a TND study with 30% of influenza controls where COVID-19 and influenza vaccine is strongly correlated in

the population. Yet, if the same scenario were applied and true COVID-19 VE was equal to 90%, COVID-19 VE would be estimated with minimal bias at 88% *(55)*.

When this bias is anticipated to have a meaningful impact on COVID-19 test-negative VE estimates (e.g. settings with highly correlated COVID-19 and influenza vaccination coverage, high influenza incidence and lower true COVID-19 VE), investigators can avoid bias by either: 1) testing for influenza and excluding influenza positive controls from study participation; or 2) performing statistical adjustment or stratification of VE estimates by influenza vaccination status. In contrast, where investigators determine that this bias is not meaningful and choose not to undertake these methods, justification should be provided to promote critical interpretation of VE results *(55)*.

6.4 Depletion of susceptibles (particularly following very large surges)

As discussed in the WHO's interim guidance on VE, bias from depletion of susceptibles can arise in studies that evaluate the duration of VE *(1, 56-58)*. Over time, more people will be infected and therefore will be at lower or no risk of reinfection (for some period of time after infection). When the vaccine is effective, the people who are infected are more likely to be unvaccinated than vaccinated – a phenomenon known as "differential depletion of susceptibles". Because depletion of susceptibles increases over time, VE may appear to wane more quickly over time than in reality (i.e. spurious waning). At this stage of the pandemic when many people have been infected, differential depletion of susceptibles between vaccinated and unvaccinated persons can also affect the overall VE estimates – even ones that include only a relatively short follow-up time. The vaccine will appear to be less effective than it actually is, biasing estimates downwards from the true estimate. In some cases, this bias may be so extreme that the VE estimates can be negative, making the vaccine incorrectly appear to be harmful.

Modelling has shown that the bias is larger when the initial VE estimates are lower, and when studies are unable to adjust for the history of prior infection among participants, than when the initial VE is high or studies are better able to capture prior infection *(59)*. True waning and lower VE against new variants both decrease the true VE and can therefore result in more bias. For example, the VE against Omicron is much lower than estimated in the original vaccine trials that were carried out when other variants were predominant, thus creating the potential for larger bias from the depletion of susceptibles. The bias may also be greater when there is a large, fast wave, such as Omicron, resulting in a substantial increase in immunity. Collecting information on prior infection status (through chart review, serological testing or self-report) and excluding from the analysis those persons with prior infection who are still likely to have substantial protection (based on time since last infection and variant of last infection) can help to minimize this bias. Alternatively, conducting analyses both with and without persons with documented prior infection can also help provide bounds for the VE estimates. Studies in which prior infection is documented and adjusted for – ideally with an ability to capture asymptomatic infection – would be the least likely to suffer from this bias. Findings of vaccine waning may reflect a combination of true waning and spurious waning due to differential depletion of susceptibles.

6.5 Treatment and passive prophylaxis

COVID-19 treatment and passive prophylaxis have been introduced since the interim guidance was published. However, little is known as to how treatment or passive prophylaxis modifies the risk of outcomes in VE studies and how much impact this could have on VE estimates. Antivirals and monoclonal antibodies can decrease progression to severe COVID-19 disease; factors such as the timing of administration in relation to when the outcome is assessed and the criteria for enrolment into a study

will drive the potential impact of severe disease outcomes on VE estimates. COVID-19 treatments should only affect VE estimates of severe disease since they are given once someone is infected. In contrast, monoclonal antibodies given as passive prophylaxis to prevent infection among high-risk populations (e.g. immunocompromised persons) can prevent infection and severe disease. Passive prophylaxis is likely to be highly correlated with vaccine use since both are recommended for the highest risk groups.

Most VE studies to date have had low rates of treatment or prophylaxis use and have been unable to evaluate the potential impact on VE estimates. Conversely, three studies have looked at the differential use and effect of antivirals stratified by vaccine status. Wong et al. found a lower risk of hospitalization with molnupiravir use among persons who were vaccinated with the primary series, while there was no benefit among those not completing the primary series *(60)*. They found no difference in hospitalization risk between vaccinated and unvaccinated persons receiving nirmatrelvir/ritonavir *(60)*. Dryden-Peterson et al. found that nirmatrelvir/ritonavir treatment was more likely to be given to unvaccinated persons, with a greater reduction in hospitalization among the unvaccinated *(61)*. Bajema et al. found that antivirals were more likely to be given to partially vaccinated persons, while persons with the primary series and/or booster dose were as likely as the unvaccinated to receive antivirals *(62)*; how this differential administration translated to antiviral effectiveness was not investigated.

Given the lack of evidence in this area to make a recommendation, investigators are encouraged to explore whether COVID-19 treatment or passive prophylaxis bias the VE estimates.

6.6 Early vaccinee bias

Persons who are vaccinated or boosted first are frequently those at highest risk of infection (e.g. health workers, essential workers) or of severe disease (e.g. care home residents, older persons, people with comorbidities) and/or may also be expected to have a poorer immune response to the vaccine (e.g. immunocompromised persons). These factors need to be considered when interpreting early VE estimates of new, additional or booster doses of vaccine. This also needs to be considered when evaluating the duration of protection as these early vaccine recipients will contribute more data to later time points. In order to minimize this impact, it is suggested that early studies of these new, additional or booster doses are either restricted to or stratified by these population groups who are vaccinated first *(63-65)*.

7. Updated resources

In addition to the previous listed resources the following resources could be valuable to VE stakeholders.

WHO's website on vaccine effectiveness and impact (): This website contains all WHO guidance on VE studies, tools such as a sample size calculator, and links to generic protocols to conduct VE studies.

WHO's Weekly Epidemiological Update (): This document provides a summary of what is known about VE on the basis of pre-print and published literature.

VIEW-hub (): The International Vaccine Access Center at Johns Hopkins Bloomberg School of Public Health (Baltimore, MD, USA) is conducting a living systematic review, the results of which are updated and summarized weekly in pdf as well as an interactive web interface which allows filtering and downloading of data based on the user's needs.

McMaster's University Evidence Products (): McMaster's University (Hamilton, Canada) is generating summaries of VE data as they relate to specific policy questions and is conducting a monthly risk-of-bias assessment on VE studies.

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