# A Southeast Asia Expert Review of Global Real-World Vaccine Effectiveness Against SARS-CoV-2

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**Systematic Review**

**Keywords:** COVID-19, COVID-19 vaccination, vaccine effectiveness, SoutheastAsia, Real-world data, AZD1222, BNT162b2, mRNA vaccine

**Posted Date:** May 9th, 2022

**DOI:** https://doi.org/10.21203/rs.3.rs-1575499/v2

# Abstract

### Background

COVID-19 vaccines have been highly effective in reducing morbidity and mortality during the pandemic. While primary series vaccination rates are generally high in Southeast Asian (SEA) countries, various factors have limited the rollout and impact of booster doses.

### Methods

To objectively review the evidence for vaccine effectiveness (VE), we extracted data from 79 studies identified in the publicly-available International Vaccine Access Center (IVAC) VIEW-hub platform reporting VE after a primary immunisation with two-dose schedules for three important clinical outcomes. We evaluated VE after primary immunisation against SARS-CoV-2 infection, and COVID-19-related hospitalisations and deaths for the most widely reported vaccines, stratified across variants of concern (VOC), age, study design and prior SARS-CoV-2 infection. The majority of studies evaluated mRNA vaccines (58 BNT162b2 studies, 34 mRNA-1273 studies and 14 combinations of both) and vector vaccines [25 COVID-19 Vaccine AstraZeneca, Vaxzevria studies (AZD1222)] with only 5 other studies available (all CoronaVac). For simplicity, mRNA studies were grouped together irrespective of which vaccine was used. VE point estimates were presented graphically with pooled means and confidence intervals were compared using standard t-tests for expert discussion.

### Findings

VE was high and equally effective for both AZD1222 and mRNA vaccines types (91%-93%) in protecting against hospitalisation and death from COVID-19, regardless of age. VE against symptomatic infections trended higher (though not significantly) for mRNA-based vaccines compared to AZD1222. Waning of VE since time of vaccination was observed for symptomatic infections but was limited for serious COVID-19 outcomes. A sub-analysis of studies with comparative arms evaluating the VE of different vaccines in the same settings also confirmed these observations for all VOC assessed, with all vaccines conferring a high level of protection against serious outcomes. For Omicron, there is limited comparative data within the IVAC dataset, however, expert review of emerging data suggests that VE against all outcomes is lower for all COVID-19 vaccines, than for the Delta variant. Importantly, data from the UK indicates that VE improves with a booster dose and that VE continues to be very similar, irrespective of the type of vaccine used. Importantly, all COVID-19 vaccines evaluated here have favourable benefit/risk profiles.

### Interpretation

Our review of the robust real-world VE data collated through the IVAC VIEW-hub platform confirms that the most studied COVID-19 vaccines in this database provide consistently high (>90%) protection against serious clinical outcomes like hospitalisations and deaths, and regardless of variant. Additionally, our observation that this protection appears equivalent for mRNA vaccines and vector vaccines like AZD1222 is supported by our analysis of local Asian and relevant international data, and by insights from SEA experts. Given the continued impact of COVID-19 hospitalisations and deaths on healthcare systems worldwide, encouraging vaccination strategies that can reduce this burden is more relevant than attempting to prevent broader but milder infections with specific variants, including Omicron.

### What this study adds

This additional context reinforces the value of real-world evidence to support efforts advocating for the completion of primary series and booster vaccinations where appropriate, especially to restore VE against emerging VOC such as Omicron. However, data gaps still persist, given the lag between the emergence of new variants, updated vaccine schedules and VE data to inform their impact.


# 1. Covid-19 In Asia (Focus On Southeast Asia)

Southeast Asian (SEA) countries were among the first to be affected by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which causes the disease, COVID-19.[1] For over 18 months, many Asian countries stemmed the virus' spread with

robust infection control measures and did not experience the devastation seen elsewhere. Until September 2021, SEA countries – specifically Indonesia, Malaysia, Philippines, Singapore, Thailand, Brunei Darussalam, Vietnam, Laos, Myanmar and Cambodia – accounted for fewer than 5% of global cases and deaths. However, since then, even some of these highly-vaccinated countries have had rapid increases in infections driven by the B.1.1.529 variant of concern (VOC), now known as Omicron.[2] Omicron is now dominant in Asia,[3] but is associated with lower rates of hospitalisation and death, particularly in vaccinated populations.[4] Asia Pacific countries that followed strict "COVID Zero" strategies are now dealing with major Omicron outbreaks,[5] including New Zealand where 95% of residents are vaccinated and 57% have had boosters,[6] and Hong Kong which saw increased deaths7[-9] especially in the elderly, a high proportion of whom were not fully vaccinated.

By March 25, 2022, over 1.18 billion people in the region (57.2% of its total population) were fully vaccinated[10] and several countries are now implementing booster programs.11 Yet, vaccine access remains an urgent and unmet need globally as only 13.7% of those in low-income countries and 56.5% of those in low-middle income countries have received at least one dose of COVID-19 vaccine.[12] The World Health Organization has highlighted the suboptimal vaccine coverage of priority populations and geographical areas in some SEA countries.1[3] This situation is further hampered by the persisting challenges of delivering different types of vaccines for primary or booster vaccinations and the increased focus on further doses in some regions when priority populations have still not had sufficient primary vaccine coverage.[13] Having endured over two years of the pandemic, SEA nations are endeavouring to resume normal economic and social activities. To provide relief for vulnerable populations in the region, decision-makers need fair, broad, and rapid access to vaccines,[14] but must also base decisions on what matters most – real-world vaccine effectiveness (VE) and safety.

Randomised controlled trials (RCTs) are conducted in controlled settings and may not reflect the real-world effectiveness (RWE) of the vaccines. RWE may be contingent on clinical factors such as the unknown level of protection mediated by antibody responses, and uncertainties regarding the real-world applicability of post-vaccination antibody responses. Issues may also arise from nonclinical factors like vaccine supply and demand dynamics, availability constraints, storage and distribution logistics across large geographical areas, and the need to cater to diverse ethnic populations. All of these factors are especially relevant in low- and middle-income countries (LMIC) in SEA.[15,16] Real-world, observational data can fulfil some of this need and help address the challenges of delivering anti-SARS-CoV-2 vaccinations. In Chile, Canada, Scotland, Qatar and Israel, such studies[17-23] already demonstrate a high VE against symptomatic disease and fatal outcomes caused by earlier VOCs. However, SEA's limited resources and surveillance systems mean that there are few large-scale studies using reliable, structured datasets from sources like registries, pharmacy databases, electronic health or insurance claims records. mRNA-based vaccines have been used more widely in Europe and the US than other vaccine platforms, causing an asymmetric accumulation of effectiveness data. This, combined with the difficulty in defining correlates of protection, has resulted in a perception that mRNA-based vaccines offer superior protection against severe SARS-CoV-2 disease compared to other types of vaccines.[24] In Asia, viral vector (e.g., AZD1222) and inactivated vaccines (e.g., CoronaVac) have been more widely available than mRNA-based vaccines (e.g., BNT162b2 and mRNA-1273) and provide a more readily deployable option for distribution and, potentially for local production.

Safety and adverse reactions (ARs) are a genuine concern for all vaccine recipients, and all vaccines are associated with common ARs but these are mostly mild and resolve quickly following vaccination. RCTs used for registration purposes specifically assessed the more common ARs but the number of participants is too few to detect rare ARs (< 1 in 10,000). As the scale of the current vaccination programmes is unprecedented, with billions of doses being distributed in the first 12 months of approvals, the emergence of some rare ARs is unfortunate but inevitable. While safety is not the primary objective of this review, it is an important counterbalance to effectiveness discussions and an expert assessment of the current status of vaccine safety is provided in context below. The International Vaccine Access Center (IVAC; Johns Hopkins Bloomberg School of Public Health, US) maintains the online, VIEW-hub resource (https://view-hub.org/covid-19/effectiveness-studies). VIEW-hub contains

epidemiological data on vaccine type and usage, country coverage and vaccine impact, and
focuses primarily on effectiveness outcomes. Unfortunately, VIEW-hub is not currently designed to capture safety outcomes.

During 2021, the primary issues countries faced related to vaccine supply, limiting population coverage rates in many parts of Asia. However, in 2022 supply is less of an issue in this part of the world and as mentioned above, two-dose coverage rates are generally quite high. The challenge now is that confidence in vaccines has been undermined by waning immunity against infections, misunderstandings and misperceptions around vaccine safety and performance, and the occurrence of highly-transmissible and immune-evasive variants. In an attempt to address some of these issues, we aimed to better understand whether VE varied between the most commonly-used vaccines for the main clinical outcomes associated with vaccine protection. To facilitate this, we leveraged the global, publicly available, RWE on VE from IVAC,[25] and assessed the relevance of these findings to SEA.

## 2. Bnt162b2, Mrna-1273 And Azd1222 Provide High And Comparable Protection Against Symptomatic Sars-cov-2-related Infections, Hospitalisations And Deaths, With Limited Waning Of Protection Against Severe Outcomes

IVAC included 79 studies with data on VE following two-dose schedules against SARS-CoV-2 infection, and COVID-19-related hospitalisations and deaths (see **Supplementary Table 1** for all studies included, **Supplementary Table 2** for study characteristics and **Supplementary Figure 1** for search strategy and selection criteria). Most of the data (28 studies) were from North America where BNT162b2 was the most-studied vaccine, followed by mRNA-1273 and AZD1222, while only two studies were from the Asia Pacific region. Given the vaccination programmes in SEA, it was also important to consider including CoronaVac (Sinovac, China) but the primary schedule was only evaluated in five studies. Due to its consistent under-representation within our dataset, we removed all CoronaVac data from the primary comparisons to prevent skewing of results and unrepresentative comparisons with AZD1222 and mRNA-based vaccines, but details of those studies can be found in **Supplementary Table 3**. Similarly, the vast majority of studies included by IVAC at our datalock point (February 10, 2022) reported VE against earlier VOCs, with limited data for Omicron, and primarily for two-dose schedules with limited data for booster study VE. To prevent skewing of vaccine comparisons, we did not perform any visualisation of the Omicron or booster VE data, but will discuss the impact of the Omicron VOC and booster vaccinations on current COVID-19 disease management and future vaccine strategies.

To simplify the comparisons, we combined datasets for BNT162b2 and mRNA-1273 as a common “mRNA” platform. We found that the three most-studied vaccines, BNT162b2, mRNA-1273 and AZD1222, had a high and comparable overall VE against symptomatic infections (average >77%) despite a wide variation (44%-100%) in study point estimates (**Figure 1a**), as well as a high and comparable VE when considering VOC, age over 60 years, study design or history of SARS-CoV-2 infection (**Figure 1b-1d**). mRNA vaccines were observed to have a non-significant trend toward higher VE against symptomatic infections. Importantly, a high overall VE (>90%) against the most serious outcomes of COVID-19-related hospitalisations (**Figure 2a**) and deaths (**Figure 3a**) was maintained regardless of the dominant circulating VOC (**Figure 2b, 3b**), age over 60 years (>84%; **Figure 2c, 3c**), different trial designs (**Figure 1d, 2d, 3d**) or previous COVID-19 infections among patients studied (**Figure 2e, 3e**).

We also performed a separate review of those studies (see **Supplementary Figure 2**) with comparative arms to assess the VE of AZD1222 and either BNT162b2 or mRNA-1273 or a heterologous mRNA schedule in the same

settings. In these 18 studies, we found that VE against hospitalisations and deaths across all age groups studied, including those over 60 years, was highly comparable between AZD1222 and mRNA-based vaccines (**Supplementary Figure 2**). We note however, that a formal meta-analysis is needed as our means and confidence intervals are purely descriptive since we did not include weighting or adjustments for the included studies.

The majority of studies included by IVAC were conducted during VOC periods prior to Omicron while most studies evaluating VE at different timepoints after vaccination were conducted during periods of high infections with the Delta variant (B.1.617.2). Against symptomatic infections, and even when measured at later points (over 140 days) after the second dose, VE declined by an average of approximately 25% for both AZD1222 and mRNA-based vaccines between the early to late periods, but remained comparable between these vaccines (**Figure 4a**). Against Delta-related hospitalisations, VE was high and comparable across the vaccines, and waning was limited (>92% after over 140 days, **Figure 4b**). A limited number of datasets to evaluate waning against Delta-related deaths prevents robust conclusions, but AZD1222 VE ranged from 88.5%-66.5% while mRNA-based VE ranged from 96%-90% over the 140-day period post-second dose (**Figure 4c**). More data is needed to confirm this observation.

## 3. Relevant Real-world Data Adds To Existing Evidence Demonstrating That Full Vaccination And Boosters Reliably Protect Against Serious Outcomes

RWE provides more contextual clarity for decision-making at local and regional levels, but some countries in SEA lack real-world VE data to assess the true impact of Omicron, or the use of mixed or heterologous vaccine schedules, a third vaccine dose or CoronaVac, a key component of vaccine supplies[28-28] in many SEA countries. A recently published observational study from Malaysia found that VE against SARS-CoV-2 infections waned significantly after 3-5 months for both BNT162b2 and CoronaVac, but VE against deaths remained high for both vaccines.2[9] RWE is also available for completed homologous primary vaccinations in Malaysia3[0] and for heterologous primary schedules in Thailand (**Table 1**).3[1,32] We also evaluated data from Chile, where CoronaVac, AZD1222, or BNT162b2 boosters were given after primary vaccinations with CoronaVac. This scenario resembles the vaccination situation of many Asian countries and potentially represents the VE that can be expected.[18] Together, these studies demonstrate that regardless of vaccine type or schedule, full vaccination effectively protects against serious outcomes. This data may also support our observations that protection can be enhanced through boosters. A high VE against serious outcomes may be achievable through a third vaccine dose or heterologous schedules, underscoring the importance of RWE in vaccine selection decisions.

## 4. Sea Experts' Insights

As our group consisted of infectious disease experts and contributors to national vaccination policies in our respective countries, we therefore considered the applicability and consistency of these findings against the limited data available for SEA and shared our recommendations on strategies for future vaccination programs.

***Insights on Safety of Available Vaccines.*** Belief in the overall safety of these vaccines is naturally of paramount importance and whilst the benefit/risk profile of the approved vaccines has been confirmed by regulators worldwide and further established through their extensive global deployment, a small number of ARs have created disproportionate concerns; in particular, thrombotic events with adenovirus vector vaccines and myocarditis or pericarditis with mRNA-based vaccines. While a small increased risk of thrombosis with thrombocytopenia syndrome (TTS) or venous thromboembolism (VTE) with thrombocytopenia (TCP) has been observed after the first dose of AZD1222 (8.1 cases per million doses), much lower rates occurred after a second dose (2.3 cases per million doses).[33] Importantly, these rates were similar to background pre-pandemic rates of autoimmune heparin-induced TCP, and were also within the estimated background rates for unvaccinated populations,3[4] as well as being much lower than TTS-like events due to COVID-19 infections (VTE with TCP was 195.9 events/million patients).[33,35] Concerns of reduced platelet levels and venous and arterial thromboses in cerebral veins also arose with AZD1222. Yet, the rates of major arterial or venous thrombotic events were not increased in adults 70 years or older[36,37] by primary vaccination with either AZD1222 or BNT162b2. In adults younger than 70 years, a small increase in the excess risk of intracranial venous thrombosis and hospitalisation with TCP after primary AZD1222 vaccination (0.9 to 3.0 events/million) is far outweighed by its reduction of COVID-19 mortality and morbidity. AZD1222 was also thought to be associated with cerebral venous sinus thrombosis (CVST),[38]

but the rate of CVST events in the four weeks following a primary dose were comparable to the rates at 90 days before vaccination. Nevertheless, given the many doses of vaccines now administered globally, CVST following a first dose of AZD1222 is still a rare clinical event and causality Is difficult to establish.[39]

In one study from a vaccine AR reporting system in the US using primarily mRNA vaccines,[40] the occurrence of most severe ARs was associated with sex, age, day of onset, and vaccine platform, with elderly individuals experiencing higher rates of thrombosis and ARs affecting the heart, blood, and nervous system. Conversely, younger individuals had a higher incidence of inflammation-related ARs such as Bell's palsy, myocarditis or pericarditis and lymphadenopathy, as well as convulsions or seizures. Nevertheless, the occurrence of severe ARs (e.g., Guillain-Barré Syndrome, deep-vein thrombosis, lymphopenia) were slightly lower than baseline for mRNA-1273 and significantly lower than baseline for BNT162b2. mRNA-based vaccines are also associated with a rarer but higher rate of vaccine-associated anaphylaxis in females than males,[41,42] and with the rare occurrence of myocarditis and pericarditis, particularly in adolescent and young adult males.[43] In Europe, myocarditis has been reported at over 26 to 57 events/million within one week of mRNA vaccination while in the US reported events estimated at a rate of 1–40.6 cases/million second doses of mRNA vaccines in males aged 12–29 years.[44,45]

CoronaVac, which is widely used across Asia, was evaluated in Brazilian healthcare workers,[46] where no severe ARs were attributed to the vaccine. While some of the initial concerns with these events led to some usage restrictions and label updates for different vaccines, the current body of evidence suggests these events are very rare and quite manageable through improved diagnosis and treatment algorithms in most circumstances with a very favourable benefit/risk profile for all COVID-19 vaccines.

Similarly, there may be concerns regarding safety of booster doses. However, the recent phase II RCT, COV-BOOST,[47] evaluated seven types of vaccines as a third or booster dose after a primary series of AZD1222 or BNT162b2, and found expected ARs due to inflammation, such as injection site pain, fatigue and headaches, all of which were well-tolerated. Importantly, social media amplification of reports about vaccine-related ARs has led to excessive worry among people even when doctors may be unconcerned.[48] We acknowledge that SEA countries do not yet have safety data on boosters, which is a gap that needs to be addressed in future studies. However, evidence available elsewhere and in COV-BOOST do not indicate any serious concerns. Healthcare providers and policymakers must address this by ensuring that accurate, updated data are widely and frequently shared with the general public and that safety concerns are not simply dismissed.

***Insights on Waning of VE or Duration of Protection.*** Our analysis consistently confirmed a high VE at preventing hospitalisations and deaths, at comparable levels across all vaccines, regardless of VOC (excluding Omicron). Numerous reports of waning antibody levels4[9-51] have driven the implementation of booster doses in many countries, based primarily on the associated waning of protection against mild infections, manifesting as breakthrough cases in vaccinated individuals.[52,53] Importantly, despite declining antibody levels, we found high and sustained VE against hospitalisations and deaths for AZD1222 and mRNA-based vaccines up to 140 days, with limited waning observed when data enabled informed assessments (**Figure 4**).

***Insights on Correlates of Protection.*** We emphasise the importance of being aware of how VE is measured and the clinical outcomes by which waning is quantified, in order to understand why vaccine-induced immunity declines against SARS-CoV-2 infection or COVID-19. Currently, protection is assumed through levels of neutralising antibodies[49] but the precise levels required to achieve this are still being established.[54] Neutralising antibodies provide initial protection against overall infection but do not provide sterilising immunity, limiting their impact on COVID-19 transmission.[49] Phase III efficacy trials for AZD1222 and mRNA-1273 both correlated the levels of immunoglobulin G (IgG) antibodies against a virus' spike or receptor-binding domain to protection against symptomatic infection.[55-58] But in the real-world, high levels of antibodies were seen in some healthcare

workers with breakthrough infections, and evidence is insufficient to support using antibody levels to predict potential infections.5[9-63] Moreover, cell-mediated immunity against COVID-19 can be induced by vaccines even when antibody-mediated mechanisms are lacking.[64] RWE indicates that COVID-19 vaccinations conferred a high level of protection against hospitalisation and death, and for at least 20 weeks after a second dose [2,17,63-65] despite VE waning against infection within six months of vaccination.[68] Breakthrough infections suggest that protection against infection may not be sufficiently durable, and that further vaccine doses are needed to support that clinical objective. With the emergence of Omicron, this waning is accentuated and underscores the need for the completion of primary series vaccinations and/or the addition of booster doses to maintain high levels of protection, especially against severe COVID-19 outcomes.[2] The minimal waning observed in our review against the Delta variant reaffirms our collective belief that VE against severe outcomes is not well correlated with antibody levels, and is indeed dependent on cellular immunity.[69,70] Consequently, T-cell responses may be a stronger indicator of protection against severe disease than neutralising antibodies[54,71-73] and we suggest that all the current vaccines induce strong T-cell responses that prevent severe disease. Thus, boosting with viral vector vaccines (which are more widely available and logistically easier to distribute than mRNA vaccines) should increase protection for un-boosted populations, regardless of the primary vaccine.

***Insights on the Impact of the Omicron Variant.*** Previous data suggests high and comparable VE against symptomatic infections by previous variants,[74-77] but data for Omicron is still accumulating. RWE data from the UK[78] provided a robust comparison of VE against Omicron and Delta for the vaccines most used there.[79] Compared to Delta, VE against symptomatic disease due to Omicron declines substantially after two-dose schedules of AZD1222 or BNT162b2, and wanes more quickly over time than for Delta, starting from 15 weeks after the second dose,[79] consistent with what has been observed elsewhere.[80] Similarly, VE against hospitalisations due to Omicron drops to 65% (range: 45% to 85%) or 70% (range: 55% to 90%) from 24 weeks after two doses of AZD1222 or BNT162b2, respectively. A high VE against Omicron hospitalisations is restored by homologous or heterologous boosters, yet VE waning appears to occur more quickly over time compared to Delta.[2,79] Importantly, with respect to Omicron, VE against overall symptomatic and serious outcomes is highly comparable for two and three dose schedules (homologous and heterologous) of AZD1222 and BNT162b2, and consistent with our review, irrespective of variant and clinical outcome.

An additional consideration, given the very high rate of infections globally, relates to the hybrid protection offered by vaccines in people with a history of COVID SARS-CoV-2 infection. Emerging data suggests that previous natural infections of SARS-CoV-2 are 56% effective against Omicron variant reinfections and 88% effective against severe, critical or fatal COVID-19.8[1] Recent data from more than 200,000 Brazilians, showed that for people who already had COVID-19, both BNT162b2 and AZD1222 offered 90% effectiveness against hospitalisation and death, consistent with the equivalent protection observed above (>89%, **Figures 2 and 3**).8[2] The same study reported that the CoronaVac vaccine provided 81% protection while one dose of the Johnson & Johnson adenovirus-vectored vaccine provided 58% protection following infection.[82]

## 5. Strengths And Limitations Of Our Review

Due to the limitations of the studies included in the IVAC database, we could not adequately stratify hospitalisation into more specific criteria like admissions or intensive care unit (ICU) usage, nor could we account for varying follow-up durations post-vaccination across studies. Hospitalisation criteria differ among countries and may not always reflect disease severity. For example, in Malaysia, hospitalisations are not a defined VE outcome as more granular criteria such as ICU admission are used instead. During Thailand's Omicron surge, the majority of patients had mild disease and were not hospitalised unless disease was severe, or they were in a high-risk group. Studies included into the IVAC database often specified open-ended age ranges, with a lack of upper-age limits restricting our ability to assess the immune dynamics and disease severity between different age groups. Additionally, we could not account sufficiently for patients with comorbidities, especially those with diabetes and hypertension, which are common in Asian populations[83] or for immunocompromised patients or those on immunosuppressive therapies. While we consider the VE of AZD1222 and mRNA-based vaccines to be equivalent against serious outcomes, further data are needed to optimise booster strategies in Asian populations. As our review only analysed primary vaccinations, we are unable to clarify

whether additional boosters would be successful against new VOCs, for how long they would be effective.8[4,85] Similarly, there is insufficient RWE on the use of heterologous vaccine schedules8[6] in this region. Future studies will need to include the most widely-used vaccine in Asia – CoronaVac – as well as offer comprehensive analysis of Asian data in the form of meta-analyses. Finally, even though death appears to be a clearly defined endpoint in some studies, its reporting as COVID-19-related is not standardised between countries.

Importantly, the strengths of our review lie in the robust dataset underpinning these observations. After applying strict inclusion/exclusion criteria and bias assessments, the IVAC database includes many large, population-level RWE studies (see **Supplementary Table 2c**). While there are geographic and schedule gaps within, the dataset provides one of the largest objective collations of RWE available publicly.

## 6. Getting Ahead Of The Virus - Critical Next Steps

Through our review, we confirm a consistently high protection of >90% against hospitalisations and deaths, and importantly, we note that this protection appeared to be equivalent with two-dose schedules of mRNA vaccines and some vector vaccines like AZD1222 (91%-93%). This observation is supported by Asian and relevant international data, all of which reinforce the value of RWE when advocating for the completion of primary series and booster vaccinations where appropriate. We also emphasise that although antibody levels are an accessible biomarker and correlate with protection against symptomatic infection, it is now clear that they decline rapidly and correlate poorly with protection against severe disease. Consequently, antibody profiles cannot accurately represent the full immune response over time and are not effective predictors of VE against severe disease. Instead, we strongly advocate considering real-world VE against severe COVID-19 outcomes. This is a more relevant metric of vaccine performance, particularly during the Omicron wave, where infection rates are high in both partially and fully vaccinated individuals.

SEA's national healthcare systems have had to strike a balance between clinical expectations based on RCT and real-world data, implementation challenges based on supply (e.g., mixed vaccination strategies) and other non-clinical considerations (e.g., cold-chain logistics). Although many SEA countries have high rates of primary vaccination, there are still challenges to achieving high booster dose coverage. In resource-limited regions, dealing with the challenges of logistics, cold-chain storage or rural vaccinations, the most effective way to achieve vaccine booster targets would simply be to consider non-mRNA vaccines which have good safety and comparable effectiveness profiles, particularly against severe outcomes, and that are accessible and optimal for the local situation (e.g., no freezer requirements). In this respect, viral vector vaccines, such as AZD1222, are attractive as they offer comparable effectiveness to mRNA-based vaccines with simpler distribution logistics. With an eye towards the future, manufacturers will need to update the first-generation vaccines to provide optimal protection against new, antigenically-distinct variants.[87] They will also need to facilitate sustainability and local manufacturing capabilities by establishing in-country expertise. In this way, vaccine production will be cost-effective while meeting the logistical challenges of current and future infectious diseases in Asia.

The COVID-19 pandemic trajectory has not been straightforward and neither have been our measures to overcome it. Booster programs have been accelerated to maintain high levels of immunity and enhance protection against serious outcomes. Confidence in vaccines has been repeatedly undermined by waning immunity against infections, misunderstandings around vaccine safety and performance, and the occurrence of highly-transmissible and immune-evasive variants. Breakthrough infections have threatened to overwhelm healthcare systems. Vaccine hesitancy and implementation challenges are likely to have been exacerbated by confusing messages. While the IVAC VIEW-hub dataset does not lend itself to a similar comparison of safety outcomes after vaccination, knowledge regarding ARs of special interest has increased substantially and provides reassurance around the safety profiles of these vaccines. Fortunately, the most widely-used vaccines have demonstrated a high level of

protection against the most serious clinical outcomes, in both controlled trials and in real-world situations. Together, these new insights into comparative VE data, combined with a greater understanding and confidence around vaccine safety, provides an opportunity to embrace a paradigm shift in vaccine perception and allows decision-makers to take control of the pandemic, now and for the future.

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## Declarations

**Competing Interest Statement:** Following International Committee of Medical Journal Editors' (ICMJE) guidelines, AOL reports honoraria for lectures from Moderna and is a member of the Technical Advisory Group, Department of Health in the Philippines. CHN, KPH, RS, and SuwC report consulting fees from AstraZeneca. DVD reports consulting fees and honoraria for advisory board attendance by AstraZeneca. NCC reports consulting fees from AstraZeneca and honoraria for scientific meeting travel and lecture from multiple companies. He is also a member of the Taiwan Vaccine Injury Compensation Program and Pediatric Infectious Disease Society of Taiwan. PIL reports grants from the Taiwan Center for Disease Control for COVID-19 vaccine immunogenicity studies, consulting fees from AstraZeneca, Merck Sharp & Dohme (MSD), and GlaxoSmithKline and payment for lectures from MSD. He also serves as the Chair, Advisory Committee on Immunization Practice in Taiwan. PSK is employed by Serum Institute of India Pvt Ltd which manufactures a COVID-19 vaccine (Covishield) that is sub-licensed from AstraZeneca. RCL reports consulting fees from AstraZeneca and honoraria for lectures from Menarini Philippines, Nestle, Mead Johnson and Novartis. He is also the vice-chair of the National Adverse Events Following Immunization committee in the Philippines. SK reports consulting fees from AstraZeneca and honoraria for lectures from AstraZeneca, Pfizer and Zuellig Pharma. EB, GT, JLS, MH, PSKT, SunC, and SS report no relevant disclosures.

**Funding Statement:** Funding for this manuscript was provided by AstraZeneca for medical writing support to summarise the International Vaccine Access Center (IVAC) data and develop draft visuals for review and interpretation by the authors. The authors were involved in the study design; in the interpretation of data; in reviewing the manuscript; and in the decision to submit the manuscript for publication. All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

**Acknowledgment:** The authors wish to thank Shawna Tan of Medical Writers Asia for manuscript writing and Manuel von Osten of GCI Health for analysis of IVAC study and data visualisations. We would also like to thank Melissa Higdon (IVAC) for review of the manuscript.

# Tables

Table 1 is in the supplementary files section.

# Figures

### Figure 1

AZD1222, BNT162b2 and mRNA-1273 Have High and Comparable Overall VE against symptomatic infections. (a) VE is shown from individual studies from IVAC, ordered from highest to lowest VE, and stratified by (b) variant of concern, (c) age over 60 years, (d) study design or (e) history of SARS-CoV-2 infection. Abbreviations: VE, vaccine effectiveness; CI, confidence interval; n.a., not applicable.

### Figure 2

AZD1222, BNT162b2 and mRNA-1273 Have High and Comparable VE Against Hospitalisations. (a) VE is shown from individual studies from IVAC, ordered from highest to lowest VE, and stratified by (b) variant of concern, (c) age over 60 years, (d) study design or (e) history of SARS-CoV-2 infection. Abbreviations: VE, vaccine effectiveness; CI, confidence interval; n.a., not applicable.

### Figure 3

AZD1222, BNT162b2 and mRNA-1273 Have High and Comparable VE Against Deaths. (a) VE is shown from individual studies from IVAC, ordered from highest to lowest VE, and stratified by (b) variant of concern, (c) age over 60 years, (d) study design or (e) history of SARS-CoV-2 infection. Abbreviations: VE, vaccine effectiveness; CI, confidence interval; n.a., not applicable.

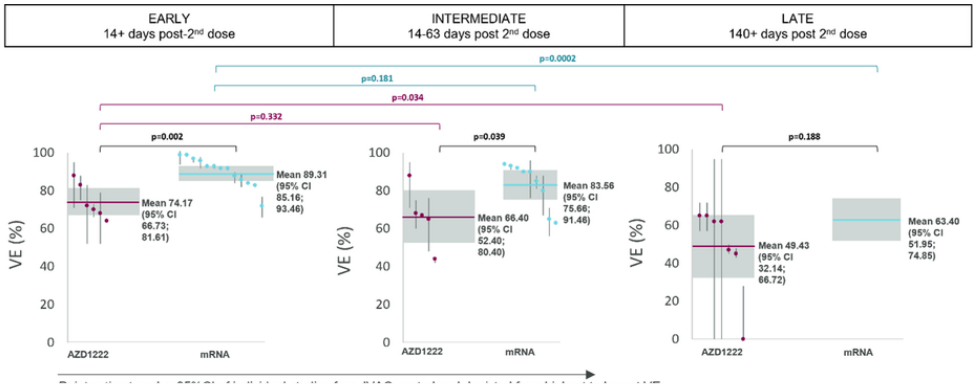


**Figure 4**

**Waning of VE with Time After Second Dose.** Abbreviations: VE, vaccine effectiveness; CI, confidence interval.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.docx
- SupplementaryData.docx