

## Expert review on global real-world vaccine effectiveness against SARS-CoV-2

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REVIEW

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## Expert review on global real-world vaccine effectiveness against SARS-CoV-2

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### ABSTRACT

**Introduction:** 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.

**Areas covered:** We reviewed 79 studies in the International Vaccine Access Center (IVAC) VIEW-hub platform on vaccine effectiveness (VE) after primary immunizations with two-dose schedules. VE data were reported for SARS-CoV-2 infection, COVID-19-related hospitalizations and deaths, and stratified across variants of concern, age, study design and prior SARS-CoV-2 infection for mRNA vaccines (BNT162b2, mRNA-1273, and combinations of both), vector vaccines (AstraZeneca, AZD1222 [ChAdOx1 nCoV-19] 'Vaxzevria'), and inactivated virus vaccines (CoronaVac).

**Expert opinion:** The most-studied COVID-19 vaccines provide consistently high (>90%) protection against serious clinical outcomes like hospitalizations and deaths, regardless of variant. Additionally, this protection appears equivalent for mRNA vaccines and vector vaccines like AZD1222, as supported by our analysis of Asian and relevant international data, and by insights from SEA experts. Given the continued impact of COVID-19 hospitalizations and deaths on health-care systems worldwide, encouraging vaccination strategies that reduce this burden is more relevant than attempting to prevent broader but milder infections with specific variants, including Omicron.

### ARTICLE HISTORY

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COVID-19; mRNA; Omicron; real-world; Southeast Asia; vaccine effectiveness; variants of concern; vector; waning immunity; AZD1222

## 1. Introduction

As of 14 June 2022 [1,2], over 535 million cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and over 6.3 million COVID-19 deaths have been reported worldwide, with over 66.3% of the global population having received nearly 11.94 billion doses of SARS-CoV-2 vaccine. Most major Western economies have passed their peaks of SARS-CoV-2 infections and COVID-19 deaths, and now have high vaccination rates [3]. Yet, the B.1.1.529 variant of concern (VOC) known as Omicron has driven a rapid increase in infections, even in highly vaccinated countries [2]. Omicron is now dominant across Asia [3] but is associated with lower rates of hospitalization and death, particularly in vaccinated populations [4]. With cases of subvariants now also increasing [4,5], it is imperative that we remain vigilant.

While at least 113 countries have started booster vaccinations, vaccine access remains an urgent and unmet need

globally as only 17.8% [2] of those in low-income countries and 53.5% [6] of those in low-middle-income countries (LMIC) have had at least one dose of a COVID-19 vaccine [7]. In fact, the WHO has voiced concerns about the suboptimal vaccine coverage of priority populations and geographical areas [8]. The challenges of delivering different types of vaccines for primary or booster vaccinations persist and are complicated by an increased focus on additional doses in some regions even when priority populations have still not had sufficient primary vaccine coverage [8]. Having endured over 2 years of the pandemic, most nations are endeavoring to resume normal activities.

To provide relief for vulnerable populations, decision-makers need fair, broad, and rapid access to vaccines [9], but must also base decisions on what matters most – real-world vaccine effectiveness (VE) and safety. Randomized controlled trials (RCTs) are conducted in controlled settings and

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**Article highlights**

- VE was high and comparable for both AZD1222 and mRNA vaccine types (91–93%) in protecting against hospitalization 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 are 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.
- Data from the UK indicate 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 favorable benefit/risk profiles.
- Although many SEA countries have high rates of primary vaccination, there are still challenges to achieving high booster dose coverage. The results of this analysis suggest that the most effective way to achieve vaccine booster targets, particularly in resource-limited settings, would simply be to consider any vaccines which have good safety and comparable effectiveness profiles, particularly against severe outcomes, and that are accessible and optimal for the local situation.
- This review 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.

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 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 LMIC [10,11].

Real-world, observational data can help address the challenges of delivering anti-SARS-CoV-2 vaccinations. In Chile, Canada, Scotland, Qatar, and Israel, such studies [12–18] already demonstrate a high VE against symptomatic disease and fatal outcomes caused by earlier VOCs. However, limitations in resources and surveillance systems mean that there are few large-scale studies using reliable, structured datasets from registries, pharmacy databases, electronic health or insurance claims records. An asymmetric accumulation of effectiveness data has resulted from the more widespread use of mRNA-based vaccines in Europe and the US than other vaccine platforms. This, combined with the difficulty in defining correlates of protection, has led to a perception that mRNA-based vaccines offer superior protection against severe SARS-CoV-2 disease compared to other types of vaccines [19]. In other regions, including SEA, viral vector (e.g. AZD1222, Ad26.CoV2.S) and inactivated vaccines (e.g. CoronaVac, BBIBP-CorV) are 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.

During 2021, vaccine supply was a key obstacle that limited population coverage rates in many countries. However, in 2022, supply is less of an issue in Asia, where two-dose coverage rates are generally 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. 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, primary series VE data from the International Vaccine Access Center (IVAC; Johns Hopkins Bloomberg School of Public Health, US), which maintains the online VIEW-hub resource. VIEW-hub contains real-world epidemiological data on vaccine type and usage, country coverage, and vaccine impact, and focuses primarily on effectiveness outcomes, but is not currently designed to capture safety outcomes [20]. It also comprises one of the most robust, independent systematic literature reviews of VE data. Our panel of South-East Asian (SEA) experts then determined the relevance of these findings to the region, specifically Indonesia, Malaysia, Philippines, Singapore, Thailand, Brunei Darussalam, Vietnam, Laos, Myanmar, and Cambodia.

Although safety is not the primary objective of this review, there are legitimate public concerns over vaccine safety and adverse reactions (ARs). 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 have had too few participants to detect rare ARs (<1 in 10,000). Given the unprecedented scale of the current vaccination programs, where billions of doses were distributed within the first 12 months of approvals, several rare ARs have inevitably emerged. A brief discourse on safety is, thus, an important counterbalance to our effectiveness discussions and we provide an expert assessment of the current status of vaccine safety.

## 2. Methods

### 2.1. Study selection

Vaccine effectiveness data was extracted from the IVAC VIEW-hub database (<https://view-hub.org/covid-19/effectiveness-studies>) up to the datalock point of 10 February 2022. We included only observational study effectiveness results that appeared in at least a detailed report or preprint, and if the comparison group included concurrent individuals (no modeled or historic controls), laboratory-confirmed outcomes, a study design that accounted for confounding, self-reported vaccination status comprised no more than 10% of participants, confidence intervals were reported, no significant bias was present, and controls were unvaccinated (e.g. excluded if ‘unvaccinated’ included days 0–12 post-vaccination). Only studies comparing persons with and without the clinical outcome under investigation, and with and without vaccination, were included (Supplementary Figure 1) [21].

Only VE data against specific disease endpoints (symptomatic disease, severe disease, 'hospitalization,' and death) were extracted. Studies reporting VE for Ad26.COV2.S ( $n = 22$ ) were excluded as we considered at least two doses necessary for full immunization. No studies reporting VE for Covaxin were included as none was available at the time of data extraction. Moreover, IVAC only included results if the interval between the final dose and case detection was at least 1 week, and excluded VE data if the follow-up after a final dose was over 6 months [21]. Effectiveness against specific SARS-CoV-2 variants was confirmed if a variant in all cases contributed to an estimate, or the variant caused the majority of cases in a study cohort or population [21]. To prevent skewed comparisons, we excluded vaccines with fewer than five VE estimates, leaving four vaccines (or combinations of) for review: BNT162b2, mRNA-1273, AZD1222 and CoronaVac (Supplementary Tables 1 and 2). As only 5 VE studies reported on CoronaVac, CoronaVac was thus excluded. Given the inclusion of mixed mRNA vaccine schedule studies, all mRNA VE data were combined into an 'mRNA vaccine platform' for a simpler comparison of mRNA vaccines (BNT162b2 and mRNA-1273) to viral vector vaccines (represented by AZD1222). To assess the VE of AZD1222 and BNT162b2 or mRNA-1273 or a heterologous mRNA schedule, we extracted VE estimates from studies with comparative arms (Supplementary Figure 2), which increased the reliability of our vaccine comparability assessments. At the time of the data lock, there were limited data available on the emerging VOC Omicron and for the VE of boosters ( $>2$  doses). To prevent skewing of vaccine comparisons, we did not perform any visualization of the Omicron or booster VE data, but discuss the impact of the Omicron VOC and booster vaccinations on current COVID-19 disease management and future vaccine strategies. A review of safety data was not possible as these data were not captured in the IVAC database at the time of study; any discussions of safety assessments are based on authors' consensus of existing safety literature.

## 2.2. Data visualization

VE estimates for each vaccine platform were combined and stratified across VOC, age, study design, and prior SARS-CoV-2 infection. VE point estimates are presented graphically with respective confidence intervals. If a meaningful estimate of the time since vaccination was extracted, the potential waning of VE over time was assessed. Studies were stratified according to VE estimates recorded as 'early' (14+ days post dose 2), 'intermediate' (14–63 days post dose 2) and 'late' ( $>140$  days post dose 2). To allow discussions on platform comparisons, means and confidence intervals were calculated for all figures. Statistical comparisons were conducted using two-tailed t-tests, with non-significance differences indicated by P-values greater than 0.05.

## 2.3. Non-IVAC data

Our IVAC dataset demonstrated several gaps in VE data for Asian populations, for the Omicron variant and for booster schedules. To enable discussion and advisories for the various vaccination situations in Southeast Asia, we addressed these gaps by including the following local or international comparative datasets:

### a. Asian data

One primary schedule study for BNT162b2, CoronaVac and AZD1222 from Malaysia [22], and several VE studies from Thailand [23, 24] provide both primary schedule VE data and data following a third booster dose, thus facilitating comparative VE studies after full vaccination in Asian settings - this is discussed in Section 3.4.

### b. Omicron data

The authors felt that Public Health England (PHE) [25, 26] primary schedule and booster data from the UK was the most credible comparison of VE against Omicron for mRNA and AZD1222.

### c. Booster data

In addition to booster data from Thailand and PHE, a Chilean study included a schedule relevant to SEA countries that evaluated AZD1222, BNT162b2, and CoronaVac VE following a third dose in individuals primed with two doses of CoronaVac [13].

## 3. Results

IVAC included 79 studies with data on VE following two-dose schedules against SARS-CoV-2 infection, and COVID-19-related hospitalizations and deaths (see Table S1 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 Asia Pacific. 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.

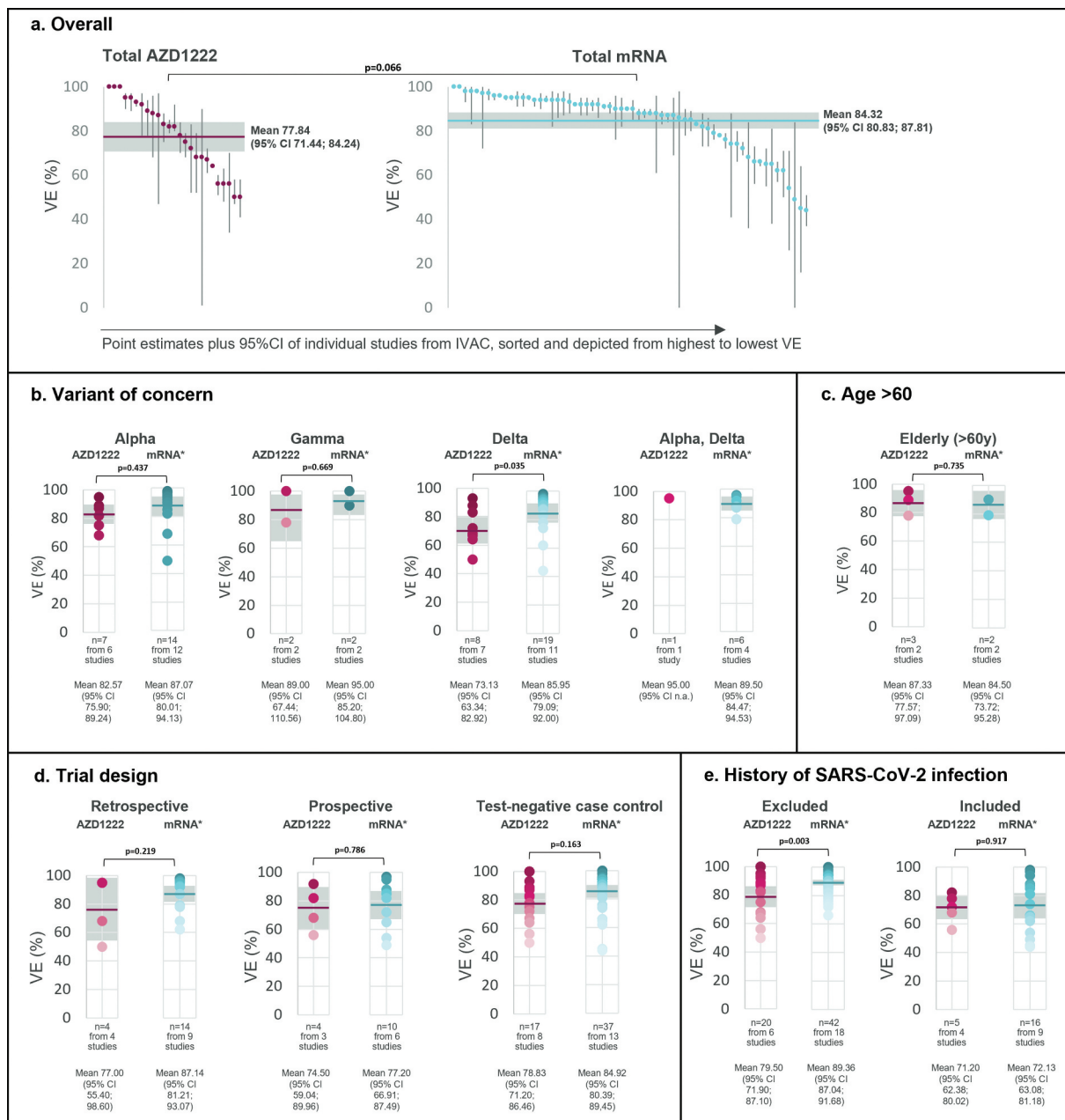
### 3.1. Vaccine effectiveness against symptomatic infection

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–d). mRNA vaccines were observed to have a non-significant trend toward higher VE against symptomatic infections.

### 3.2. VE against serious outcomes of hospitalization and death

Importantly, a high overall VE ( $>90\%$ ) against the most serious outcomes of COVID-19-related hospitalizations (Figure 2a) and deaths (Figure 3a) was maintained regardless of the dominant circulating VOC (Figure 2b, 3b), age over 60 years ( $>84\%$ ;





**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.

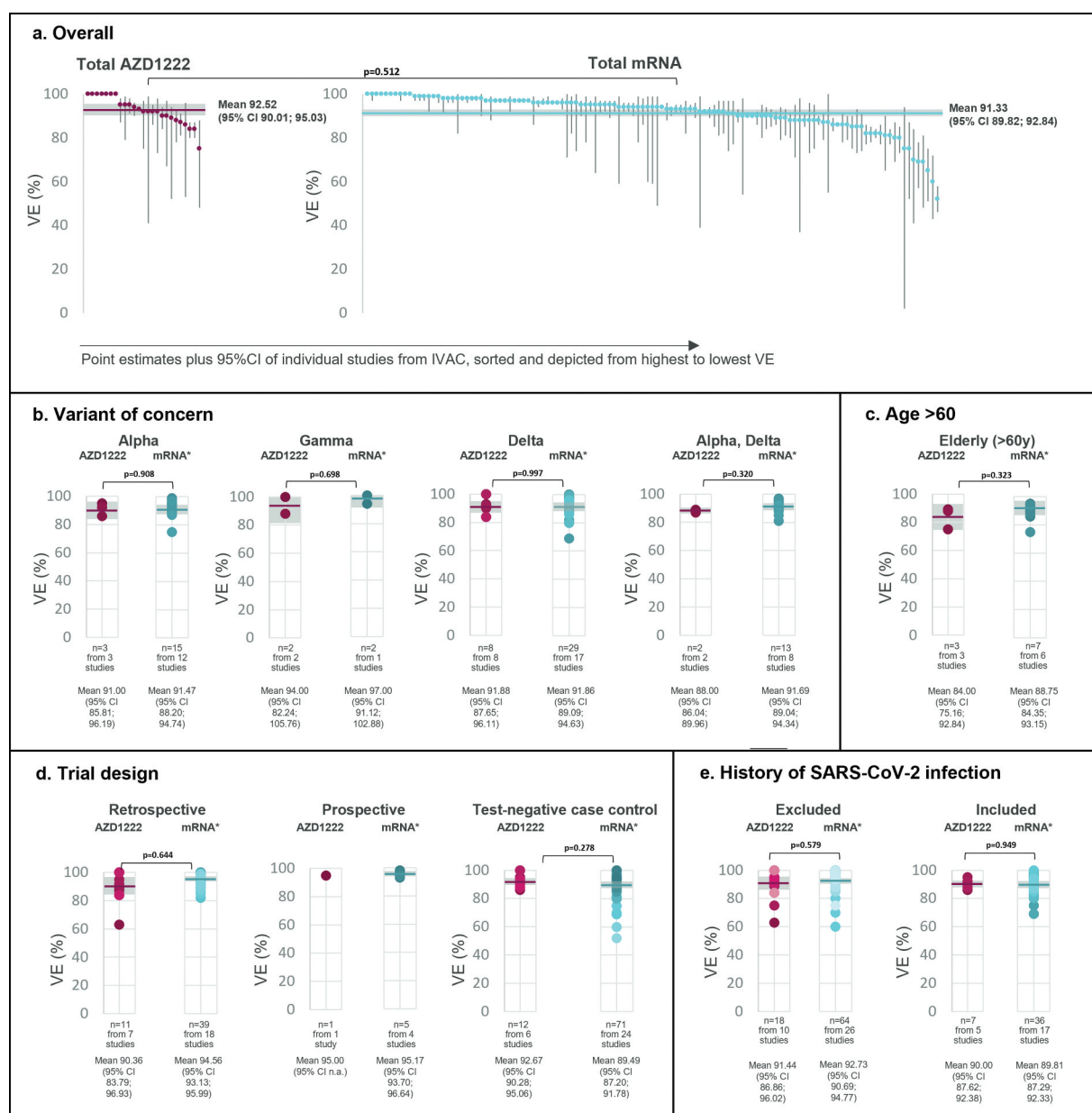
Figure 2c, 3c), different trial designs (Figure 1d, 2d, 3d) or previous COVID-19 infections among patients studied (Figure 2e, 3e).

In a separate analysis of 18 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, we found that VE against hospitalizations and deaths across all age groups studied, including those over 60 years, was highly comparable between AZD1222 and mRNA-based vaccines (Supplementary Figure 2). This merits further study in a formal meta-analysis, as the means and confidence intervals

in our analysis were purely descriptive and did not include weighting or adjustments for these studies.

### 3.3. VE against symptomatic infections and serious outcomes over time

At the time of datalock, most studies evaluating VE at different timepoints after vaccination were conducted during periods of high infections with the Delta variant (B.1.617.2) and the Omicron VOC had only begun to emerge. Against this backdrop, in terms of symptomatic

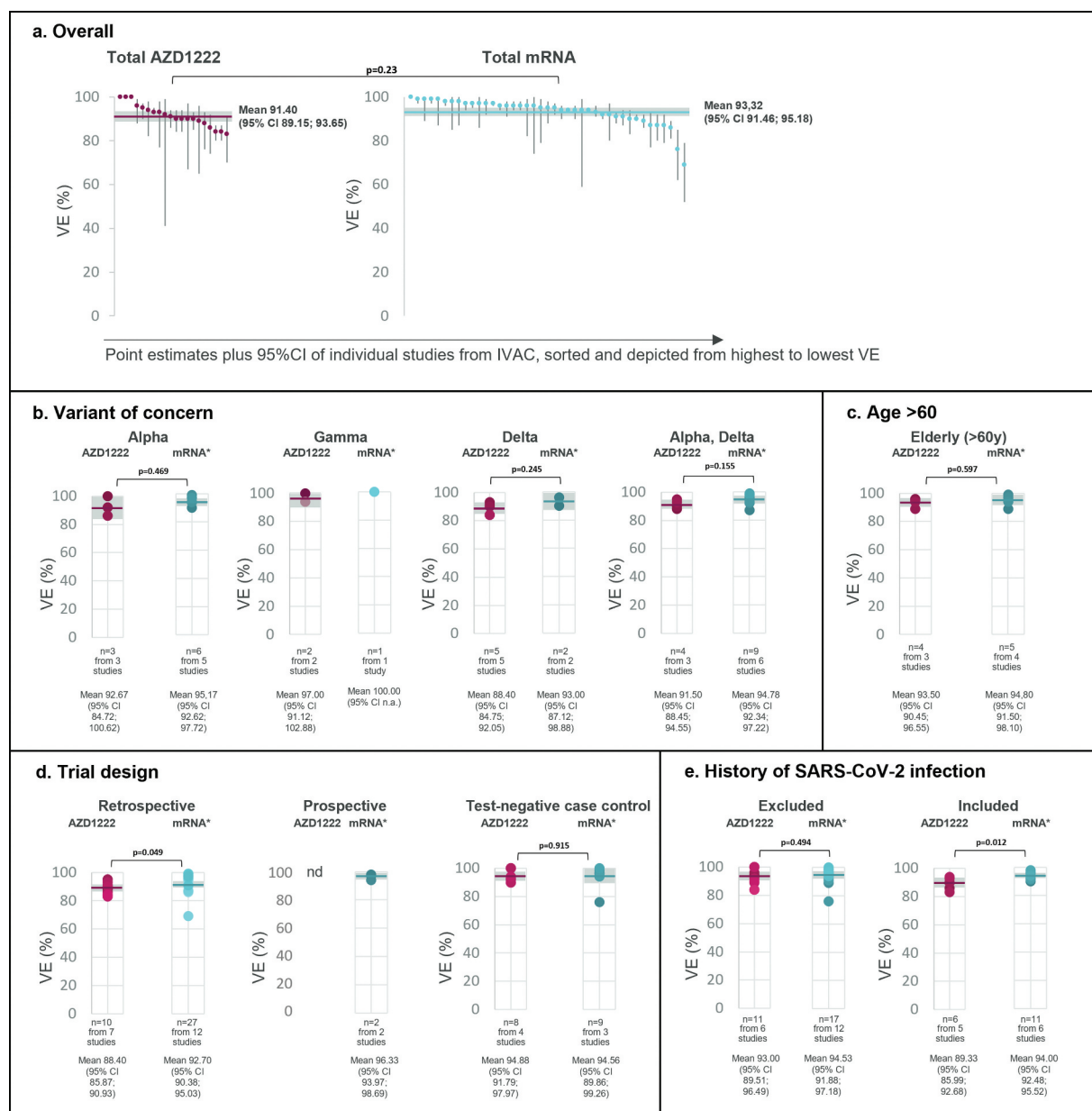


**Figure 2.** AZD1222, BNT162b2, and mRNA-1273 have high and comparable VE against hospitalizations. (a) VE is shown from individual studies from IVAC, ordered from highest to lowest VE, and stratified by (b) variant of concern, (c) age over 60 years, (d) study design, or (e) history of SARS-CoV-2 infection.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

infections, even when measured at later points (>140 days) after the second dose, VE declined by an average of approximately 25% for both AZD1222 and mRNA-based vaccines between early and late periods, and remained comparable between all vaccines (Figure 4a). Against Delta-related hospitalizations, 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% to 66.5%, while mRNA-based VE ranged from 96% to 90% over the 140-day period post-second dose (Figure 4c). More data are needed to confirm this observation.

### 3.4. Additional relevant real-world data

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 [27]. RWE is also available for completed homologous primary vaccinations in Malaysia [28] and for heterologous primary schedules in Thailand (Table 1) [23, 29]. 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 LMIC countries and potentially represents the VE that can be expected [13]. Together,



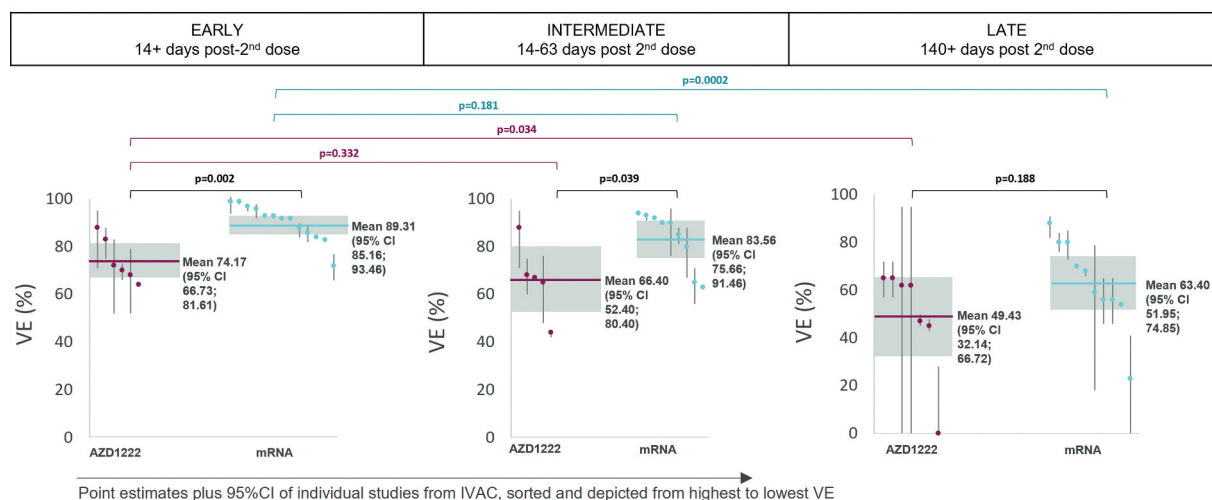
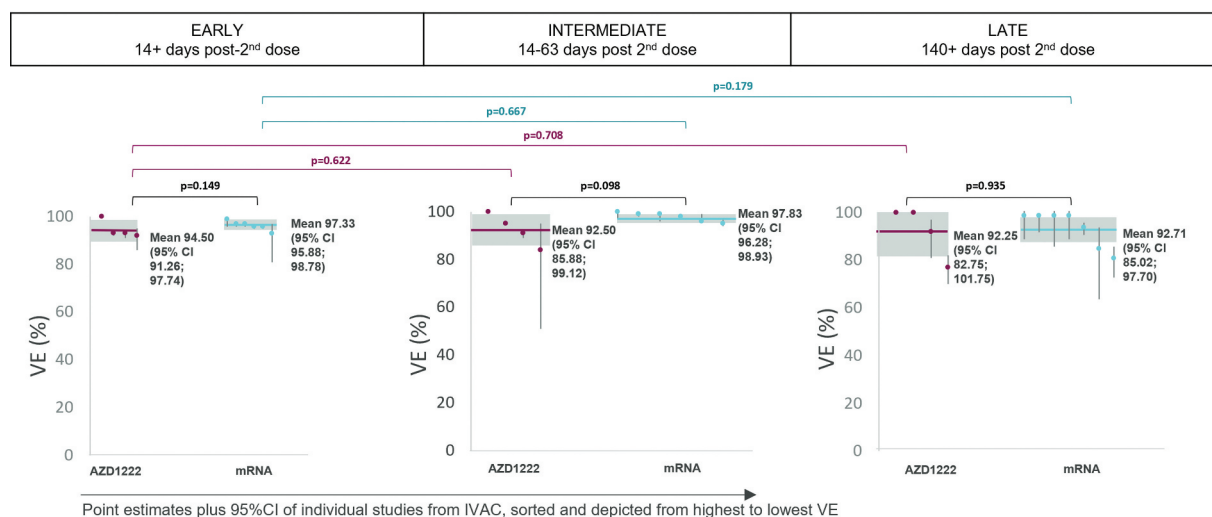
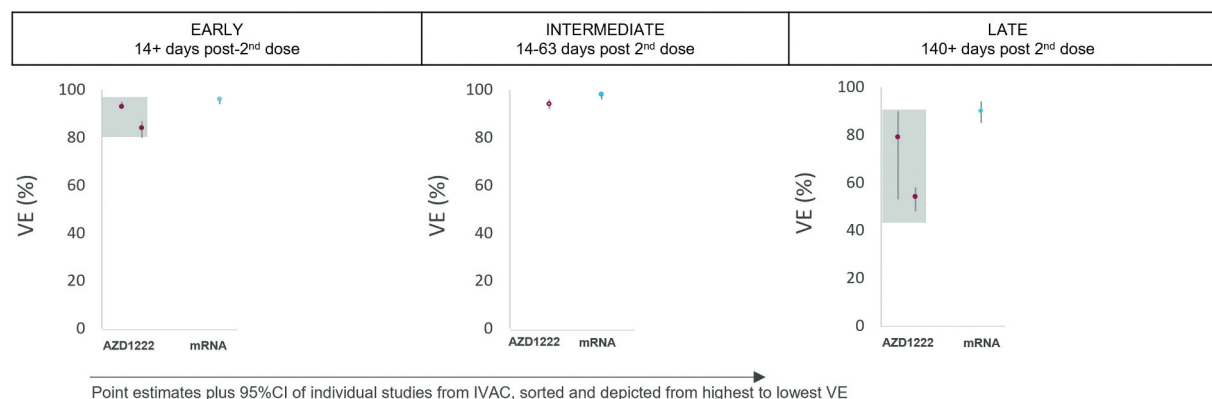
**Figure 3.** AZD1222, BNT162b2, and mRNA-1273 have high and comparable VE against deaths. (a) VE is shown from individual studies from IVAC, ordered from highest to lowest VE, and stratified by (b) variant of concern, (c) age over 60 years, (d) study design, or (e) history of SARS-CoV-2 infection. Abbreviations: VE, vaccine effectiveness; CI, confidence interval; n.a., not applicable.

these studies demonstrate that, regardless of vaccine type or schedule, full vaccination effectively protects against serious outcomes. These 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. Expert opinion: Southeast Asia experts' insights

RWE provides more contextual clarity for decision-making at local and regional levels, but some countries lack real-world VE data to assess, for example, the true impact of VOCs such as

Omicron; the use of mixed or heterologous vaccine schedules; a third vaccine dose; or CoronaVac, a key component of vaccine supplies [22, 30, 31] in many LMIC countries. Because of a dearth of VE studies from Southeast Asia, we analyzed global data to understand the potential impact of different vaccination strategies on VE in this region. The results showed that the three most studied vaccines, BNT162b2, mRNA-1273, and AZD1222, had comparable effectiveness profiles, particularly against severe outcomes and reinforces the value of real-world evidence, particularly in an evolving area of clinical practice. Nevertheless, data gaps still persist, given the lag between the emergence of new variants, updated vaccine schedules, and VE data to inform their impact. Our working

**a. Symptomatic infection****b. Hospitalisation****c. Death****Figure 4.** Waning of VE with time after second dose.

Abbreviations: VE, vaccine effectiveness; CI, confidence interval.



**Table 1.** VE in relevant real-world studies. Data were not directly compared, and this summary is non-exhaustive because of differences between studies. For example, some studies did not assess VE against infections, while others assessed province-level rather than nationwide data, and not all studies listed exact vaccine schedules or vaccine demographics. Follow-up durations may also vary. Abbreviations: VE, vaccine effectiveness; ICU, intensive care unit.

	Malaysia	Thailand – Chiang Mai*	Thailand – Bangkok and vicinity*	Chile
Vaccine(s) evaluated for VE (Approximate follow-up duration)	AZD1222 BNT162b2 CoronaVac (Up to 5.5 months) 87.8%	AZD1222 BNT162b2 CoronaVac (Undeclared) 28% with CoronaVac primary 93% with AZD1222 primary 92% with BNT162b2 primary 93% with CoronaVac/AZD1222	AZD1222 BNT162b2 CoronaVac (Up to 3 months) 98% with 2-dose CoronaVac plus BNT162b2 booster 86% with 2-dose CoronaVac plus AZD1222 booster 83% with 2-dose AZD1222 74% with CoronaVac/AZD1222 60% with 2-dose CoronaVac High but variable VE depending on vaccine schedule	CoronaVac primary with AZD1222, BNT162b2 or CoronaVac booster (Up to 9 months) No data
VE against infection				
VE against symptomatic disease	85.4%	No data		78.8% with CoronaVac, 96.5% with BNT162b2, 93.2% with AZD1222
VE against hospitalization	No data	<sup>†</sup> 97% for 2-dose schedules 99% for 3-dose schedules No data	No data	86.3% with CoronaVac, 96.1% with BNT162b2, 97.7% with AZD1222
VE against ICU admission	79.1% overall 95.6% with AZD1222 90.3% with BNT162b2 72.0% with CoronaVac		No data	92.2% with CoronaVac, 96.2% with BNT162b2, 98.9% with AZD1222
VE against death	86.7% overall 95.3% with AZD1222 92.7% with BNT162b2 82.4% with CoronaVac	<sup>†</sup> 97% for 2-dose schedules 99% for 3-dose schedules	No data	86.7% with CoronaVac, 96.8% with BNT162b2, 98.1% with AZD1222
Study limitations of relevance to our analysis	Hospitalization is not an evaluable VE outcome	<sup>†</sup> Data on hospitalizations and deaths were combined	Almost 30% of the study cohort were healthcare workers	None noted
Reference	Suah JL et al., 2021	Faculty of Public Health, Chiang Mai University and Chiang Mai Provincial Health Office	Sritipsukho P et al., 2022	Jara AJ et al., 2022

\* Vaccines were administered in various schedules, either as primary schedules of two doses of a single type of vaccine, or a primary schedule of two doses of a single type of vaccine plus one booster of a different vaccine, or heterologous primary schedules of one dose of two different vaccine types.

group of SEA infectious disease experts and contributors to national vaccination policies discussed the applicability and consistency of these findings against the limited data available for Southeast Asia, as well as safety considerations, and shared our insights and recommendations on strategies for future vaccination programs.

#### 4.1. Insights on safety of available vaccines

Overall safety of these vaccines is of paramount importance. While 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. Reports of thrombosis with thrombocytopenia syndrome (TTS) or venous thromboembolism (VTE) with thrombocytopenia (TCP) were observed after a first dose of AZD1222 (8.1 cases per million doses) and after a second dose (2.3 cases per million doses) [32, 33]. These rates appear to vary substantially according to geographical area [32, 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 [32], as well as being much lower than TTS-like events due to COVID-19 infections (VTE with TCP was 195.9 events/million patients) [32, 33]. 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 aged 70 years or older [35, 36] 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 hospitalization with TCP after primary AZD1222 vaccination (0.9 to 3.0 events/million) was far outweighed by its reduction of COVID-19 mortality and morbidity. AZD1222 was also thought to be associated with cerebral venous sinus thrombosis (CVST) [37], but the rate of CVST events in the 4 weeks following a primary dose was 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 very rare clinical event and causality is difficult to establish [38].

In one study from a vaccine AR reporting system in the US using primarily mRNA vaccines [39], 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) was slightly lower than baseline for mRNA-1273 and significantly lower than baseline for BNT162b2. mRNA-based vaccines are also associated with a rare but higher rate of vaccine-associated anaphylaxis in females than males

[40, 41], and with the rare occurrence of myocarditis and pericarditis, particularly in adolescent and young adult males [42]. In Europe, myocarditis has been reported at over 26 to 57 events/million within 1 week of mRNA vaccination while, in the US, reported events were estimated at a rate of 1 – 40.6 cases/million second doses of mRNA vaccines in males aged 12 – 29 years [43, 44].

CoronaVac, which is used widely across Asia, was evaluated in Brazilian health-care workers [45], 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 favorable 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 [46], 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 [47]. 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. Health-care 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.

#### 4.2. Insights on waning of VE or duration of protection

Our analysis consistently confirmed a high VE at preventing hospitalizations and deaths, at comparable levels across all vaccines, regardless of VOC (excluding Omicron). Numerous reports of waning antibody levels [48,49,50] 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 [51,52]. Importantly, despite declining antibody levels, we found high and sustained VE against hospitalizations and deaths for AZD1222 and mRNA-based vaccines up to 140 days, with limited waning observed when data enabled informed assessments (Figure 4).

#### 4.3. Insights on correlates of protection

We emphasize 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 neutralizing antibodies [48] but the precise levels required to achieve this are still being established [53]. Neutralizing antibodies provide initial protection against overall infection but do not provide

sterilizing immunity, limiting their impact on COVID-19 transmission [48]. Phase III clinical 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 [54,55,56,57]. But in the real world, high levels of antibodies were detected in some health-care workers with breakthrough infections, and evidence is insufficient to support using antibody levels to predict potential infections [58,59,60,61,62]. Moreover, cell-mediated immunity against COVID-19 can be induced by vaccines even when antibody-mediated mechanisms are lacking [63]. RWE indicates that COVID-19 vaccinations conferred a high level of protection against hospitalization and death, and for at least 20 weeks after a second dose [12, 25, 62,63,64] despite VE waning against infection within 6 months of vaccination [65]. 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 [25]. 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 [66, 67]. Consequently, T-cell responses may be a stronger indicator of protection against severe disease than neutralizing antibodies [53, 68,69,70] 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.

#### 4.4. Insights on the impact of the Omicron variant

Previous data suggest high and comparable VE against symptomatic infections by previous variants [71,72,73,74], but data for Omicron are still accumulating. RWE data from the UK [75] provided a robust comparison of VE against Omicron and Delta for the vaccines most used there [76]. 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 [76], consistent with what has been observed elsewhere [77]. Similarly, VE against hospitalizations 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 hospitalizations is restored by homologous or heterologous boosters, yet VE waning appears to occur more quickly over time compared to Delta [25, 76]. 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 suggest 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 [78]. 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 hospitalization and death, consistent with the equivalent protection observed above (>89%, Figures 2 and 3). 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 [79].

#### 4.5. Insights on vaccine strategy

Southeast Asia's national health-care 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 toward the future, manufacturers will need to update the first-generation vaccines to provide optimal protection against new, antigenically distinct variants [80]. 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.

#### 5. Strengths and limitations of our review

The real-world studies included in this review encompass a wide range of methodologies, populations, and outcome measures. Due to the limitations of the individual studies included in the IVAC database, we could not adequately stratify hospitalization 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. Hospitalization criteria differ among countries and may not always reflect disease severity. For example, in Malaysia, hospitalizations 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 hospitalized 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 commonly-occurring comorbidities like diabetes and hypertension [81] 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 optimize booster strategies. As our review only analyzed primary vaccinations, we are unable to clarify whether additional boosters would be successful against new VOCs, for how long they would be effective [82, 83]. Similarly, there is insufficient RWE on the use of heterologous vaccine schedules [84] in this region. Future studies will need to include the most widely used vaccine in LMICs – CoronaVac – and offer comprehensive meta-analyses. Finally, even though death appears to be a clearly defined endpoint in some studies, its reporting as COVID-19-related is not standardized 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. Conclusion

The COVID-19 pandemic trajectory has not been straightforward and neither have been our measures to overcome it. Breakthrough infections have threatened to overwhelm health-care systems and, although booster programs have been accelerated, public confidence in vaccines has been undermined by waning immunity against infections, misunderstandings around vaccine safety and performance, and the emergence of highly transmissible and immune-evasive variants. Moreover, vaccine hesitancy and implementation challenges are likely to have been exacerbated by confusing messages.

Against this backdrop, our review provides reassuring data to show that some of the most commonly used vaccines provide a consistently high protection of >90% against hospitalizations and deaths, and importantly, this protection appeared to be equivalent with two-dose schedules of mRNA vaccines and some vector vaccines like AZD1222 (91–93%). This finding was further supported by RWE data from Malaysia and Thailand, among other countries, reinforcing the value of RWE in helping to inform clinicians and public health systems about the benefits of completing the primary vaccine series and of booster vaccinations.

We also emphasize that although antibody levels are an accessible biomarker and correlate with protection against symptomatic infection, it is clear that these levels 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.

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. Together, these new insights into VE and safety provide an opportunity and confidence to embrace a paradigm shift in vaccine perception and allow decision-makers to take control of the pandemic, now and for the future.

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## Declaration of Interest

Following International Committee of Medical Journal Editors' (ICMJE) guidelines, A Ong-Lim reports honoraria for lectures from Moderna and is a member of the Technical Advisory Group, Department of Health in the Philippines. C Huu Nghia, KP Hwang, R Solante, and S Chariyalertsak report consulting fees from AstraZeneca. D Do-Van reports consulting fees and honoraria for advisory board attendance by AstraZeneca. NC Chiu 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. PI Lee 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. PS. Kulkarni is employed by Serum Institute of India Pvt Ltd., which manufactures a COVID-19 vaccine (Covishield) that is sub-licensed from AstraZeneca. Rommel Crisenio Lobo 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. S Kiertiburanakul reports consulting fees from AstraZeneca and honoraria for lectures from AstraZeneca, Pfizer and Zuellig Pharma. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.



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