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COVID-19 Vaccine Effectiveness During JN.1 and Later Omicron Subvariant Predominance: A Systematic Review

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INTRODUCTION

Evidence of COVID-19 vaccine efficacy from randomized controlled trials (RCTs) was available for the early COVID-19 period for ancestral vaccines, mainly in 2020-2021 (pre-Omicron) when population immunity was low. These trials showed high efficacy against symptomatic disease but were not powered to assess severe disease and death.¹ When it became unethical to withhold vaccines, RCTs were no longer feasible; thus, evidence of the vaccine performance thereafter came from observational studies after vaccine introduction starting in early 2021. This real-world evidence of vaccine effectiveness (VE) from millions of vaccinated individuals confirms the vaccines' ability to reduce COVID-19-associated severe disease and death.¹

Previous systematic reviews have shown VE is generally highest shortly after the last dose and remains substantial over time against severe disease from Omicron and its sublineages, but protection against mild/moderate disease and infection is lower than against pre-Omicron variants of concern and declines rapidly.² mRNA vaccines have demonstrated the strongest overall performance across age groups and variants. Booster doses increase neutralizing antibody titres and improve protection, particularly against variants with immune escape.³

After JN.1 or later Omicron subvariants predominated (January 2024 and later), most people had acquired some immunity either through prior infection or vaccination, and studies could no longer compare vaccinated individuals to immune-naïve individuals. The more recent studies from 2024-25 assess up-to-date or relative VE (rVE) which compares individuals recently vaccinated with a currently recommended vaccine to those who have not received them, but who often received older vaccines in the past or who have protection from prior infection. This has the effect of lowering the VE estimates because the studies assess the added protection above existing protection rather than compared to no protection as was done in earlier studies assessing absolute VE (aVE). Up-to-date and relative VE is particularly useful, however, for assessing the added value of annual (or semi-annual) boosters.

Monovalent JN.1 or KP.2 COVID-19 vaccines were introduced into some vaccination programmes in the second half of 2024. The benefit of updated vaccines depends on antigenic match to circulating variants. We sought to summarize the VE of observational studies with study periods in which JN.1 (including BA.2.86) or later Omicron subvariants were predominant ($\geq 50\%$), between January 2024-December 2025.

METHODS

We conducted a living systematic review of COVID-19 vaccine effectiveness studies from March 2021 through December 2025. Databases searched included PubMed, Embase, the WHO COVID-19 database (through July 2023), Web of Science, medRxiv, bioRxiv, SSRN, Europe PMC, Research Square, and Knowledge Hub.²⁻⁴ Searches were conducted on a weekly basis, with team meetings including experienced epidemiologists held regularly to review newly identified studies. Authors were contacted as needed to resolve questions about inclusion or exclusion criteria.



We abstracted observational studies that assessed COVID-19 VE against SARS-CoV-2 laboratory-confirmed death, severe disease (primarily defined as hospitalization with COVID-like illness, severe acute respiratory illness (SARI), or a primary diagnosis of COVID-19), symptomatic disease (including medically attended illness such as emergency department or urgent care visits for COVID-like illness), and, any SARS-CoV-2 infection regardless of symptoms. A study or citation could provide multiple VE assessments, for example, for multiple time periods post-vaccination, age groups, vaccine regimens, outcomes, or subvariant periods.

Populations evaluated in this analysis included older adults (defined as aged ≥ 60 years), healthy adults, children aged 6 months to 17 years, pregnant persons and their infants, and adults with immunocompromising conditions, comorbidities or underlying conditions. We also looked for studies evaluating VE against transmission in healthcare workers, and conducted a targeted review for VE against absenteeism.

Studies included in this review provided VE estimates from periods in which JN.1 (including its precursor BA.2.86) or later Omicron subvariants were predominant, defined as comprising $\geq 50\%$ of circulating strains over the study period; this corresponds approximately to January 2024 or later. However, for pregnant persons and their infants and for healthcare workers, due to the scarcity of studies conducted during that period, evidence was drawn from the entire Omicron period (December 2021 onward).

Except where noted otherwise, included studies compared recently vaccinated individuals (i.e., “up-to-date”) to those not recently vaccinated. That is, rather than comparing to an unvaccinated group, the comparison group included individuals who may have received any number of previous COVID-19 vaccines or who may be unvaccinated. Some studies assessed “relative” VE in which the comparison group consists exclusively of previously vaccinated persons. During the period studied, both the vaccinated group and the comparison group may have had previous infections which likely provided some protection. Therefore, VE estimated in these analyses represent the incremental protection provided by the most recent dose beyond existing protection.

Generally, VE estimates for time intervals <14 days after the final dose in the primary vaccination course and <7 days after booster doses were excluded; exceptions included wide intervals that included these early time periods (e.g., 0-60 days). VE estimates across the full study follow-up period were presented (“overall” VE). To better compare studies, we also presented estimates within 3 months of vaccination which ensures similar follow-up time between studies and shows VE when it is closer to its peak (“early” VE). Duration of VE was explored by showing estimates across multiple time intervals post-vaccination within a study; these often also show peak VE estimates assessed approximately 1-month post-vaccination.

Because studies varied substantially in comparison group definitions, duration of follow-up, and circulating subvariants, a meta-analysis was not conducted. Instead, we have presented results descriptively, with ranges, medians, and interquartile ranges of VE estimates where appropriate, stratified by outcome severity, vaccine type, and time since vaccination.



RESULTS

Of over 2,500 studies reviewed across the full search period (March 2021–December 2025), approximately 30% met inclusion criteria. For this analysis during the JN.1 and later subvariant predominant period, 32 eligible studies were included across six population groups: 27 studies among older adults (≥ 60 years), six among immunocompromised adults, three among adults with comorbidities, five among healthy adults aged 18–64 years, three among children aged 6 months to 17 years, and one among healthcare workers, with some studies evaluating more than one population. For pregnant persons and their infants, 17 studies from the earlier Omicron period were included (eight in pregnant persons, nine in infants through six months of age). Most studies were conducted in high-income countries, predominantly in Europe and the United States, and all but one evaluated mRNA vaccines. XBB.1.5-adapted monovalent vaccines were the most frequently studied (2023–2024 formulation), with JN.1- and KP.2-adapted vaccines (2024–2025 formulation) in a smaller but growing body of evidence. As of 31 December 2025, no studies had been published on LP.8.1 vaccine effectiveness.

OLDER ADULTS

Nearly all (26/27) studies were from high-income countries—mainly European countries (12 studies)^{5–16} and the United States (10 studies),^{17–26} with 2 from Australia^{27,28} and 2 from Canada^{29,30}; 1 was from a middle-income country (China).³¹ The study from China (Tang #416) evaluated VE of a protein subunit vaccine (WSK-V102C) against symptomatic disease, while the remaining studies evaluated VE of mRNA vaccines, including XBB.1.5 adapted monovalent vaccines (16 studies),^{5–8,10,11,13,15–17,19,23,25,27,28,30} JN.1-adapted monovalent vaccines (4 studies),^{9,10,12,28} KP.2 adapted monovalent vaccines (7 studies),^{18,20–22,24,26,29} or any JN.1/KP.2 vaccine (1 study).¹⁴

There was a general trend of higher effectiveness against more severe outcomes, with the greatest effectiveness against death and progressively lower VE against severe disease and symptomatic disease, respectively (Figures 1–2). VE tended to be lower for XBB.1.5-adapted vaccines compared to JN.1 or KP.2 vaccines (with evidence limited for JN.1 and KP.2 vaccines); however, the duration since vaccination in assessments of XBB.1.5 vaccines tended to be longer, which can reduce VE. Variability between study designs and settings further limit interpretation of VE comparisons across studies.

Death

There were 16 estimates of VE against death due to COVID-19 from 8 studies with follow-up time ranging from approximately 4 to 10.5 months since vaccination (Figure 1).^{5,6,9,11–13,19,20} VE ranged from -21% to 96% (median 58%, IQR 25–66). Among the 4 studies (7 estimates) that assessed VE within ~22 weeks (5 months) of vaccination, VE was higher, ranging from 48% to 96%.^{5,6,9,12} The lowest estimate of -21% was in a study that assessed cases up to 10 months since vaccination in adults age ≥ 80 years; the same study estimated VE to be 18% for individuals 65–79 years of age from the same country and 19–38% in adults age ≥ 80 years from different countries.¹¹

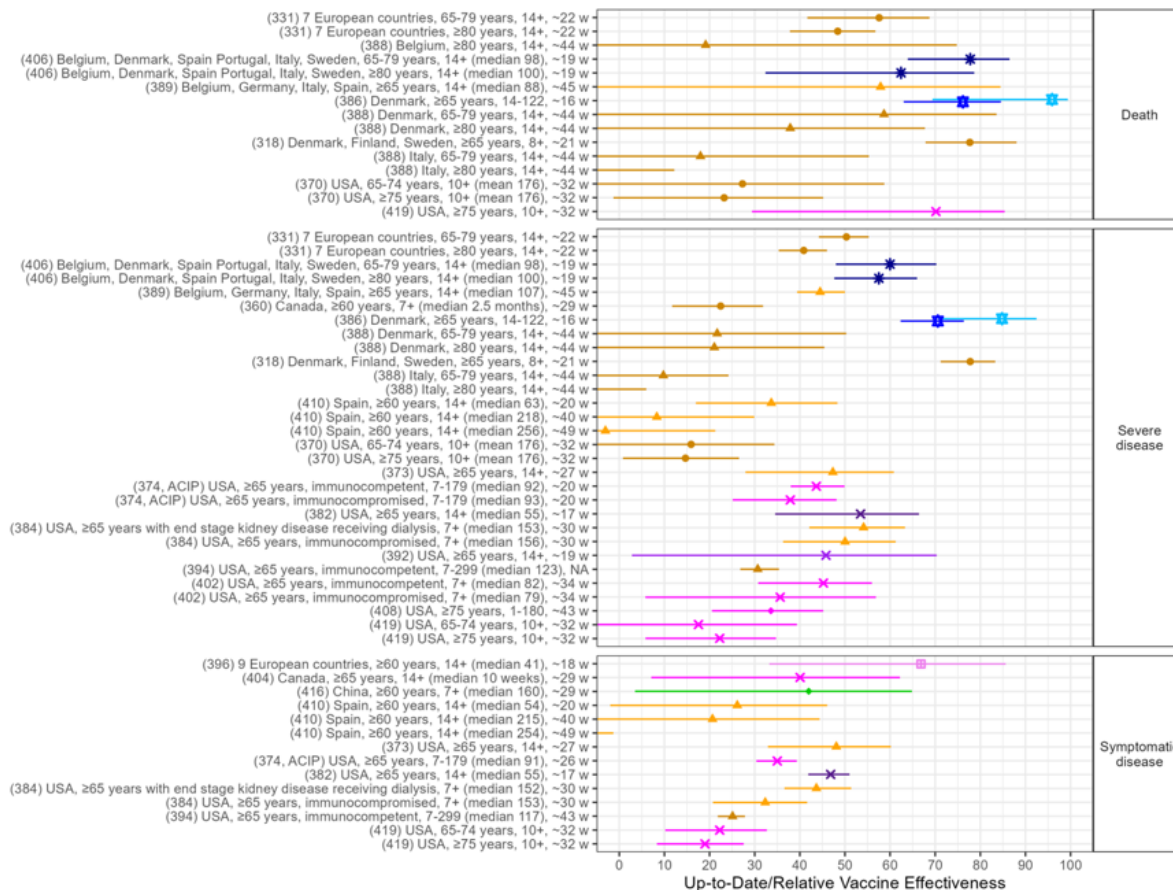
Estimates of early VE within 3 months of vaccination varied less than those for overall VE, and differences by vaccine type appeared less prominent, further suggesting that such variation may largely reflect differences in duration of follow-up since vaccination. Early VE ranged from 18 to 86% (n=6 studies, 9



estimates; median 60%, IQR 51-82%; Figure 2).^{5,6,9,12,27,28} Early VE of XBB vaccines ranged from 18 to 83% (n=4 studies, 5 estimates),^{5,6,27,28} while VE of JN.1 vaccines ranged from 48 to 86% (n=3 studies, 4 estimates)^{9,12,28}; no studies evaluated KP.2 vaccines (Figure 2). Liu et al. (#415) found XBB vaccines had lower VE than JN.1 vaccines (18% vs. 48%, respectively), but XBB vaccine recipients were likely vaccinated earlier and thus had longer follow-up time within the 3-month interval compared to JN.1 vaccine recipients, suggesting that longer time since vaccination may still be impacting VE even in estimates restricted to ≤ 3 months follow-up.²⁸

Figure 1. Overall Relative and Up-to-Date COVID-19 Vaccine Effectiveness during Omicron JN.1 and Later Subvariant Predominance, Older Adults

Study ID, Country, Population, Subvariant, days post final dose, max possible duration of follow-up



Range of VE

XBB vaccine: -21 to 78%
JN.1 vaccine: 62-96%
KP.2 vaccine: 70%

Evaluated dose

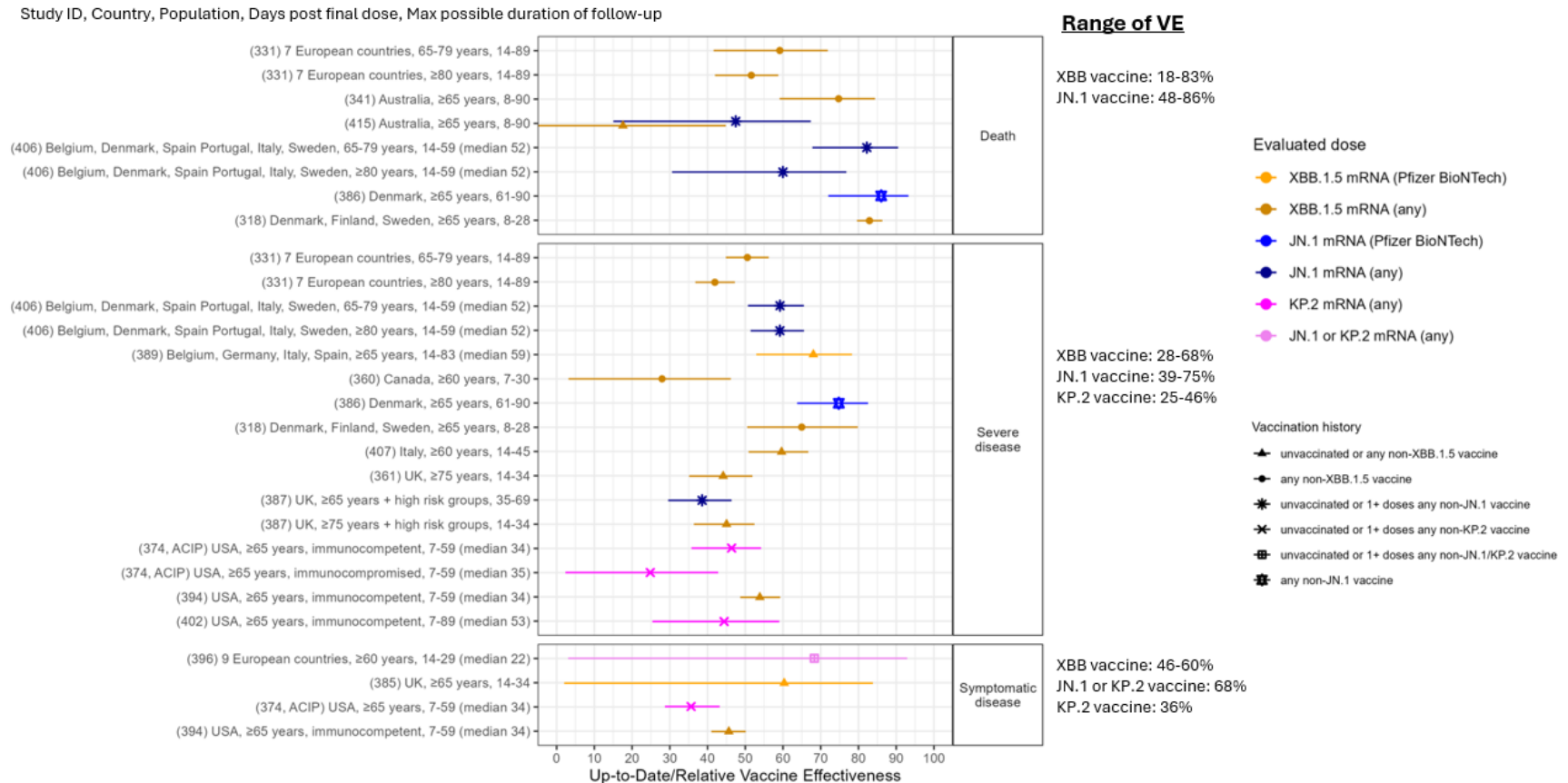
- XBB.1.5 mRNA (Pfizer BioNTech)
- XBB.1.5 mRNA (any)
- JN.1 mRNA (Pfizer BioNTech)
- JN.1 mRNA (Moderna)
- JN.1 mRNA (any)
- KP.2 mRNA (Pfizer BioNTech)
- KP.2 mRNA (Moderna)
- KP.2 mRNA (any)
- JN.1 or KP.2 mRNA (any)
- WSK-V102C protein (WestVac Bipharm)

Vaccination history

- unvaccinated or any non-XBB.1.5 vaccine
- any non-XBB.1.5 vaccine
- unvaccinated or 1+ doses any non-JN.1 vaccine
- unvaccinated or 1+ doses any non-KP.2 vaccine
- unvaccinated or 1+ doses any non-JN.1/KP.2 vaccine
- any non-JN.1 vaccine
- unvaccinated or any prior COVID vaccine
- any non-KP.2 vaccine

XBB vaccine: -39 to 48%
JN.1 or KP.2 vaccine: 67%
KP.2 vaccine: 19-47%
WSKV102C: 42%

Figure 2. Early (<3m) Relative and Up-to-Date COVID-19 Vaccine Effectiveness during Omicron JN.1 and Later Subvariant Predominance, Older Adults





Severe Disease

Eighteen studies (31 VE estimates) evaluated overall VE against severe disease with follow-up times varying widely, between approximately 4 to 11 months since vaccination (Figure 1).^{5,6,9,11–13,16–21,23–26,30,32} VE ranged from -6 to 85% (median 44%, IQR 22–52) overall and from 34% to 85% (median 50%, IQR 44–60) among estimates assessed within 27 weeks (6 months) of vaccination. As with VE against death, the range in estimates likely reflect variability between study designs, settings, and follow-up times since vaccination.

Early VE against severe disease ranged from 25 to 75% (n=12 studies, 16 estimates; median 53%, IQR 42–59%; Figure 2).^{5–7,9,10,12,13,16,26,30,32,33} VE ranged from 28 to 68% for XBB vaccines (n=8 studies, 9 estimates),^{5–7,10,13,16,30,33} 39 to 75% for JN.1 vaccines (n=3 studies, 4 estimates),^{9,10,12} and 44 to 46% for KP.2 vaccines (n=2 studies, 2 estimates among immunocompetent older adults),^{26,32} suggesting VE from JN.1 vaccines may be higher than for KP.2 vaccines, but study settings might have impacted results, as JN.1 vaccines were evaluated in Europe and KP.2 vaccines were evaluated in the USA.

Symptomatic Disease

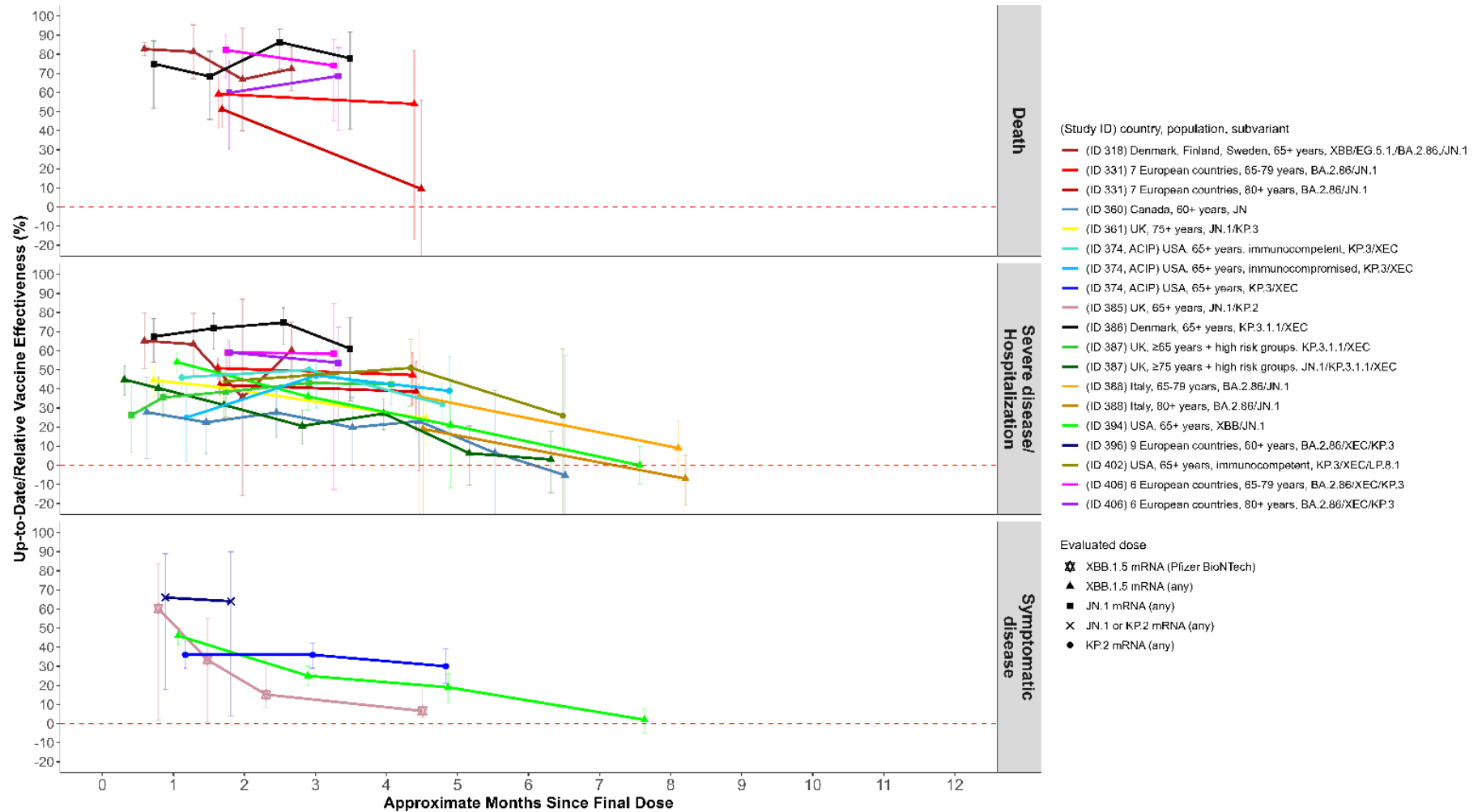
Fourteen estimates from 10 studies evaluated overall VE against symptomatic disease among older adults, also with a wide range in follow-up, between 17–49 weeks (~4–11 months) from vaccination (Figure 1).^{14,16,17,20,23,24,26,29,31,33} One negative VE estimate (-39%) was observed in a study that estimated VE of XBB.1.5 mRNA vaccines during KP.3 predominance among individuals vaccinated many months prior (median of 8.3 months); during BA.2.86 predominance, the same study estimated VE of 26% and 21% among older adults vaccinated a median of 1.8 and 7.1 months prior, respectively.¹⁶ Excluding this outlier, overall VE ranged from 19–67% (median 38%, IQR 25–45); VE within 20 weeks (~4.5 months) ranged from 26–67% (3 studies, 3 estimates).^{14,16,24} Only 4 studies (4 estimates) assessed early VE, which had a similar range (36–68%) but higher median (53%, IQR 44–62%; Figure 2).^{8,14,26,33}

No studies estimated VE for JN.1 vaccines alone and only one study assessed VE for JN.1 and KP.2 vaccination combined (overall VE=67%).¹⁴ For XBB vaccines (n=4 studies, 7 estimates), overall VE ranged from -39% to 48% and from 26–48% among assessments with follow-up time ≤6 months^{16,17,23,33}; for KP.2 vaccines (n=4 studies, 5 estimates) overall VE ranged 19–47% and from 35–47% among assessments with study follow-up time <7 months (median time post vaccination 2–3 months).^{20,24,26,29} One study assessed the protein subunit WSKV102C vaccine, finding 42% VE with a follow-up period of ~7 months (median time post vaccination ~5 months). Early VE was similar: VE estimates for the two XBB evaluations were 46% and 60%, KP.2 VE was 36%, and the study of JN.1 or KP.2 vaccines reported VE of 68%.^{8,33}

Duration of Protection in older adults

Figure 3 summarizes available evidence on the duration of protection among older adults. Because the comparison group includes individuals who had not been recently vaccinated but who had been previously vaccinated and/or had a prior infection(s), waning of VE implies the risk of COVID-19 becomes similar over time between the groups. Furthermore, as both the recently vaccinated group and the comparison group can have long-lasting protection against severe disease from prior vaccinations and infections, a VE of 0% does not mean no protection but rather similar protection between the groups.

Figure 3. Duration of Relative and Up-to-Date COVID-19 Vaccine Effectiveness during Omicron JN.1 and Later Subvariant Predominance, Older Adults



Footnote: Each line represents an assessment of VE over time for a particular vaccine type, population, and outcome within a study.



Four studies (6 assessments over time) provided evidence for duration of protection against death but only up to between 3 to 4.5 months post vaccination (Figure 3).^{5,6,9,12} VE against death remained generally stable for 5 of the 6 estimates but decreased from 51% to 9% between months 2 and 5 in one study of adults ≥ 80 years of age who received XBB.1.5 mRNA vaccination during BA.2.86/JN.1 subvariant period (Nunes #331); a younger subgroup (age 65-79) in the study experienced minimal decline (VE was 59% and 54% at months 2 and 5, respectively) though 95% CIs at month 5 were wide for both groups.⁶

More studies ($n=11$, 16 assessments over time) evaluated waning of relative VE against severe disease and for longer duration, up to at least 6 months for 6 assessments.^{5-7,9-12,26,30,32,33} VE appeared generally stable through 5 months since vaccination and then declined in all estimates with longer follow-up, generally towards VE of 0% (i.e., protection waned to a similar level as those who had not been recently vaccinated).

Only 4 studies (4 assessments over time) provided evidence on the duration of protection against symptomatic disease among older adults and only 3 assessments had data beyond 2 months post-vaccination (to 5-8 months).^{8,14,26,33} These studies showed different waning patterns (one was stable while the other two declined), but all showed modest or low additional protection beyond 2 months after the recent vaccination ($\leq 40\%$ VE). However, the study with follow-up up to only 2 months had higher VE (65%) for the first 2 months compared to the other studies, indicating more evidence is needed to assess waning of relative VE against symptomatic disease.¹⁴

Three studies, Nunes et al. (#331), Humphreys et al. (#388), and Humphreys et al. (#406), assessed VE over time among older adults stratified by age group (65-79 vs. ≥ 80 years) against both death and severe disease.^{6,11,12} While Nunes et al. reported steeper declines against death among adults ≥ 80 years than 65-79-year-olds (discussed above), the study saw minimal differences in duration of VE against severe disease between the two age groups.⁶ Duration of VE was also similar between adults ≥ 80 years and 65-79 years in the two studies by Humphreys et al., with VE for the older age group tending to be somewhat lower at most time points.^{11,12} In addition, two studies by Ioannou et al. (#370 and #419) estimated similar VE against death (XBB vaccines), severe disease (XBB and KP.2 vaccines), and symptomatic disease (KP.2 vaccines) over the entire study period between adults 65-74 years and ≥ 75 years (Figure 2).^{19,20} Variation between the waning patterns of VE may be due to differences in post-vaccination intervals and follow-up time, vaccines evaluated, study design and setting, and outcome definitions for symptomatic disease. More follow-up time is needed to fully assess duration of protection against JN.1 outcomes, as studies of previous variants showed significant waning after 6 months.

PERSONS WITH IMMUNOCOMPROMISING CONDITIONS

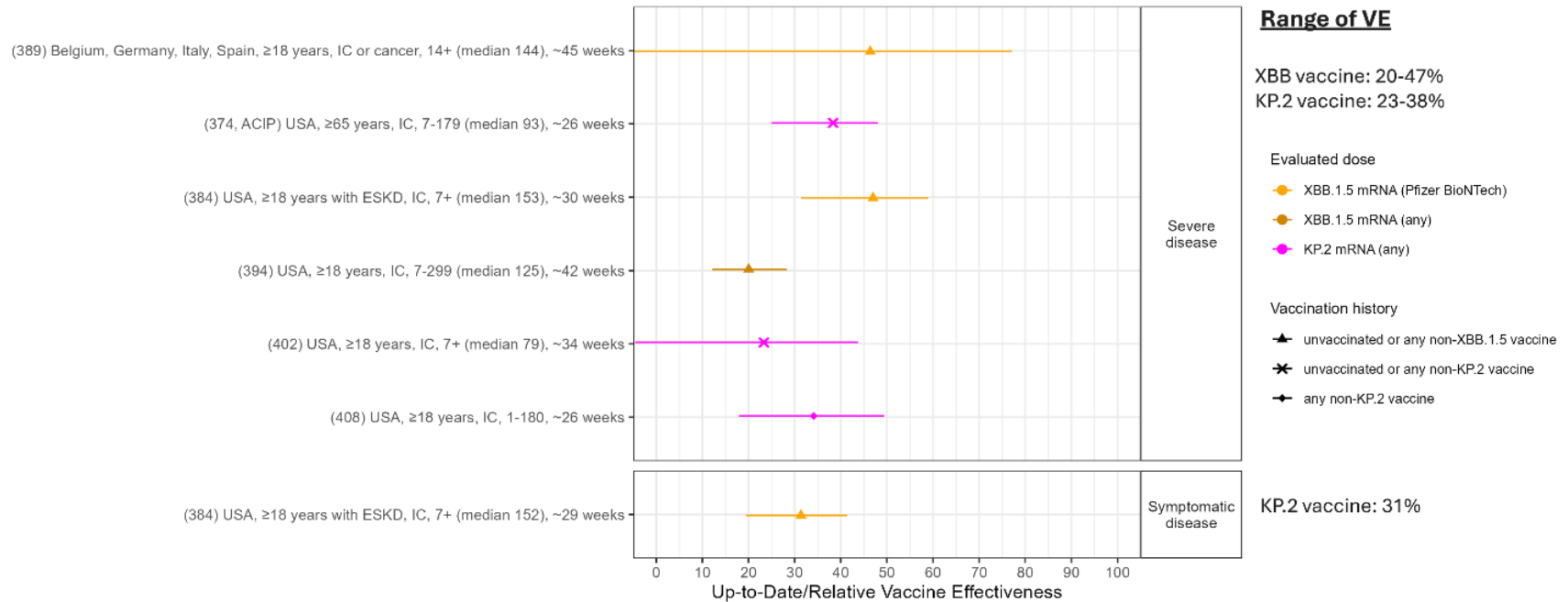
Of the 6 studies assessing VE in immunocompromised persons, 3 evaluated VE of XBB mRNA vaccines while the remaining 3 evaluated VE of KP.2 mRNA vaccines.^{13,21,23,26,32,33} In general, VE provided modest protection against severe disease—even over long study periods. Evidence was scarce for VE against symptomatic disease but indicated some protection. There was little evidence available assessing early VE among immunocompromised persons.



Overall VE in immunocompromised persons

Six VE estimates from 6 studies assessed VE over the full study duration (“overall”) against severe disease, with maximum follow-up time ranging from approximately 6 to 10 months (median was within 6 months for all).^{13,21,23,26,32,33} VE ranged from 20% to 47% (median 36%, IQR 26-45%; Figure 4). Protection from KP.2 vaccines (VE 23-38%; n=3 studies, 3 estimates)^{21,26,32} was comparable to that from XBB vaccines (VE 20-47%; n=3 studies, 3 estimates)^{13,23,33}. Only 1 study (1 estimate, XBB vaccines) assessed overall VE against symptomatic disease, which was a study of adults with end stage kidney disease (ESKD) receiving dialysis; VE was 31% among immunocompromised adults ≥ 18 years.²³

Figure 4. Overall Relative and Up-to-Date COVID-19 Vaccine Effectiveness during Omicron JN.1 and Later Subvariant Predominance, Immunocompromised Individuals ESKD = end stage kidney disease and receiving dialysis



Early VE (≤ 3 months) in immunocompromised persons

Early VE (within 7-59 days of vaccination) against severe disease ranged between 25% among immunocompromised older adults (KP.2 vaccine), 39% among immunocompromised adults of all ages (XBB vaccine), and 63% among immunocompromised adults with ESKD receiving dialysis (XBB vaccine) (3 studies, 3 estimates).^{23,26,33} However, the low KP.2 VE of 25% (#374) was higher when estimated ~3 and 5 months post-vaccination in the same study (47% and 39%, respectively), suggesting presence of confounding or other unknown factors as VE is expected to peak in the first couple of months (Figure 5).²⁶

Early VE against symptomatic disease was assessed in only 1 study (1 estimate: VE=50%), which evaluated XBB vaccination among immunocompromised adults with ESKD receiving dialysis.²³

VE of immunocompromised adults compared to immunocompetent adults

VE of immunocompromised adults was compared to that among immunocompetent adults in the same study who were the same age and received the same vaccine (13 comparisons in 5 studies; Table 1).^{21,23,26,32,33} No substantial differences in VE were observed, and VE was not always higher in the immunocompetent group (VE was greater in the immunocompetent group for 10 of 13 estimates). Since immunocompromised persons have a higher risk of disease, more disease could be prevented from vaccination of these groups, even with lower relative VE.

Table 1: Within-study comparisons of Up-to-Date VE among immunocompetent vs. immunocompromised persons (overall and/or early time periods, depending on availability)

Study	Population	Outcome	Days post vaccination (median)	VE Immuno-compromised	VE Immuno-competent
384 Payne ²³ (XBB vaccines)	18+ years with ESKD	Symptomatic disease (medically attended COVID-19)	7+ (150-152)	31 (19-41)	43 (36-50)
			7-59 (53)	50 (35-62)	47 (37-56)
	65+ years with ESKD		7+ (152-153)	32 (21-42)	44 (37-51)
	18+ years with ESKD	Severe disease	7+ (151-153)	47 (31-59)	50 (40-59)
			7-59 (53)	63 (40-77)	52 (36-64)
	65+ years with ESKD		7+ (153-156)	50 (36-61)	54 (42-63)
394 Link-Gelles ³³ (XBB vaccines)	18+ years	Severe disease	7-299	20 (12-28)	29 (25-33)
			7-59	39 (26-49)	51 (46-56)
374 Link-Gelles ²⁶ (KP.2 vaccines)	65+ years	Severe disease	7-179 (92-93)	38 (25-48)	44 (38-50)
			7-59 (34-35)	25 (2-43)	46 (26-60)
408 Cai ²¹ (KP.2 vaccines)	18+ years	Severe disease	1-180	34.4 (18.0-49.2)	25.5 (15.5-35.2)
402 Ma ³² (KP.2 vaccines)	18+ years	Severe disease	7+ (79-80)	23 (-5 to 44)	40 (27-51)
	65+ years		7+ (79-82)	36 (6-57)	45 (31-56)

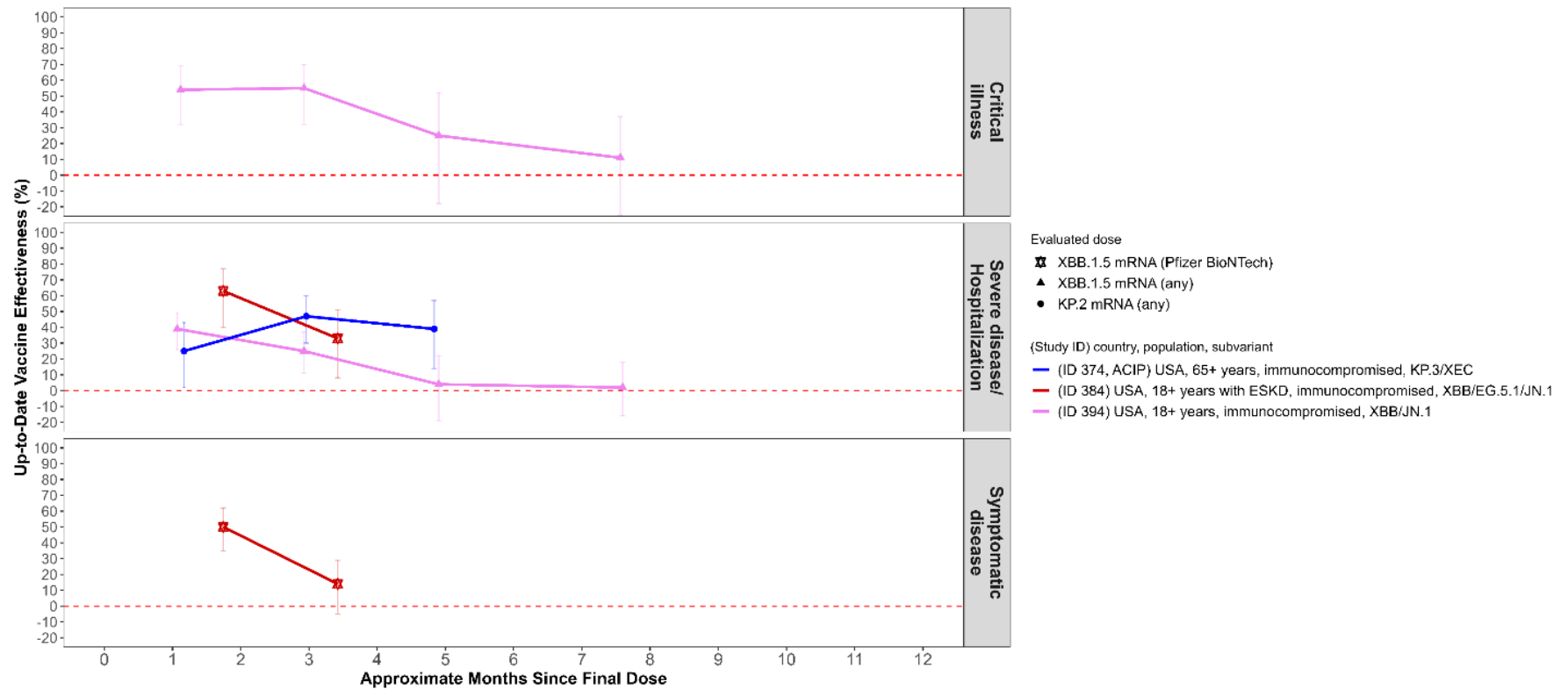
ESKD = end stage kidney disease and receiving dialysis. Shaded cells describe early VE (here defined as within 2 months of vaccination). Numbers in parentheses represent 95% confidence intervals.



Duration of Protection in immunocompromised persons

Only 3 studies (5 assessments of waning) estimated duration of vaccine protection in immunocompromised persons out to 3.5, 5, and 8 months post-vaccination respectively, but findings differed (Figure 5).^{23,26,33} One study (Payne #384) showed declines in VE of XBB vaccines against both severe disease and symptomatic disease between 1.5 and 3.5 months, from 63% and 50% to 33% and 14%, respectively. In the second study (Link-Gelles #394), protection from XBB vaccination against severe disease also declined, from 39% to negligible (2%) between 1 and 8 months post-vaccination; VE against critical disease was higher than severe disease but showed a similar pattern of waning.^{23,33} The third study (Link-Gelles #374) observed an increase in VE against severe disease from 25% at 1 month to 47% at 3 months, and then a small decline to 39% at 5 months post-vaccination.²⁶

Figure 5. Duration of Up-to-Date COVID-19 Vaccine Effectiveness during Omicron JN.1 and Later Subvariant Predominance, Immunocompromised Individuals





PERSONS WITH COMORBIDITIES

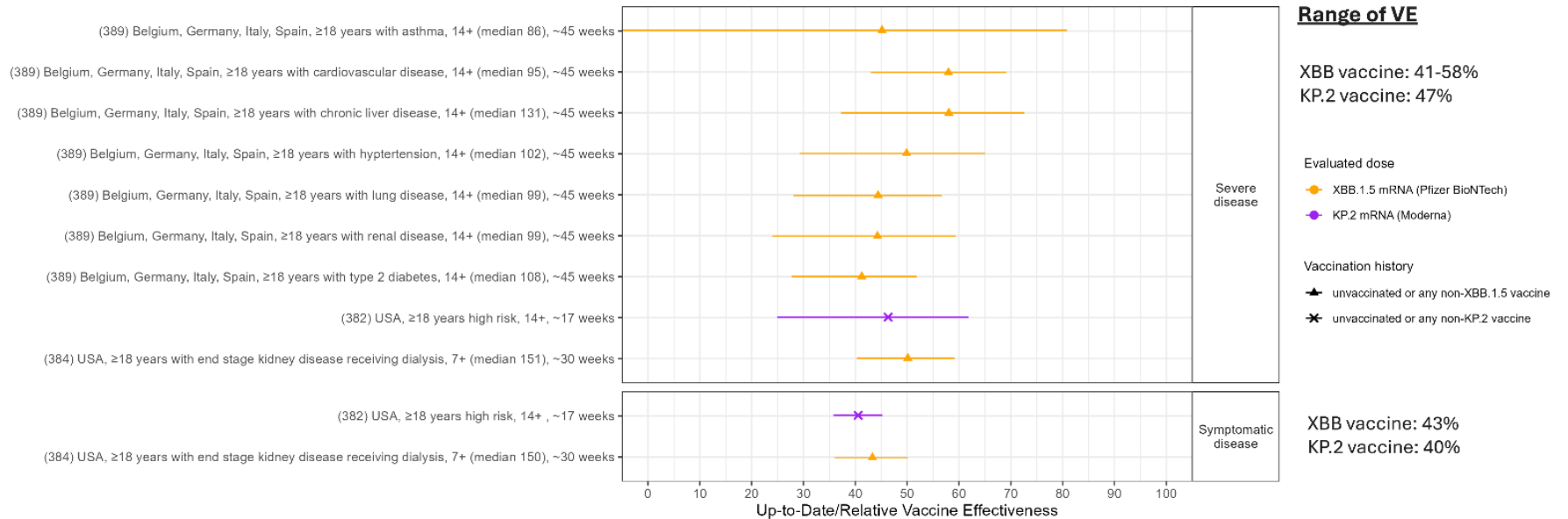
Three studies assessed VE in adults (18+ y) with comorbidities, including adults with end-stage kidney disease (ESKD, Payne #384), adults with a medical condition making them “high risk” for severe outcomes of COVID-19 (Wilson #382), and adults with various specific comorbidities such as lung disease, cardiovascular disease, and type 2 diabetes (Volkman. #389).^{13,23,24} Two studies evaluated XBB vaccines^{13,23} while the third assessed VE of KP.2 vaccines.²⁴ The limited available evidence indicated moderate protection against severe disease and modest protection against symptomatic disease among those with comorbidities.

Overall VE in persons with comorbidities

Against severe disease, overall VE ranged from 41 to 58% (median 47%, IQR 45-50; n=3 studies, 9 VE estimates; Figure 6).^{13,23,24} Maximum follow up time ranged from about 4 to 11 months, with median follow up times within 6 months. Evidence by vaccine type was scarce and showed no differences between XBB (n=2 studies, 8 VE estimates)^{13,23} and KP.2 (n=1 study, 1 VE estimate)²⁴ vaccines. One study (Volkman #389) demonstrated comparable VE against severe disease for different types of comorbidities (range 41 to 58%, n=7 VE estimates for 7 types of comorbidities).¹³

Overall VE against symptomatic disease was assessed by 2 studies (Wilson #382 and Payne #384) with maximum follow up times of about 4 months and 7.5 months, respectively.^{23,24} VE was similar in both studies: 40% VE for KP.2 vaccines among high-risk adults (Wilson #382), and 43% VE for XBB vaccines among adults with ESKD (Payne #384).^{23,24}

Figure 6. Overall Relative and Up-to-Date COVID-19 Vaccine Effectiveness during Omicron JN.1 and Later Subvariant Predominance, Individuals with Comorbidities





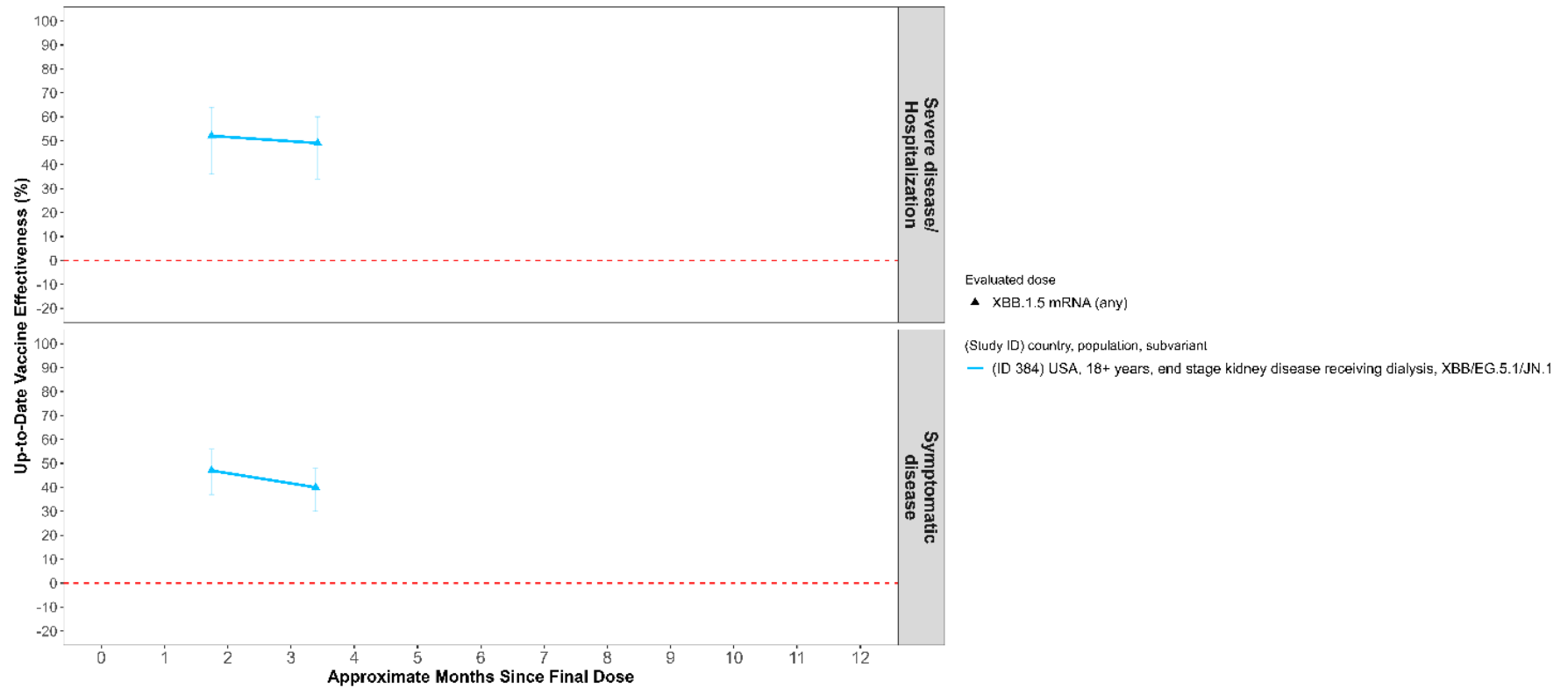
Early VE (≤ 3 months) in persons with comorbidities

Payne et al (#384) was the only study to evaluate early protection among persons with comorbidities. Among adults with ESKD receiving dialysis, VE of XBB vaccines within 2 months of vaccination was 52% against severe disease and 47% against symptomatic disease.²³

Duration of Protection in persons with comorbidities

Payne (#384; Figure 7) was also the only study to evaluate duration of protection, finding little decline in VE of XBB vaccines from 1 to 4.5 months among persons with ESKD receiving dialysis; VE declined from 52 to 49% and from 47 to 40% against severe and symptomatic disease, respectively.²³

Figure 7. Duration of Up-to-Date COVID-19 Vaccine Effectiveness during Omicron JN.1 and Later Subvariant Predominance, Individuals with Comorbidities





PREGNANT PERSONS AND INFANTS (≤6 MONTHS OF AGE)

Due to the scarcity of studies conducted during JN.1 or later subvariant predominance among pregnant persons and infants born to mothers vaccinated during pregnancy, evidence from the entire Omicron period was considered for these populations (study periods occurring predominantly in December 2021 or later). Seventeen studies met inclusion criteria, including 8 among pregnant persons^{34–41} and 9 among infants through 6 months of age (assessing protection via maternal vaccination).^{34,42–49} Ten studies evaluated absolute VE of primary series vaccination in mothers or their infants (Figures 8 and 10)^{35–37,42–47,50} and 14 assessed absolute or relative or up-to-date VE of a booster dose (Figures 9 and 11).^{34–41,43,45,47–50}

All primary and most booster VE studies evaluated ancestral mRNA vaccines (n=10 primary, n=12 booster),^{34–38,40,43,45,47–50} while 1 evaluated absolute VE of Omicron BA.4/5 bivalent booster doses⁴¹ and another assessed up-to-date VE of Omicron XBB.1.5 monovalent boosters.⁵¹ Most evidence was from North America and Europe while 1 study was from Singapore (Goh #431), 1 from Brazil (Florentino #B163), and 1 study used data from 18 countries across the world (Villar #362).^{36,38,47}

Pregnant persons

Absolute VE (Reference group: Unvaccinated)

Absolute VE in pregnant persons was highest against severe disease, decreasing with severity of outcome, and higher for booster vaccination than primary series vaccination (Figure 8). All included absolute VE studies among pregnant persons (n=4 studies) were conducted during earlier periods of Omicron.^{34–37}

Among pregnant persons, 4 VE estimates from 4 included studies showed strong protection of an ancestral mRNA booster dose against severe disease (median VE: 79%, IQR: 73–84; Figure 8).^{34–37} For primary series vaccination, absolute VE against severe disease from the same 4 studies was moderate, ranging from 21–77% (n=4 estimates, median 54%, IQR 44–61). The lower VE for primary series may be due in part to the longer follow-up time post vaccination for primary series estimates (~55–75 weeks) compared to booster dose estimates (~18–66 weeks), with some pregnant persons vaccinated prior to pregnancy.

Evidence was more limited for symptomatic disease but showed some protection. One study estimated absolute VE of bivalent BA.4/5 booster vaccination to be 53%.⁴¹ Absolute VE of an ancestral mRNA booster dose was moderate (54–65% VE, n=2 estimates from 2 studies), while VE of primary series vaccination appeared to be lower (VE 16–41%, n=2 estimates, same 2 studies), again likely due to the longer follow-up time, allowing for more waning for evaluations of primary series VE.^{35,36}

Two studies evaluated absolute VE of ancestral mRNA vaccines against infection and found similar, albeit slightly lower VE compared to symptomatic disease.^{36,37}

Relative and up-to-date VE

Relative and up-to-date VE of a booster dose among pregnant persons was assessed by 5 studies, including the only study meeting criteria from the JN.1 or later subvariant predominant period (Ciesla #418).^{34,37,38,40,51} Despite some variation, the limited available evidence indicated moderate incremental benefit of a booster dose across outcomes and vaccine types.

Figure 8. Overall Absolute COVID-19 Vaccine Effectiveness during Omicron Predominance, Pregnant Individuals

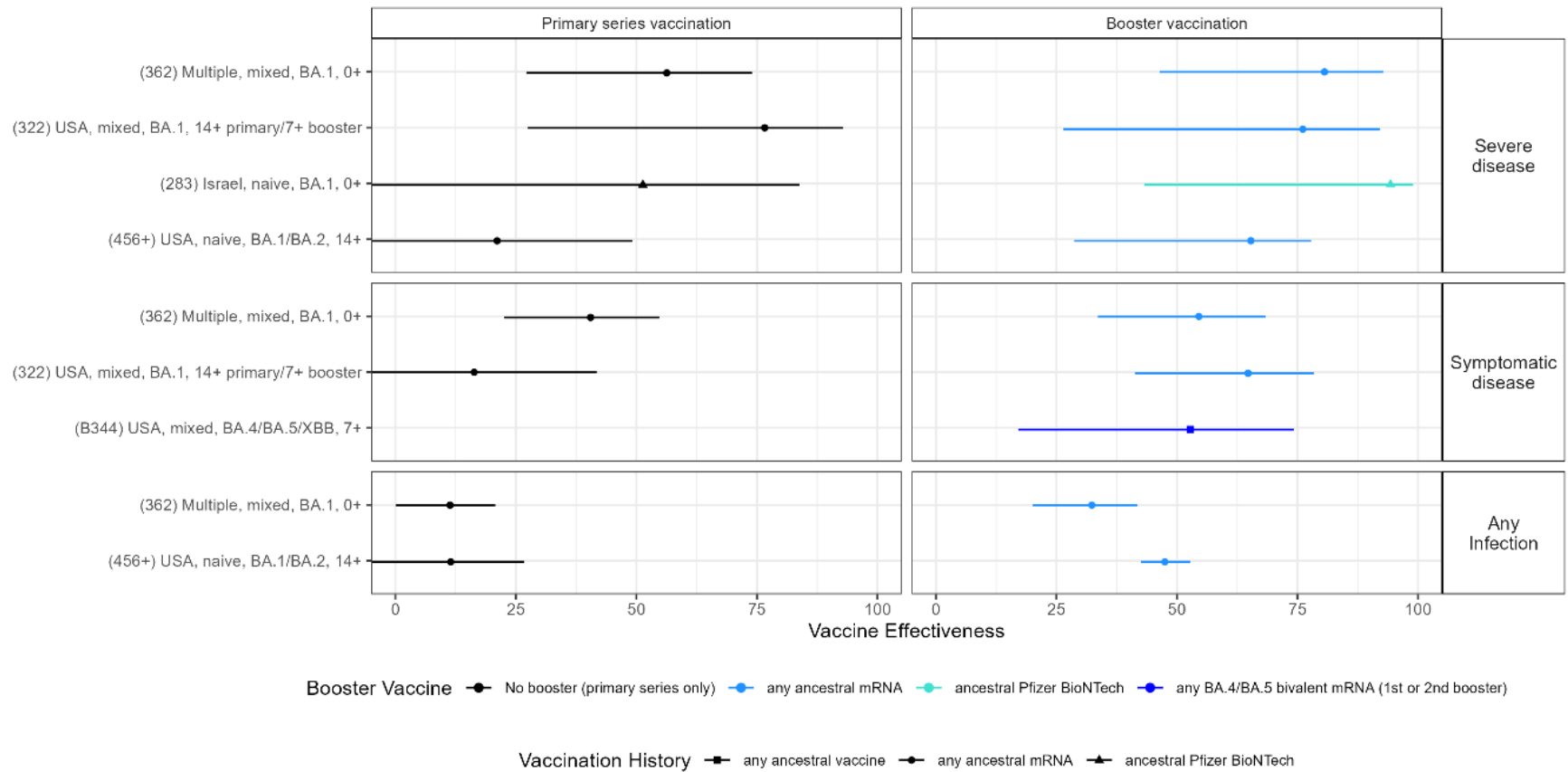
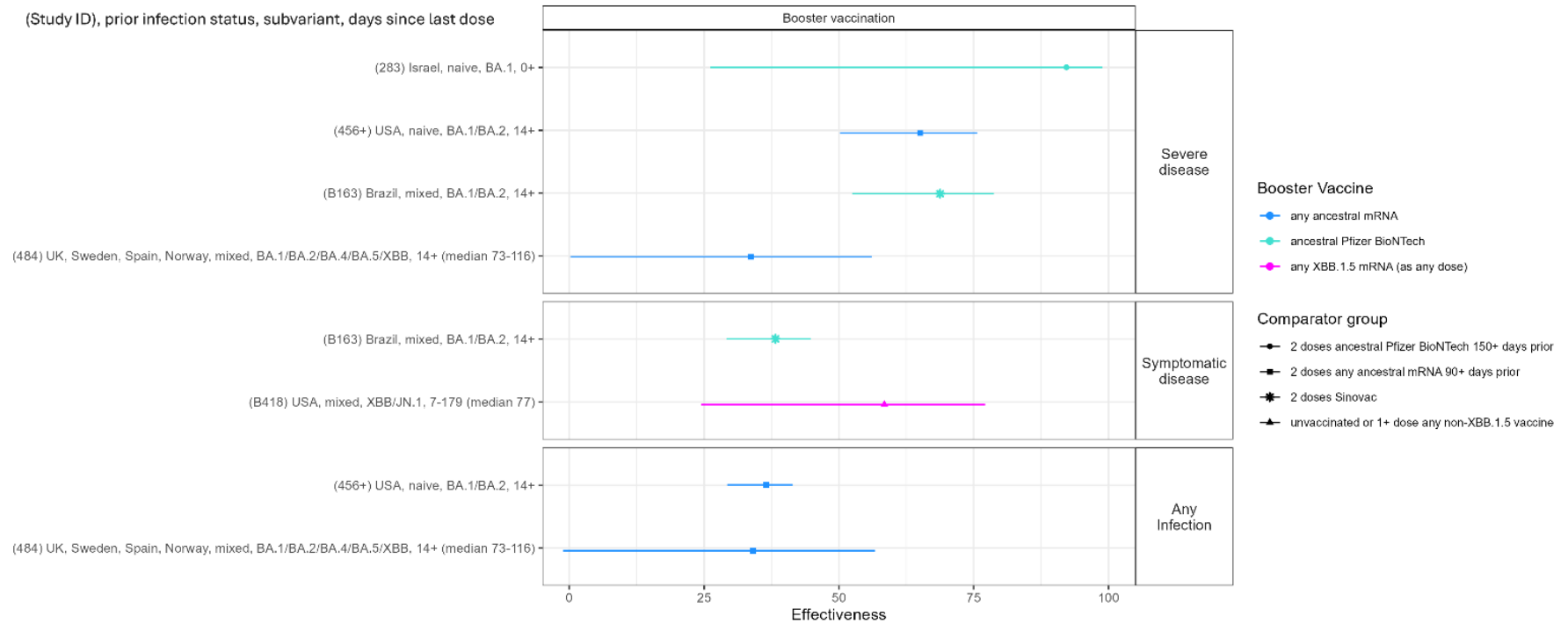


Figure 9. Overall Relative or Up-to-date COVID-19 Vaccine Effectiveness during Omicron Predominance, Pregnant Individuals





VE of an ancestral mRNA booster dose against severe disease ranged from 34%-92% across 4 studies.^{34,37,38,40} Differences in study design, setting, and comparator groups could contribute to the variation in VE across the studies. For example, the reference group in the study from Brazil (Florentino #B163) received a primary series of CoronaVac while those in the other two studies received an mRNA primary series.³⁸ Additionally, the reference group in the study from Israel (Guedalia #283) restricted the reference group to individuals vaccinated at least 5 months prior whereas the other studies either restricted to those vaccinated at least 3 months (Mercade-Besore #484, Qin #456) or did not apply any restriction (Florentino #B163).^{34 37,38,40}

Against symptomatic disease, VE of ancestral mRNA booster vaccination was slightly lower (38%, n=1 estimate) compared to VE of the Omicron XBB.1.5 monovalent vaccines (58%, n=1 estimate).^{38,51} The longer maximum follow-up time post vaccination for the ancestral mRNA estimate (~35 weeks vs. ~25 weeks), differences in the circulating subvariants, as well as differences in reference groups, study design, and setting may contribute to differences in VE.

Two studies assessed relative VE against infection among pregnant persons, finding similar, modest relative VE of ancestral mRNA vaccines (34% and 36% VE).^{37,40}

Duration of Protection in pregnant persons

There was little evidence (n=2 studies) on the duration of protection of vaccination among pregnant persons; both studies included pregnant persons vaccinated before and during pregnancy.^{35,40} One study showed large declines in absolute booster VE from about 2 to 4 months against severe disease (VE fell from 86% to -53%) and symptomatic disease (VE fell from 79% to -124%), though the 95% confidence intervals for were extremely wide due to small sample sizes.³⁵ The same study showed modest declines in primary series VE against severe disease (86% to 64% from 2 to 9 months) and an increase in primary series VE against symptomatic disease during the same time interval (from 3% to 42%). Substantial uncertainty around these estimates limit conclusions around the duration of protection of COVID-19 vaccination among pregnant persons.

In a second study relative VE of a booster dose against severe disease was modest at 29-60 days (25%, 95%CI: 0-52) but remained stable at 91-180 days (23%, 95% CI: -40 to 62); VE against infection declined from 55% at 15-28 days to 30% at 181-365 days after vaccination.⁴⁰

Infants (≤6 months of age)

Available evidence (n=9 studies) showed moderate to strong protection conferred to infants by maternal vaccination against different outcomes.⁴²⁻⁵⁰ Absolute VE of booster vaccination was moderate to high against severe disease and moderate against infection, while VE of primary series vaccination was moderate to high. There were no clear differences by timing during pregnancy of maternal vaccinations, but most estimates demonstrated that maternal doses received during or after pregnancy conferred some protection to infants. Relative VE of a booster dose showed added protection of a booster dose compared to primary series vaccination against severe disease and infection, though evidence was more limited. Note that in the summary below, if a study provides estimates by trimester of maternal vaccination and over the entire course of pregnancy, the estimate over the entire course of pregnancy is used when



describing ranges and medians. Also note that one study (Jorgensen, #375) evaluated VE of maternal post-natal vaccination on preventing severe disease and infection in infants.⁴⁶ Finally, please note that some estimates reflect maternal vaccination received both before as well as during pregnancy.

Absolute VE (Reference group: Unvaccinated)

Four studies evaluated absolute VE of maternal ancestral mRNA booster vaccination in infants^{43,45,47,50}, and six studies assessed VE of maternal primary series vaccination.^{42–47} Absolute VE of booster vaccination against severe disease in infants through 6 months of age ranged from 64% to 80% (n=2 estimates from 2 studies),^{45,50} with maximum follow-up time post vaccination ranging from approximately 33-36 weeks (Figure 10). Primary series VE against severe disease ranged from 36-58% VE (median 38%, IQR 37-48; n=3 estimates from 3 studies) with longer maximum follow-up time post maternal vaccination of 34-67 weeks.^{42,45,46}

Absolute booster dose VE against infection ranged from 73-78% (n=3 estimates from 3 studies),^{43,45,47} while primary series VE against infection ranged from 3-73% VE (median 19%, IQR 16-34; n=7 estimates from 5 studies).^{43–47}

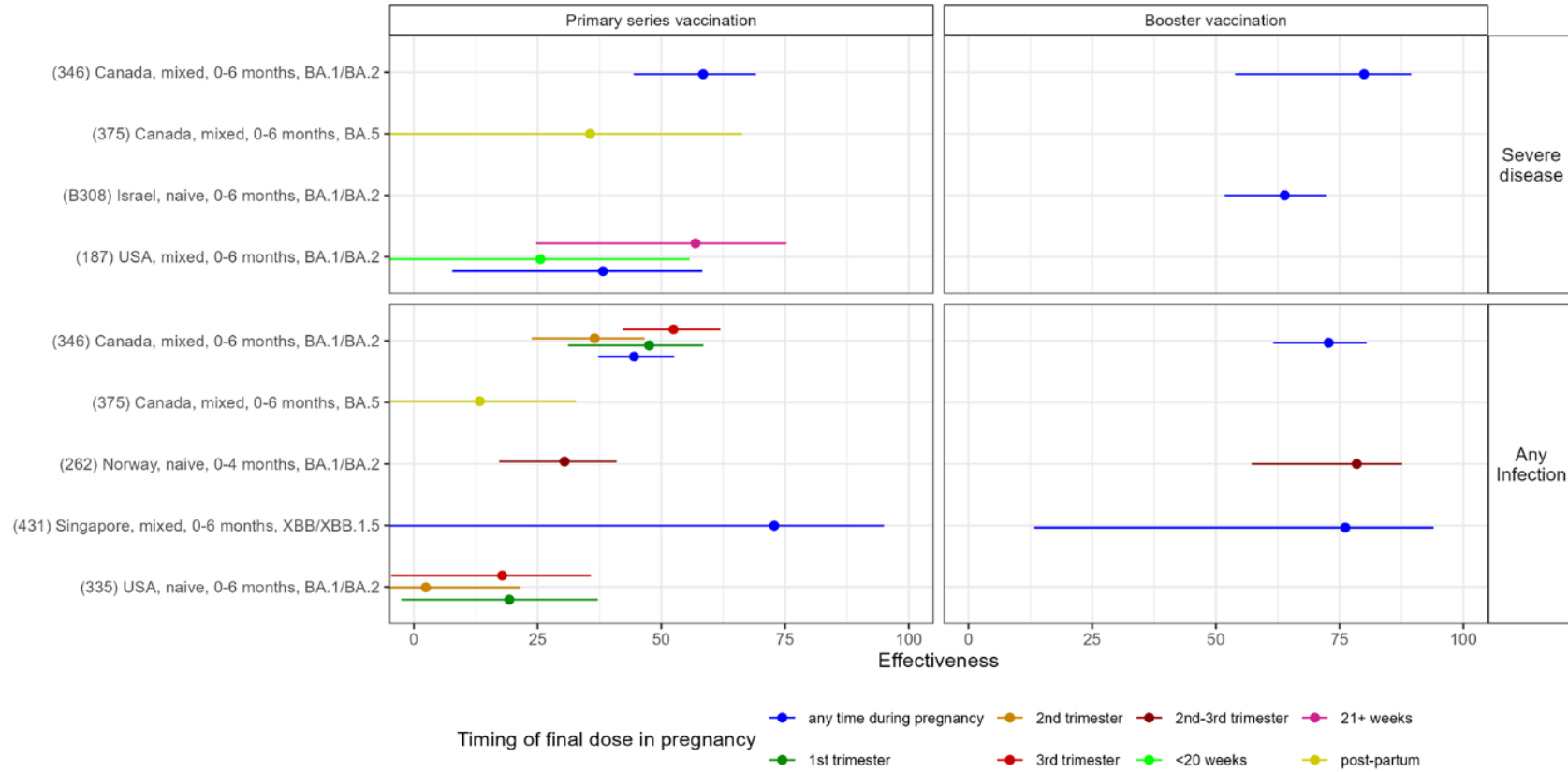
Five studies assessed VE by timing of vaccination during pregnancy.^{42,44–47} In one study (Halasa #187), protection of maternal primary series vaccination against severe disease was higher among infants whose mothers were vaccinated later in pregnancy compared to earlier (57% vs. 25% VE for mothers vaccinated at ≥ 21 weeks gestation and < 21 weeks gestation, respectively).⁴² However, evidence for primary series VE against infection showed no clear pattern by trimester of maternal vaccination among 2 studies (Jorgensen #346 and Zerbo #335).^{44,45} One study (Jorgensen #375) found some indirect protection conferred to infants even when mothers were vaccinated after giving birth (36% VE against severe disease and 13% VE against infection).⁴⁶

Relative VE

Evidence was limited for relative VE of a maternal booster dose versus primary series maternal vaccination in infants (2 estimates from 2 studies), and all evaluated ancestral mRNA vaccines.^{52 53} One study estimated relative VE of 65% against severe disease among infants within 30 days of birth, while the other estimated relative VE of 56% against infection in infants ≤ 6 months of age.

Figure 10. Overall Absolute COVID-19 Vaccine Effectiveness during Omicron Predominance, Infants born to Mothers Vaccinated during Pregnancy

(ref no) country, prior infection status, subvariant





HEALTHY ADULTS (18-64 YEARS)

Evidence for VE among healthy, younger adults (ages 18-64 years) during JN.1 or later subvariant predominance was fairly limited (n= 5 studies).^{13,19,20,26,51} All included studies evaluated up-to-date or relative VE. Most of the studies (n=4) were from the United States,^{19,20,26,51} while 1 was conducted across four western European countries.¹³ Three studies evaluated VE of XBB.1.5 mRNA vaccines,^{13,19,51} while the remaining 2 evaluated KP.2 mRNA vaccines.^{20,26} One study assessed VE against death,¹⁹ 3 against severe disease,^{13,19,20} 3 against symptomatic disease,^{20,26,51} and 2 evaluated VE against infection.^{19,20}

Overall VE in healthy adults

One study evaluated overall VE against death among healthy adults during JN.1 or later subvariant predominance, finding strong protection (VE 84%) at a mean of 25 weeks post vaccination, though confidence intervals are wide (Figure 11).¹⁹ Three VE estimates from 3 studies evaluated overall VE against severe disease among adults 18-64 years, with varied results.^{13,19,20} VE of XBB vaccines against severe disease was 30% and 66% in 2 studies, with median follow-up times of 25 and 15 weeks, respectively.^{13,19} The VE of the KP.2 vaccine against severe disease was low, though the confidence interval was wide (VE 12%, 95% CI -50 to 43%).²⁰ The two VE estimates against severe disease that were ≤30% were among veterans 18-64 years in the United States with a higher proportion of underlying conditions relative to the general population and, thus, may not reflect a truly healthy adult population.^{19,20} The study in Europe (Volkman #389) may be more representative of a healthy adult population (VE 66%).¹³

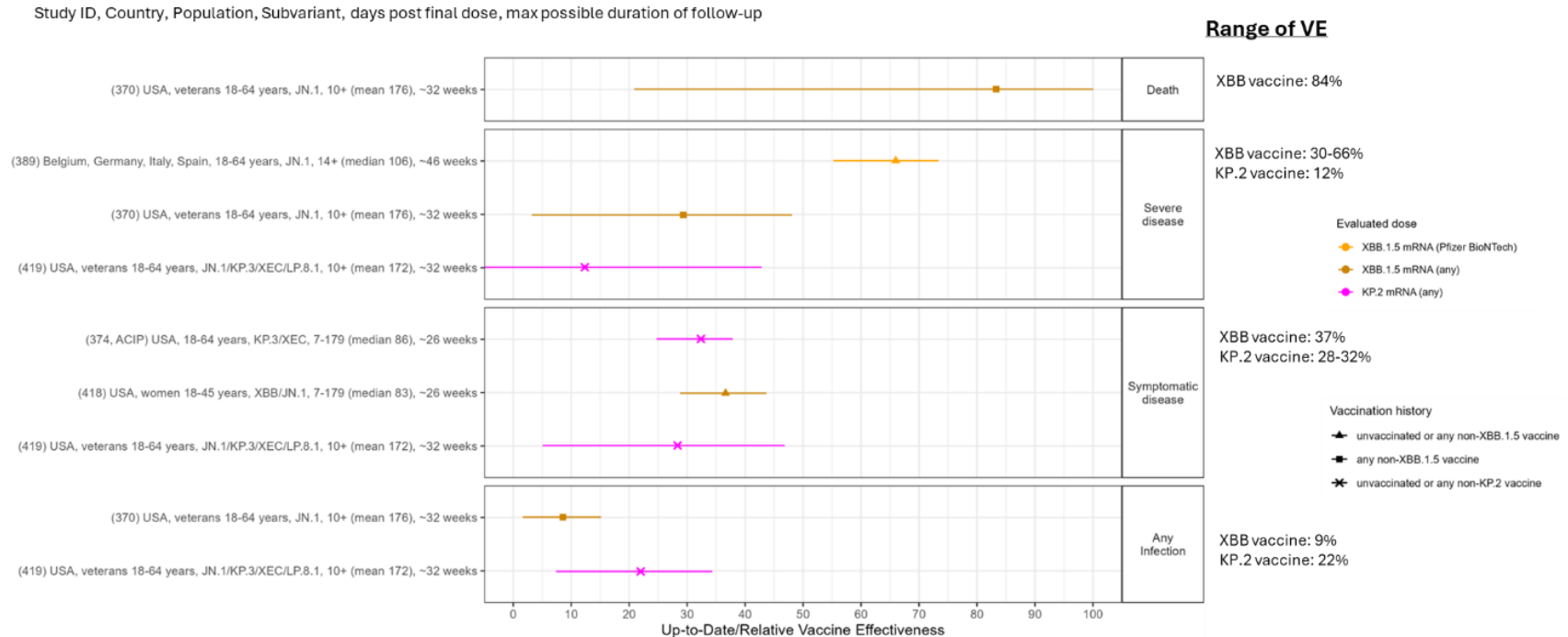
Against symptomatic disease, 3 estimates from 3 studies showed modest protection among adults 18-64 years; 1 of the 3 estimates (Ioannou #419) was among veterans in the United States.^{20,26,51} Overall VE of XBB vaccines was 37% against symptomatic disease (n=1 estimate from 1 study).⁵¹ Overall VE of KP.2 vaccination ranged from 28-32% (n=2 estimates from 2 studies).^{20,26} The maximum follow up time since vaccination across the three studies ranged from 26 to 32 weeks.

Two VE estimates from 2 studies showed low protection against infection. One study estimated a VE of 9% for XBB vaccines, while the other reported a VE of 22% for KP.2 vaccines against infection.^{19,20} Both studies were conducted among veterans in the United States.

Duration of Protection in healthy adults

Two assessments from 2 studies (Link-Gelles #374 & Volkman 389) evaluated the duration of protection of vaccination among healthy adults.^{13,26} In one study, VE of XBB vaccination against severe disease started high, peaking at 85%, and remained strong (>75%) up to about 6 months following vaccination.¹³ Beyond 6 months, VE against severe disease dropped, reaching 24% VE 8-12 months following vaccination. In the second assessment of duration of protection, VE of KP.2 vaccination against symptomatic disease fell from 39% at about 1 month to 20% at about 5 months following vaccination.²⁶

Figure 11. Overall Relative and Up-to-Date COVID-19 Vaccine Effectiveness during Omicron JN.1 and Later Subvariant Predominance, Adults 18-64 years



CHILDREN (6 MONTHS-17 YEARS)

Limited evidence was available on VE among children (6 months - 17 years) during JN.1 or later subvariant predominance (n=5 VE estimates from 3 studies).^{54,55,56} All 3 studies were conducted in the United States and estimated up-to-date VE of a booster dose (Figure 12).

Overall VE in children

Only 1 study (Tartof #365) evaluated VE against severe disease (Figure 12), finding moderately strong protection of an XBB.1.5 mRNA booster dose against severe disease among children aged 5-17 years (VE 65%, 95% CI 36-81%), with a median follow up time of about 11 weeks since vaccination.⁵⁴ This study also provided VE estimates stratified by younger children and adolescents, with no substantial difference in VE between age groups (68% vs. 63% among children aged 5-11 and 12-17 years, respectively).

Four estimates from 2 studies (Irving #413 & Irving #417) from the same US surveillance network (VISION) estimated moderate protection against symptomatic disease among children.^{55,56} The VE against symptomatic disease ranged from 35-44% for XBB vaccines and was slightly higher for JN.1 and KP.2 vaccines (56% and 66%, respectively). The differences may be due to the greater mismatch between the XBB vaccines and circulating subvariants as well as longer maximum follow up time for these estimates with more opportunity for waning (~47 weeks for the XBB VE estimates vs. ~26 weeks for the JN.1 and KP.2 vaccine estimates), though median follow up times differed only slightly (~13 weeks vs. ~11 weeks). Within each of these two studies, no notable differences in VE between younger and older children were observed (66% vs. 56% and 35% vs. 44% among children aged 9 months-4 years vs. 5-17 years).

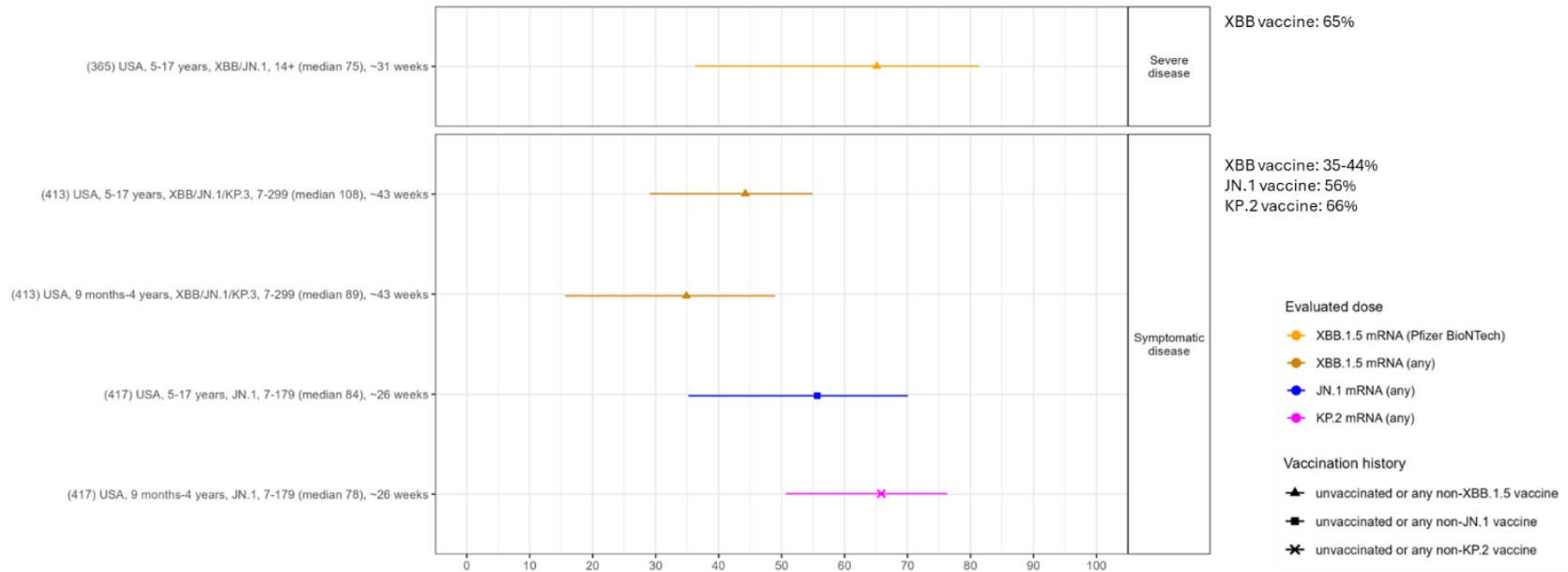
Duration of Protection in children

Two assessments from one study (Irving #413) evaluated duration of protection against symptomatic disease in children.⁵⁵ Early VE (≤ 60 days post vaccination) was moderate but decreased notably between 60-299 days (from 53% to 23% among children 9 months to 4 years and from 64% to 34% among children 5-17 years).

Figure 12. Overall Relative and Up-to-Date COVID-19 Vaccine Effectiveness during Omicron JN.1 and Later Subvariant Predominance, Children 6 months – 17 years

Study ID, Country, Population, Subvariant, days post final dose, max possible duration of follow-up

Range of VE



HEALTHCARE WORKERS

The key issue for healthcare workers is not their individual risk, which has already been addressed above for healthy adults, but rather whether current vaccines reduce any nosocomial transmission that healthcare workers may be contributing to. Only one VE study met inclusion criteria for the JN.1 or later period, but it was against any infection, not transmission; VE was 23% (95% CI 6-38%) in this US study evaluating an XBB.1.5 mRNA booster dose out to 7 months (Shrestha #314).⁵⁷ In an attempt to find more studies, we looked for any studies during Omicron, including excluded studies, and also looked for outcomes against absenteeism. We found two more VE studies, but only for absenteeism and they did not meet inclusion criteria so have risk of bias.

The first study was conducted in the UK during JN.1 and evaluated absenteeism among healthcare workers in secondary care settings (Foulkes 2025).⁵⁸ COVID-19 caused four times more infections and absences than did influenza or RSV. Absences due to symptomatic infections were fewer among vaccinated healthcare workers compared to unvaccinated healthcare workers and were 1 day shorter; no such differences were seen with influenza vaccine. However, the study observed only 5% (-38–34%) VE for episodes of absence associated with any COVID-19 infection over the 6-month period, though CIs were wide, and overall they found no differences by vaccine status in the proportion absent among all healthcare workers for any absence, including non-infectious reasons.

The second study was conducted in hospital healthcare workers in Greece over a 5-year period that included pre-Omicron variants (Maltezou 2026).⁵⁹ In this study, COVID-19 was the most common cause of absence among healthcare workers each year, and, as in the other study, also caused more absences than influenza, about twice as many. VE against COVID-19-associated absenteeism was 56% across the 5-year time period, but policies around testing and absenteeism changed over the years, as did the disease severity and population immunity, so it may not be representative of today's context. Furthermore, COVID-19 vaccination was very low (0-8%) in the most recent 3 years of the study, so protection in most individuals would be from being vaccinated in 2021-2022 when coverage was 90%. They also found that COVID-19-vaccinated healthcare workers were absent fewer days than unvaccinated, whereas there was no difference for influenza vaccine, but absences were shorter by only half a day in 2024; none were vaccinated in 2025 so they could not evaluate for the most recent year. But there is evidence of possible bias as they also found that absences were shorter among those who were vaccinated in previous years (88% of which were 3 years prior) where we would have expected almost no effect due to waning effects of vaccine and increases in population immunity. Thus, selection bias as to who gets vaccinated and why may play a role; perhaps HCWs that got vaccinated in the more recent years were also more committed to their work and caring for patients, so less likely to take leave.

DISCUSSION

This living systematic review synthesized real-world COVID-19 vaccine effectiveness evidence during the JN.1 and later Omicron subvariant predominant period across six population groups including all persons over 6 months of age, both healthy and immunocompromised or with comorbidities, as well as children born to mothers vaccinated during pregnancy. Recent COVID-19 vaccination with variant-adapted mRNA vaccines continues to provide clinically meaningful protection against severe disease beyond that from



prior vaccination and infection alone across all populations studied. Early VE against severe disease was moderate to high across all groups examined, ranging from 25-86%. This incremental protection is especially important for older adults, high risk groups and immune-naïve babies protected via maternal immunization, all of whom face substantially higher absolute risk of severe COVID-19 and its complications.⁶⁰

Protection was higher and more durable against more severe outcomes (death and severe hospitalization) than less severe (symptomatic illness and infection), but protection against severe disease declined and became similar to that in the comparison group approximately 6-8 months after vaccination. These findings support the rationale for annual (or biannual) vaccination and the framework in which the primary goal is to prevent severe disease, hospitalization, and death, rather than to prevent mild illness or asymptomatic infection.⁶⁰

When vaccine types were compared within similar early follow-up windows, JN.1-, KP.2- and XBB.1.5-adapted vaccines tended to show similar VE in the context of JN.1 or later Omicron subvariants. However, no head-to-head comparisons within the same study and time window exist. Although the expectation is that a better antigenic match between the vaccine and circulating strains improves effectiveness, this finding is reassuring as it supports the use of updated vaccine formulations even in a context when they become available only after the virus has already transitioned to another subvariant.

VE among adults with immunocompromising conditions or with comorbidities was broadly similar to that of immunocompetent adults, which is both reassuring and important for policy. The substantially higher risk in these groups means that the same VE translates into greater absolute benefit, with more hospitalizations and deaths prevented per person immunized.

Some key limitations of this synthesis include the very small number of studies in children, lack of outcomes of interest from the JN.1 or later period for pregnant persons and healthcare workers, and lack of studies on LP.8.1-adapted vaccines. Results also reflect only mRNA vaccines in high-income country settings, predominantly in Europe and the United States, limiting the generalizability of these findings to global vaccination policy contexts. The duration of VE beyond six months was unknown for most populations and outcomes, which impacts guidance on how frequently to re-vaccinate; however, declines towards no additional protection relative to the comparison group was observed by 6-8 months in older adults and is likely similar or shorter for other populations based on comparisons of other VE measurements across populations such as peak VE within 3 months of vaccination. Although we could account for some of varying factors across estimates, such as time since vaccination, other factors that we could not control for contributed to the heterogeneity in estimates across studies that prevented precise estimation or meta-analysis of the data. The comparison group varied substantially across studies: some included both unvaccinated and previously vaccinated persons, while others were restricted to previously vaccinated persons only. Additionally, as population immunity from prior vaccination and infection becomes more universal, the expected incremental VE from an additional dose is reduced; as the incremental benefit of booster doses wear off over time, VE approaches zero, which can result in negative VE estimates (i.e., estimated VE is just as likely to be negative as positive when VE is expected to be 0). Negative VE estimates in this context should generally be interpreted as consistent with no additional

protection from the recent dose compared to underlying protection. However, negative VE estimates were rare and not observed after recent (<3 months) vaccination. Finally, these are observational studies and who gets vaccinated and why may be correlated with risk of disease, either positively or negatively.

Taken together, these findings provide evidence that continued annual or biannual (every 6 months) COVID-19 vaccination with variant-adapted mRNA vaccines in high-priority groups including older adults, immunocompromised individuals, adults with comorbidities, and pregnant persons, provide meaningful protection against severe outcomes in the early months post-vaccination.

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