Duration of protection from COVID-19 Vaccines: SAGE presentation December 7, 2021

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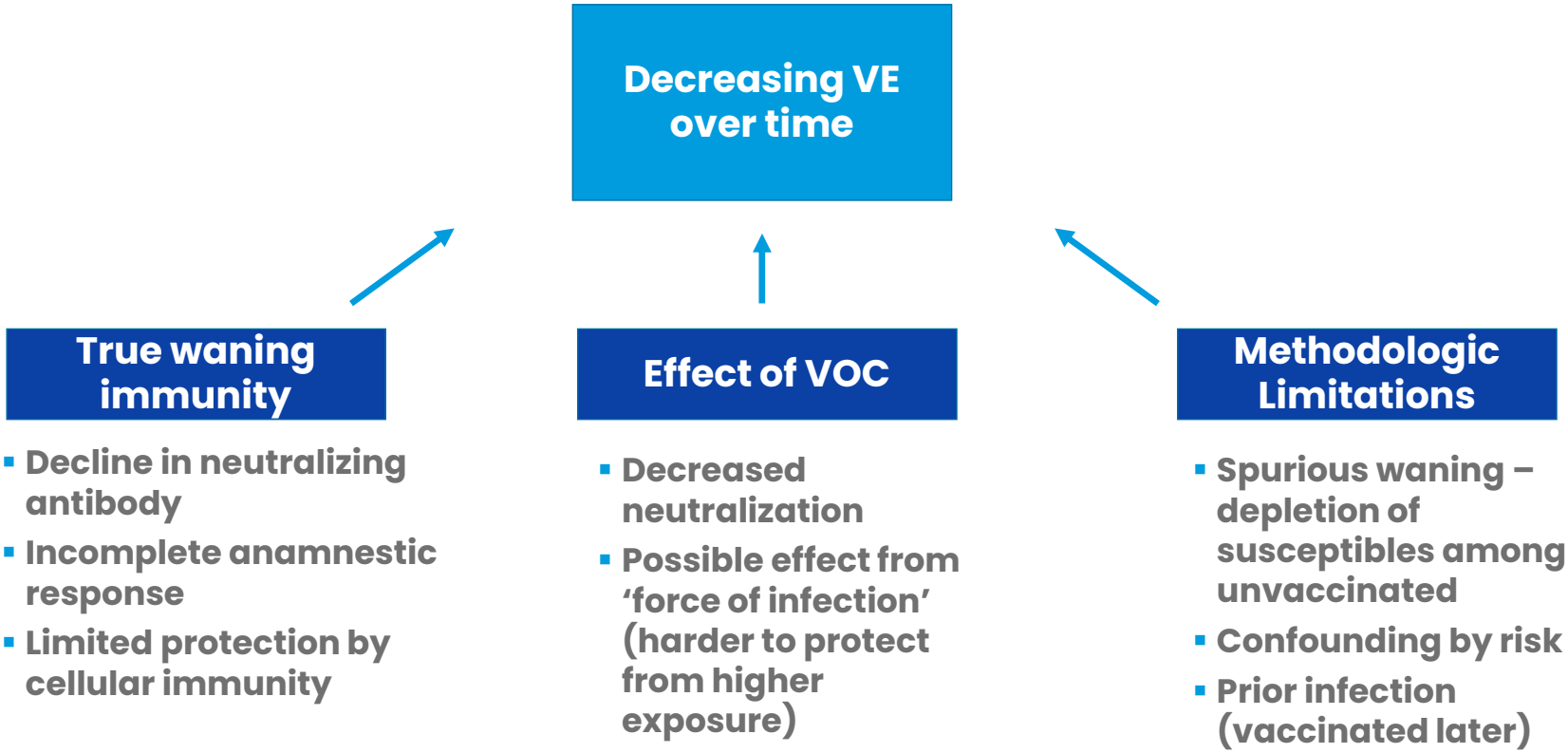
Overview

- Vaccine Effectiveness Studies. Systematic review and meta-regression
- Breakthrough infections among vaccinated persons


Decreasing VE over time
True waning immunity
Decline in neutralizing antibody
Incomplete anamnestic response
Limited protection by cellular immunity
Effect of VOC
Decreased neutralization
Possible effect from 'force of infection' (harder to protect from higher exposure)
Methodologic Limitations
Spurious waning – depletion of susceptibles among unvaccinated
Confounding by risk
Prior infection (vaccinated later)

Systematic Review

- Most studies of VE provide cumulative VE since time of vaccination which can obscure a decrease in VE due to changing COVID-19 incidence over time
- Focused on studies that provided VE at discrete time intervals after vaccination
- Systematic search of pre-print and published literature of multiple databases
- Apply two sets of inclusion/exclusion criteria
    - 1. adjust for confounders, compare to unvaccinated group, do not include partially vaccinated
    - 2. VE at discrete time intervals, VE provided ≥3 months post-vaccination, VE of single vaccines
- Looked separately at studies that evaluated VE for a single variant, and those that looked at mixed variants

Systematic Review

- 18 studies included between June 17-December 2
  - 15 Pfizer/BioNTech-Comirnaty, 11 Moderna-mRNA-1273, 4 Janssen-Ad26.COV2.S, 4 AstraZeneca-Vaxzevria
  - 3 RCT, 7 TND case-control studies, 6 retrospective and 2 prospective cohort studies,
  - Locations: Canada (1), Israel (1), Finland (1), Qatar (1), Spain (1), Sweden (1), United Kingdom (2), United States (8), multi-country clinical trials (2)
- Graphed the VE at the median time point for each time interval separately by outcome, age group, vaccine and variant context (single variants vs. mixed variants)
- Random effects meta-regression was used to estimate the average change in VE from 1-6 months after full vaccination

Risk of bias of studies included in analysis, by domain of bias

Study	tool used (robinsi or rob2)	Bias due to randomization	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to departures from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result
El Sahly et al	ROB2	Low	n/a	n/a	n/a	Low	Low	Low	Low
Janssen VRBPAC	ROB2	Low				Low	Low	Low	Low
Thomas et al	ROB2	Low				Low	Low	Low	Low
Andrews et al	ROBINSI		Moderate	Low	Low	Low	Low	Moderate	Moderate
Bruxvoort et al	ROBINSI		Moderate	Moderate	Low	Low	Low	Moderate	Moderate
Chemaitelly et al	ROBINSI		Serious	Low	Low	Low	Low	Low	Moderate
Goldberg et al	ROBINSI		Serious	Low	Low	Low	Low	Low	Moderate
Lin et al	ROBINSI		Serious	Low	Low	Low	Low for infection	Low	Moderate
Martinez-Bas et al	ROBINSI		Serious	Serious	Low	Low	Low	Low	Moderate
Nordstrom et al	ROBINSI		Moderate	Low	Low	Low	Low	Moderate	Moderate
Self et al	ROBINSI		Moderate	Low	Low	Low	Low	Low	Low
Tartof et al	ROBINSI		Moderate	Low	Low	Low	Low	Moderate	Low
Thompson et al	ROBINSI		Moderate	Low	Low	Low	Low	Low	Low
Skowronski et al	ROBINSI		Serious	Low	Low	Low	Low	Low	Moderate
Poukka et al	ROBINSI		Serious	low	Low	Low	low	Low	Moderate
Irizarry et al	ROBINSI		Serious	low	Low	Low	low	Low	Moderate
Tenforde et al	ROBINSI		Moderate	Low	Low	Low	low	Low	Low

Bias due to confounding, mostly due to lack of adjustment for comorbidity and time;
Bias in measurement mostly antigen test not confirmed by PCR;
Bias in selection of reported result if no public protocol.

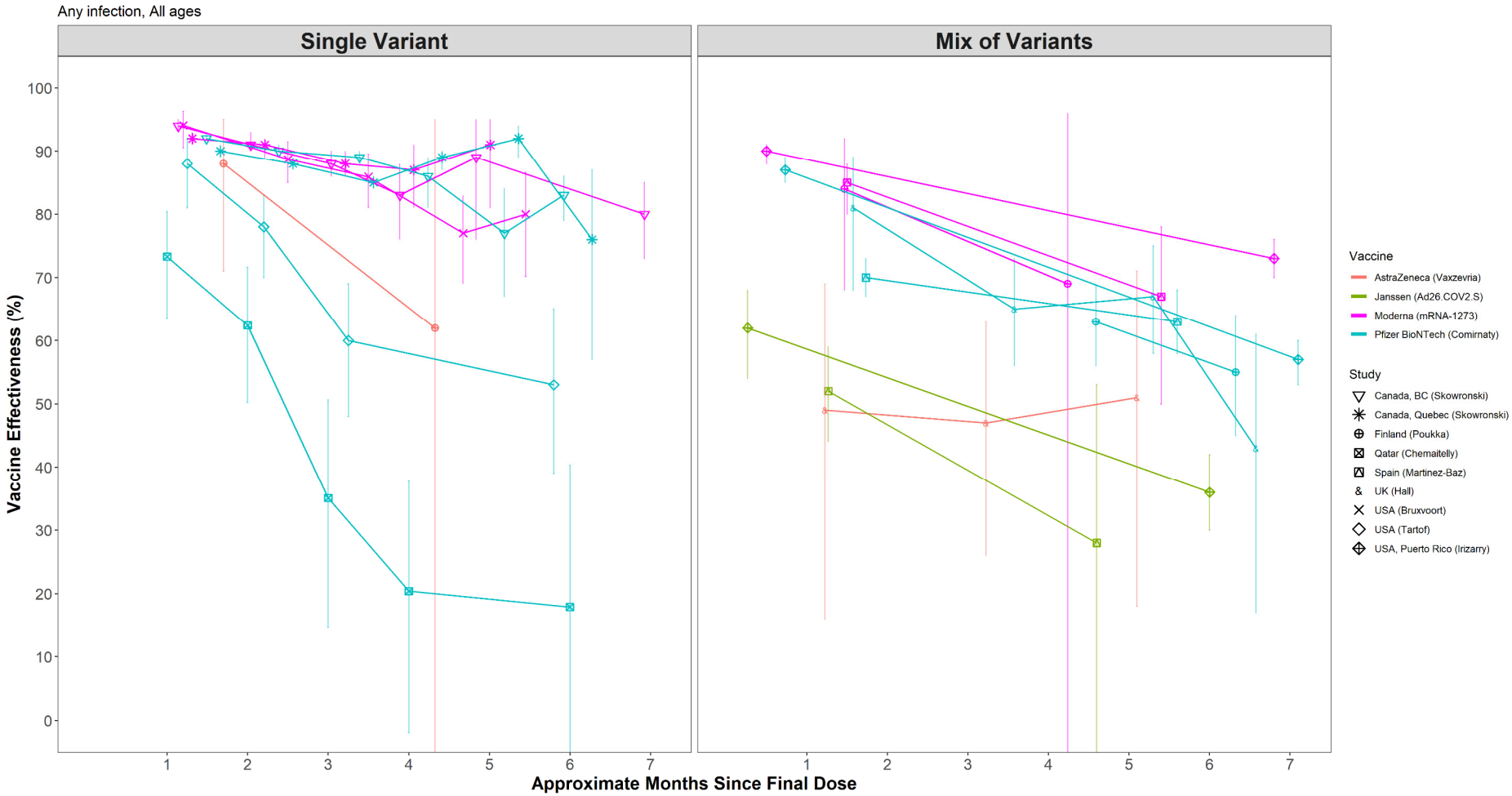
*One study, Hall et al., has not been evaluated yet

Overall Risk of Bias of studies included in the analysis

Study	Overall Bias, WHO/JHSPH review; ROBINS-i	McMasters; overall bias; modified ROBINS-I	Cochrane ; overall bias; ROBINS-I
El Sahly et al	Low		
Janssen VRBPAC	Low		
Thomas et al	Low		
Andrews et al	Moderate	Moderate	Moderate
Bruxvoort et al	Moderate	Serious	Moderate
Chemaitelly et al	Serious	Serious	Serious
Goldberg et al	Serious	Serious	Serious
Lin et al	Serious	Serious	Serious
Martinez-Bas et al	Serious	Serious	Serious
Nordstrom et al	Moderate	Serious	
Self et al	Moderate		Serious
Tartof et al	Moderate	Moderate	Serious
Thompson et al	Moderate	Serious	Moderate
Skowronski et al	Serious	Serious	
Poukka et al	Serious		
Irizarry et al	Serious		
Tenforde et al	Moderate		Serious

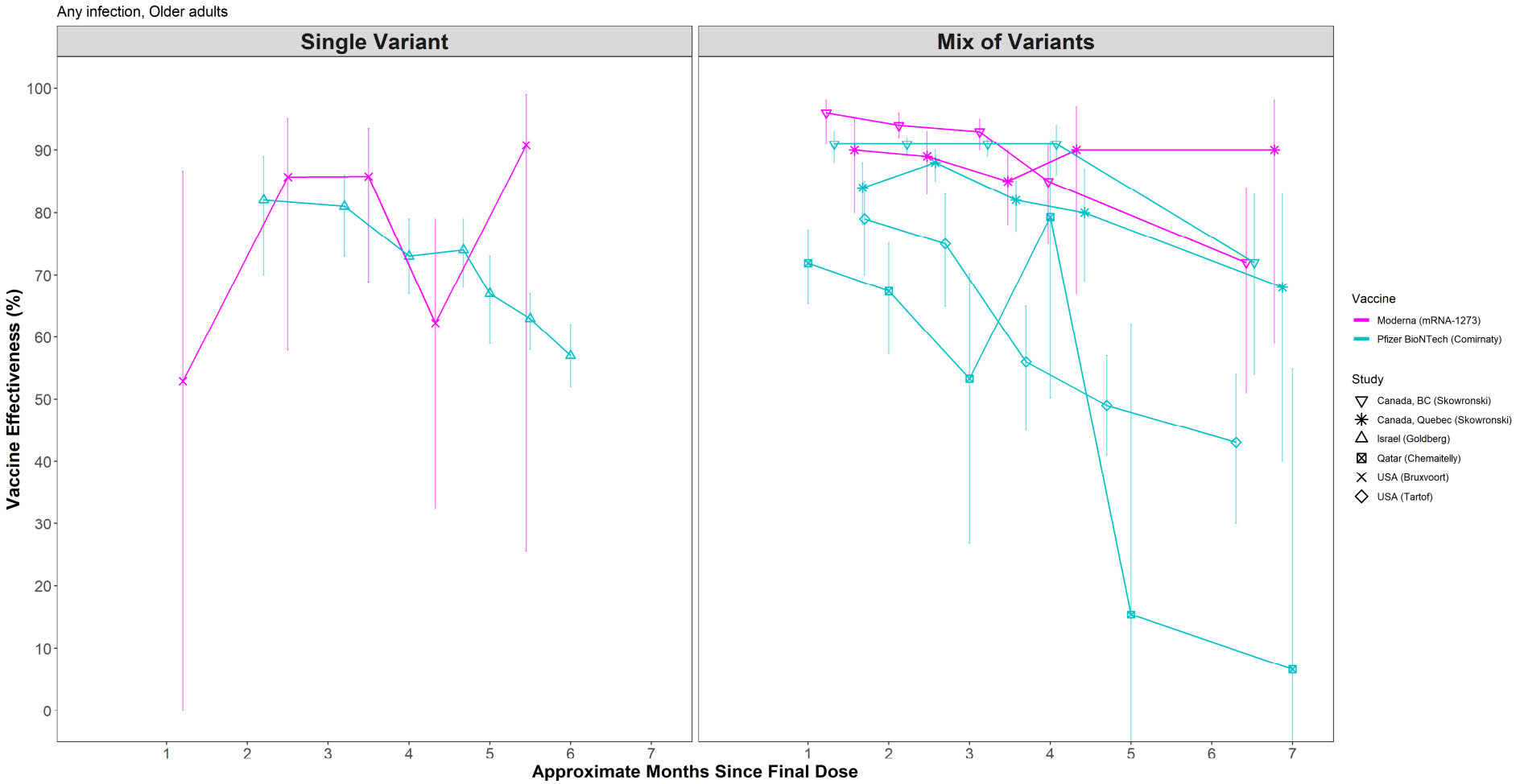
*One study, Hall et al., has not been evaluated yet

Any Infection, All Ages



*All single variant studies evaluated Delta

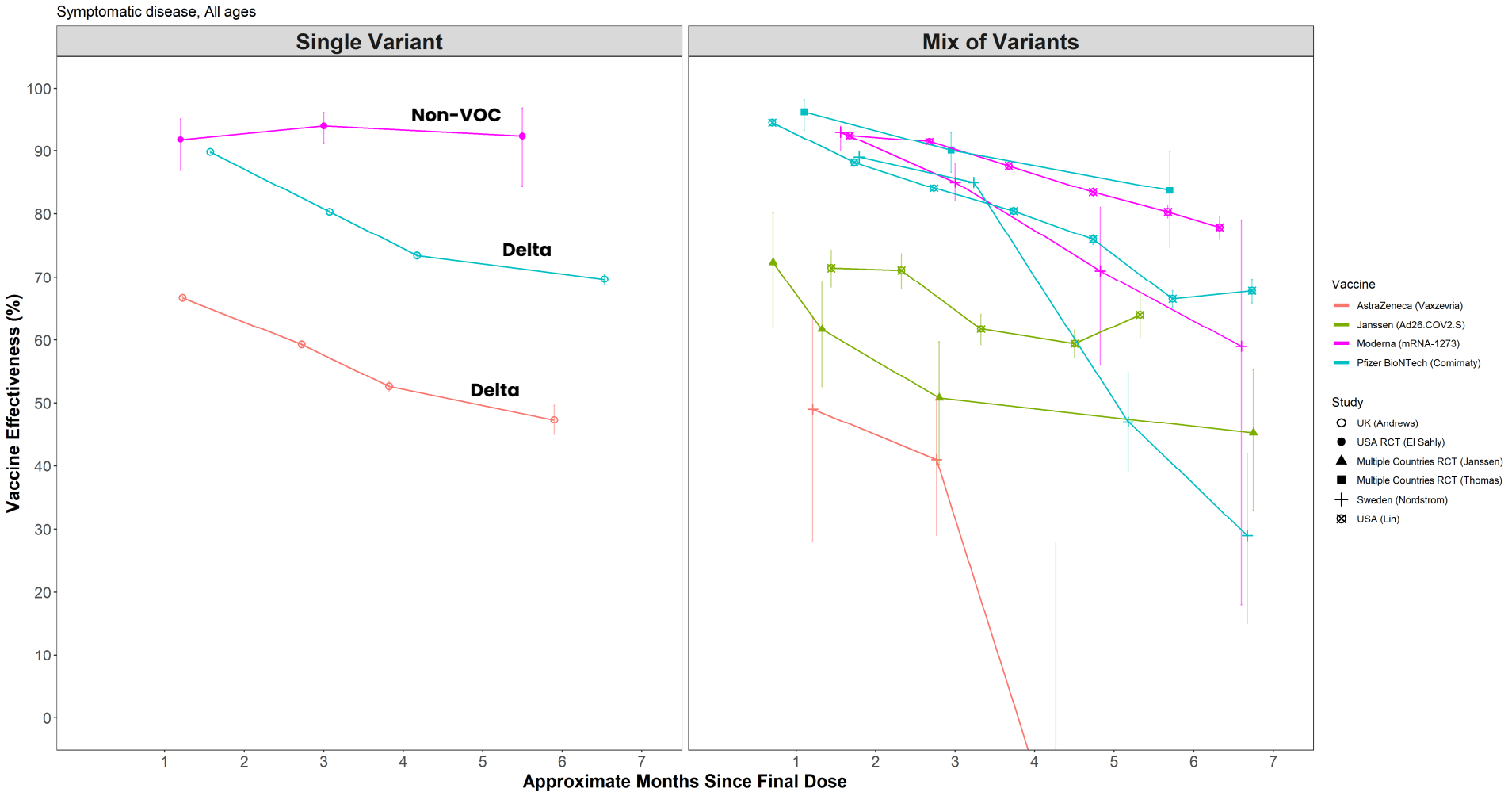
Any Infection, Older adults



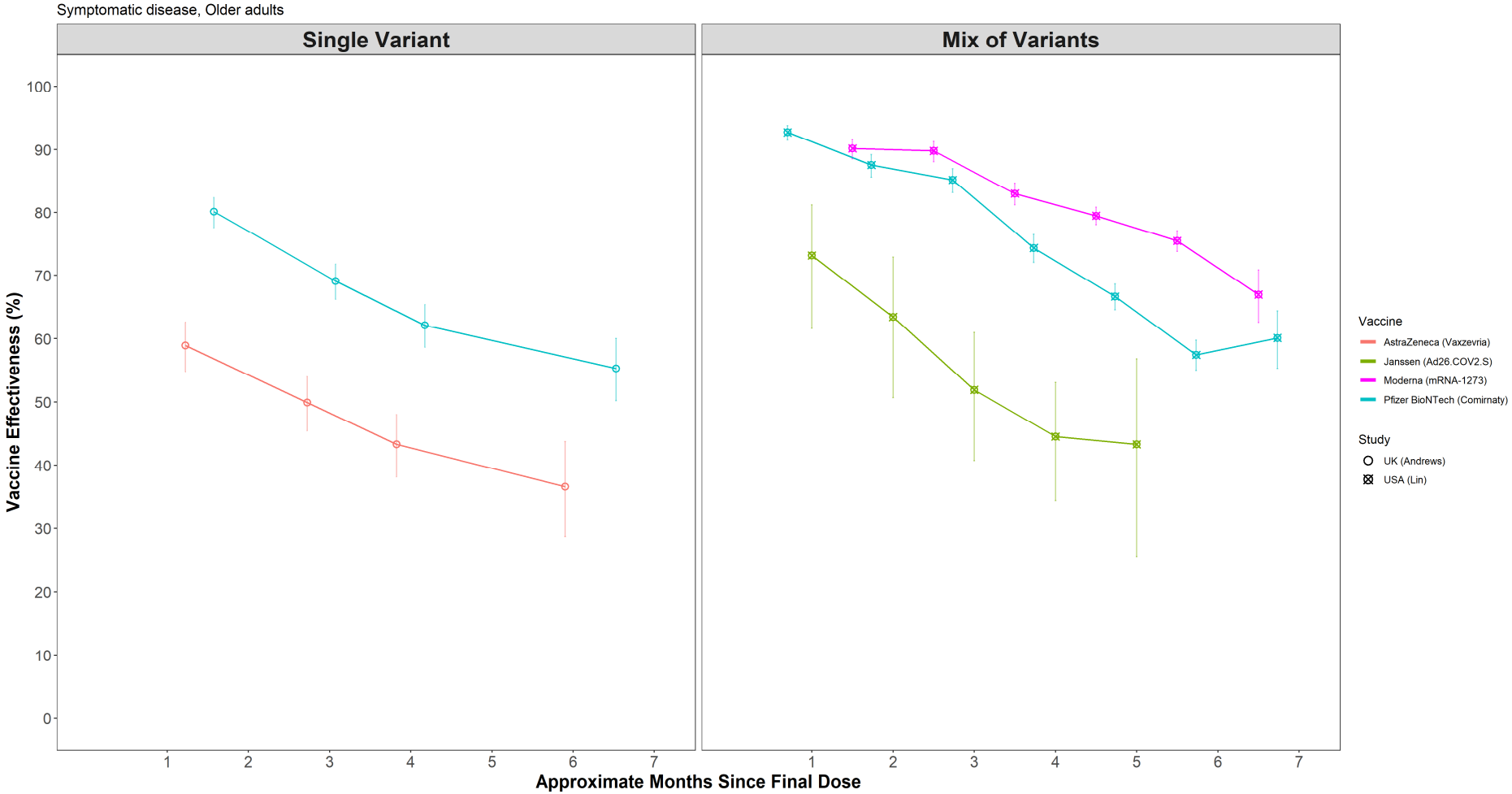
Goldberg: estimates in Delta plot are for Delta period.

*All single variant studies evaluated Delta

Symptomatic Disease, All Ages

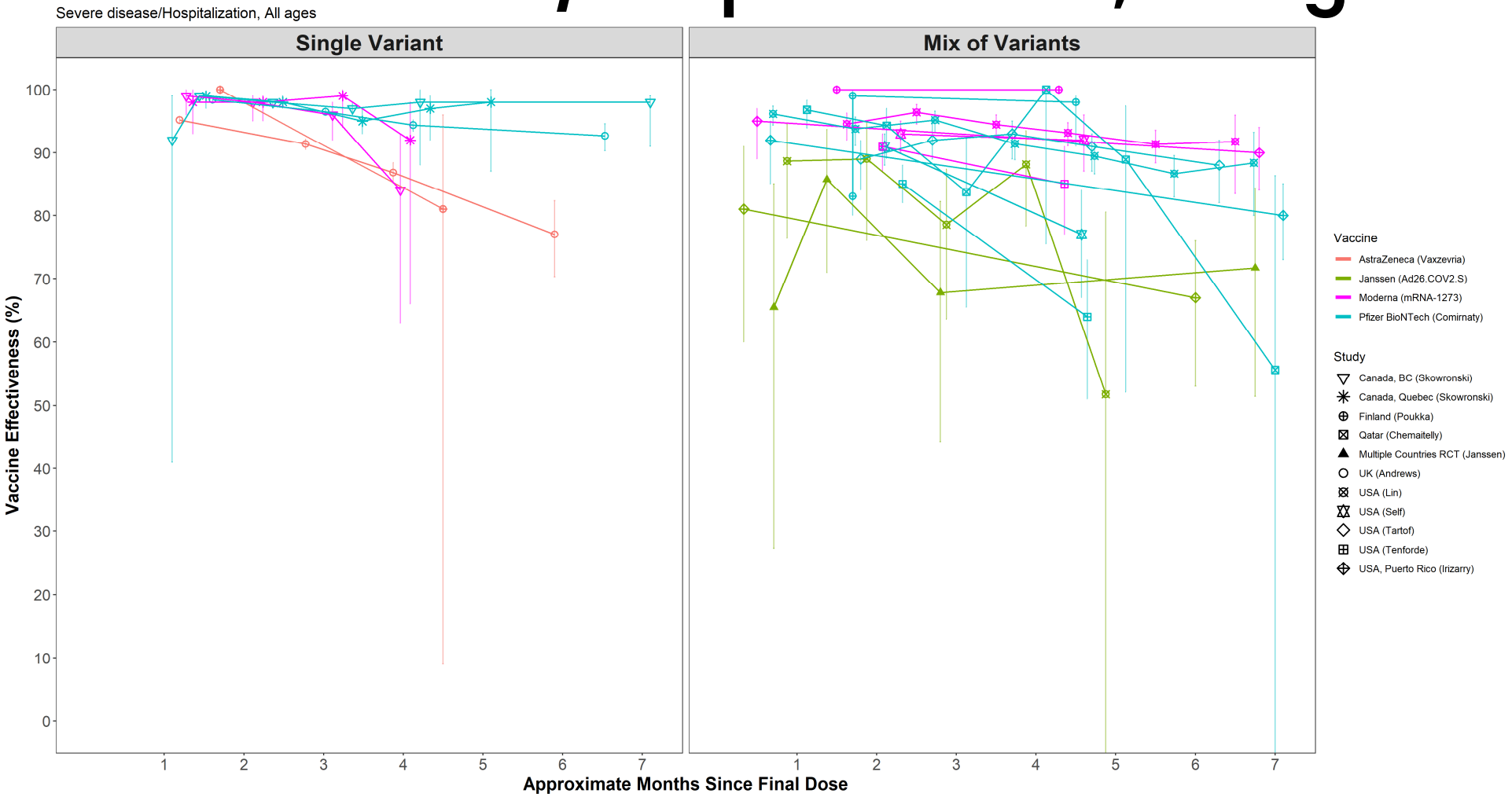


Symptomatic Disease, Older Ages



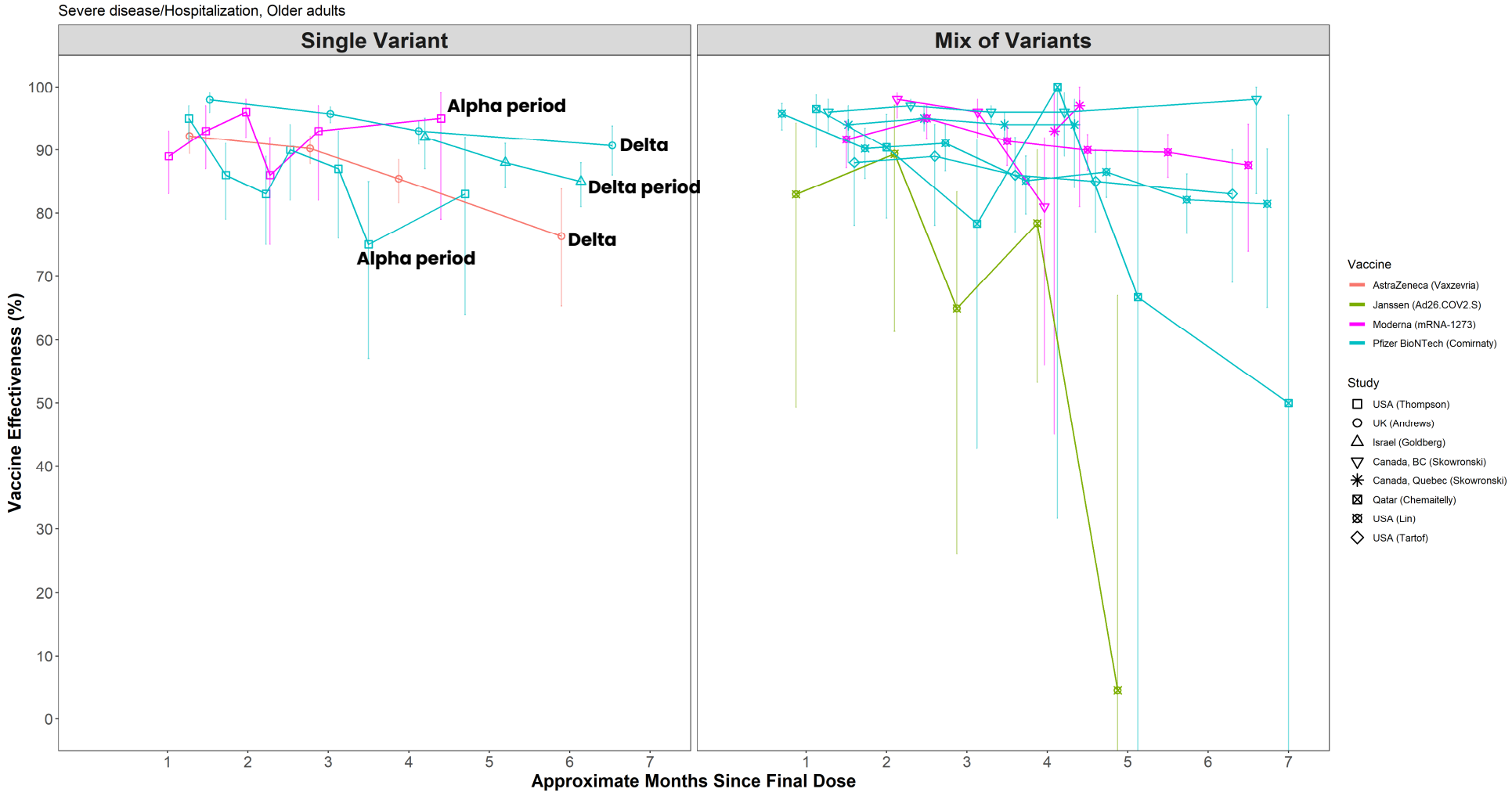
*All single variant studies evaluated Delta

Severe Disease/Hospitalization, All Ages



*All single variant studies evaluated Delta

Severe Disease/Hospitalization, Older Adults



Meta-Regression of decrease in VE over time

Outcome	Decrease in % points in VE from 1 to 6 months after final dose (95% CI), p value*	
	All Ages	Older Adults
SARS-CoV-2 Infection	18·5 (8·4-33.4)	19·9 (9.2-36.7)
Any Symptomatic Disease	25·4 (13.7-42.4)	32·0 (11-69.0)
Severe Disease	8·0 (3.6-15.2)	9·7 (5.9-14.7)

*Combined for single/non VOC and mixed variants due to no notable difference in decrease in VE

From SSRN preprint, Nov 18. will be updated based on addition of 4 studies; minimal change expected

Decreased VE in progression to very severe disease if hospitalized?

Effectiveness of mRNA Vaccines for Preventing COVID-19 Hospitalizations and Attenuating Disease Severity

- Case-control study from IVY network
- Immunocompetent adults (≥18 years) hospitalized at 21 hospitals in 18 states from 11 March – 15 September 2021
- Case status:
  - Cases with COVID-19-like illness and positive SARS-CoV-2 molecular or antigen test within 10 days of illness onset
  - Controls SARS-CoV-2 negative by RT-PCR
- Vaccination status:
  - Fully vaccinated with mRNA vaccine (dose 2 of Bnt162b2 or mRNA-1273 ≥14 days prior to illness onset) or unvaccinated

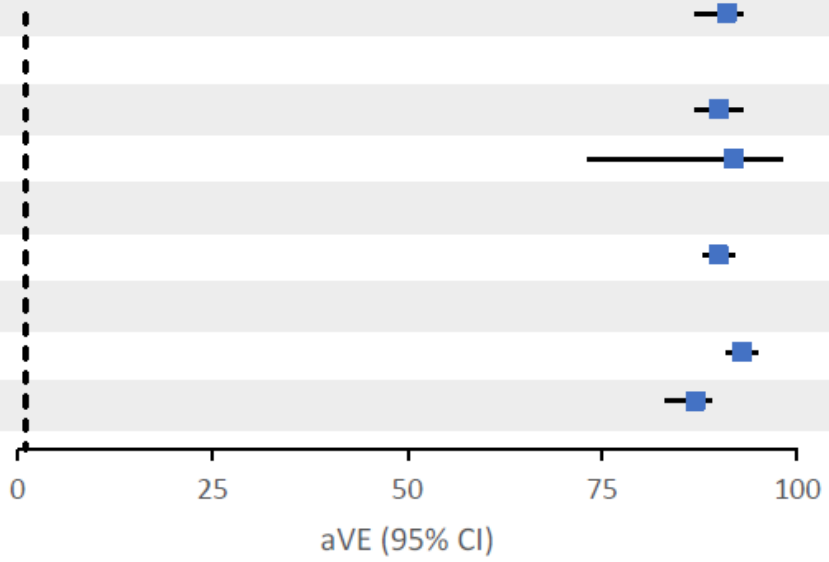
IVY

INFLUENZA AND OTHER VIRUSES IN THE ACUTELY ILL

*IVY slides courtesy of Mark Tenforde, CDC

Vaccine effectiveness against hospitalization

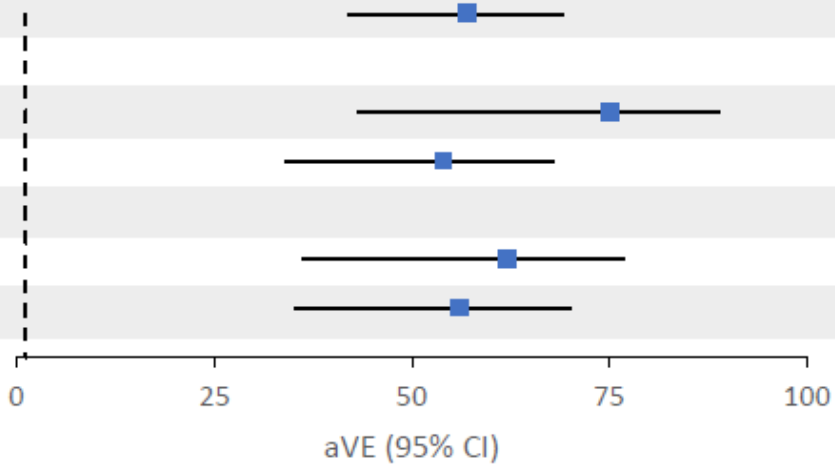
Subgroup	Adjusted VE against hospitalization, % (95% CI)*
Pre-Delta period (March-June 2021)	
Overall	91 (87-93)
By time since vaccination	
14-120 days since dose 2	90 (87-93)
>120 days since dose 2	92 (73-98)
Delta period (July-September 2021)	
Overall	90 (88-92)
By time since vaccination	
14-120 days since dose 2	93 (91-95)
>120 days since dose 2	87 (83-89)



* VE calculated by logistic regression, comparing the odds ratio of vaccination in COVID-19 case patients versus COVID-19-negative controls: (1 – aOR) × 100; models adjusted for calendar time, US geographic region, age, sex, and race and ethnicity

Among adults hospitalized with COVID-19, VE against progression to invasive mechanical ventilation or death

Subgroup	Adjusted VE against progression to mechanical ventilation or death, % (95% CI)*
Overall	57 (42-69)
By time period	
March-June (pre-Delta period)	75 (43-89)
July-September (Delta period)	54 (34-68)
By time since vaccination (March-September)	
14-120 days since dose 2	62 (36-77)
>120 days since dose 2	56 (35-70)



* VE calculated by logistic regression, comparing the odds ratio of vaccination in COVID-19 case patients who progressed to invasive mechanical ventilation or in-hospital death within 28 days and COVID-19 case patients who did not: (1 – aOR) × 100; models adjusted for age, sex, race and ethnicity, and number of baseline chronic medical conditions

Analysis of breakthrough infections among vaccinated persons

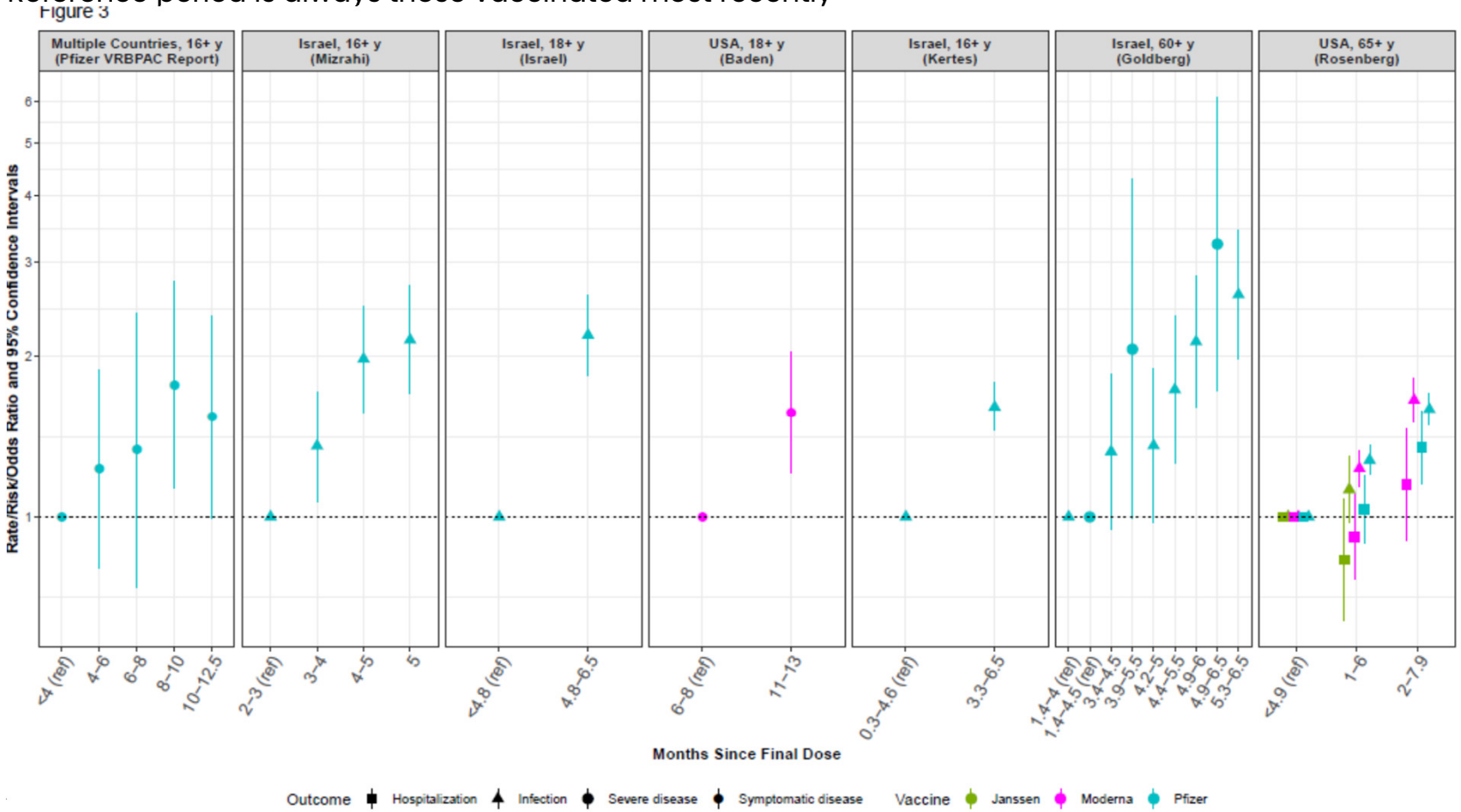
- Studies that evaluated breakthrough infections among fully vaccinated persons (e.g., infections, symptomatic, hospitalized)
- Rates of breakthrough infection stratified by time since vaccination
- Only breakthrough infection due to **Delta** variant
- Comparison of risk ratios comparing most recently vaccinated group with groups vaccinated further in the past

Analysis of breakthrough infections among vaccinated persons

- 2 studies of cross-over vaccination of placebo group in RCTs (Moderna and Pfizer)
- 4 observational studies in Israel
- 1 observational study in the U.S.A.

Risk Among Early vs Late Vaccinees

Reference period is always those vaccinated most recently



From SSRN preprint, Nov 18. will be updated slightly

Potential biases in assessing waning VE

Remaining unvaccinated persons have differential risk of exposure at high coverage in population
Earliest vaccinated group has sustained higher risk
Vaccinated persons change behavior over time in a way different to unvaccinated persons
Vaccinated persons have differential testing behavior over time relative to unvaccinated.
Vaccine-derived immunity increases among unvaccinated persons (i.e., spurious waning)
Changes in dosing interval over time

Summary

- Moderate decrease in VE in 6 months after vaccination for infection and any symptomatic disease
  - Both for Delta and for mixed variants
- Minimal decrease of VE over time against severe disease
- Waning is a likely cause of the decrease in VE, although cannot rule out bias
- Continued follow-up of VE >6 months is needed and for more vaccines
- The impact of Omicron on waning VE is not known

IVB

Extra slides

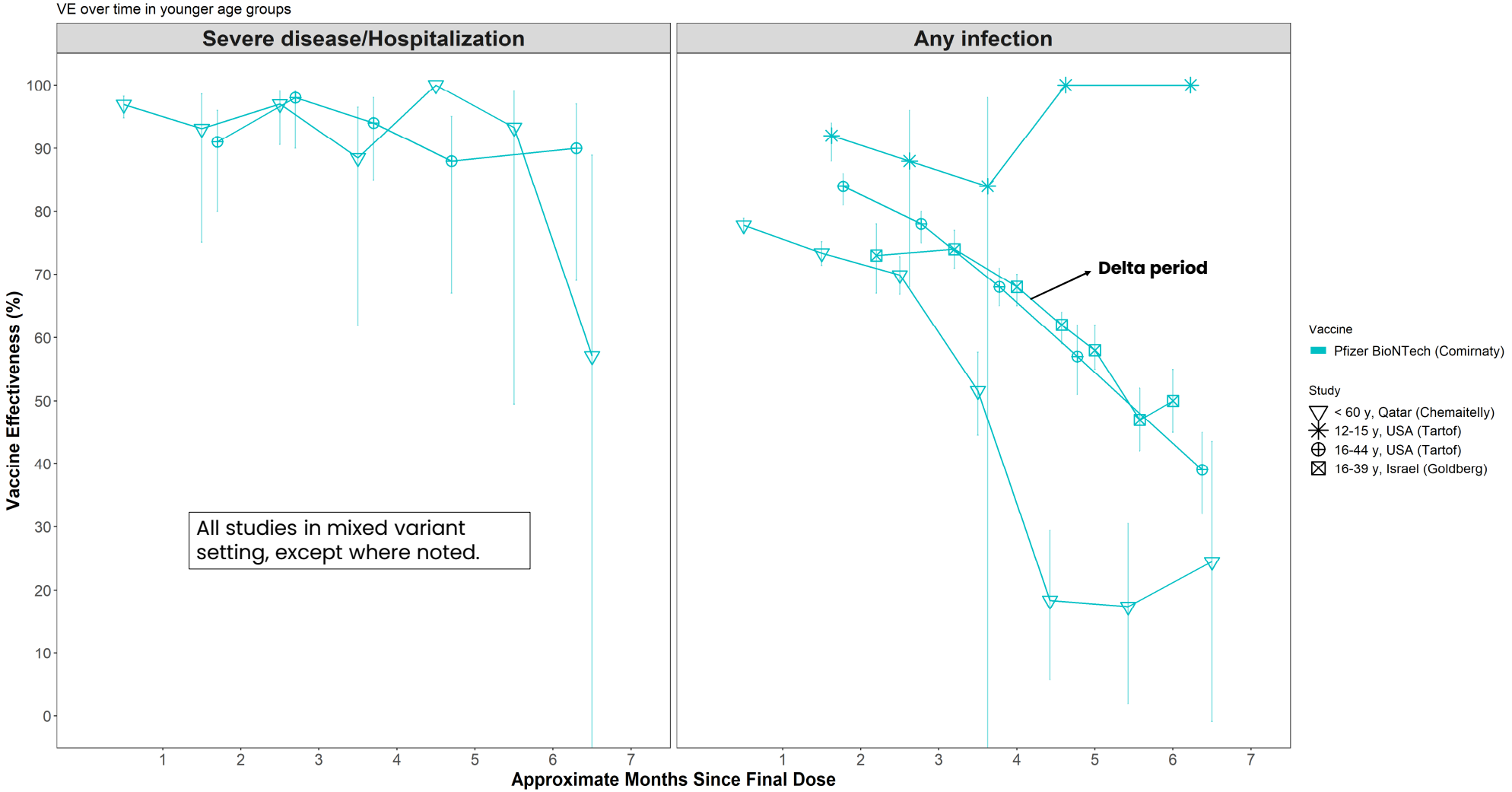
Severe disease definitions by study

Poukka	Hospitalization	
Irizarry	Hospitalization+death	Assessed together
Tenforde	1) Hospitalization, 2) Disease progression to death or invasive mechanical ventilation (among hospitalized)	
Skowronski	Hospitalization	
Lin	1) Hospitalization, 2) Death	Assessed separately
Tartof	Hospitalization	
Self	Hospitalization	
Andrews	1) Hospitalization, 2) Death	Assessed separately
Thompson	1) Hospitalization and ICU admissions, 2) ED/UC visits	ICU admission as subset of hospitalization. ED/UC visits assessed separately from hospitalizations.

Janssen	Severe/critical disease {
	Positive test in addition to any of the following criteria:
	- Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥30 breaths/minute, heart rate ≥125 beats/minute, oxygen saturation (SpO2) ≤93% on room
	air at sea level*, or partial pressure of oxygen/fraction of inspired oxygen (PaO2/FiO2)
	<300 mmHg)
	- Respiratory failure (defined as needing high-flow oxygen, non-invasive ventilation,
	mechanical ventilation, or extracorporeal membrane oxygenation [ECMO])
	-Evidence of shock (defined as systolic blood pressure <90 mmHg, diastolic blood pressure <60 mmHg, or requiring vasopressors)
	- Significant acute renal, hepatic, or neurologic dysfunction
	- ICU admission
	- Death
	}
		Evaluated by the Clinical Severity Adjudication Committee.

Chemaitelly	Severe, critical, or fatal disease, as per WHO definitions (see comment)	Severe disease definition: SARS-CoV-2 infected person with "oxygen saturation of <90% on room air, and/or respiratory rate of >30 breaths/minute in adults and children >5 years old (or ≥60 breaths/minute in children <2 months old or ≥50 breaths/minute in children 2-11 months old or ≥40 breaths/minute in children 1–5 years old), and/or signs of severe respiratory distress (accessory muscle use and inability to complete full sentences, and, in children, very severe chest wall indrawing, grunting, central cyanosis, or presence of any other general danger signs)". Critical disease definition: SARS-CoV-2 infected person with "acute respiratory distress syndrome, sepsis, septic shock, or other conditions that would normally require the provision of life sustaining therapies such as mechanical ventilation (invasive or non-invasive) or vasopressor therapy" COVID-19 death definition: death resulting from a clinically compatible illness, in a probable or confirmed COVID-19 case, unless there is a clear alternative cause of death that cannot be related to COVID-19 disease (e.g. trauma). There should be no period of complete recovery from COVID-19 between illness and death. A death due to COVID-19 may not be attributed to another disease (e.g. cancer) and should be counted independently of preexisting conditions that are suspected of triggering a severe course of COVID-19.
Goldberg	Severe disease {resting respiratory rate of more than 30 breaths per minute, oxygen saturation of less than 94% while the person was breathing ambient air, or a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen of less than 300.}	Persons who died from Covid-19 during the follow-up period were included in the study and categorized as having had severe dise

VE over time for younger adults (<60 yrs)



Meta

Meta-regression results by variant type from Nov 18 preprint

Outcome	Age group	Variant context	Vaccines evaluated	Percentage point decrease from peak VE		Decrease in % points in VE from 1 to 6 months after final dose (95% CI), p value†	
				≥10%, n (%)	≥25%, n (%)	Stratified by variant context	Combined
SARS-CoV-2 Infection	All ages	Single or non-VOC	Comirnaty (n=4), mRNA-1273 (n=3)	6 (86%)	2 (29%)	17·7 (6·2 to 37·9), p=0.003	18·5 (33·4 to 8·4) p=0·0006
		Mixture of variants	Comirnaty(n=1), mRNA-1273 (n=1), Ad26.COV2.S (n=1)	2 (66%)	0	21·4 (-7·8 to 99·5), p=0·16	
	Older adults	Single or non-VOC	Comirnaty (n=1), mRNA-1273 (n=1)	2 (100%)	0	31·9 (7·6 to 100), p=0·11	19·9 (36.7 to 9.2) p=0·0007
		Mixture of variants	Comirnaty (n=4), mRNA-1273 (n=2)	5 (83%)	2 (33%)	17·1 (6·0 to 35·7), p=0·004	
COVID-19 Symptomatic Disease	All ages	Single or non-VOC	Comirnaty (n=1), mRNA-1273 (n=1), AstraZeneca-Vaxzevria (n=1)	2 (66%)	0	22·5 (-6·6 to 100), p=0·12	25·4 (42.4 to 13.7) p<0·0001
		Mixture of variants	Comirnaty (n=3), mRNA-1273 (n=2), Vaxzevria (n=1), Ad26.COV2.S (n=2)	8 (100%)	4 (57%)	28·8 (12·4 to 56·5), p=0·0007	
	Older adults	Single or non-VOC	Comirnaty (n=1), Vaxzevria (n=1)	2 (100%)	0	27·2 (-20·2 to 100), p=0·14	32·0 (69.0 to 11.0) p=0·0002
		Mixture of variants	Comirnaty (n=1), mRNA-1273 (n=1), Ad26.COV2.S (n=1)	3 (100%)	3 (100%)	36·1 (16·3 to 70·5), p=0·007	
COVID-19 Severe Disease	All ages	Single or non-VOC	Comirnaty (n=3), mRNA-1273 (n=2), Vaxzevria (n=1)	2 (33%)	0	6·5 (2·1 to 16·0), p=0·004	8·0 (15.2 to 3.6) p=0·0002
		Mixture of variants	Comirnaty (n=4), mRNA-1273 (n=2), Ad26.COV2.S (n=2)	4 (50%)	2 (25%)	9·1 (2·5 to 20·3), p=0·007	
	Older adults‡	Single or non-VOC	Comirnaty (n=3), mRNA-1273 (n=1), Vaxzevria (n=1)	2 (40%)	0	11·8 (3·5 to 28·3), p=0·008	9·7 (14.7 to 5.9) p<0·0001
		Mixture of variants	Comirnaty (n=5), mRNA-1273 (n=3), Ad26.COV2.S (n=1)	3 (38%)	2 (25%)	8·1 (2·7 to 17·2), p=0·003	