Effectiveness of Covid-19 vaccines in ambulatory and inpatient care settings, by Thompson, *et al.*

Nadja Vielot, PhD – University of North Carolina

Cindy Zhou, PhD – US Food and Drug Administration

Celebrating 1 year of ISPE-BC Journal Club!

Special thanks to:

- BC: Fred Varricchio, Bob Chen, Emalee Martin
- ISPE: Cathy Panozzo, Bradley Layton, Jen Gerber, Cindy Zhou
- Journal club leaders: Victoria Abbing

Please share your ideas for papers and special events!

Upcoming events

- Seeking volunteers!
- Vaccine safety lectures/discussions
  - Safety definition working group members
- ISPE events open to BC membership

Coming full circle!

- October 7, 2020: Alternative observational designs to estimate the effectiveness of one dose of oral cholera vaccine in Lusaka, Zambia
  - Focus on test negative design

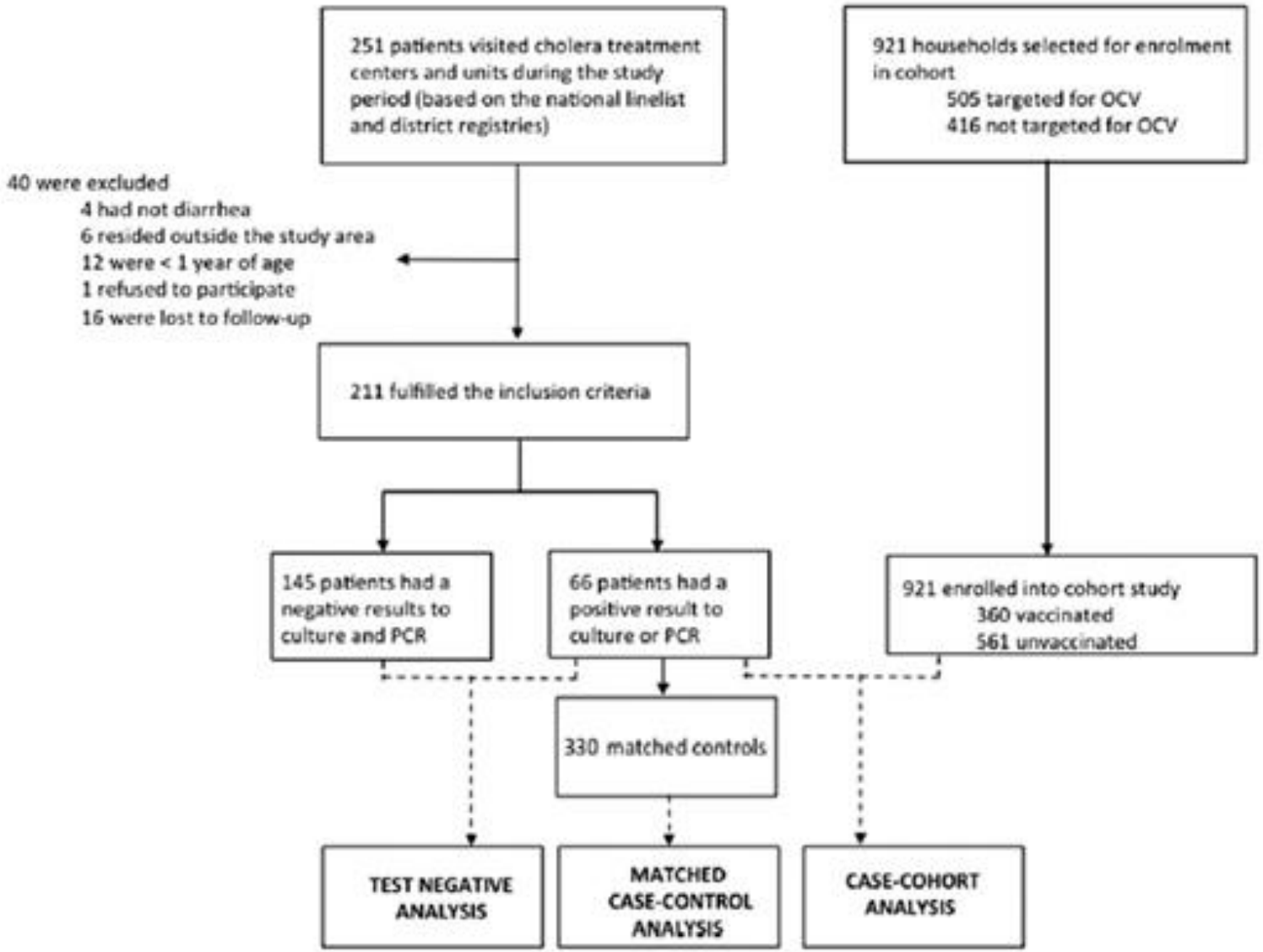


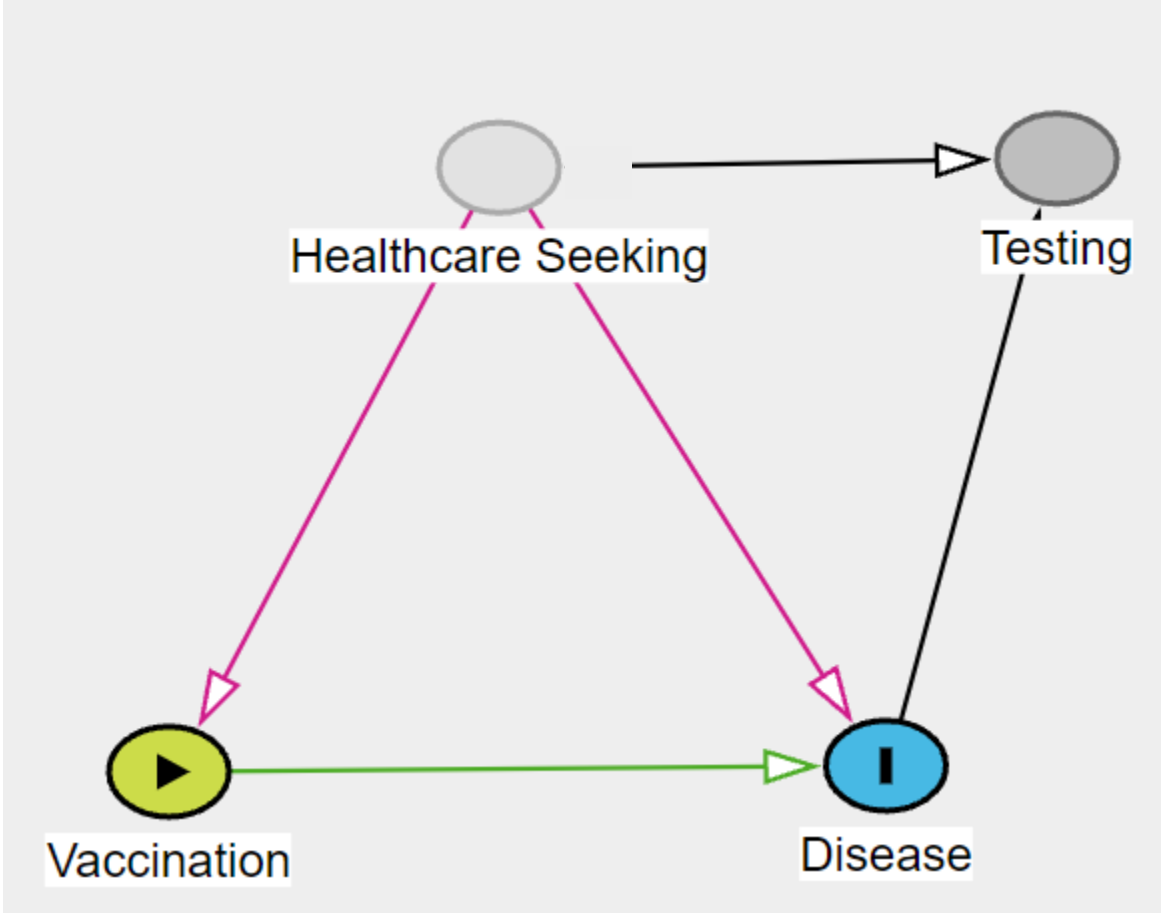
Fig. 2. Study flowchart.

Test Negative Case Control

- **Strategy**
- Controls selected from those who test negative for the disease

- **Pros/Cons**
- More efficient in outbreak settings
- Controls for healthcare utilization, catchment areas, geographical factors, but not completely
- Limited external validity
- Classification dependent on test characteristics

Selection bias in test-negative studies



Sullivan SG, Tchetgen Tchetgen EJ, Cowling BJ. Theoretical Basis of the Test-Negative Study Design for Assessment of Influenza Vaccine Effectiveness. Am J Epidemiol. 2016;184(5):345-353. doi:10.1093/aje/kww064
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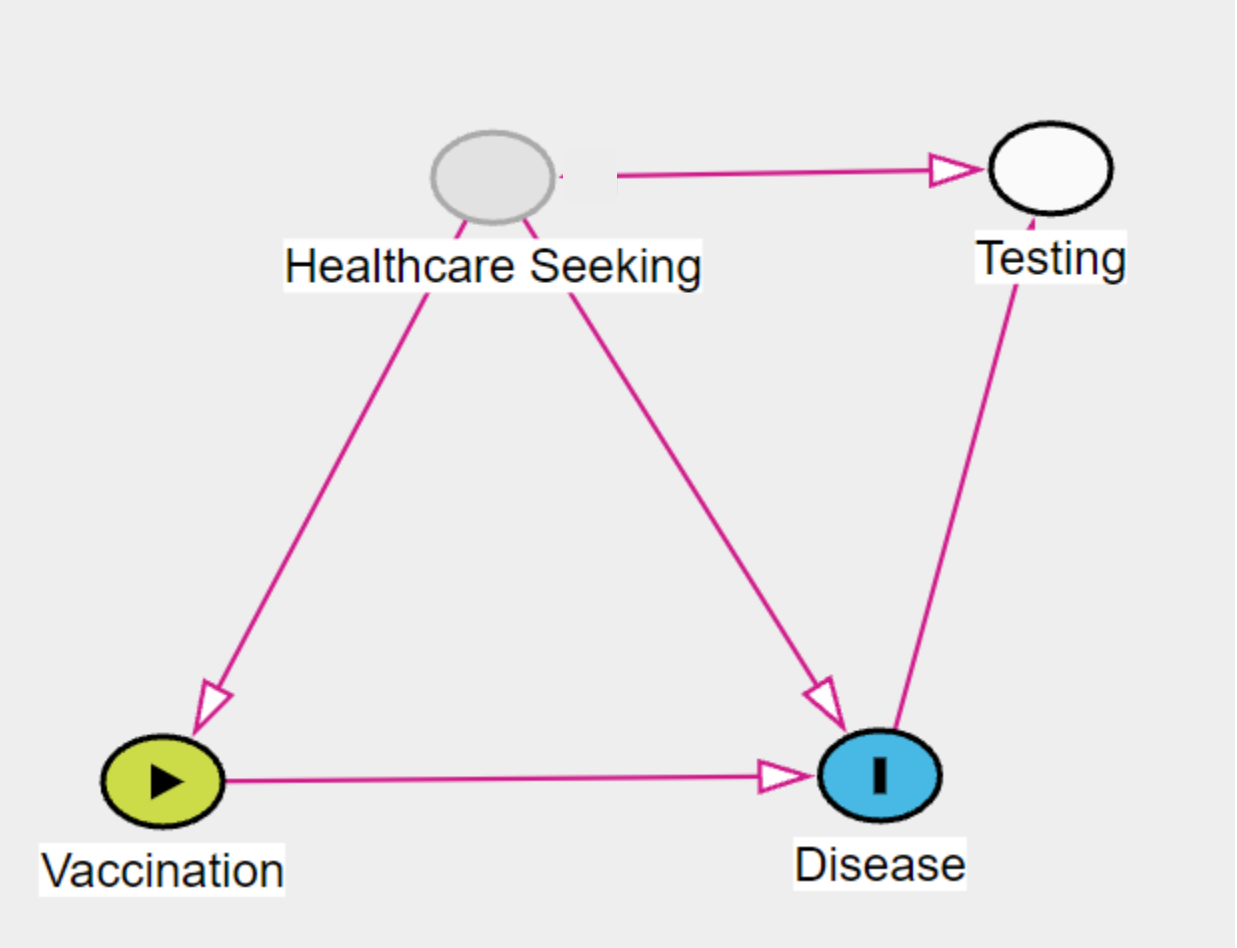

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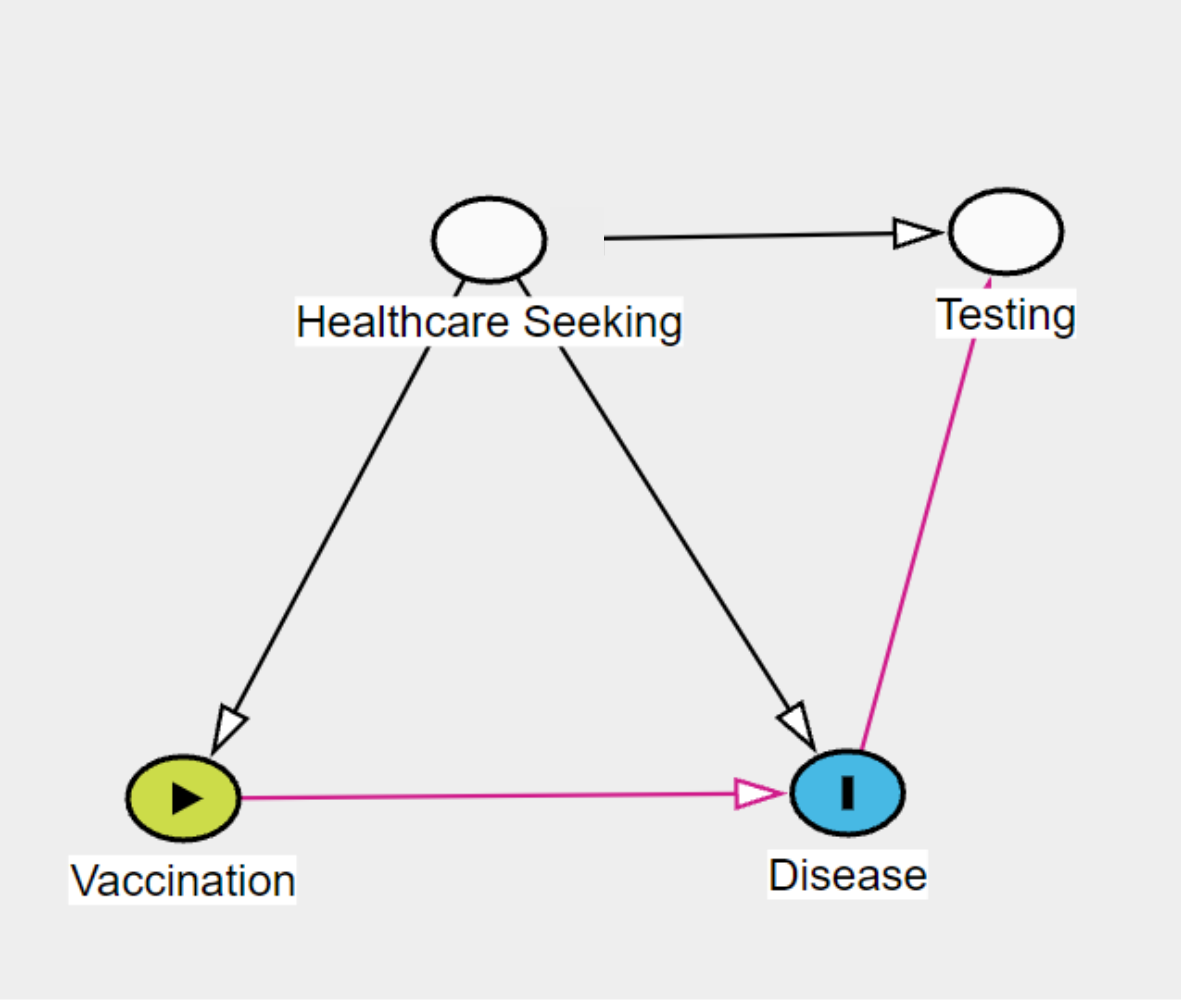

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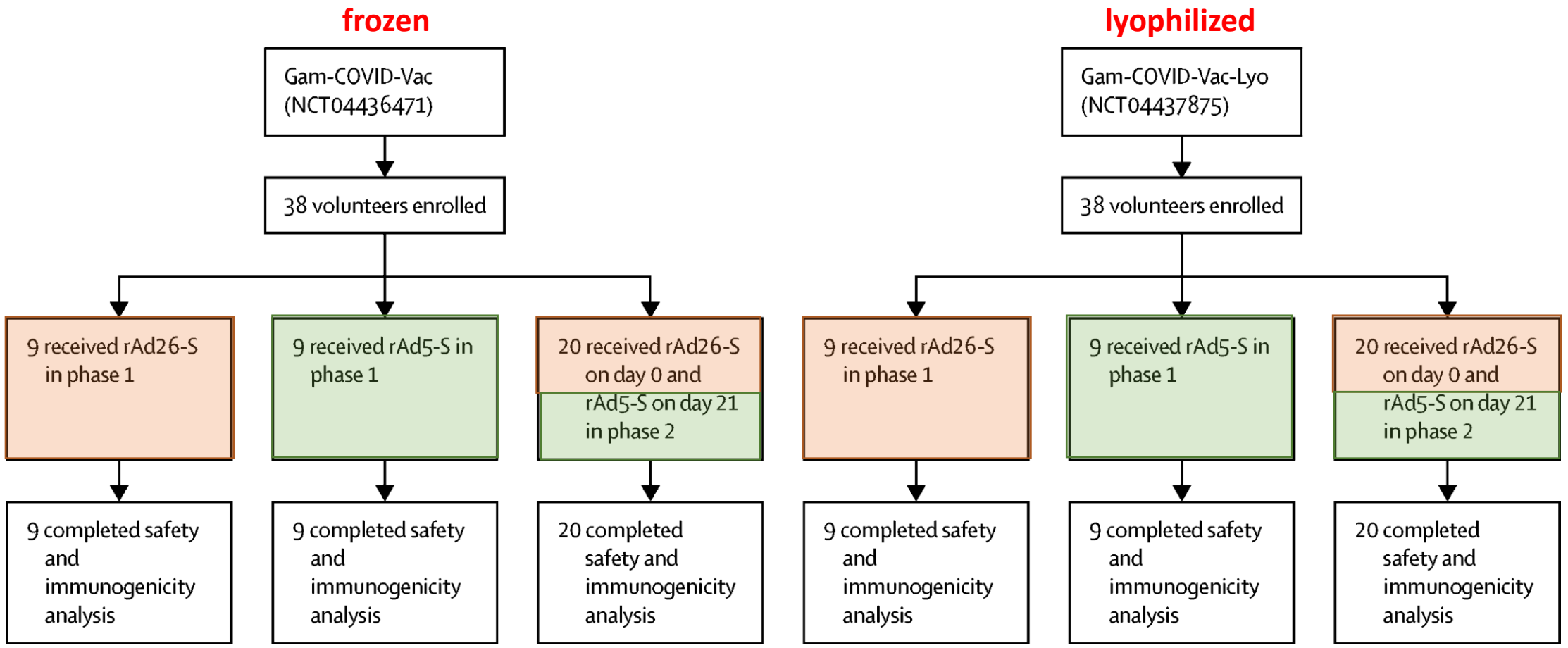
Coming full circle!

- January 6, 2021: Safety and immunogenicity of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine in two formulations: two open, non-randomised phase 1/2 studies from Russia
  - Covid-19 vaccines go live with lots of new RCT data

Sputnik V clinical trial schematic



Leading vaccines

Developer	How It Works	Phase	Status
Pfizer-BioNTech	mRNA	2 3	Approved in U.S., other countries. Emergency use in E.U., other countries.
Moderna	mRNA	3	Approved in Switzerland. Emergency use in U.S., E.U., other countries.
Gamaleya	Ad26, Ad5	3	Emergency use in Russia, other countries.
Oxford-AstraZeneca	ChAdOx1	2 3	Approved in Brazil. Emergency use in U.K., E.U., other countries.
CanSino	Ad5	3	Approved in China. Emergency use in other countries.
Johnson & Johnson	Ad26	3	Emergency use in U.S., E.U., other countries.
Vector Institute	Protein	3	Approved in Turkmenistan. Early use in Russia.
Novavax	Protein	3	
Sinopharm	Inactivated	3	Approved in China, U.A.E., Bahrain. Emergency use in other countries.
Sinovac	Inactivated	3	Approved in China. Emergency use in other countries.
Sinopharm-Wuhan	Inactivated	3	Approved in China. Limited use in U.A.E.
Bharat Biotech	Inactivated	3	Emergency use in India, other countries.

https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html

Coming full circle!

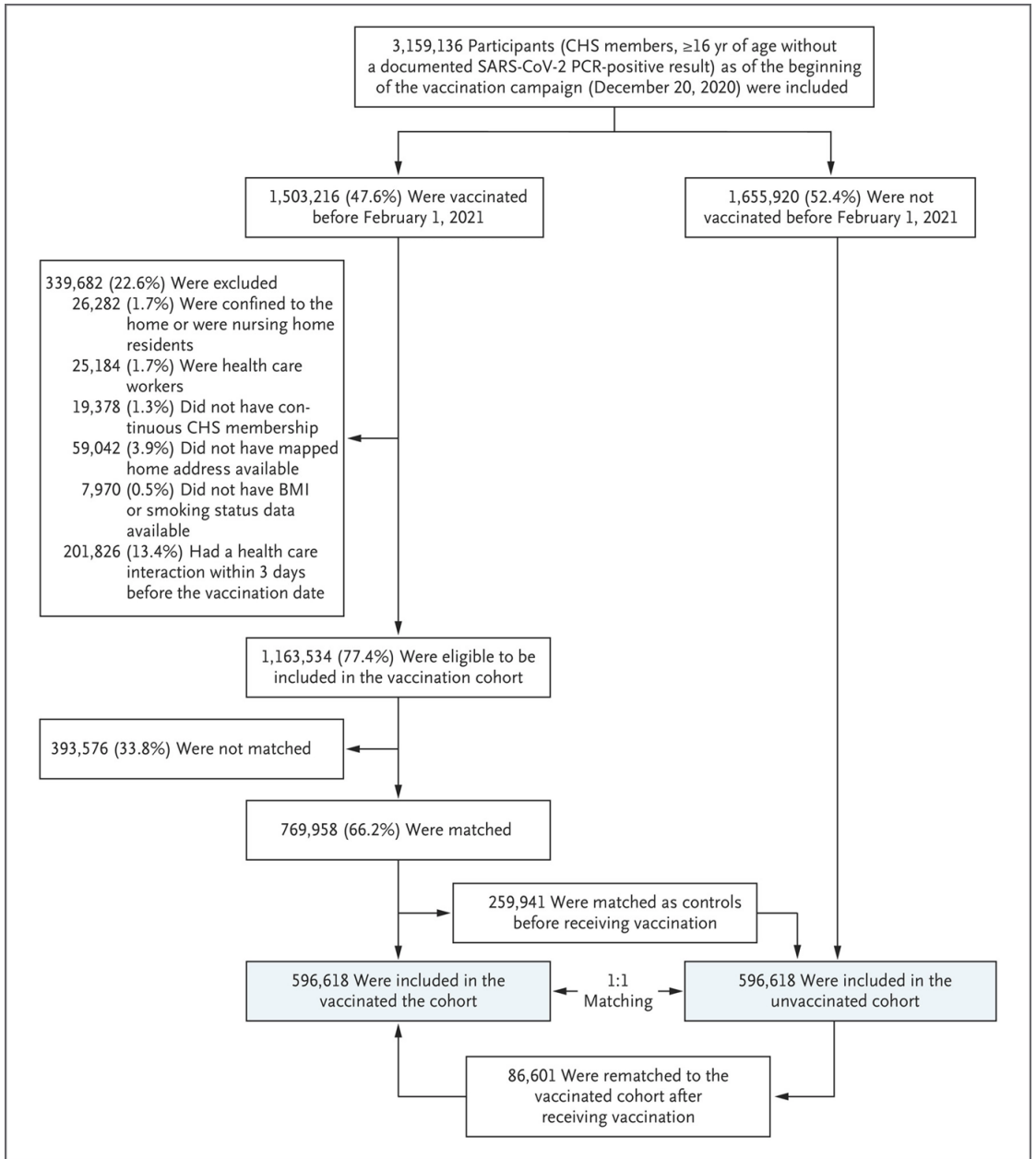
- April 7, 2021: BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting
  - Importance of real-world data (RWD) for real-world evidence (RWE)

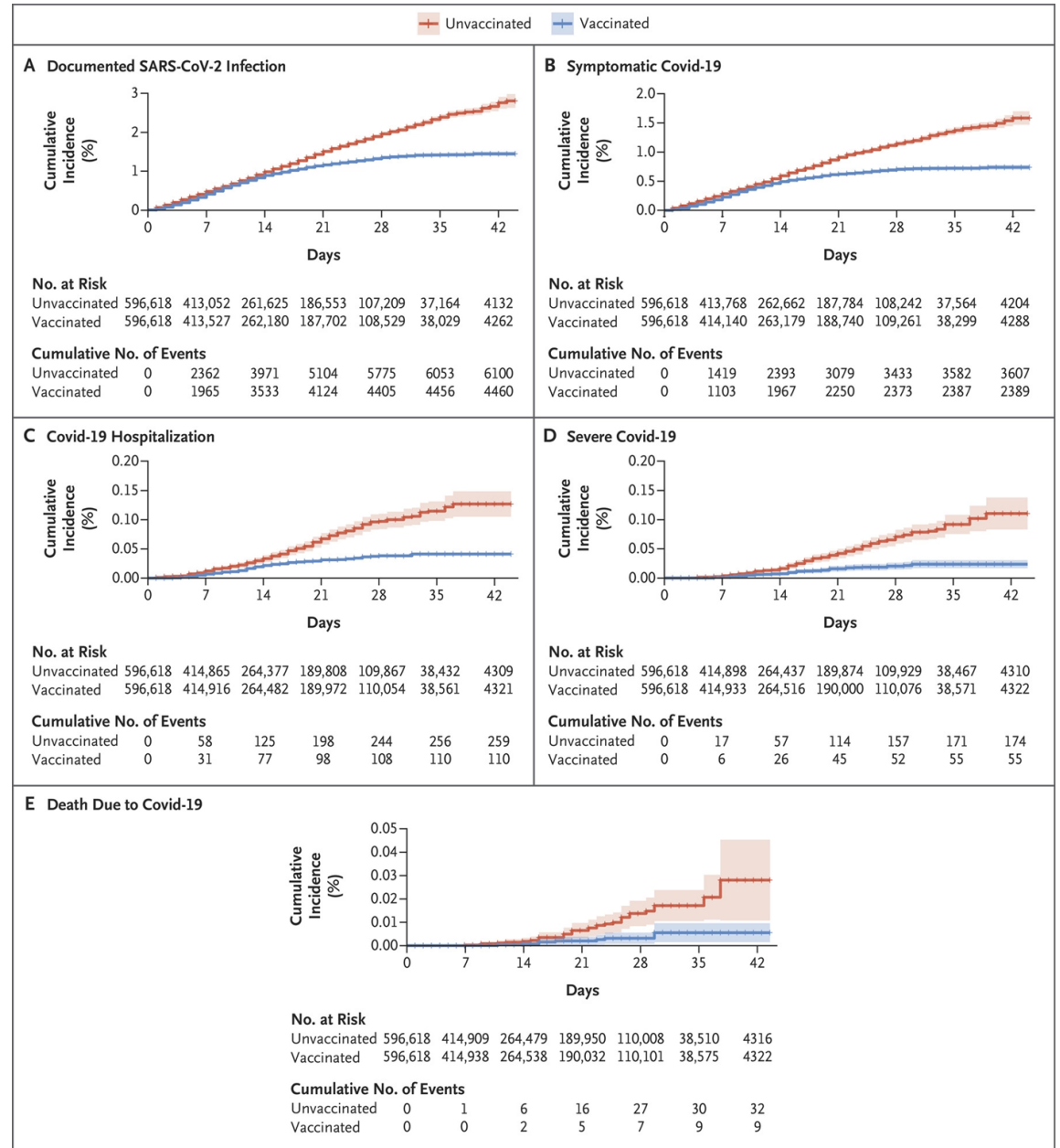
Real-Word Data for Real-World Evidence

- “Real-world data are the data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.” (FDA)
  - Electronic health records
  - Claims and billing data
  - Registries
- RWD → RWE
- RWE plays an increasingly important role in development and regulation of vaccines

“https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence

Clalit Health Services Data





Clalit Health Services Data

Table 2. Estimated Vaccine Effectiveness against Covid-19 Outcomes during Three Time Periods.*

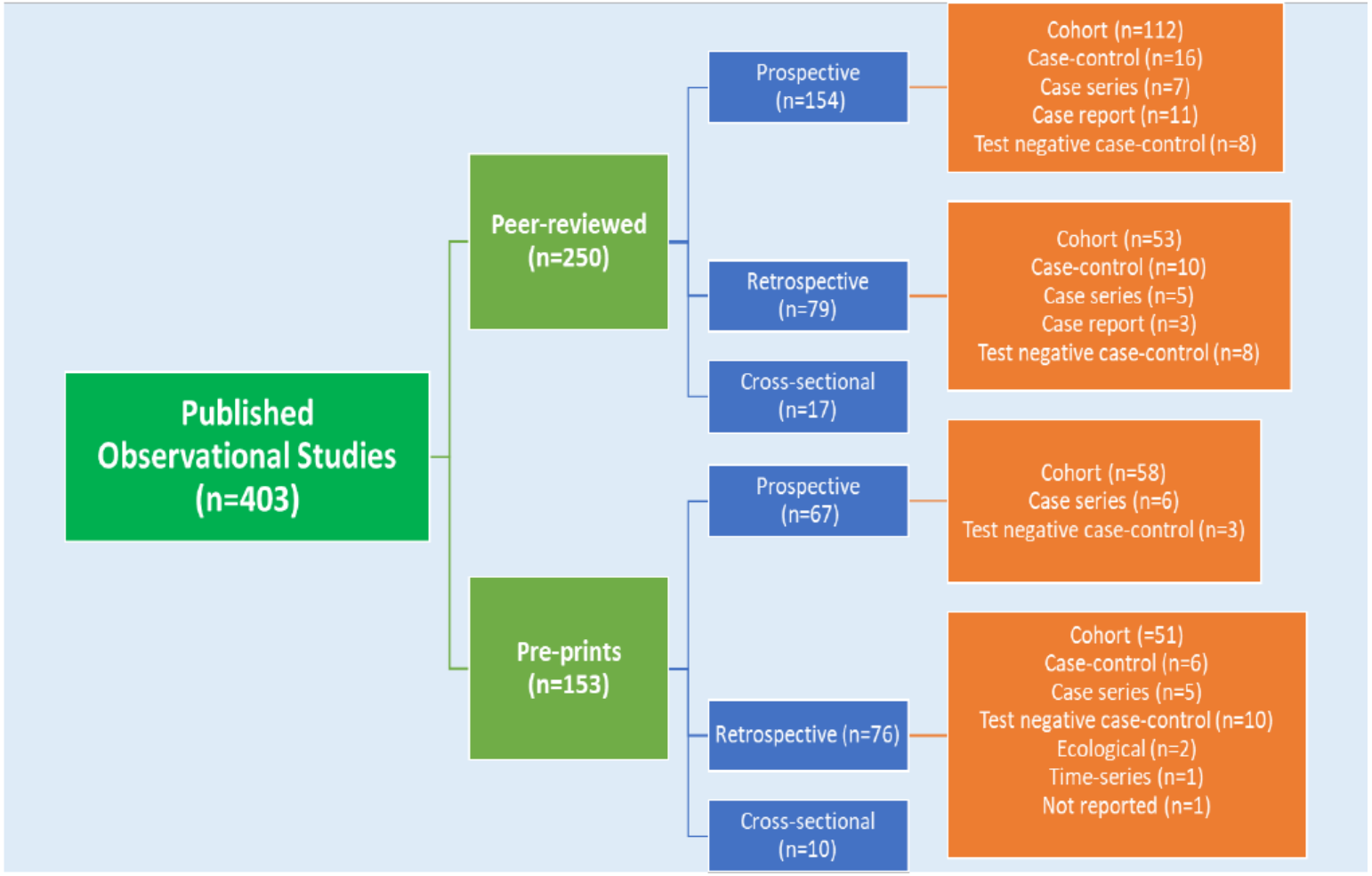
Period	Documented Infection		Symptomatic Illness		Hospitalization		Severe Disease		Death	
	1–RR	Risk Difference	1–RR	Risk Difference	1–RR	Risk Difference	1–RR	Risk Difference	1–RR	Risk Difference
	% (95% CI)	*no./1000 persons (95% CI)*	% (95% CI)	*no./1000 persons (95% CI)*	% (95% CI)	*no./1000 persons (95% CI)*	% (95% CI)	*no./1000 persons (95% CI)*	% (95% CI)	*no./1000 persons (95% CI)*
14 to 20 days after first dose	46 (40–51)	2.06 (1.70–2.40)	57 (50–63)	1.54 (1.28–1.80)	74 (56–86)	0.21 (0.13–0.29)	62 (39–80)	0.14 (0.07–0.21)	72 (19–100)	0.03 (0.01–0.07)
21 to 27 days after first dose	60 (53–66)	2.31 (1.96–2.69)	66 (57–73)	1.34 (1.09–1.62)	78 (61–91)	0.22 (0.13–0.31)	80 (59–94)	0.18 (0.10–0.27)	84 (44–100)	0.06 (0.02–0.11)
7 days after second dose to end of follow-up	92 (88–95)	8.58 (6.22–11.18)	94 (87–98)	4.61 (3.29–6.53)	87 (55–100)	0.22 (0.08–0.39)	92 (75–100)	0.32 (0.13–0.52)	NA	NA

* Confidence intervals were estimated using the percentile bootstrap method with 500 repetitions. Estimates were calculated only for cells with more than 10 instances of an outcome across the two groups. NA denotes not available, and RR risk ratio.

Coming full circle!

- October 6, 2021: Effectiveness of Covid-19 vaccines in ambulatory and inpatient care settings
  - All of the above!

Landscape of observational study designs on the effectiveness of COVID-19 vaccination

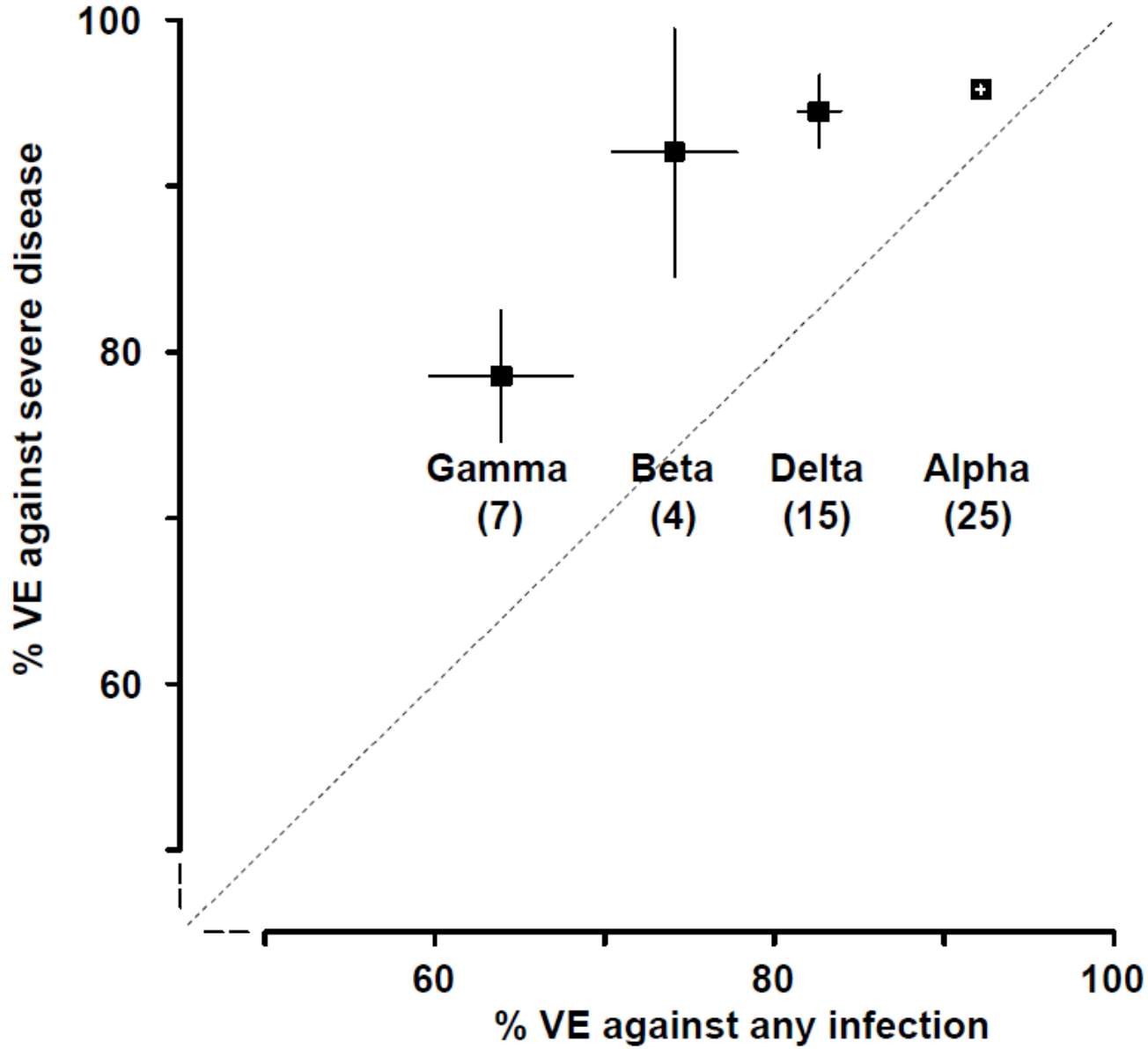


https://www.who.int/publications/m/item/draft-landscape-of-observational-study-designs-on-the-effectiveness-of-covid-19-vaccination

Landscape of observational study designs on the effectiveness of COVID-19 vaccination

- Case reports/Case series?
  - Immunogenicity studies
  - Reports of breakthrough infections
  - Lab studies

Efficacy by viral variant



https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-september-17-2021-meeting-announcement#event-materials

Effectiveness of Covid-19 Vaccines in Ambulatory and Inpatient Care Settings

10/6/2021

ISPE VAXSIG & Brighton Collaboration Joint Journal Club

Nadja Vielot (UNC-CH)

Cindy Zhou (FDA-CBER-OBE)

Thompson MG, Stenehjem E, Grannis S, et al. Effectiveness of Covid-19 Vaccines in Ambulatory and Inpatient Care Settings [published online ahead of print, 2021 Sep 8]. N Engl J Med. 2021;NEJMoa2110362. doi:10.1056/NEJMoa2110362

Disclaimer

- Cindy Zhou is an employee of the FDA. The views expressed in this presentation are those of the presenter and do not necessarily reflect those of the FDA.

Study Population

- Adults (≥50 years of age) with Covid-19–like illness who underwent molecular testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).
  - Covid-19–like illness: A clinical diagnosis of acute respiratory illness or signs or symptoms that have been associated with Covid-19 in previous studies.
  - Covid-19–like illness using discharge codes.

Study Period

- January 1 through June 22, 2021

The highly contagious delta variant accounts for 52% (45%-59%) of COVID-19 cases in the U.S. by June 20, 2021, according to CDC. https://covid.cdc.gov/covid-data-tracker/#variant-proportions

Data Sources

- VISION network: 7 U.S. health care systems and research centers with integrated medical, laboratory, and vaccination records.
  - Columbia University Irving Medical Center (CUIMC; New York)
  - HealthPartners Institute (Minnesota and Wisconsin)
  - Intermountain Healthcare (Utah)
  - Kaiser Permanente Northern California (KPNC)
  - Kaiser Permanente Northwest Center for Health Research (KPNW; Oregon and Washington)
  - Regenstrief Institute (Indiana)
  - University of Colorado

Outcomes

- Hospitalization lasting more than 24 hours
- ICU admission (as a subset of hospitalization)
- Emergency department or urgent care clinic visit (ED/UC)

associated with laboratory-confirmed SARS-CoV-2 infection within 14 days before and up to 72-hours after (i.e., 17 days) the hospital admission or ED/UC encounter date. (sup p. 83)

  - Patients tested using only a non-molecular assay (e.g., rapid SARS-CoV-2 antigen test) were excluded.
  - Hierarchy rule was used if multiple tests occurred in the 17-day window.

Exposure/Vaccination Status

- The patients' vaccination status was documented in electronic health records and immunization registries (CUIMC by a city registry).
- Full series or partially vaccinated

Study Design

- Test-negative design to estimate vaccine effectiveness by comparing the odds of a positive test for SARS-CoV-2 infection among vaccinated patients with those among unvaccinated patients.

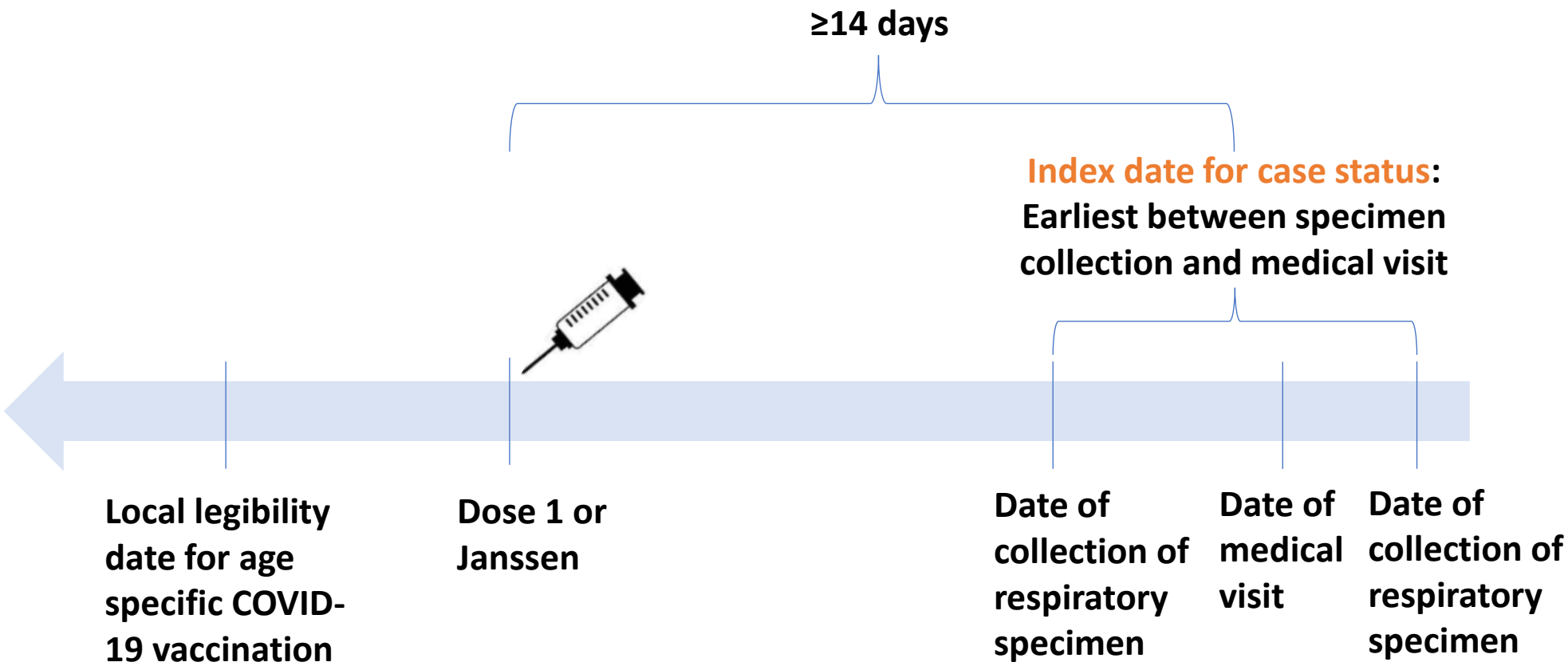
Cases vs. Controls

Cases	Controls
• ≥1 qualified CLI diagnosis either at hospital discharge or associated with the ED/UC medical event; AND • ≥1 positive result from a qualified test during the 17-day window.	• ≥1 qualified CLI diagnosis either at hospital discharge or associated with the ED/UC medical event; AND • Negative result from a qualified test during the 17-day window.

Inclusion/Exclusion Criteria

- Inclusion criteria:
  - Medical encounters that occurred since January 1, 2021, among adults (aged ≥50 years) with a qualified COVID-like illness (CLI) diagnosis
  - A positive or negative result from a molecular SARS-CoV-2 laboratory test within the 14 days before and up to 72-hours after the hospital admission or Emergency Department or Urgent Care (ED/UC) encounter
  - An opportunity to be at least partially vaccinated on the index date (defined as 14 days after the partner-specific date of when vaccines became widely available to adults in each age group).
- Exclusion criteria:
  - Medical events were also excluded if no molecular SARS-CoV-2 testing was performed within 14 days to 72-hours after admission or if they occurred in patients who received a first dose of a COVID-19 vaccine

Study Design



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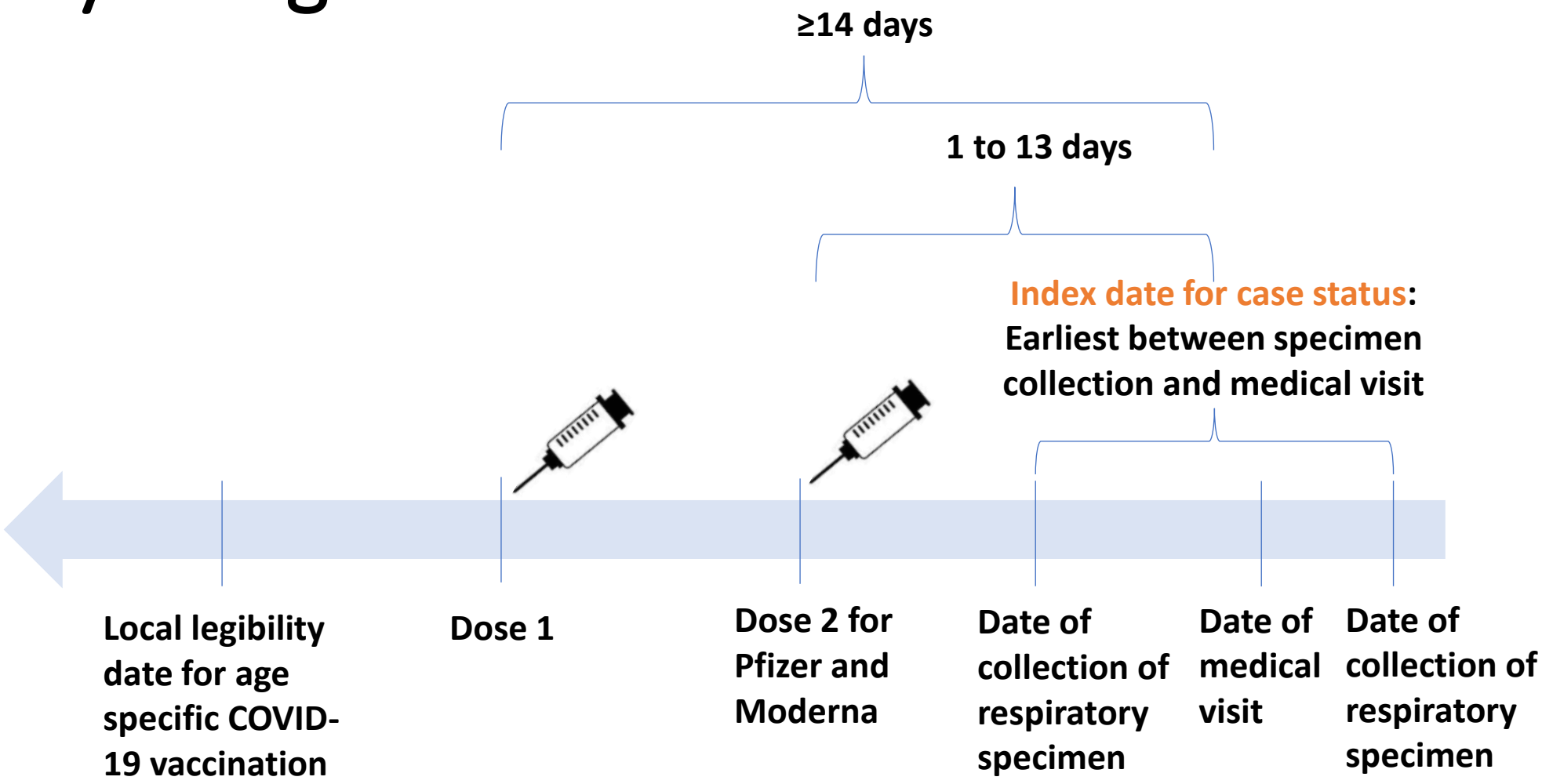

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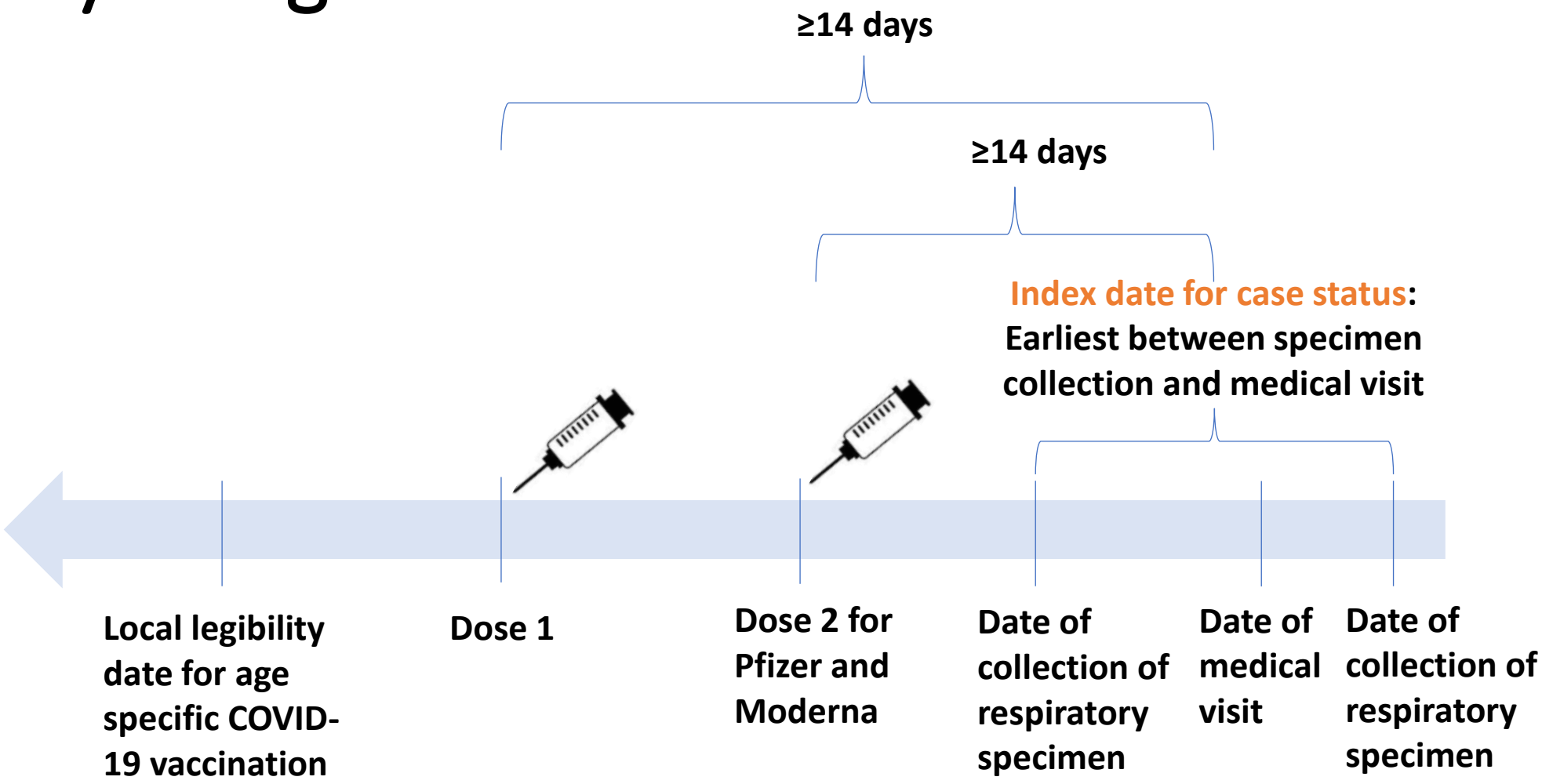


Statistical Analysis

- Multivariable logistic-regression models adjusted with weights based on propensity-for-vaccination scores and according to age, geographic region, calendar time (days from January 1, 2021, to the index date for each medical visit), and local virus circulation.
  - Propensity-for-vaccination scores
  - Local SARS-CoV-2 circulation on the day of each medical visit, the 7-day moving average of the percentage of RT-PCR tests that were SARS-CoV-2–positive within each of the 36 geographic subregions was extracted from public health records

Secondary/Sensitivity Analysis

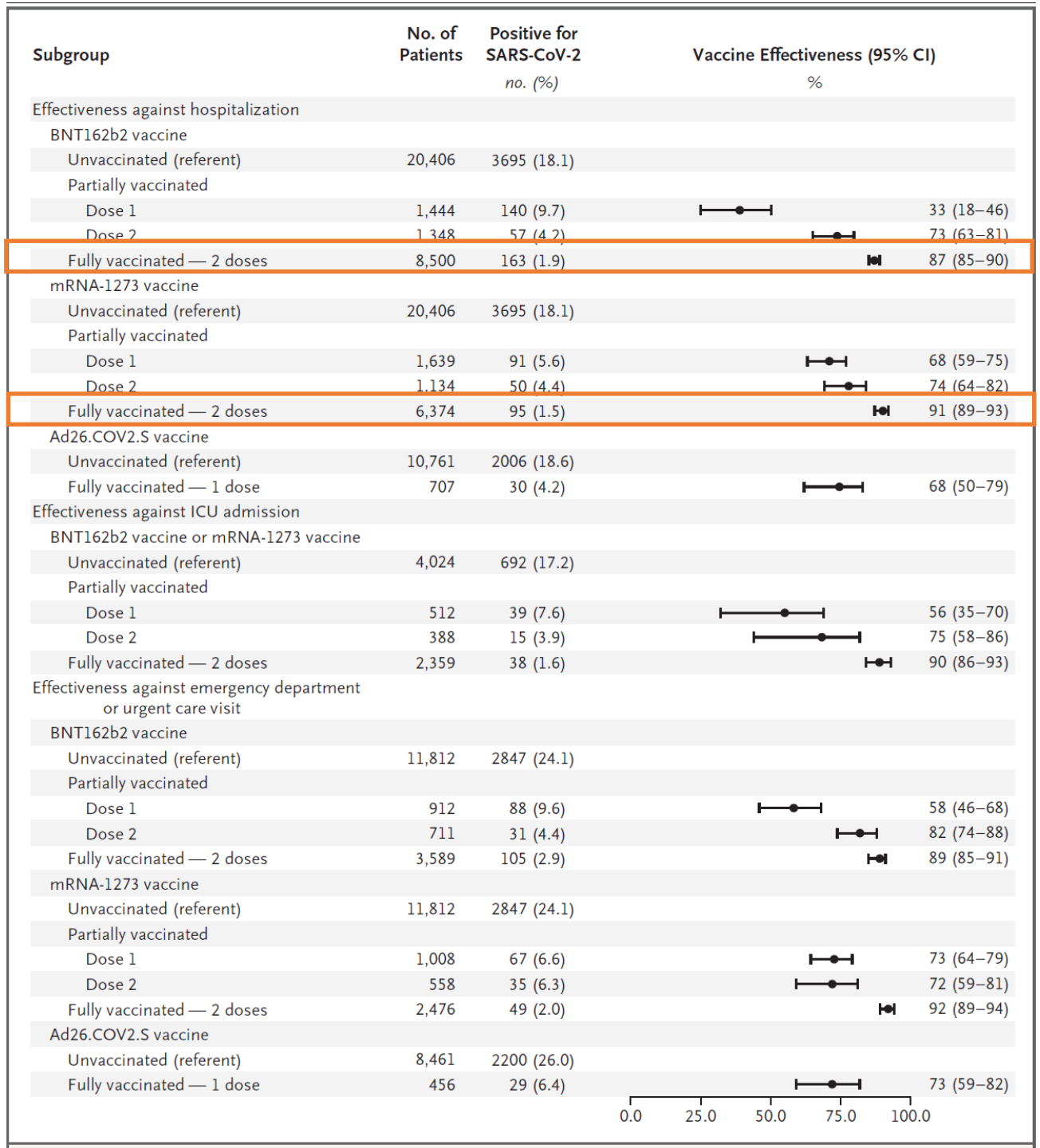
- Vaccine effectiveness was estimated for patients at 14-day intervals after each dose of vaccine
  - Negative control: VE among Patients who received dose 1 <14 days before the index date should approach zero in an unbiased model.
- Sensitivity analysis:
  - Stratified by network partner
  - Restricted to first or primary diagnosis code to identify CLI
  - Excluded patients with any SARS-CoV-2–positive result on molecular or antigen assays more than 14 days before the index date
  - Calculated inverse weights that accounted for both the propensity to be vaccinated and the propensity to be tested

Results

Table 2. Characteristics of the Patients According to SARS-CoV-2 Test Results and Vaccination Status.*

Characteristic	All Visits	Assay for SARS-CoV-2		Standardized Mean Difference†	Vaccination Status‡					Standardized Mean Difference§
		Negative	Positive		Unvaccinated	Partial, 1 Dose of mRNA Vaccine	Partial, 2 Doses of mRNA Vaccine	Full, 2 Doses of mRNA Vaccine	Full, Ad26.COV2.S Vaccine	
	number (percent of all visits)				*number (percent of all visits)*					
Hospitalization										
All hospitalizations	41,552 (100)	37,231 (90)	4321 (10)	−0.13	20,406 (49)	3083 (7)	2482 (6)	14,874 (36)	707 (2)	0.05
First	40,367 (97)	36,096 (89)	4271 (11)		19,903 (49)	3003 (7)	2456 (6)	14,361 (36)	644 (2)	
Repeat	1,185 (3)	1,135 (96)	50 (4)		503 (42)	80 (7)	26 (2)	513 (43)	63 (5)	
ED or urgent care visit										
All ED or urgent care visits	21,522 (100)	18,271 (85)	3251 (15)	0.09	11,812 (55)	1920 (9)	1269 (6)	6,065 (28)	456 (2)	0.00
First	18,537 (86)	15,822 (85)	2715 (15)		10,190 (55)	1688 (9)	1088 (6)	5,181 (28)	390 (2)	
Repeat	2,985 (14)	2,449 (82)	536 (18)		1,622 (54)	232 (8)	181 (6)	884 (30)	66 (2)	
Medical setting				0.00						0.14
ED	18,375 (85)	15,598 (85)	2777 (15)		10,351 (56)	1582 (9)	1069 (6)	5,000 (27)	373 (2)	
Urgent care clinic	3,147 (15)	2,673 (85)	474 (15)		1,461 (46)	338 (11)	200 (6)	1,065 (34)	83 (3)	

Main Results (Fig 1)



Subgroup	No. of Patients	Positive for SARS-CoV-2 no. (%)	Vaccine Effectiveness (95% CI) %
Effectiveness against hospitalization			
BNT162b2 vaccine			
Unvaccinated (referent)	20,406	3695 (18.1)	
Partially vaccinated			
Dose 1	1,444	140 (9.7)	33 (18–46)
Dose 2	1,348	57 (4.2)	73 (63–81)
Fully vaccinated — 2 doses	8,500	163 (1.9)	87 (85–90)
mRNA-1273 vaccine			
Unvaccinated (referent)	20,406	3695 (18.1)	
Partially vaccinated			
Dose 1	1,639	91 (5.6)	68 (59–75)
Dose 2	1,134	50 (4.4)	74 (64–82)
Fully vaccinated — 2 doses	6,374	95 (1.5)	91 (89–93)
Ad26.COV2.S vaccine			
Unvaccinated (referent)	10,761	2006 (18.6)	
Fully vaccinated — 1 dose	707	30 (4.2)	68 (50–79)
Effectiveness against ICU admission			
BNT162b2 vaccine or mRNA-1273 vaccine			
Unvaccinated (referent)	4,024	692 (17.2)	
Partially vaccinated			
Dose 1	512	39 (7.6)	56 (35–70)
Dose 2	388	15 (3.9)	75 (58–86)
Fully vaccinated — 2 doses	2,359	38 (1.6)	90 (86–93)
Effectiveness against emergency department or urgent care visit			
BNT162b2 vaccine			
Unvaccinated (referent)	11,812	2847 (24.1)	
Partially vaccinated			
Dose 1	912	88 (9.6)	58 (46–68)
Dose 2	711	31 (4.4)	82 (74–88)
Fully vaccinated — 2 doses	3,589	105 (2.9)	89 (85–91)
mRNA-1273 vaccine			
Unvaccinated (referent)	11,812	2847 (24.1)	
Partially vaccinated			
Dose 1	1,008	67 (6.6)	73 (64–79)
Dose 2	558	35 (6.3)	72 (59–81)
Fully vaccinated — 2 doses	2,476	49 (2.0)	92 (89–94)
Ad26.COV2.S vaccine			
Unvaccinated (referent)	8,461	2200 (26.0)	
Fully vaccinated — 1 dose	456	29 (6.4)	73 (59–82)

Main Results (Fig 1)

Full two dose mRNA-based vaccination, effectiveness=89% (87%, 91%)

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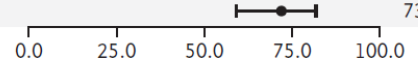

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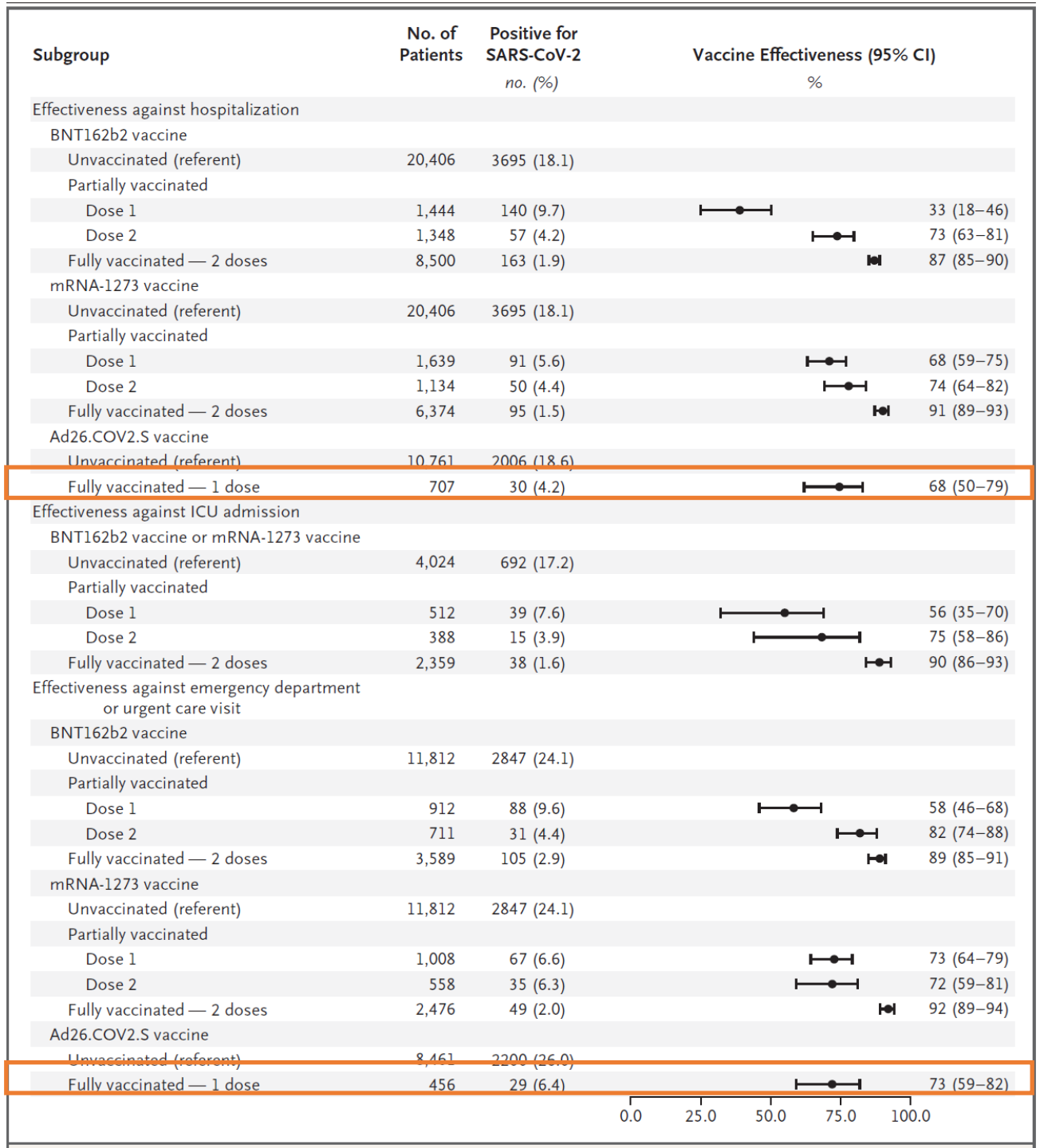

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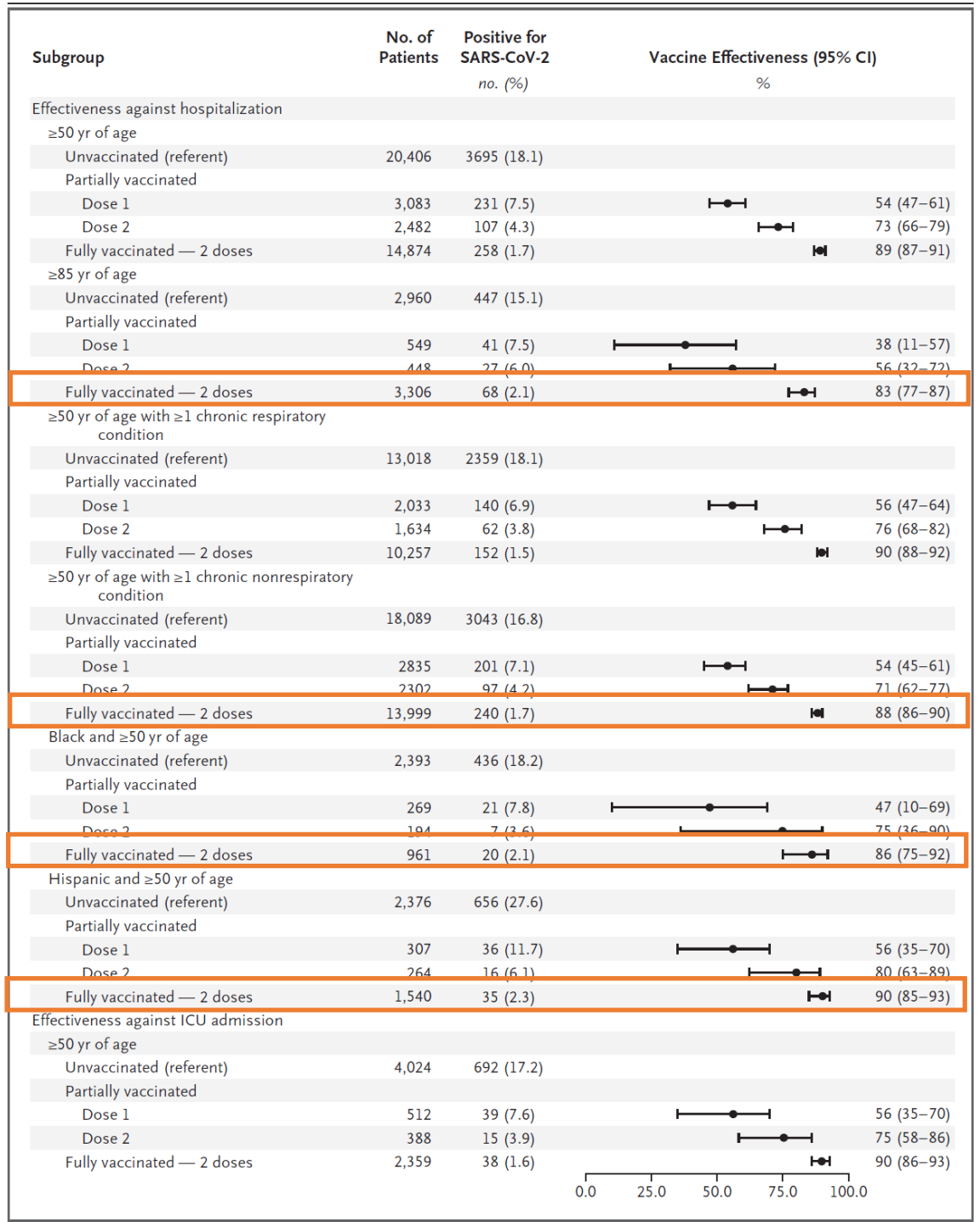
Fully vaccinated — 1 dose	456	29 (6.4)	73 (59–82)

Results according to age, race or ethnic group, and underlying medical conditions (Fig 2)



Subgroup	No. of Patients	Positive for SARS-CoV-2	Vaccine Effectiveness (95% CI)
		no. (%)	%
Effectiveness against hospitalization			
≥50 yr of age			
Unvaccinated (referent)	20,406	3695 (18.1)	
Partially vaccinated			
Dose 1	3,083	231 (7.5)	54 (47–61)
Dose 2	2,482	107 (4.3)	73 (66–79)
Fully vaccinated — 2 doses	14,874	258 (1.7)	89 (87–91)
≥85 yr of age			
Unvaccinated (referent)	2,960	447 (15.1)	
Partially vaccinated			
Dose 1	549	41 (7.5)	38 (11–57)
Dose 2	448	27 (6.0)	56 (32–72)
Fully vaccinated — 2 doses	3,306	68 (2.1)	83 (77–87)
≥50 yr of age with ≥1 chronic respiratory condition			
Unvaccinated (referent)	13,018	2359 (18.1)	
Partially vaccinated			
Dose 1	2,033	140 (6.9)	56 (47–64)
Dose 2	1,634	62 (3.8)	76 (68–82)
Fully vaccinated — 2 doses	10,257	152 (1.5)	90 (88–92)
≥50 yr of age with ≥1 chronic nonrespiratory condition			
Unvaccinated (referent)	18,089	3043 (16.8)	
Partially vaccinated			
Dose 1	2835	201 (7.1)	54 (45–61)
Dose 2	2302	97 (4.2)	71 (62–77)
Fully vaccinated — 2 doses	13,999	240 (1.7)	88 (86–90)
Black and ≥50 yr of age			
Unvaccinated (referent)	2,393	436 (18.2)	
Partially vaccinated			
Dose 1	269	21 (7.8)	47 (10–69)
Dose 2	194	7 (3.6)	75 (36–90)
Fully vaccinated — 2 doses	961	20 (2.1)	86 (75–92)
Hispanic and ≥50 yr of age			
Unvaccinated (referent)	2,376	656 (27.6)	
Partially vaccinated			
Dose 1	307	36 (11.7)	56 (35–70)
Dose 2	264	16 (6.1)	80 (63–89)
Fully vaccinated — 2 doses	1,540	35 (2.3)	90 (85–93)
Effectiveness against ICU admission			
≥50 yr of age			
Unvaccinated (referent)	4,024	692 (17.2)	
Partially vaccinated			
Dose 1	512	39 (7.6)	56 (35–70)
Dose 2	388	15 (3.9)	75 (58–86)
Fully vaccinated — 2 doses	2,359	38 (1.6)	90 (86–93)

Results by 14-day interval (Fig 3)

Subgroup	No. of Patients	Positive for SARS-CoV-2	Vaccine Effectiveness (95% CI)
		no. (%)	%
Effectiveness against hospitalization			
≥50 yr of age			
Unvaccinated (referent)	20,618	3711 (18.0)	
Indeterminate vaccination			
0–13 Days after dose 1	1,751	290 (16.6)	−4 (−21 to 10)
Partially vaccinated — 1 dose			
14–27 Days after dose 1	1,895	181 (9.6)	44 (33 to 53)
28–41 Days after dose 1	479	30 (6.3)	70 (56 to 80)
42–55 Days after dose 1	189	4 (2.1)	91 (74 to 97)
≥56 Days after dose 1	561	17 (3.0)	83 (71 to 90)
Partially vaccinated — 2 doses			
0–13 Days after dose 2	2,497	107 (4.3)	74 (67 to 79)
Fully vaccinated — 2 doses			
14–27 Days after dose 2	2,754	48 (1.7)	88 (84 to 92)
28–41 Days after dose 2	2,783	41 (1.5)	92 (88 to 94)
42–55 Days after dose 2	2,603	41 (1.6)	90 (87 to 93)
56–69 Days after dose 2	2,394	51 (2.1)	86 (82 to 90)
70–83 Days after dose 2	2,048	24 (1.2)	93 (89 to 95)
84–97 Days after dose 2	1,528	27 (1.8)	86 (79 to 91)
98–111 Days after dose 2	971	23 (2.4)	82 (72 to 89)
≥112 Days after dose 2	568	11 (1.9)	86 (74 to 93)
Effectiveness against emergency department			

New findings

- mRNA-based vaccines were highly effective among adults who were 85 years of age or older and persons with chronic medical conditions.
- In Black adults and Hispanic adults, mRNA-based vaccines were similarly effective with respect to Covid-19–associated hospitalization and an emergency department or urgent care clinic visit.
- The effectiveness of full mRNA-based vaccination remained consistently high at least until 112 days (~4 months) after the second dose.

Limitations

- Unmeasured and residual confounding may have biased our estimates, e.g., occupation.
- Percentage of patients who were clinically tested for SARS-CoV-2 by molecular assay differed across network partners and clinical settings.
- Potential misclassification of vaccine exposures or outcomes.
- Circulation of SARS-CoV-2 variants, e.g., delta

Discussion

Assumptions of test-negative design

- The incidence of Covid-19–like illness that was unrelated to Covid-19 (i.e., in SARS-CoV-2–negative patients) should not vary according to Covid-19 vaccination status.
- Vaccine effectiveness should be the same among patients who would seek and receive medical attention and those who would not, given similar Covid-19 severity.