RESEARCH LETTER

Genomic Characterization of RSV in the US by Vaccination Status

Respiratory syncytial virus (RSV) causes lower respiratory tract infections with a high serious disease burden in infants and older adults.[1,2] The viral surface glycoproteins G and F mediate viral attachment and fusion, respectively.[3] Strains of RSV are grouped into subtypes (A and B) and clades based on the sequence for G.

Supplemental content

The prefusion stabilized F protein is the antigenic target for recently approved vaccines; 6 antigenic sites have been defined (0, I, II, III, IV, and V), and sites 0 and V induce the most potent neutralizing antibodies.[4] Surveillance of RSV from vaccinated and unvaccinated individuals helps determine the extent of antigenic drift in F and the potential need for updating vaccine composition. This report describes RSV genomic surveillance results from 2 large US networks in the first season after the introduction of RSV vaccines.

Methods | Samples from 2 large, geographically diverse surveillance networks in the US were collected: the Investigating Respiratory Viruses in the Acutely Ill network, a surveillance network funded by the Centers for Disease Control and Prevention, enrolls hospitalized individuals with acute respiratory illness at 26 medical centers in 20 US and the Veterans Health Administration. Demographic data, vaccination history, and respiratory specimens were collected from individuals with acute respiratory illness who had a positive nucleic acid test result for RSV within 10 days of symptom onset and 3 days of admission (Investigating Respiratory Viruses in the Acutely Ill) or specifically from RSV-positive individuals with documented prior RSV vaccination (Veterans Health Administration). Specimens were processed for whole genome sequencing and

Table. Characteristics of US Adults With Respiratory Syncytial Virus (RSV), September 2023-April 2024

	No. (%)		
	All patients (N = 482)	IVY Network (n = 414)[a]	Veterans Health Administration (n = 68)[b]
Age, median (IQR), y	68 (58-77)	67 (56-77)	76 (69-80)
Age group, y		n = 413	
18-59	136 (28.2)	129 (31.2)	7 (10.3)
60-74	176 (36.5)	155 (37.4)	21 (30.9)
≥75	169 (35.1)	129 (31.2)	40 (58.8)
Female sex	215 (44.6)	212/413 (51.2)	3 (4.4)
Male sex	266 (55.2)	201/413 (48.6)	65 (95.6)
Race and ethnicity[c]			
Black, non-Hispanic	87 (18.0)	82 (19.8)	5 (7.4)
Hispanic or Latino, any race	70 (14.5)	66 (15.9)	4 (5.9)
White, non-Hispanic	285 (59.1)	233 (56.3)	52 (76.5)
Other race, non-Hispanic	24 (5.0)	22 (5.3)	2 (2.9)
Unknown	16 (3.3)	11 (2.7)	5 (7.4)
US Department of Health and Human Services region			
1	98 (20.3)	96 (23.2)	2 (2.9)
2	26 (5.4)	26 (6.3)	0
3	13 (2.7)	1 (0.2)	12 (17.6)
4	69 (14.3)	60 (14.5)	9 (13.2)
5	54 (11.2)	51 (12.3)	3 (4.4)
6	35 (7.3)	35 (8.5)	0
7	16 (3.3)	15 (3.6)	1 (1.5)
8	78 (16.2)	78 (18.8)	0
9	81 (16.8)	40 (9.7)	41 (60.3)
10	12 (2.5)	12 (2.9)	0

(continued)

Table. Characteristics of US Adults With Respiratory Syncytial Virus (RSV), September 2023-April 2024 (continued)

	No. (%)		
	All patients (N = 482)	IVY Network (n = 414)[a]	Veterans Health Administration (n = 68)[b]
Comorbidities[d]			
Heart failure	124 (25.7)	101 (24.4)	23 (33.8)
Chronic obstructive pulmonary disease	131 (27.2)	109 (26.3)	22 (32.4)
Chronic kidney disease or kidney failure	82 (17.0)	62 (15.0)	20 (29.4)
Immunocompromised[e]	124 (25.7)	111 (26.8)	13 (19.1)
RSV subtype			
A	94 (19.5)	75 (18.1)	19 (27.9)
B	374 (77.6)	325 (78.5)	49 (72.1)
Unknown subtype	14 (2.9)	14 (3.4)	0
RSV vaccination status[f]			
Unvaccinated	441 (91.5)	399 (96.4)	42 (61.8)
Partially vaccinated	9 (1.9)	8 (1.9)	1 (1.5)
Vaccinated	32 (6.6)	7 (1.7)	25 (36.8)
GSK (Arexvy)	10 (31.3)	2 (28.6)	8 (32.0)
Pfizer (Abrysvo)	19 (59.4)	2 (28.6)	17 (68.0)
Unknown vaccine type	3 (9.4)	3 (42.9)	0

[a] The Investigating Respiratory Viruses in the Acutely Ill (IVY) Network includes 26 hospitals in 20 US states.

[b] The Veterans Health Administration (VHA) serves more than 9 million enrolled veterans each year at 1380 care sites in all US states and territories.

[c] Race and ethnicity from IVY were self-reported and categorized as Black, non-Hispanic; Hispanic or Latino, any race; White, non-Hispanic; or Other race, non-Hispanic ethnicity (American Indian or Alaska Native, Asian, and Native Hawaiian or Other Pacific Islander and those who reported as "Other"). Race and ethnicity in VHA were categorized by grouping all with Hispanic/Latino ethnicity as Hispanic or Latino regardless of race; persons with reported race and unknown or missing ethnicity were grouped by race category; and persons with missing or unknown race and missing or unknown ethnicity are categorized as unknown. Other race, non-Hispanic includes American Indian or Alaska Native, Asian, and Native Hawaiian or Other Pacific Islander.

[d] In IVY, comorbidities were abstracted from chart reviews. In VHA, comorbidities were based on presence of *International Classification of Diseases, Tenth Revision* codes documented prior to RSV specimen collection date: heart failure (I50); COPD (J42, J43, J44); chronic kidney disease/end-stage renal disease (N18); immunocompromised (based on AHRQ Immunocompromised State Diagnosis Codes).

[e] Immunocompromised in IVY was defined as active solid tumor or hematologic malignancy (ie, newly diagnosed malignancy or treatment for a malignancy within past 6 months), solid organ transplant, hematopoietic cell transplant, HIV infection, primary immunodeficiency, use of immunosuppressive medication in the past 30 days, or other conditions that cause moderate or severe immunosuppression.

[f] Unvaccinated: no prior receipt of RSV vaccine; partially vaccinated: RSV vaccination 0-13 days before illness onset; vaccinated: RSV vaccination ≥14 days before illness onset.

phylogenetic analysis. Detailed methods are provided in Supplement 1.

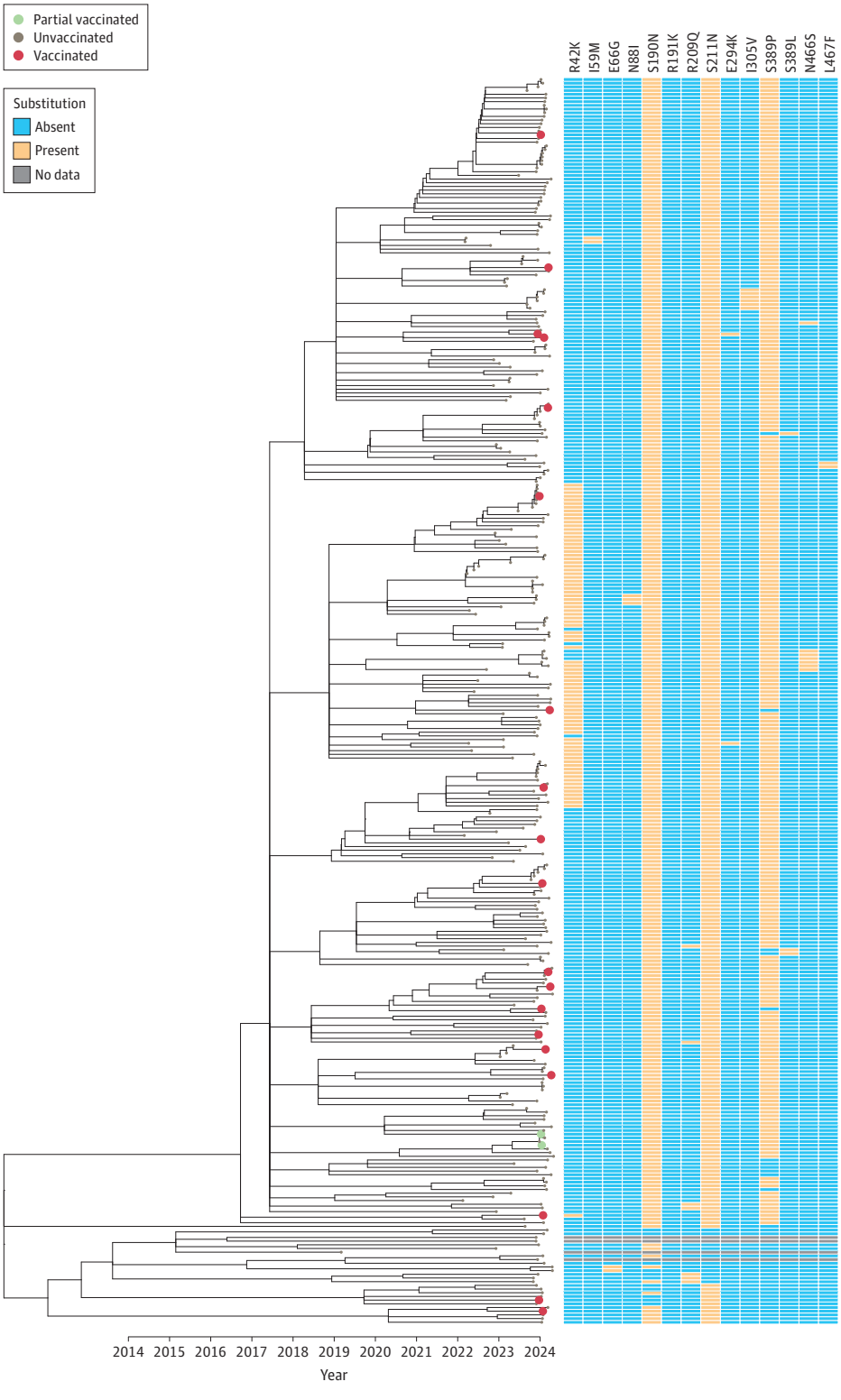
Results | From September 21, 2023, through April 30, 2024, a total of 482 specimens were obtained; 32 (6.6%) from individuals vaccinated 14 days or more before illness onset, 9 (1.9%) from individuals vaccinated 0 to 13 days before illness onset, and 441 (91.5%) from individuals not vaccinated for RSV (**Table**). Among 32 vaccinated individuals, 10 (31.3%) received the GSK (Arexvy) vaccine,[5] 19 (59.4%) received the bivalent A/B Pfizer (Abrysvo) vaccine,[6] and 3 (9.4%) had unknown vaccine type. RSV-B predominated, with 374 (77.6%) RSV-B viruses and 94 (19.5%) RSV-A viruses identified.

Whole genome sequences were obtained from 60 (64%) RSV-A and 270 (72%) RSV-B specimens. A maximum likelihood phylogenetic analysis demonstrated significant diversity in circulating RSV-A and RSV-B, representative of strains circulating in the US during this period. In a similar analysis of the RSV-B F gene (**Figure**), sequences from vaccinated individuals were distributed across the tree and did not appear to associate with specific subclades, clusters, or variants, consistent with lack of antigenic drift. Three substitutions in RSV-B antigenic sites—S190N, S211N, and S389P—are nearly fixed in circulating RSV during the analysis period and from historical RSV comparators recovered since 2022. A fourth substitution, R42K, was common in the sample set and datasets of circulating strains.

Amino acid substitutions in vaccinated and partially vaccinated individuals were further analyzed, including additional F sequences from individuals for whom complete genomic data were not available (RSV-A: n = 13; RSV-B: n = 31). In RSV-A antigenic sites, I57V was present in 1 sequence, S377N was present in 2 sequences, and I384V was present in 1 sequence. In RSV-B antigenic sites, besides the R42K substitution mentioned above, R191K was present in 1 sequence and E294K was present in 1 sequence. Thus, in 44 vaccine breakthrough infections, there were no common or recurring variants.

Discussion | This study found little evidence for antigenic drift in the F protein of circulating viruses in this first season after the introduction of RSV vaccines. Because only 24% of eligible US adults were estimated to have received an RSV vaccine

Figure. Time-Resolved Phylogenetic Tree of Respiratory Syncytial Virus (RSV)-B F Gene



Time-resolved maximum likelihood phylogenetic tree of 270 RSV-B sequences from US adults September 2023 to April 2024 and 70 contextual RSV-B sequences from 2022-2023 in the Investigating Respiratory Viruses in the Acutely Ill network, available on GISAID.org. The heat map shows amino acid substitutions (top) in antigenic sites identified across the cohort relative to the reference sequence hRSV/B/Australia/VIC-RCH056/2019 (EPI_ISL_1653999).

during 2023-2024 and infants had limited uptake of nirsevimab, the selective pressure for antigenic drift variants in RSV F is likely to be low relative to the pressure from background immunity. Study strengths include whole genome viral sequencing from adults in 2 large geographically diverse US surveillance networks with linkage to verified vaccination status. Limitations include the lack of serological analysis of recovered viruses and no pediatric data. Continued genomic

surveillance should continue as community uptake of RSV prevention products increases.

Adam S. Lauring, MD, PhD
Connor Edson, BS
Diya Surie, MD
Fatimah S. Dawood, MD
Wesley H. Self, MD, MPH
Cynthia Lucero-Obusan, MD
Mark Holodniy, MD
for the IVY Network

Author Affiliations: Division of Infectious Diseases and Department of Microbiology and Immunology, University of Michigan, Ann Arbor (Lauring); Department of Veterans Affairs Public Health Reference Laboratory, Palo Alto, California (Edson, Holodniy); Coronavirus and Other Respiratory Viruses Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia (Surie, Dawood); Vanderbilt Institute for Clinical and Translational Research, and Department of Emergency Medicine, Vanderbilt University Medical Center, Nashville, Tennessee (Self); Department of Veterans Affairs, Public Health National Program Office, Palo Alto, California (Lucero-Obusan); Department of Veterans Affairs, Public Health National Program Office, Washington, DC (Lucero-Obusan).

Accepted for Publication: January 27, 2025.

Published Online: March 10, 2025. doi:10.1001/jama.2025.1225

Corresponding Authors: Adam Lauring, MD, PhD, University of Michigan, 1137 Catherine St, Medical Sciences 2 4742C, Ann Arbor, MI 48109 (alauring@med.umich.edu); Mark Holodniy, MD, Veterans Affairs Public Health Reference Laboratory, Office of Patient Care Services, Department of Veterans Affairs, 3801 Miranda Ave (132), Palo Alto, CA 94304 (Mark.Holodniy@va.gov).

Author Contributions: Dr Lauring had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Lauring, Edson, Surie, Dawood, Lucero-Obusan.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Lauring, Edson, Holodniy.
Critical review of the manuscript for important intellectual content: All authors.
Statistical analysis: Lauring, Edson.
Obtained funding: Lauring, Surie, Self, Holodniy.
Administrative, technical, or material support: Lauring, Edson, Surie, Dawood, Self, Holodniy.
Supervision: Lauring, Holodniy.

Conflict of Interest Disclosures: Dr Lauring reported receiving personal fees from Roche outside the submitted work. Dr Self reported receiving grants from the Centers for Disease Control and Prevention during the conduct of the study. No other disclosures were reported.

Funding/Support: This work was funded by the Centers for Disease Control and Prevention (CDC) (contract No. 75D30122C14944; paid to Vanderbilt University Medical Center), National Institute of Allergy and Infectious Diseases 1U19AI181767-01 (to Dr Lauring), and US Department of Veterans Affairs (VA) internal operational funding.

Role of the Funder/Sponsor: Investigators from the CDC were involved in all aspects of the study, including the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The CDC had the right to control decisions about publication via the CDC publication clearance process. The National Institutes of Health and VA had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Group Information: The IVY Network members appear in Supplement 2.

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the VA and the CDC.

Data Sharing Statement: See Supplement 3.

1. Shi T, McAllister DA, O'Brien KL, et al; RSV Global Epidemiology Network. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study. *Lancet*. 2017;390(10098):946-958. doi:10.1016/S0140-6736(17)30938-8

2. Falsey AR, Hennessey PA, Formica MA, Cox C, Walsh EE. Respiratory syncytial virus infection in elderly and high-risk adults. *N Engl J Med*. 2005;352(17):1749-1759. doi:10.1056/NEJMoa043951

3. Battles MB, McLellan JS. Respiratory syncytial virus entry and how to block it. *Nat Rev Microbiol*. 2019;17(4):233-245. doi:10.1038/s41579-019-0149-x

4. Gilman MSA, Castellanos CA, Chen M, et al. Rapid profiling of RSV antibody repertoires from the memory B cells of naturally infected adult donors. *Sci Immunol*. 2016;1(6):eaaj1879. doi:10.1126/sciimmunol.aaj1879

5. Papi A, Ison MG, Langley JM, et al; AReSVi-006 Study Group. Respiratory syncytial virus prefusion F protein vaccine in older adults. *N Engl J Med*. 2023;388(7):595-608. doi:10.1056/NEJMoa2209604

6. Walsh EE, Pérez Marc G, Zareba AM, et al. Efficacy and safety of a bivalent RSV prefusion F vaccine in older adults. *New Engl J Med*. 2023;388(16):1465-1477. doi:10.1056/NEJMoa2213836