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BRIEF REPORT

Bivalent RSVpreF Effectiveness Against Respiratory Syncytial Virus (RSV)-Related Respiratory Disease Hospitalization and Emergency Department Visits Across Three RSV Seasons

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ABSTRACT

Introduction: Respiratory syncytial virus (RSV) protein subunit vaccines reduce the risk of severe outcomes such as hospitalization and emergency department (ED) visits for at least two RSV seasons following vaccination. No data have been published on real-world RSV vaccine effectiveness (VE) beyond the second season after vaccination. This study evaluates bivalent RSVpreF VE against RSV-related respiratory disease hospitalizations/ED visits throughout three seasons after vaccination.

Methods: This retrospective test-negative case–control study evaluates bivalent RSVpreF VE among adults aged ≥60 years at Kaiser Permanente Southern California, USA, with lower respiratory tract disease (LRTD) or acute respiratory illness (ARI) over three RSV seasons (11/24/2023–4/18/2026). Cases were RSV-positive without coinfection. Controls were negative for RSV, hMPV, influenza, SARS-CoV-2, and positive for a non-vaccine preventable disease pathogen. Exposure was bivalent RSVpreF (Abrysvo) receipt ≥ 21 days before LRTD/ARI. Adjusted VE was estimated using odds ratios from multivariable logistic regression or generalized estimating equations.

Results: Overall adjusted VE against RSV-related LRTD hospitalization/ED visits was 80% (95% CI 68–87), 70% (95% CI 53–81), and 51% (95% CI —12–78) in the first, second, and third season after vaccination, respectively. Overall adjusted VE against RSV-related ARI hospitalization/ED visits was 81% (71–87), 64% (48–75),

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and 60% (15–81), respectively. Adjusted VE among non-immunocompromised individuals trended 4–7% higher than corresponding overall estimates. Overall adjusted VE across the three combined seasons was 73% (95% CI 64–80) and 73% (95% CI 65–79) against RSV-related LRTD and ARI, respectively.

Conclusion: Bivalent RSVpreF provides protection against RSV-related respiratory hospitalization/ED visits for at least three seasons after vaccination in this population of older adults with a high prevalence of comorbidities. Estimates in the third season for ARI were more definitive, while those for LRTD were imprecise due to limited event numbers. This suggests bivalent RSVpreF vaccination results in substantial individual and public health benefit.

Trial Registration: ClinicalTrials.gov ID: NCT06077968

Keywords: Respiratory syncytial virus; Bivalent RSVpreF; Lower respiratory tract disease; Acute respiratory illness; Vaccine effectiveness; Test-negative; Hospitalization

Key Summary Points

Why carry out this study?
Protein subunit respiratory syncytial virus (RSV) vaccines reduce the risk of severe outcomes such as hospitalization and emergency department (ED) visits for at least 2 RSV seasons after vaccination.
Real-world RSV vaccine effectiveness (VE) beyond the second season after vaccination is currently unknown.
This study evaluates bivalent RSVpreF VE against RSV-related respiratory disease hospitalizations/ED visits throughout three seasons after vaccination.

What was learned from the study?
VE against RSV-related lower respiratory tract disease hospitalization/ED visits was 80% (95% CI 68–87), 70% (95% CI 53–81), and 51% (95% CI —12–78) in the first, second, and third season after vaccination, respectively, and 73% (95% CI 64–80) across the 3 combined seasons.
VE against RSV-related acute respiratory illness hospitalization/ED visits was 81% (95% CI 71–87), 64% (95% CI 48–75), and 60% (95% CI 15–81) in the first, second, and third season after vaccination, respectively, and 73% (95% CI 65–79) across the three combined seasons.
Bivalent RSVpreF provides protection against RSV-related respiratory disease hospitalization/ED visits for at least three seasons after vaccination in this population of older adults with a high prevalence of comorbidities.
Bivalent RSVpreF vaccination results in substantial individual and public health benefit.

INTRODUCTION

Severe respiratory illness due to respiratory syncytial virus (RSV) causes hundreds of thousands of hospitalizations and tens of thousands of deaths in older adults annually in high-income countries [1, 2]. RSV protein subunit vaccines reduce the risk of severe outcomes such as hospitalization and emergency department (ED) visits for at least 2 RSV seasons following vaccination [3–6]. No data have been published on real-world RSV vaccine effectiveness (VE) beyond the second season after vaccination. This study evaluates bivalent RSVpreF VE against RSV-related respiratory disease hospitalizations/ED visits throughout three seasons after vaccination.

METHODS

This is a retrospective test-negative case–control study evaluating VE among adults aged ≥ 60 years at Kaiser Permanente Southern California (KPSC), USA, over three RSV seasons (11/24/2023–4/18/2026). Events were defined as first hospitalization/ED visit in each season with ≥ 1 lower respiratory tract disease (LRTD) or acute respiratory illness (ARI) ICD-10 discharge code in any position and concurrent multiplex polymerase chain reaction (PCR) respiratory specimen testing (Roche Diagnostics cobas eplex RP2) of a nasal/nasopharyngeal swab collected 14 days prior to 3 days after admission. Full inclusion and exclusion criteria have been detailed previously [1]. As RSV testing is infrequent in practice among hospitalized adults with LRTD [7], we supplemented standard-of-care (SOC) testing with study-initiated salvage and RSV testing of swabs collected for SARS-CoV-2 and/or influenza testing using the same PCR assay as the SOC specimens. Cases were RSV-positive without coinfection. Controls were negative for RSV, human metapneumovirus (hMPV), influenza, SARS-CoV-2, and positive for a non-vaccine preventable disease pathogen [3, 8, 9]. Exposure was defined as bivalent RSVpreF (Abrysvo) receipt ≥ 21 days before LRTD/ARI admission date [3, 8, 9]. Adjusted VE was estimated using odds ratios from multivariable logistic regression or generalized estimating equations in analyses where individuals contributed multiple events. The pre-specified primary analysis used individually specified models for each season after vaccination given each analysis contained a unique population [3]. Findings from the Phase 3 studies, expert opinion, and published studies of clinical/biologic factors were used to identify potential covariates for inclusion in the models. Covariates were assessed for completeness, distributions, and bivariate associations with the outcome, exposure, and each other. Variables were selected based on a combination of a priori decisions and a qualitative assessment of empirical relationships. Age, sex, race/ethnicity, Charlson comorbidity index, encounter month, encounter facility, and prior receipt of influenza vaccination were pre-specified as important confounders incorporated into all models. Other model-specified covariates are listed in the Fig. 1 footnote, with immunocompromise defined in the Supplementary Material. [3, 8, 9] A separate sensitivity analysis was conducted using a single harmonized model covariate set across all VE estimates. Analyses were performed using SAS version 9.4 (SAS Institute). KPSC's institutional review board approved this study and waived informed consent requirements (IRB #13943). This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

RESULTS

Of 6813 LRTD events and 10,296 ARI events among individuals aged ≥ 60 years with LRTD or ARI hospitalization/ED visits at study sites during the study period, 3131 (46.0%) LRTD and 4797 (46.6%) ARI events met inclusion criteria. Of the included LRTD and ARI events, 2206 (70.5%) and 2722 (56.7%), respectively, were hospitalizations (Table 1). Overall, 637 (20.3%) LRTD and 967 (20.2%) ARI events were vaccinated with bivalent RSVpreF and 911 (29.1%) LRTD and 1261 (26.3%) ARI events were RSV-positive cases. The median age among LRTD and ARI events was 78 years (interquartile range (IQR) 70–85) and 77 years (IQR 69–84), respectively. The median Charlson comorbidity index was 4 (IQR 2–7) among LRTD and 4 (IQR 2–6) among ARI, and 22.8% and 22.1% of LRTD and ARI, respectively, were immunocompromised. In both the LRTD and ARI analyses, RSV-positive cases were more likely to be hospitalized, female, and non-Hispanic white (Table 1). RSV-positive cases were more likely to be immunocompromised in the LRTD analysis and more likely to be older in the ARI analysis.

Adjusted VE against RSV-related LRTD hospitalization/ED visits was 80% (95% CI 68–87), 70% (95% CI 53–81), and 51% (95% CI —12–78) in the first, second, and third season after vaccination, respectively (Fig. 1). Adjusted VE against RSV-related ARI hospitalization/ED visits was 81% (95% CI 71–87), 64% (95% CI 48–75), and 60% (95% CI 15–81) in the first, second,

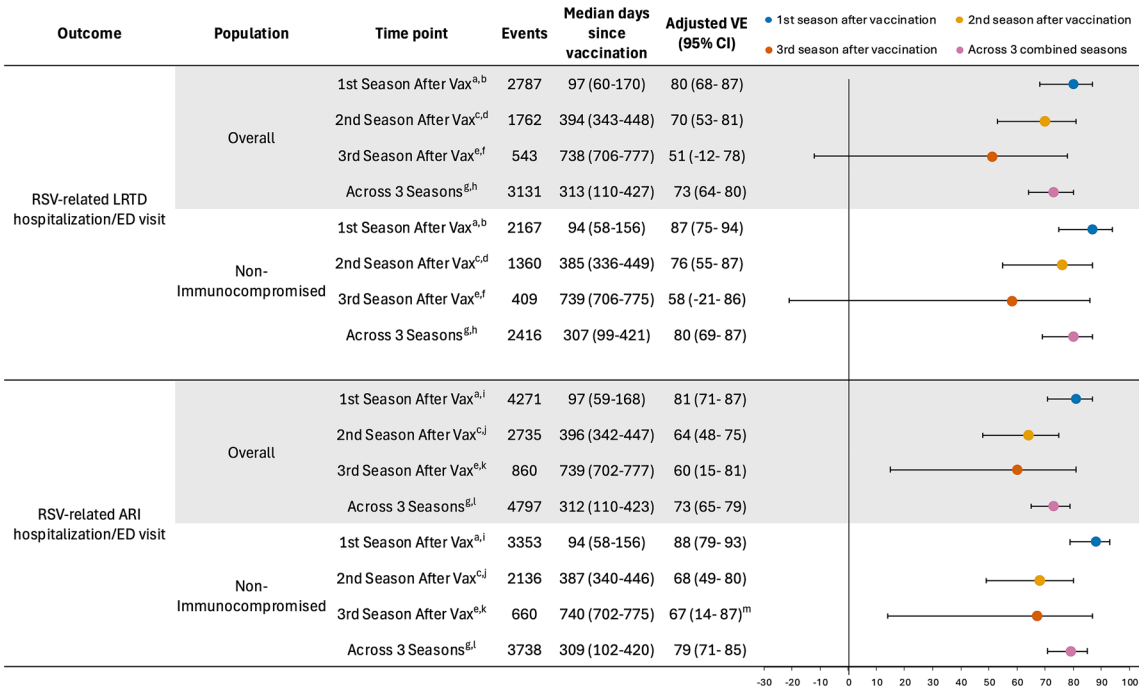

Fig. 1 Bivalent RSVPreF vaccine effectiveness estimates against respiratory syncytial virus (RSV)-related respiratory disease hospitalization and emergency department visits across three RSV seasons. a Includes those vaccinated from October 2023 to March 2024 and all unvaccinated with events during the 2023-2024 RSV season, those vaccinated from April 2024 to March 2025 and all unvaccinated with events occurring during the 2024-2025 RSV season, and those vaccinated from April 2025 to March 2026 and all unvaccinated with events occurring during the 2025-2026 RSV season. **b** Models for LRTD 1st season after vaccination were adjusted for age, sex, race/ethnicity, Charlson index score, encounter month, encounter facility, flu vaccination in the year prior to index, diabetes, smoking, number of inpatient encounters in the year prior to index, and median household income. **c** Includes those vaccinated from October 2023 to March 2024 and all unvaccinated with events during the 2024-2025 RSV season and those vaccinated from April 2024 to March 2025 and all unvaccinated with events during the 2025-2026 RSV season. **d** Models for LRTD 2nd season after vaccination were adjusted for age, sex, race/ethnicity, Charlson index score, encounter month, encounter facility, flu vaccination in the year prior to index, BMI category, diabetes, and immunocompromised. **e** Includes those vaccinated from October 2023 to March 2024 and all unvaccinated with events during the 2025-2026 RSV season. **f** Models for LRTD 3rd season after vaccination were adjusted for age, sex, race/ethnicity, Charlson index score, encounter month, encounter facility, flu vaccination in the year prior to index, diabetes, immunocompromise, neighborhood deprivation index quartile, number of virtual encounters in the year prior to index, and smoking status. **g** Includes those vaccinated from October 2023 to March 2026 and all unvaccinated with events during the 2023-2024, 2024-2025, and 2025-2026 RSV seasons; **h** Models for LRTD across three seasons were adjusted for age, sex, race/ethnicity, Charlson index score, encounter month, encounter facility, flu vaccination in the year prior to index, and diabetes. **i** Models for ARI 1st season after vaccination were adjusted for age, sex, race/ethnicity, Charlson index score, encounter month, encounter facility, and flu vaccination in the year prior to index. **j** Models for ARI 2nd season after vaccination were adjusted for age, sex, race/ethnicity, Charlson index score, encounter month, encounter facility, flu vaccination in the year prior to index, BMI category, and diabetes. **k** Models for ARI 3rd season after vaccination were adjusted for age, sex, race/ethnicity, Charlson index score, encounter month, encounter facility, flu vaccination in the year prior to index, BMI, smoking, number of virtual encounters in the year prior to index, and neighborhood deprivation index. **l** Models for ARI across three seasons were adjusted for age, sex, race/ethnicity, Charlson index score, encounter month, encounter facility, and flu vaccination in the year prior to index. **m** $n = 3$ with unknown BMI excluded to achieve model convergence

Table 1 Characteristics of patients ≥60 years of age with acute respiratory illness or lower respiratory tract disease hospitalization or ED visit during three respiratory syncytial virus (RSV) seasons (2023–2026)

	Lower respiratory tract disease				Acute respiratory illness			
	Total study population	**Cases**	**Controls**	***p* value[a]**	**Total study population**	**Cases**	**Controls**	***p* value[a]**
	***n* = 3131**	***n* = 911**	***n* = 2220**		***n* = 4,797**	***n* = 1,261**	***n* = 3,536**	
Age at index date				0.0815				0.0128
60–74	1243 (39.7%)	340 (37.3%)	903 (40.7%)		2087 (43.5%)	511 (40.5%)	1576 (44.6%)	
75+	1888 (60.3%)	571 (62.7%)	1317 (59.3%)		2710 (56.5%)	750 (59.5%)	1960 (55.4%)	
Median (interquartile range)	78 (70, 85)	78 (70, 86)	77 (70, 85)		77 (69, 84)	77 (70, 85)	76 (69, 84)	
Sex				< 0.0001				< 0.0001
Female	1718 (54.9%)	558 (61.3%)	1160 (52.3%)		2640 (55%)	767 (60.8%)	1873 (53%)	
Male	1413 (45.1%)	353 (38.7%)	1060 (47.7%)		2157 (45%)	494 (39.2%)	1663 (47%)	
Race/ethnicity				0.0372				0.0109
Non-Hispanic Asian/Pacific Islander	431 (13.8%)	120 (13.2%)	311 (14%)		643 (13.4%)	175 (13.9%)	468 (13.2%)	
Non-Hispanic Black	412 (13.2%)	112 (12.3%)	300 (13.5%)		675 (14.1%)	161 (12.8%)	514 (14.5%)	
Hispanic	1103 (35.2%)	296 (32.5%)	807 (36.4%)		1782 (37.1%)	433 (34.3%)	1349 (38.2%)	
Non-Hispanic Multiple/Other/Unknown	53 (1.7%)	15 (1.6%)	38 (1.7%)		80 (1.7%)	20 (1.6%)	60 (1.7%)	
Non-Hispanic White	1132 (36.2%)	368 (40.4%)	764 (34.4%)		1617 (33.7%)	472 (37.4%)	1145 (32.4%)	

Table 1 continued

	Lower respiratory tract disease				Acute respiratory illness			
	Total study population	**Cases**	**Controls**	***p* value**[a]	**Total study population**	**Cases**	**Controls**	***p* value**[a]
	***n* = 3131**	***n* = 911**	***n* = 2220**		***n* = 4,797**	***n* = 1,261**	***n* = 3,536**	
Encounter Setting				0.001				< 0.0001
Hospital[b]	2206 (70.5%)	680 (74.6%)	1526 (68.7%)		2722 (56.7%)	786 (62.3%)	1936 (54.8%)	
Emergency Department	925 (29.5%)	231 (25.4%)	694 (31.3%)		2075 (43.3%)	475 (37.7%)	1600 (45.2%)	
Charlson Index Score				0.7585				0.8535
0	179 (5.7%)	53 (5.8%)	126 (5.7%)		413 (8.6%)	101 (8%)	312 (8.8%)	
1	283 (9%)	89 (9.8%)	194 (8.7%)		495 (10.3%)	135 (10.7%)	360 (10.2%)	
2	379 (12.1%)	106 (11.6%)	273 (12.3%)		603 (12.6%)	165 (13.1%)	438 (12.4%)	
3	345 (11%)	107 (11.7%)	238 (10.7%)		558 (11.6%)	146 (11.6%)	412 (11.7%)	
4+	1945 (62.1%)	556 (61%)	1389 (62.6%)		2728 (56.9%)	714 (56.6%)	2014 (57%)	
Median (interquartile range)	4 (2, 7)	5 (2, 7)	4 (2, 7)		4 (2, 6)	4 (2, 6)	4 (2, 6)	
High-risk chronic medical conditions[c]				0.4947				0.7862
No	172 (5.5%)	54 (5.9%)	118 (5.3%)		389 (8.1%)	100 (7.9%)	289 (8.2%)	
Yes	2959 (94.5%)	857 (94.1%)	2102 (94.7%)		4408 (91.9%)	1161 (92.1%)	3247 (91.8%)	

Table 1 continued

	Lower respiratory tract disease				Acute respiratory illness			
	Total study population	**Cases**	**Controls**	***p* value[a]**	**Total study population**	**Cases**	**Controls**	***p* value[a]**
	***n* = 3131**	***n* = 911**	***n* = 2220**		***n* = 4,797**	***n* = 1,261**	***n* = 3,536**	
Immunocompromising conditions and medications				0.0247				0.2168
No	2416 (77.2%)	679 (74.5%)	1737 (78.2%)		3738 (77.9%)	967 (76.7%)	2771 (78.4%)	
Yes	715 (22.8%)	232 (25.5%)	483 (21.8%)		1059 (22.1%)	294 (23.3%)	765 (21.6%)	
Abrysvo vaccination				< 0.0001				< 0.0001
No	2494 (79.7%)	854 (93.7%)	1640 (73.9%)		3830 (79.8%)	1184 (93.9%)	2646 (74.8%)	
Yes	637 (20.3%)	57 (6.3%)	580 (26.1%)		967 (20.2%)	77 (6.1%)	890 (25.2%)	

[a]*p* value calculated using chi-square, compares characteristics of RSV cases versus strict controls negative for RSV, human metapneumovirus (hMPV), and other vaccine preventable diseases (VPD) (influenza and SARS-CoV-2), and positive for ≥ 1 non-VPD pathogen, [i.e., adenovirus, coronavirus (229E, HKU1, NL63, OC43), human rhinovirus/enterovirus, Parainfluenza 1–4, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*)]

[b]Hospital encounters include < 24-h hospital stays

[c] High-risk conditions include asthma, COPD, CHF, coronary artery disease, other chronic lung disease, cardiac, renal, liver diseases, diabetes mellitus, neurological conditions, stroke, autoimmune disorders, immunocompromising conditions and medications (e.g., HIV, AIDS, cancers, organ transplant, and blood disorders, etc.)

and third season after vaccination, respectively (Fig. 1). Among non-immunocompromised individuals, adjusted VE against RSV-related LRTD and ARI trended 4–7% higher than corresponding overall VE estimate (Fig. 1). Adjusted VE across three seasons was similar for both LRTD and ARI at 73% (95% CI 64–80) and 73% (95% CI 65–79), respectively. Adjusted VE estimates from the sensitivity analysis using harmonized adjustment models were consistent with the primary analysis, though trended lower for the third season VE estimate for LRTD and ARI as compared to the primary analysis; for example, overall ARI third season VE was 52% (95% CI 1–77) versus 60% (95% CI 15–81) for the primary analysis. (Table S1).

DISCUSSION

In this population of older adults with a high prevalence of comorbidities, our results suggest bivalent RSVpreF provides clinically relevant protection against RSV-related hospitalization and ED visits across three seasons after

vaccination. These data are the first available real-world RSV VE for the third season after vaccination. The consistency of findings across ARI and LRTD is notable, as these outcomes reflect a similarly meaningful clinical construct, as LRTD is a subset of ARI. Overall, VE waned modestly across three seasons. For LRTD, the absolute VE decrease was 10% in the first year and 19% in the second. For ARI, 17% in the first year and 4% in the second year. Similar declines were observed among non-immunocompromised persons but VE trended 4—7% higher than the overall estimates.

The only other available third season RSV vaccine effectiveness is from RSVpreF3's randomized phase 3 trial, which showed 48% efficacy against symptomatic RSV-LRTD [3]. These trial data are limited by exclusion of immunocompromised persons and lack of statistical power to assess events requiring hospitalization or ED visit [10]. Our findings expand on this by examining bivalent RSVpreF, focusing on a clinically meaningful measure of severe disease, RSV-related hospitalization/ED visit, and including a diverse real-world population at risk for severe disease, including those with immunocompromise.

Confidence intervals for third season after vaccination estimates were wide and crossed the null for the LRTD analysis, and the small immunocompromised population's estimate was not reported because it was too imprecise to allow meaningful interpretation. Further data are needed to more conclusively determine duration of protection amongst different populations, including immunocompromised individuals, to inform potential revaccination intervals. As the study is ongoing, this will be re-evaluated in future seasons.

The sensitivity analysis using a harmonized model across all estimates showed identical estimates for the first and second seasons after vaccination compared to the prespecified primary analysis, but slightly lower VE and less precision for both LRTD/ARI endpoints in the third season after vaccination. This may be due to inherent differences in the early adopters who contributed events to the third season estimates, and who followed the original Advisory Committee on Immunization Practices recommendations [11], meriting further assessment in future analyses.

Study strengths include minimal exposure misclassification with vaccination defined by electronic health record augmented by bidirectional data exchange with the California Immunization Registry, specimen salvage and RSV-testing to boost power and generalizability of RSV case detection, a multi-pathogen PCR to define a control group which minimizes bias, and a socio-demographically diverse study population. Limitations include lower RSV vaccine uptake in the first season after vaccine availability, decreasing number of available events for each additional season post-vaccination limiting statistical power, reliance on data from a single health system, and possible residual confounding. Exclusion of 48 LRTD and 59 ARI RSV coinfections may also limit generalizability, though previously published data from this study and others showed similar VE with and without coinfections included [9, 12]. The purpose of this exclusion is to remove cases for which the primary cause of hospitalization may have been the co-infecting pathogen. Although the strict control definition requiring a positive test for a non-vaccine preventable disease pathogen reduces bias from limited sensitivity of single specimen RSV testing and correlated respiratory virus vaccine uptake [13, 14], seasonality of some of the non-vaccine preventable pathogens may not overlap with RSV. Our previous work has shown VE derived from strict-control analyses is similar to VE from traditional RSV-negative control analyses but it remains possible that the non-VPD seasonality could influence VE estimates [3, 8, 9].

CONCLUSION

Bivalent RSVpreF provides protection against RSV-related respiratory disease hospitalization/ED visits for at least three seasons after vaccination, resulting in substantial individual and public health benefit. While estimates in the third season for ARI were more definitive, those for LRTD were imprecise due to limited event numbers. Additional studies and analyses are needed

to further define durability of protection in specific population subgroups.

Author Contributions. Sara Y Tartof (SYT), Negar Aliabadi (NA), Elizabeth Begier (EB), and Evan J Zasowski (EJZ) conceived this study. Jeff Slezak (JS), Gabriella Goodwin (GG), Timothy B Frankland (TBF), and Vennis Hong (VH) conducted the analysis. SYT, NA, JS, GG, Qing Liu, and EB wrote the first draft of the protocol. SYT, EJZ, NA, JS and EB wrote the first draft of the manuscript. All authors contributed to the study design, drafting the protocol, and edited the manuscript for important intellectual content. All authors gave final approval of the version to be published. All authors had final responsibility for the decision to submit for publication. VH, Banshri Kapadia, GG, TBF and JS had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Data Availability. Deidentified participant data and protocol that support the findings of this study may be made available from the investigative team following publication in the following conditions: (1) agreement to collaborate with the study team on all publications, (2) provision of external funding for administrative and investigator time necessary for this collaboration, (3) demonstration that the external investigative team is qualified and has documented evidence of training for human subjects protections, and (4) agreement to abide by the terms outlined in data use agreements between institutions. Inquiries may be sent to Sara Tartof, PhD MPH at sara.y.tartof@kp.org.

Declarations

Conflict of Interest. Evan J Zasowski, Negar Aliabadi, Qing Liu, Sabrina Welsh, Michael Dutro, Erica Chilson, Alejandro Cane, Kyla Hayford, Elizabeth Begier are employees of and hold stock and/or stock options in Pfizer Inc. Sara Y Tartof, Gabriella Goodwin, Jeff Slezak, Vennis Hong, Timothy B Frankland, Bradley Ackerson, Sally Shaw, Banshri Kapadia, Brigitte C Spence, Gregg S Davis, and Hina Chowdhry are employees of KPSC, which received funding from Pfizer in connection with the development of this manuscript. Bradley Ackerson received research support for work unrelated to this study provided by Pfizer, Moderna, Dynavax, Seqirus, GlaxoSmithKline, Genentech, F2G, Merck, AstraZeneca. Jeff Slezak received research support from Dynavax for work unrelated to this study. Timothy B Frankland previously owned stock in Pfizer Inc., Ishares Biotechnology ETF, Abbvie, CVS, Merck & Co. Inc. Timothy B Frankland owns stock in Astrazeneca Plc ADR, Regeneron Pharmaceutical, Stryker Corp. Sara Y Tartof received research support from Pfizer for work unrelated to this study. Joseph A Lewnard received honoraria from Pfizer for work unrelated to this study, as well as other honoraria from Valneva, Vaxcyte, and CSL Seqirus.

Ethical Approval. KPSC's institutional review board approved this study and waived informed consent requirements (IRB #13943). This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

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