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Influenza Vaccine Effectiveness Against Illness and Asymptomatic Infection in 2022–2023: A Prospective Cohort Study

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Abstract

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Background. Previous estimates of vaccine effectiveness (VE) against asymptomatic influenza virus infection based on seroconversion have varied widely and may be biased. We estimated 2022–2023 influenza VE against illness and asymptomatic infection in a prospective cohort.

Methods. In the HEROES-RECOVER cohort, adults at increased occupational risk of influenza exposure across 7 US sites provided weekly symptom reports and nasal swabs for reverse transcription–polymerase chain reaction (RT-PCR) influenza testing. Laboratory-confirmed influenza virus infections were classified as symptomatic (≥ 1 symptom) or asymptomatic during the week of testing. Participants reported demographic information and vaccination through surveys; most sites verified vaccination through medical record and immunization registry review. Person-time was calculated as days from the site-specific influenza season start (September–October 2022) through date of infection, study withdrawal, or season end (May 2023). We compared influenza incidence among vaccinated versus unvaccinated participants overall, by symptom status, and by influenza A subtype, using Cox proportional hazards regression adjusted for site and occupation. We estimated VE as $(1 - \text{adjusted hazard ratio}) \times 100\%$.

Results. In total, 269 of 3785 (7.1%) participants had laboratory-confirmed influenza, including 263 (98%) influenza A virus infections and 201 (75%) symptomatic illnesses. Incidence of laboratory-confirmed influenza illness among vaccinated versus unvaccinated participants was 23.7 and 33.2 episodes per 100 000 person-days, respectively (VE: 38%; 95% CI: 15%–55%). Incidence of asymptomatic influenza virus infection was 8.0 versus 11.6 per 100 000 (VE: 13%; 95% CI: –47%, 49%).

Conclusions. Vaccination reduced incidence of symptomatic but not asymptomatic influenza virus infection, suggesting that influenza vaccination attenuates progression from infection to illness.

Keywords

influenza; vaccines; cohort; asymptomatic infection; symptomatic illness

Influenza vaccines are an important tool for preventing seasonal influenza. The effectiveness of influenza vaccines is assessed each year, most commonly against outcomes such as medically attended illness and influenza-associated hospitalization. However, there has been an increasing recognition of the importance of non–medically attended illnesses and asymptomatic infections in the transmission dynamics of respiratory pathogens [1, 2]. For influenza, understanding the proportion of viral infections that remain asymptomatic is important to guide the public health response to seasonal influenza epidemics. Recommendations such as masking, hand washing, physical distancing, and vaccination have the potential to limit transmission of influenza by both symptomatically and asymptotically infected persons.

The proportion of influenza virus infections that are asymptomatic and vaccine effectiveness (VE) against asymptomatic infection have been challenging to measure. Cohort and household transmission studies have demonstrated seroconversion in the absence of symptoms [3]. However, these studies have limitations, including lack of systematic viral testing in the absence of symptoms and potential recall bias arising from retrospective self-report of symptoms. Seroconversion may overestimate VE because vaccinated people

are less likely to have a 4-fold increase in antibody titer after infection [4]. As a result, the prevalence of asymptomatic influenza virus infections and VE against asymptomatic infection versus symptomatic illness are not well understood. Cohort studies with active surveillance for respiratory illness and systematic swabbing for viral infections provide valuable information on the incidence of viral infection and transmission but are resource intensive and infrequently conducted for influenza [5].

The Arizona Healthcare, Emergency Response, and Other Essential Workers Surveillance (HEROES) and Research on the Epidemiology of SARS-CoV-2 in Essential Response Personnel (RECOVER) studies were established during the coronavirus disease 2019 (COVID-19) pandemic. Testing for influenza was later added to the protocol, providing an opportunity to assess the effectiveness of the 2022–2023 seasonal influenza vaccine against infection and illness. The objectives of this analysis were to compare the incidence of laboratory-confirmed influenza virus infection and illness during the 2022–2023 influenza season among vaccinated and unvaccinated participants in the HEROES-RECOVER cohort and to estimate influenza VE against illness and asymptomatic infection.

METHODS

Cohort and Study Population

The HEROES-RECOVER studies were prospective cohorts of frontline workers participating in active surveillance for COVID-19 and influenza. The protocol and methods have been described previously [6, 7]. HEROES-RECOVER has documented the natural history of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and COVID-19 before vaccines became available, as well as VE of COVID-19 vaccines against infection and illness through active surveillance and systematic collection of respiratory and serum specimens [8–10]. Molecular testing for influenza began in November 2021; we used data from August 2022–May 2023 to assess influenza VE during the 2022–2023 influenza season.

Participants included primary healthcare personnel (physicians, physician assistants, nurse practitioners, dentists), allied healthcare personnel (eg, nurses, therapists, technicians, medical assistants, and orderlies), first responders (eg, law enforcement, firefighters, and other emergency services), and other frontline workers (eg, education, food production, and service occupations) [9]. During the 2022–2023 influenza season, participants were enrolled in 5 states: Arizona, Florida, Minnesota, Texas, and Utah. Participants from HEROES-RECOVER were eligible for inclusion in the current study if they were continuously enrolled during the 2022–2023 influenza season (September/October 2022–31 May 2023), participated in active surveillance, and provided complete data on vaccination status and date of vaccination. All participants provided informed consent, and the HEROES-RECOVER protocol was reviewed and approved by the institutional review boards at participating sites or under a reliance agreement.

Measurements

Sociodemographic and health characteristics, including underlying medical conditions, were reported by participants in surveys completed at enrollment and updated quarterly. Active monitoring for illness symptoms was conducted through weekly surveillance questionnaires administered by text message and email, with a checklist where participants indicated whether they were experiencing any of the following: cough (wet or dry), nasal congestion, fatigue, febrile symptoms (fever or chills or both), headache, aches, sore throat, joint pain, shortness of breath, nausea, diarrhea, vomiting, abdominal pain, change in taste or smell, or rash. Self-reported mask use at work was collected monthly and averaged over the study period. Participants self-collected weekly mid-turbinate nasal swabs regardless of symptom status and provided additional nasal and saliva samples during the weeks in which they were experiencing any symptoms. Specimens were tested by reverse transcription–polymerase chain reaction (RT-PCR) for influenza virus and SARS-CoV-2; a subset of influenza A viruses were sub-typed. Influenza vaccination and date were ascertained by self-report through electronic surveys. Sites in Arizona, Minnesota, Texas, and Utah also had access to electronic medical records and state registries to verify vaccination dates; this date was used if it differed from self-reported vaccination history.

Each participant's follow-up start date was the later of their enrollment date or the beginning of influenza virus circulation at their site (ie, the first week with an influenza-positive test among participants at that site). Participants who were vaccinated at least 14 days before their start date began contributing vaccinated person-time. Participants vaccinated 0–13 days before their start date began contributing vaccinated person-time on day 14 post-vaccination (ie, they were censored from their start date until day 14 post-vaccination). Participants who were unvaccinated on their start date began contributing unvaccinated person-time; if they received an influenza vaccination midway through follow-up, they were censored for days 0–13 post-vaccination and then contributed vaccinated person-time beginning 14 days post-vaccination. Follow-up ended at the earliest of the following: date of influenza virus infection, study withdrawal date, or the end of the influenza season (31 May 2023). Influenza virus infections occurring within 0–13 days post-vaccination were not included in VE analyses, as these participants were censored during that time.

The date of influenza virus infection was defined as the sample collection date of a specimen that tested positive by RT-PCR for influenza. Consecutive influenza detections within a 30-day period were considered a single infection. There were 3 infection outcomes of interest: (1) laboratory-confirmed influenza virus infection defined as a positive RT-PCR with or without associated symptoms, (2) asymptomatic infection, and (3) influenza illness, defined as a positive test with any associated symptom. We also explored another definition of symptomatic influenza illness: positive influenza PCR test plus febrile symptoms. For participants reporting symptoms through active surveillance, additional illness surveys were sent every 7 days until illness resolution was reported; asymptomatic participants did not receive illness surveys but confirmed absence of symptoms at the time RT-PCR test results were communicated. Clinical outcomes such as medical care-seeking were also self-reported via the illness survey.

Statistical Analyses

First, we compared participant vaccination status by study site, race and ethnicity, gender, age group, occupation, pre-existing conditions, smoking status, and mask-wearing practices at work. We calculated rates of all laboratory-confirmed influenza virus infection, asymptomatic influenza virus infection, and illness per 100 000 vaccinated versus unvaccinated person-days of follow-up. We summarized the symptomatic fraction of influenza virus infections, frequency of specific symptoms among participants with influenza illness, and medical care-seeking.

Next, we estimated adjusted hazard ratios (aHRs) comparing rates of laboratory-confirmed influenza, asymptomatic infection, and influenza illness among vaccinated versus unvaccinated participants. For the outcome of laboratory-confirmed influenza, aHRs were also stratified by influenza A subtype [A(H1N1)pdm09 and A(H3N2)] (described in the Supplementary Methods). We used the Andersen-Gill extension of the Cox proportional hazards regression model [11], controlling for participant occupational category (primary healthcare personnel, allied healthcare personnel, first responder, or frontline worker) and site. Asymptomatic infections were included as a competing hazard in the model of VE against influenza illness [12]. We also assessed whether aHRs differed between asymptomatic and symptomatic cases using a similar model including an interaction term between the binary vaccination status measure and a binary measure for presence of symptoms. A statistically significant aHR for this interaction term would be interpreted as rejecting the null hypothesis that aHRs were equivalent across symptomatic and asymptomatic cases. Vaccine effectiveness was calculated as $(1 - \text{aHR}) \times 100\%$.

We conducted 3 sensitivity analyses for potential bias in VE estimates. First, we calculated VE against laboratory-confirmed influenza virus infection excluding SARS-CoV-2 co-positive illness episodes from the analysis. Second, we calculated VE excluding participants who had less than 80% adherence to weekly swabbing. Third, we calculated influenza VE against non-influenza, SARS-CoV-2-negative illness episodes (ie, participants reporting symptoms without an influenza or SARS-CoV-2-positive test result) to assess potential under-ascertainment of influenza in the cohort or residual bias in VE estimates.

RESULTS

Study Population and Vaccination

Of 3990 HEROES-RECOVER participants who were enrolled during the 2022–2023 influenza season, we excluded 10 (0.3%) who were not continuously enrolled, 136 (3.4%) with missing influenza vaccination status in 2022–2023, and 52 (1.3%) who indicated they were vaccinated but did not report a date, resulting in 3785 eligible participants. These participants had high adherence to weekly surveillance; the median (interquartile range [IQR]) percentage of weeks during the study period when participants submitted respiratory specimens was 91% (74%–97%).

In all, 2465 (65%) participants received an influenza vaccine and 1320 (35%) remained unvaccinated for the entire 2022–2023 season. Influenza vaccination rates varied by gender (72% among females vs 54% among males), race and ethnicity (50% among Hispanic

participants vs 69% among White, non-Hispanic and Asian, non-Hispanic participants), and occupation (36% among first responders vs 90% among primary healthcare personnel). Vaccination rates also varied by study site, with the highest vaccine coverage in Minnesota (85%) and the lowest in Florida (27%); Florida had a higher proportion of participants who were first responders (58%) than did sites in other states (5%–22%) (Table 1). Vaccinated participants were more likely than unvaccinated participants to wear a mask at work (median percentage of time wearing a mask at work was 50% vs 7%).

Influenza Virus Infections and Symptoms

Between 1 July 2022 and 31 May 2023, 279 RT-PCR–confirmed influenza virus infections and 1044 PCR–confirmed SARS-CoV-2 infections were identified. There were 12 coinfections of influenza virus and SARS-CoV-2; all were symptomatic. Ten participants experienced 2 laboratory–confirmed influenza virus infections more than 30 days apart during the study period, resulting in 269 first influenza virus infections during 703 326 person-days of follow-up (38.2 per 100 000 person-days). Among these 269 infections, 68 (25%) were asymptomatic. The presence of symptoms did not vary significantly by age group (range: 74%–75%) or occupation (range: 68% among primary healthcare personnel to 83% among allied healthcare personnel; $P = .22$). Of 201 (75%) infections associated with at least 1 symptom, 81% of participants reported cough, 66% reported febrile symptoms, and 55% reported sore throat. In addition, 76% of participants reported nasal congestion, 72% reported fatigue, and 57% reported body aches (Supplementary Table 1). Among 185 symptomatic participants with confirmed infection who reported the number of days they were sick in bed, the median (IQR) was 2 (0–3) days. Percentages of participants with RT-PCR–confirmed influenza virus infection during the 2022–2023 season were similar by study site, gender, occupation, presence of a chronic condition, and current smoking status (Table 1). Similar proportions of vaccinated (19%) and unvaccinated (21%) participants with an influenza virus infection sought medical care for illness, with 1 hospitalization in an unvaccinated participant.

Vaccine Effectiveness

Ten participants' influenza virus infections occurred within 14 days of vaccination; these participants were censored at their vaccination date, resulting in 259 infections being included in VE analyses. The incidence of any influenza virus infection per 100 000 person-days was 31.6 among vaccinated participants and 44.8 among unvaccinated participants (aHR: .68; 95% CI: .51–.90) (Figure 1, Table 2); influenza vaccination was associated with a 32% reduced risk of any influenza virus infection (VE: 32%; 95% CI: 10%–49%). The incidence of symptomatic illness per 100 000 person-days was 23.7 among vaccinated participants and 33.2 among unvaccinated participants (aHR: .62; 95% CI: .45–.85); influenza vaccination was associated with a 38% reduced risk of symptomatic illness (VE: 38%; 95% CI: 15%–55%). The aHR was similar when using the alternate definition of symptomatic illness requiring febrile symptoms (aHR: .72; 95% CI: .49–1.05). The incidence of asymptomatic infection per 100 000 person-days was 8.0 among vaccinated and 11.6 among unvaccinated participants (aHR: .87; 95% CI: .51–1.47); VE against asymptomatic influenza was not statistically significant (VE: 13%; 95% CI: –47%, 49%) (Table 2). In the interaction model, aHRs were statistically significantly different between

symptomatic and asymptomatic infections (interaction term coefficient: .60; 95% CI: .03–1.16). Vaccine effectiveness was similar against A(H1N1)pdm09-associated (VE: 47%; 95% CI: 9%–69%) and A(H3N2)-associated (VE: 52%; 95% CI: 26%–69%) infections, although the 95% CI for VE against A(H1N1)pdm09 was wider (Table 2 and Supplementary Table 2). Only 3 influenza B infections occurred in this population, and therefore VE against influenza B was not estimated.

In sensitivity analyses, VE against symptomatic illness was similar when excluding 12 coinfections of influenza and SARS-CoV-2 (VE: 35%; 95% CI: 12%–53%). When we excluded 1142 (29%) participants with less than 80% adherence to swabbing, VE was slightly higher against symptomatic illness (VE: 44%; 95% CI: 24%–59%), and VE against asymptomatic infection remained not statistically significant (VE: 29%; 95% CI: –23%, 60%). Influenza vaccination was not associated with rates of non-influenza, SARS-CoV-2–negative illness (237 per 100 000 vaccinated person-days vs 252 per 100 000 unvaccinated person-days; aHR: 1.01; 95% CI: .92–1.10).

DISCUSSION

Cohort studies such as HEROES-RECOVER provide a valuable opportunity for further evidence on the role of vaccination in preventing infection and reducing illness severity. The 2022–2023 influenza season was notable for an early start of influenza virus circulation, with increases in influenza-associated outpatient visits and hospitalizations beginning in October 2022 [13]. The majority of influenza viruses detected and subtyped during the 2022–2023 season were A(H3N2) viruses, with less circulation of A(H1N1)pdm09 viruses; most [14] were genetically and antigenically similar to the viruses included in the 2022–2023 Northern Hemisphere influenza vaccine [15, 16]. This analysis found that influenza vaccination provided protection against illness associated with both A(H1N1)pdm09 and A(H3N2) infections, but did not reduce rates of asymptomatic infection. Overall, there was a 38% reduction in influenza illness.

In this cohort of individuals at increased occupational risk of influenza virus exposure, overall rates of influenza virus infection and illness were low; fewer than 6% of vaccinated participants and 10% of unvaccinated participants had laboratory-confirmed influenza virus infection during the 2022–2023 season. While this cohort consists of individuals with frequent occupational exposures to respiratory viruses, participants may have had reduced susceptibility due to prior infection. The cohort included highly vaccinated healthcare workers and less vaccinated first responders, which is consistent with reported COVID-19 vaccine uptake in these groups [17]. The effectiveness of influenza vaccination against symptomatic infection during the 2022–2023 season in this cohort was similar to estimates from other observational studies using the test-negative study design [18–20]. Our findings are also consistent with studies from previous influenza seasons among highly exposed healthcare workers, which is important because influenza is a major cause of missed work, burden on healthcare and emergency response systems, and economic losses [21, 22]. We also found that influenza vaccination did not reduce the risk of asymptomatic infection, both in the stratified VE model and in the interaction model directly comparing symptomatic and asymptomatic infection, indicating that this finding is unlikely to be due solely to the

relatively smaller number of asymptomatic infections. This finding is consistent with a test-negative study of COVID-19 VE against symptomatic illness among healthcare personnel and persons with direct contact with persons with laboratory-confirmed COVID-19 [23]. Together, this evidence suggests that vaccination against influenza and COVID-19 may provide protection against illness in individuals at increased risk of infection.

Prospective cohort studies like HEROES-RECOVER that include regular testing and symptom assessments are critical for understanding the asymptomatic fraction and VE against asymptomatic infection. In this analysis, we did not find evidence that seasonal influenza vaccine prevented asymptomatic infection but did see evidence of protection against symptomatic infection. The role of vaccines against viral respiratory pathogens in protecting against symptomatic illness has been increasingly recognized, including for SARS-CoV-2. Prospective cohorts have found evidence of protection against both SARS-CoV-2 infection and symptom progression following vaccine booster doses [24, 25], but additional research is needed to further understand vaccine protection against influenza infection versus disease. Understanding the protection provided by viral respiratory vaccines is important to guide efforts to decrease the transmission of these pathogens, as well as public health messaging about the importance of vaccines.

This analysis has limitations. First, influenza virus infections may have gone undetected, especially if they were asymptomatic. However, one of the unique strengths of this cohort was the weekly swabbing regardless of symptom status. We found high adherence to weekly testing and null VE against illnesses with unknown etiology, suggesting a high probability of detecting influenza virus infections. Second, although we controlled for occupational and site differences, there might be residual sources of unmeasured confounding. For example, if vaccinated persons were more engaged with symptom reporting and more likely to report even mild symptoms, then we might have underestimated VE against symptomatic illness. Finally, the HEROES-RECOVER cohort is more likely to be vaccinated (including a history of prior vaccination) and exposed to influenza virus than the general population [26]. Vaccine effectiveness against asymptomatic infection among children may differ. However, our estimates of VE against influenza illness were similar to those reported among adults in other studies during the 2022–2023 season [20].

Conclusion

During the 2022–2023 influenza season, influenza vaccination provided a significant reduction in the risk of any symptomatic influenza illness, but not asymptomatic infection, in a prospective occupational cohort. Protection was similar against infection with influenza A(H3N2) as with influenza A(H1N1) pdm09. Asymptomatic infections represented a substantial proportion of all influenza virus infections, highlighting the importance of further research to understand VE and transmission of influenza among those with asymptomatic infections.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability.

For questions about data availability, please contact the corresponding author.

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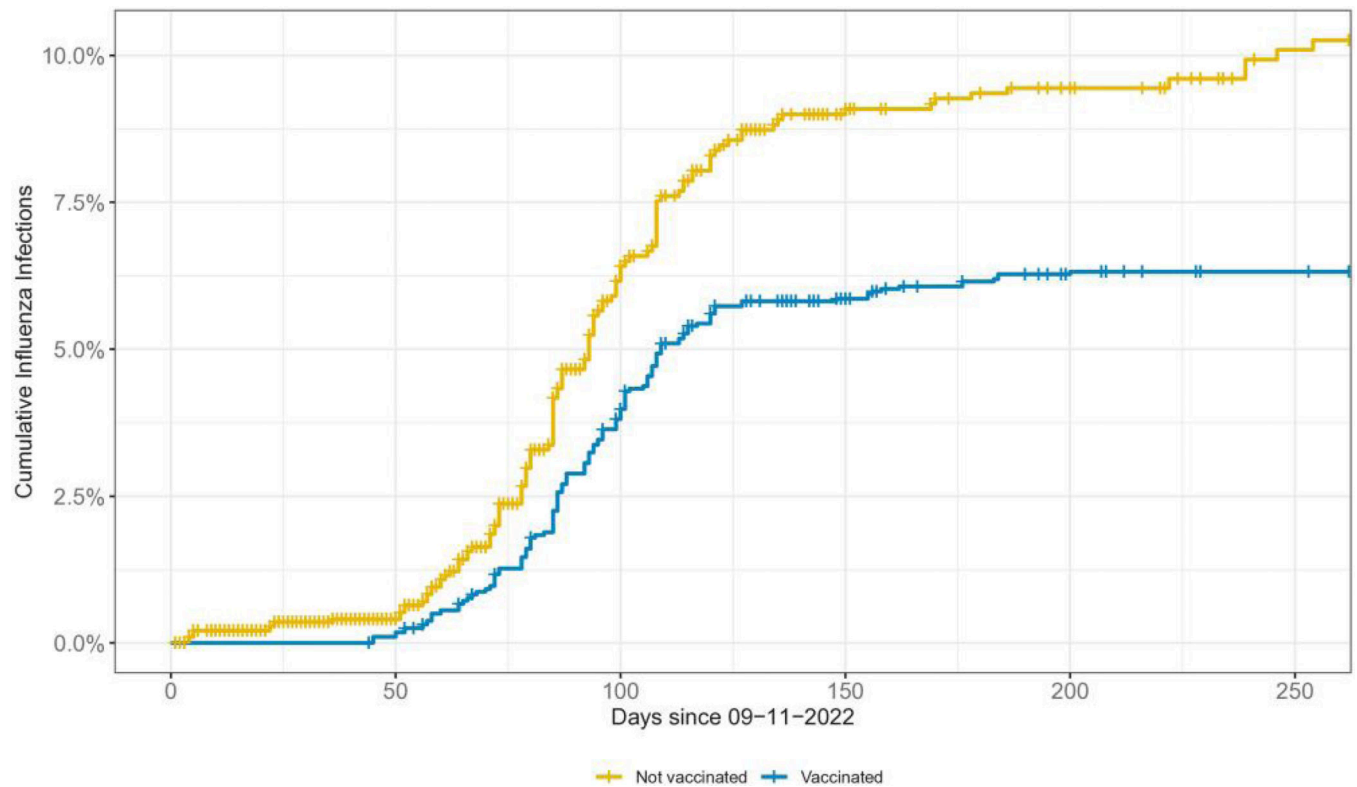


Figure 1.

Cumulative incidence of 259 laboratory-confirmed influenza virus infections among the HEROES-RECOVER cohort, by 2022–2023 seasonal influenza vaccination status. Abbreviation: HEROES-RECOVER, Healthcare, Emergency Response, and Other Essential Workers Surveillance–Research on the Epidemiology of SARS-CoV-2 in Essential Response Personnel.

Table 1. Characteristics, Infections, and Vaccination Among the HEROES-RECOVER Cohort Participants During the 2022–2023 Influenza Season

	Overall No. (%) ^a	PCR-Confirmed Influenza During 2022–2023 Season, ^b n (%)	Received Influenza Vaccine After 1 July 2022, ^b n (%)
Total participants	3785	269 (7.1)	2465 (65)
Cohort site			
Texas	271 (7.2)	22 (8.1)	203 (75)
Minnesota	618 (16)	40 (6.5)	525 (85)
Arizona	1771 (47)	115 (6.5)	1167 (66)
Utah	700 (18)	59 (8.4)	455 (65)
Florida	425 (11)	33 (7.7)	115 (27)
Gender ^c			
Female	2396 (63)	153 (6.4)	1722 (72)
Male	1380 (37)	115 (8.3)	739 (54)
Age group			
18–49 y	1423 (38)	108 (7.6)	907 (64)
≥50 y	2362 (62)	161 (6.8)	1558 (66)
Race/ethnicity			
White, NH	2770 (74)	191 (6.9)	1925 (69)
Black, NH	124 (3.3)	9 (7.3)	74 (60)
Asian, NH	98 (2.6)	10 (10)	68 (69)
Hispanic	684 (18)	54 (7.9)	340 (50)
Another race	86 (2.2)	4 (4.7)	45 (52)
Occupation ^d			
Primary healthcare personnel	568 (15)	34 (6.0)	509 (90)
Allied healthcare personnel	1276 (34)	76 (6.0)	1038 (81)
First responder	774 (20)	69 (8.9)	279 (36)
Frontline worker	1167 (31)	90 (7.7)	639 (55)
Chronic conditions ^e			
None	2688 (71)	189 (7.0)	1675 (62)
≥1	1097 (29)	80 (7.3)	790 (72)
Current smoker			

	Overall No. (%) ^a	PCR-Confirmed Influenza During 2022–2023 Season, ^b n (%)	Received Influenza Vaccine After 1 July 2022, ^b n (%)
Yes	797 (22)	51 (6.4)	528 (66)
No	2901 (78)	211 (7.3)	1894 (65)

Abbreviations: HEROES-RECOVER, Healthcare, Emergency Response, and Other Essential Workers Surveillance—Research on the Epidemiology of SARS-CoV-2 in Essential Response Personnel; NH, non-Hispanic; PCR, polymerase chain reaction.

^aColumn percentages.

^bRow percentages.

^cAn additional 9 (<1%) participants self-reported as transgender, another gender not listed, or did not provide a gender.

^dPrimary healthcare personnel = physicians, physician assistants, nurse practitioners, dentists; Allied healthcare personnel = nurses, therapists, technicians, medical assistants, and orderlies; First responder = fire services, law enforcement, or other emergency services; Frontline worker = both public- and non-public-facing essential workers including education, food production and service occupations.

^eChronic conditions = asthma, chronic lung diseases (eg, chronic obstructive pulmonary disease [COPD], emphysema), cancer, diabetes, heart disease, hypertension, immunosuppression, kidney disease, liver disease including chronic hepatitis, autoimmune disease, or any other condition requiring clinical care for at least 6 months.

Table 2.
Influenza Vaccine Effectiveness Against All Infections, Symptomatic Illnesses, and Asymptomatic Infections

	Person-Days	PCR-Positive	Rate Per 100 000 Person-Days	Unadjusted Hazard Ratio (95% CI)	Adjusted ^a Hazard Ratio (95% CI)	VE (95% CI), %
<i>All infections^b</i>						
Unvaccinated	276 730	124	44.8	Ref	Ref	Ref
Vaccinated	426 596	135	31.6	.64 (.50–.82)	.68 (.51–.90)**	32 (10–49)**
<i>A(H1N1)pdm09</i>						
Unvaccinated	290 739	39	13.5	Ref	Ref	Ref
Vaccinated	441 817	33	7.47	.47 (.29–.74)	.53 (.31–.91)*	47 (9–69)*
<i>A(H3N2)</i>						
Unvaccinated	294 878	50	17.0	Ref	Ref	Ref
Vaccinated	445 883	52	11.7	.54 (.42–.68)	.48 (.31–.74)**	52 (26–69)**
<i>Symptomatic</i>						
Unvaccinated	276 730	92	33.2	Ref	Ref	Ref
Vaccinated	426 596	101	23.7	.63 (.47–.83)	.62 (.45–.85)**	38 (15–55)**
<i>Asymptomatic</i>						
Unvaccinated	276 730	32	11.6	Ref	Ref	Ref
Vaccinated	426 596	34	8.0	.68 (.42–1.12)	.87 (.51–1.47)	13 (–47, 49)

* $P < .05$

** $P < .01$.

Abbreviations: PCR, polymerase chain reaction; Ref, reference; VE, vaccine effectiveness.

^a Adjusted for study site (Arizona, Minnesota, Utah, Texas, Florida) and occupation (primary healthcare personnel, secondary healthcare personnel, first responder, or frontline worker).

^b Includes 193 symptomatic and 66 asymptomatic infections; 254 influenza A [72 A(H1N1)pdm09, 102 A(H3N2), 82 subtype unknown] and 3 influenza B infections.