

# Pragmatic Assessment of Influenza Vaccine Effectiveness in the Department of Defense (PAIVED): Updates from Year 4 of a Multi-site Trial



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## Background

The SARS-CoV-2 pandemic has emphasized the need for effective vaccines to combat the burden of respiratory infections. The SARS-CoV-2 vaccines authorized to date have been remarkably effective at preventing severe disease.

Despite a well-established program, influenza vaccine effectiveness (VE) remains suboptimal. Influenza VE is dependent on many factors including the match of the circulating strain to the vaccine, as well as the timing of influenza spread in a community. The platform in which the vaccine is developed, e.g., egg-based vs non-egg based, has been hypothesized as a potential contributor.

The Pragmatic Assessment of Influenza Vaccine Effectiveness in the DoD (PAIVED) study is a randomized clinical trial of three FDA-licensed vaccine types (egg-based, cell-based, and recombinant), designed to determine which of these vaccines performs best among adults in a military setting.

## Methods

### Primary objective

Compare the relative effectiveness of 3 types of licensed influenza vaccines for prevention of laboratory-confirmed influenza

- 4 influenza seasons: 2018/19, 2019/20, 2020/21, 2021/22

### Participants

- DoD healthcare beneficiaries aged 18+
  - Active duty (AD), dependents, and retirees

### Locations

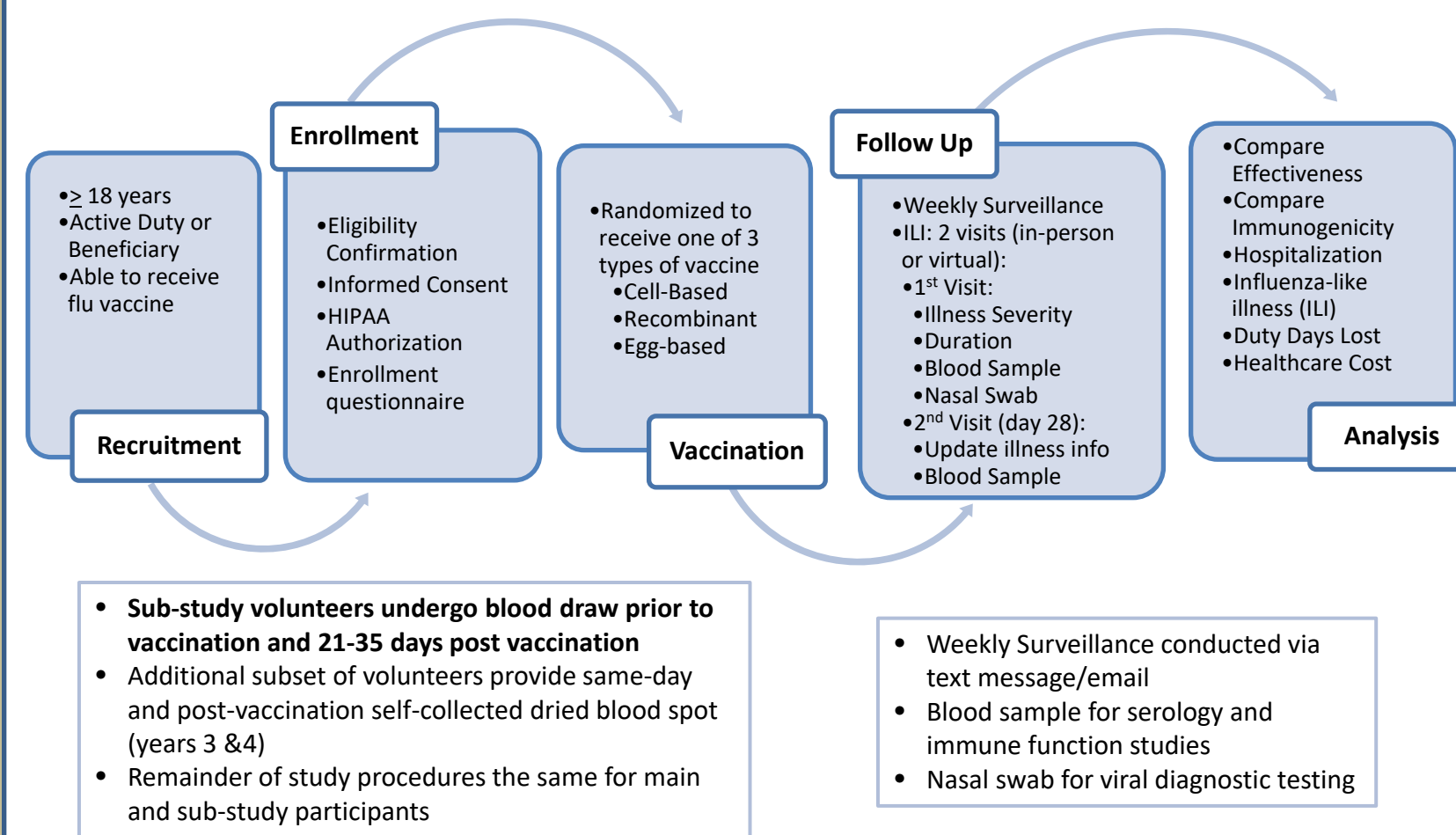
San Diego, CA (NMCS/D/MCRD); Annapolis, MD (USNA); Bethesda, MD (WRNMMC, USU); Fort Bragg, NC (WAMC); Fort Hood, TX (CRDAMC); San Antonio, TX (BAMC, WHASC); Portsmouth, VA (NMCP); Tacoma, WA (MAMC)

### Study Procedures (Figure 1)

- Randomized (1:1:1) to receive 1 of 3 licensed influenza vaccine formulations (egg-based, recombinant, or cell-culture derived)
- Weekly surveys throughout the influenza season querying the development of **influenza like illness (ILI)**, defined as:
  - Cough or sore throat, **and**
  - Feverish or having chills, **or**
  - Body aches or fatigue
- When ILI identified, participants completed:
  - Daily symptom diary (Flu-Pro) x 7 days
  - 2 visits (virtual or in person), 4 weeks apart
    - Nasal swab for viral PCR (acute)
    - Blood sample (acute & convalescent)

## Results

Figure 1. PAIVED summary flow chart



- Sub-study volunteers undergo blood draw prior to vaccination and 21-35 days post vaccination
- Additional subset of volunteers provide same-day and post-vaccination self-collected dried blood spot (years 3 & 4)
- Remainder of study procedures the same for main and sub-study participants
- Weekly Surveillance conducted via text message/email
- Blood sample for serology and immune function studies
- Nasal swab for viral diagnostic testing

Figure 2. Pathogens identified in PAIVED participants with ILI, by influenza season

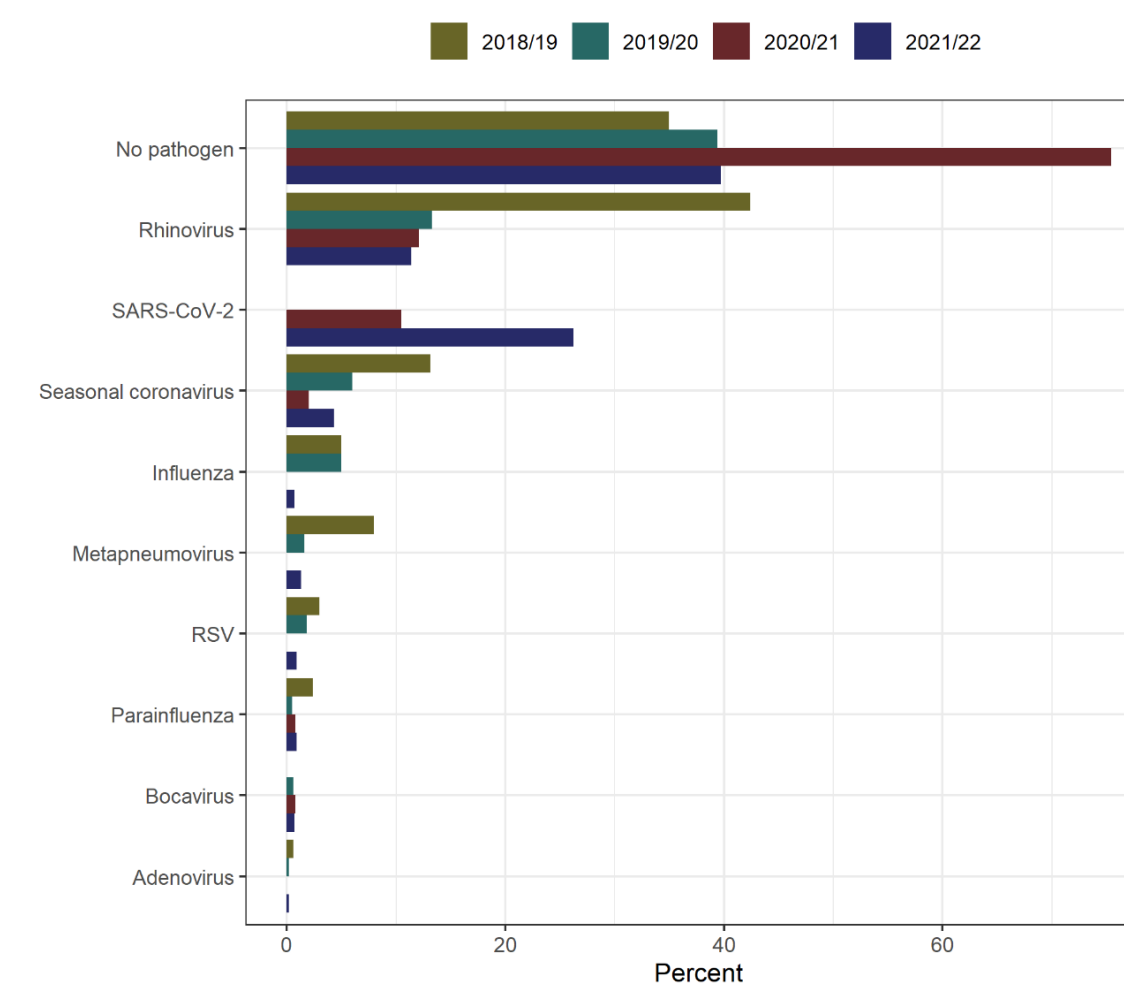


Table 1. PAIVED summary over four seasons<sup>1</sup>

	2018/19 (N=1623)	2019/20 (N=5879)	2020/21 (N=3259)	2021/22 (N=4690)	Total (N=15451)
# military bases	5	9	10	9	10
# in immunogenicity substudy <sup>2</sup>	179	362	296	321	1,158
Age					
Mean (SD)	35.7 (19.2)	33.6 (14.6)	33.6 (12.5)	34.1 (12.6)	34.0 (14.2)
Sex					
Missing	0 (0.0%)	1 (0.0%)	2 (0.1%)	0 (0.0%)	3 (0.0%)
Female	412 (25.4%)	1820 (31.0%)	1034 (31.7%)	1696 (36.2%)	4962 (32.1%)
Male	1211 (74.6%)	4058 (69.0%)	2223 (68.2%)	2994 (63.8%)	10486 (67.9%)
Race					
White	875 (53.9%)	3456 (58.8%)	1839 (56.4%)	2649 (56.5%)	8819 (57.1%)
Hispanic	453 (27.9%)	1114 (18.9%)	598 (18.3%)	789 (16.8%)	2954 (19.1%)
Black	139 (8.6%)	666 (11.3%)	373 (11.4%)	551 (11.7%)	1729 (11.2%)
Asian	76 (4.7%)	359 (6.1%)	255 (7.8%)	368 (7.8%)	1058 (6.8%)
Multiple races	59 (3.6%)	207 (3.5%)	134 (4.1%)	258 (5.5%)	658 (4.3%)
Unknown/Other	21 (1.3%)	77 (1.3%)	60 (1.8%)	75 (1.6%)	233 (1.5%)
Military status					
Active duty	982 (60.5%)	4465 (75.9%)	2703 (82.9%)	3980 (84.9%)	12130 (78.5%)
Retired military	310 (19.1%)	715 (12.2%)	317 (9.7%)	409 (8.7%)	1751 (11.3%)
Dependent	331 (20.4%)	699 (11.9%)	231 (7.1%)	296 (6.3%)	1557 (10.1%)
Missing	0 (0.0%)	0 (0.0%)	7 (0.2%)	5 (0.1%)	12 (0.1%)
# with at least 1 ILI	330 (20.3%)	1628 (27.7%)	315 (9.7%)	1291 (27.5%)	3564 (23.1%)
Total ILIs	351	1988	357	1564	4260
Mean duration (days) (SD)	12.0 (11.1)	10.9 (9.6)	10.6 (8.2)	11.0 (6.6)	11.0 (8.7)
Mean days of limited activity (SD)	5.1 (9.3)	5.3 (5.9)	5.4 (5.8)	5.2 (4.7)	5.2 (5.9)
Mean days of missed work (SD)	1.2 (2.2)	1.4 (2.7)	3.4 (5.8)	2.7 (3.5)	2.2 (3.5)

<sup>1</sup> Individuals considered enrolled if they enrolled in the study and did not withdraw within one day  
<sup>2</sup> Participants with both pre- and post-vaccination blood draw

## Results (continued)

- PAIVED year 4 enrolled 4,690 participants (Table 1)
- A total of 1,564 ILIs were reported in the 2021-22 season
  - 1053 participants reported a single ILI, 203 participants reported two ILIs, and 35 participants reported three ILIs
- Few (n=3) hospitalizations reported this season, however ILIs were associated with substantial burden of illness
  - Average of 5.2 days of limited activity & 2.7 days missed work
- SARS-CoV-2 was the most common pathogen identified from nasal swabs collected during acute ILI in year 4 (26%), followed by rhinovirus (11%) and seasonal coronaviruses (4%) (Figure 2)
  - Influenza was identified in ten participants

## Conclusions

The fourth year of PAIVED was characterized by early (pre-enrollment) spread of influenza in some areas, as well as the nationwide surge of the SARS-CoV-2 Omicron variant in December. Influenza attack rates during the last two seasons of the study were far lower than historical averages, likely due to pandemic precautions, making the data from identified cases highly valuable. Additional cases of laboratory confirmed influenza are being sought via electronic medical record data abstraction. Comparative influenza vaccine effectiveness calculations will be performed to inform future vaccine purchasing decisions, however statistical power may be limited by the relatively small number of influenza cases.

## Acknowledgments

### Disclaimer

Views expressed are those of the author(s) and do not reflect the official policy/position of USUHS, DoD, Department of the Army, Navy, or Air Force, or the DHA, Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc. (HJF), BAMC, MAMC, WRNMMC, US Army Medical Dept, US Army Office of the SG, or the USG. Investigators followed human subjects protection 45CFR46 policies.

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