

Pathogen Co-infections and Trends in Influenza-like Illness in PAIVED

Stephanie A. Richard^{1,2}, Christina Schofield³, Limone Collins⁴, Christina Spooner⁴, Srihari Seshadri⁴, Anuradha Ganesan^{1,2,5}, Wesley Campbell⁵, David Hrcncir^{4,6,7}, Tahaniyat Lalani^{1,2,8}, Tyler Warkentien⁸, Katrin Mende^{1,2,9}, Ana E. Markelz⁹, Catherine M. Berjohn^{1,10}, Bruce McClenathan^{4,11}, Jitendrakumar R. Modi¹², Alan Williams¹³, Timothy H. Burgess¹, Rhonda E. Colombo^{1,2,3,14}

¹Infectious Disease Clinical Research Program, Department of Preventive Medicine and Biostatistics, Uniformed Services University of the Health Sciences, Bethesda, MD, USA, ²The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., Bethesda, MD, USA, ³Madigan Army Medical Center, Tacoma, WA, USA, ⁴Immunization Healthcare Division, Defense Health Agency, Bethesda, MD, Falls Church, VA, Fort Bragg, NC, and San Diego, CA, USA, ⁵Walter Reed National Military Medical Center, Bethesda, MD, USA, ⁶Carl R. Darnall Army Medical Center, Fort Hood, TX, USA, ⁷Wilford Hall Ambulatory Surgical Center, LAFB, San Antonio, TX, USA, ⁸Naval Medical Center Portsmouth, Portsmouth, VA, USA, ⁹Brooke Army Medical Center, San Antonio, TX, USA, ¹⁰Naval Medical Center San Diego, San Diego, CA, USA, ¹¹Womack Army Medical Center, Fort Bragg, NC, USA, ¹²Naval Health Clinic, Annapolis, MD, USA, ¹³Department of Family Medicine, Uniformed Services University of the Health Sciences, Bethesda, MD, USA, ¹⁴Department of Medicine, Uniformed Services University of the Health Sciences, Bethesda, MD, USA



Background

The Pragmatic Assessment of Influenza Vaccine Effectiveness in the Department of Defense (DoD) (PAIVED) is a multicenter, multiservice study assessing influenza vaccine effectiveness in active-duty service members, retirees, and dependents that spans four influenza seasons (2018/19, 2019/20, 2020/21, and 2021/22).

PAIVED offers a unique opportunity to examine influenza-like illness (ILI) trends prior to and during the COVID-19 pandemic in a prospectively followed, well-defined cohort. In addition, the PAIVED study provides insight into the frequency of respiratory virus coinfections, which are of particular concern during the current season.

Methods

Objective

Describe ILI trends among DoD beneficiaries enrolled in PAIVED across the four influenza seasons

Study Locations

Annapolis, MD; Bethesda, MD; Portsmouth, VA; Fort Bragg, NC; Fort Hood, TX; San Antonio, TX; San Diego, CA; Tacoma, WA

Participants

- Adults eligible for medical care in DoD seeking influenza vaccination and able to provide informed consent

Study Procedures

- Randomized (1:1:1) to receive one of three licensed, quadrivalent inactivated influenza vaccines (egg-based, cell-culture, and recombinant)
- Weekly surveillance for ILI symptoms (email or text)
- ILI defined *a priori* as having a cough or sore throat AND
 - Fever/feeling feverish or having chills/night sweats, OR
 - Having muscle/body aches or fatigue

Participants with Confirmed ILI

- Online symptom questionnaire (Flu-PRO) x 7 days
- 2 study visits: in-person or virtual as needed during pandemic (per infection control procedures)
 - Visit 1 (0 - 14d): interview & nasal swab & blood draw
 - Visit 2 (28 ± 7d): interview & blood draw

Statistical Analysis

- Descriptive statistics exclude those who dropped out prior to completing any ILI surveillance
- Tested for differences in demographics & ILI experience using chi-squared or Kruskal-Wallis tests as appropriate

Results

- 3,564 participants reported a total of 4,260 ILIs. Those who reported an ILI were more likely to be older, female, healthcare workers, or have more than a high school education (Table 1)
- ILI prevalence was highest in 2019-20 (27.7%), followed by 2021/22 (27.5%), 2018/19 (20.3%), and 2020/21 (9.7%)
- The weekly incidence of participants reporting ILI never exceeded 1% in 2020/21 (Figure 1)
- In the 2021/22 season, percent of participants reporting ILI peaked in late December/early January (at the time of Omicron surge)
- Among those with nasal swabs, no pathogen was detected in 53% of the episodes reported, 1 pathogen was detected in 43%, and multiple pathogens identified in 3.3% (Figure 2)
 - 2 pathogens: 3.2%; 3 pathogens: 2 swabs; 4 pathogens: 1 swab
 - 70% of episodes with multiple pathogens included rhinovirus
 - SARS-CoV-2 was most frequently co-detected with rhinovirus (n=13), seasonal coronaviruses (n=4), human bocavirus (n=5), and influenza (n=2)

Table 1. Self-reported demographics for PAIVED cohort at enrollment

	No ILI reported (N=11887)	Reported ILI (N=3564)	Total (N=15451)	p value
Age				< 0.01
Mean (SD)	33.8 (14.5)	34.5 (13.0)	34.0 (14.2)	
N missing	49	3	52	
Sex				< 0.01
Female	3531 (29.7%)	1433 (40.2%)	4964 (32.1%)	
Male	8353 (70.3%)	2131 (59.8%)	10484 (67.9%)	
Missing	3 (0.0%)	0 (0.0%)	3 (0.0%)	
Race				0.26
White	6818 (57.4%)	2000 (56.1%)	8818 (57.1%)	
Hispanic	2247 (18.9%)	709 (19.9%)	2956 (19.1%)	
Black	1344 (11.3%)	385 (10.8%)	1729 (11.2%)	
Asian	807 (6.8%)	250 (7.0%)	1057 (6.8%)	
Multiple races	488 (4.1%)	171 (4.8%)	659 (4.3%)	
Unknown/Other	183 (1.5%)	49 (1.4%)	232 (1.5%)	
Military status				< 0.01
Active duty	9355 (78.7%)	2775 (77.9%)	12130 (78.5%)	
Retired military	1375 (11.6%)	377 (10.6%)	1752 (11.3%)	
Dependent	1145 (9.6%)	412 (11.6%)	1557 (10.1%)	
Missing	12 (0.1%)	0 (0.0%)	12 (0.1%)	
Healthcare worker	3545 (29.8%)	1316 (36.9%)	4861 (31.5%)	< 0.01
Educational background				< 0.01
High school or less	5307 (44.6%)	1324 (37.1%)	6631 (42.9%)	
More than high school	6568 (55.3%)	2240 (62.9%)	8808 (57.0%)	
Missing	12 (0.1%)	0 (0.0%)	12 (0.1%)	

Figure 1. Percentage of PAIVED participants (a) reporting ILI, (b) with SARS-CoV-2, (c) with influenza, and (d) with rhinovirus, by week of year, according to ILI season

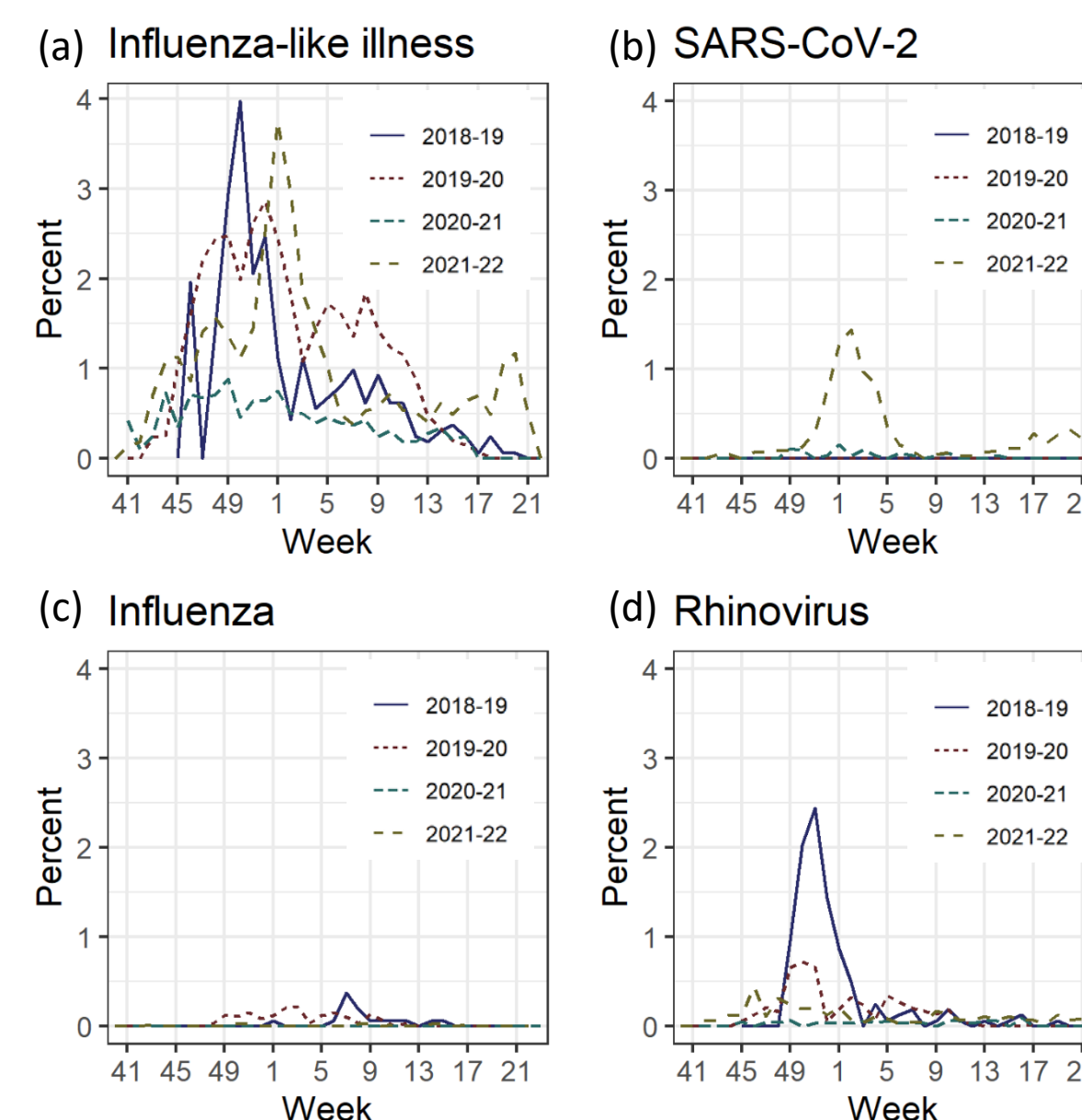
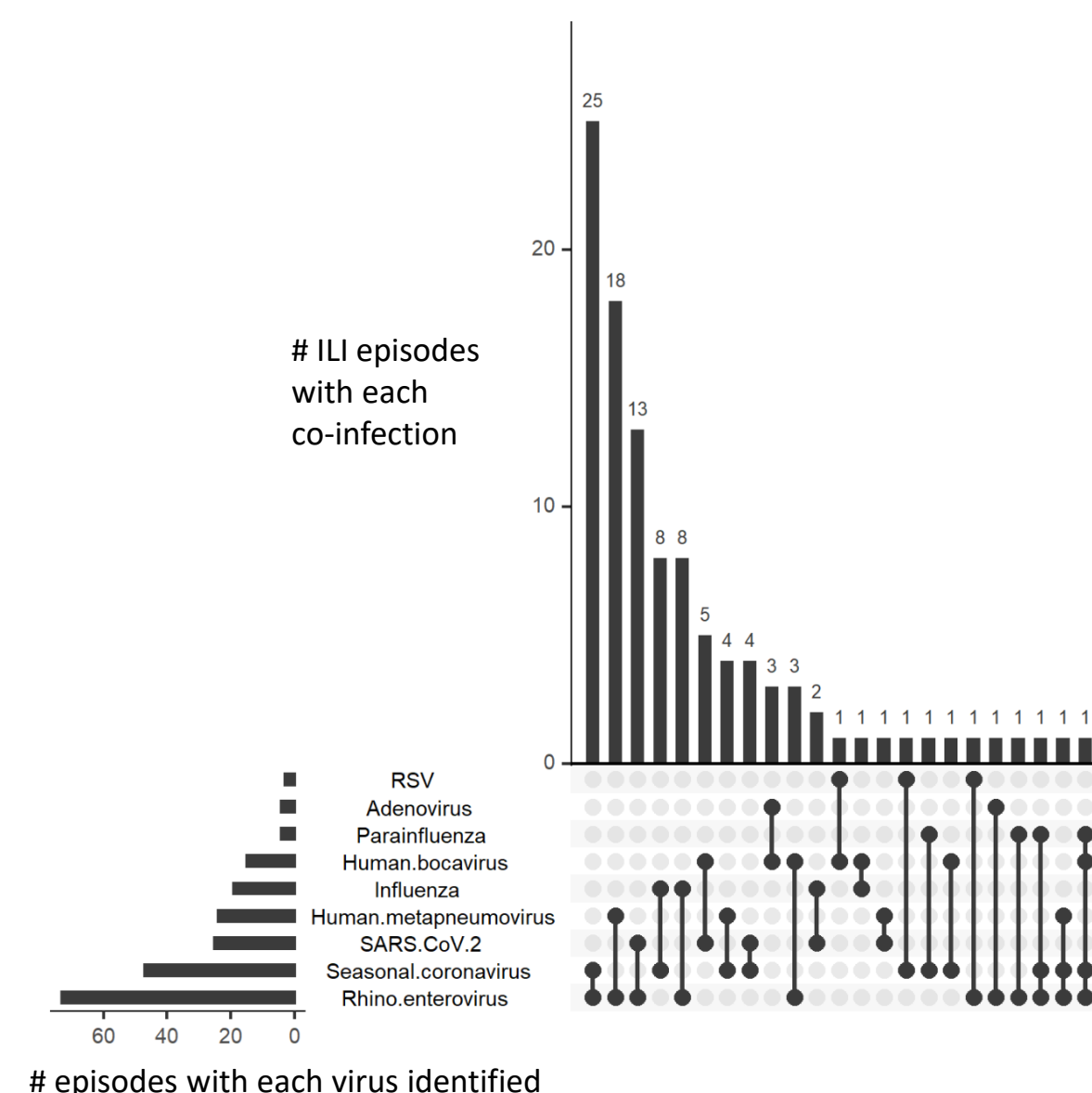


Figure 2. Pathogens co-identified in PAIVED nasal swabs collected during ILI episodes



Conclusions

ILI incidence was highest in the first two years and dropped precipitously during the third year (2020/21), consistent with national surveillance reports of influenza and outpatient ILI activity. The lack of ILI activity during 2020/21 suggests that measures taken to reduce transmission of SARS-CoV-2 hindered the spread of other respiratory viruses that season. However, emergence of the SARS-CoV-2 Omicron variant was associated with a resurgence of ILI reporting in the 2021/22 season.

Multiple pathogens were identified in approximately 5% of nasal swabs collected during acute ILIs across the four seasons, with rhinovirus and seasonal coronavirus being most commonly co-detected. Co-infections with SARS-CoV-2 and other viruses, primarily rhinovirus, were observed. Influenza and SARS-CoV-2 were only co-detected in two instances in this fully-influenza vaccinated cohort.

We plan to further evaluate the clinical, immunologic, and virologic characteristics associated with the two influenza and SARS-CoV-2 co-infection 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.

Funding

This work (IDCRP-120) was conducted by the Infectious Disease Clinical Research Program (IDCRP), a Department of Defense (DoD) program executed by the Uniformed Services University of the Health Sciences (USU) through a cooperative agreement with The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc. (HJF). This project has been supported with federal funds from the National Institute of Allergy and Infectious Diseases, National Institutes of Health (NIH), under Inter-Agency Agreement Y1-AI-5072 and from and from the Defense Health Program, U.S. Department of Defense, and Defense Health Agency Immunization Healthcare Division, under award HU0001190002

Correspondence

Rhonda E. Colombo, MD, MHS
rcolombo@idcrp.org

