Vaccines and Related Biological Products Advisory Committee Meeting

DEFENSE HEALTH AGENCY • DEPARTMENT OF DEFENSE •

DoD Influenza Surveillance and Mid-Season Vaccine Effectiveness

Armed Forces Health Surveillance Division (AFHSD)
Naval Health Research Center (NHRC)
Naval Medical Research Center (NMRC)
United States Air Force School of Aerospace Medicine (USAFSAM)
DoD Global Respiratory Pathogen Surveillance Program Partners

Presentation to the Vaccines and Related Biological Products Advisory Committee (VRBPAC) – 3 March 2022

LCDR Courtney Gustin, DrPH, MSN**

**Representing the DoD CONUS and OCONUS lab-based influenza surveillance activities

Briefing Outline

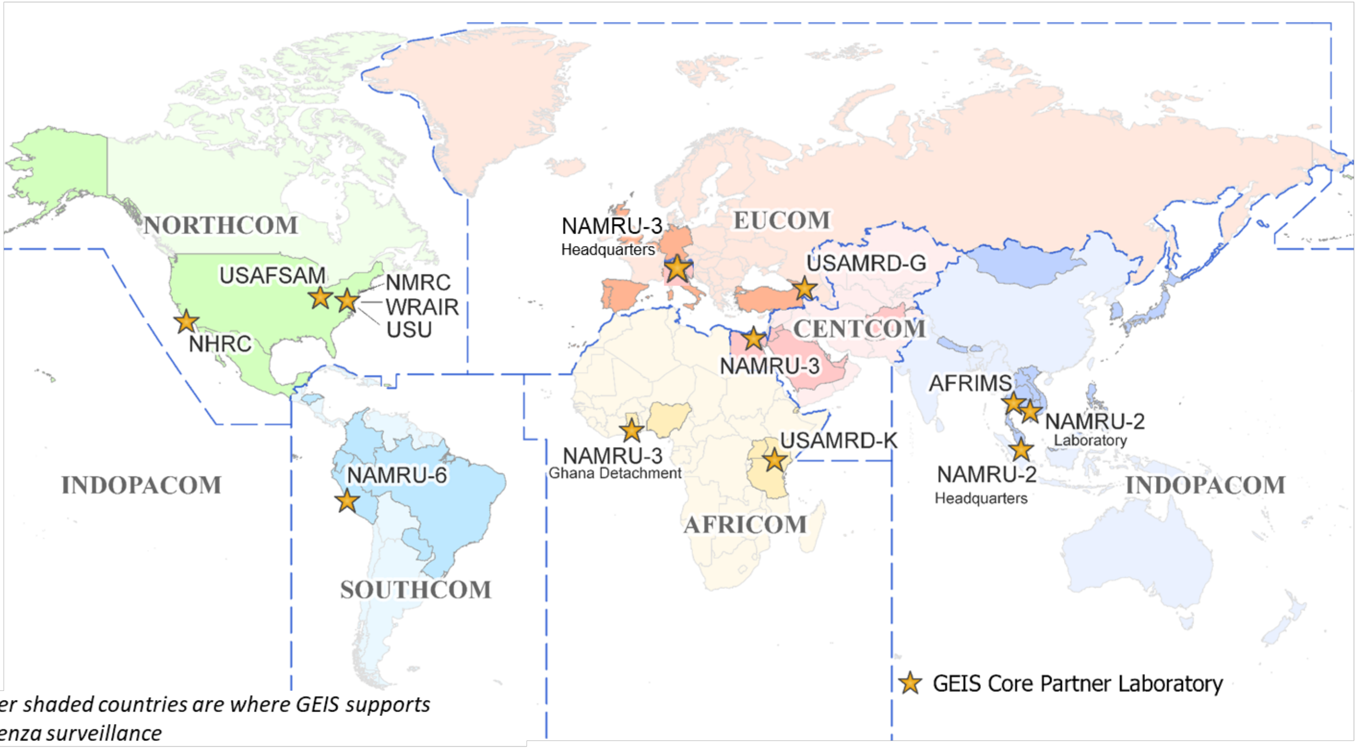
Purpose: Provide an update to the VRBPAC on DoD influenza surveillance activities for 2022 -2022

1. Program Description
2. DoD Influenza Subtype Circulation
3. Antigenic Characterization
4. Vaccine Effectiveness in US Service Members
5. Vaccine Strain Recommendations

Breadth of DoD Influenza Surveillance

- **Global Influenza Surveillance**
  - Approximately 400 locations in over 30 countries
    - ✓ Military; local government/academic
  - Extensive characterization capabilities within the DoD
    - ✓ Culture, PCR, sequencing, serology
  - Rapid sharing of results with CDC and/or regional WHO reference centers
    - ✓ Yearly average: ~30,000 samples collected and analyzed each year
- **Comprehensive Epidemiology and Analysis Capabilities**
  - 1.33 Million Active Duty records (health care utilization, immunizations, deployment, reportable diseases, etc.)
    - ✓ Produce Medical Surveillance Monthly Report (MSMR), ad-hoc requests, studies/analyses,
    - ✓ Weekly influenza reports
    - ✓ Vaccine safety and effectiveness studies

GEIS-Supported Influenza Surveillance Footprint



Darker shaded countries are where GEIS supports influenza surveillance

DoD Influenza Subtype Circulation

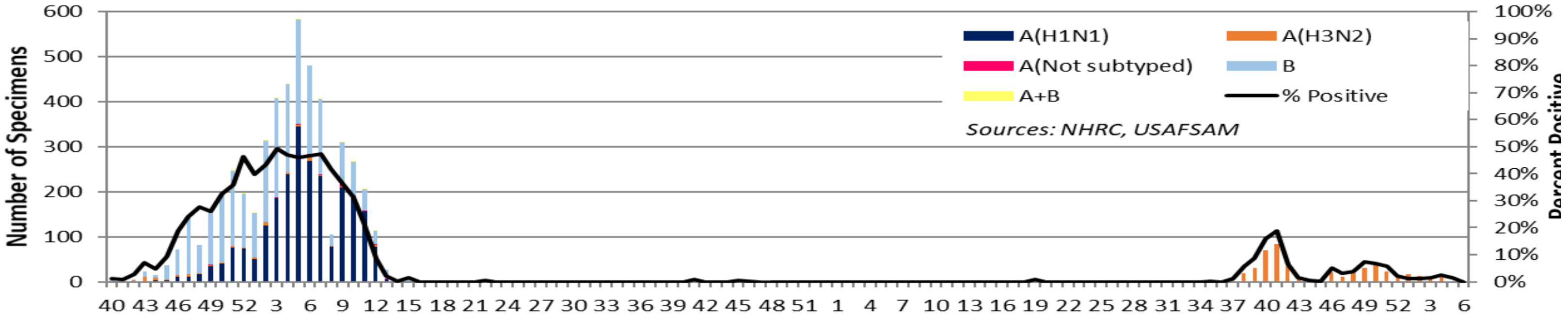
DoD Influenza Subtype Circulation

- **Common themes for the 2021-2022 season**
    - ALL laboratories and nations continued to be affected by the **SARS-CoV-2 pandemic**
    - Concurrent testing and assay validation for SARS-CoV-2 and influenza
    - While surveillance estimates for DoD on the next few slides are lower than usual, influenza was detected in all GCCs (in some places for the first time since the beginning of the pandemic)
- **Region-specific examples**
    - North America: installation-wide influenza A outbreaks
    - Africa: frequent detection of Influenza A Virus (IAV) and Influenza B Virus (IBV), including A(H1N1) in West Africa
    - Southeast Asia: persistent influenza in Nepal

Subtype Circulation: North America

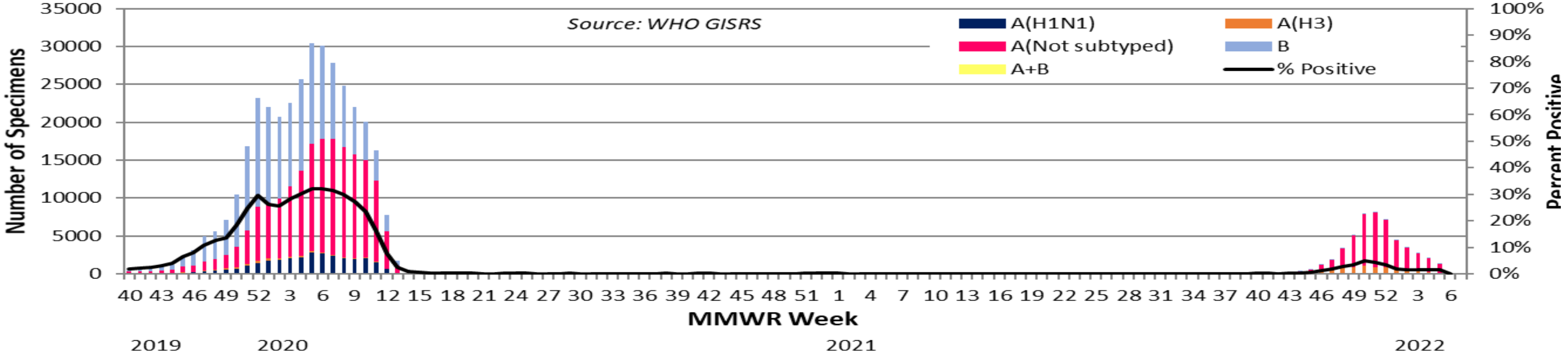
Number and Proportion of Specimens Positive for Influenza by Subtype

DoD
Surveillance



Sources: NHRC, USAFSAM

WHO
Surveillance

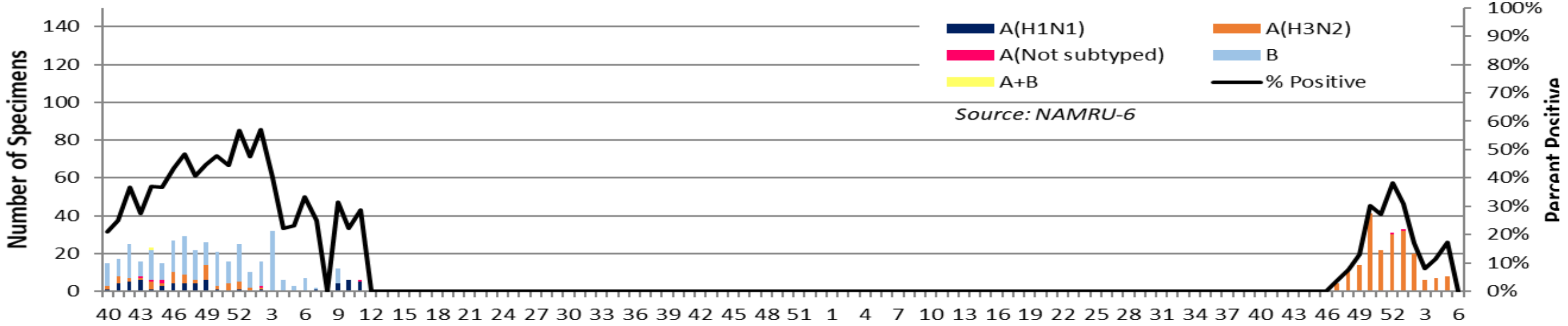


Source: WHO GISRS

Subtype Circulation: South America

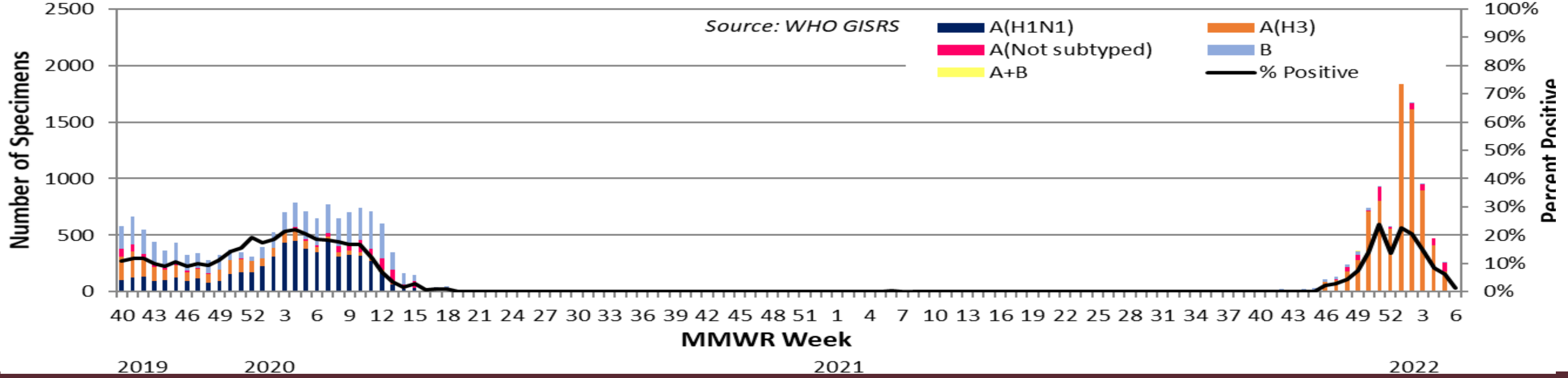
Number and Proportion of Specimens Positive for Influenza by Subtype

DoD Surveillance



Source: NAMRU-6

WHO Surveillance

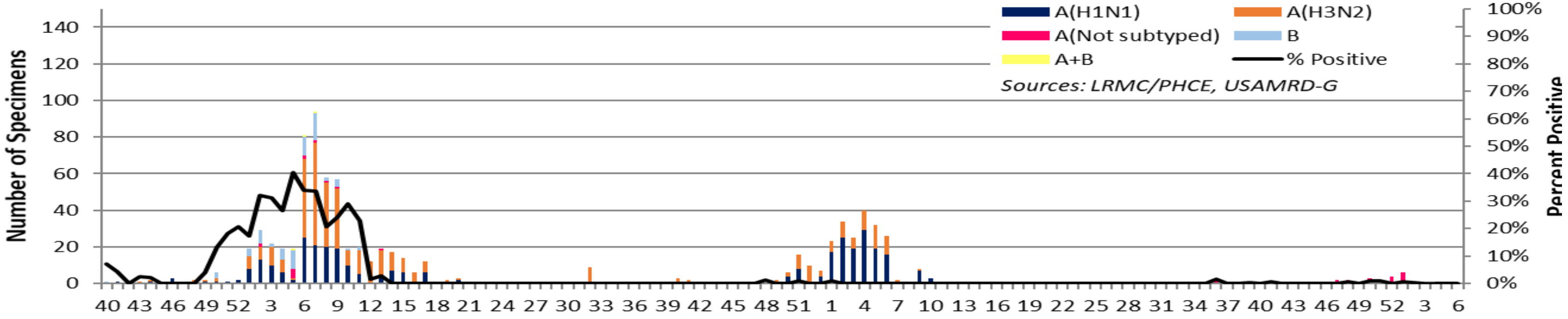


Source: WHO GISRS

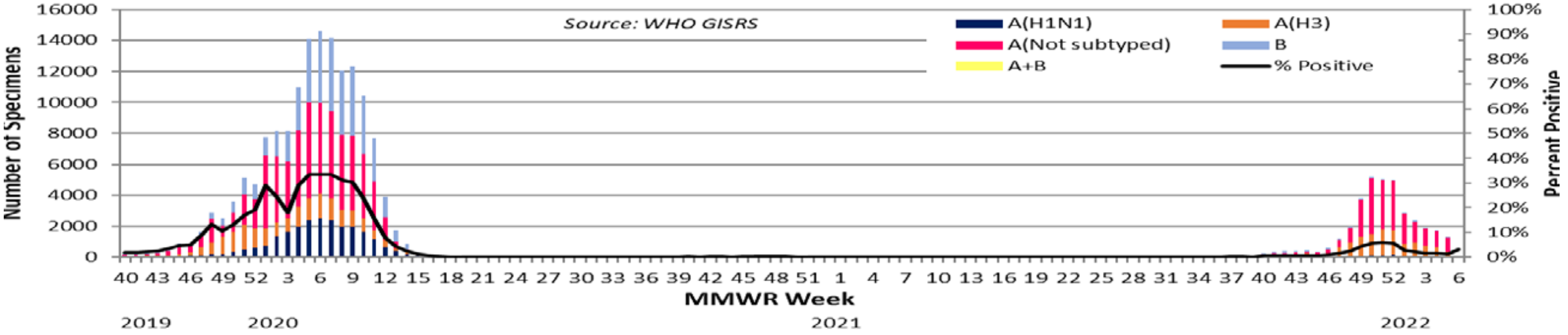
Subtype Circulation: Europe

Number and Proportion of Specimens Positive for Influenza by Subtype

DoD
Surveillance



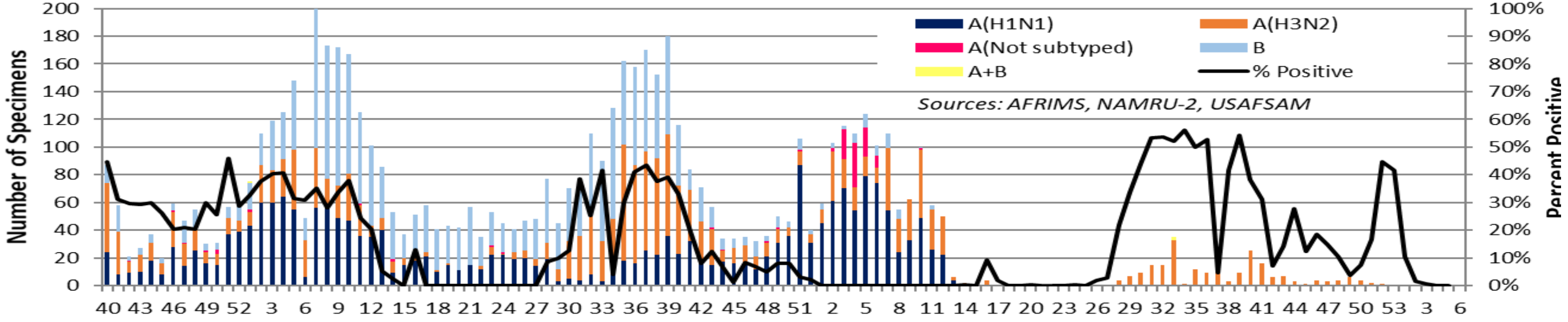
WHO
Surveillance



Subtype Circulation: Asia

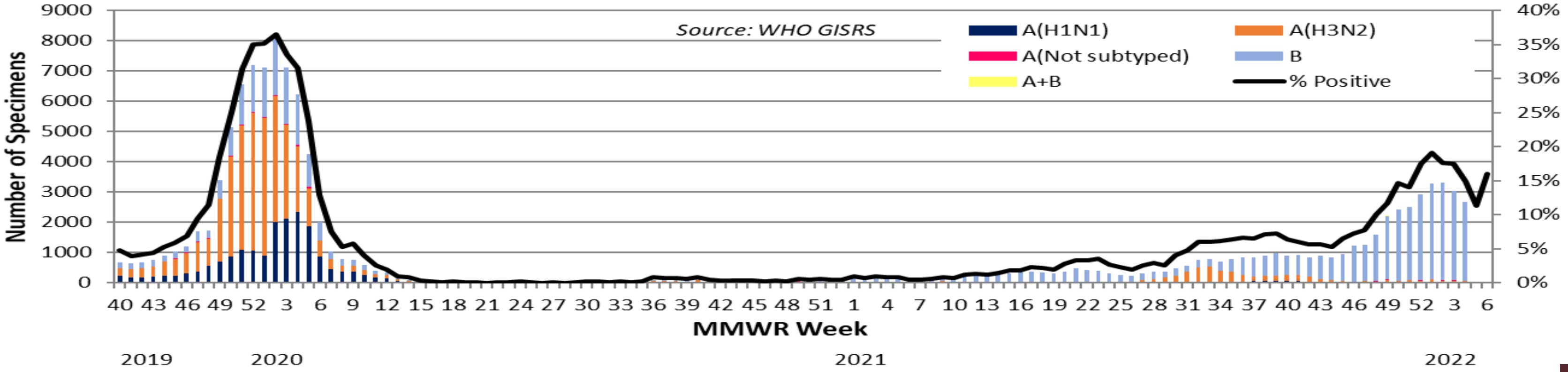
Number and Proportion of Specimens Positive for Influenza by Subtype

DoD
Surveillance



Sources: AFRIMS, NAMRU-2, USAFSAM

WHO
Surveillance

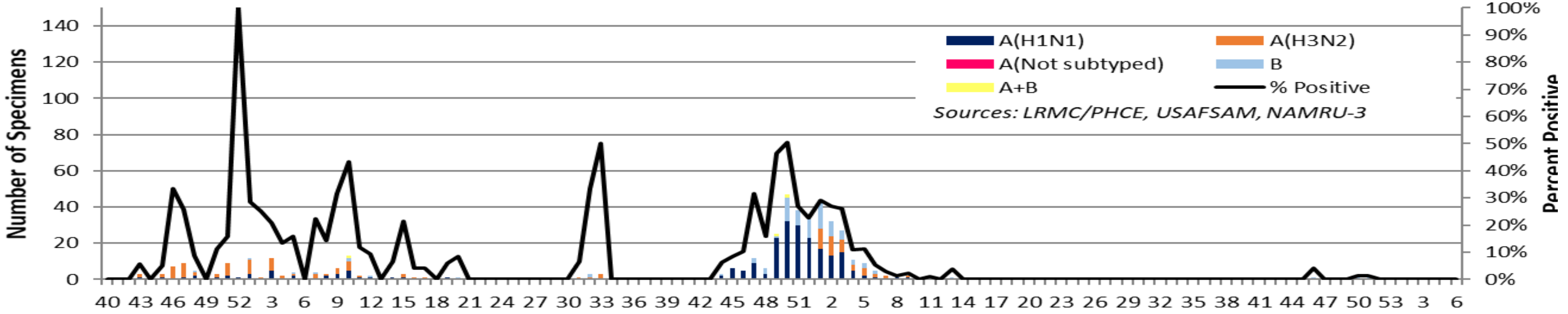


Source: WHO GISRS

Subtype Circulation: Middle East

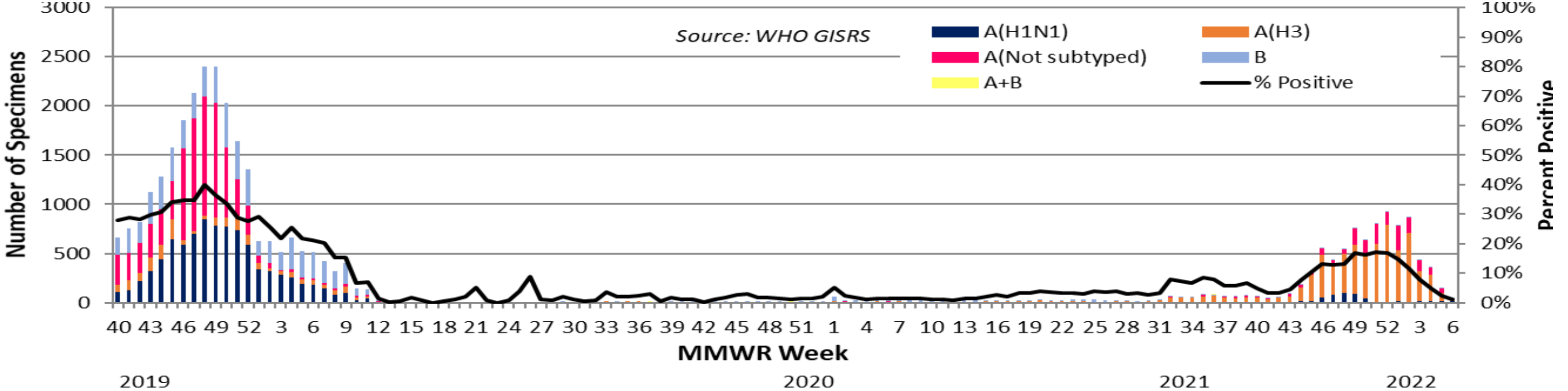
Number and Proportion of Specimens Positive for Influenza by Subtype

DoD Surveillance



Sources: LRMC/PHCE, USAFSAM, NAMRU-3

WHO Surveillance

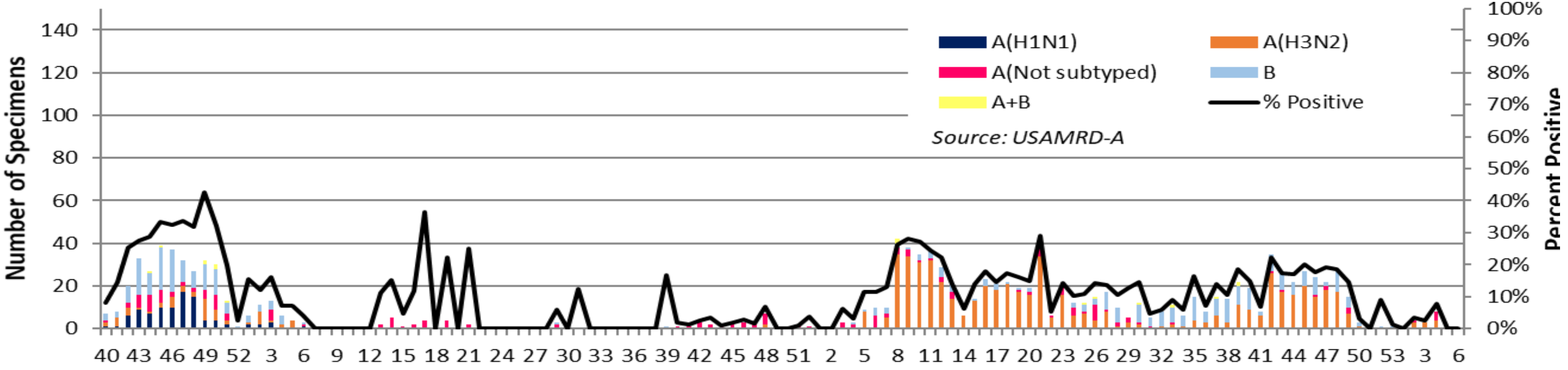


Source: WHO GISRS

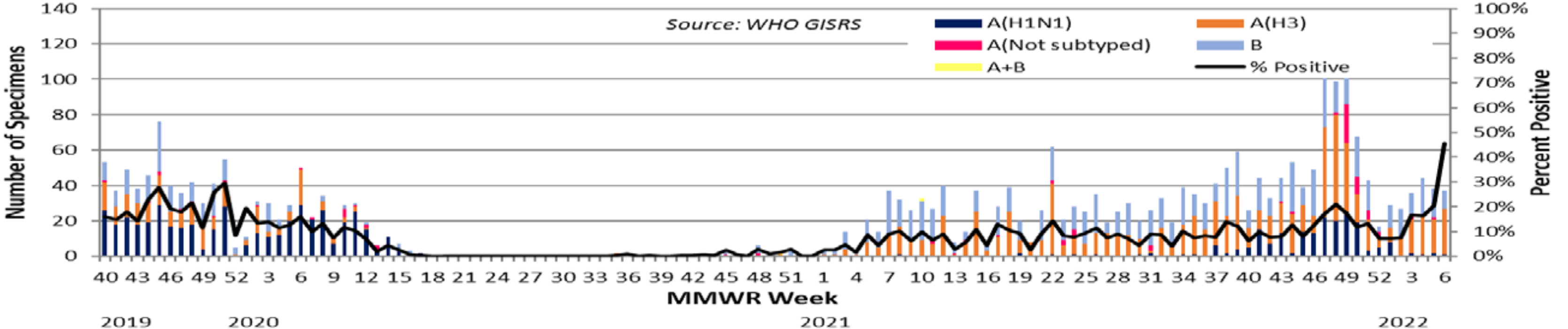
Subtype Circulation: East Africa

Number and Proportion of Specimens Positive for Influenza by Subtype

DoD
Surveillance



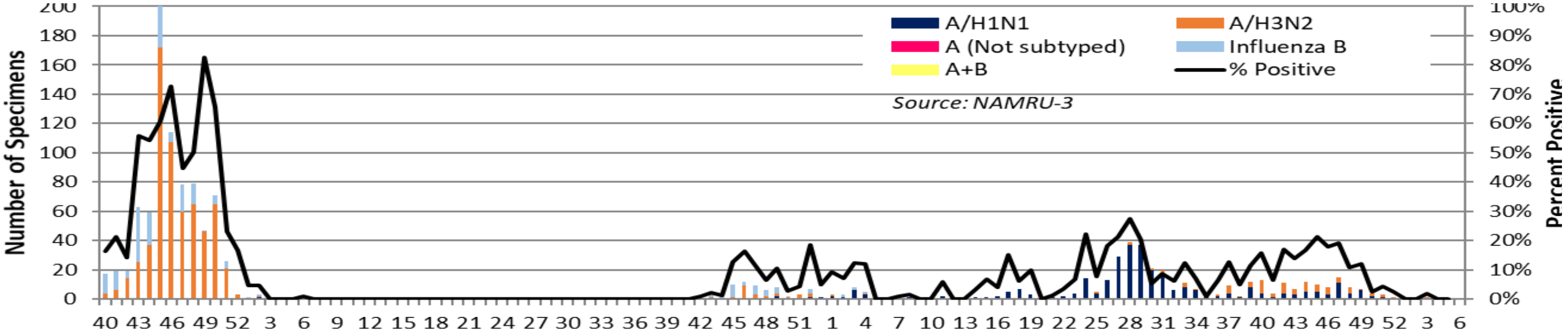
WHO
Surveillance



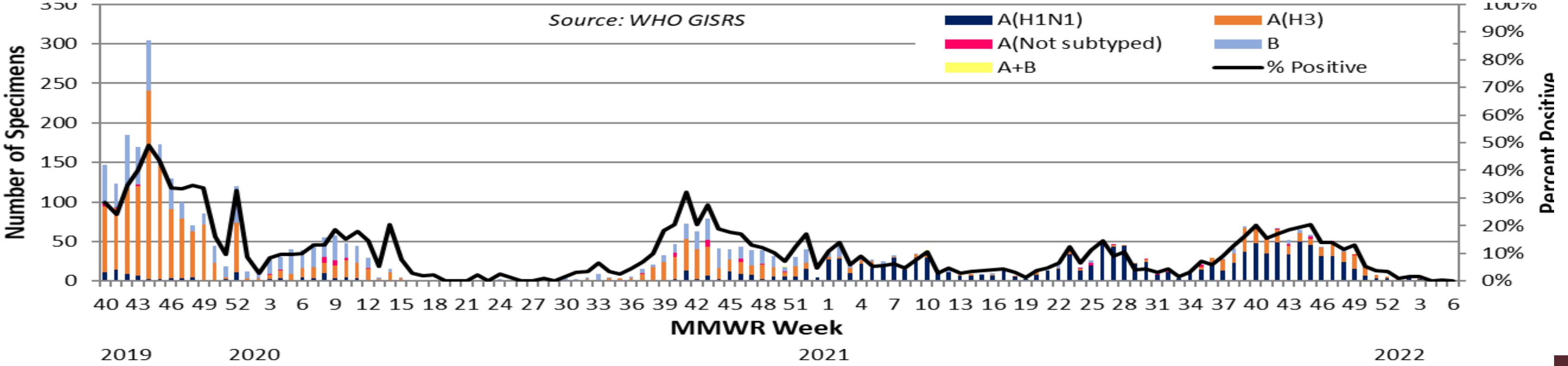
Subtype Circulation: West Africa (Ghana)

Number and Proportion of Specimens Positive for Influenza by Subtype

DoD Surveillance



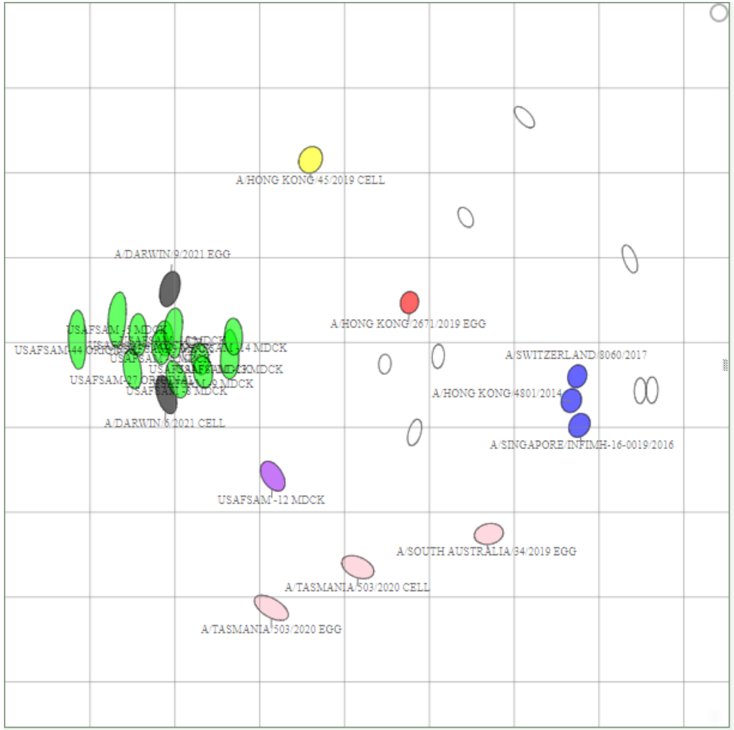
WHO Surveillance



High-content Imaging Neutralization Test (HINT) using reference Antisera

	Reference Antiserum											
Reference Viruses	A/Tasmania/503/2020 Egg	A/Tasmania/503/2020 Cell	A/Darwin/9/2021 Egg	A/Darwin/6/2021 Cell	A/Hong Kong/2671/2019 Egg	A/Hong Kong/45/2019 Cell	A/South Australia/34/2019 Egg	A/Switzerland/8060/2017	A/Singapore/INFIMH-16-0019/2016	A/Hong Kong/4801/2014		
A/Tasmania/503/2020 Egg	1810	80	640	640	40	40	57	80	113	160		
A/Tasmania/503/2020 Cell	226	1810	320	226	113	226	226	113	160	160		
A/Darwin/9/2021 Egg	160	226	3620	2560	160	160	160	160	80	80		
A/Darwin/6/2021 Cell	226	160	2560	5120	113	80	160	113	113	113		
A/Hong Kong/2671/2019 Egg	1810	905	905	3620	5120	1810	905	452	1280	905		
A/Hong Kong/45/2019 Cell	160	1810	452	320	320	640	160	160	113	160		
A/South Australia/34/2019 Egg	452	452	226	320	160	80	452	320	1280	905		
A/Switzerland/8060/2017	640	640	320	320	320	320	320	5120	5120	5120		
A/Singapore/INFIMH-16-0019/2016	320	640	320	320	320	226	226	640	5120	5120		
A/Hong Kong/4801/2014	320	640	452	320	320	320	320	1280	5120	5120		
test Samples											subclade	Other substitutions from Darwin/6 and Darwin/9
USAFSAM-27 Original	160	113	3620	5120	80	80	160	80	80	57	3C.2a1b.2a2-D53G	
USAFSAM-44 Original	113	80	1810	3620	80	80	57	57	40	40	3C.2a1b.2a2-D53G	
USAFSAM-3 MDCK	113	160	5120	5120	160	113	160	113	160	80	3C.2a1b.2a2-D53G	
USAFSAM-4 MDCK	113	113	3620	5120	160	80	160	113	80	57	3C.2a1b.2a2-D53G	D375N
USAFSAM -5 MDCK	80	113	2560	3620	113	80	113	113	57	80	3C.2a1b.2a2-D53G	
USAFSAM -6 MDCK	160	113	5120	5120	113	113	226	160	80	80	3C.2a1b.2a2-D53G	D408G
USAFSAM -7 MDCK	452	452	5120	5120	226	113	160	113	113	113	3C.2a1b.2a2-D53G	
USAFSAM -8 MDCK	226	226	2560	5120	160	113	226	113	113	80	3C.2a1b.2a2-D53G	
USAFSAM -9 MDCK	320	320	3620	5120	160	160	226	113	160	113	3C.2a1b.2a2-D53G	F79L
USAFSAM -10 MDCK	160	160	3620	5120	160	160	226	160	113	80	3C.2a1b.2a2-D53G	
USAFSAM -12 MDCK	640	320	1280	1280	160	160	226	226	160	160	3C.2a1b.2a2	S156H, S205F, A212T
USAFSAM -13 MDCK	320	320	2560	5120	320	160	320	160	160	160	3C.2a1b.2a2-D53N	
USAFSAM -14 MDCK	320	452	3620	5120	452	160	320	160	160	160	3C.2a1b.2a2-D53N	

Antigenic Cartography Map Generated using ACMACS Program



Antigenic Metadata

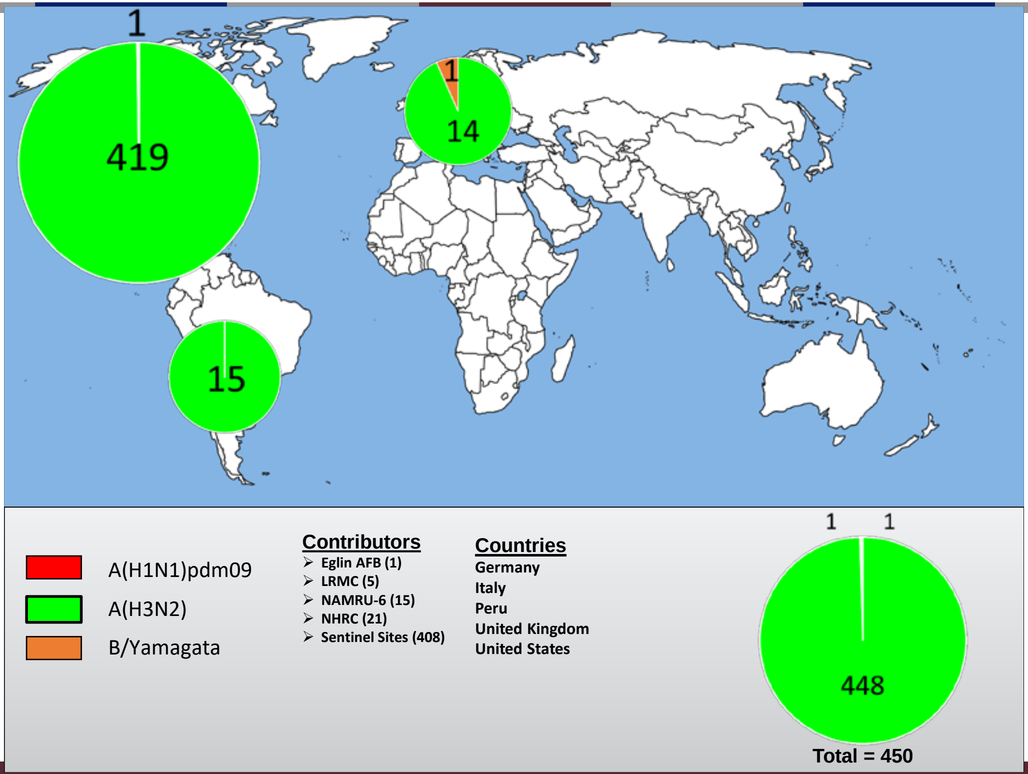
Sample #	Collection Month	State/Country	Clade	Notes	Subclade	Other substitutions from Darwin/6 and Darwin/9
27	October	Maryland	3C.2a1b.2a2	D53G/D104G/L157I/S262N/K276R group	3C.2a1b.2a2-D53G	
44	November	South Carolina	3C.2a1b.2a2	D53G/D104G/L157I/S262N/K276R group	3C.2a1b.2a2-D53G	
3	November	Florida	3C.2a1b.2a2	D53G/D104G/L157I/S262N/K276R group	3C.2a1b.2a2-D53G	
4	November	Florida	3C.2a1b.2a2	D53G/D104G/L157I/S262N/K276R group	3C.2a1b.2a2-D53G	D375N
5	November	Florida	3C.2a1b.2a2	D53G/D104G/L157I/S262N/K276R group	3C.2a1b.2a2-D53G	
6	November	Florida	3C.2a1b.2a2	D53G/D104G/L157I/S262N/K276R group	3C.2a1b.2a2-D53G	D408G
7	November	Georgia	3C.2a1b.2a2	D53G/D104G/L157I/S262N/K276R group	3C.2a1b.2a2-D53G	
8	November	Georgia	3C.2a1b.2a2	D53G/D104G/L157I/S262N/K276R group	3C.2a1b.2a2-D53G	
9	November	Georgia	3C.2a1b.2a2	D53G/D104G/L157I/S262N/K276R group	3C.2a1b.2a2-D53G	F79L
10	November	Georgia	3C.2a1b.2a2	D53G/D104G/L157I/S262N/K276R group	3C.2a1b.2a2-D53G	
12	September	Germany	3C.2a1b.2a2		3C.2a1b.2a2	S156H, S205F, A212T
13	October	Germany	3C.2a1b.2a2	D53N/N96S/I192F/N378S group	3C.2a1b.2a2-D53N	
14	October	Germany	3C.2a1b.2a2	D53N/N96S/I192F/N378S group	3C.2a1b.2a2-D53N	

Summary of Circulating Subtype 2021-2022 Influenza Season

- Influenza surveillance has continued during the 2021-2022 season and influenza activity has been detected in all regions after a period of relative inactivity in 2020-2021.
  - **North America: A(H3N2)** has been the dominant type detected
  - **South America:** positivity increased in recent months (**A/H3N2**)
  - **Europe:** low levels of influenza detected
  - **Asia:** moderate influenza driven recently by **A(H3N2)** and **influenza B**
  - **Middle East:** low levels of influenza detected, primarily **influenza A**
  - **East Africa:** moderate influenza with all subtypes detected
  - **West Africa:** primarily detecting influenza A; one of the only regions with **A(H1N1)** circulating

DoD / USAFSAM Phylogenetic Analysis
2021-2022 Influenza Season

Geographical Distribution of Influenza Sequences, 2021-2022

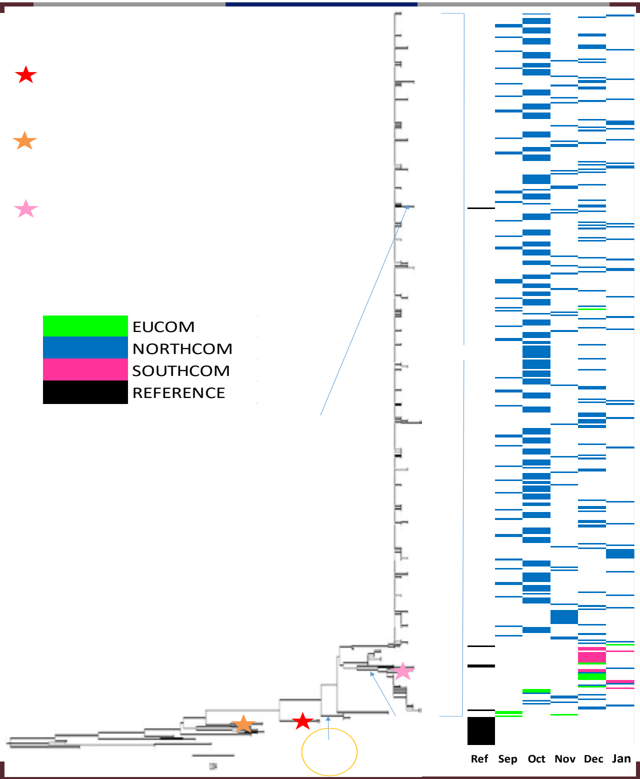


- 🟥 A(H1N1)pdm09
- 🟩 A(H3N2)
- 🟧 B/Yamagata

Contributors
- Eglin AFB (1)
- LRMC (5)
- NAMRU-6 (15)
- NHRC (21)
- Sentinel Sites (408)

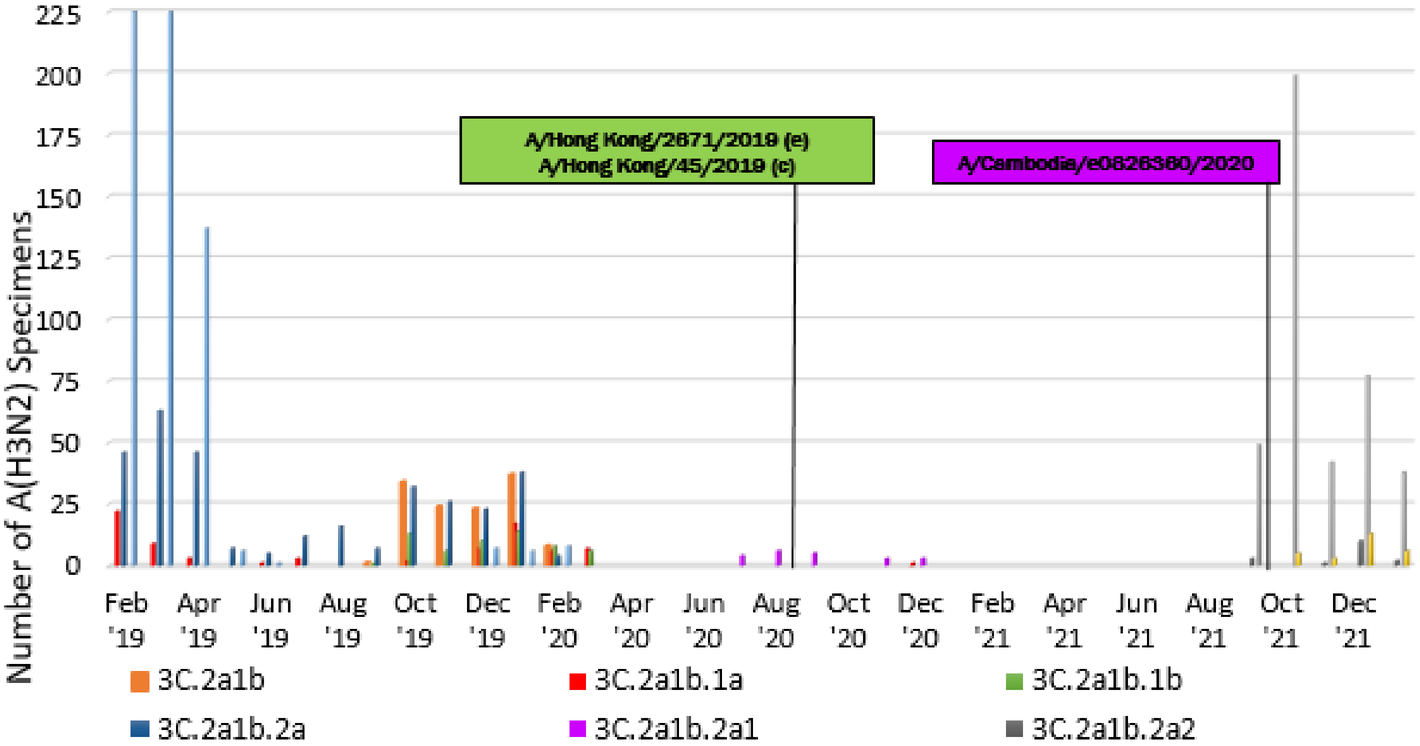
Countries
- Germany
- Italy
- Peru
- United Kingdom
- United States

2021-2022 A(H3N2) HA Phylogenetic Tree



- 448 influenza A(H3N2) HA sequences
- All in clade 3C.2a1b.2a2
- The majority from NORTHCOM and sharing D53G/D104G/L157I/S262N/K276R
- D53N/N96S/I192F/N378S group mostly from EUCOM and SOUTHCOM
- One major addition and two single losses of glycosylation motifs
- 2020-2021 and 2021-2022 NH vaccine strains and 2022 SH vaccine strains indicated on tree by stars
- A/Maryland/02/2021 most closely related reference strain
- Virus with S205F and A212T showed antigenic distinction from reference vaccine viruses

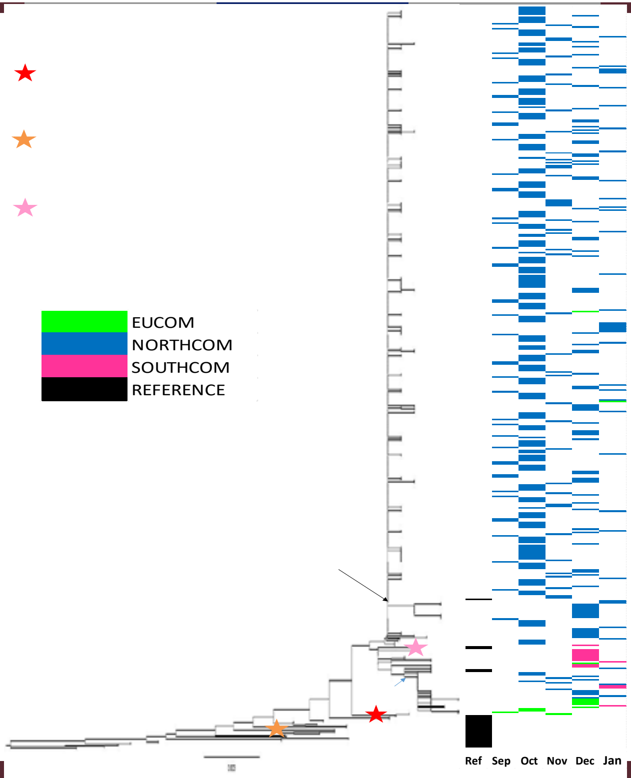
A(H3N2) HA Clades Feb 2019 – Jan 2021



A/Hong Kong/2671/2019 (e)
A/Hong Kong/45/2019 (c)

A/Cambodia/e0826360/2020

2021-2022 A(H3N2) NA Phylogenetic Tree



- 428 influenza A(H3N2) NA sequences
- NA phylogenetic tree similar in structure to HA
- Addition of glycosylation motif by S329N
- Again, A/Maryland/02/2021 most closely related reference strain

Discussion

- A total of 450 influenza sequences were available for analysis from the DoD, including contributions from LRMC, NHRC, NAMRU-6, and USAFSAM.
- Only one influenza A(H1N1)pdm09 specimen from NORTHCOM was sequenced and was clade 6B.1A-5A.1, the same clade as the 2020-2021 influenza vaccine A(H1N1)pdm09 strain and shares the substitutions R113K and H399N similar to reference virus A/Pennsylvania/02/2021.
- Only one influenza B specimen from EUCOM was sequenced and was a B/Yamagata lineage in clade Y3, the same clade as the 2021-202 influenza vaccine B/Yamagata strain.
- 448 influenza A(H3N2) sequences were analyzed and were all clade 3C.2a1b.2a2, with 6% sharing substitutions D53N/N96S/I192F/N378S and 90% sharing D53G/D104G/L157I/S262N/K276R.
- One HA substitution in the first group, N96S, causes the addition of a glycosylation motif.
- Four sequences (0.9%) that were not in the D53N or D53G groups, shared S205F and A212T. One representative from this group displayed the most antigenic distinction from reference and vaccine strains.

Service Member Vaccine Effectiveness Estimates

Analysis Overview

- Mid-year estimates provided by:
  - AFHSD AF Satellite - US Air Force School of Aerospace Medicine (USAFSAM)
  - Naval Health Research Center (NHRC)
  - AFHSD Epidemiology and Analysis Section (E&A)
- Case test-negative control studies used to estimate VE
  - All studies used case test-negative control method
  - Each influenza infection from USAFSAM and NHRC was confirmed by RT-PCR or viral culture; AFHSD also used positive rapid tests (but excluded rapid test negatives)
  - Analyses performed for influenza types and subtypes

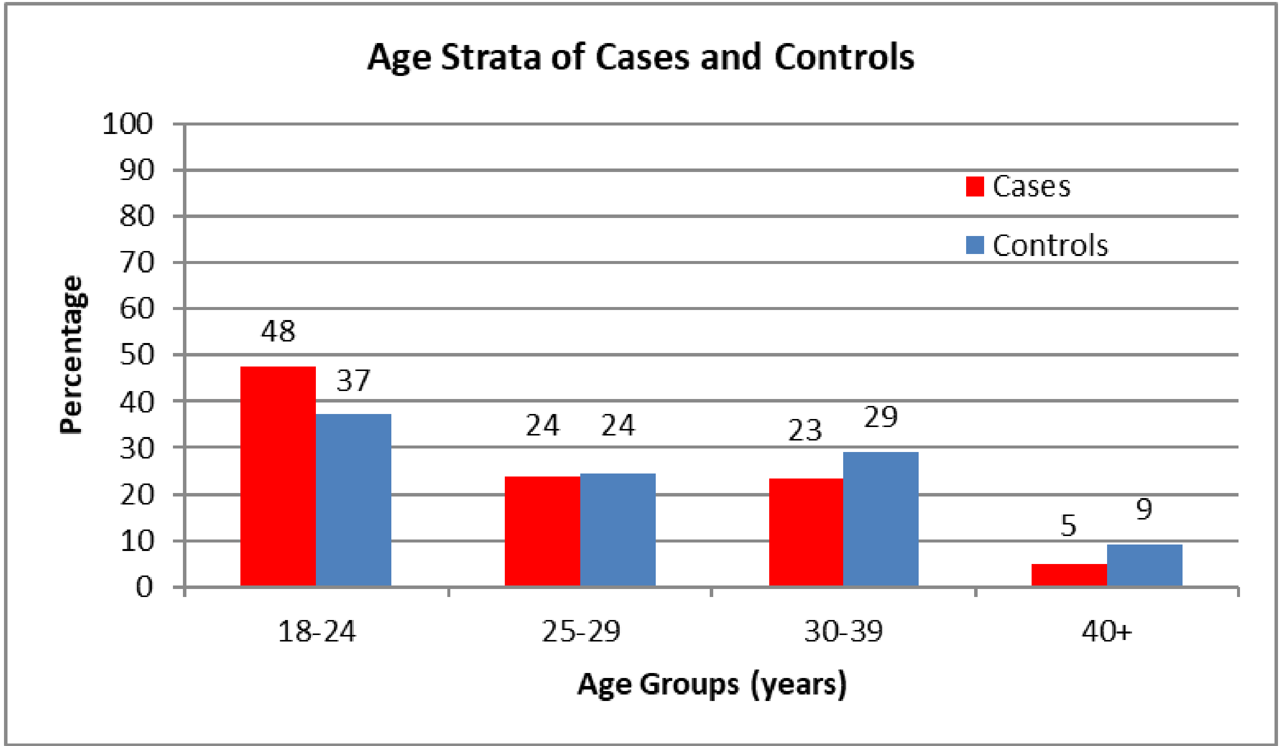
Service Members: Study Design

- Case / Test-negative control design
- Population: Active component Service Members
  - Army, Navy, Air Force, Marines
  - CONUS and OCONUS
- Time Period: September 1, 2021 – February 12, 2022
- Lab-confirmed flu cases: positive by rapid, RT-PCR, or culture assays
- Test-negative Controls: negative by RT-PCR or culture assays (subjects with negative rapid excluded)
- Models adjusted for sex, age category, prior vaccination, and month of diagnosis
- Overall and type-specific VE calculated

Service Members: Vaccination Information & Case Subtypes

- Vaccination
  - IIV was the only vaccine type among the study subjects
  - 85% of subjects had prior flu vaccine in previous 5 years
- Cases
  - Influenza A (any subtype) = 1,303
  - Influenza A(H3N2) = 155
  - Influenza A(H1N1) = 1
  - Influenza B = 165

Service Members: Cases and Controls by Age Group



Service Members: Interim VE Estimates 2021-2022

Influenza Type	Vaccination Status	Cases N (%)	Controls N (%)	Crude VE (95% CI)	Adjusted VE (95% CI)*
Any Influenza	Vaccinated	946 (65)	33,851 (69)	**18 (9, 27)**	**36 (28, 44)**
	Unvaccinated	513 (35)	14,962 (31)		
Influenza A	Vaccinated	862 (66)	33,851 (69)	**14 (3, 23)**	**33 (24, 41)**
	Unvaccinated	441 (34)	14,962 (31)		
A/H3N2	Vaccinated	103 (66)	33,851 (69)	12 (-22, 37)	**32 (3, 53)**
	Unvaccinated	52 (34)	14,962 (31)		
Influenza B	Vaccinated	87 (53)	33,851 (69)	**51 (33, 64)**	**59 (42, 71)**
	Unvaccinated	78 (47)	14,962 (31)		

*Adjusted for sex, age, and month of diagnosis

Service Members: VE Summary

Among Service Members, the 2021-2022 influenza vaccine provided:

- Low to moderate protection against any influenza (36%), influenza A (33%) and A/H3N2 (32%)
- Moderate protection against influenza B (59%)

Notes on Vaccine Strain Recommendations

The WHO influenza vaccine strain recommendations for the 2022-2023 Northern Hemisphere season are:

- For the 2022-2023 influenza vaccine A(H1N1) component: A/Victoria/2570/2019-like virus for the egg-based vaccine and A/Wisconsin/588/2019-like virus for the cell- or recombinant-based vaccine

Based on our 2021-2022 data, we cannot agree or disagree with this recommendation

- For the 2022-2023 influenza vaccine A(H3N2) component: A/Darwin/9/2021-like virus for the egg-based vaccine and A/Darwin/6/2021-like virus for the cell- or recombinant-based vaccine

Based on our 2021-2022 genetic and antigenic data, we agree with this recommendation

- For the 2022-2023 influenza vaccine B/Victoria component: B/Austria/1359417-like virus for the egg-based and cell- or recombinant-based vaccines

We do not have 2021-2022 data to agree or disagree with this recommendation

- The above three influenza strains are recommended for the trivalent vaccine, and for the quadrivalent vaccine to include these three in addition to the B/Yamagata component, B/Phuket/3073/2013-like virus for the egg-based and cell- or recombinant-based vaccines

Based on our 2021-2022 data, we cannot agree or disagree with this recommendation

Acknowledgements

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Ms. Denise Kramer
Mr. Matthew Sanders
Ms. Aleta Yount
Ms. Debby Koontz
Mr. Don Johson
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Recruit Surveillance Sites
Marine Corps Recruit Depot San Diego
Marine Corps Recruit Depot Parris Island
Recruit Training Command Great Lakes
Fort Leonard Wood
Fort Benning
Fort Jackson
Lackland Air Force Base
Coast Guard Training Center Cape May

CDC-California Department of Health Border Infectious Disease Surveillance Sites
Clinica de Salud del Pueblo Brawley
Clinica de Salud del Pueblo Calexico
Clinica de Salud del Pueblo El Centro
San Ysidro Health Center
Pioneers Memorial Healthcare
El Centro Regional Medical Center
Sharp Chula Vista Hospital
Mexicali General Hospital

DoD Beneficiary Surveillance Sites
Branch Health Clinic/ Marine Corps Air Station Yuma
Naval Hospital Camp Pendleton
Captain James A. Lovell Federal Health Care Center (Naval Hospital Great Lakes)
Robert E. Bush Naval Hospital Twenty Nine Palms
Naval Training Center San Diego
Naval Medical Center San Diego
Naval Branch Health Clinic Kearny Mesa
Naval Health Clinic Lemoore
Naval Hospital Yokosuka
Naval Branch Health Clinic Naval Base San Diego
Naval Medical Center Portsmouth
Boone Branch Health Clinic
Oceana Branch Health Clinic

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