

Influenza Update

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What is Influenza?

- Contagious respiratory virus that infects the nose, throat, and lungs.
- Signs and symptoms
 - Fever or feeling feverish/chills
 - **Not everyone will experience a fever**
 - Cough
 - Sore throat
 - Runny or stuffy nose
 - Muscle or body aches
 - Headaches
 - Fatigue (very tired)
 - Vomiting and diarrhea (more common in children)

Influenza Virus

- Orthomyxoviridae family
 - A, B and C
 - Influenza A and B viruses cause seasonal epidemics
 - Influenza C viruses cause mild disease
 - Influenza A viruses are classified into subtypes
 - Two surface glycoproteins
 - Hemagglutinin
 - H1-H16 (birds)
 - H17-H18 (bats)
 - Neuraminidase
 - N1-N19 (birds)
 - N10-N11 (bats)
 - Influenza B
 - Two lineages:
 - Victoria
 - Yamagata

Nomenclature of Influenza Virus

- *The antigenic type (e.g., A, B, C)*
- *The host of origin (e.g., swine, equine, chicken, etc. For human-origin viruses, no host of origin designation is given.)*
- *Geographical origin (e.g., Denver, Taiwan, etc.)*
- *Strain number (e.g., 15, 7, etc.)*
- *Year of isolation (e.g., 57, 2009, etc.)*
- *For influenza A viruses, the hemagglutinin and neuraminidase antigen description in parentheses e.g., (H1N1), (H5N1)*
 - *For example:*
 - *A/duck/Alberta/35/76 (H1N1) for a virus from duck origin*
 - *A/Perth/16/2009 (H3N2) for a virus from human origin*

Introduction to Influenza

- Two forms of Influenza occur globally
 - Epidemic (seasonal or interpandemic) influenza caused by Influenza A and B
 - Sporadic Pandemics caused by Influenza A
- Antigenic Drift vs Antigenic Shift
 - Drift:
 - Continuous process that occurs in both influenza A and B virus, due to accumulation of point mutations in the viral hemagglutinin and neuraminidase genes
 - This allows the virus to escape immunity induced through previous exposure or vaccination resulting in seasonal epidemics
 - Shift:
 - Sporadic event, restricted to Influenza A
 - Introduction of human beings into a novel virus strain to which a large proportion of the population does not have immunity

Introduction to Influenza

- Antigenic Shift (continued)
 - If the novel influenza virus spreads efficiently and sustainably from person to person → global pandemic
 - Four Influenza Pandemics:
 - 1918 Spanish Influenza (H1N1)
 - 1957 Asian Influenza (H2N2)
 - 1968 Hong Kong (H3N2)
 - 2009 Swine Influenza (H1N1)
 - Most Severe Pandemic Occurred in 1918, led to 50 million deaths
 - In the years following each pandemic, descendants of the pandemic strain established a new viral lineage in human beings and either replaced or co-circulated with previously circulating strains
 - Currently:
 - Pandemic 2009 H1N1 (H1N1pdm09)
 - H3N2
 - Influenza B

Vaccination Strategies

- Since 1977, inactivated vaccines have contained three components – called this trivalent formulation (IIV3)
 - Recent H1N1 virus
 - H3N2 Virus
 - Influenza B Virus
- 1980:
 - Two antigenically distinct lineage of influenza B have co-circulated; and now we have a quadrivalent formulation (IIV4)
- Studies have demonstrated that the addition of the fourth component does not interfere with the immune response to the other three components
- Two vaccines which use substrates other than chicken eggs:
 - CCIIV4 – Mammalian Cell Culture
 - RIV3 – Recombinant Baculovirus – expressed HA proteins produced in insect eggs
- One Live Attenuated Vaccine
 - LAIV4 – Intranasal vaccine

Influenza Vaccine Composition 2019-2020

- 2019-2020 Trivalent Influenza Vaccine:
 - A(H1N1)pdm09 vaccine component A/Brisbane/02/2018 (H1N1)pdm09-like virus
 - A(H3N2) vaccine component A/Kansas/14/2017 (H3N2)-like virus
 - B/Colorado/06/2017-like (Victoria lineage) virus
- 2019-2020 Quadrivalent Influenza Vaccine:
 - Includes all component of the Trivalent Influenza Vaccine
 - B/Phuket/3073/2013-like (Yamagata lineage) virus

Grohskopf LA, Alyanak E, Broder KR, Walter EB, Fry AM, Jernigan DB. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2019–20 Influenza Season. *MMWR Recomm Rep* 2019;68(No. RR-3):1–21

Influenza Vaccines-2019-2020

Trade name (Manufacturer)	Presentation	Age Indication	HA (IIVs and RIV4) or Virus Count (LAIV4) for each vaccine virus (per dose)	Route	Mercury (from Thimerosal) (ug/0.5mg)
IIV4 – Standard Dose – Egg Based					
Afluria Quadrivalent (Seqirus)	0.25-mL PFS	6 through 35 mos	7.5 µg/0.25 mL 15 µg/0.5 mL	IM	----
	0.5 – mL PFS	≥3 yrs			----
	5.0 – mL MDV	≥6 mos (needle/syringe) 18 through 64 yrs (jet injector)			24.5
Fluarix Quadrivalent (GlaxoSmithKline)	0.5-mL PFS	≥6 mos	15 µg/0.5 mL	IM	----
FluLaval Quadrivalent (GlaxoSmithKline)	0.5-mL PFS	≥6 mos	15 µg/0.5 mL	IM	----
	5.0-mL MDV	≥6 mos			< 25
Fluzone Quadrivalent (Sanofi Pasteur)	0.25-mL PFS	6 through 35 mos	7.5 µg/0.25 mL 15 µg/0.5 mL	IM	----
	0.5-mL PFS	≥6 mos			----
	0.5-mL SDV	≥6 mos			----
	5.0-mL MDV	≥6 mos			< 25

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Influenza Vaccines-2019-2020

Trade name (Manufacturer)	Presentation	Age Indication	HA (IIVs and RIV4) or Virus Count (LAIV4) for each vaccine virus (per dose)	Route	Mercury (from Thimerosal) (ug/0.5mg)
IIV4—Standard Dose—Cell culture based (cclIV4)					
Flucelvax Quadrivalent (Seqirus)	0.5-mL PFS	≥4 yrs	15 µg/0.5 mL	IM	----
	5.0-mL MDV	≥4 yrs			25
IIV3—High Dose—Egg based (HD-IIV3)					
Fluzone High-Dose (Sanofi Pasteur)	0.5-mL PFS	≥65 yrs	60 µg/0.5 mL	IM [†]	—
IIV3—Standard Dose—Egg based[†] with MF59 adjuvant (aIIV3)					
Fluad (Seqirus)	0.5-mL PFS	≥65 yrs	15 µg/0.5 mL	IM [†]	—
RIV4—Recombinant HA					
Flublok Quadrivalent (Sanofi Pasteur)	0.5-mL PFS	≥18 yrs	45 µg/0.5 mL	IM [†]	—
LAIV4—Egg based					
FluMist Quadrivalent (AstraZeneca)	0.2-mL prefilled single-use intranasal sprayer	2 through 49 yrs	10 ^{6.5-7.5} fluorescent focus units/0.2 mL	NAS	—

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Contraindications and Precautions to the Use of Influenza Vaccines – United States, 2019-2020 Influenza Season

Vaccine type	Contraindications and conditions for which use is not recommended	Precautions
IIV	History of severe allergic reaction to any component of the vaccine or to a previous dose of any influenza vaccine	Moderate or severe acute illness with or without fever History of Guillain-Barré syndrome within 6 weeks after receipt of influenza vaccine
RIV4	History of severe allergic reaction to any component of the vaccine	Moderate or severe acute illness with or without fever History of Guillain-Barré syndrome within 6 weeks after receipt of influenza vaccine

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Contraindications and Precautions to the Use of Influenza Vaccines – United States, 2019-2020 Influenza Season

Vaccine type	Contraindications and conditions for which use is not recommended	Precautions
LAIV4	History of severe allergic reaction to any component of the vaccine or to a previous dose of any influenza vaccine Concomitant aspirin- or salicylate-containing therapy in children and adolescents Children aged 2 through 4 years who have received a diagnosis of asthma or whose parents or caregivers report that a health care provider has told them during the past 12 months that their child had wheezing or asthma or whose medical record indicates a wheezing episode has occurred within the past 12 months Children and adults who are immunocompromised due to any cause (including immunosuppression caused by medications or HIV infection) Close contacts and caregivers of severely immunosuppressed persons who require a protected environment Pregnancy Receipt of influenza antiviral medication within the past 48 hours	Moderate or severe acute illness with or without fever History of Guillain-Barré syndrome within 6 weeks after receipt of influenza vaccine Asthma in persons aged ≥5 years Other underlying medical conditions that might predispose to complications after wild-type influenza infection (e.g., chronic pulmonary, cardiovascular [excluding isolated hypertension], renal, hepatic, neurologic, hematologic, or metabolic disorders [including diabetes mellitus])

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Vaccine Effectiveness 2018-2019

Age group (years)	Influenza positive Total	Influenza positive (% Vaccinated)	Influenza negative Total	Influenza negative (% Vaccinated)	Adjusted VE %	Adjusted 95% CI
All ages	2795	48	7246	56	29%	(21 to 35)
6 mos–8	759	40	1675	58	49%	(38 to 58)
9–17	493	45	772	41	6%	(-22 to 27)
18–49	831	39	2435	44	25%	(10 to 37)
50–64	448	60	1324	62	12%	(-12 to 31)
≥65	264	81	1040	83	12%	(-29 to 41)

Xu X, Blanton L, Elal AI, et al. Update: Influenza Activity in the United States During the 2018–19 Season and Composition of the 2019–20 Influenza Vaccine. MMWR Morb Mortal Wkly Rep 2019;68:544–551

Influenza Specific Vaccine Effectiveness 2018-2019

Influenza A (H1N1) Viruses

Age group (years)	Influenza positive Total	Influenza positive (% Vaccinated)	Influenza negative Total	Influenza negative (% Vaccinated)	Adjusted VE %	Adjusted 95% CI
All ages	1342	(43)	7246	(56)	44%	(36, 51)

Influenza A (H3N2) viruses

Age group (years)	Influenza positive Total	Influenza positive (% Vaccinated)	Influenza negative Total	Influenza negative (% Vaccinated)	Adjusted VE %	Adjusted 95% CI
All ages	1350	(52)	7246	(56)	9%	(-4, 20)

Xu X, Blanton L, Elal AI, et al. Update: Influenza Activity in the United States During the 2018–19 Season and Composition of the 2019–20 Influenza Vaccine. MMWR Morb Mortal Wkly Rep 2019;68:544–551

Guidelines for Use In Specific Populations

- **Pregnant Women**
 - All women who are pregnant or who might be pregnant during the influenza season should receive influenza vaccine.
 - An age-appropriate IIV or RIV4 may be used.
 - LAIV4 should not be used during pregnancy.
 - Influenza vaccine can be administered at any time during pregnancy

Guidelines for Use In Specific Populations

- **Adults Aged ≥ 65 years**
 - Persons aged ≥ 65 years may receive any age-appropriate IIV (standard- or high-dose, trivalent or quadrivalent, adjuvanted or unadjuvanted) or RIV4.
 - High-dose IIV3 exhibited superior efficacy over a comparator standard-dose IIV3 in a large randomized trial, and may provide better protection than standard dose IIV3 for this age group.
 - However, vaccination should not be delayed to find a particular product if an appropriate one is available.

Guidelines for Use In Specific Populations

- **Persons With Chronic Medical Conditions:**
 - LAIV is not recommended for persons with some chronic medical conditions
- **Caregivers and Contacts of High-Risk Persons**
 - Caregivers and contacts (including those of immunosuppressed persons) may receive any age-appropriate IIV or RIV4.
 - LAIV4 may be given to caregivers and contacts of persons who are not severely immunocompromised (i.e., who do not require a protected environment).
 - Health care personnel or hospital visitors who receive LAIV4 should avoid providing care for severely immunosuppressed persons requiring a protected environment for 7 days after vaccination.

Guidelines for Use In Specific Populations

- **Persons with Egg Allergy**
 - Persons who are able to eat lightly cooked egg (e.g., scrambled egg) without reaction are unlikely to be egg-allergic.
 - Persons who have experienced only hives after exposure to egg should receive any licensed, recommended, age-appropriate influenza vaccine (i.e., IIV, RIV4, or LAIV4).
 - Persons reporting symptoms other than hives after exposure to egg (such as angioedema, respiratory distress, lightheadedness, or recurrent emesis; or who required epinephrine or another emergency medical intervention) may also receive any licensed and recommended influenza vaccine that is otherwise appropriate.
 - Additionally, for these persons, vaccine should be administered in an inpatient or outpatient medical setting and supervised by a health care provider who is able to recognize and manage severe allergic reactions.
 - A previous severe allergic reaction to influenza vaccine, regardless of the component suspected of causing the reaction, is a contraindication to future receipt of the vaccine.

Guidelines for Use In Specific Populations

- **Immunocompromised Persons**
 - Immunocompromised persons should receive an age-appropriate IIV or RIV4.
 - LAIV4 should not be used for immunocompromised persons.
 - Immune response to vaccines might be blunted in immunocompromised persons, and might be reduced or minimal as a result of medications, chemotherapy, or transplant regimens.

Vaccine Strategies for High Risk Populations

Solid Organ Transplant Recipients

- Incidence varies among transplanted organ
 - In Liver Transplant Recipients:
 - 2.8 cases/1000 person years
 - In Lung Transplant Recipients:
 - 41.8 cases/1000 person years
- Population is high risk for influenza related complication
 - Mortality 4-17%
- Influenza can lead to allograft dysfunction along with acute and chronic rejection in lung transplant recipients

Solid Organ Transplant Recipients

- Influenza vaccine:
 - Inactivated trivalent → Two Influenza A strains, and one Influenza B strain
 - Inactivated quadrivalent → Two Influenza A strains, and two Influenza B strains
- How do we know if Influenza vaccine is effective?
 - Check HAI titers
 - A titer of 1:40 is defined to be seroprotective (in nonimmunocompromised patient) and are associated with 50% strain-specific protection
 - However, it is not known if the titer of 1:40 provides the same degree of protection in immunocompromised individuals

Immunogenicity in SOTR

- Different Influenza Vaccines reviewed:
 - High Dose (unadjuvanted) inactivated influenza vaccine
 - Unadjuvanted inactivated influenza vaccine booster dose in same season
 - MF59 adjuvanted inactivated influenza vaccine

High Dose Vaccine

- Inactivated standard dose Influenza Vaccine contains 15ug of HA protein (in both trivalent or quadrivalent vaccine)
- Inactivated high dose vaccine contains 60 ug of HA
 - Approved for population age at least 65 years in North America
 - Demonstrated greater efficacy as well as reduced influenza mortality in this population
 - Demonstrated to be more immunogenic than standard-dose vaccine in pediatric and adult patients receiving chemotherapy

Adjuvant Influenza Vaccine

- **Adjuvant:**
 - An Oil-in-water emulsion that contains squalene, sorbitan trioleate and polysorbate-90 and acts via attracting inflammatory cells to the site of injection
- RCT of Adult Kidney Transplant (n=68); patients were either allocated to receive nonadjuvanted standard-dose influenza vaccine or MF59 adjuvanted vaccination
 - Neither the seroconversion or seroprotection rate or GMT were different in the two study groups
- There was a questionable link to Narcolepsy with the adjuvant 2009 H1N1 Vaccine in Europe, CDC published a study and found vaccination was NOT associated with an increased risk for narcolepsy

Diagnosis of Influenza

Diagnosis

	Sensitivity	Turnaround Time	Advantages	Disadvantages
Viral Cultures	Close to 100%	3-10 days	High sensitivity and specificity; virus available for characterization (recovery of new and divergent strains); ability to recover other viruses	Poor specimen quality might affect yield; results not available in time to inform clinical decision making; time and labor intensive; specialized labs required
Rapid Viral Culture	70-90%	1-3 days	Faster than traditional viral culture, less expertise needed than for traditional cell culture	Less sensitive than traditional viral culture, might miss divergent influenza viruses
Rapid Antigen Detection: DFA	70-90%	1-4 hours	Rapid turnaround, can identify additional pathogens (different staining methods); can assess sample quality	Sensitivity and Specificity technician dependent
Rapid antigen detection: Immunochromatogenic assay	59-93%	< 30 min	No specialized equipment; rapid result	Least sensitive method
RT-PCR	Close to 100%	1-8 hours	High sensitivity and specificity, typing and subtyping possible	Expensive, potential for cross contamination

Clinical Microbiology

- Available tests:
 - Rapid
 - Alerie I Influenza A & B
 - 1 hour turn around time
 - First line test
 - >95% sensitivity and specificity
 - PCR
 - Simplexa Flu A, B, & RSV Direct assay
 - Reserved for negative rapid, but high clinical suspicion
 - 24 hour turn around time
 - >99% sensitivity and specificity
 - Panel
 - Immunosuppressed patients only
 - New bacterial targets included this year
 - Not a stat test
 - Proper collection is key

Treatment Options

Treatment

- Six licensed AntiFour were recommended by U.S. FDA
- Three neuraminidase inhibitors:
 - Oral Oseltamivir
 - Inhaled Zanamivir
 - Intravenous Peramavir
- Cap-dependent endonuclease inhibitor:
 - Oral Baloxavir
- Adamantanes:
 - Not recommended due to high level of resistance (>99%)
- Resistance:
 - Antiviral resistance and reduced susceptibility to the neuraminidase inhibitors and to baloxavir is low
 - Concern with emergence of viruses with molecular markers associated with reduced susceptibility to baloxavir viral Drugs approved in United States:
 - following treatment
- Clinical data demonstrates best time to initiate therapy is within 48 hours of symptoms

Treatment

- Baloxavir was approved as a new antiviral treatment for influenza in October of 2018
- Blocks a different step in viral replication than neuraminidase inhibitors
- Is a single dose tablet vs five days of oral oseltamivir
- Shortened duration of influenza from a median of 80 to 54 hours
- Postmarket Adverse Event Data:
 - 382 reports received
 - All but 14 had serious or fatal outcome
 - 50 cases of anaphylactic shock
 - Concern for Hypersensitivity

Infection Control

Infection Control

- **Prevention Strategies for Seasonal Influenza in Healthcare Settings**
 - 5 to 20% of U.S. residents acquire influenza virus infection and will seek medical care in ambulatory health care settings
 - 200,000 persons are hospitalized each year for influenza-related complications
 - Healthcare-associated influenza can, and prevention measures must be implemented in all healthcare settings
- **Mode of Transmission:**
 - Large particle respiratory droplet transmission (travel short distance which is approximately six feet or less)
 - Indirect contact transmission via hand transfer

Infection Control

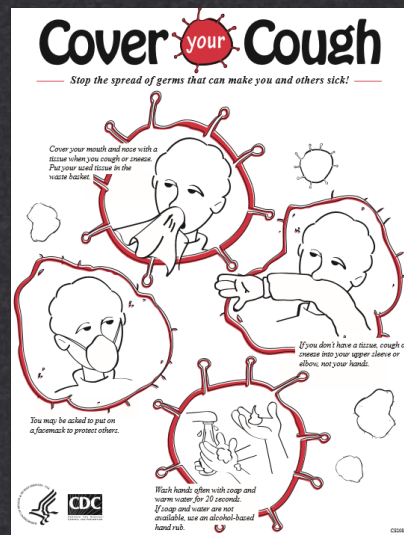
- **Promote and administer seasonal influenza vaccine**
- **Take Steps to Minimize Potential Exposures**
- **Monitor and Manage Ill Healthcare Personnel**
- **Adhere to Standard Precautions**
- **Adhere to Droplet Precautions**
- **Use Caution when Performing Aerosol-Generating Procedures**
- **Manage Visitor Access and Movement Within the Facility**
- **Monitor Influenza Activity**

Infection Control

- Implement Environmental Infection Control
- Implement Engineering Controls
- Train and Educate Healthcare Personnel
- Administer Antiviral Treatment and Chemoprophylaxis of Patients and Healthcare Personnel when Appropriate
- Consideration for Healthcare Personnel at Higher Risk for Complication of Influenza

Respiratory Hygiene/Cough Etiquette in Healthcare Settings

- Visual Alerts
 - Cover your Cough
- Respiratory Hygiene/Cough Etiquette
- Masking and Separation of Persons with Respiratory Symptoms
- Droplet Precautions



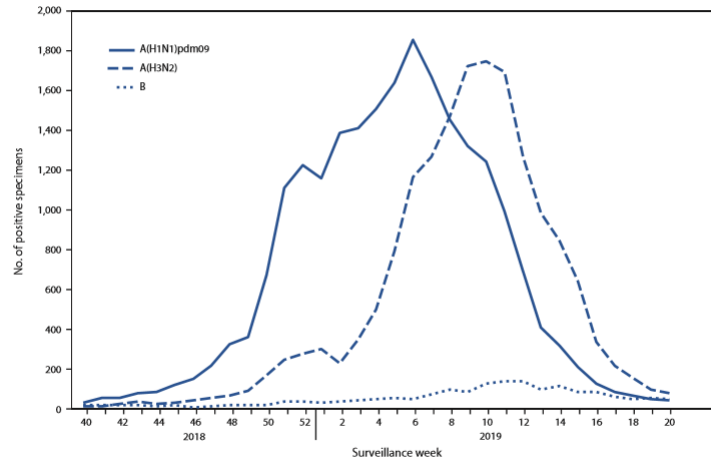
Interim Guidance for Influenza Outbreak Management in Long-Term Care and Post-Acute Care Facilities

- Institutions such as nursing homes and skilled nursing facilities that provide health care to people (including children) who are unable to manage independently in the community
- Preventing transmission of influenza virus requires a multi-faceted approach:
 - Influenza Vaccination
 - Influenza Testing
 - Infection Prevention and Control Measures
 - Antiviral Treatment
 - Antiviral Chemoprophylaxis

Post Exposure Prophylaxis

- Immunization is the best way to prevent influenza, and antiviral drugs should not be used as a substitute for influenza vaccination
- It is appropriate in certain target populations – outbreaks in nursing homes, hospitals, and other long-term care facilities
- Target Population for Prevention:
 - Residents of nursing homes and chronic care facilities
 - Adults \geq 65 years of age
 - Pregnant women and women up to two weeks postpartum
 - Chronic Medical Conditions
- Generally not recommended in instances patients who have been vaccinated during a season where there is a match between vaccine and circulating virus

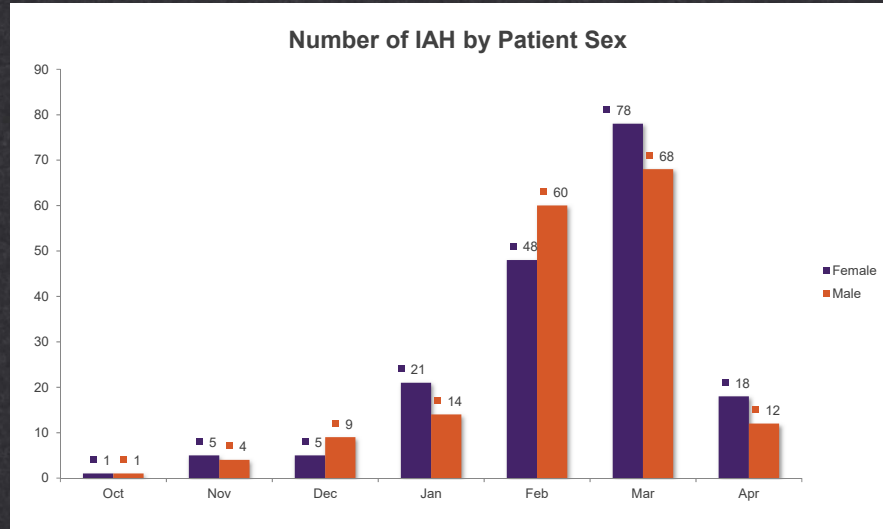
FIGURE 1. Number* of respiratory specimens testing positive for influenza reported to CDC by public health laboratories, by influenza virus type, subtype,[†] and surveillance week — United States, September 30, 2018–May 18, 2019[‡]



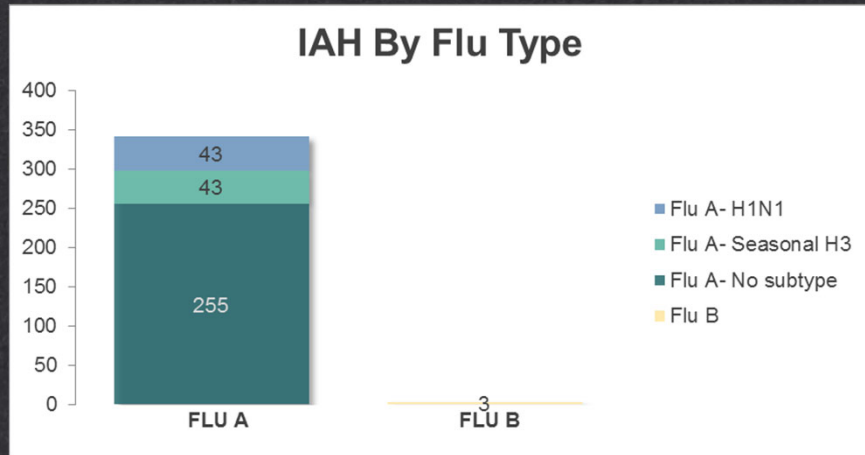
* N = 40,674.
[†] 1,629 influenza A viruses not subtyped are excluded.
[‡] As of June 14, 2019.

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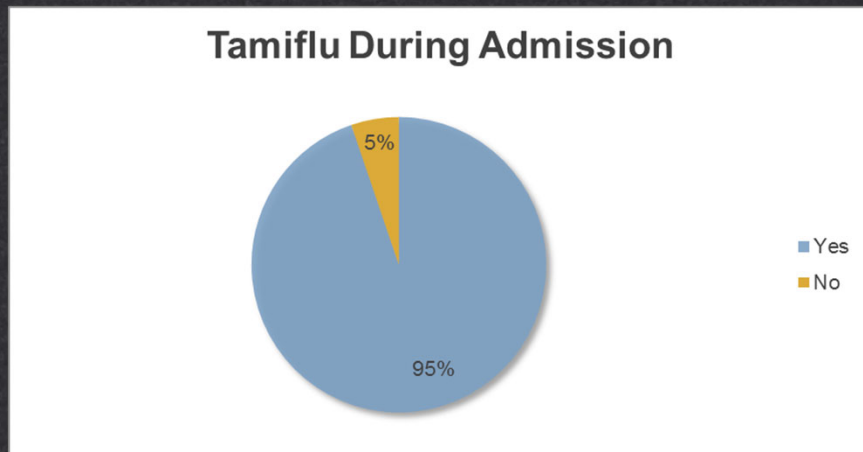
Influenza Data 2018-2019



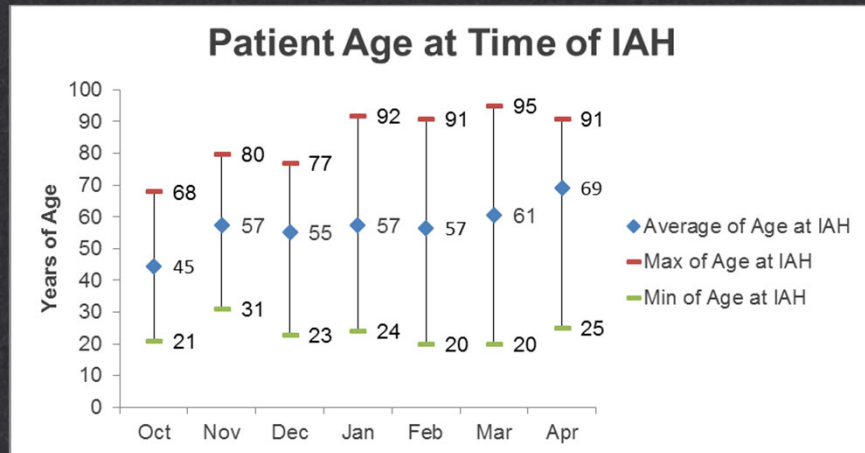
Influenza Data 2018-2019



Influenza Data 2018-2019



Influenza Data 2018-2019



OSU Wexner Medical Center Influenza Data 2018-2019

