# *Clostridium difficile* and Influenza

Prabhu Gounder, MD, MPH
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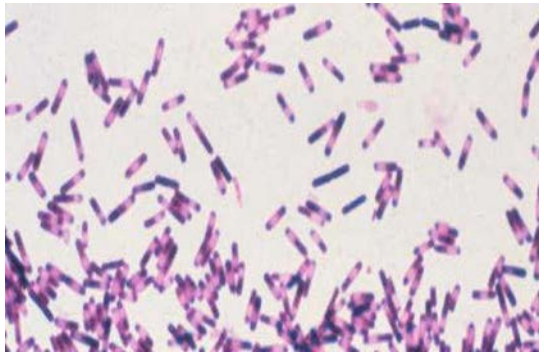
Los Angeles County Department of Public Health

# *Clostridium difficile*

# What is *C. difficile*?

- Anaerobic spore-forming bacillus
- Some strains can produce toxins
  - Toxin A - enterotoxin
  - Toxin B – cytotoxin
- Toxin B
  - 10x more potent than toxin A
  - Strains without toxin A as virulent as those with both toxins
- ~10-30% of C. difficile strains do not produce any toxins
  - Not pathogenic
- Most common bacterial infectious diarrhea in nosocomial settings

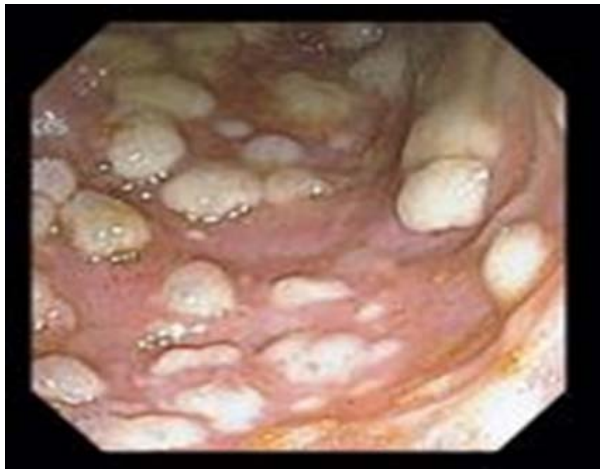


# Risk Factors

- **Antimicrobial exposure**
- **Acquisition of *C. difficile***
- Advanced age
- Severe illness
- Immunosuppression
- Tube feeds
- Gastric acid suppression

# What diseases result from *C. difficile*?

- Asymptomatic carriage
  - Colonization with non-toxin producing *C. difficile*
  - Up to 20% of hospitalized adults
  - Up to 50% of long-term care facility residents
- *C. difficile* infection (CDI) – symptomatic illness
- *C. difficile*-associated disease (CDAD) – spectrum of illnesses
  - pseudomembranous colitis (PMC)
  - toxic megacolon
  - perforations of the colon
  - sepsis
  - death (rarely)



# What are the main clinical symptoms of CDI?

- Watery diarrhea (3 loose stools in 24 hours)

- Other manifestations
  - lower abdominal pain and cramping
  - low-grade fever
  - Nausea
  - anorexia

# How does *C. difficile* spread and cause disease?

Susceptible host
(≥1 risk factors)

→ Loss of normal protective flora
(Antibiotic use or decreased stomach acidity)

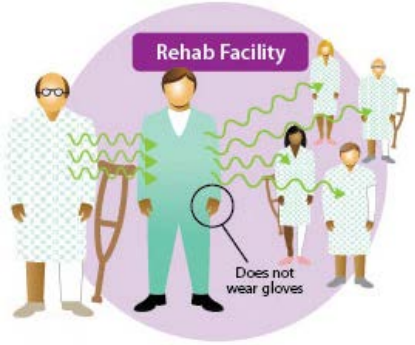
→ Exposure to C. difficile spores
(Bedside items, caregivers' hands)

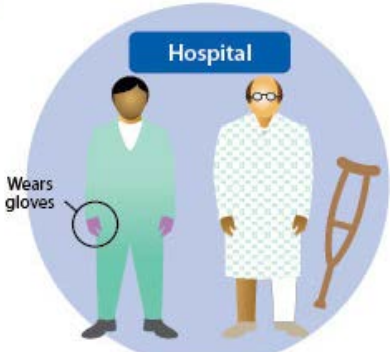
→ Ingestion of spores
(Transmission via fecal-oral route)

→ Proliferation of C. difficile bacteria
(Secretion of toxins A and B)

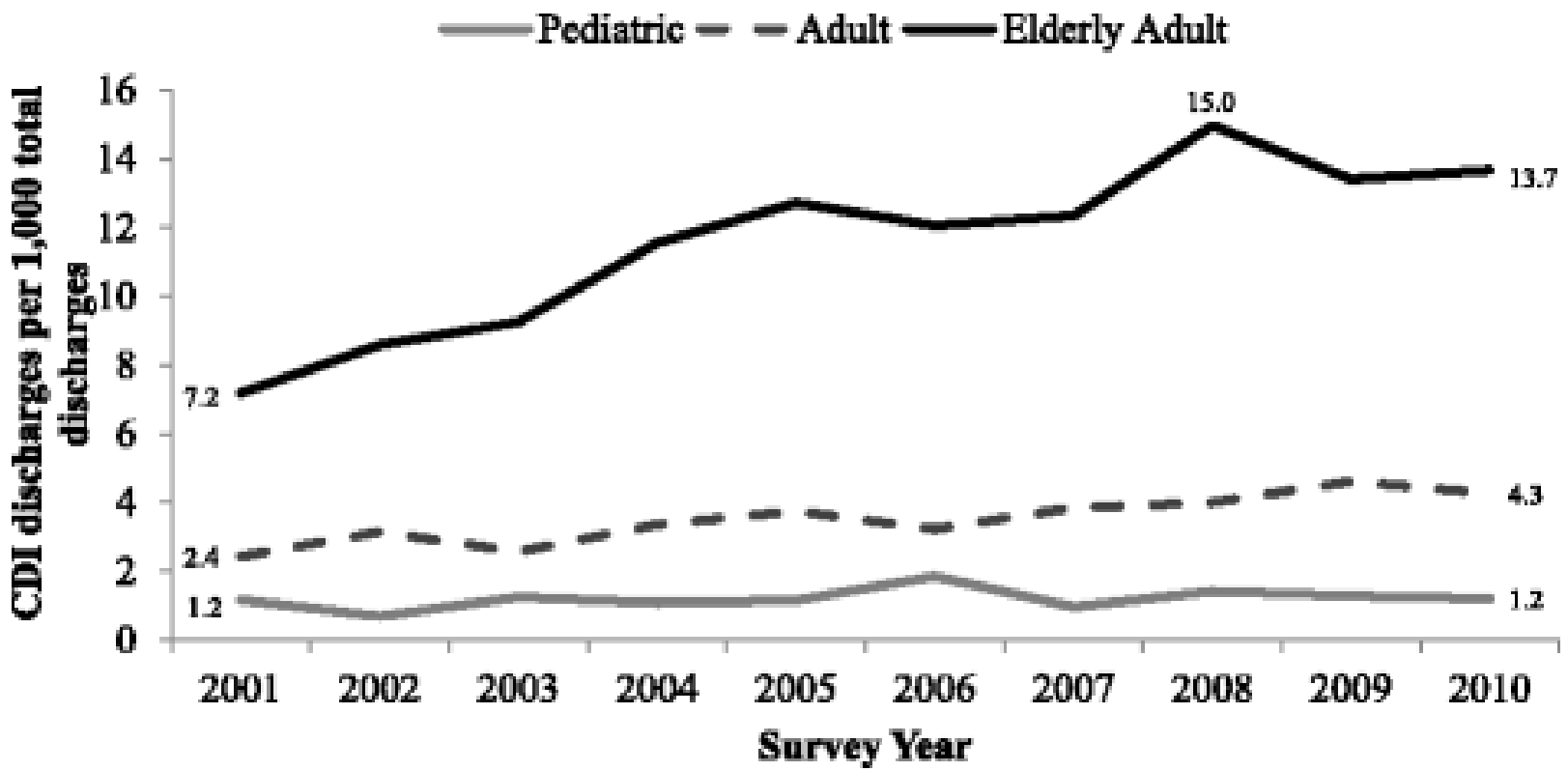
→ Profound colonic inflammatory response
(Diarrhea results)





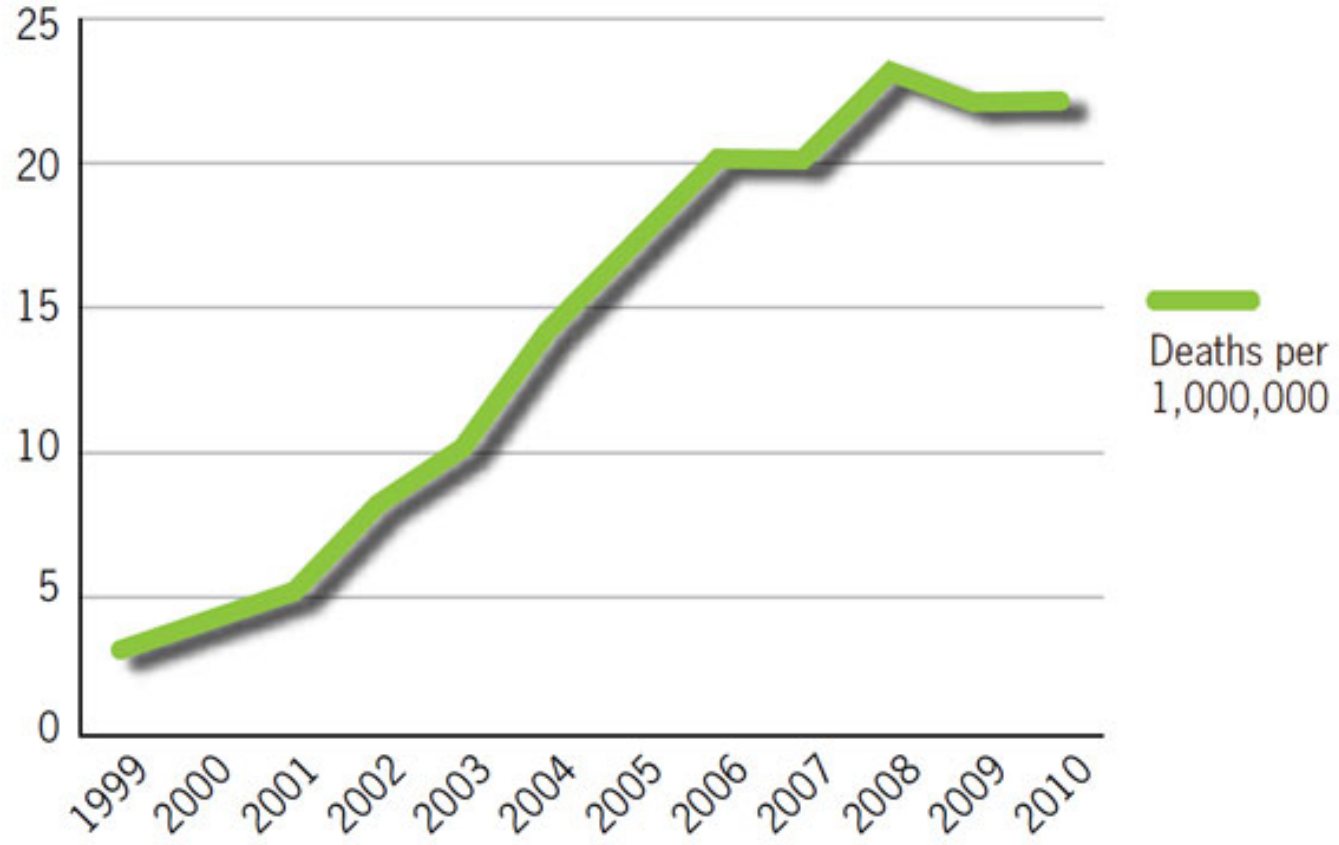



# *C. difficile* Infection Incidence Among Hospitalized Patients by Age Group (Age <18, 18-64, ≥65 years) --- United States, 2001-2010




BMC Infect Dis. 2016 Nov 17;16(1):682.

# Deaths Caused by C. difficile Infections --- United States, 1999-2010




* Age-adjusted Rate of *C. difficile* as the Primary (Underlying) Cause of Death.

Source: CDC National Center for Health Statistics, 2012

# Why the increase in *C. difficile* incidence and mortality?

- Increasing use of antibiotics
  - Across all age groups
- Aging population in all medical care settings
  - SNF, acute inpatient care and outpatient
- Introduction of a new hypervirulent *C. difficile* strain BI/NAP1/027
  - First detected in Pittsburgh (2000)
  - Spread widely leading to large outbreaks in 2000s
  - Produces more toxin (23x more toxin B)
  - Produces another toxin (binary toxin)

# Diagnosis of CDI

- Suspect CDI in patients with
  - Acute diarrhea
  - CDI risk factors
  - No alternative explanation (e.g., laxatives)
- Send liquid unformed stool for testing
- Do not test asymptomatic patients with formed stool
  - Asymptomatic carriage is common and does not warrant treatment
- Stool assays may remain positive after clinical recovery
  - Testing for cure or repeated testing during same episode is not warranted

# Common *C. difficile* diagnostic tests

- EIA for *C. difficile* toxins A and B (2 hours)
  - 79-80% sensitive
  - 99% specific
- Nucleic acid amplification test such as PCR (1 hour)
  - Detects toxin genes; does not test for active toxin production
  - Cannot distinguish toxin producing from non-producing strains
  - Can result in overdiagnosis of CDI
- Other tests: EIA for *C. difficile* GDH antigen, toxigenic culture, and endoscopy

# Treatment of CDI

- Stop inciting drugs (20-25% respond)
- Preferred antibiotics
  - Vancomycin
  - Fidaxomicin
  - If above unavailable – metronidazole
- Fecal microbiota transplantation
  - Preferred for recurrent CDI despite appropriate antibiotic therapy
- Surgery for complications

# Infection Control and Prevention: Core Prevention Strategies

Guidelines for prevention and control of *C. difficile* and multi-drug resistant organisms available on LA County DPH website: http://publichealth.lacounty.gov/acd/docs/LAC%20Guidelines_AcuteCare206-2-09rev.pdf

- Antimicrobial stewardship program (~50% antibiotic use unnecessary)
- Hand hygiene **with soap and water (not sanitizer)**
- Contact precautions for duration of diarrhea
- Disinfection equipment/environment
- Laboratory-based alert system for immediate notification of positive test results
- Education about CDI: HCP, housekeeping, administration, patients, families

# Supplemental Prevention Strategies

- Extend use of Contact Precautions beyond duration of diarrhea (e.g., 48 hours)
- Presumptive isolation for symptomatic patients
- Evaluate and optimize testing for CDI
- Implement universal glove use on units with high CDI rates
- Use sodium hypochlorite (bleach 1:10) – containing agents for environmental cleaning

# Common Challenge: Patient Placement

- Long-term care placement should not be refused based on *C. difficile* status; instead:
  - Place resident in private room
  - If private room unavailable
    - Cohort with other CDI-positive patients
    - Provide a dedicated bedside commode

# Influenza

# The Influenza Virus

- Genome ~13,000 base pairs
- Viral replication highly error prone (~1/10,000 bp)
- Advantages
  - Increased adaptability to selection pressures (e.g. antivirals)
  - Evade host immunity
- Influenza survives as a population of viruses, not a single virus
  - Requires continuous viral surveillance
  - Necessitates frequent updates to the vaccine

# Antigenic "Drift" and "Shift"

## Drift

- Point mutations (1/10,000 bp)
- Minor changes, within subtypes
- Occurs in A and B subtypes
- May cause epidemics

⇛ Occurs frequently

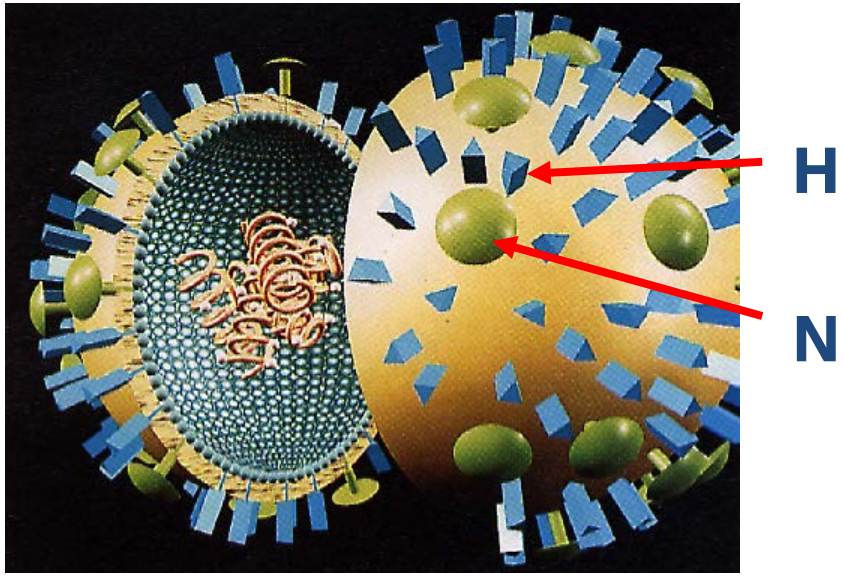
## Shift

- Major change, new subtypes
- Exchange of gene segments
- Occurs in A subtypes only
- May cause pandemics

⇛ Occurs infrequently

# Influenza A Virus Divided into Subtypes

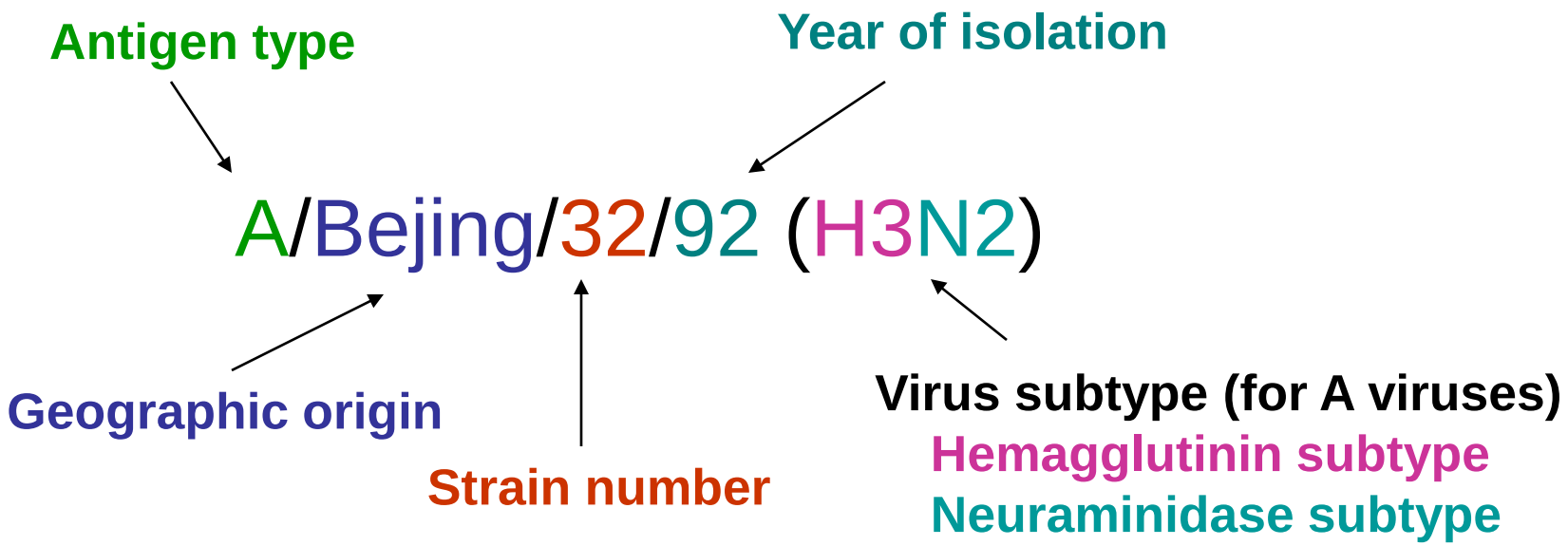
- Based on surface glycoproteins
  - Hemagglutinin (H) – vaccines induce antibodies to block this protein
  - Neuraminidases (N) – Antiviral drugs inhibit this protein
- Current human subtypes:
  - A(H1N1)pdm09
  - A(H3N2)



# Classifying Influenza B Viruses

- Not divided into subtypes
- Characterized by lineage (geographic origin) and strain
- Currently circulating influenza B viruses belong to two lineages
  - B/Victoria
  - B/Yamagata

# WHO Nomenclature for Naming Influenza Viruses



# Pandemic Influenza

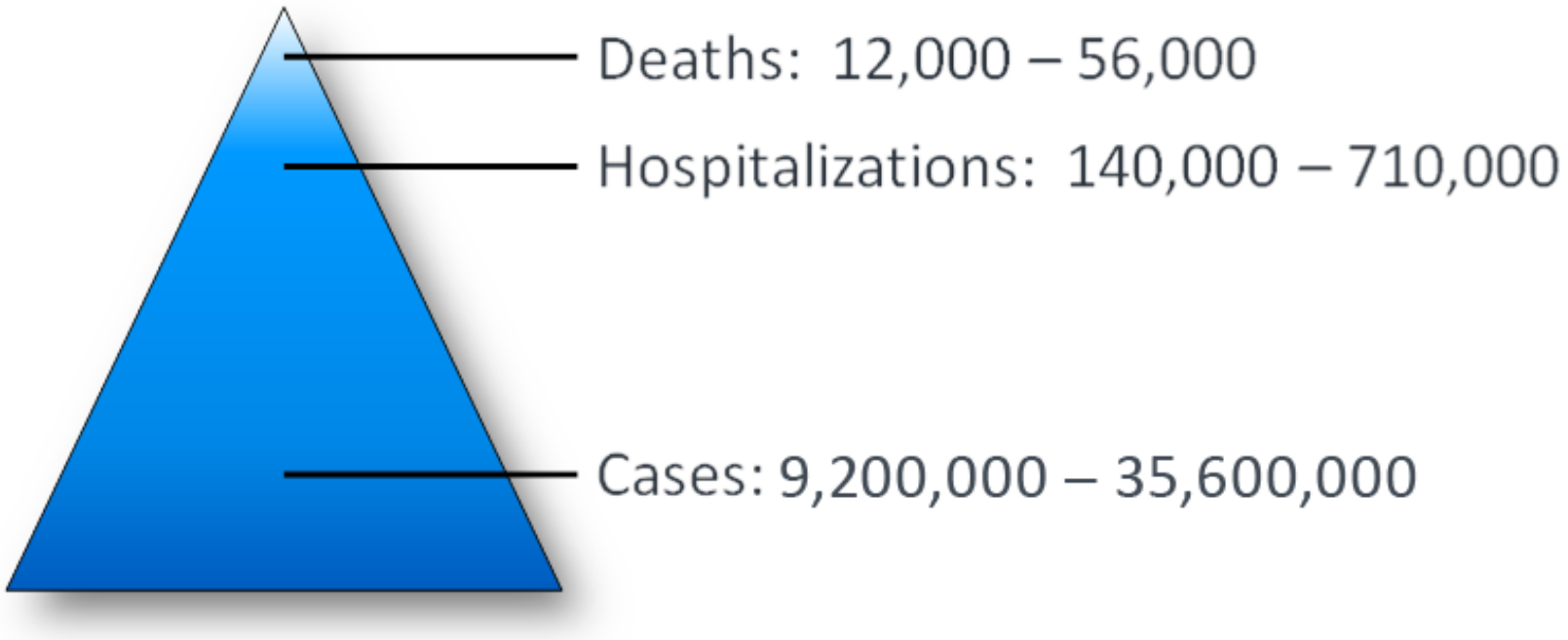
- Emergence and spread of “novel” influenza A virus
  - Results from antigenic shift
  - Sustained and efficient  human-human transmission
- Potential for global spread within months
- Potential to kill millions - All age groups
- Two modern pandemics
  - “Spanish” pandemic – H1N1 in 1918
  - “Hong Kong” pandemic – H3N2 in 1958

# Challenges with Counting Influenza Cases, Hospitalizations, and Deaths

- Many flu hospitalizations/deaths occur 1-2 weeks after illness
  - Secondary bacterial infection
  - Exacerbation of underlying chronic illness
- Most people with flu-related complications are not tested for flu
- Commonly used flu tests not highly sensitive – result in false negative results
- No requirement to report individual cases or deaths

## Impact of Influenza in the U.S.

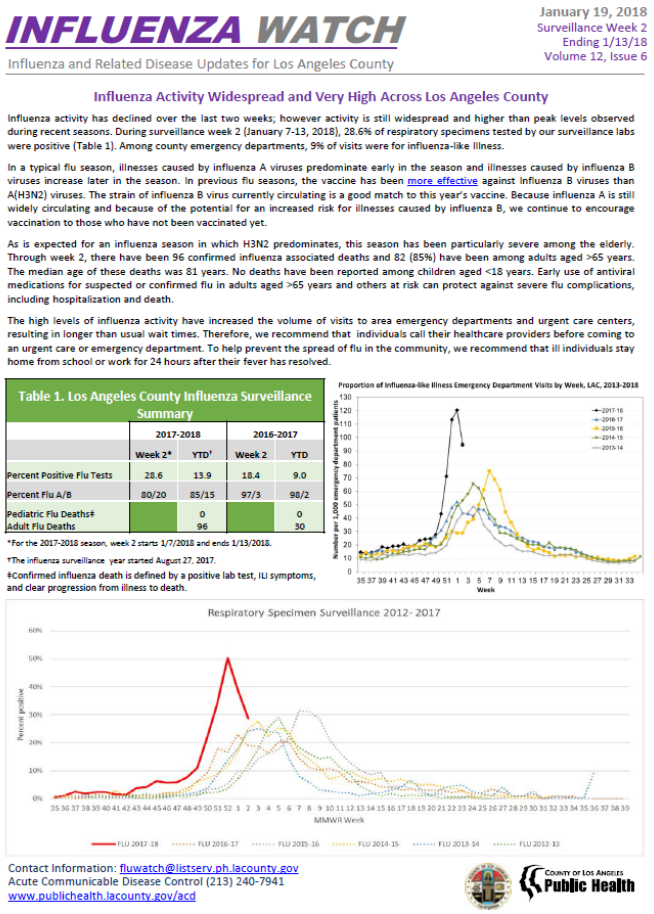
- Best obtained by modelling




(CDC estimates for 2010–2016)

# Overview of Influenza Surveillance in LA County

- Begins in October and ends mid-May
- Surveillance concentrated during this period
  - Year round surveillance activities
- Data collected and analyzed weekly
  - Published weekly or bi-weekly during flu season through *Influenza Watch*



**INFLUENZA WATCH**

Influenza and Related Disease Updates for Los Angeles County

January 19, 2018
Surveillance Week 2
Ending 1/13/18
Volume 12, Issue 6

**Influenza Activity Widespread and Very High Across Los Angeles County**

Influenza activity has declined over the last two weeks; however activity is still widespread and higher than peak levels observed during recent seasons. During surveillance week 2 (January 7-13, 2018), 28.6% of respiratory specimens tested by our surveillance labs were positive (Table 1). Among county emergency departments, 9% of visits were for influenza-like illness.

In a typical flu season, illnesses caused by influenza A viruses predominate early in the season and illnesses caused by influenza B viruses increase later in the season. In previous flu seasons, the vaccine has been more effective against Influenza B viruses than A(H3N2) viruses. The strain of influenza B virus currently circulating is a good match to this year's vaccine. Because influenza A is still widely circulating and because of the potential for an increased risk for illnesses caused by influenza B, we continue to encourage vaccination to those who have not been vaccinated yet.

As is expected for an influenza season in which H3N2 predominates, this season has been particularly severe among the elderly. Through week 2, there have been 96 confirmed influenza associated deaths and 82 (85%) have been among adults aged >65 years. The median age of these deaths was 81 years. No deaths have been reported among children aged <18 years. Early use of antiviral medications for suspected or confirmed flu in adults aged >65 years and others at risk can protect against severe flu complications, including hospitalization and death.

The high levels of influenza activity have increased the volume of visits to area emergency departments and urgent care centers, resulting in longer than usual wait times. Therefore, we recommend that individuals call their healthcare providers before coming to an urgent care or emergency department. To help prevent the spread of flu in the community, we recommend that ill individuals stay home from school or work for 24 hours after their fever has resolved.

**Table 1. Los Angeles County Influenza Surveillance Summary**

| | 2017-2018 | | 2016-2017 | |
|---|---|---|---|---|
| | Week 2* | YTD† | Week 2 | YTD |
| Percent Positive Flu Tests | 28.6 | 13.9 | 18.4 | 9.0 |
| Percent Flu A/B | 80/20 | 85/15 | 97/3 | 98/2 |
| Pediatric Flu Deaths‡ | | 0 | | 0 |
| Adult Flu Deaths | | 96 | | 30 |

*For the 2017-2018 season, week 2 starts 1/7/2018 and ends 1/13/2018.

†The influenza surveillance year started August 27, 2017.

‡Confirmed influenza death is defined by a positive lab test, ILI symptoms, and clear progression from illness to death.

Proportion of Influenza-like Illness Emergency Department Visits by Week, LAC, 2013-2018

Respiratory Specimen Surveillance 2012- 2017

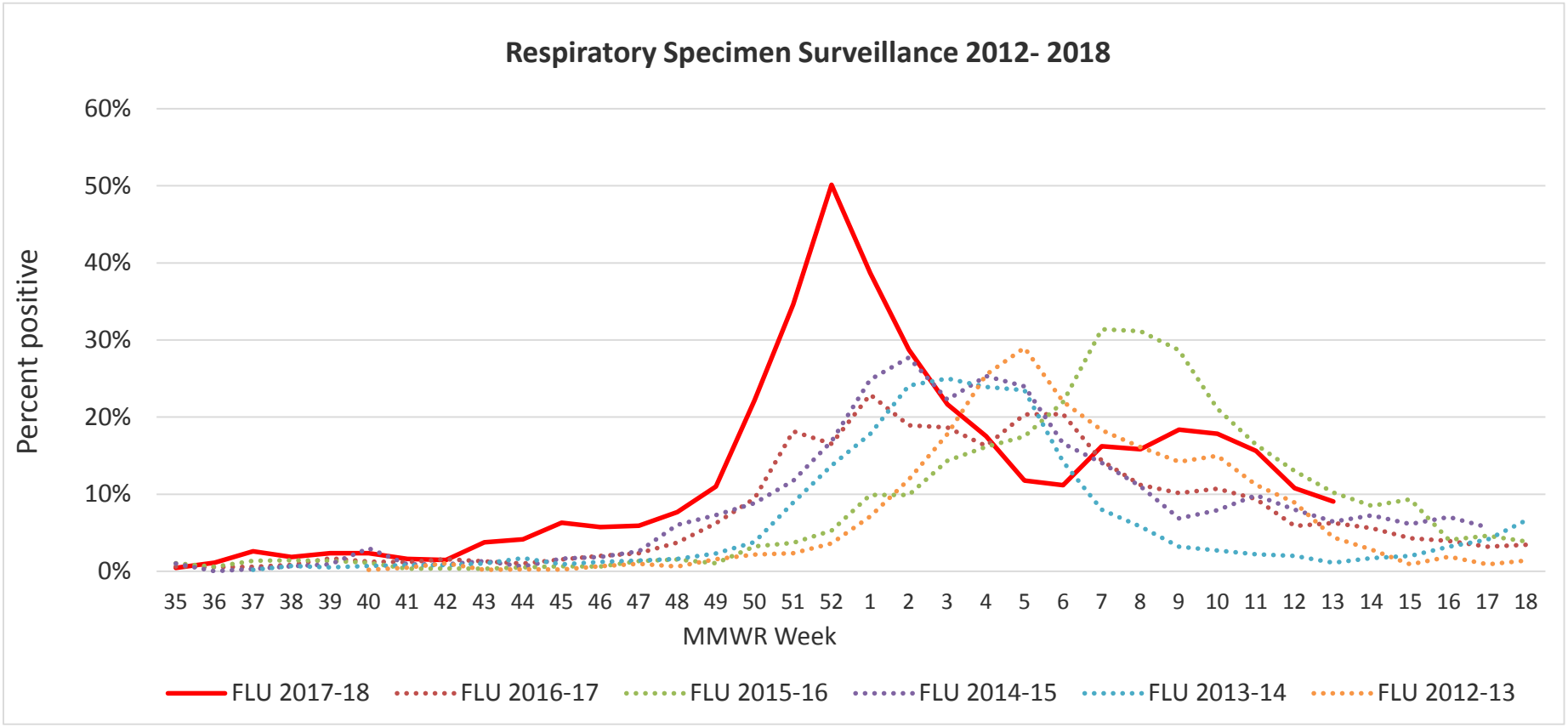
Contact Information: fluwatch@listserv.ph.lacounty.gov
Acute Communicable Disease Control (213) 240-7941
www.publichealth.lacounty.gov/acd

# Influenza Surveillance Data Sources

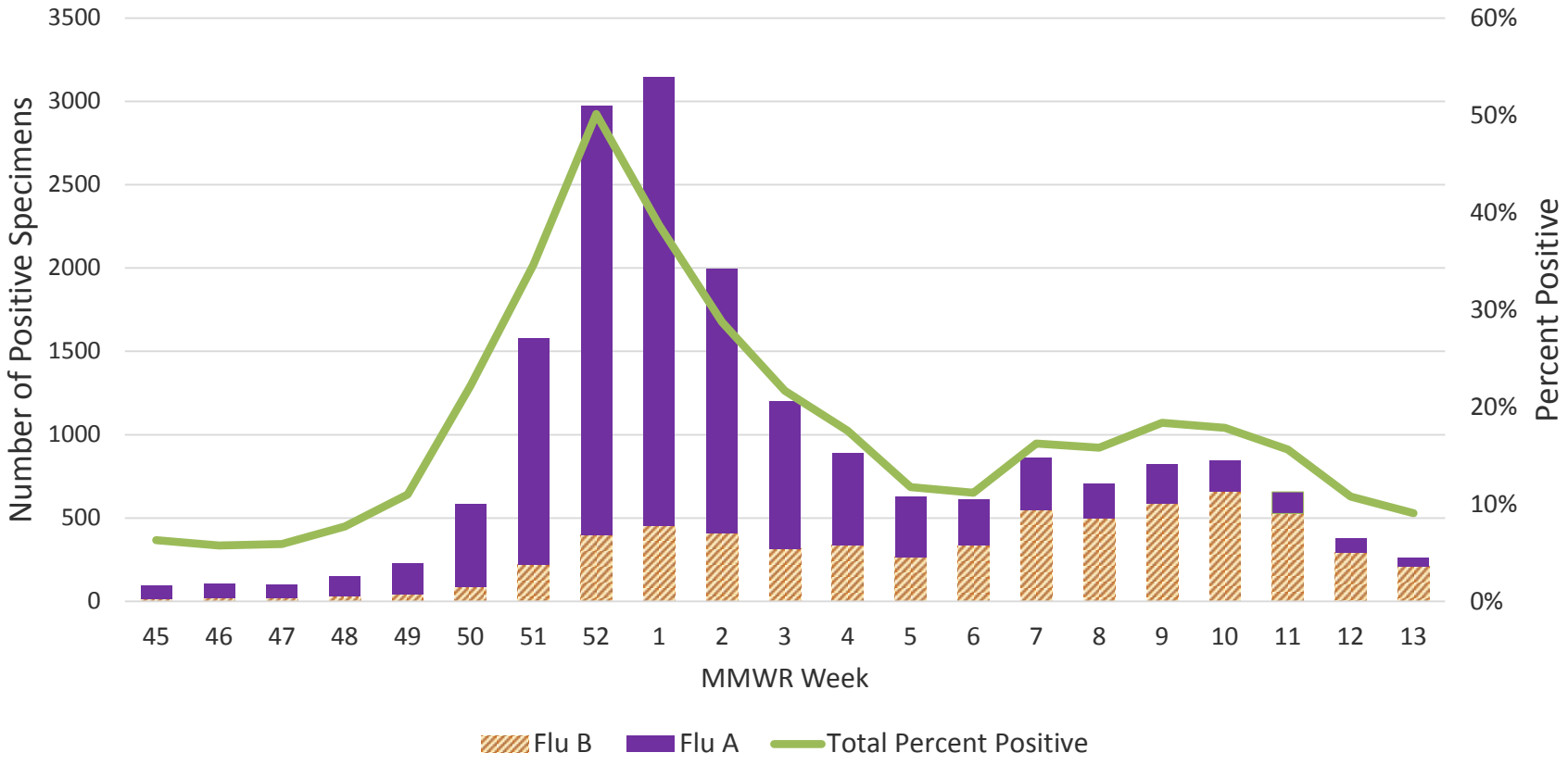
- Sentinel surveillance
  - Laboratory-based reporting – 9 participating laboratories
  - Influenza-associated fatalities – reportable since 2010
  - Outbreak surveillance
- Syndromic surveillance
  - ED visits for influenza-like illness (ILI) symptoms
- P&I Deaths – death certificate data
- Other – Kaiser Permanente, Biofire

# LA County Laboratory-Based Sentinel Surveillance, 2012-13 to 2017-18

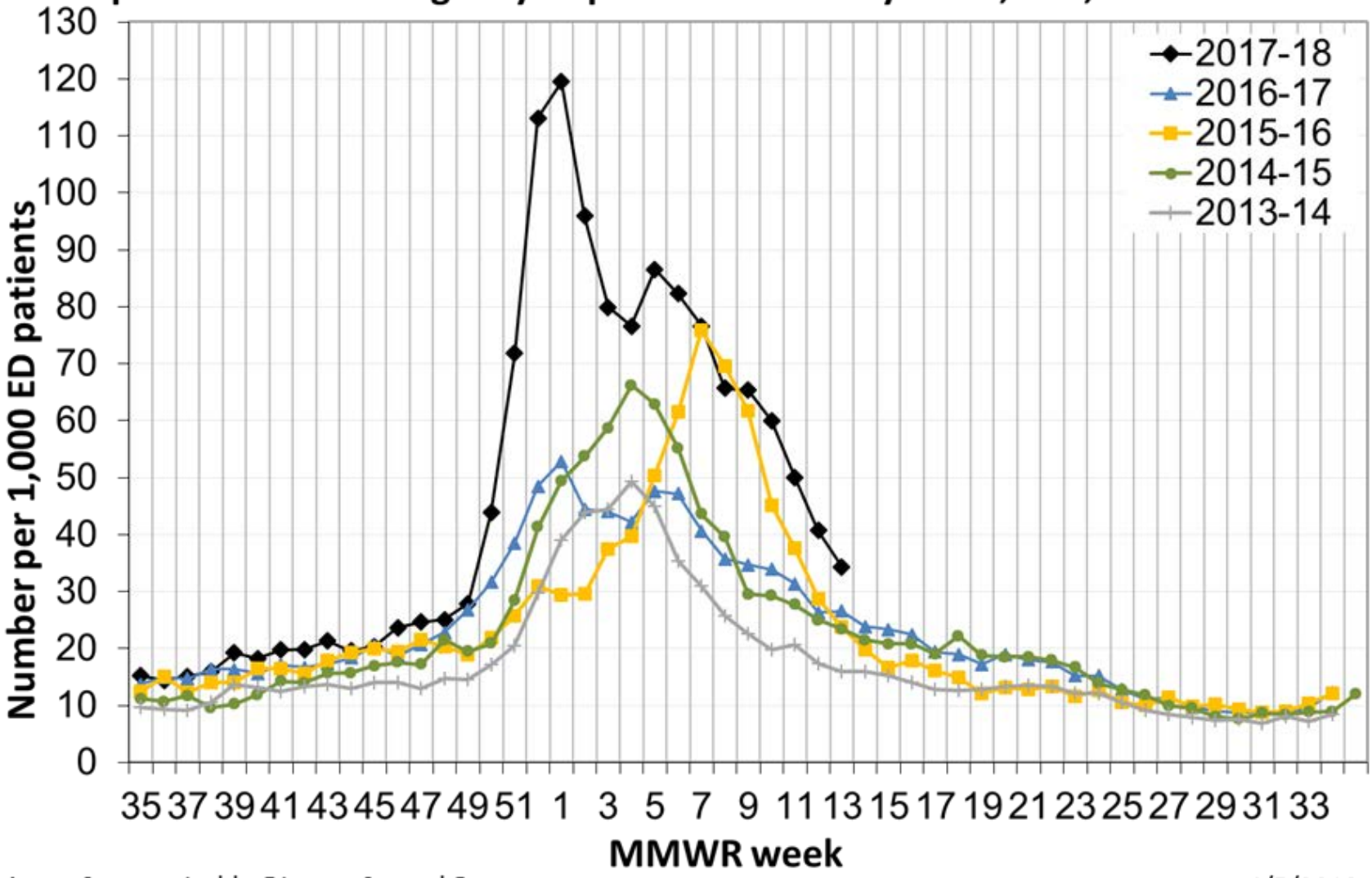
- Used to define the beginning and end of flu season
  - % positive >5% or <5%



# Influenza Positive Tests from Sentinel Laboratories Los Angeles County, 2017-18 Season



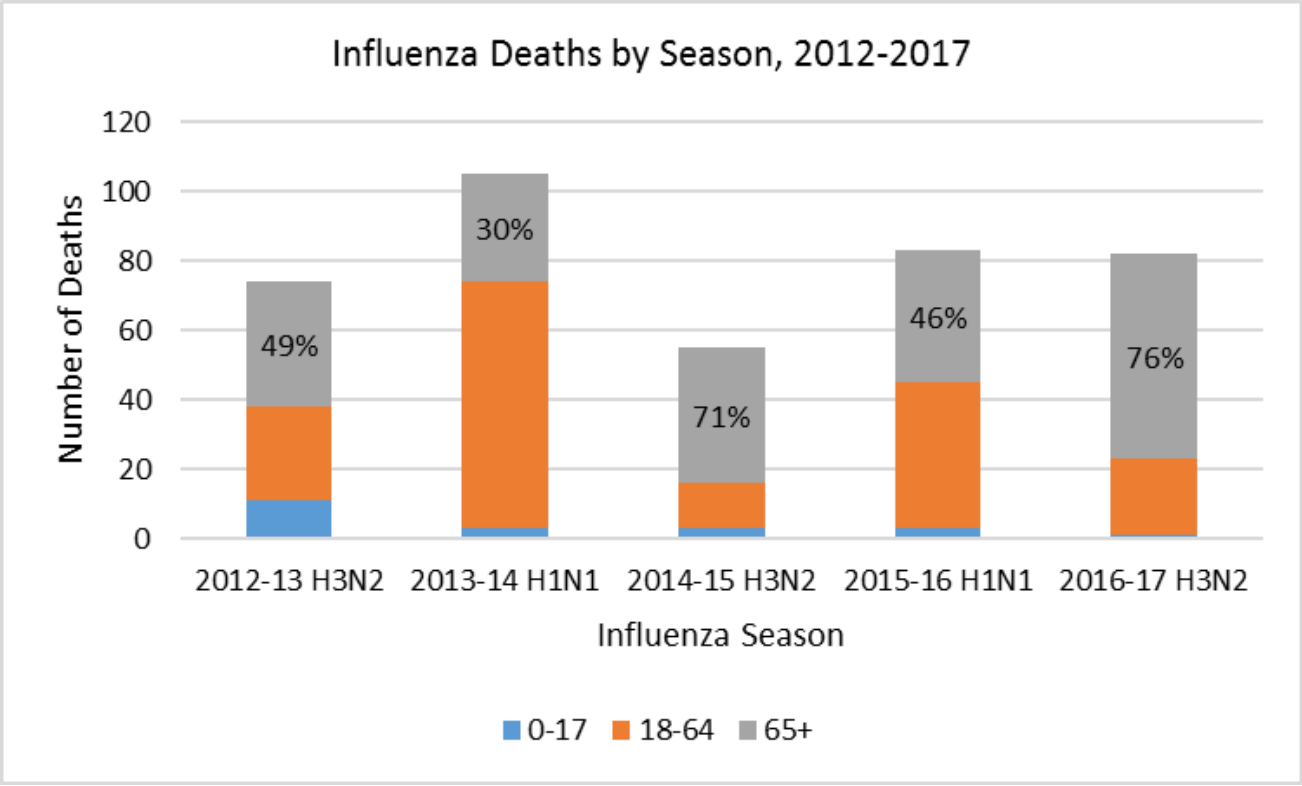
## Proportion of ILI Emergency Department visits by week, LAC, 2013 to 2018




Acute Communicable Disease Control Program

4/5/2018

# Influenza-Associated Deaths in LA County, 2012-13 to 2016-17

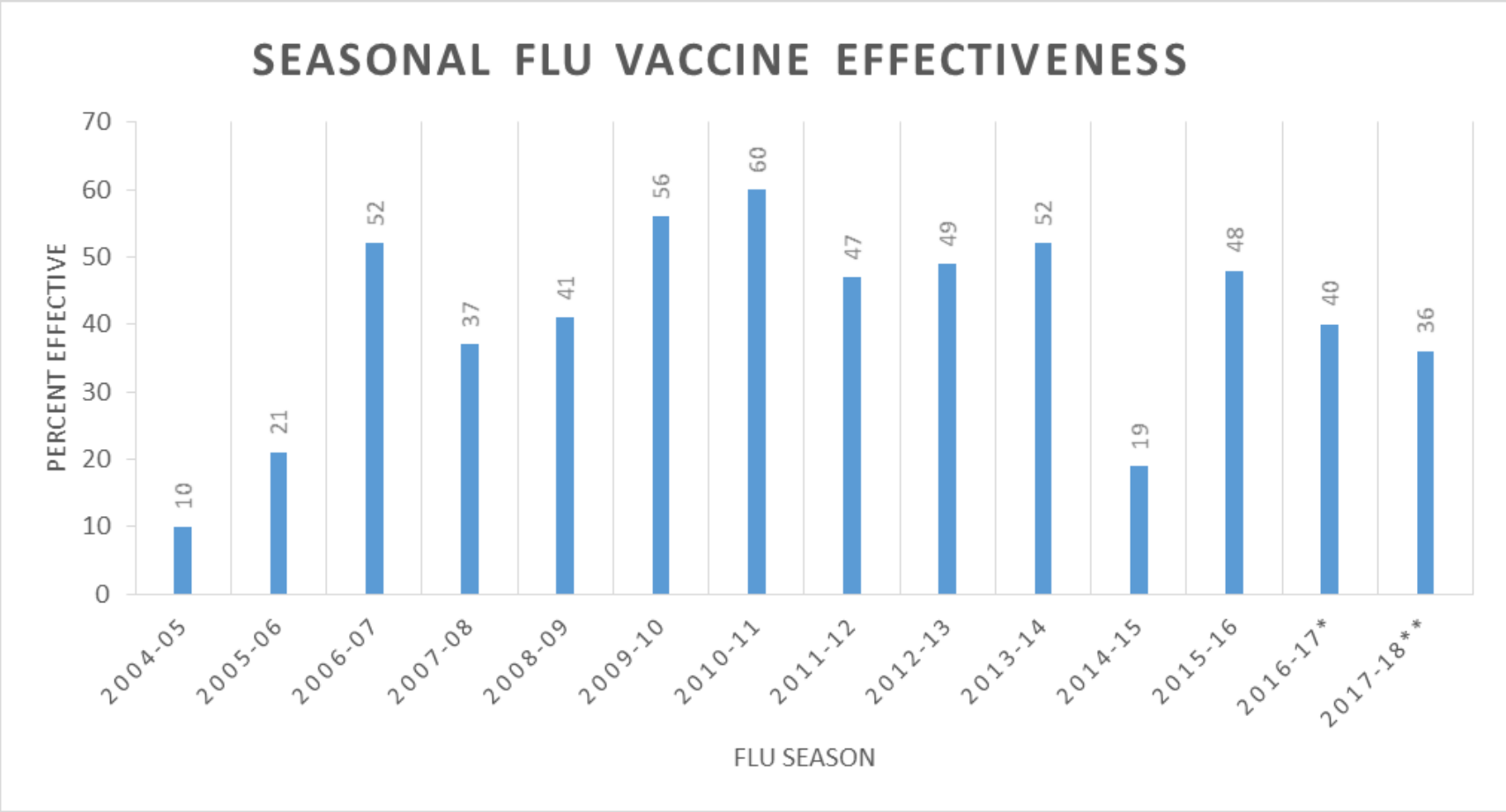



- 239 influenza-associated deaths in 2017-18 season
  - 193 (81%) aged 65+ years

# Influenza Vaccination Recommendations for 2017-18 Season

- All persons aged >6 months without contraindications should be vaccinated annually
- Timing of vaccination: Ideally before onset of influenza activity
- Vaccine formulation
  - Live attenuated vaccine not recommended
  - Higher dose formulation for elderly and immunocompromised
  - CDC does not state preference between trivalent or quadrivalent vaccine (theoretical benefit to quadrivalent)

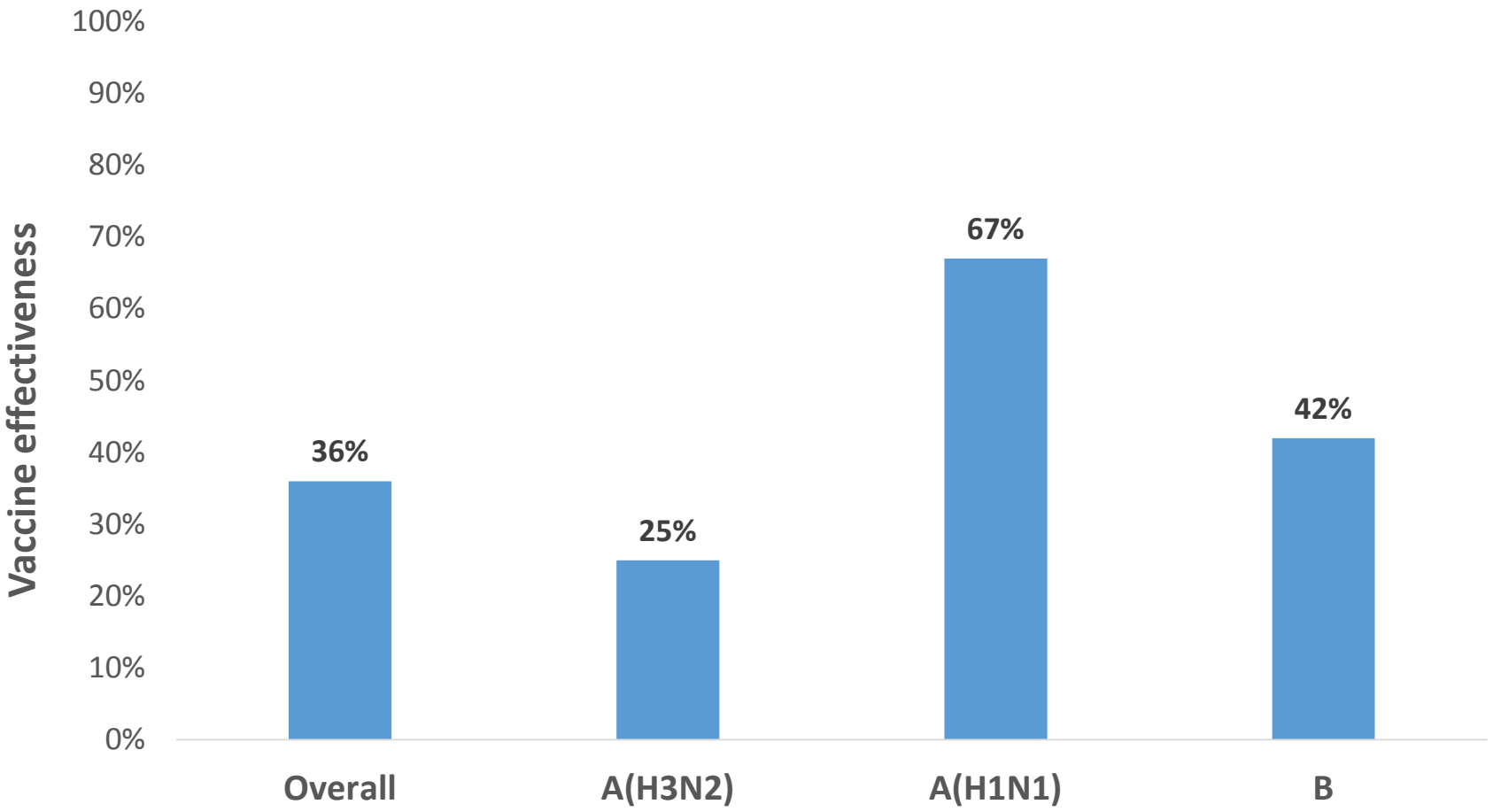
# Seasonal Influenza Vaccine Effectiveness (VE) for 13 Seasons, 2004-05 to 2016-17




*Interim 2016-2017 VE Estimates (4/20/2016-4/9/2017) were presented to ACIP in June 2017

**Interim early estimates may differ from final end-of-season estimates

# 2017-18 Interim Seasonal Influenza VE



A vaccine *not* given

is

100% *not* effective

# What is Considered a Flu Outbreak in a SNF?

- >1 case of laboratory confirmed flu in the setting of a cluster (≥2 cases) of ILI in a 72 hour period

- LAC Department of Public Health responded to
  - 30 flu outbreaks at SNFs during the 2016-17 flu season
  - 73 flu outbreaks at SNFs from Nov 2017 to Mar 2018

# Laboratory Confirmation of Influenza

- Recommended tests (in order of preference):
  - rRT-PCR – most sensitive and accurate test
  - Immunofluorescence
  - Rapid antigen tests
    - Low sensitivity (62%)
    - High specificity (98%)

# Antiviral Chemoprophylaxis During Outbreaks

- To all non-ill residents regardless of vaccination status
- Minimum 2 weeks and continued for 7-10 days after last known case identified
- Consider for all staff regardless of vaccination status if outbreak caused by a strain that is not well matched by the vaccine

# Other Outbreak Control Measures

- Droplet precautions for ill residents
- Place ill residents in a private room or cohort with other ill residents
- Dedicate separate staff to ill and non-ill residents
- Limit group activities and serve meals in room
- Avoid new admissions to facility or unit with ill residents (7 days after symptom onset of last ill resident)

# Influenza Outbreak Prevention

- *Vaccinate* all residents and staff
- *Surveillance* of all residents, staff, and visitors for ILI during flu season (Oct-May)
- *Test* for flu anytime resident develops ILI
- *Exclude* ill staff and visitors from facility

# Questions?