Influenza and RSV in Adults

Kansas City Southwest Clinical Society

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February 2, 2024

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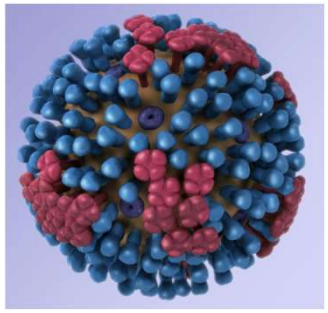
METRO INFECTIOUS DISEASE CONSULTANTS

Outline

- Influenza
  - Virology
  - Epidemics vs. Pandemics
  - Clinical course
  - Testing
  - Treatment
  - Prevention



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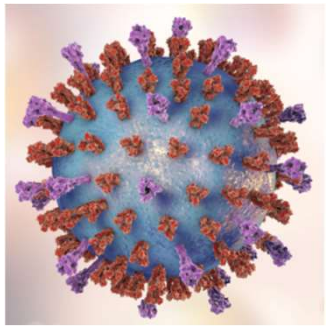
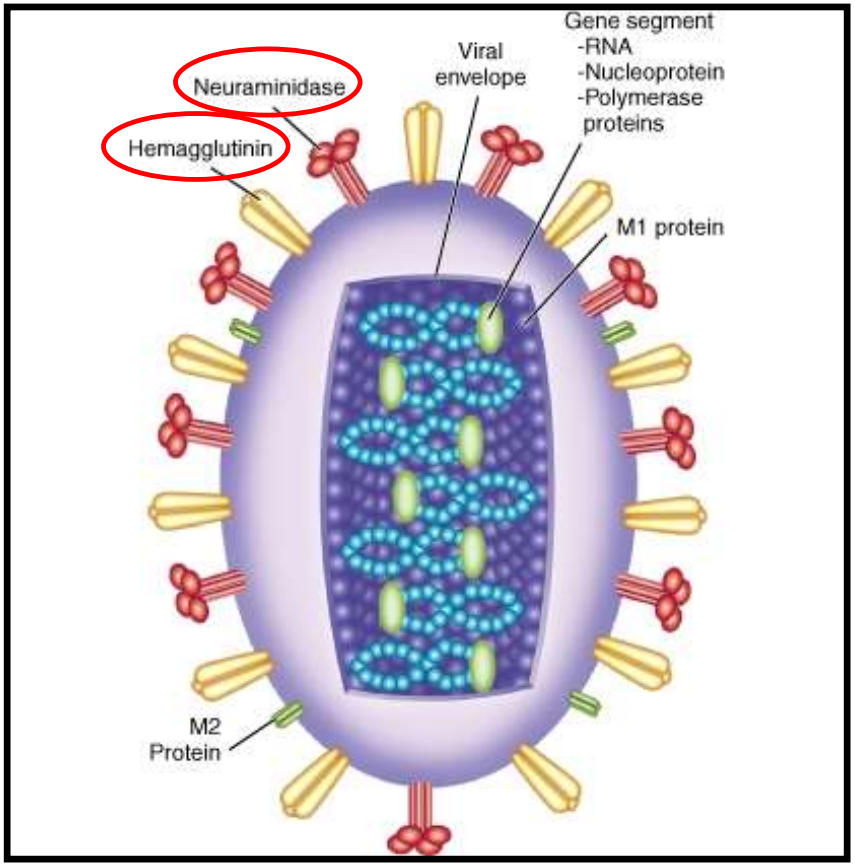
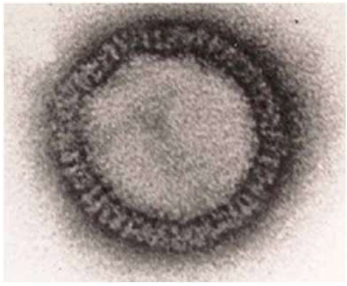


- Closing Thoughts

Influenza Virus Structure





H: Hemagglutinin
Viral attachment to cell membranes; membrane fusion

At least 18 highly divergent, antigenically distinct HAs in influenza A viruses
(H1 to H18)
[H17 & H18 have thus far only been found in bats]

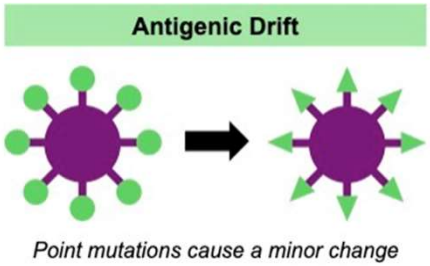
N: Neuraminidase
Cleaves sialic acid from cell surface; released from membranes; prevents aggregation

At least eleven distinct NAs (N1 to N11)

Mandell, Principles and Practice of Infectious Diseases

PLOS Pathogens https://doi.org/10.1371/journal.ppat.1010062 May 19, 2022

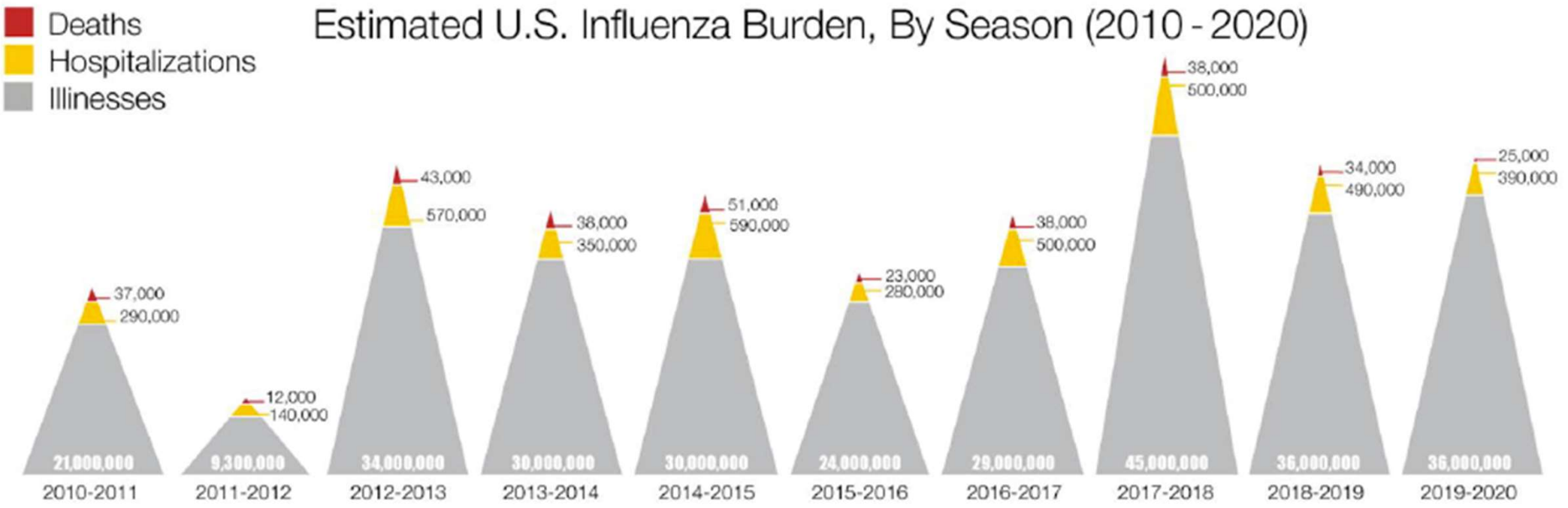
Influenza



- Recurrent epidemics of febrile respiratory disease have occurred every 1 to 3 years for at least the past 400 years
- Epidemics – "*Seasonal Influenza*" occur most years (a result of antigenic drift)

  From 2010 – 2018 in the U.S.[1]
  - 4.3 – 23 million medical visits yearly
  - 140,000 – 960,000 influenza-related excess hospitalizations yearly
  - 12,000 – 79,000 annual deaths
  - 90% of deaths in persons 65 and older[2]
  - 37% of hospitalizations among persons younger than 65[2]
  - average annual total economic burden $11.2 billion[3]

[1]*Clinical Infectious Diseases* 2019;68(6):e1–47 [2]*PLOS Medicine* 2013; 10(11):e1001558 [3]*Vaccine* 2018;36(27):3960-3966



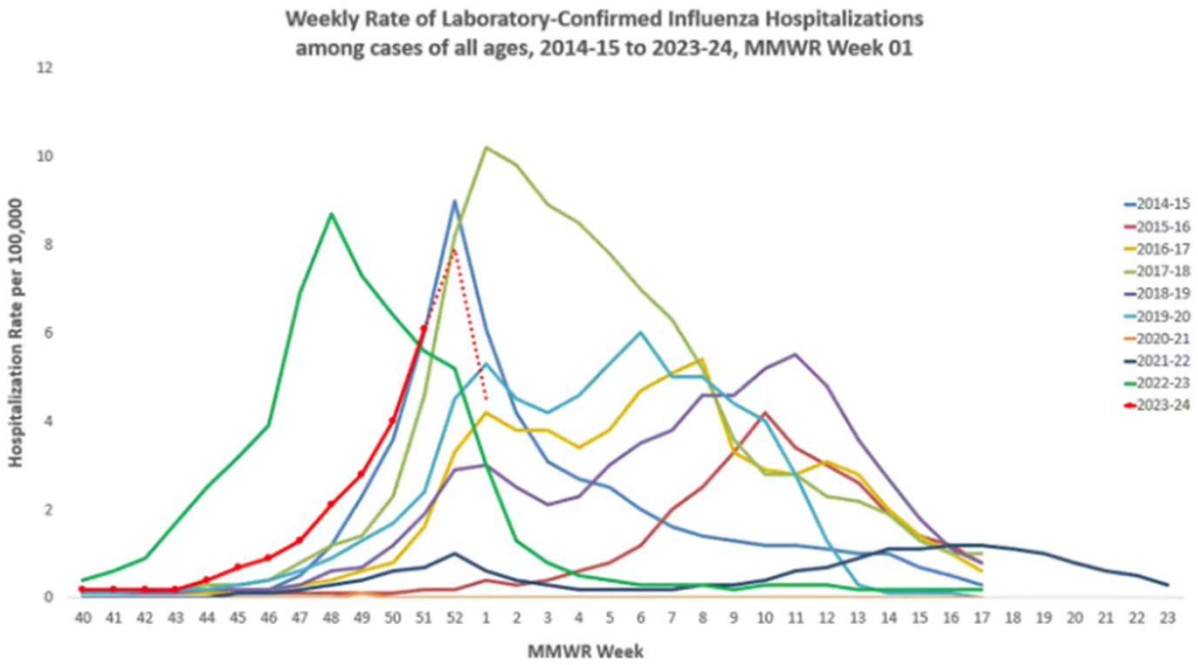
Hospitalization
+ Death
= 2.14%

Hospitalization
+ Death
= 1.20%

https://www.cdc.gov/flu/about/burden/index.html

Variation in Timing and Magnitude of Seasonal Influenza

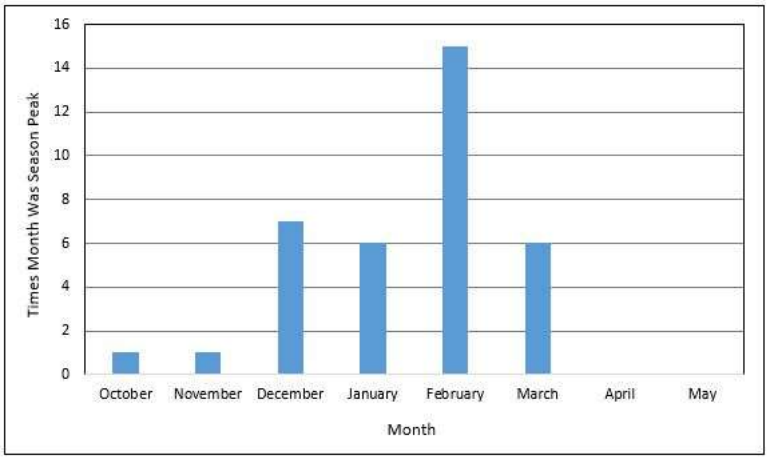
Hospitalization Rate per 100,000



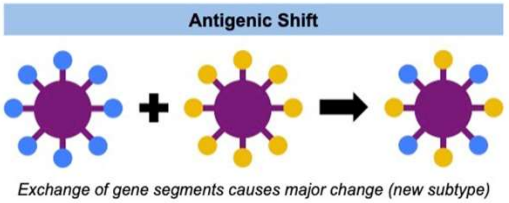
CDC.gov accessed 1/14/24

MMWR 68(3):1-21, August 23, 2019

Peak Month of Flu Activity (nationwide)
1982-1983 through 2017-2018



Influenza



Exchange of gene segments causes major change (new subtype)

- Pandemics – global epidemics, occur erratically[2] (a result of antigenic shift)
- Pandemics occur when a 'new' influenza virus capable of human-to-human transmission enters the population
- The first recorded pandemic that clearly fits the description of influenza occurred in 1580

  (32 pandemics have been recorded since – on average one every ~14 years)
- The worst pandemic in recorded history occurred in 1918-1919

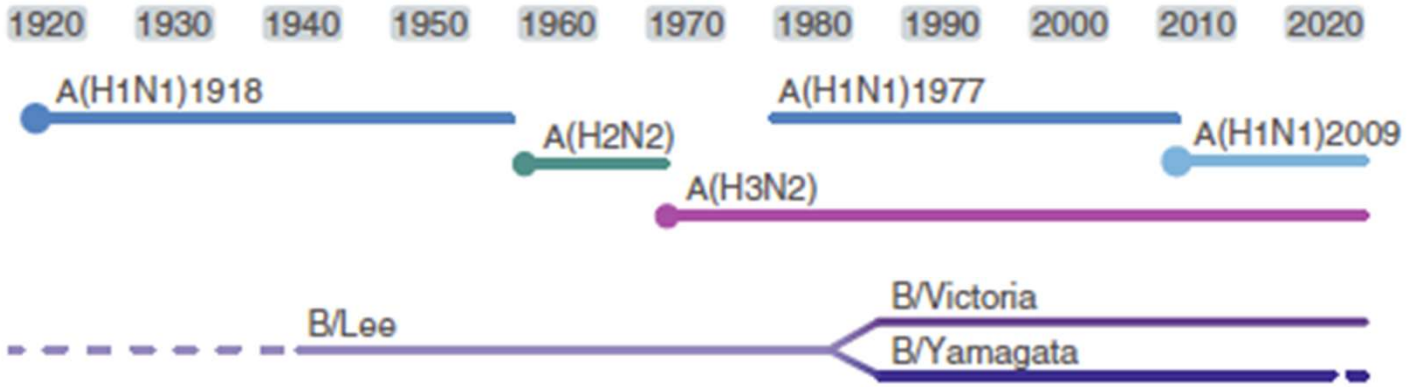
Pandemic	U.S. Deaths	World Deaths
2009 H1N1	12,000	284,000
1968-69 H3N2 "Hong Kong Flu"	34,000	1 Million
1957-58 H2N2 "Asian Flu"	70,000	2 Million
1918-19 H1N1 "Spanish Flu"	>550,000 U.S. population was ~1/3 of current #	20-50 Million

Mandell, *Principles and Practice of Infectious Diseases*

[2]*Emerging Infectious Diseases* 12(1):15, 2006

Pandemic Influenza A Strains Become the Seasonal Influenza Strains

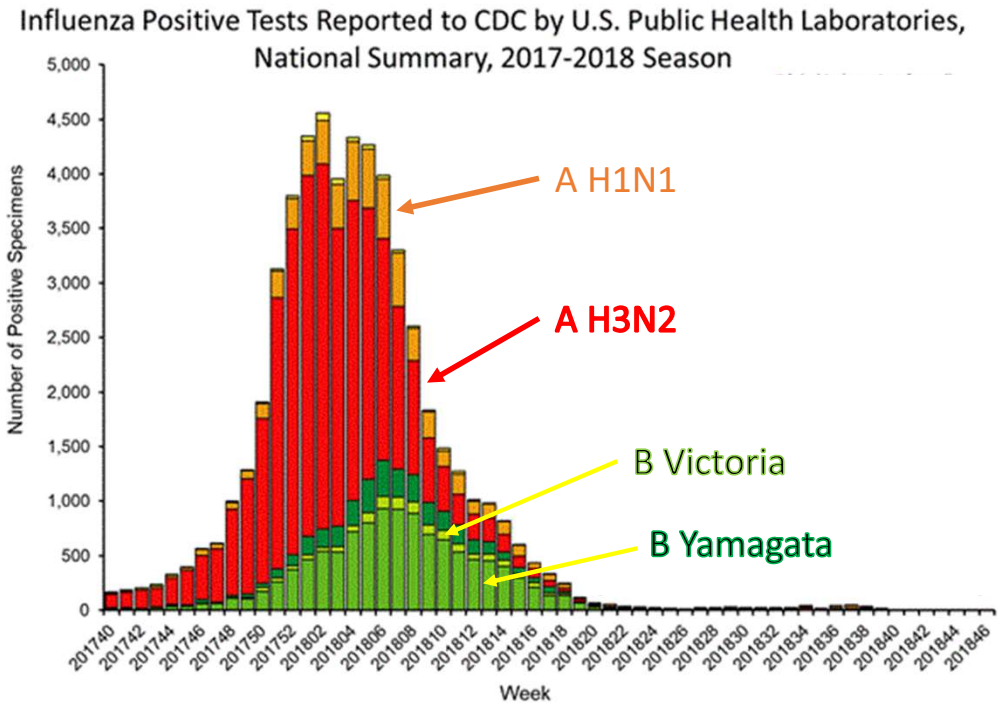
Historical circulation of influenza viruses in the last century

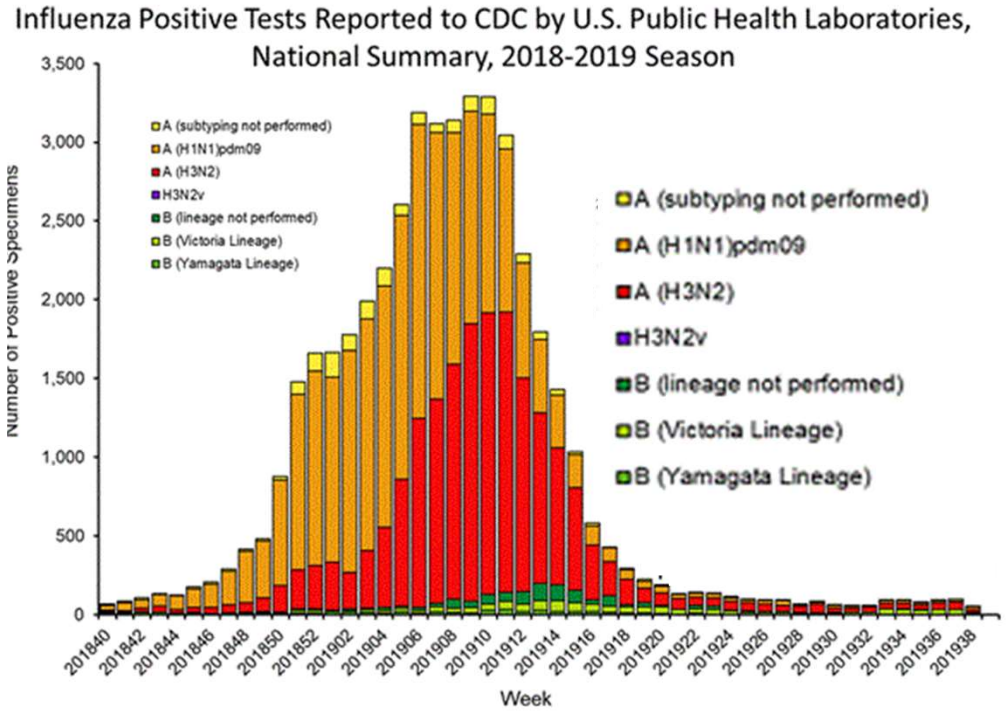


Nature Communications (2022) 13:1721

Seasonal Influenza

In recent years, two dominant strains of Influenza A and two strains of Influenza B have circulated.
The proportions of these vary year by year and vary throughout an epidemic.





CDC.gov WHO.int

It appears that as an indirect result of the COVID-19 pandemic, Influenza B Yamagata may have become extinct

Clinical Aspects of Influenza

"We've got that durned influenzy agin" by A.B. Frost
Kansas City Star November 27, 1918

Seasonal Influenza Clinical Course

- Incubation period 1 – 2 days
- Sudden onset of:
  - Fever, usually lasts 3 days, up to 8
  - Chills, Body aches, Sore throat
  - Non-productive cough, Runny nose, Headache
  - Emesis and diarrhea (more common in children)
- Viral pneumonia uncommon
- Low death rate except in the elderly
- High attack rate in those living in close proximity

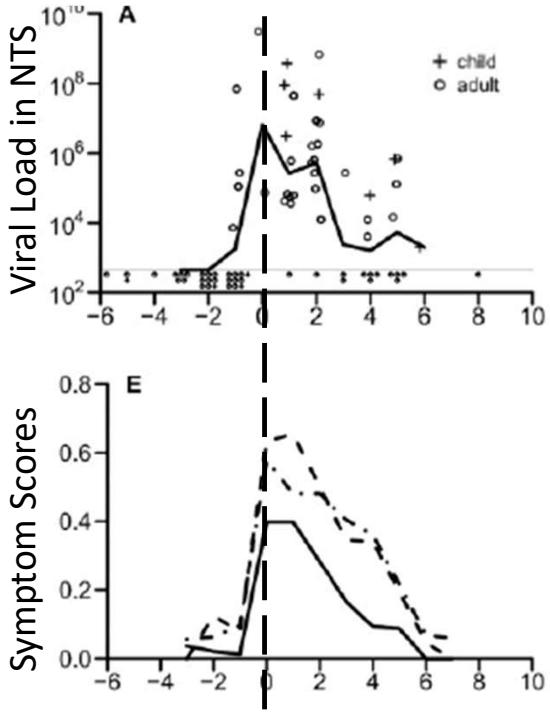
Symptom or sign	No. (%) of symptoms reported at illness onset	
	Influenza A (n = 26)	Influenza B (n = 18)
Runny nose or nasal congestion	19 (73)	11 (61)
Cough	18 (69)	14 (78)
Sore throat	14 (54)	7 (39)
Headache	14 (54)	5 (28)
Phlegm	12 (46)	5 (28)
Myalgia	9 (35)	6 (33)
Fever ⩾37.8°C	8 (31)	8 (44)

NOTE. ARI onset is defined as the first day with ⩾2 of the 7 signs or symptoms listed.

J Infect Dis 2010 May; 201(10): 1509–1516

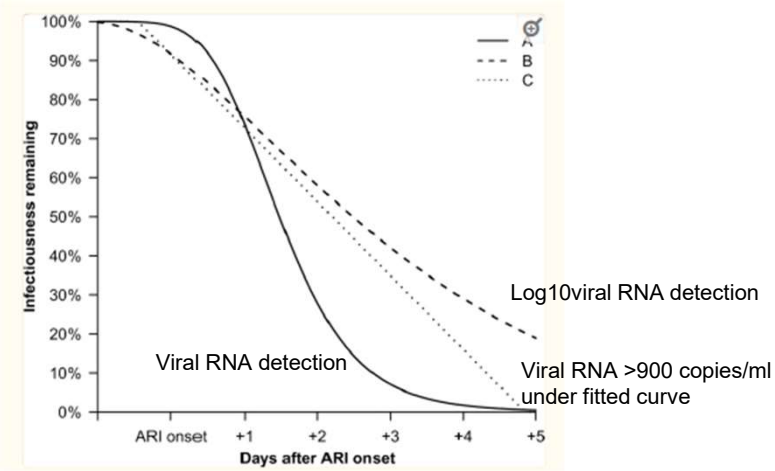
Duration of Viral Shedding in Influenza

Influenza A



(NTS = nose and throat swab)

- **Virus can be detected the day before illness onset, virus levels peak within 24 hours after onset**
  - **Highest infectious period is within 3 days after symptom onset**
- Young children can be infectious for longer periods
- Critically ill patients might have longer influenza viral replication in the lower respiratory tract
- Severely immunocompromised persons can be infectious for weeks to months



In a study of household contacts of people with Influenza

J Infect Dis 2010 May; 201(10): 1509–1516

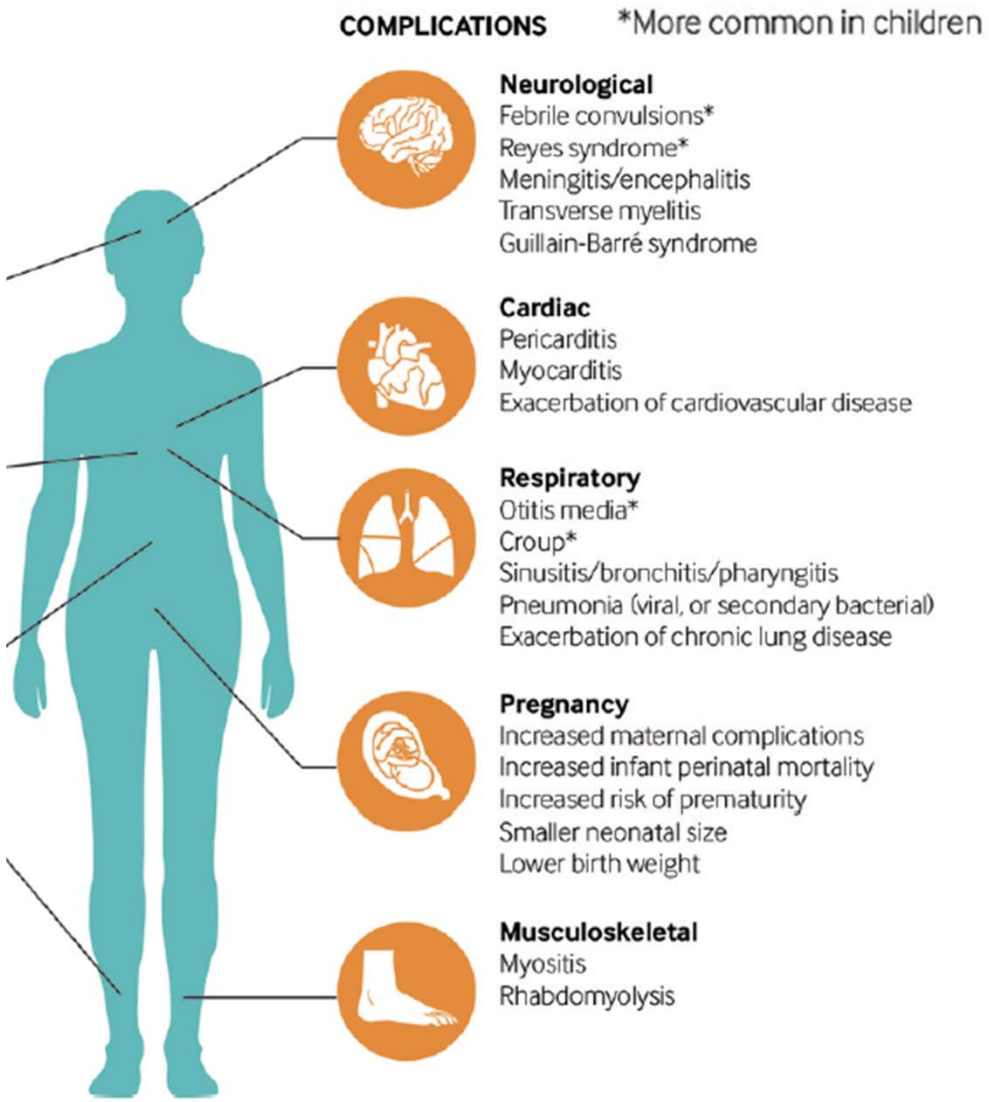
Seasonal Influenza Clinical Course

- Most people recover from uncomplicated influenza
- Complications resulting in severe illness and death can occur, particularly among:
  - very young children
  - older adults
  - pregnant and postpartum women within 2 weeks of delivery
  - people with certain chronic medical conditions including chronic pulmonary, cardiac, and neurologic disorders, and metabolic disease
  - those who are immunocompromised

Clinical Infectious Diseases 2019;68(6):e1–47

Complications of Influenza

- Exacerbation of chronic disease
- Bacterial superinfection
  - Staphylococcus aureus (MSSA, MRSA), Streptococcus pneumoniae, Group A Streptococcus
    → may result in sepsis, severe sepsis, or septic shock
- Multi-organ failure
- Healthcare-associated infections
  - Bacterial, fungal, ventilator-associated pneumonia
- Death



BMJ 2016; 355:i6258 doi: 10.1136/bmj.i6258

Influenza Testing

- Rapid antigen test: fast and inexpensive but low sensitivity
  (Helpful if positive, but high false-negative rate)

10 minutes, ~$10
Point Of Care (POC)
Sensitivity ~50%

- Rapid molecular assay: fast, not expensive, good sensitivity

15-30 minutes, POC but requires a lab, ~$25, Sensitivity ~90%

- PCR: slow, expensive, very good sensitivity
  - Multiplex PCR detects other pathogens but more expensive →

60-120 minutes, ~$100-150,
Requires a High Complexity Lab
Sensitivity ~99%

Adenovirus (PCR)
B. pertussis DNA (PCR)
B.parapertussis DNA PCR
C. pneumoniae DNA (PCR)
Coronavirus OC43 (PCR)
Coronavirus HKU1 (PCR)
Coronavirus 229E (PCR)
Coronavirus NL63 (PCR)
Human Metapneumovir PCR
Influenza A (H1) PCR
Influ A (H1N1/09) PCR
Influenza A (H3) PCR
Influenza Type A (PCR)
Influenza Type B (PCR)
M. pneumoniae (PCR)
Parainfluenza 1 (PCR)
Parainfluenza 2 (PCR)
Parainfluenza 3 (PCR)
Parainfluenza 4 (PCR)
RSV (PCR)
Entero/Rhino (PCR)

Annals Int Med 2017 Sep 19;167(6):394-409

Clinical Infectious Diseases 2019 69(7):1243–1253

Which Influenza Test is Recommended?

- Outpatients:
  - Rapid influenza molecular assays are recommended over rapid influenza antigen detection tests
- Hospitalized patients:
  - RT-PCR or other molecular assays are recommended
  - Rapid antigen detection tests are not recommended and should not be used unless molecular assays are not available
    - follow-up testing with RT-PCR or other molecular assays should be performed to confirm negative rapid antigen results
  - Immunocompromised patients: Multiplex RT-PCR assays targeting a panel of respiratory pathogens, including influenza viruses are recommended

Influenza A&B PCR or 'combo' flu/RSV/COVID-19 PCR

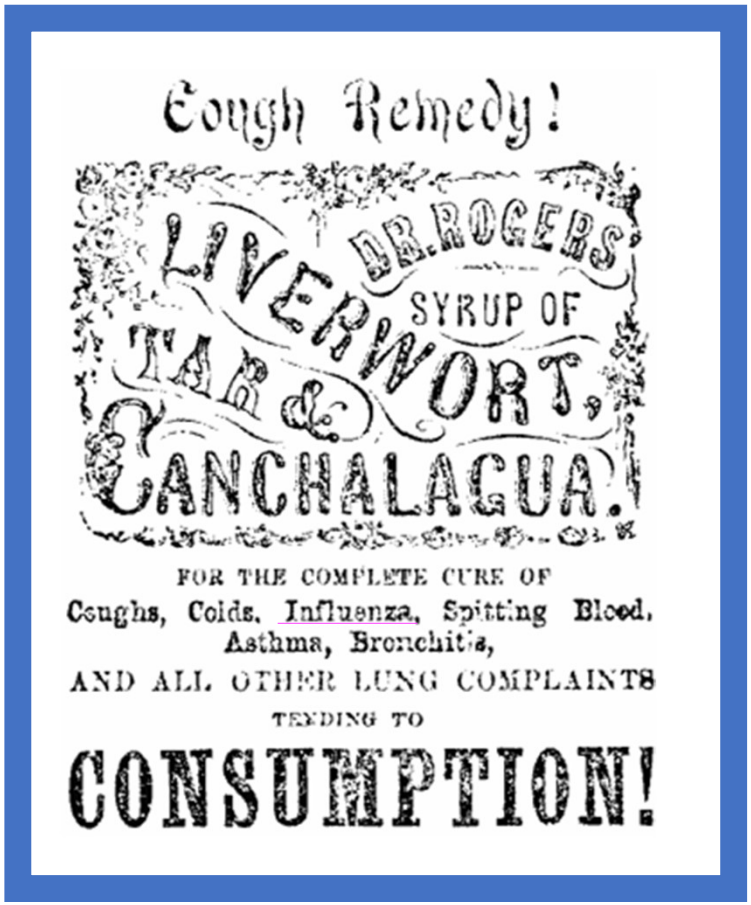
Clinical Infectious Diseases
IDSA GUIDELINE

Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 Update on Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenza[a]

Clinical Infectious Diseases 2019;68(6):e1–47

RT-PCR on lower respiratory tract specimen if nasopharyngeal PCR is negative (10-19% in intubated patients)

INFLUENZA TREATMENT



Liberty, MO
Weekly Tribune
February 10, 1854

Recommended Antivirals for Treatment of Influenza, U.S. 2023-24

Four antivirals are available to treat influenza:

- All have demonstrated efficacy and are FDA-approved for early treatment (<2 days of illness onset) in outpatients with uncomplicated influenza

Neuraminidase inhibitors

Antiviral Drug	Route of Administration	Recommended Ages for Treatment	COST
Oseltamivir	Oral (twice daily x 5d)	All ages	~$25-70*
Zanamivir	Inhaled (twice daily x 5d)	≥7 years	~$70*
Peramivir	Intravenous (single infusion)	≥6 months	~$1000*
Baloxavir	Oral (single dose)	≥5 years (otherwise healthy) ≥12 years (high-risk)	~$170*

Cap-dependent endonuclease inhibitor

CDC.gov
https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

* per Dr. Google 1/2024

Influenza Treatment Summary

For Adults

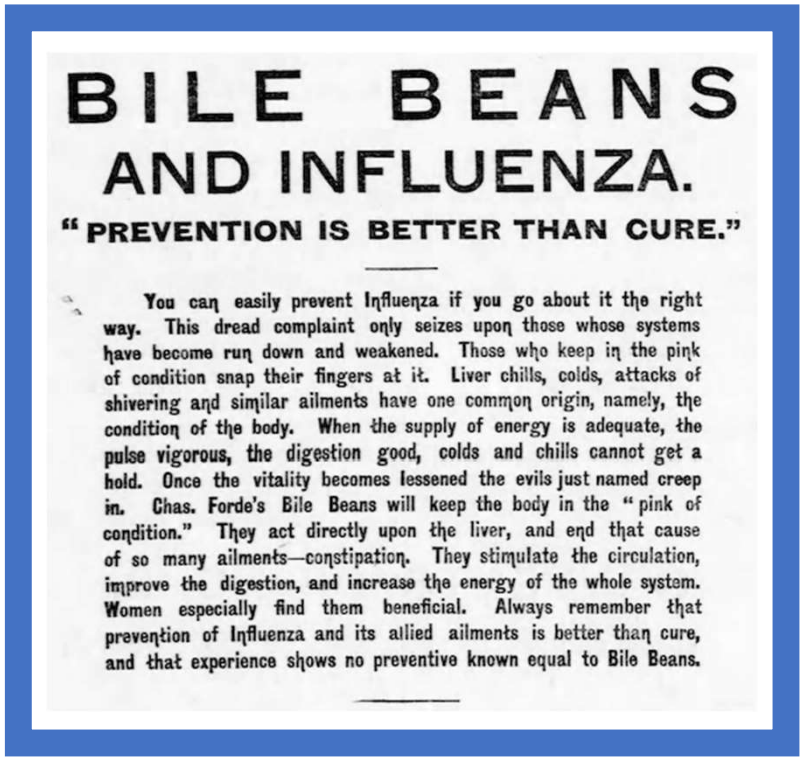
- Treatment started within 36 hours of symptom onset reduced illness duration by 25.2 hours and reduced the risk of lower respiratory tract complications by 44%
- Single-dose baloxavir had similar median time to alleviation

Special Populations

- Pregnant women and up to two weeks postpartum
  - Oseltamivir is recommended (lack of data for others)
- Immunocompromised patients
  - Baloxavir is not recommended (risk of resistance emergence due to prolonged viral replication)
- Hospitalized patients
  - Antiviral treatment is recommended ASAP even if beyond 48 hours from symptom onset
  - Inhaled zanamivir and oral baloxavir are not recommended (lack of data)
- Critically ill patients
  - Optimal duration of oseltamivir is unclear

https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

INFLUENZA PREVENTION



BILE BEANS
AND INFLUENZA.
"PREVENTION IS BETTER THAN CURE."

You can easily prevent Influenza if you go about it the right way. This dread complaint only seizes upon those whose systems have become run down and weakened. Those who keep in the pink of condition snap their fingers at it. Liver chills, colds, attacks of shivering and similar ailments have one common origin, namely, the condition of the body. When the supply of energy is adequate, the pulse vigorous, the digestion good, colds and chills cannot get a hold. Once the vitality becomes lessened the evils just named creep in. Chas. Forde's Bile Beans will keep the body in the "pink of condition." They act directly upon the liver, and end that cause of so many ailments—constipation. They stimulate the circulation, improve the digestion, and increase the energy of the whole system. Women especially find them beneficial. Always remember that prevention of Influenza and its allied ailments is better than cure, and that experience shows no preventive known equal to Bile Beans.

The Daily Telegraph (London)
21 Nov 1902, Fri · Page 4

Influenza Vaccine Recommendations

Vaccinate everyone >6 months old every year

Which vaccine?

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Recommendations and Reports / Vol. 72 / No. 2
August 25, 2023

Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2023–24 Influenza Season

TABLE 1. Influenza vaccines — United States, 2023–24 influenza season*

Trade name (manufacturer)	Presentation	Age indication	µg HA (IIV4s and RIV4) or virus count (LAIV4) for each vaccine virus (per dose)	Route	Mercury (from thimerosal, if present) µg/0.5 mL
IIV4 (standard-dose, egg-based vaccines†)					
Afluria Quadrivalent (Seqirus)	0.5-mL PFS§	≥3 yrs§	15 µg/0.5 mL	IM¶	—**
	5.0-mL MDV§	≥6 mos§ (needle and syringe) 18 through 64 yrs (jet injector)	7.5 µg/0.25 mL 15 µg/0.5 mL	IM¶	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¶	—
Fluzone Quadrivalent (Sanofi Pasteur)	0.5-mL PFS††	≥6 mos††	15 µg/0.5 mL	IM¶	—
	0.5-mL SDV††	≥6 mos††	15 µg/0.5 mL	IM¶	—
	5.0-mL MDV††	≥6 mos††	7.5 µg/0.25 mL 15 µg/0.5 mL	IM¶	25.0
ccIIV4 (standard-dose, cell culture–based vaccine)					
Flucelvax Quadrivalent (Seqirus)	0.5-mL PFS	≥6 mos	15 µg/0.5 mL	IM¶	—
	5.0-mL MDV	≥6 mos	15 µg/0.5 mL	IM¶	25.0
HD-IIV4 (high-dose, egg-based vaccine†)					
Fluzone High-Dose Quadrivalent (Sanofi Pasteur)	0.7-mL PFS	≥65 yrs	60 µg/0.7 mL	IM¶	—
aIIV4 (standard-dose, egg-based vaccine† with MF59 adjuvant)					
Fluad Quadrivalent (Seqirus)	0.5-mL PFS	≥65 yrs	15 µg/0.5 mL	IM¶	—
RIV4 (recombinant HA vaccine)					
Flublok Quadrivalent (Sanofi Pasteur)	0.5-mL PFS	≥18 yrs	45 µg/0.5 mL	IM¶	—
LAIV4 (egg-based vaccine†)					
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	—

5 types
9 options

MMWR 72(2):1-25, August 25, 2023

Flu Shot – What to Do

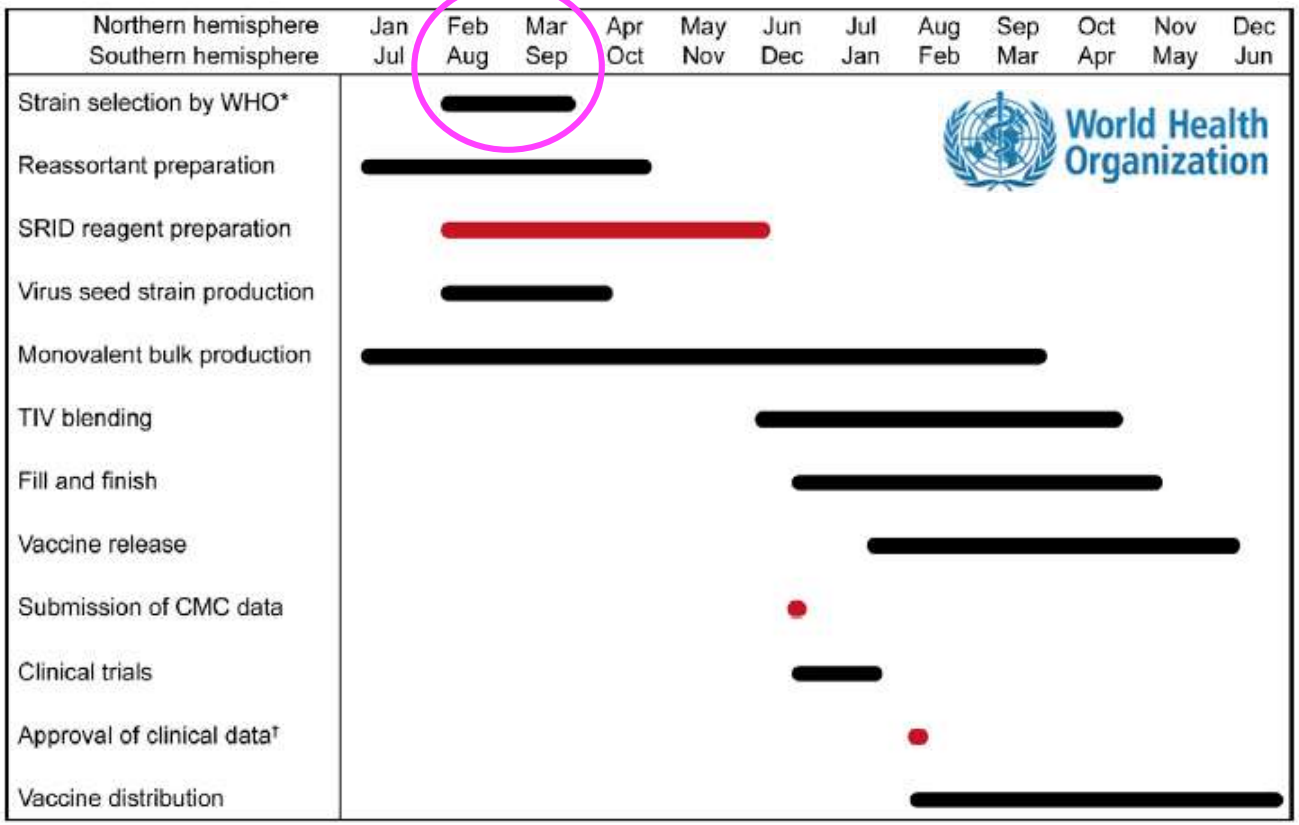
- Use what you have, try to vaccinate everyone >6 months old
- 65 and over: high-dose or adjuvant
- Concern about egg allergy: cell-based or recombinant

  (since 2016 egg allergies are no longer considered a contraindication to flu vaccine)
- Concern about thimerosal: single dose

  (Data from many studies show no evidence of harm caused by the low doses of thimerosal in vaccines. Studies reveal no link between thimerosal and autism.)
- FluMist (nasal spray) available but injection preferred

www.cdc.gov

Vaccine Strain Selection



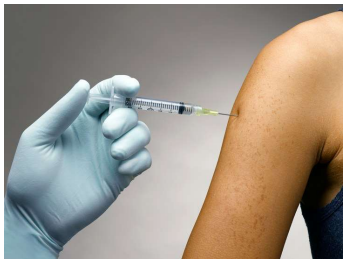
European Journal of Pharmaceutics and Biopharmaceutics 2015; 94:251–263

In some years, circulating strains of influenza change considerably over the months leading to vaccine distribution

Some years the vaccine is a “good match”, some years not

(2023-24 vaccine appears to be an excellent match)

Flu Vaccine Effectiveness



- Varies year to year
- During the six influenza seasons from 2010–11 through 2015–16, influenza vaccination prevented an estimated
  - 1.6–6.7 million illnesses
  - 790,000–3.1 million outpatient medical visits
  - 39,000–87,000 hospitalizations
  - and 3,000–10,000 respiratory and circulatory deaths

    Average PER SEASON

- During the severe 2017–18 influenza season, notable for an unusually long duration of widespread high influenza activity, flu vaccine is estimated to have prevented
  - 7.1 million illnesses, 3.7 million medical visits, 109,000 hospitalizations, and 8,000 deaths, despite an overall estimated vaccine effectiveness of 38%

MMWR 68(3):1-21, August 23, 2019

Universal Influenza Vaccine

- Several strategies under development

Researchers getting closer to a "universal" flu vaccine

With new vaccine targets and more powerful delivery platforms, researchers are making inroads toward an influenza vaccine that could offer better, longer-lasting protection.

Carolyn Beans, *Science Writer*

When urgent coronavirus disease 2019 (COVID-19) vaccine development efforts began in earnest in early 2020, researchers were by no means starting from scratch. That's in part attributable to the decades of research dedicated to creating better influenza vaccines. Indeed, many flu vaccinologists pivoted to COVID-19 two years ago, bringing to bear the knowledge and tools they'd developed to fight a seasonal menace that has the potential to spark pandemics.

But these vaccinologists haven't turned away from their longstanding goal: an influenza vaccine that protects against all strains. Such an achievement could save hundreds of thousands of lives every year. And COVID-19 vaccine efforts may end up helping to accelerate that work.

A universal influenza vaccine represents a game changer that could take the threat of both seasonal and pandemic influenza "off the table," according to a November 2021 report, one of four from the

PNAS 2022 Vol. 119 No. 5 e2123477119

NIH National Institutes of Health
Turning Discovery Into Health

NEWS RELEASES

Monday, May 15, 2023

Clinical trial of mRNA universal influenza vaccine candidate begins

NEWS RELEASES

Friday, September 15, 2023

NIH clinical trial of universal flu vaccine candidate begins

Vaccine targets six flu strains.

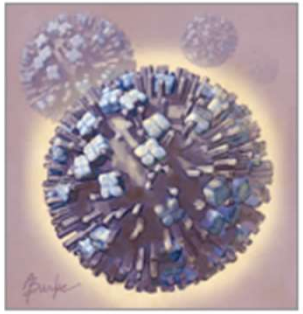
Twenty-Strain "Universal" mRNA Flu Vaccine Effective in Animal Studies

An investigational messenger RNA (mRNA) vaccine encoding hemagglutinin antigens from all 20 known influenza A virus subtypes and B virus lineages protected mice and ferrets from a wide range of matched and mismatched virus strains in a recent study.

The vaccine was developed on the same nucleic acid-based platforms behind the COVID-19 mRNA vaccines. The mRNA platforms make it possible to incorporate many more antigens than protein-based multivalent vaccine technologies can. This could make the new approach effective against a broader range of potential pandemic influenza strains circulating in animal reservoirs, the study's authors wrote in *Science*.

To ensure that each encoded antigen generated an immune response to its target strain, the authors first tested the antigens individually in 20 separate mRNA vaccines. Each individual vaccine induced antibodies in mice that were reactive against the target strains, as well as antibodies that were cross-reactive to some degree against other strains.

Next, mice were injected with the multivalent mRNA vaccine that encoded all 20 strain-specific antigens. The rodents produced antibodies to all the strains for at least 4 months. The multivalent vaccine also boosted existing H1N1 antibodies in mice previously infected with that influenza strain, while inducing new antibodies against the other 19 strains.



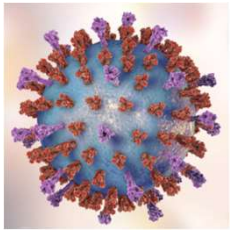
When challenged with a variety of matched and mismatched influenza viruses 28 days after vaccination, mice that received the multivalent vaccine lost less weight, showed fewer clinical symptoms, and were less likely to die than mice that received a single-strain vaccine that did not target the challenge virus. Mice injected with a 19-strain vaccine that lacked the H1N1 antigen were highly susceptible to 1 H1N1 virus sample but survived infection with virus from another sample. The multivalent vaccine also protected ferrets against an antigenically mismatched avian H1N1 virus, according to the report.

According to the authors, the results suggest that the multivalent mRNA flu vaccine protects against matched antigens by inducing neutralizing antibodies, and against mismatched antigens with some other mechanism, such as antibody-mediated cell toxicity.

"This provides a pathway to a universal influenza vaccine," wrote the authors of a commentary accompanying the study.

JAMA January 10, 2023
Volume 329, Number 2

Respiratory Syncytial Virus

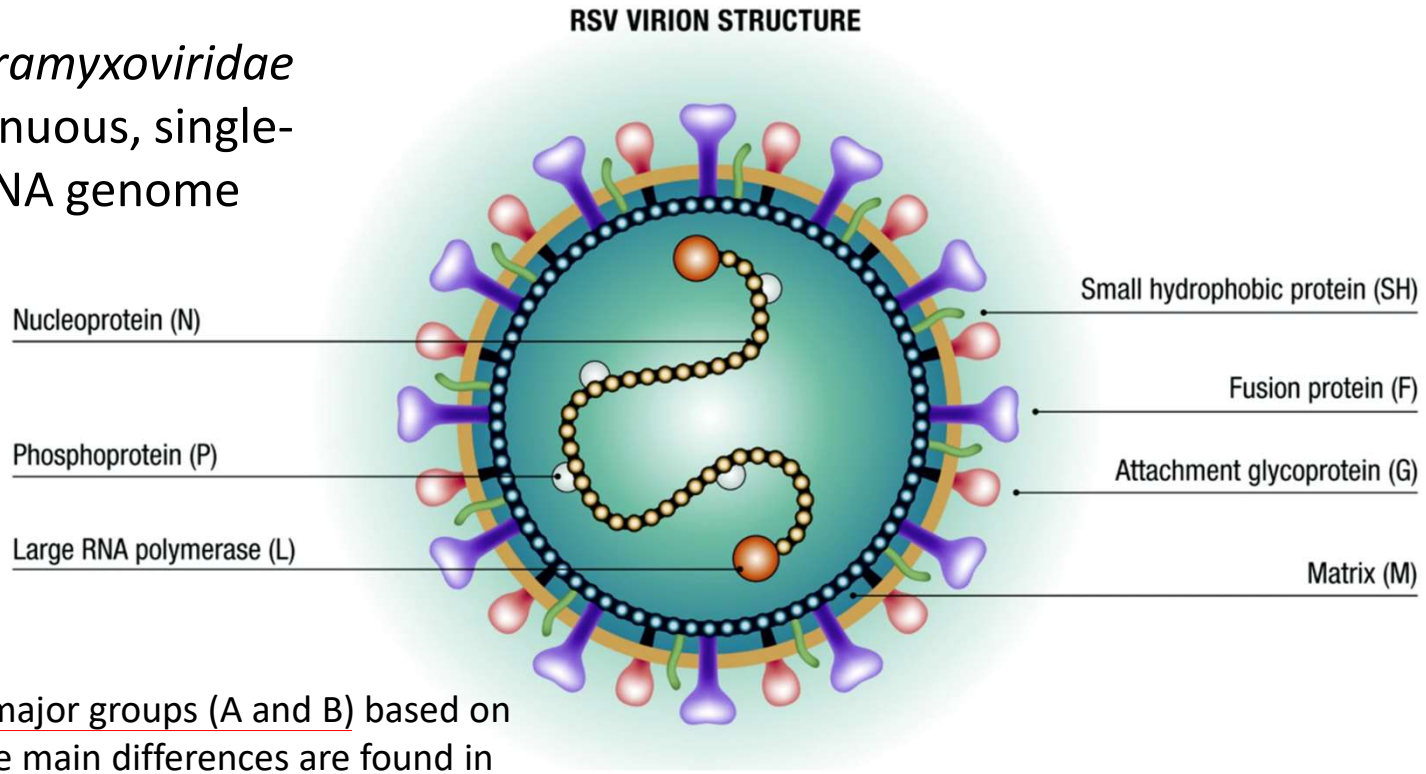


- In children:
  - RSV is the most common cause of bronchiolitis and pneumonia in children under 12 months of age
  - In the U.S. there are between 75,000 and 125,000 children hospitalized each year due to complications of RSV infection
  - Est. globally there are 64 million cases of RSV annually that result in 253,500 deaths
  - Almost all children will have had an RSV infection by their second birthday
- In adults:
  - RSV is associated with up to 12% of medically attended acute respiratory illnesses
  - <1% require hospitalization
  - RSV is the third most commonly identified viral cause among respiratory viruses resulting in hospitalization (pre-COVID-19 pandemic)

J Virology July 2014 88(13): 7602–7617 CDC.gov PLoS ONE 2017 12(8): e0182321 *Influenza Other Resp Viruses* 2022;16:1133–1140

RSV is a member of the *Paramyxoviridae* family and contains a continuous, single-stranded negative-sense RNA genome

RSV has a non-segmented genome, so unlike Influenza it cannot reassort genome segments and thus does not cause large-scale pandemics



RSV strains are separated into two major groups (A and B) based on antigenic and genetic variability. The main differences are found in the attachment glycoprotein G. RSV G protein interacts with host cell receptors, is a target for neutralizing antibodies, and is highly variable. This variability might contribute to the ability of the virus to cause yearly outbreaks.

Other members of the *Paramyxoviridae* family include measles, mumps, human metapneumovirus, and the zoonoses Hendra and Nipah viruses

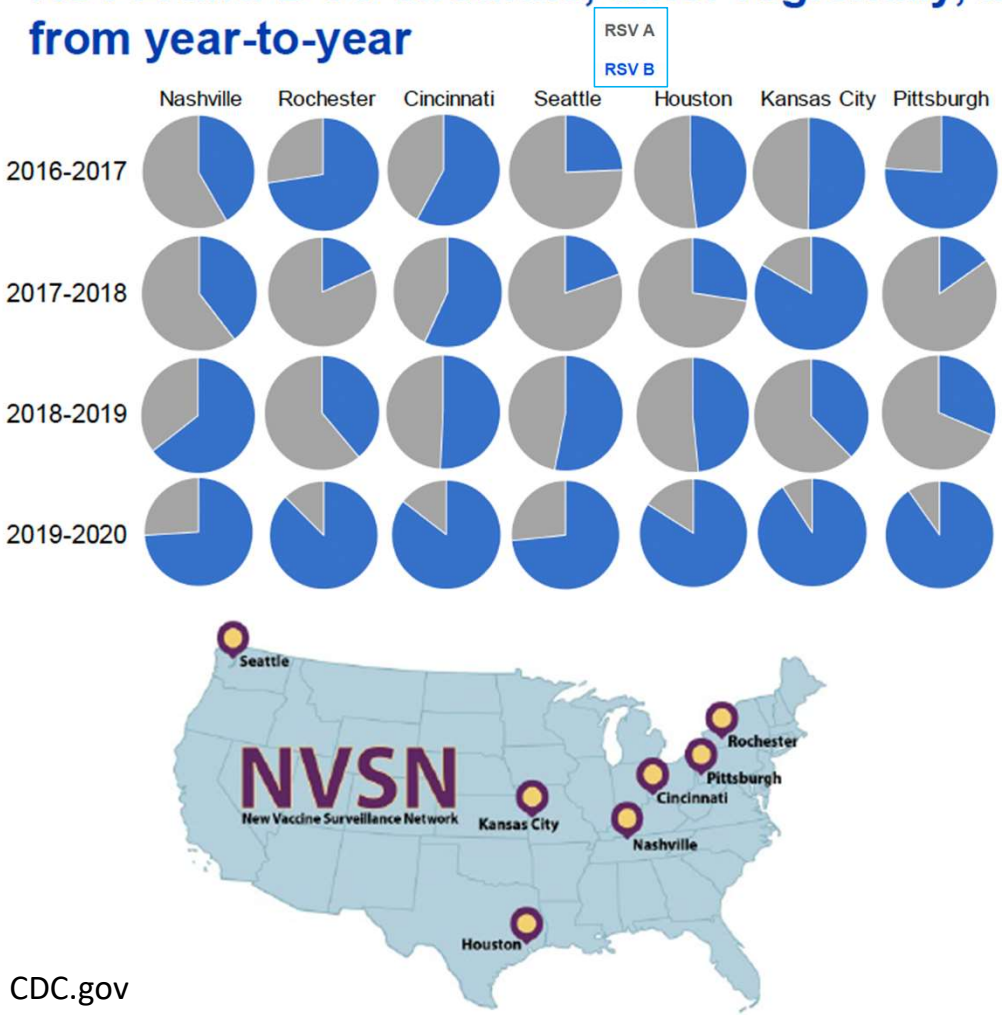
Journal of Virology July 2014 Volume 88 Number 13 p. 7602–7617
Cureus 15(3): e36342 *Virology Journal* 2014, 11:36 *Italian J Pediatrics* 47, 198 (2021)

RSV Immunity after Natural Infection

- Natural RSV infection does not provide durable or complete protection from reinfection.
- Anti-RSV antibodies return to pre-infection levels within 6 months after infection.
- Reinfection can occur within two months of last infection.
- Older adults have weaker IFNy responses to RSV than younger adults, likely making them more susceptible to infection and to severe infection.

J Infectious Diseases 1991; 163:693-698 *Am J Respir Crit Care Med* 2015; 191(9): 1040–1049 *J Medical Virology* 2006; 78:1493-1497

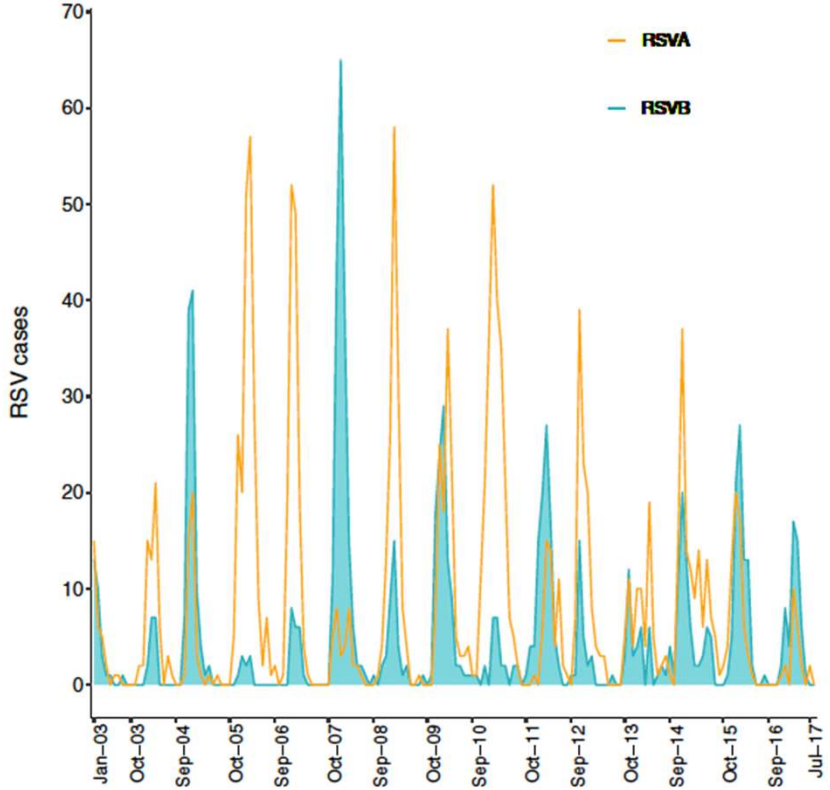
RSV A and B co-circulate, differ regionally, and from year-to-year



CDC.gov

Epidemic patterns of RSV antigenic groups A & B

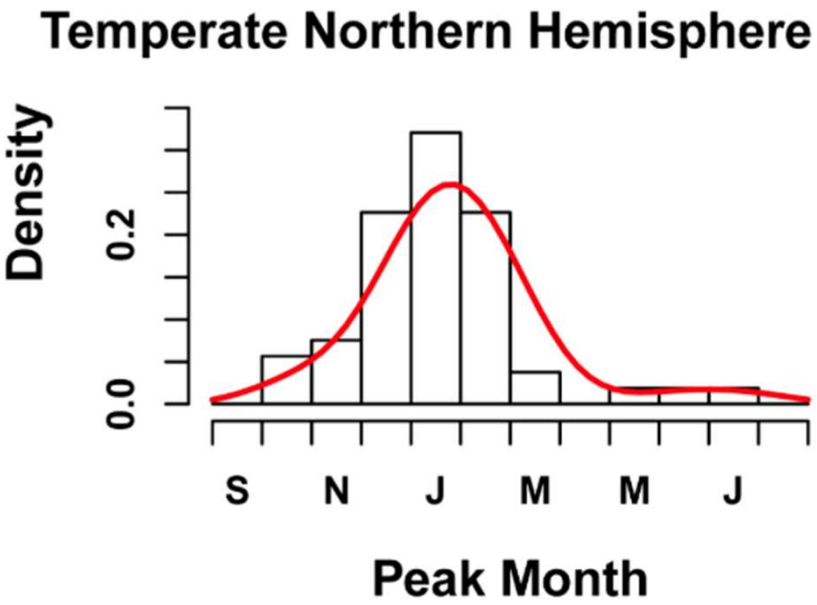
Kilifi, Kenya 2002 to 2017



Nature Scientific Reports (2020) 10:21176

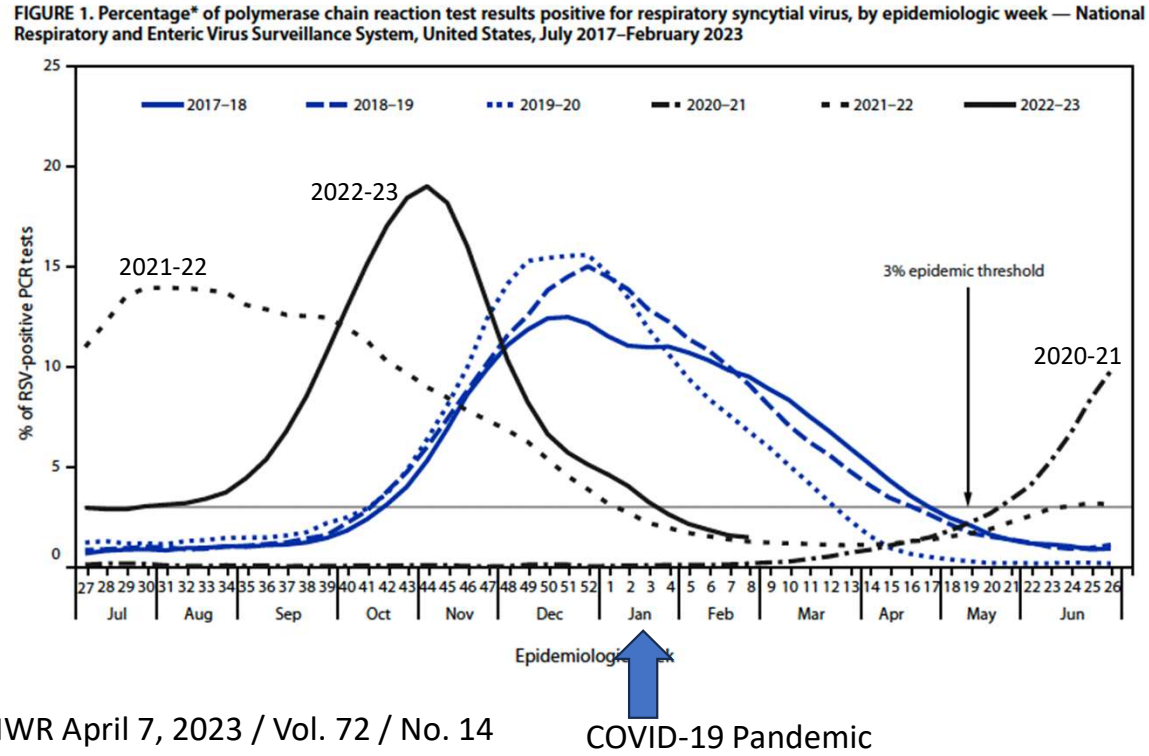
RSV Seasonality

Peak Month of RSV Activity 1990 - 2009



PLOS ONE 2013 8(2):e54445

Perturbation of RSV Seasonality by the COVID-19 Pandemic



MMWR April 7, 2023 / Vol. 72 / No. 14

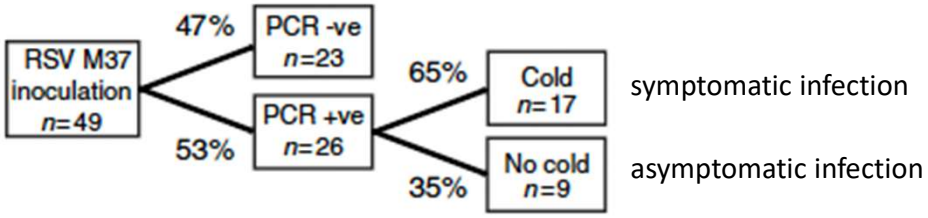
Symptoms of RSV Infection

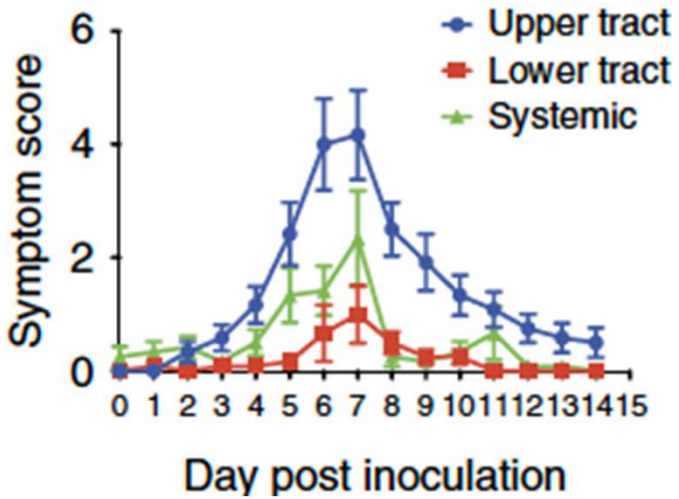
- Runny nose
- Coughing
- Sneezing
- Fever
- Wheezing (more common with RSV than other respiratory viruses)
- Decrease in appetite

CDC.gov

Experimental RSV Infection

49 healthy adults aged 18-50 (median 20.5)





Incubation period 4-6 days
Illness typically lasts 7-10 days, worst symptoms on days 3-5
Cough may linger 3-4 weeks
Duration of shedding by PCR 11 days, by viral culture 3-8 days

Upper: sneezing, nasal discharge, nasal obstruction or sore throat
Lower: cough, wheeze, shortness of breath
Systemic: headache, malaise, fever

Nature communications (2015) 6:10224

Prevalence of RSV in Older Adults

Study of ~5000 Episodes of Illness in Adults >65
in 14 countries on 3 continents in the Northern Hemisphere, 2008-10 (before COVID-19)

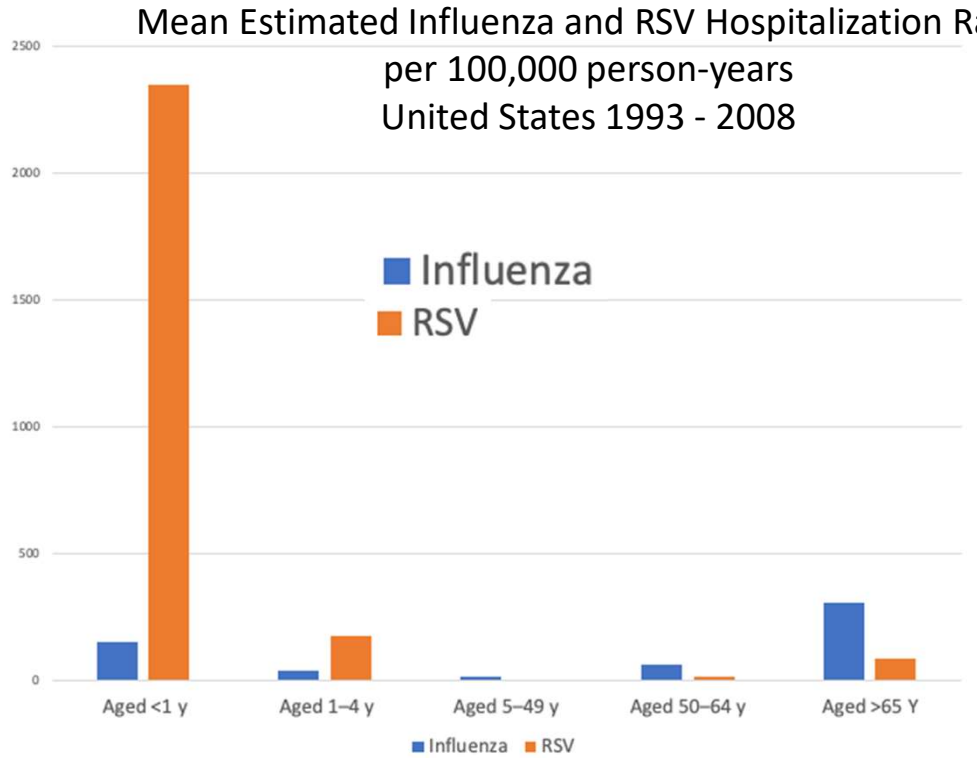
- RSV was the third leading viral cause of moderate-to-severe* 'Influenza-Like Illness' (ILI)
  - Influenza 37.2%
  - Enterovirus/Rhinovirus 25.6%
  - RSV 12.8%
  - Coronavirus 10.0% [pre-pandemic]
  - Human Metapneumovirus 10.0%
  - Parainfluenza 7.5%
- Hospitalization among RSV-positive moderate-to-severe ILI episodes (19.5%) was about twice as common than hospitalization among episodes positive for any other virus (8.6%) and 5-fold more common compared to influenza A (3.8%)

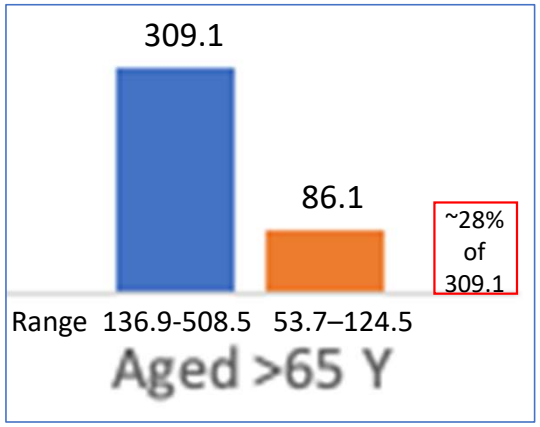
*defined as ILI with pneumonia, hospitalization, or maximum daily influenza symptom severity score (ISS) >2

J Infectious Diseases 2014 Jun 15; 209(12): 1873–1881

Severe RSV in Adults

- Most adult RSV hospitalizations occur in older adults
  - est 60,000 – 160,000 hospitalizations and 6,000 – 10,000 deaths annually among adults aged ≥65 years (U.S.)

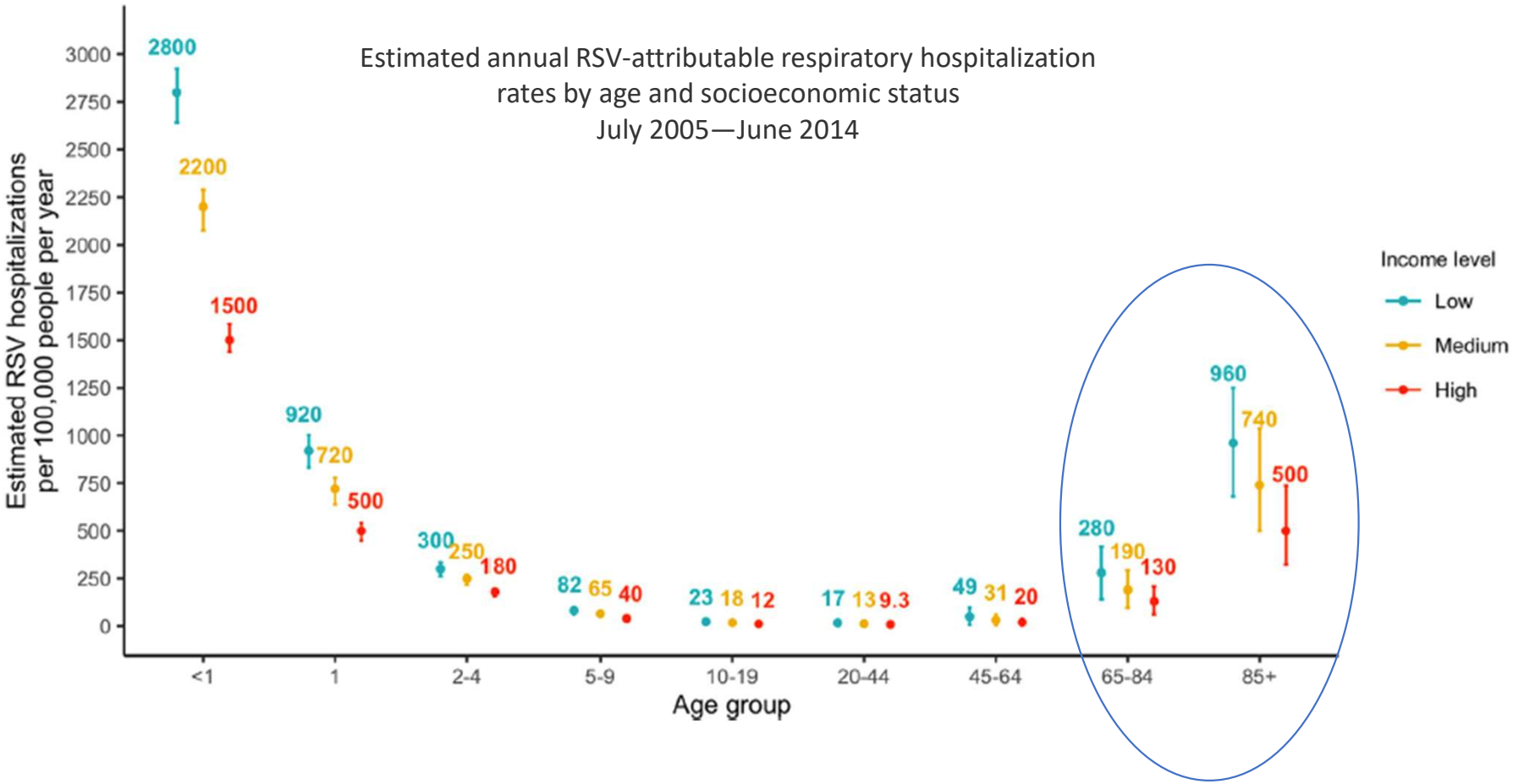




MMWR July 21, 2023 Vol. 72 No. 29 pages 793-801

data from *Clinical Infectious Diseases* 2012;54(10):1427–36

Severe RSV in Adults



Pneumonia (2022) 14:6

Morbidity and Mortality in Older Adults (aged ≥60 years) Hospitalized with RSV

Characteristics of a random sample of patients aged ≥60 years hospitalized with laboratory-confirmed RSV infection (N = 1,634), RSV–Associated Hospitalization Surveillance Network, 12 states, October 2022–April 2023

Characteristic	Overall No.	Overall Weighted % (95% CI)
Underlying medical condition		
≥1 underlying medical condition***	1,584	95.5 (93.2–97.2)
Chronic lung disease	813	49.2 (45.7–52.7)
COPD	552	33.7 (30.5–37.0)
Asthma	332	19.1 (16.6–21.8)
Other†††	72	5.4 (3.8–7.3)
Cardiovascular disease	1,108	67.1 (63.7–70.5)
CHF§§§	545	33.2 (30.0–36.5)
CAD¶¶¶	435	26.4 (23.5–29.5)
CVA****	253	13.7 (11.7–15.9)
Immunocompromising condition	292	18.6 (16.0–21.4)
Diabetes mellitus	553	32.6 (29.5–35.8)
Neurologic condition	439	27.3 (24.3–30.5)
Dementia††††	183	12.4 (10.1–15.0)
Other	256	14.9 (12.6–17.4)
Kidney disorder	477	29.3 (26.3–32.5)
Obesity	572	37.8 (34.3–41.4)

Hospitalization outcome§§		%
Hospital stay, days, median (IQR)	4.1 (2.2–7.6)	—
BiPAP/CPAP	339	19.8 (17.3–22.6)
High-flow nasal cannula	80	4.3 (3.2–5.7)
≥1 severe outcome¶¶	332	18.5 (15.9–21.2)
ICU admission	297	17.0 (14.5–19.7)
Invasive mechanical ventilation	94	4.8 (3.5–6.3)
In-hospital death	98	4.7 (3.6–6.1)

¶¶ Severe outcome is defined as requiring ICU admission or mechanical ventilation or experiencing in-hospital death

*** Defined as one or more of the following: chronic lung disease, including asthma; chronic metabolic disease including diabetes mellitus; blood disorder or hemoglobinopathy; cardiovascular disease; neurologic disorder; immunocompromising condition; renal disease; gastrointestinal or liver disease; rheumatologic, autoimmune, or inflammatory condition; obesity; feeding tube dependency; and wheelchair dependency

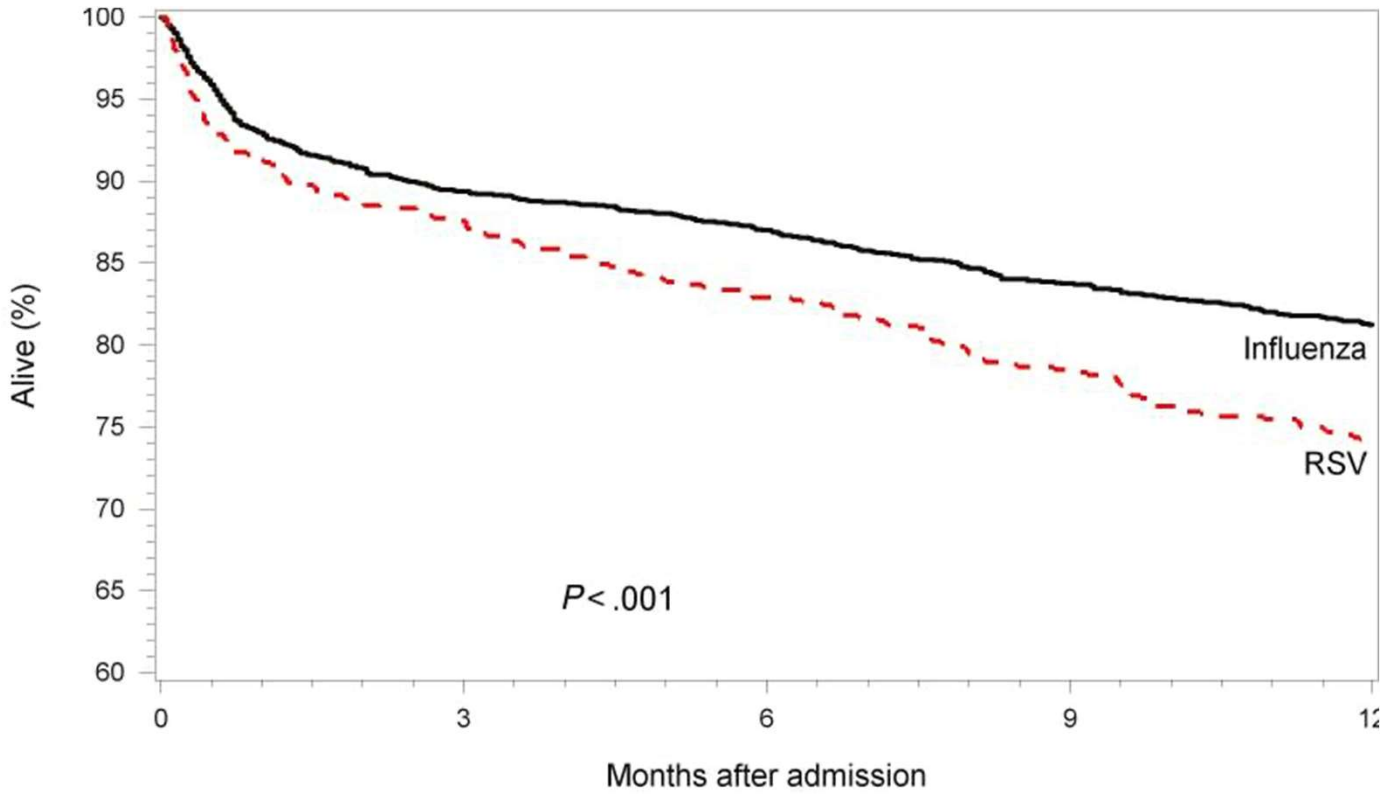
MMWR October 6, 2023 Vol. 72 No. 40 pages 1075-1082

One-year Survival After Hospitalization

in Adults 60 and over

with RSV (n=645) or Influenza (n=1878)

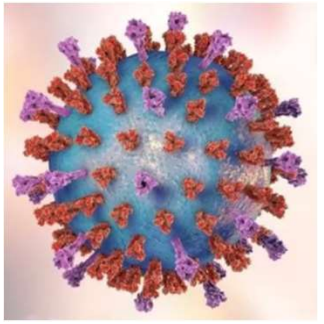
Southern California, 2011-15



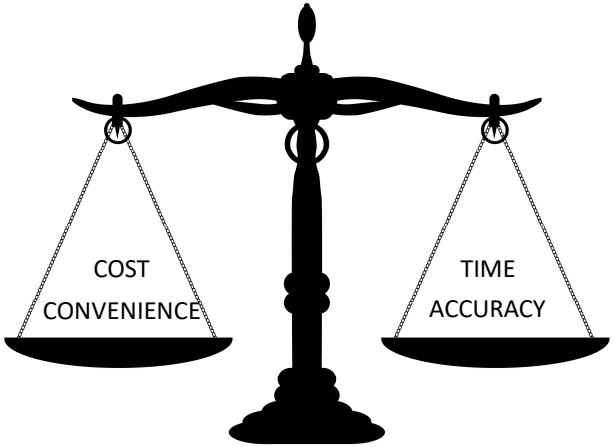
Note that in this era vaccination and treatment was available for Influenza

Clinical Infectious Diseases 2019 Jul 15; 69(2): 197–203

RSV Testing



- Current rapid antigen tests
  - Sensitivity ~80%, specificity ~95%
- Rapid molecular test
  - Sensitivity 90-98%, specificity 99-100%
- Multiplex PCR
  - Sensitivity 95-100%, specificity 99-100%



Clin Microbiol Rev 2017 Jan; 30(1): 277–319

RSV Treatment in Adults

- For most adults, treatment is supportive
- For those with lower tract infection who present with cough and wheezing, bronchodilators may result in symptom relief, particularly if the patient has underlying reactive airway disease
- Treatment in immunocompromised patients has not been well studied and the optimal approach is uncertain
  - Ribavirin (oral vs. inhaled) and IVIG can be used in those who are severely immunocompromised, such as hematopoietic cell and lung-transplant recipients and selected persons with leukemia

Clinical Infectious Diseases 2013;56(2):258–66

RSV Vaccine in Adults

- On June 21, 2023, ACIP voted to recommend that adults aged ≥60 years may receive a single dose of an RSV vaccine, using shared clinical decision-making. ("Talk to your doctor.")

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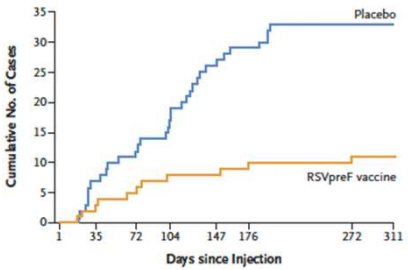

Efficacy of RSV Vaccines

TABLE 1. Efficacy of 1 dose of GSK respiratory syncytial virus RSVpreF3 vaccine against respiratory syncytial virus–associated disease among adults aged ≥60 years — multiple countries, 2021–2023

Efficacy evaluation period	Vaccine efficacy against outcome*	
	RSV-associated LRTD†	RSV-associated medically attended LRTD§
Season 1¶	82.6 (57.9–94.1)**	87.5 (58.9–97.6)††
Season 2§§	56.1 (28.2–74.4)††	—¶¶
Combined seasons 1 and 2 (interim)***	74.5 (60.0–84.5)†††	77.5 (57.9–89.0)††

LRTD = lower respiratory tract disease

† LRTD defined as two or more lower respiratory symptoms (new or increased sputum, cough, and dyspnea) or signs (new or increased wheezing, crackles or rhonchi detected during chest auscultation, respiratory rate ≥20 respirations per minute, low or decreased oxygen saturation [<95% or ≤90% if baseline was <95%] and need for oxygen supplementation) for ≥24 hours, including one or more lower respiratory signs, or three or more lower respiratory symptoms for ≥24 hours.

§ Medically attended RSV-associated LRTD defined as LRTD plus attention at one or more inpatient or outpatient health care service. Estimates were not included in per-protocol assessments.

N Engl J Med 2023;388:1465-77.
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TABLE 3. Efficacy of 1 dose of Pfizer respiratory syncytial virus RSVpreF vaccine against respiratory syncytial virus–associated disease among adults aged ≥60 years — multiple countries, 2021–2023

Efficacy evaluation period	Vaccine efficacy against outcome, % (95% CI)*	
	RSV-associated LRTD†	RSV-associated medically attended LRTD§
Season 1¶	88.9 (53.6–98.7)	84.6 (32.0–98.3)
Season 2 (interim)**	78.6 (23.2–96.1)	—††
Combined seasons 1 and 2 (interim)§§	84.4 (59.6–95.2)	81.0 (43.5–95.2)

Neither of the two clinical trials that led to FDA approval of RSV vaccines for older adults was powered to assess protection against hospitalization, though both trials showed moderate to high efficacy of RSV vaccination against LRTD, which is in the causal pathway leading to severe disease

Safety of RSV Vaccines

TABLE 2. Safety* of 1 dose of GSK respiratory syncytial virus RSVPreF3 vaccine in adults aged ≥60 years — multiple countries, 2021–2023

Safety event	Risk for event: RSVPreF3 recipients no./No. (%)†	Placebo recipients no./No. (%)§	Relative risk (95% CI)¶
Serious AE**	549/12,570 (4.4)	540/12,604 (4.3)	1.02 (0.91–1.15)
Severe reactogenicity events††	37/979 (3.8)	9/976 (0.9)	4.10 (1.99–8.45)
Inflammatory neurologic events§§	3 events in trials without placebo recipients¶¶	—¶¶	—¶¶

One case of GBS and two cases of acute disseminated encephalomyelitis in 17,922 doses given over all trials

TABLE 4. Safety* of 1 dose of Pfizer respiratory syncytial virus RSVpreF vaccine in adults aged ≥60 years — multiple countries, 2021–2023

Safety event	Risk for event: RSVpreF recipients no./No. (%)†	Placebo recipients no./No. (%)§	Relative risk (95% CI)¶
Serious AE**	792/18619 (4.3%)	749/18334 (4.1%)	1.04 (0.94–1.15)
Severe reactogenicity events††	36/3673 (1.0%)	24/3491 (0.7%)	1.43 (0.85–2.39)
Inflammatory neurologic events§§	3/18622 (—)¶¶	0/18335 (—)	—¶¶

One case each of GBS, Miller Fisher syndrome (a GBS variant), and undifferentiated motor-sensory axonal polyneuropathy

GBS = Guillain-Barre Syndrome

Whether these events occurred due to chance, or whether RSV vaccination increases the risk for inflammatory neurologic events is currently unknown. Until additional evidence becomes available, RSV vaccination in older adults should be targeted to those who are at highest risk for severe RSV disease and therefore most likely to benefit from vaccination.

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Underlying Medical Conditions and Other Factors Associated with Increased Risk for Severe RSV Disease

Chronic underlying medical conditions associated with increased risk

- Lung disease (such as chronic obstructive pulmonary disease and asthma)
- Cardiovascular diseases (such as congestive heart failure and coronary artery disease)
- Moderate or severe immune compromise*
- Diabetes mellitus
- Neurologic or neuromuscular conditions
- Kidney disorders
- Liver disorders
- Hematologic disorders
- Other underlying conditions that a health care provider determines might increase the risk for severe respiratory disease

Other factors associated with increased risk

- Frailty†
- Advanced age§
- Residence in a nursing home or other long-term care facility
- Other underlying factors that a health care provider determines might increase the risk for severe respiratory disease

Abbreviation: RSV = respiratory syncytial virus.

*A list of potentially immune compromising conditions is available at https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-who-are-immunocompromised.html.

†Frailty is a multidimensional geriatric syndrome and reflects a state of increased vulnerability to adverse health outcomes. Although there is no consensus definition, one frequently used tool is the Fried frailty phenotype in which frailty is defined as a clinical syndrome with three or more of the following symptoms present: unintentional weight loss (10 lbs in past year), self-reported exhaustion, weakness (grip strength), slow walking speed, and low physical activity.

§Among adults aged ≥60 years, RSV incidence increases with advancing age. Although age may be considered in determining an older adult patient's risk for severe RSV-associated disease, there is no specific age threshold at which RSV vaccination is more strongly recommended within the age group of adults aged ≥60 years.

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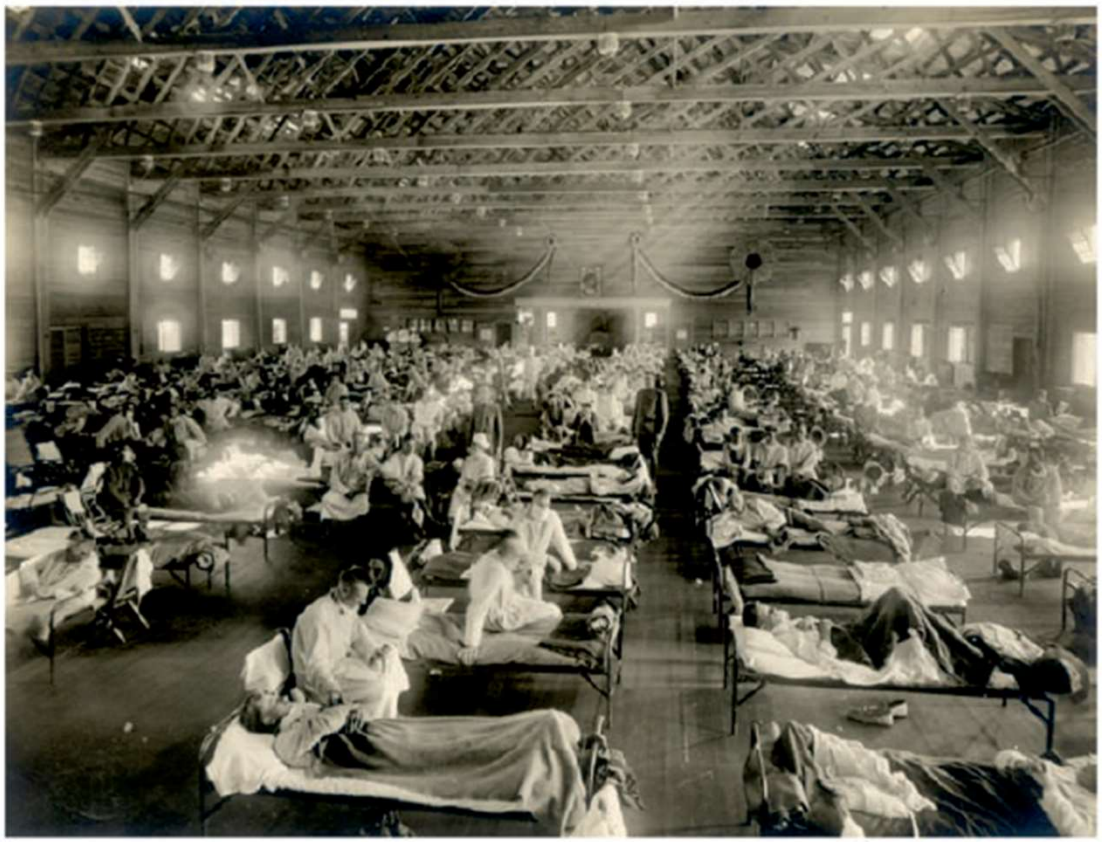
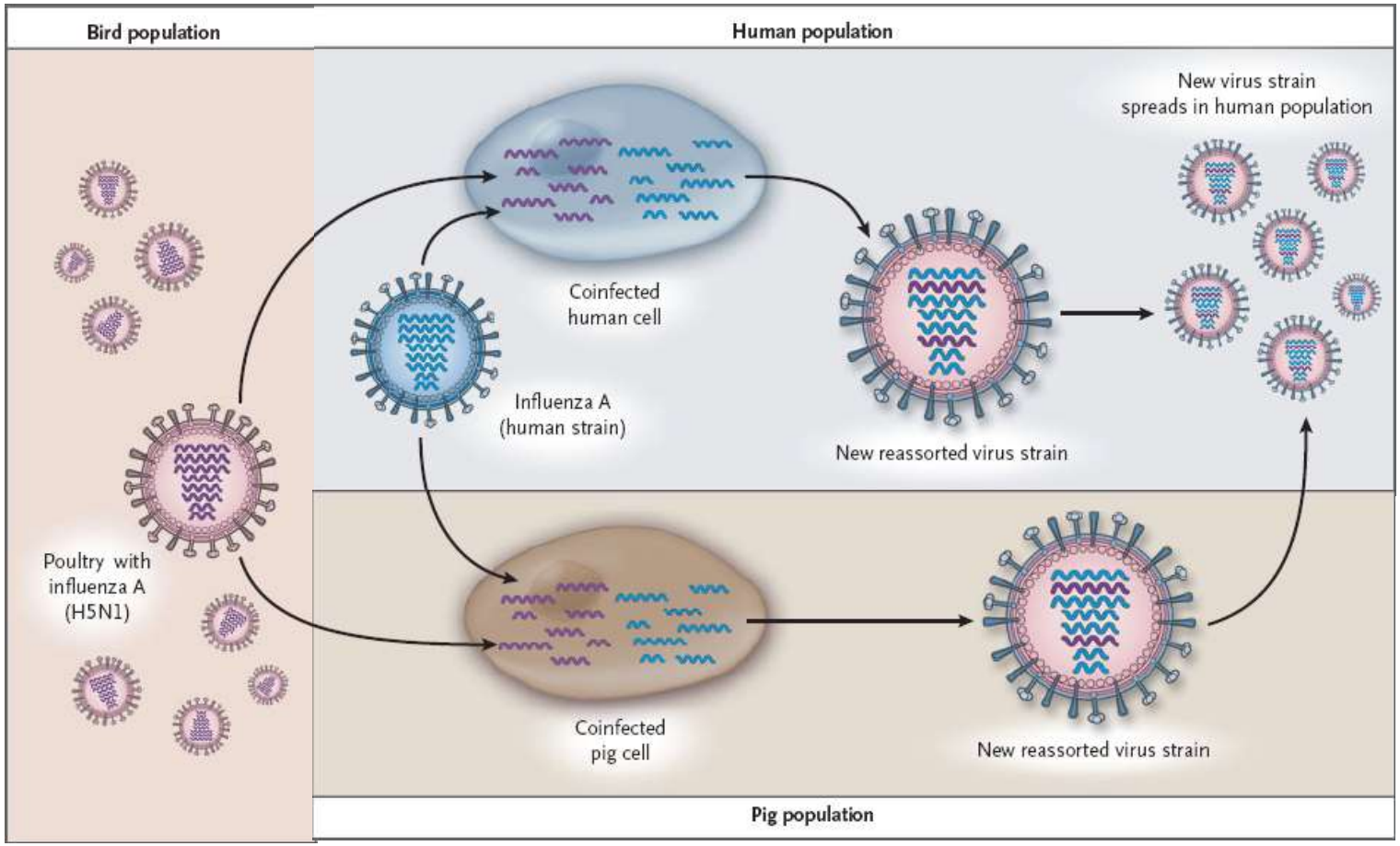
The Next Pandemic



Missouri Medicine May/June 2018; 115(3):183

Camp Funston (now Fort Riley) Kansas, 1918

Why do Pandemics Occur?



Antigenic Shift

New England Journal of Medicine 351(23):2363, 2004

H5N1 in Migratory Birds

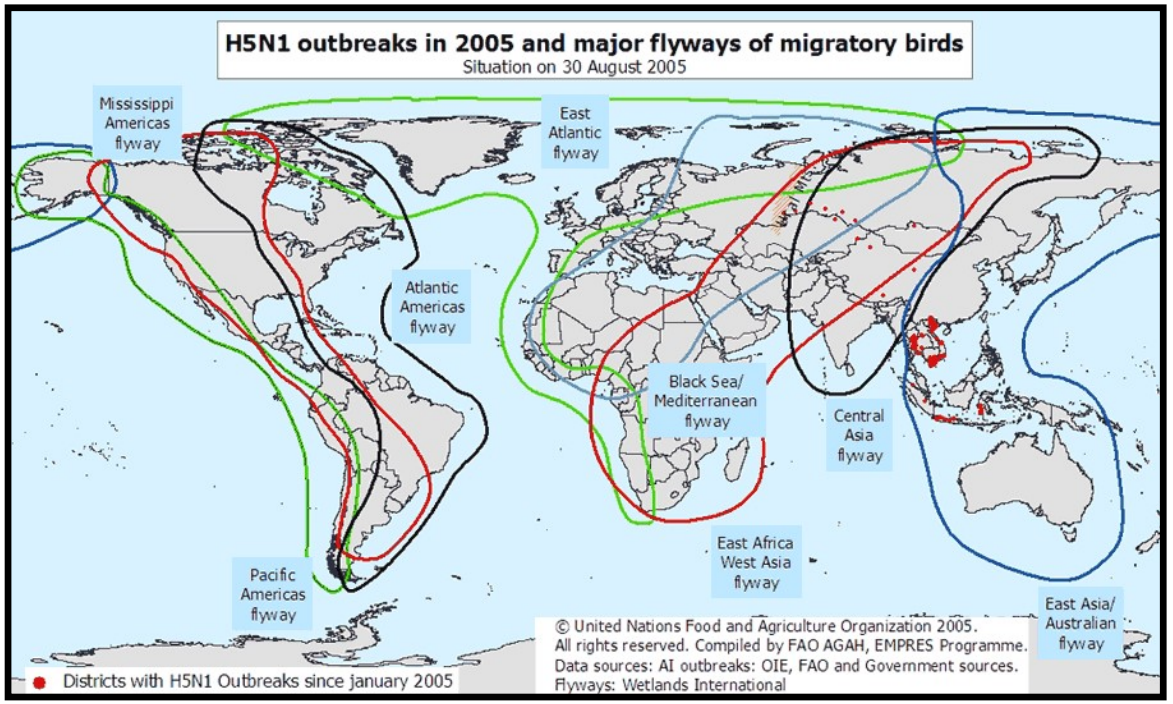
16 of the 18 known hemagglutinin (HA) subtypes and 9 of the 11 known neuraminidase (NA) subtypes have been identified in aquatic birds[1]

AVIAN INFLUENZA

Evidence Points to Migratory Birds in H5N1 Spread

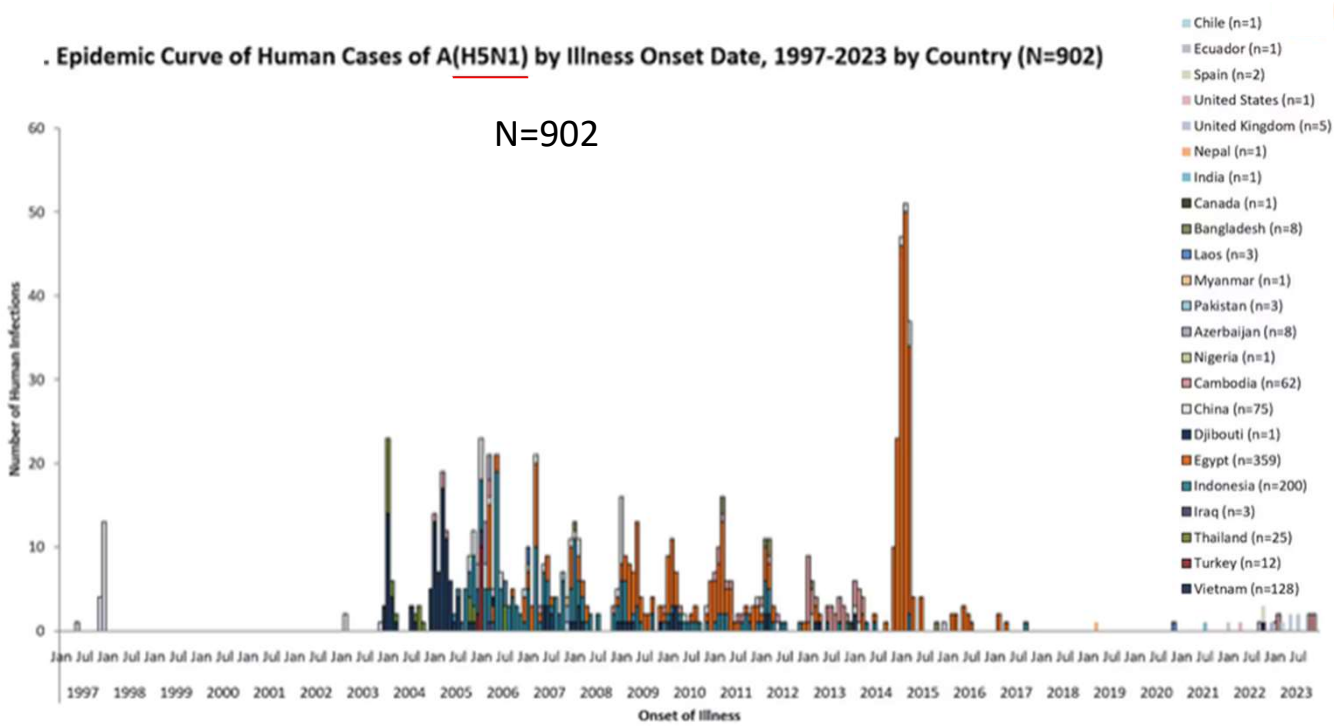
With the H5N1 avian influenza virus racing across the globe, scientists are debating new evidence on the role of migratory birds. As *Science* went to press, the virus had just been confirmed in a third African nation, Niger, one of the world's poorest countries. It had spread further in Europe and Asia, with 13 countries confirming outbreaks in just the past 2 months. And France reported the European Union's first outbreak in domestic poultry.

SCIENCE VOL 311 3 MARCH 2006
Published by AAAS

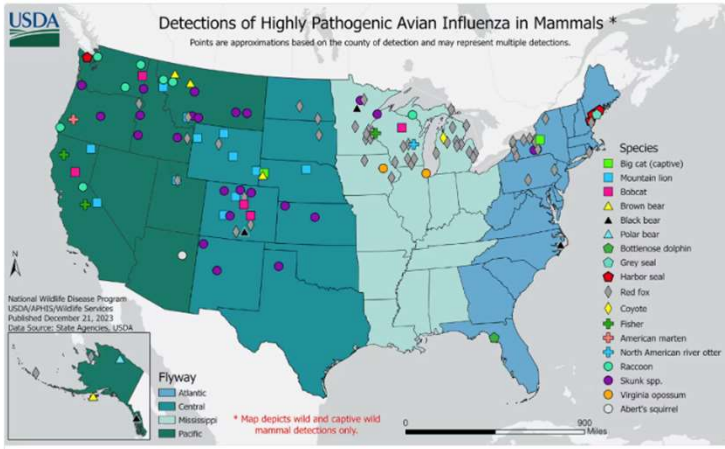


http://www.fao.org/ag/againfo/subjects/en/health/diseases-cards/migrationmap.html

[1]PLOS Pathogens https://doi.org/10.1371/journal.ppat.1010062 May 19, 2022



Country of Case	Month of illness onset or case detection	Disease Severity and Outcome	Virus Clade by sequencing or associated poultry outbreaks
Cambodia	February 2023	Critical illness, died	Clade 2.3.2.1c
	February 2023	Mild illness, survived	Clade 2.3.2.1c
	October 2023	Critical illness, died	Clade 2.3.2.1c
	October 2023	Critical illness, died	Clade 2.3.2.1c
	November 2023	Critical illness, died	Clade 2.3.2.1c
	November 2023	Mild illness, survived	Clade 2.3.2.1c
Chile	March 2023	Critical illness	Clade 2.3.4.4b
China	September 2022	Critical illness, died	Clade 2.3.4.4b
	January 2023	Hospitalized, outcome not reported	Clade 2.3.4.4b
Ecuador	December 2022	Critical illness, survived	Clade 2.3.4.4b
Spain	September 2022	Asymptomatic	Clade 2.3.4.4b
	October 2022	Asymptomatic	Clade 2.3.4.4b
United Kingdom	January 2022	Asymptomatic	Clade 2.3.4.4b
	May 2023	Asymptomatic	Clade 2.3.4.4b
	May 2023	Asymptomatic	Clade 2.3.4.4b
	July 2023	Asymptomatic	Clade 2.3.4.4b
	July 2023	Asymptomatic	Clade 2.3.4.4b
United States	April 2022	Fatigue only, survived	Clade 2.3.4.4b
Vietnam	October 2022	Critical illness, survived	Not reported

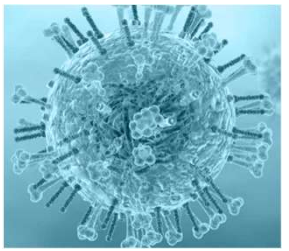


Source: USDA APHIS | 2022-2023 Detections of Highly Pathogenic Avian Influenza in Mammals

Technical Report: Highly Pathogenic Avian Influenza A(H5N1) Viruses

CDC.gov accessed 1/20/24

‘Spillover Events’ Continually Occur



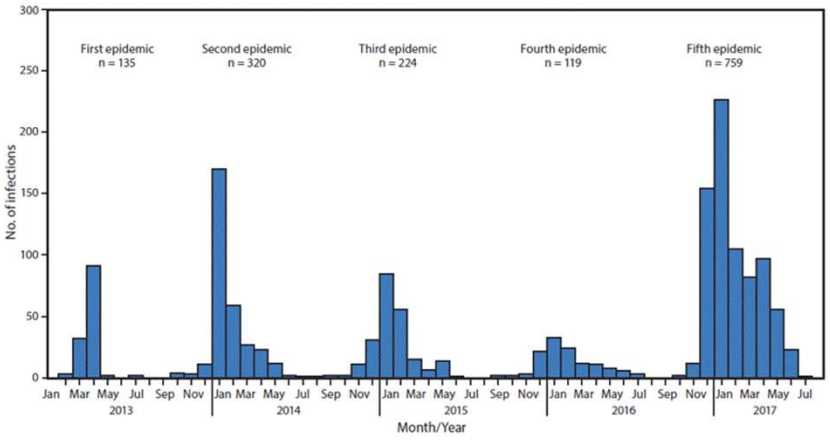
Morbidity and Mortality Weekly Report (*MMWR*)

Update: Increase in Human Infections with Novel Asian Lineage Avian Influenza A(H7N9) Viruses During the Fifth Epidemic — China, October 1, 2016–August 7, 2017

Weekly / September 8, 2017 / 66(35);928–932

During March 31, 2013–August 7, 2017, a total of 1,557 human infections with Asian H7N9 viruses were reported; at least 605 (39%) of these infections resulted in death. All infections were either detected in mainland China, Hong Kong, and Macao, or associated with travel from mainland China (29 cases were exported to

FIGURE 1. Confirmed Asian lineage avian influenza A(H7N9) virus infections of humans reported to the World Health Organization (N = 1,557),* by month of illness onset — China,† February 19, 2013–August 7, 2017



Transboundary and Emerging Diseases

ORIGINAL ARTICLE

H9N2 influenza virus spillover into wild birds from poultry in China bind to human-type receptors and transmit in mammals via respiratory droplets

Xinghai Zhang, Yuanguo Li, Song Jin, Tiecheng Wang, Weiyang Sun, Yiming Zhang, Fangxu Li, Menglin Zhao, Leiyun Sun, Xinyu Hu, Na Feng, Ying Xie, Yongkun Zhao ... See all authors

First published: 10 February 2021 | https://doi.org/10.1111/tbed.14033 | Citations: 9

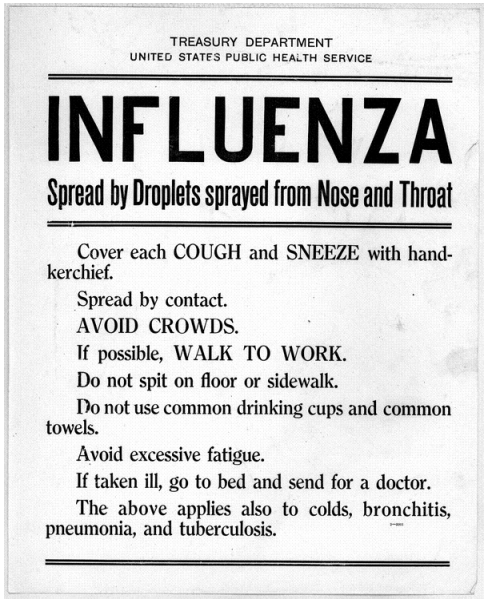
The Next Pandemic

- It is not a question of if, but when the next influenza pandemic will occur, and how severe it will be.

  (Unless a universal influenza vaccine is developed, widely distributed, and accepted.)

- Recent events associated with the COVID-19 pandemic are worrisome
  - Significant deterioration of public health infrastructure in the face of direct threats
  - Lack of trust in public health measures and authorities
  - Legislative actions to try to limit the ability of public health to implement public health measures in a crisis
  - Lack of respect for the needs of the community vs. the individual
  - Lack of widespread (global) availability of effective prevention and treatment measures

Influenza pandemics occur on average every 14 years, the last was in 2009



TREASURY DEPARTMENT
UNITED STATES PUBLIC HEALTH SERVICE

INFLUENZA

Spread by Droplets sprayed from Nose and Throat

Cover each COUGH and SNEEZE with handkerchief.

Spread by contact.

AVOID CROWDS.

If possible, WALK TO WORK.

Do not spit on floor or sidewalk.

Do not use common drinking cups and common towels.

Avoid excessive fatigue.

If taken ill, go to bed and send for a doctor.

The above applies also to colds, bronchitis, pneumonia, and tuberculosis.

Influenza and RSV in Adults

Kansas City Southwest Clinical Society

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