



Updates in the Treatment of Influenza

What Pharmacists Need to Know



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Faculty

Jeffery A. Goad, PharmD, MPH, FISTM, FAPhA

Professor and Chair, Department of Pharmacy Practice

Chapman University School of Pharmacy

Irvine, CA



Dr. Goad is Professor and Chair of the Department of Pharmacy Practice in the Chapman University School of Pharmacy. He received his Doctor of Pharmacy degree from the USC School of Pharmacy and Masters of Public Health from the Keck School of Medicine at USC. He completed a residency in pediatric pharmacy practice at Children's Hospital, Los Angeles and holds a Certificate of Knowledge in Travel Health from the International Society of Travel Medicine. Dr. Goad has presented at over 200 pharmacy and medical conferences and published more than 80 articles and book chapters.

A woman with curly hair is shown in a close-up, looking down at a light blue mug she is holding with both hands. She has a slight smile and is wearing a blue top. The background is dark and out of focus.

Disclosures

Dr. Goad has disclosed that he is/has served as a consultant for Sanofi Pasteur and PaxVax and the Merck & Co. speaker's bureau.

The clinical reviewer, Lisa C. Hutchison, PharmD, has no actual or potential conflicts of interest in relation to this program.

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Type of Activity: Application



Learning Objectives

- **Identify** patients who should receive influenza antiviral therapy according to current recommendations
- **Compare and contrast** current and newly available influenza antiviral medications
- **Discuss** expected outcomes of influenza antiviral medications and the evidence to support their place in therapy

The Burden of Influenza: 2017-2018

During the 2017-2018 flu season, CDC estimates flu caused:

49 million
flu **illnesses**

960,000
flu **hospitalizations**

79,000
flu **deaths**

*Influenza
vaccine
effectiveness
& coverage*

Age group (years)	Adjusted VE%	IZ rate
All ages	38%	
6 months-8	68%	68% (6 m-4 y)
9-17	32%	55% (5-17 y)

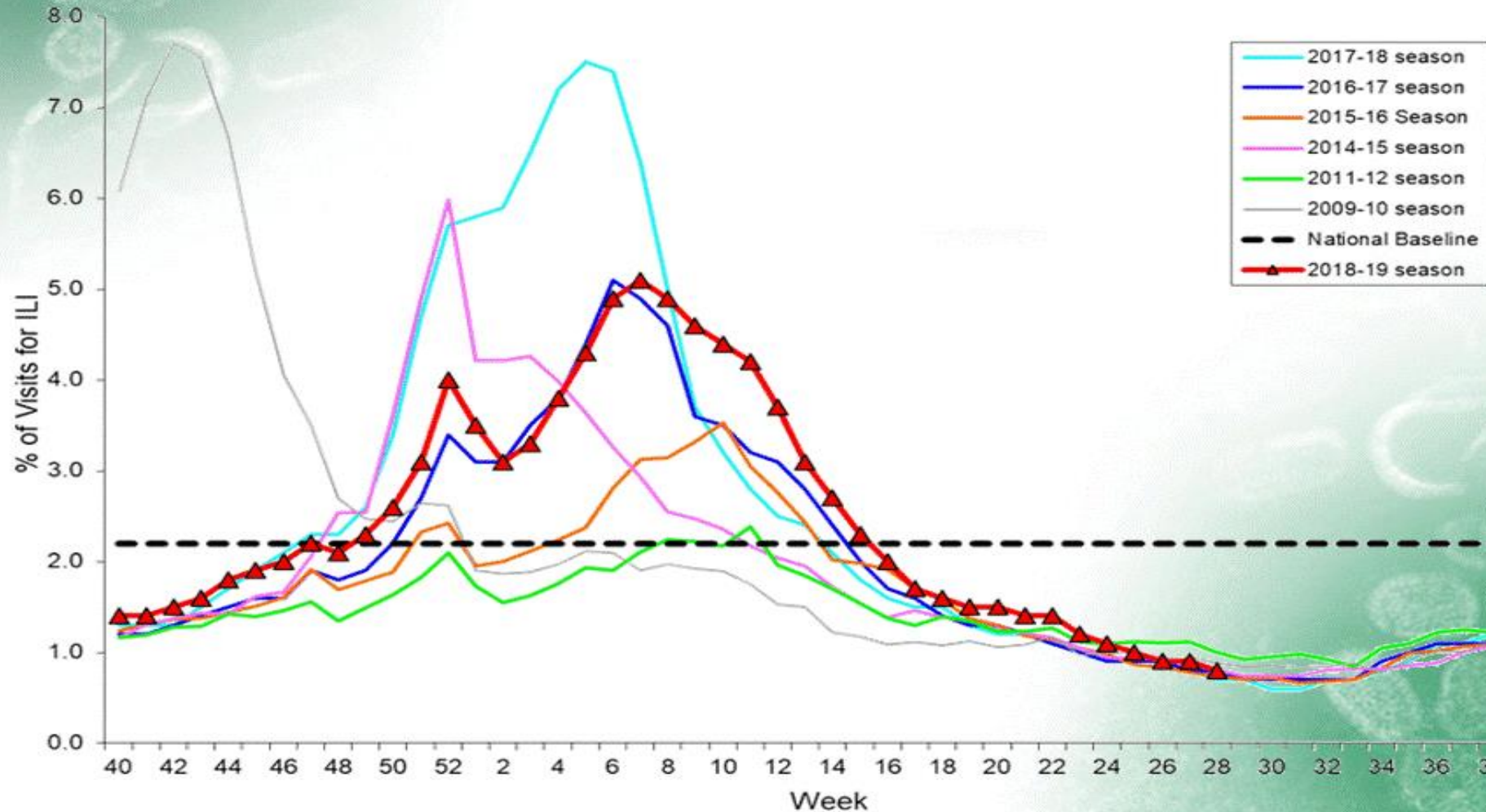
Age group (years)	Adjusted VE%	IZ rate
18-49	33%	27%
50-64	30%	40%
≥65	17%	60%

FLUVIEW



A Weekly Influenza Surveillance Report Prepared by the Influenza Division

Percentage of Visits for Influenza-like Illness (ILI) Reported by the U.S. Outpatient Influenza-like Illness Surveillance Network (ILINet), Weekly National Summary, 2018-2019 and Selected Previous Seasons



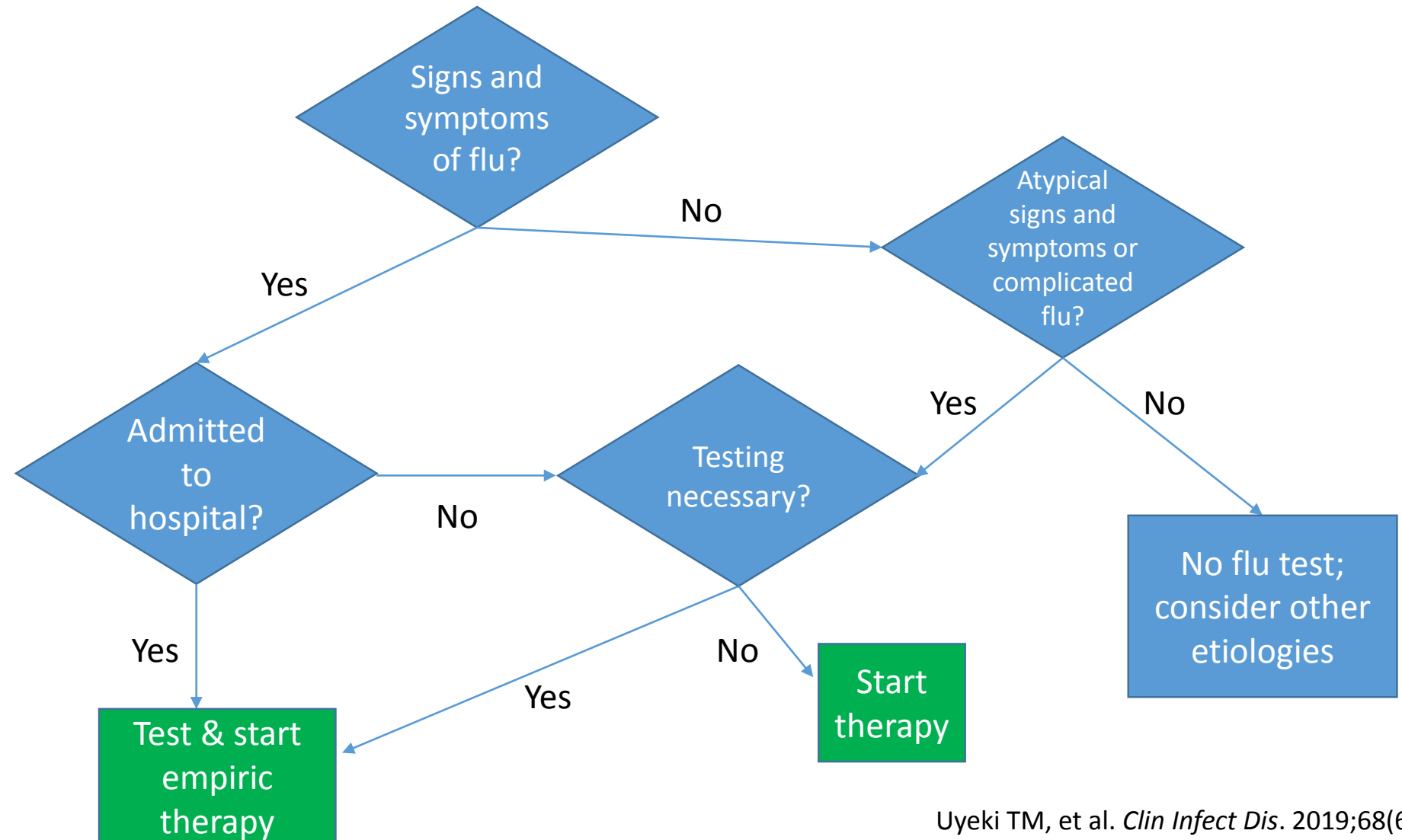
Cold vs. Influenza



Signs and Symptoms	Cold	Influenza (Flu)
Symptom onset	Gradual	Abrupt
Fever	Rare	Usual; lasts 3-4 days
Aches	Slight	Usual; often severe
Chills	Uncommon	Fairly common
Fatigue, weakness	Sometimes	Usual
Sneezing	Common	Sometimes
Chest discomfort, cough	Mild to moderate; hacking cough	Common; can be severe
Stuffy nose	Common	Sometimes
Sore throat	Common	Sometimes
Headache	Rare	Common

Influenza Testing and Treatment Guide

IDSA 2018 Clinical Practice Guidelines for Influenza Diagnosis and Treatment



Rapid Diagnostic Test vs. Rapid Molecular Assay

Rapid, point-of-care testing is commonly used in the outpatient setting

Rapid Molecular Assay	Rapid Influenza Diagnostic Test
Nucleic acid amplification	Antigen detection
Flu A and B	Flu A and B
CLIA waived	CLIA waived
15-30 min	10-15 min
High sensitivity and specificity	Low/moderate sensitivity & high specificity
Nasal swab	Nasal swab



High Risk for Complications from Influenza

- Children < 5 years old
- Adults \geq 65 years old with
 - Chronic pulmonary, cardiovascular, renal, hepatic, metabolic, or neurologic diseases
 - Moderate to severe developmental delay
- Immunosuppression
- Pregnant
- < 18 years old and on aspirin
- Extreme obesity (body mass index > 40 kg/m²)
- Chronic care facility residents

Influenza Vaccination



**GET YOURSELF
AND YOUR FAMILY
VACCINATED!**

A yearly flu vaccine is the first and most important step in protecting against flu viruses.

Everyone 6 months or older should get an annual flu vaccine. Protect Yourself. Protect Your Family. Get Vaccinated. #FightFlu

Contraindication: Severe allergy
Reduced effectiveness: Immunosuppressed

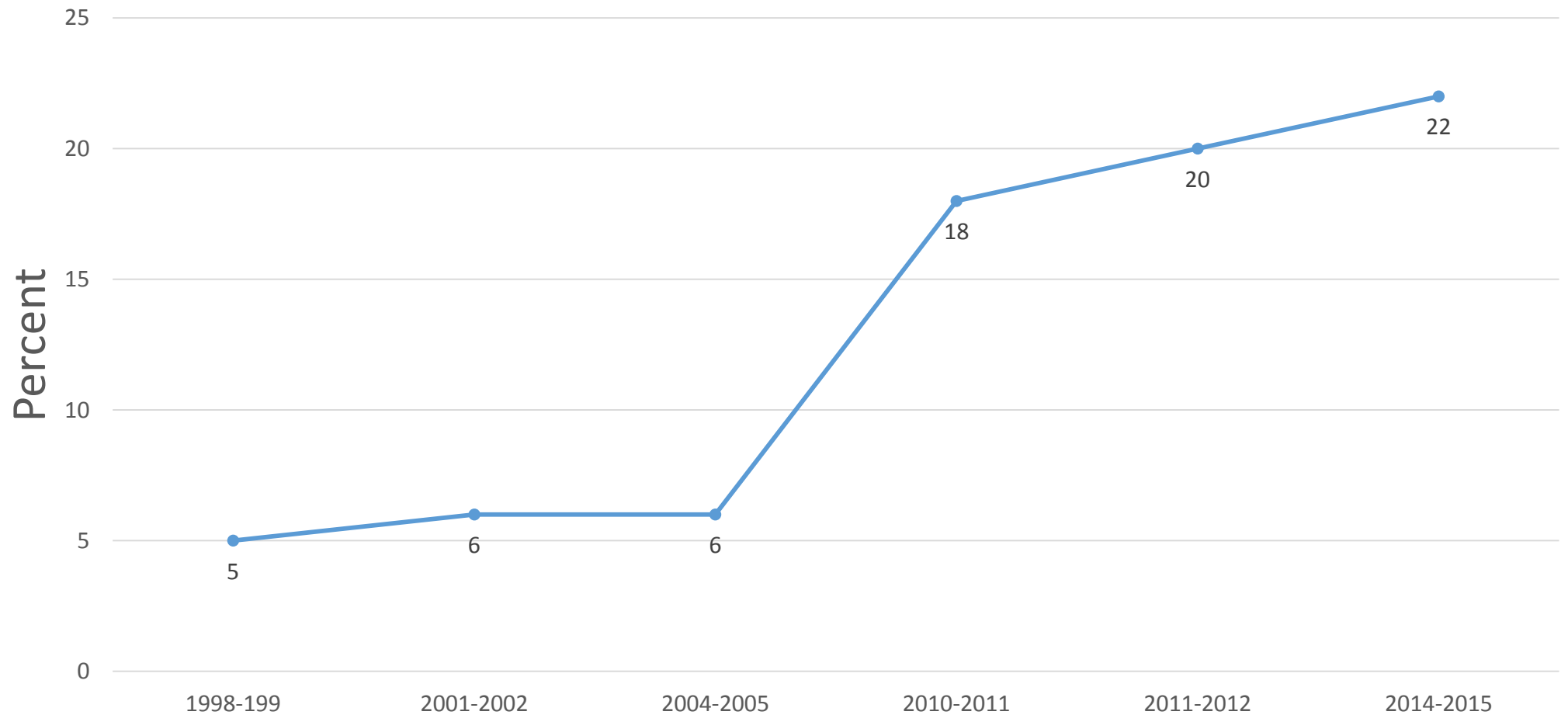
Influenza vaccines 2018-2019

Grohskopf LA, et al.
MMWR Recomm Rep.
2018;67(No. RR-3):1-20.

HA, hemagglutinin;
LAIV, live, attenuated
influenza vaccine;
RIV, recombinant
inactivated influenza
vaccine.

Trade name (Manufacturer)	Age indication	Egg-grown virus, [†] cell culture-grown virus, or recombinant HA	Adjuvanted (yes/no)
Quadrivalent IIVs (IIV4s)—Standard dose—Contain inactivated virus			
Afluria Quadrivalent (Seqirus)	≥ 5 years	Egg	No
Fluarix Quadrivalent (GlaxoSmithKline)	≥ 6 months	Egg	No
Flulaval Quadrivalent (ID Biomedical Corp. of Quebec)	≥ 6 months	Egg	No
Fluzone Quadrivalent (Sanofi Pasteur)	≥ 6 months	Egg	No
Flucelvax Quadrivalent (Seqirus)	≥ 4 years	Cell culture	No
Trivalent IIV (IIV3)—Standard dose—Contains inactivated virus			
Afluria (Seqirus)	≥ 5 years	Egg	No
Trivalent IIV3—High dose—Contains inactivated virus			
Fluzone High-Dose (Sanofi Pasteur)	≥ 65 years	Egg	No
Trivalent IIV3—Adjuvanted—Contains inactivated virus			
Fluad (Seqirus)	≥ 65 years	Egg	Yes (MF59)
Quadrivalent RIV (RIV4)—Contains recombinant HA			
Flublok Quadrivalent (Sanofi Pasteur)	≥ 18 years	Recombinant	No
Quadrivalent LAIV (LAIV4)—Contains live, attenuated, cold-adapted virus			
FluMist Quadrivalent (AstraZeneca)	2-49 years	Egg	No

Percent of Influenza Vaccine Administered at the Pharmacy: 1998 - 2015



Source: Behavioral Risk Factor Surveillance System (BRFSS)

Influenza Antivirals

TAKE ANTIVIRAL DRUGS IF YOUR DOCTOR PRESCRIBES THEM!

or
Pharmacist!



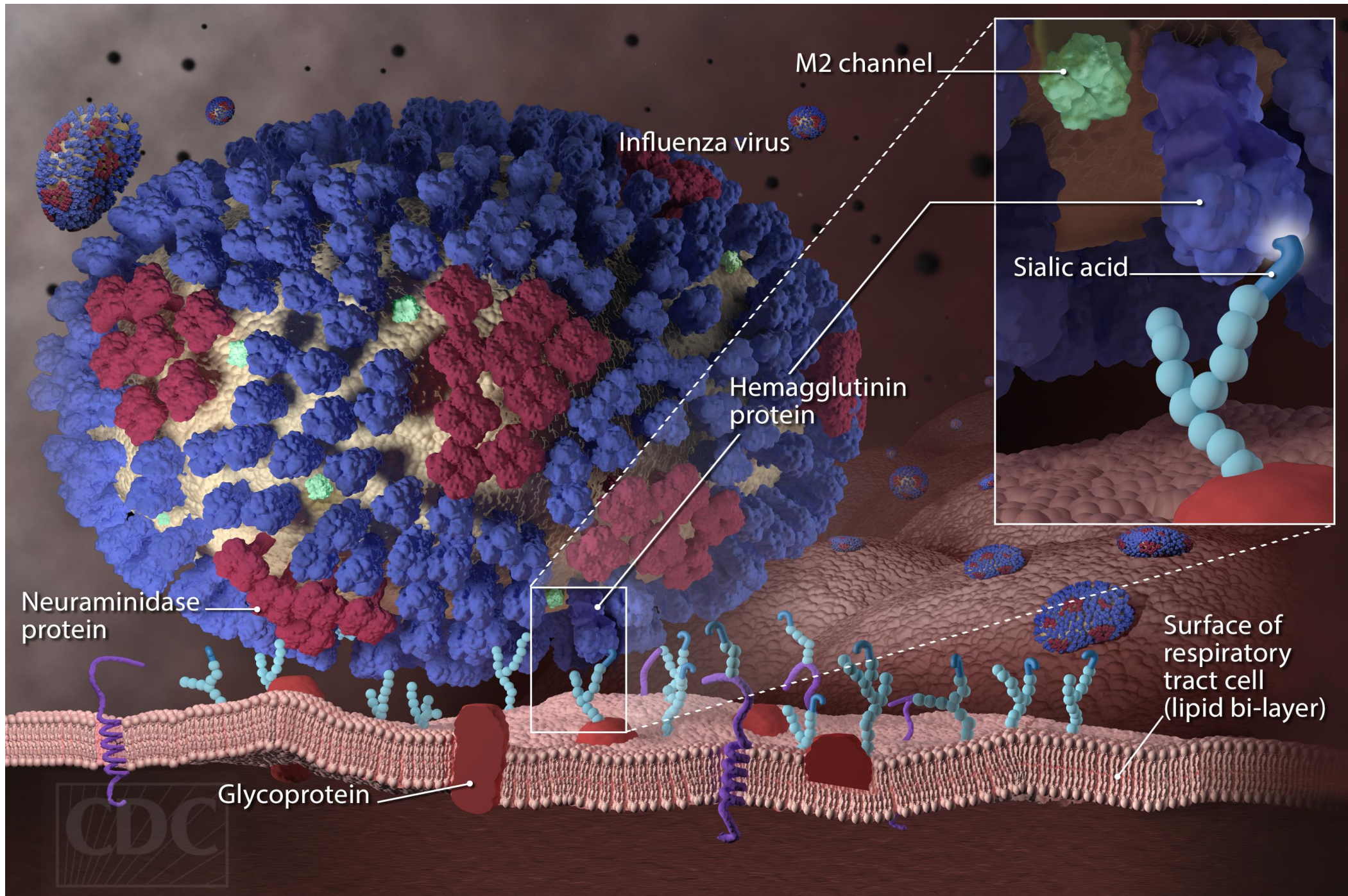
**FLU
ANTIVIRALS**

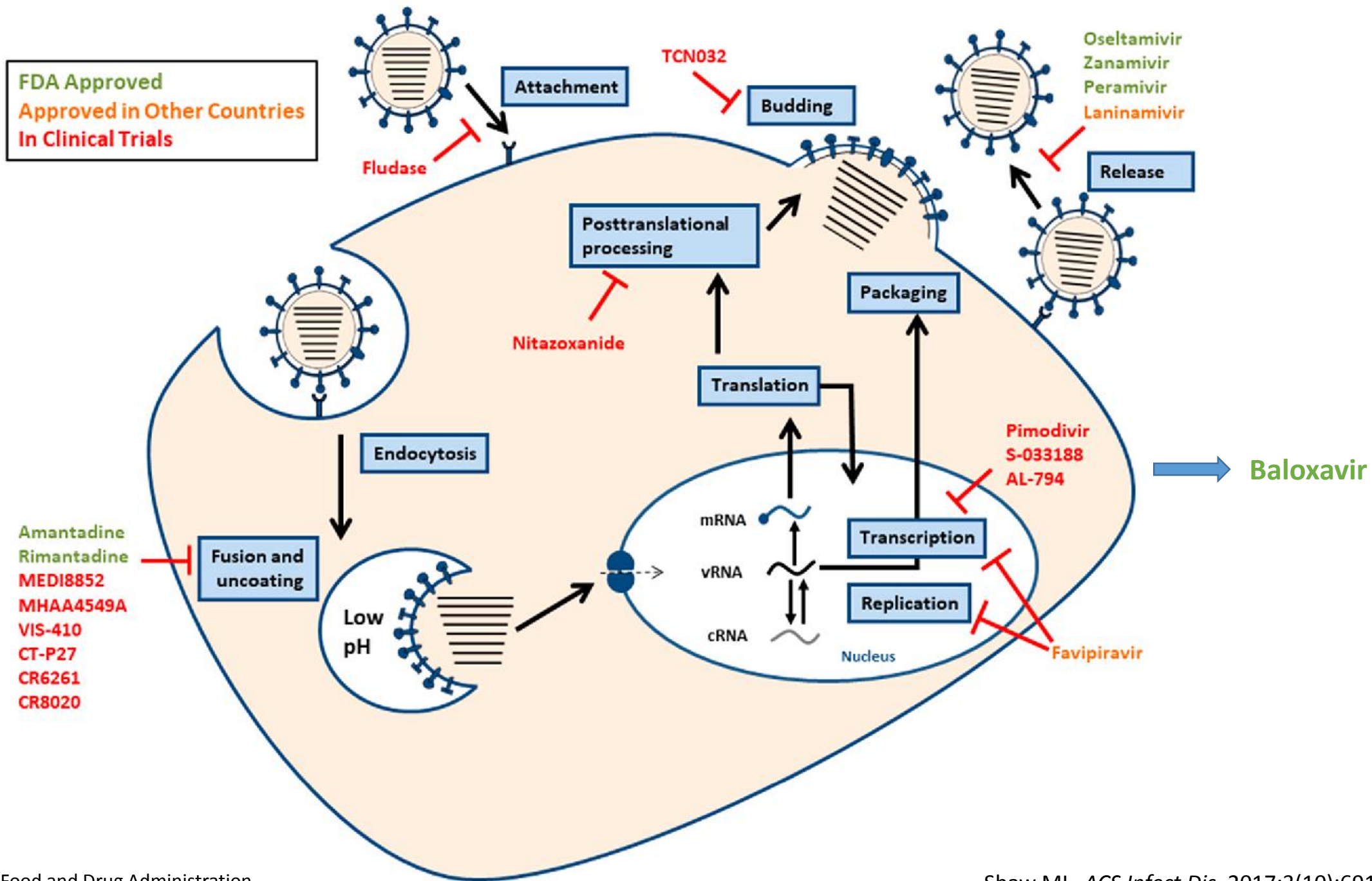


Influenza Treatment Timing



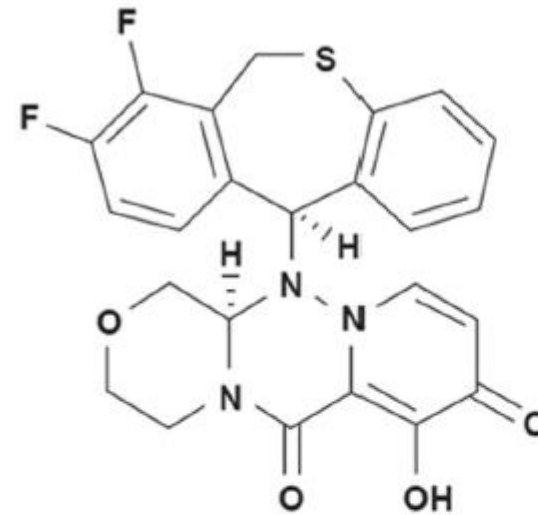
48 hours



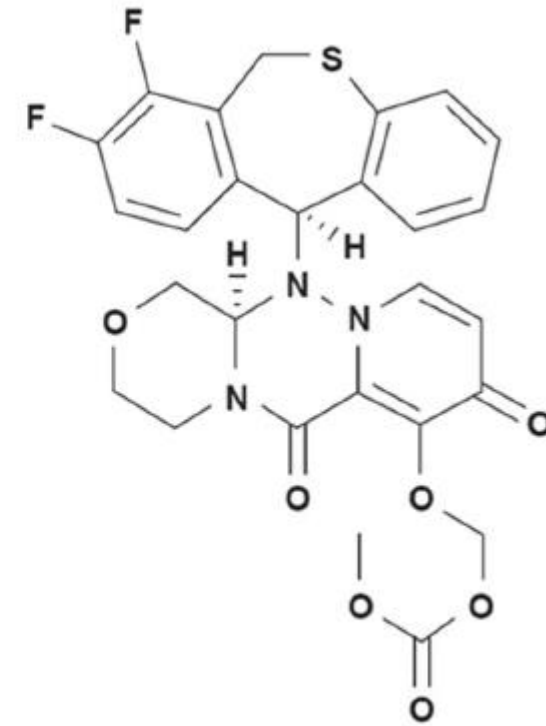


Baloxavir Marboxil (Xofluza)

- Cap-dependent endonuclease inhibitor
- Pro-drug, rapidly converted
- Pharmacokinetics
 - 4 hours to peak
 - Food ↓ C_{max} by 48%
 - Especially Ca, Al, Mg, Fe (chelates)
 - T_{1/2} = 79.1 hours
 - Metabolized by UGT1A3 and CYP3A4
 - No clinically significant interactions



Baloxavir acid (BXA)



Baloxavir marboxil (BXM)

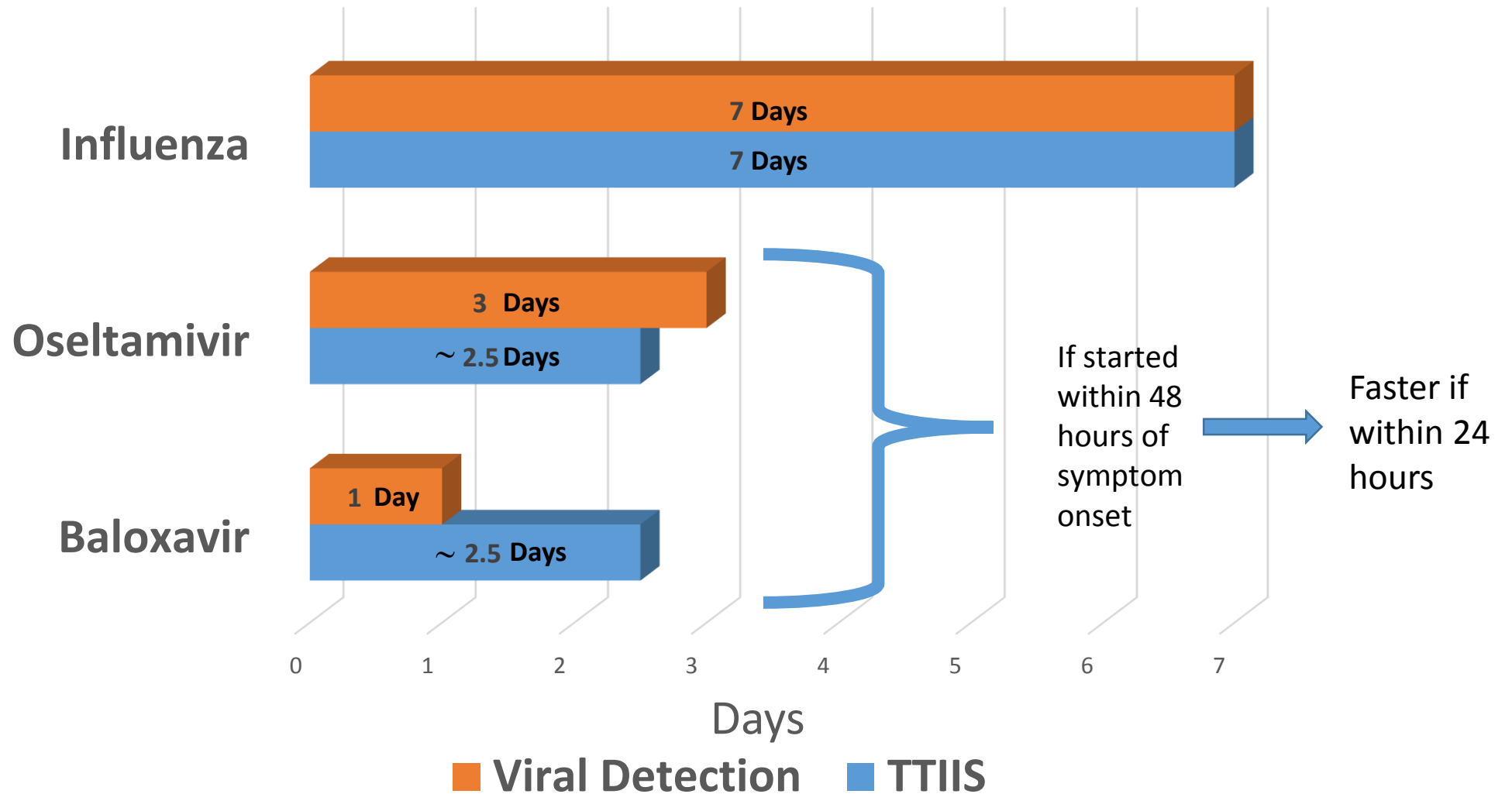
Influenza Antiviral Agents

Antiviral	Mode of action	Route	Indication
Amantadine/rimantadine	M2 ion channel inhibitor	PO	Treatment (uncomplicated) and prophylaxis, influenza A ONLY
Oseltamivir	Neuraminidase inhibitor	PO	Treatment (uncomplicated) and prophylaxis, influenza A/B
Zanamivir	Neuraminidase inhibitor	Oral INH	Treatment (uncomplicated) and prophylaxis, influenza A/B
Peramivir	Neuraminidase inhibitor	IV	Treatment, acute and uncomplicated influenza A/B
Baloxavir	Polymerase inhibitor (PA endonuclease)	PO	Treatment, uncomplicated influenza A/B

IV, intravenously; PA, polymerase acidic; PO, by mouth.

Pregnancy: CDC recommends oseltamivir but not baloxavir

Antiviral Efficacy



TTIIS, median time to improvement of influenza symptoms.

Hayden F, et al. *N Engl J Med.* 2018;379(10):913-23.

Treatment & Chemo-prophylaxis



Influenza antiviral agents	Use	Recommended for	Adult Regimen
Oral oseltamivir	Treatment	Any age	75 mg BID x 5 days
	Chemo-prophylaxis (household)	> 3 months	75 mg QD x 7 days or greater
Inhaled zanamivir	Treatment	7 years and older	10 mg BID x 5 days
	Chemo-prophylaxis (household)	5 years and older	10 mg QD x 10 days
Intravenous peramivir	Treatment	2 years and older	600 mg 15-30 min infusion
	Chemo-prophylaxis	Not recommended	N/A
Oral baloxavir	Treatment	12 years and older	QD x 1 day
	Chemo-prophylaxis	Not recommended	N/A

BID, twice daily; QD, once daily.

Influenza Antiviral Resistance

Virus ¹	Oseltamivir	Zanamivir	Adamantanes
A/H3N2	<3%	Rare	>99%
A/H1N1	<3%	Rare	Rare
B	Rare	Rare	100%

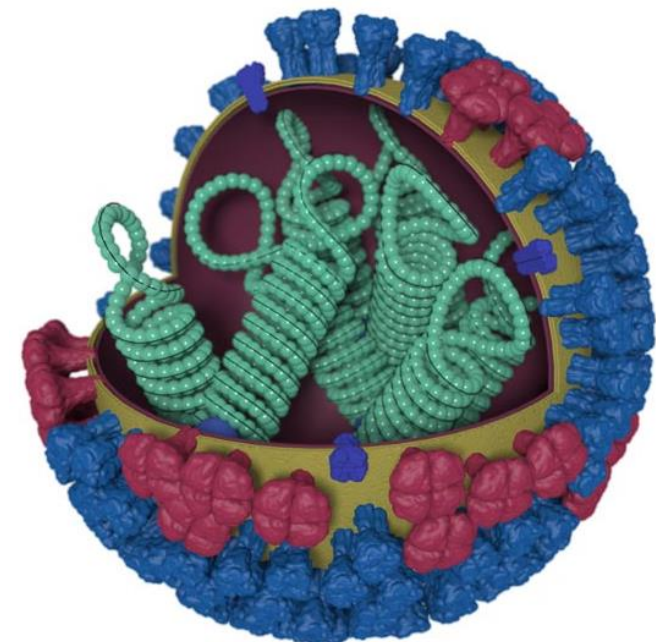
- Baloxavir resistance²
 - 10% had viral escape mutants
 - Reduced drug susceptibility
 - Still infectious 5 days after therapy
- No cross resistance of NAIs to baloxavir
- Amantadine/rimantadine not recommend by CDC for influenza treatment or prevention

NAI, neuraminidase inhibitor.

¹ Li T, et al. *Viruses*. 2015;7(9):4929-44.

² Omoto S, et al. *Sci Rep*. 2018;8(1):9633.

AN INFLUENZA VIRUS



Adverse Events – Phase III Study



Event	Baloxavir (N=610)		Placebo (N=309)		Oseltamivir (N=513)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
	<i>Percent</i>					
Any adverse event	20.7	1	24.6	1.3	24.8	0.2
Adverse events reported in ≥1% of patients in any group						
Diarrhea	3	0.2	4.5	0.3	2.1	0
Bronchitis	2.6	0	5.5	0.3	3.5	0
Nausea	1.3	0.2	1.3	0.3	3.1	0
Headache	0.8	0.2	1	0	0.8	0
Vomiting	0.8	0.2	0.6	0	1.2	0
Dizziness	0.5	0	1.3	0	0.2	0
Adverse event considered to be related to the trial regimen	4.4	0.3	3.9	0.3	8.4†	0
Adverse events considered to be related to the trial regimen and reported in ≥1% of patients in any group						
Diarrhea	1.8	0.2	1.3	0	1.4	0
Nausea	0.3	0.2	0.6	0.3	1.6	0
Serious adverse event	0.3	0.3	0	0	0	0
Adverse event leading to discontinuation of the trial regimen	0.3	0	0.3	0.3	0.4	0

† Statistically significant difference

Pharmacy-based POC Testing and Treatment



POC, point-of-care.

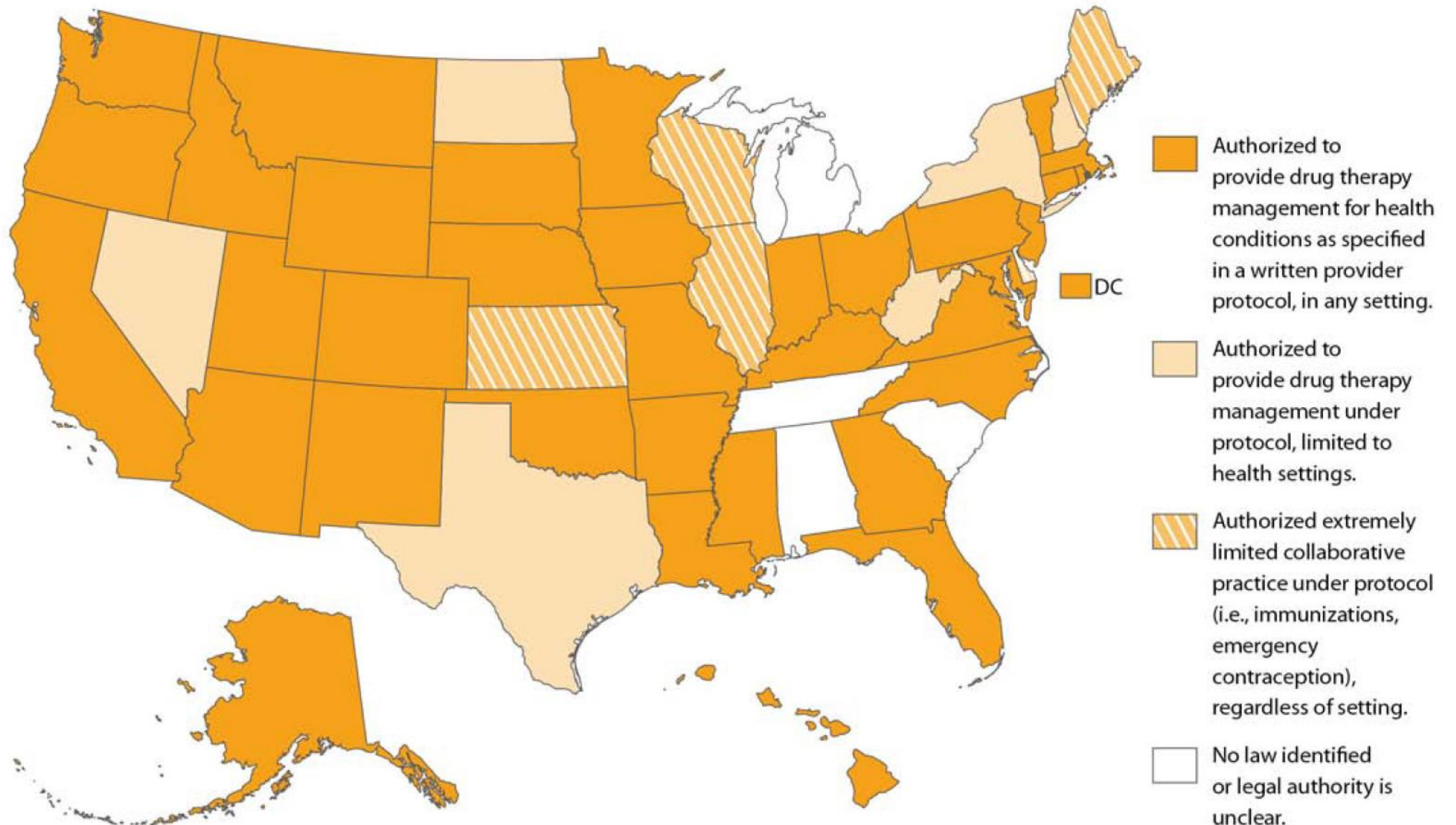
Implementation

- State law allows pharmacists to perform CLIA-waived tests
 - Who can serve as the CLIA-waived lab director?
 - State/county regulations
- State law allows pharmacists to initiate antivirals
 - Collaborative practice agreement (40+ states)
 - Some states are silent on “diagnosis” of influenza
 - Must be able to initiate without obtaining a prescription
 - Independent authority
- Training
 - Performing nasopharyngeal swab
 - Performing POC testing, including QA/QC

States with Laws Explicitly Authorizing Pharmacist Collaborative Practice Agreements, 2012



Centers for Disease Control and Prevention, 2012.



POC Influenza Screening & Treatment Considerations

Screen



Test



Treat

EXCLUSIONS to testing

- Symptoms >48 hours
- Receipt of LAIV within the previous 2 weeks
- Immunocompromised state
- Receipt of an NAI within the previous 2 weeks
- Pulmonary disease requiring home oxygen therapy
- Women who are pregnant or breastfeeding
- Known renal disease or dysfunction
- Known asthma, COPD, or heart failure

Automatic referral to provider

- Altered mental status
- Pulse >125 beats/minute
- Systolic BP <90 mmHg or diastolic BP <60 mmHg
- Respiratory rate >30 breaths/minute
- Temperature >103°F
- Oxygen sat <92% on room air or using oxygen
- *Test negative, but definite flu symptoms present*

EXCLUSION to treatment

- Known hypersensitivity to NAI/baloxavir

BP, blood pressure; COPD, chronic obstructive pulmonary disease.



Question & Answer



Thank you!