Fighting the Flu in Older Adults

Marilyn N. Bulloch PharmD, BCPS, FCCM
mjn004@auburn.edu

Objectives

1. Describe the pathophysiology, clinical presentation, and disease burden of influenza in geriatrics
2. Identify geriatric specific considerations for medications and vaccinations used in the treatment or prevention of influenza
3. Discuss literature and clinical studies involving older adults evaluating medications and vaccinations used in the treatment or prevention of influenza

Disclosures

- Pharmacy Times Contributor
- Genetech Speaker's Bureau for Xofluza (baloxavir)

All content discussed in this presentation will remain unbiased

Brief Review of Influenza

Contagious RNA viral infection

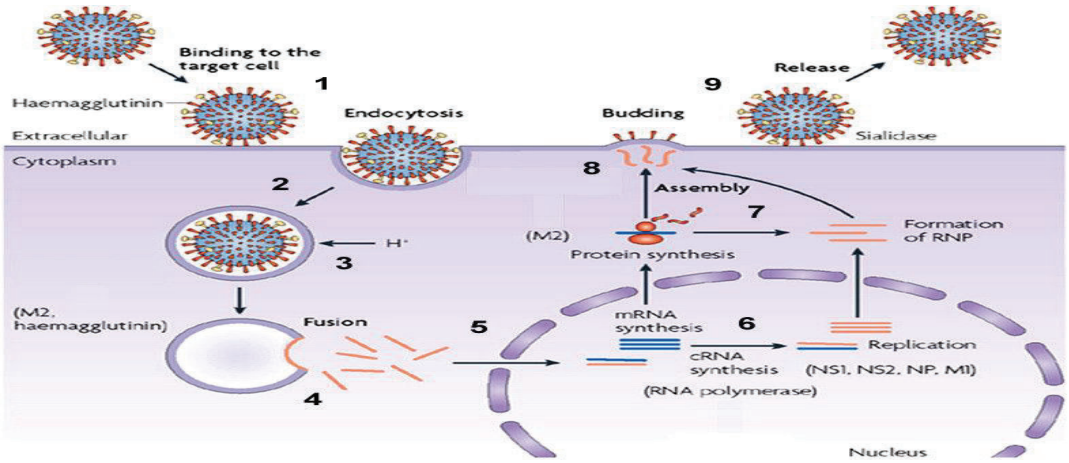
Spread via respiratory droplets

Can infect anyone at any time

More commonly appears during “seasons”

- Southern Hemisphere: April – September
- Northern Hemisphere: October – March
- Tropics : year round

Influenza Replication

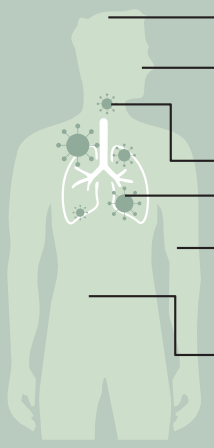


Scolari S. Lateral organization of the transmembrane domain and cytoplasmic tail of influenza virus hemagglutinin revealed by time resolved imaging. 2009. Thesis

Influenza Categorization

	Influenza A	Influenza B	Influenza C	Influenza D
Infections in:	Humans (“flu”) Animals (birds, pigs, ect)	Humans (“flu”)	Humans	Animals (cattle)
Severity	Mild-severe	Mild-severe	Mild	
Categorized by:	Hemagglutinin Neuraminidase	Lineages: Victoria and Yamagata		
Pearls	• Most common in average year • Most virulent • Mutates more quickly • Susceptible to antigenic shift – implicated in pandemics	• Mutates more slowly • Rarely if ever cause pandemics		

Classic Presentation



Headache
Fever (Usually high)
Chills
Congestion or runny nose
Cough (usually non-productive)
Sore throat
Shortness of breath or difficulty breathing
Fatigue
Muscle or body aches
Nausea
Vomiting
Diarrhea

Symptoms vary WIDELY by patient

Patients may not have all or even most of the known symptoms

- Symptoms appear 1-4 days after exposure
- People are contagious ~ 1 day before symptoms appear
- Most contagious in first 3-4 days
  Patients remain contagious ~ 7 days
  (up to 2 weeks in immunocompromised)
- Gastrointestinal symptoms are more common in Influenza B (all patients) and in pediatrics (all strains)
- Cough and fatigue may last > 2 weeks

https://www.cdc.gov/flu/symptoms/symptoms.htm

Flu Burden 2021-22

Up to 13 million cases

Up to 6.1 million visits to health care providers

Up to 170K hospitalizations

Up to 14 K deaths

Preliminary estimates for October 1, 2021 to June 11, 2022. Final data available Fall 2022

Source: https://www.cdc.gov/flu/about/burden/preliminary-in-season-estimates.htm

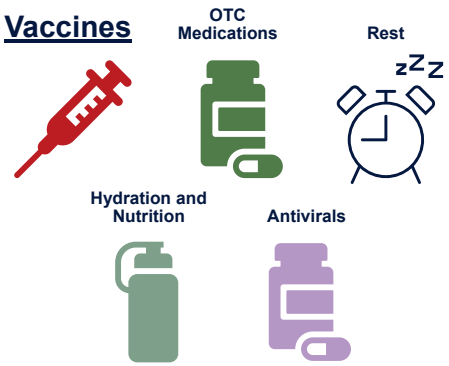
Risk Factors Associated with 30-day Mortality in Older Adults

- Retrospective cohort study of patients ≥ 75 years with influenza
- Mean Age 87.9 years [Survivors 87.3 years vs. Non-Survivors 91.5 years; p=0.006]
- Mean # medications 6.32 [Survivors 6.15 vs. Non-Survivors 7.5; p=0.026]

	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Age	1.18 (1.04;1.35)	0.013	1.37 (1.05;1.79)	0.021
Female	0.97 (0.28;3.36)	0.964	3.01 (0.31;29.20)	0.342
Charlson Comorbidity Index	1.31 (0.96;1.80)	0.092	1.39 (0.78;2.48)	0.268
Diabetes	0.56 (0.12;2.68)	0,466	0.60 (0.06;5.91)	0.662
Chronic respiratory disease	1.83 (0.45;7.43)	0.401	0.27 (0.02;3.91)	0.334
Chronic cardiac disease	3.26 (1.04;10.24)	0.043	6.48 (0.56;74.69)	0.134
Immunosuppression	0.94 (0.19;4.65)	0.944	1.62 (0.16;16.40)	0.683
ADL score	0.69 (0.50;0.95)	0.027	0.36 (0.17;0.75)	0.006
Number of drugs	1.16 (0.96;1.40)	0.128	1.15 (0.83;1.61)	0.405
Nosocomial infection	0.58 (0.15;2.22)	0.426	2.17 (0.18;26.76)	0.545
Antiviral < 48 h	0.33 (0.09;1.27)	0.107	0.04 (0.002;0.78)	0.034
Antibiotic prescription	3.67 (0.97;13.94)	0.057	0.64 (0.07;6.28)	0.704
SOFA score	1.83 (1.27;2.64)	0.001	2.30 (1.07;4.94)	0.034
Lymphopenia	2.17 (0.45;10.45)	0.336	0.42 (0.04;4.03)	0.453

OR, Odds Ratios; ADL, Activities of Daily Living; SOFA, Sequential Organ Failure Assessment .

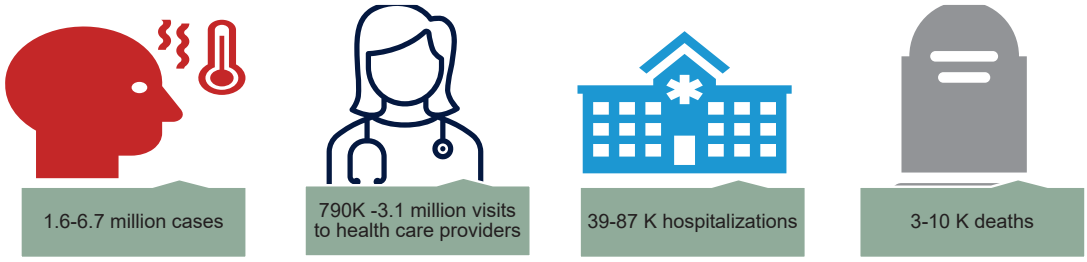
Guesneau C et al. J. Clin Med.2021;10:3521



Approach to Influenza Management

Vaccine Prevented Flu Burden 2011-16

Each season, the influenza vaccine prevented:



https://www.cdc.gov/mmwr/volumes/70/rr/rr7005a1.htm
Grohskopf LA, Alyanak E, Ferdinands JM, et al. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices, United States, 2021–22 Influenza Season. MMWR Recomm Rep 2021;70(No. RR-5):1–28.

Vaccine Indications

Everyone over 6 months without contraindications

Patients at High Risk for Complications

Children aged 6 months – 5 years	**Age ≥50 years**	Chronic lung, kidney, liver, neurologic, or hematologic disease	Chronic heart disease (except hypertension)
Metabolic disorders (including diabetes)	Immunocompromised	Pregnant women	Children on salicylates
Long-term care and nursing home residents	Alaska Natives	American Indians	BMI ≥ 40

- Workers in healthcare settings
- Household contacts and caregivers of children < 5 years and adults ≥50 years
- Household contacts and caregivers of people at high risk for severe complications
- High risk for flu-related complications

Grohskopf LA, Alyanak E, Ferdinands JM, et al. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices, United States, 2021–22 Influenza Season. MMWR Recomm Rep 2021;70(No. RR-5):1–28.

2022-23 Influenza Vaccine Composition

Egg-Based Vaccines	Cell-or Recombinant-Based Vaccines
A/Victoria/2570/2019 (H1N1)pdm09-like virus	A/Wisconsin/588/2019 (H1N1)pdm09-like virus
A/Darwin/9/2021 (H3N2)-like virus	A/Darwin/6/2021 (H3N2)-like virus
B/Austria/1359417/2021 (B/Victoria lineage)-like virus	B/Austria/1359417/2021 (B/Victoria lineage)-like virus
B/Phuket/3073/2013 (B/Yamagata lineage)-like virus	B/Phuket/3073/2013 (B/Yamagata lineage)-like virus

Source: Weir JP. Food and Drug Administration. Influenza Virus Vaccine Strain Selection 2022-2023 Northern Hemisphere. March 3, 2022
https://www.precisionvaccinations.com/vaccines/influenza-vaccines-2022

Vaccinating Older Adults

- "Enhanced" Vaccines – designed to create a stronger immune response in older adults
  - High-dose or Adjuvanted
  - May have more explicit recommendation for preference for 2022-23
- Recombinant
- 2020 study of 800 patients aged 65-82 years
  - Titers were significantly higher in patients who received an adjuvanted, high-dose, or recombinant vaccine vs. standard doses
  - Titers: recombinant > high dose > adjuvanted
  - Enhanced vaccines resulted in boosting T-cell responses
- Any vaccine is better than no vaccine
  - In most patients
- Do not vaccinate too early – no data that a booster is helpful in most

https://www.cdc.gov/flu/season/faq-flu-season-2021-2022.htm#what-virus
Crowling BJ et al. Clin Infect Dis.2020;71:1704-1714
Grohskopf LA, Alyanak E, Ferdinands JM, et al. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices, United States, 2021–22 Influenza Season. MMWR Recomm Rep 2021;70(No. RR-5):1–28.

Vaccine Administration Timing

Ideal	• September • October
Avoid too early vaccination in some people	• July or August • **Especially in older adults** • Protection may decrease over time
When early vaccination is okay	• Children • Third trimester of pregnancy

Grohskopf LA, Alyanak E, Ferdinands JM, et al. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices, United States, 2021–22 Influenza Season. MMWR Recomm Rep 2021;70(No. RR-5):1–28.

Vaccine Interactions

"Acceptable" to give IIV_4 or RIV_4 while a patient is getting antivirals

Data on $LAIV_4$ administration to patients on antivirals is limited

- In theory – antivirals will interfere with LAIV4 action
- Labeling – 48 hours before and 14 days after vaccination
- Baloxavir and peramivir may interfere if given > 48 hours before
  - ACIP – "Reasonable" to assume 5 days before with peramivir and 17 days before with baloxavir and 2 weeks after vaccination

Unless given at same time, separate $LAIV_4$ four weeks from administration of another live vaccine

Simultaneous administration of IIV_4 with PPSV23 in geriatrics was associated with lower seroprotection to one influenza B antigen at 4-6 weeks postvaccination vs. sequential administration 2 weeks apart

Grohskopf LA, Alyanak E, Ferdinands JM, et al. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices, United States, 2021–22 Influenza Season. MMWR Recomm Rep 2021;70(No. RR-5):1–28.

Reduction in Dementia Risk with Flu Vaccination

Rationale

- Influenza vaccine previously shown to increase microglia activity – causing clearance of amyloid-beta in animals
- Influenza vaccine may decrease neuroinflammation

Meta-analysis of 5 articles published through September 2021

297,157 older adults free from dementia at baseline

- Mean age 75.5 years (± 7.4 years)
- 46.8% female
- Mean follow-up 9 years

All studies of high quality, observational, and included validated diagnosis of dementia

Results

- Influenza vaccination reduced risk of dementia by 3% (RR=0.91, 95% CI 0.94-1.00; p=0.04)
- Vaccination associated with 29% reeducation in studies that adjusted for potential confounders (including age, gender, medical conditions, substance abuse, education, smoking history, and other cofounders)

Veronese N et al. *Ageing Res Rev*. 202;73:1015342

Vaccines in Development

Flu-v

- Novel peptide SQ vaccine designed to produce cellular immunity
- Potential universal vaccine candidate

NasoVAX

- Recombinant intranasal vaccine
- Designed for seasonal and pandemic use
- Activate humoral, mucosal, and cellular immunity in unison – thought to cause a more comprehensive immune response comparable to available traditional influenza vaccine
- Phase2a study – well tolerated and achieved 100% seroprotection with serum antibody response

RedeeFlu

- Nasal vaccine
- Uses a proprietary M2 deleted, single replication influenza virus
- Supra-seasonal, live, single- replication vaccine that does not shed virus
- Phase 2a study – showed protection against a highly drifted H3N2 influenza virus

https://www.precisionvaccinations.com/vaccines/influenza-vaccines-2022

Vaccines in Development

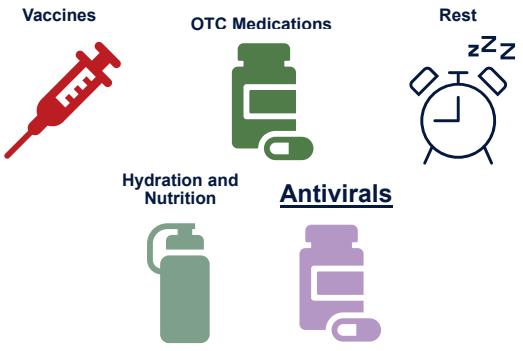
NanoFlu	•Quadrivalent recombinant hemagglutinin protein nanoparticle IM vaccine •Produced in SF insect cell baclovirus system •Uses HA amino acid protein sequences similar to the wild-type circulated virus HA sequences •Contains patented adjuvant •Older adults are a targeted population •Phase 3 study in older adults – well tolerated and produced enhanced immune response vs. IIV4.
CD388 (drug-FC conjugate)	•Potent, long-acting antiviral to provide universal prevention and treatment of both seasonal and pandemic influenza •Single dose
CVSQIV	•Second generation-mRNA vaccine •Multiple non-chemically modified mRNA constructs – produce immune responses vs. relevant targets of 4 different influenza strains

https://www.precisionvaccinations.com/vaccines/influenza-vaccines-2022

Vaccines in Development

Moderna mRNA-1230	• Annual combination booster for influenza, RSV, and SARS-CoV-2
REVTx-99a	• Intranasal • For prevention of H3N2 in healthy humans • Also for parainfluenza, rhinovirus, RSV, and SARS-CoV-2

https://www.precisionvaccinations.com/vaccines/influenza-vaccines-2022



Approach to Influenza Management

CDC Algorithm for Testing and Treatment

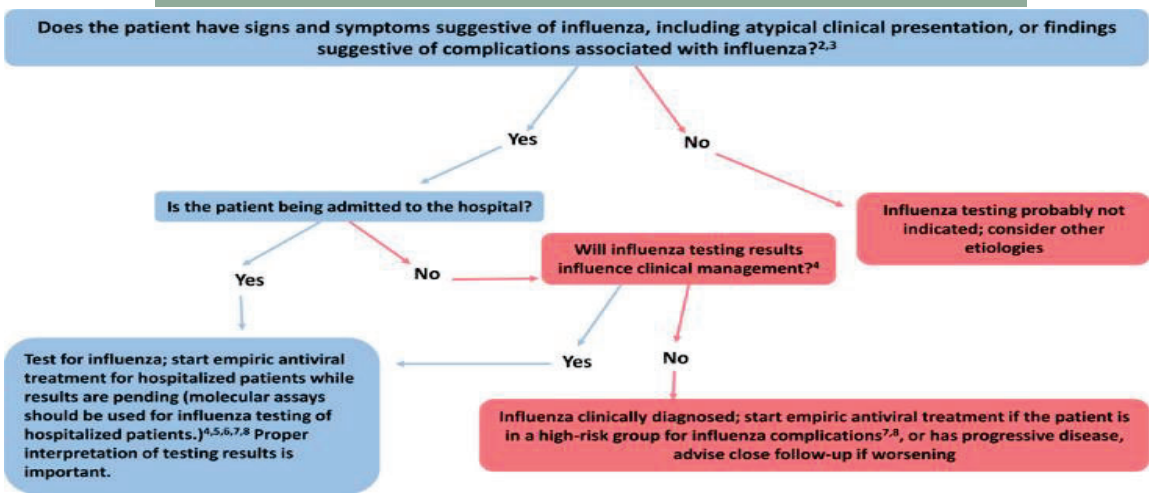


Figure 4: https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

Key Points: Treatment

Start within 48 hours of symptoms onset

- Relates to virus replication and antiviral pharmacology

When treatment is recommended:

- Hospitalized
- Severe, complicated, or progressive illness
- High risk for influenza complications
- Anyone with symptoms based on clinical judgement

Influenza antiviral medications: summary for clinicians. https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

Key Points: Prophylaxis

Antiviral prophylaxis should not be a substitute in most patients for immunization

Start within 48 hours of exposure to be helpful

CDC decreased minimum duration of therapy for oseltamivir and zanamivir from 10 to 7 days

In LTC facilities – prophylaxis should continue for 7 days after the last influenza case identified

Neuraminidase inhibitors are ~ 70-90% effective at protecting against susceptible influenza viruses

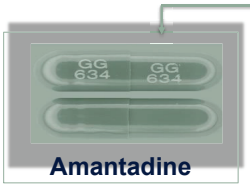
When recommended:

- High risk patients during 1st 2 weeks following vaccination after exposure
- High risk patients who have a vaccine contraindication and have exposure
- Patients with severe immune deficiencies or others who may not respond to a vaccine and have exposure
- All nursing home residents – regardless of vaccination status

Influenza antiviral medications: summary for clinicians. https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

Antivirals

No Longer Recommended



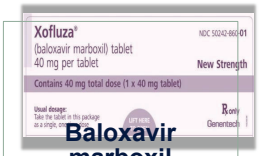
Amantadine

Rimantadine

Oseltamivir

Zanamivir

Peramivir



Baloxavir marboxil

Influenza antiviral medications: summary for clinicians. https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

Oseltamivir

For treatment and prophylaxis

Frequency and Duration of Therapy

- Treatment – Twice daily x 5 days
- Prophylaxis – Once daily x 7-10 days

Adverse Effects

- Nausea/vomiting
- Headache
- Transient psychiatric reactions (e.g. hallucinations)
- Skin reactions

Influenza antiviral medications: summary for clinicians. https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

Oseltamivir is the *only* recommended antiviral in outpatients with severe, complicated, or progressive illness

Influenza antiviral medications: summary for clinicians. https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

Oseltamivir Considerations

- Prodrug
- Only generic antiviral for influenza
- Available as a capsule or suspension
- Request flavoring for any suspension being administered via traditional oral route

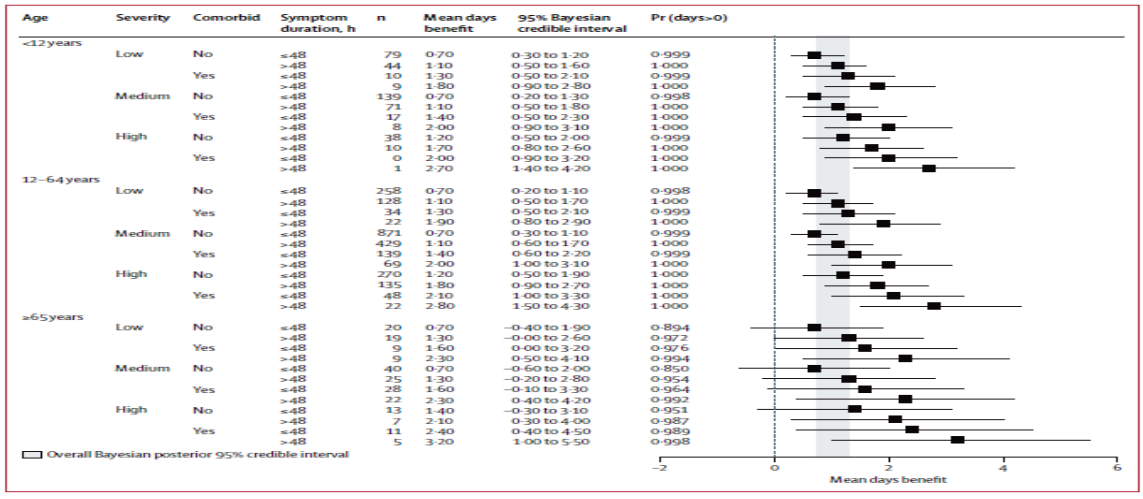
Uyeki TM, et al. *Clin Infect Dis*. 2019;68(6):e1-e47
Influenza antiviral medications: summary for clinicians. www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm.
Kawai N, et al. *J Infect*. 2008;56(1):51-57
Chairat K, et al. *Brit J Clin Pharmacol*. 2016;81(6):1103-1112
Dutkowski R, et al. *Int J Antimicrob Agents*. 2010;35(5):461-467.

ALIC⁴E Trial

Open-label pragmatic, response-adaptive platform randomized controlled trial January 2016-April 2018	• 3,059 patients ≥ 1 year of age with influenza symptoms < 72 hours • Excluded: CKD, immunosuppression, hospitalization, liver impairment, and scheduled procedures requiring general anesthesia in next 2 weeks
Groups	• Usual Care vs. Usual Care with Oseltamivir
Results	• Faster overall recovery with oseltamivir vs. usual care [5.71 days vs. 6.73 days; HR 1.29, 95%CI 1.2-1.39) • No evidence of difference in results between type of influenza or season

Butler CC, et al. *Lancet*. 2020;395:42-52

ALIC⁴E Trial



Butler CC, et al. *Lancet*. 2020;395:42-52

ALIC⁴E Trial: Impact of Oseltamivir on Quality-Adjusted Life Years

14-day symptom diaries returned by 2,234 adults and 363 children

Addition of oseltamivir in adults:

- Reduced influenza-related QALY loss at 14-day and 28-day follow-up (p<0.00 and p=0.002)
- Increased QALYs gained by 0.0006 at 14-days and 0.0008 at 28-days

Geriatric specific results

- Increased QALYs gained by 0.0006 at 14-days and 0.0008 at 28-days

Effectiveness of Oseltamivir Prophylaxis in Influenza Outbreaks in Residential Aged Care

Large cohort study using prospective administration data from database of aged care facilities in Australia that reported influenza outbreaks between 2015-2018

- 86 outbreaks in 49 facilities

Considerations

- Oseltamivir prophylaxis failure: new clinical case of influenza occurring in a patient on oseltamivir prophylaxis calculated as the attack rate in patients on prophylaxis divided by attack rate in patients not on prophylaxis

Patients

- 10,064 total patients
- 16% patients diagnosed with influenza (9% confirmed by PCR)
- Vaccination rates 88% for patients and 37% for staff

Results Overall

- Attack rate significantly lower in facilities that used oseltamivir prophylaxis compared to those who did not (1.9% vs. 18.9%; ARR 17%; NNT 6)
- Oseltamivir 90% effective at preventing new cases of influenza (RR of OP failure 0.1; p<0.0001)
- Increased risk of failure in facilities with high prophylaxis utilization rate (RR 6.5; 95% CI 2.86-14.77)

Dronavalli et al. *J Epidemiol Glob Health*.2020;10:184-89

Effectiveness of Oseltamivir Prophylaxis in Influenza Outbreaks in Residential Aged Care

- Facilities with dementia wards had 30% more influenza cases and more use of oseltamivir for treatment (34%) than prophylaxis (12%) vs. those without dementia wards
- Facilities with dementia wards had lower prophylaxis failure rates (44%)

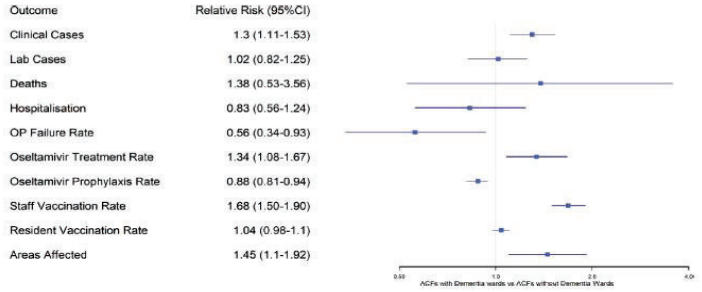


Figure 1 | Relative risk of clinical outcomes in influenza outbreaks in dementia wards compared with non-dementia wards in ACFs. ACF, aged care facility; OP, oseltamivir prophylaxis; deaths, any deaths occurring in residents of the ACF during the outbreak.

Dronavalli et al. *J Epidemiol Glob Health*.2020;10:184-89

Effectiveness of Oseltamivir Prophylaxis in Influenza Outbreaks in Residential Aged Care

- Facilities with only high care wards had 29% fewer cases of influenza
- Rates of oseltamivir prescriptions were similar between facilities with only high care wards vs. other facilities
- Prophylaxis failure rate was 87% lower in facilities with high care wards

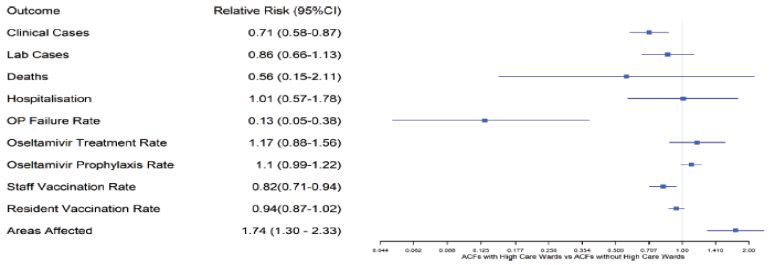


Figure 2 | Relative risk of clinical outcomes in influenza outbreaks in high care wards compared with non-high care wards in ACFs. ACF, aged care facility; OP, oseltamivir prophylaxis; deaths, any deaths occurring in residents of the ACF during the outbreak.

Dronavalli et al. *J Epidemiol Glob Health*.2020;10:184-89

Effectiveness of Oseltamivir in Reducing Complications and 30-day Mortality in Hospitalized Adults

Multi-center, retrospective cohort study in the Netherlands

- 390 hospitalized adults with confirmed influenza
- Mean age 65 years(49% patients > 65 years)
- Other demographics: 42% female, 80% had comorbidities, 60% had cardiovascular comorbidities 42% lung comorbidities, and 46% were immunocompromised

Median duration between symptom onset and drug initiation: 3 days

Patients more likely to receive oseltamivir

- Younger adults
- Patients with comorbidities
- Given concomitant antibiotics
- Admitted to ICU within 48 hours of hospital admission

Table 3
Outcome using propensity score matching in the group of influenza patients treated with oseltamivir within 48 h of hospital admission compared with the group of patients without this treatment

Outcome variable	Untreated (%)	Treated (%)	Difference (%)	OR	95% CI	*P*
30-day mortality	12/88 (13.6)	4/88 (4.6)	-8/88 (9.1)	0.30	0.07-1.07	0.04
In-hospital mortality	9/88 (10.2)	3/88 (3.4)	-6/88 (6.8)	0.31	0.05-1.31	0.13
Composite endpoint	14/88 (15.9)	4/88 (4.6)	-10/88 (11.4)	0.25	0.06-0.86	0.02
Median (IQR) length of hospital stay (days)	6 (2.8-11.0)	4 (2.6-8.0)	-	-	-	0.14

OR, odds ratio; CI, confidence interval; ICU, intensive care unit; IQR, interquartile range; composite endpoint, 30-day mortality and/or ICU admission >48 h after hospital admission.

Groeneveld et al. *Int J Antimicrob Agents*.2020;56:106155

Zanamivir

For treatment and prophylaxis

Dose – 2 inhalations

Frequency and Duration of Therapy

- Treatment – Twice daily x 5 days
- Prophylaxis – Once daily x 7-10 days

Contraindications

- Reactive lung disease and/or bronchospasm
- Milk protein allergy

Influenza antiviral medications: summary for clinicians. https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

Zanamivir Adverse Effects

- Diarrhea
- Bronchospasm
- Headache
- Dizziness
- Cough
- Nasal congestion
- Nausea
- Oropharyngeal/facial edema
- Allergic reaction

Uyeki TM, et al. *Clin Infect Dis.* 2019;68(6):e1-e47;
Heneghan CJ, et al. *BMJ.* 2014;348:g2547
Influenza antiviral medications: summary for clinicians. www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm.

Zanamivir vs. Oseltamivir in COPD patients with Influenza

Randomized controlled trial of 160 adult patients with COPD and influenza in China

No difference in influenza A (O 52.5% vs. Z 55%) or influenza B (O 47.5% vs. 45%)

Table 2. Changes in body temperature (°C) on days 1, 3, and 7 of treatment of chronic obstructive pulmonary disease patients with influenza virus infection treated with oral oseltamivir (OSELTA group) or inhaled zanamivir (ZANA group).

Assessment day	OSELTA group (N=80)	ZANA group (N=80)	Statistics
Day 1	38.2 ± 0.8	38.2 ± 0.7	Δ*=0.02; 95%CI=–0.2049 to 0.2833 *t*=0.148; P=0.882
Day 3	37.0 ± 0.6	37.3 ± 0.7	Δ*=0.23; 95%CI=–0.4507 to –0.0270 *t*=2.631; P=0.009
Day 7	36.6 ± 0.2	36.5 ± 0.3	Δ*=–0.04; 95%CI=–0.0193 to 0.1379 *t*=–0.918; P=0.360

Table 3. Comparison of clinical improvement of influenza non-specific symptoms on days 3 and 7 of treatment of chronic obstructive pulmonary disease patients with influenza virus infection treated with oral oseltamivir (OSELTA group) or inhaled zanamivir (ZANA group).

Assessment day	OSELTA group (N=80)	ZANA group (N=80)	Statistics
Day 3			
Body temperature returned to normal	41 (51.3%)	32 (40.0%)	χ^2=2.041; P=0.153
Improvement in clinical symptoms	68 (85.0%)	55 (68.8%)	χ^2=5.942; P=0.015
Day 7			
Body temperature returned to normal	80 (100.0%)	77 (96.3%)	χ^2=3.057; P=0.080
Improvement in clinical symptoms	78 (97.5%)	67(83.8%)	χ^2=8.901; P=0.003

Li et al. *Braz J Med Biol Res.*2021;54:e9542

Peramivir

- **Treatment only**
- **One-dose**
- **IV Therapy**
- **15-30 minute infusion**
- **Requires renal dosing**

Major ADRS

- Diarrhea
- Skin Reactions
- Psychiatric effects (transient)

Considerations

- Approved primarily from studies of Influenza A
- Reimbursed as outpatient infusion therapy
- May alleviate fever faster than oseltamivir (Difference -7.83 hours)

Uyeki TM, et al. *Clin Infect Dis.* 2019;68(6):e1-e47
Su et al. *J Infect Chemother.*2022;28:158-68
Influenza antiviral medications: summary for clinicians. www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm.

Peramivir

Open-label RCT at 2 academic emergency departments (Johns Hopkins Hospital and Maricopa Medical Center)

Compared oral oseltamivir (n=84) to IV peramivir (n=95)

Both groups received first dose in ED

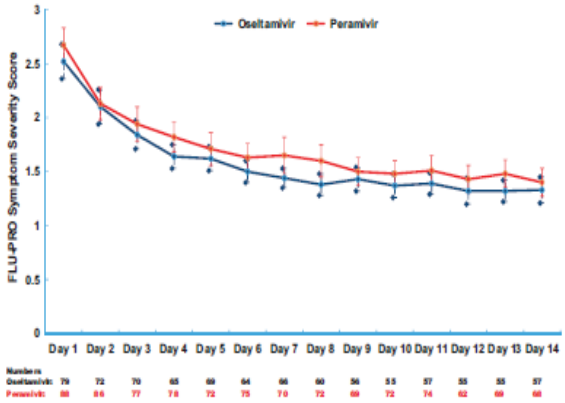
- Oseltamivir group took remaining 4 days either as outpatient or inpatient
- Peramivir could be continued in patients admitted to hospital based on physician discretion

Average FLU-PRO score similar at baseline (P 2.67 vs. O 2.52)

Decrease in scores non-inferior (P<0.05 at day 5, day 10, and day 14)

No difference in all influenza-related complications (31% vs 21%; p> 0.05) or pneumonia (11% vs. 14% ; p> 0.05)

FLU-PRO Symptom Severity Score for 14 Days of Follow-up



Hsieh Y et al. Influenza Other Respir Viruses.2021;15:121-131

Other Peramivir Studies

Study	Design	Results
Kato et al. 1	• 2 week randomized open-label study in 209 patients • Evaluated Peramivir repeat (600 mg IV on 2 consecutive days) vs. peramivir single (300 mg IV single dose) vs. oseltamivir in adults with influenza and chronic respiratory disease	• NO difference in peramivir repeat or single • Cumulative area of time vs. symptoms (CATVS) shorter for peramivir single vs. oseltamivir (Treatment difference -1.45.07) • CATVS shorter for peramivir single vs. oseltamivir in patients with **influenza A** (TD -206.61; p=0.0231), **bronchial asthma** (-156.57;p=0.0328), **baseline respiratory severity score** < 5 (TD-265.32;p=0.012) and **age < 65** (TD – 184.3;p=0.0249)
Kato et al. 2	• Additional outcomes from 2-week open label study	• Both peramivir regiments reduces COPD Assessment Test (CAT) score on day 3 more than oseltamivir (Repeat -0.45 vs. O -0.9 p=0.0032) (single -3.8 vs. O -0.9 p=0.0203) • Median time to alleviation of 3 respiratory symptoms longer with repeat vs. single (68.9 hours vs. 50.6 hours, HR 1.57; p=0.0191) and shorter with single vs. oseltamivir (50.6 hours vs. 78.8 hours, HR 0.62 p=0.0141) • Alleviation of 7 influenza symptoms shorter with single vs. repeat (70.3 vs. 103.8 hours, HR 1.62, 95% CI 1.12-2.34) and vs. oseltamivir (70.3 vs. 102 hours, HR 0.59, 95% CI 0.41-0.86), but no difference between repeat and oseltamivir (HR 0.96, 95% CI 0.65-1.41)
Chen et al.	• Single center RCT in 40 adults in China with severe influenza A with primary viral pneumonia from December 2018-April 2019 • Compared Peramivir (300 mg IV daily for 5 days) vs. oseltamivir	• No difference between oseltamivir and peramivir in duration of viral positivity (2.95 vs. 2.8 days; p>0.05), remission of symptoms (3.9 vs. 3.25 days;p=0.29), or time to cough alleviation (75.53 vs. 63.89 hours; p=0.51) • Peramivir had a shorter duration of time to fever alleviation (12.32 vs. 23.67 hours; p=0.034)

Kato et al. Influenza Other Respir Viruses.2021;15:132-141
Kato et al. Influenza Other Respir Viruses.2021;15:651-660
Chen et al. Open Forum Infec Dis.2020;8:ofaa562

Comparison Of Neuraminidase Inhibitors

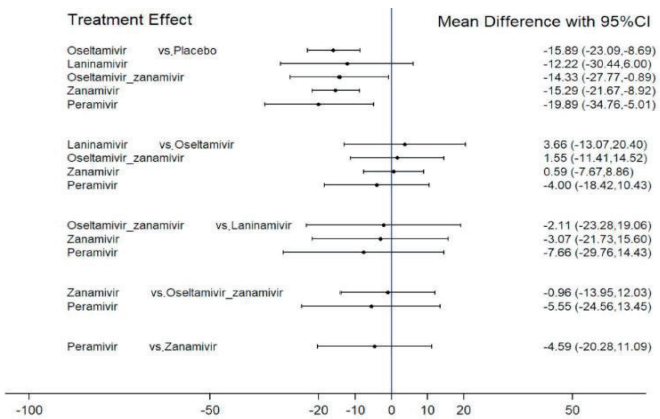
Network Meta-Analysis of NAIs

Focused on reducing influenza symptoms

58 two-arm studies published 1997-2018.

22,250 patients total

Summarized Mean Difference for Multiple Treatment Comparisons of Symptom Alleviation

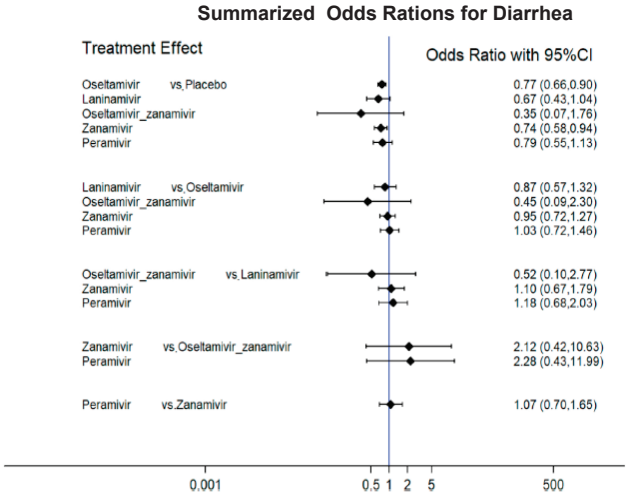


Su et al. *J Infect Chemother*.2022;28:158-68

Comparison Of Neuraminidase Inhibitors

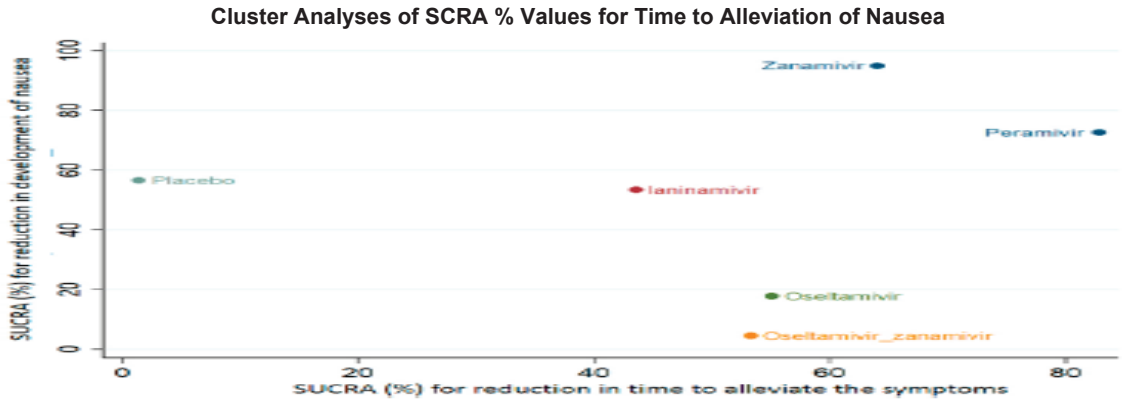
Geriatric Results

No significant effect on symptom alleviation from any NAI



Su et al. *J Infect Chemother*.2022;28:158-68

Comparison of Neuraminidase Inhibitors



Greater SUCRA (%) indicate a shorter time or a lower risk of nausea

Su et al. *J Infect Chemother*.2022;28:158-68

Neuraminidase Inhibitors Adverse Effects

Retrospective study of the U.S. FDA adverse event reporting systems (FAERS) and WebMD data from 2013-2018

Results

- 16,729 adverse effects from 4,598 patients in FAERS and 575 adverse effects from 440 patients in WebMD
- FAERS: adverse effects in older adults more common with peramivir (63.51%) and in pediatrics with zanamivir (30.67%)
- Peramivir – abnormal liver function, cardiac failure, shock, respiratory failure
- WebMD: Oseltamivir associated with GI symptoms in older adults

Han et al. Sci Rep.2020;10:3116

Baloxavir marboxil

40 to < 80 kg (88 lb to < 176 lbs)		≥ 80 kg (≥ 176 lbs)	
One	**40-mg Tablet**	**One**	**80-mg Tablet**
20 mL	40 mg/20 mL Oral suspension	40 mL	40 mg/20 mL Oral suspension

Oral suspension is FDA approved – but not (yet) currently available for use

Approved for treatment and prophylaxis of uncomplicated influenza within 48 hours of symptom onset

Compound summary baloxavir marboxil. National Center for Biotechnology Information website. pubchem.ncbi.nlm.nih.gov/compound/124081896.
Influenza antiviral medications: summary for clinicians. www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm.

Baloxavir Considerations

Adverse Effects
- Diarrhea
- Nausea
- Headache
- Bronchitis
- Nasopharyngitis

Interactions
- Live influenza vaccine
- Laxatives
- Antacids
- Calcium
- Iron
- Magnesium
- Selenium
- Zinc

Administration
- One dose
- Separate from products containing calcium or polyvalent cations

Compound summary baloxavir marboxil. National Center for Biotechnology Information website. pubchem.ncbi.nlm.nih.gov/compound/124081896.
Influenza antiviral medications: summary for clinicians. www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm.

CAPSTONE 2 Study

- Double-blind, placebo-controlled and oseltamivir-controlled trial
- Outpatients with symptoms ≤ 48 hours
- Aged ≥12 years
- ≥ 1 risk factor for influenza-associated complications
- 17 countries and 551 sites

	Baloxavir marboxil	Placebo	P-value
Median to symptom alleviation	73.2 hours	102.3 hours	<0.001
Influenza A (H3N2)	75.4 hours	100.4 hours	0.0141
Influenza B	74.6 hours	100.6 hours	0.0138
Median duration of viral shedding	48 hours	96 hours	<0.001
Antibiotic use/secondary infection	3.4%	7.5%	0.01
Development of flu complication	2.8%	10.4%	0.0112

	Baloxavir marboxil	Oseltamivir	P-value
Median to symptom alleviation	73.2 hours	81 hours	>0.05
Influenza A (H3N2)	75.4 hours	No data	>0.05
Influenza B	74.6 hours	101.6 hours	0.0251
Median duration of viral shedding	48 hours	96 hours	<0.001
Development of flu complication	2.8%	4.6%	>0.05

Ison MG, et al. *Lancet Infect Dis*.2020;20"1204-1214

Baloxavir Prophylaxis in Household Contacts

	Baloxavir (n=374)	Placebo (N=375)	Adjusted Risk Ratio (95% CI)
Lab confirmed influenza	7 (1.9%)	51 (13.6%)	0.14 (0.06-0.3)
Negative PCR at baseline but contact with PCR positive index patient	5/344 (1.5%)	39/337 (11.6%)	0.13 (0.05-0.31)
Patients < 12 years	3/71 (4.2%)	11/71 (15.5%)	0.27 (0.08-0.9)
Patients ≥ 12 years	4/303 (1.3%)	40/304 (13.2%)	0.1 (0.04-0.28)
Patients with high-risk factors	1/46 (2.2%)	8/52 (15.4%)	0.13 (0.02-0.94)
Lab confirmed influenza regardless of fever or symotoms	49 (13.1%)	114 (30.4%)	0.43 (0.32-0.58)
PCR confirmed illness	20 (5.3%)	84 (22.4%)	0.24 (0..15-0.38)

Ikematsu et al. *N Eng J Med*.2020;383:309-320

Baloxavir vs. Neuraminidase Inhibitors on House Transmissions

Retrospective study using Japanese claims database

1st family members with influenza in 2018-19 identified as index patient

Families classified into

- Oral baloxavir (BXM) vs. 3 controls
  - Oral oseltamivir (OTV) (Primary control)
  - Inhaled zanamivir (ZNV)
  - Inhaled laninamivir (LNV)

Household transmission defined as influenza diagnosis in family during days 3-8

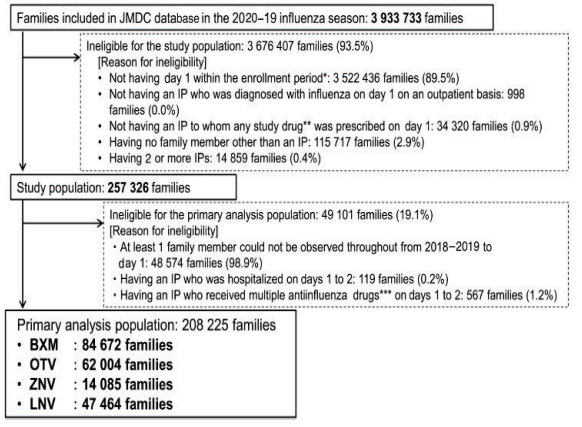


Figure 1. Flow of identification of families included in the study population and analysis population. *1 October 2018 to 23 April 2019. **BXM, OTV, ZNV, LNV. ***Anti-influenza drugs: BXM, OTV, ZNV, LNV, or peramivir hydrate. Abbreviations: BXM, baloxavir marboxil; IP, index patient; LNV, laninamivir octanoate hydrate; OTV, oseltamivir; ZNV, zanamivir hydrate.

Komeda T, et al. *Clin Infect Dis*.2021;72:e859-67

Baloxavir vs. Neuraminidase Inhibitors on House Transmissions

Lower transmission with Baloxavir vs. Oseltamivir (17.98% vs. 24.16%)

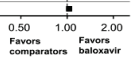
Higher odds of transmission in Baloxavir than Zanamivir, although the proportion of families with household transmission was lower in Baloxavir (17.95% vs. 18.41%)

Odds of transmission high if index patient was ≤ 12 years

Drug	N	Household transmission	%	Unadjusted OR*	Adjusted** OR (95%CI)
BXM	84 672	15 226	17.98	---	---
OTV	62 004	14 983	24.16	1.45	1.09 (1.05–1.12)
ZNV	14 085	2 593	18.41	1.03	0.93 (.89–.97)
LNV	47 464	8 272	17.43	0.96	0.99 (.96–1.02)

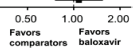
A Influenza A

Drug	N	Household transmission	%	Unadjusted OR*	Adjusted** OR (95%CI)
BXM	61 246	11 106	18.13	---	---
OTV	42 883	10 727	25.01	1.51	1.11 (1.07–1.15)
ZNV	9188	1717	18.69	1.04	0.92 (.87–.98)
LNV	33 353	6079	18.23	1.01	1.03 (.99–1.07)



B Influenza B

Drug	N	Household transmission	%	Unadjusted OR	Adjusted OR (95%CI)
BXM	818	89	10.88	---	---
OTV	570	74	12.98	1.22	1.06 (.71–1.56)
ZNV	193	26	13.47	1.28	1.15 (.70–1.89)
LNV	594	67	11.28	1.04	1.08 (.76–1.54)



Komeda T, et al. *Clin Infect Dis*.2021;72:e859-67

Questions