Antivirals Improve Outcomes in Influenza

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KEYWORDS

• Influenza • Antiviral • Neuraminidase • Oseltamivir • Zanamivir • Peramivir

KEY POINTS

- For healthy adults, antivirals offer approximately 1 day symptoms reduction and require shared decision-making due to potential side effects like nausea and vomiting.
- Antiviral therapy should be considered early in the course of high-risk ED patients especially prior to admission. Critically ill patients can benefit most from early antiviral initiatiion.
- Although use of neuraminidase inhibitors can lead to antiviral-resistant strains, there is no clinical decrease in the effectiveness against influenza in the community.

INTRODUCTION

Influenza remains one of the most common and clinically meaningful viral illnesses encountered in the emergency department (ED). In the United States, it recurs annually, generally rising in the fall, peaking between December and February, and tapering through spring. Although seasonal epidemics are expected each year, the intensity, age distribution, and circulating strains vary markedly by season—making influenza a perennial driver of outpatient visits, ED crowding, hospital strain, and excess mortality. Clinically, influenza is characterized by the abrupt onset of fever, myalgias, cough, and malaise, and can produce anything from a brief, self-limited febrile illness to fulminant respiratory failure and multiorgan dysfunction. Globally, there are around 1 billion cases of seasonal influenza annually, including an estimated 3 to 5 million cases of severe illness.[1]

The 2023 to 2024 season offers a recent snapshot of this burden. The US Centers for Disease Control and Prevention (CDC) estimated approximately 40 million influenza cases during the 2023 to 2024 season. Of these, approximately 18 million (45%) sought medical care, approximately 470,000 (1.2%) required hospitalization, and approximately 28,000 (0.07%) died.[2] Older adults were disproportionately

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Emerg Med Clin N Am 44 (2026) 495–505
https://doi.org/10.1016/j.emc.2026.01.005 **emed.theclinics.com**

Abbreviations	
ED	emergency department
CDC	Centers for Disease Control and Prevention
CI	confidence interval
FDA	Food and Drug Administration
HA	Hemagglutinin
ICU	intensive care unit
IV	Intravenous
NA	neuraminidase
NAIs	neuraminidase inhibitors
NNT	number needed to treat

affected, accounting for roughly half of hospitalizations and more than two-thirds of deaths, despite representing a minority of outpatient visits. Pediatric impact remained substantial as well, with 197 laboratory-confirmed influenza-associated deaths reported in children.[2]

Seasonal influenza, therefore, represents a massive and recurring public health problem. Prevention remains the cornerstone of control. CDC modeling for the 2023 to 2024 season estimated that vaccination prevented approximately 9.8 million illnesses, 4.8 million medical visits, 120,000 hospitalizations, and 7900 deaths[3] (**Fig. 1**).

Antiviral medications can reduce symptom duration and may reduce some complications if started early. In the United States, 4 Food and Drug Administration (FDA)-approved agents have activity against influenza A and B.

- Oseltamivir (oral),
- Zanamivir (inhaled),
- Peramivir (intravenous [IV]), and
- Baloxavir marboxil (single-dose oral; cap-dependent endonuclease inhibitor).

In the ED, clinicians must frequently make decisions about antiviral initiation before confirmatory diagnostic testing is available. These decisions often occur under significant operational pressure—including high patient volume, the need for rapid disposition, and limited availability of appropriate isolation spaces—which further underscores the importance of understanding which patients are most likely to benefit from treatment. Understanding who benefits, what the realistic effect size is, and what harms and trade-offs exist is essential for emergency physicians. This article reviews

Fig. 1. Oseltamivir (Tamiflu), oral NAI packaging (Adobe Stock #288160471).[4] (Genentech USA, Inc./Stuart Monk – stock.adobe.com.)

the virology and pharmacology relevant to antiviral therapy, summarizes the evidence for benefit and harm, addresses timing and special populations, and offers an approach to shared decision-making in the ED.

VIRUS AND ANTIVIRALS: CORE CONCEPTS

The influenza virus surface displays 2 major glycoproteins: hemagglutinin (HA) and neuraminidase (NA). HA binds to sialic acid residues on respiratory epithelial cells, mediating viral entry. NA then cleaves sialic acid to facilitate the release and spread of newly formed virions from infected cells.[5] These antigens define strain subtypes (eg, H1N1 and H3N2). HA undergoes frequent mutation, driving antigenic drift and immune escape, whereas the active site of the NA enzyme is comparatively conserved, making NA an attractive antiviral target[5,6] (**Fig. 2**).

After entry, viral uncoating is driven by the M2 ion channel, which acidifies the virion interior and allows release of viral RNA.[8] Because M2 is a membrane channel, it was historically targetable from outside the cell. Once in the host cell nucleus, influenza hijacks host transcriptional machinery via a "cap-snatching" mechanism to initiate viral mRNA synthesis—another exploitable target for antiviral development.[9] In clinical practice, the 3 major antiviral classes historically relevant to influenza are

1. *M2 ion channel inhibitors (adamantanes)*—amantadine and rimantadine, active only against influenza A;
2. *Neuraminidase inhibitors (NAIs)*—oseltamivir, zanamivir, peramivir, active against influenza A and B; and
3. *Polymerase acidic endonuclease inhibitors*—baloxavir, which targets viral RNA transcription.

Adamantanes were the first widely used influenza antivirals. Amantadine (FDA-approved 1966) and rimantadine (1993) block the influenza A M2 proton channel, preventing uncoating and halting replication early in the viral life cycle.[10–13] These drugs

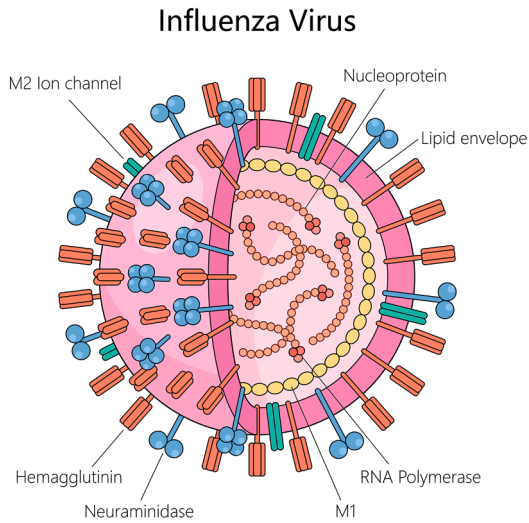

Fig. 2. Influenza virion schematic highlighting the hemagglutinin (HA) and neuraminidase (NA) surface glycoproteins (Adobe Stock #834865757).[7] (Oleksandr Pokusai – stock.adobe.com.)

have little or no activity against influenza B because the influenza B M2 analog differs structurally.[8] Unfortunately, M2-target mutations conferring adamantane resistance spread globally: resistance among circulating influenza A (H3N2) strains escalated dramatically in the 1990s and 2000s.[14] As a result, adamantanes are no longer recommended for routine influenza treatment. The CDC explicitly recommends against their use because of widespread resistance.[15]

By contrast, NA inhibitors act later in replication by blocking NA, thereby limiting virion release from infected cells and reducing spread along the respiratory epithelium.[16,17] Oseltamivir and zanamivir were the first NAIs in common use, followed by peramivir. Zanamivir (approved 1999) is delivered by inhalation; when started within 48 hours of symptom onset, it has been associated with shorter symptom duration, quicker return to normal activity, and less antibiotic use for presumed secondary complications.[10,18] However, its inhaled route limits use in patients with reactive airway disease because of risk of bronchospasm, and it is technically more cumbersome than taking pills. Oseltamivir (Tamiflu) is oral (capsule or liquid) and therefore avoids bronchospasm concerns; started within 48 hours, it has been associated with decreased symptom duration and intensity and lower rates of influenza-associated complications such as pneumonia.[19–21] Peramivir (Rapivab) is an IV NAI that can be given as a single dose.[2]

Baloxavir marboxil represents a newer class: a cap-dependent endonuclease inhibitor that interferes with viral RNA transcription. Approved in 2018, baloxavir is active against both influenza A and B and has demonstrated reduced viral shedding compared with oseltamivir in both otherwise-healthy and high-risk adults.[10,22]

ROUTES OF ADMINISTRATION AND PRACTICAL EQUIVALENCE

Multiple NAIs are now available in different formulations (oral, inhaled, and IV). A randomized controlled trial conducted in ED patients at high risk for influenza complications compared a standard 5 day oral oseltamivir course (first dose given in the ED, remaining doses taken at home) with a one-time IV dose of peramivir administered during the ED visit.[23] Patients in both arms had similar illness trajectories, including comparable symptom duration and recovery metrics. The authors concluded that IV peramivir and oral oseltamivir were clinically noninferior in this population.[23]

This has practical implications. If the clinician is concerned that a patient will not complete a multiday outpatient course—because of unreliable follow-up, limited access to medications, cognitive barriers, housing insecurity, and so forth—a single-dose IV antiviral given under supervision before discharge may be preferable. Conversely, in a clinically stable patient who does not otherwise need IV access and is comfortable taking oral medication at home, oral oseltamivir is reasonable. In short, when efficacy is essentially equivalent, the decision between IV and oral NA inhibition should be individualized around adherence, ED throughput, and resource use.[23]

MYTHS AND MISCONCEPTIONS

Influenza is an acute viral infection of the respiratory tract, typically presenting with sudden fever, cough, myalgias, and fatigue. Most otherwise healthy individuals experience an uncomplicated, self-limited illness that resolves over several days to a week or 2 without specific antiviral therapy. For these low-risk outpatients, supportive care—hydration, antipyretics/analgesics, and self-isolation to prevent transmission—is appropriate.[1]

In contrast, prompt antiviral therapy is recommended for

- Patients who are hospitalized,
- Patients with severe or progressive disease, and
- Patients at an increased risk for complications (eg, pregnant or recently postpartum individuals, adults aged ≥65 years, those with chronic cardiopulmonary disease, and immunocompromised patients).[24,25]

Antivirals work best if started within 48 hours of symptom onset. Early initiation can shorten symptom duration by roughly 1 day and may reduce certain lower respiratory complications.[24,26] Importantly, even within that early window, high-risk patients are on a steeper trajectory toward serious outcomes such as bronchitis, primary viral pneumonia, and secondary bacterial pneumonia.[24] The threshold to treat this group is therefore low.

That said, much of the randomized trial evidence for antivirals comes from relatively healthy outpatients with self-limited disease.[26] Watchful waiting—allowing the illness to run its course while managing symptoms and giving clear return precautions—is an appropriate strategy in young, otherwise healthy, low-risk individuals.[25]

Recent high-quality evidence reinforces this selective-use approach. A 2025 network meta-analysis of 73 randomized trials (34,332 patients) compared multiple antivirals for nonsevere influenza and found that, overall, antivirals had little or no effect on mortality for either low-risk or high-risk patients, and generally did not reduce hospital admission in low-risk patients.[27] Even in high-risk patients, oseltamivir showed little to no effect on admission risk (risk difference 0.4%; 95% confidence interval [CI] 1.0 to −0.4; high-certainty evidence), while baloxavir may have reduced admission risk (risk difference 1.6%; 95% CI 2.0 to −0.4), although that signal was based on low-certainty evidence.[27] These findings align with evolving World Health Organization guidance, which recommends against routine antivirals for nonsevere influenza in most patients, with a conditional exception for baloxavir in patients at high risk of progression.[28]

Observational analyses from the 2009 H1N1 pandemic suggest that NA inhibitor treatment is associated with reduced mortality in hospitalized adults, particularly when started early, which supports aggressive use in severe cases even when presentation is delayed.[29] Age is also a key modifier of risk: during the 2009 H1N1 outbreak in Hong Kong, infection fatality was less than 1 per 100,000 infections in children but approximately 1 per 1000 infections in adults aged 50 to 59 years, underscoring the sharp increase in severity with advancing age.[30]

TIMING OF ANTIVIRAL ADMINISTRATION

Timing matters. In hospitalized adults with influenza, receiving oseltamivir within 48 hours of symptom onset has been associated with a shorter length of stay, although not a statistically significant difference in 90 day mortality compared with later initiation.[31] Current CDC guidance recommends antiviral therapy for hospitalized patients, patients with severe/progressive illness, and high-risk patients, even if they present greater than 48 hours after symptom onset, to mitigate complications.[15]

Delayed administration is not benign. A multicenter CDC-supported analysis of adults hospitalized with influenza-associated pneumonia (FluSurv-NET, 2012–2019) found that starting antiviral therapy more than 48 hours after hospital admission was associated with approximately 40% increase in 30 day mortality compared with starting on hospital day 0. Each additional day of delay increased the likelihood of intensive care unit (ICU) admission, need for invasive mechanical ventilation, and

death.[32] These data reinforce a "treat now" mentality for critically ill and high-risk inpatients.

THE ORIGINS AND PERSISTENCE OF THE "ANTIVIRAL FOR EVERYONE" MYTH

NAIs (especially oseltamivir) were widely adopted in guidelines and practice with the expectation that they would substantially change outcomes. However, much of that enthusiasm was built on early trials and expert opinion rather than consistent, contemporary evidence across all patient groups.

The original proantiviral narrative came from studies in mostly healthy outpatients showing modest reductions—often about 1 day—in overall symptom duration when therapy began within 48 hours. This relatively small symptomatic benefit for low-risk patients was generalized into a broader "antivirals help everyone" mindset, which then migrated into ED practice.[26]

Two forces helped entrench this

1. *Extrapolation bias*—Data from ambulatory or general medicine populations were assumed to apply equally to acutely ill ED patients or critically ill inpatients.[26]
2. *Action bias*—Patients or providers may prefer to "do something," especially in a febrile patient with dyspnea during peak flu season, even if the absolute benefit for that particular patient is uncertain.

ADVERSE EFFECTS

NAIs can provide benefit, but they are not benign. Every antiviral carries the potential for adverse effects, drug–drug interactions, and downstream consequences that may outweigh modest symptomatic gains in low-risk patients. The conversation with the patient should, therefore, include not only potential benefit but also potential harm.

A systematic safety review of NAIs compiled adverse event data for oseltamivir and zanamivir.[33] In adults treated with oseltamivir, increased reports of nausea, vomiting, bronchitis, insomnia, and vertigo were observed compared with placebo in manufacturer data. During prophylaxis, oseltamivir was also associated with gastrointestinal complaints (nausea, vomiting, diarrhea, and abdominal pain), neurologic symptoms (dizziness, headache, insomnia, and vertigo), and fatigue.[33] Higher oseltamivir doses (150–300 mg/d vs the standard 75 mg twice daily) correlated with a higher incidence of nausea.[33]

Zanamivir showed a generally cleaner systemic side-effect profile: rates of nausea, diarrhea, and sinusitis were similar to placebo in both treatment and prophylaxis trials.[33] However, zanamivir carries a known risk of bronchospasm in patients with reactive airway disease.[18] This practical limitation—together with inhaler technique requirements—has contributed to its decreased use compared with oral oseltamivir.

Across multiple outpatient studies, NAI shortens the duration of influenza symptoms by roughly 1 day, on average, versus no antiviral therapy. There is no universally reliable number needed to treat (NNT) for "global clinical improvement," because the effect size varies with age, baseline health status, timing of initiation, circulating strain, and how "symptom resolution" is defined.[34]

Looking at complications rather than symptom relief, the absolute benefit appears even smaller. Pooled analyses suggest that in adults, the NNT with oseltamivir to prevent one additional self-reported case of pneumonia is on the order of 100.[34] During prophylaxis (ie, postexposure prevention in adults), the estimated NNT with zanamivir to prevent one self-reported pneumonia case is approximately 311.[34] These are extremely high NNTs, implying a very small absolute benefit at the individual patient level.

On the harm side, the signal is stronger. The number needed to harm for oseltamivir in adults is approximately 28 for nausea and 22 for vomiting.[34] Put differently: for every 22 adults treated, one will experience drug-related vomiting who would not have vomited otherwise. For every 28 treated, 1 will develop drug-related nausea.[34] For a generally healthy outpatient who is likely to recover fully without antivirals, those trade-offs are not trivial.

This balance of modest benefit and nontrivial harm is consistent with comparative safety findings. In the same 2025 synthesis, oseltamivir was associated with an increased rate of treatment-related adverse events (risk difference 1.23%; 95% CI 1.10–1.39; moderate-certainty evidence), including gastrointestinal and neurologic complaints.[27] By contrast, baloxavir was associated with few or no excess adverse events (risk difference 3.2%; 95% CI 5.2 to −0.6; high-certainty evidence) and likely shortened symptom duration by about 1 day (mean difference ∼1.0 day faster vs standard care; moderate-certainty evidence).[27] Taken together with earlier study, this suggests that while oseltamivir is widely used and familiar, its benefit in uncomplicated outpatient influenza is modest and its side-effect signal is real, whereas baloxavir may offer similar (or slightly greater) symptom reduction with fewer adverse effects but also raises ongoing concerns about resistance emergence.[27,35]

Taken together, NAIs can modestly shorten illness, but they have not been shown to meaningfully reduce hospitalization in otherwise healthy, low-risk adults with uncomplicated influenza, and they do carry gastrointestinal and other adverse effects. The prescribing decision in the ED for low-risk outpatients should, therefore, be framed as preference-sensitive: a roughly 1 day faster recovery versus a nonnegligible chance of nausea/vomiting and the cost/inconvenience of the medication.[33,34]

DRUG–DRUG INTERACTIONS

A common bedside question is whether antivirals interact with medications patients are already taking (eg, acetaminophen, nonsteroidal anti-inflammatory drugs, antibiotics, and anticoagulants). Oseltamivir has been studied with common antipyretics, amoxicillin, and warfarin, with no clinically meaningful changes in pharmacokinetics.[36] No significant interactions were seen with calcineurin inhibitors such as cyclosporine or tacrolimus.[36] Overall, NAIs have a relatively favorable drug–drug interaction profile. Clinicians should still use judgment in patients with significant renal or hepatic dysfunction, given the need for dose adjustment.

ANTIVIRAL RESISTANCE

Widespread antiviral use naturally raises concerns about resistance. We have already seen this story with the adamantanes (amantadine and rimantadine): initially highly effective against influenza A via M2 ion channel blockade, they became essentially obsolete as resistance skyrocketed globally after 2000.[10–14,37] The CDC now advises against their use.[15]

Resistance to NAI is more nuanced. Oseltamivir resistance in influenza A was rare (<5%) in clinical trials before 2007, but by 2008 to 2009, some countries reported greater than 90% prevalence of oseltamivir-resistant seasonal H1N1 strains.[37] Crucially, resistant strains were documented even in patients with no prior oseltamivir exposure, confirming person-to-person transmission of resistant virus.[37] A well-described mechanism is the H275Y mutation in the NA of influenza A (H1N1), which substitutes tyrosine for histidine and impairs oseltamivir binding. Peramivir, which binds similarly to the NA active site, can also be affected. Zanamivir binding is less impacted by H275Y and often remains active.[37]

Pediatric patients, particularly those aged under 5 years, appear more prone to developing resistance during therapy—possibly because immunologically naïve children sustain higher viral loads for longer, giving more opportunity for resistant variants to emerge.[37,38] Nevertheless, even when resistance is detected, available data do not clearly show worse clinical outcomes compared with susceptible virus.[38]

Importantly, global surveillance from 2020 to 2023 indicates that less than 1% of circulating influenza viruses displayed resistance to NAIs or to baloxavir.[39,40] In other words, while vigilance is necessary, current first-line antivirals remain largely active against circulating strains.

SUMMARY

For ED clinicians, the key is not simply "give antivirals or withhold antivirals," but "who benefits, how much, and at what cost."

In otherwise healthy adults with uncomplicated influenza presenting within 48 hours, antiviral therapy is expected to reduce symptom duration by approximately 1 day. The absolute reduction in serious complications remains minor, and the probability of developing nausea or vomiting is a relevant consideration. Therefore, prescribing antivirals in this cohort necessitates a shared decision-making conversation rather than an automatic prescription.

Conversely, in high-risk patients—including those aged 65 years or older, pregnant or recently postpartum individuals, immunocompromised patients, or those with serious chronic comorbidities—and in any patient presenting with severe or progressive illness, the immediate initiation of early antiviral therapy is warranted, ideally commencing in the ED. This initiation should proceed without waiting for confirmatory testing if the pretest probability of influenza is high. The initial dose should be administered in the ED, with appropriate adjustment of oseltamivir dosage for renal function. Furthermore, enteral or nasogastric dosing is indicated for intubated patients when necessary.

Hospitalized and critically ill patients derive the greatest benefit from the prompt commencement of antiviral treatment. Delays, even as short as 1 or 2 days, in patients with influenza-associated pneumonia correlate with elevated mortality rates, increased ICU admissions, and a greater need for mechanical ventilation. Consequently, the ED represents the critical window of opportunity for intervention.

Peramivir (IV) and oseltamivir (oral) demonstrate clinically comparable efficacy in high-risk ED patients. The selection between these agents should be based on factors such as anticipated adherence, the requirement for IV access, and considerations of ED throughput.

Baloxavir is a single-dose oral antiviral exhibiting potent virologic suppression. Pooled trial data indicate that it offers an approximate 1 day reduction in symptom duration compared with standard care in nonsevere influenza. Baloxavir may also reduce the risk of hospital admission in high-risk patients, although this signal is supported by low-certainty evidence and did not achieve statistical robustness. Adverse events associated with baloxavir appear infrequent relative to oseltamivir. However, documentation of treatment-emergent resistance to baloxavir exists, rendering its broad, indiscriminate use in the ED controversial, particularly for patients requiring hospitalization.

Antibiotic stewardship remains a paramount concern. In confirmed, uncomplicated influenza without evidence of bacterial coinfection, the routine administration of antibiotics is unnecessary. In such cases, explicit return precautions must be provided,

detailing signs such as worsening dyspnea, persistent fever extending beyond the expected course, or indications of dehydration.

Bottom Line

Early recognition of high-risk patients and timely antiviral initiation can reduce morbidity and may reduce mortality in the sickest patients. (24,26,30,37) For everyone else, antivirals are a preference-sensitive therapy with modest symptomatic benefit and nontrivial side effects.

CLINICS CARE POINTS

- In healthy adults, the absolute reduction in serious complications when given antivral therapy is minor compared to the non trivial side effects so it should be a preference-sensitive therapy.
- In confirmed uncomplicated influenza, routine antibiotic therapy is not warranted unless there is evidence of bacterial co-infection.
- Early ED initiation of antiviral therapy in ctitically ill or hospitalized patients can be benefitial if the pretest probability of influenza is high even prior to confirmatory testing.

DISCLOSURE

The authors have no conflicts to disclose.

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