Consensus

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Chinese expert consensus on the combined use of antiviral drugs for influenza

Jing Yuan[1,§], Haimei Zhang[1,§], Rongrong Zou[1,§], Weizhen Weng[1], Honglian Bai[2], Jun Chen[3], Yutian Chong[4], Xilong Deng[5], Liang Fu[1], Yingyun Fu[6], Wenjun Gao[7], Zuojiong Gong[8], Chenghui Huang[9], He Huang[10], Jia Huang[1], Jianning Jiang[11], Rongmeng Jiang[12], Yongfang Jiang[13], Linghua Li[5], Bingliang Lin[4], Xi Liu[14], Feng Lin[15], Jie Peng[16], Qingsong Qi[17], Bo Qin[18], Zhijun Qu[19], Fei Shi[6], Gang Wu[20], Tao Wu[21], Hui Wang[22], Lingwei Wang[7], Yan Wang[23], Fei Xiao[14], Feng Xu[24], Juan Xu[17], Kaijin Xu[25], Haipeng Zhu[17], Guanlin Zhou[26], Guangbin Chen[1,*], Hongzhou Lu[1,*]; National Medical Research Center for Infectious Diseases

[1] The Third People's Hospital of Shenzhen, Shenzhen, Guangdong, China;
[2] Foshan First People's Hospital, Foshan Hospital Affiliated to Southern University of Science and Technology, Foshan, Guangdong, China;
[3] Shanghai Public Health Clinical Center, Fudan University, China;
[4] The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, China;
[5] Guangzhou Eighth People's Hospital, Guangzhou Medical University, Guangzhou, China;
[6] Shenzhen People's Hospital, Shenzhen, Guangdong, China;
[7] Zhongshan Second People's Hospital, Zhongshan, Guangdong, China;
[8] Renmin Hospital of Wuhan University, Wuhan, Hubei, China;
[9] Shenzhen Bao'an People's Hospital, Shenzhen, Guangdong, China;
[10] Shenzhen Second People's Hospital, Shenzhen, Guangdong, China;
[11] The First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi, China;
[12] Beijing Ditan Hospital, Capital Medical University, Beijing, China;
[13] The Second Xiangya Hospital of Central South University, Changsha, Hunan, China;
[14] The Fifth Affiliated Hospital, Sun Yat-sen University, Zhuhai, Guangdong, China;
[15] Hainan General Hospital, Haikou, Hainan, China;
[16] Nanfang hospital, Southern Medical University, Guangzhou, Guangdong, China;
[17] The Ninth People's Hospital of Dongguan, Dongguan, Guangdong, China;
[18] The First Affiliated Hospital of Chongqing Medical University, Chongqing, China;
[19] Longgang Central Hospital of Shenzhen, Shenzhen, Guangdong, China;
[20] The Affiliated Hospital of Southwest Medical University, Luzhou, Sichuan, China;
[21] Hainan Public Health Clinical Center, Haikou, Hainan, China;
[22] Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China;
[23] Peking University First Hospital, Beijing, China;
[24] The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China;
[25] The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China;
[26] The Fifth People's Hospital of Ganzhou, Ganzhou, Jiangxi, China.

SUMMARY: Influenza is an acute respiratory infectious disease caused by influenza viruses, and it poses a serious threat to global public health. High-risk groups include the elderly, infants and young children, pregnant women, and patients with chronic underlying diseases. These groups are prone to developing severe illness after infection, which can lead to serious complications and even death. Early antiviral treatment is key to reducing the rate of severe illness and death. Currently, authoritative guidelines at home and abroad recommend early, single-agent antiviral therapy as the standard regimen. However, anti-influenza virus monotherapy has problems such as drug resistance and poor therapeutic effect. To address these problems, this consensus was developed by organizing experts from the departments of Infectious Diseases, Respiratory Medicine, Critical Care Medicine, and Pharmacy. These experts systematically sorted out domestic and international evidence on combined antiviral therapy for influenza and formulated expert recommendations on combined antiviral therapy for influenza in specific populations.

Keywords: influenza viruses, influenza antiviral therapy, resistance, combined therapy

1. Introduction

Influenza viruses cause seasonal influenza and influenza pandemics, posing a serious threat to human health and public health. According to the 2017 Global Burden of Disease Study (GBD 2017), up to 145,000 people worldwide die each year due to influenza-associated lower respiratory tract infection (LRTI) (*1*). A study showed that during the period 2010–2015, there were an average of 88,100 influenza-related respiratory disease deaths per year in mainland China, equivalent to 8.2% of all respiratory disease deaths (*2*). Dr Tedros Adhanom Ghebreyesus, Director-General of the World Health Organization(WHO), has warned that the threat of a pandemic flu remains a constant concern. Risk of new influenza viruses crossing from animals to humans and causing a real pandemic is ongoing. We must remain vigilant and be well-prepared (*3*).

Antiviral drugs play a crucial role in controlling influenza outbreaks and epidemics. Up to now, the primary antiviral medications approved for treating influenza virus infections include three classes: transmembrane protein M2 ion channel inhibitors, neuraminidase inhibitors (NAIs), and RNA-dependent RNA polymerase (RdRp) inhibitors (*4*). Recently, new anti-influenza virus drugs such as ZSP1273 have been launched. Meanwhile, more anti-influenza virus drugs with new targets and completely new mechanisms of action are under development. However, the types of currently available antiviral drugs for influenza remain relatively limited. Moreover, influenza viruses are highly prone to mutations, and the number of drug-resistant virus strains is constantly increasing. Drug resistance caused by viral mutations and drug abuse remains a serious issue, and monotherapy for influenza viruses is facing the challenge of drug resistance. For instance, the detection rate of neuraminidase inhibitor-resistant strains is on the rise among immunocompromised patients. Typical cases include the H275Y mutation in Influenza A virus (IAV) subtype H1N1 and the I221T/V mutation in Influenza B virus (IBV). In addition, the polymerase inhibitor baloxavir can induce the PA/I38T mutation. Furthermore, antiviral treatment of severe influenza still faces many challenges and uncertainties at present. According to relevant data, the diagnosis time of patients with severe influenza in China is relatively late, which may lead to delays in treatment timing. As a result, most patients miss the optimal time window for antiviral treatment (*5*). Patients with severe influenza may experience prolonged replication and shedding of the virus in the upper and lower respiratory tracts. The virus excretion time of severe patients is prolonged, and the duration of antiviral treatment may need to be extended (*6,7*).

Combination drug therapy has emerged as a key strategy to address drug resistance and enhance therapeutic efficacy in severe influenza cases. By leveraging synergistic effects to inhibit viral replication through multiple targets, this approach offers distinct clinical advantages (*8*). Specifically, combination drug therapy can reduce emergence of drug-resistant viral strains and mitigate treatment-related adverse effects, which may in turn lower incidence of severe influenza and improve the success rate of treating severe cases. Han J *et al* (*9*) pointed out a critical issue: currently circulating IAV strains (such as H1N1 and H3N2) have developed resistance to neuraminidase inhibitors. What is worse, they are almost completely resistant to M2 ion channel inhibitors. This growing resistance problem is further exacerbated by the use of subtherapeutic doses in both clinical treatment and chemoprophylaxis. Novel therapies targeting host components and new strategies for combination therapy show potential for maximizing the reduction of viral resistance.

Currently, anti-influenza virus therapy recommended in national and international expert consensus statements and clinical practice guidelines is typically based on monotherapy. However, in specific clinical scenarios (such as severe infections, patients at risk of drug resistance, or patients with immunosuppression), combination therapy strategies should be considered. This approach is also expected to become one of the future development trends in influenza treatment. By using drugs that act on different targets, we can not only reduce the development of viral drug resistance and minimize adverse reactions caused by the dosage of a single drug but also formulate individualized treatment plans based on the severity of the patient's condition. Especially for patients with severe influenza, special attention should be paid to host immune regulation therapy (*10*).Therefore, the combination regimens proposed in this consensus are expert recommendations. They apply to populations that are critically ill, immunosuppressed, or suspected of having drug resistance.

These recommendations are intended to inform clinical decision-making, and they are not routine first-line recommendations. Any off-guideline medication must undergo individualized risk-benefit assessment and be fully communicated with the patient or their family.

2. Methods

To ensure this consensus has a solid evidence-based foundation, we conducted systematic searches in multiple well-known medical databases (including PubMed and Web of Science) by September 25, 2025, using the search formula "Combination Therapy" AND "Influenza Virus". We aimed to collect key studies in all relevant fields through comprehensive literature searches, to ensure this consensus was developed based on the best available evidence. The evidence-based medicine (EBM) evidence of this expert consensus adopts the 2011 Oxford Centre for Evidence-Based Medicine (OCEBM) Levels of Evidence and Grades of Recommendations (*11*) (Table 1).

Table 1. Level of evidence

Recommendation Strength	Evidence Level	Description
A	1a	System review of randomized controlled trials (RCTs))
	1b	RCTs with small confidence intervals for results
	1c	Any evidence showing an "all or nothing effect"
B	2a	Systematic evaluation of cohort studies
	2b	Individual cohort studies (including low-quality RCTs, *e.g.*, those with >20% loss-to-follow-up rates)
	2c	Studies based on patient outcomes
	3a	Systematic evaluation of case-control studies
	3b	Single case-control study
C	4	Case series reports, low-quality cohort studies and low-quality case-control studies
D	5	Expert opinion (*i.e.*, speculation based solely on basic research or clinical experience that is not supported by clinical studies)

3. Current primary antiviral drugs for influenza

3.1. Life cycle of influenza viruses and targets and mechanisms of antiviral drug action

The replication process of influenza virus comprises six core steps, including viral entry, viral uncoating, viral genome replication and transcription, viral protein translation, viral assembly, and viral budding (*12*). This series of highly ordered steps provides clear targets for antiviral drug development. First, during the viral invasion stage, hemagglutinin (HA) inhibitors block fusion of the virus with the host cell membrane to prevent infection. After virus entry, during the uncoating stage, M2 ion channel inhibitors and HA inhibitors suppress acidification inside the virus to prevent the release of the virus's genetic material. Subsequently, in the core process of viral genome replication and transcription in the cell nucleus, RdRp inhibitors can directly inhibit the replication of viral genetic information. RdRp inhibitors include three categories: RNA polymerase acidic protein inhibitors (PA), RNA polymerase basic protein 1 inhibitors (PB1), and RNA polymerase basic protein 2 inhibitors (PB2). When newly formed vRNPs need to be transported from the nucleus to the cytoplasm for assembly, vRNP export inhibitors can interrupt this process. During the viral assembly stage, NAIs, M2 ion channel inhibitors, and HA maturation inhibitors interfere with the correct processing of viral proteins. Finally, when progeny virus particles bud on the cell surface, NAIs prevent the virus from detaching from the host cell surface (Figure 1).

3.2. Anti-influenza virus treatment drugs

The current major anti-influenza virus therapies are listed in Table 2.

4. The necessity of combination antiviral therapy

4.1. Antiviral drug resistance in influenza viruses

Influenza virus is a pathogen with rapid mutation ability, and its genome can evolve through multiple mechanisms such as point mutations (such as variations in PB2, PA, and NA genes), segmental recombination and genomic recombination. At present, multiple key drug resistance sites have been identified: the S31N mutation of the M2 protein confers resistance to amantadine drugs; the H274Y and R292K mutations in the NA gene significantly reduce sensitivity to neuraminidase inhibitors (*e.g.*, oseltamivir); and the I38T mutation in the PA protein significantly diminishes the antiviral activity of baloxavir. In addition, novel mutations such as the K229R mutation in the PB1 gene and the P653L mutation in the PA gene also indicate a potential risk of resistance to favipiravir (*13*).

Between 2018 and 2020, the resistance rate of Influenza A (H1N1)pdm09 strains to NAIs reached 1.3% worldwide. Meanwhile, IBV also exhibited a resistance rate of approximately 1% (*14*). Children, patients receiving prophylactic drug treatment, and individuals with impaired immune function (such as hematopoietic stem cell transplant recipients or immunocompromised patients) have become high-risk groups for NAI resistance (*15-17*). More notably, among the more than 30 newly identified drug-resistant mutations from 2016 to 2024, approximately 80% are distributed in IBV.These mutations can lead to a drastic reduction in drug sensitivity: a single mutation can reduce the inhibitory effect by 10 to 1,000 times, while multi-site synergistic mutations (such as the combination of H274Y and I222R) can even increase drug resistance by more than 10,000 times. In addition, some mutation combinations can also cause cross-resistance or multidrug resistance phenotypes. Particularly, after some drug-resistant strains acquire compensatory mutations (such as the H274Y variant accompanied by D354G), their replication fitness and transmission ability are restored.

Drug resistance of influenza viruses to antiviral agents has become a major challenge in clinical practice. Faced with the constantly evolving drug resistance of influenza viruses, there is an urgent need to optimize

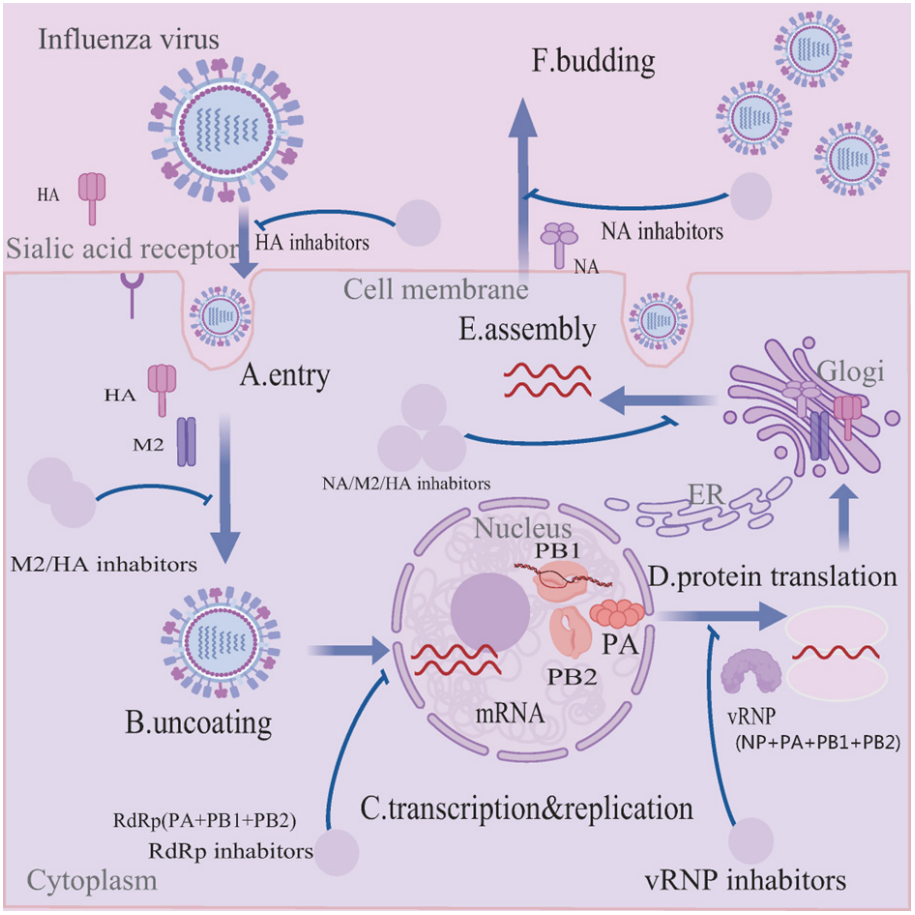

Figure 1. Replication cycle of influenza virus and crucial steps targeted by virus-directed antiviral compounds. Replication cycle of influenza virus encompassing six core steps (viral entry, uncoating, replication and transcription, protein translation, assembly, and budding) and the key stages targeted by virus-directed antiviral compounds. Approved drugs for influenza treatment are indicated in bold. (Figure created with MedPeer)

Table 2. The main anti-influenza virus treatment drugs

Category	Mechanism	Representative drugs
M2 ion channel inhibitors	Inhibits M2 ion channel function and interferes with viral capsidization.	Amantadine, Rimantadine
Neuraminidase inhibitors	Inhibits neuraminidase activity and blocks virus budding	Oseltamivir, Zanamivir, Peramivir, Laninamivir
RNA polymerase acid protein inhibitors	Inhibits viral RNA polymerase activity and prevents viral synthesis	Baloxavir marboxil, Baloxavir, Suraxavir Marboxil
RNA polymerase basic protein 1 inhibitors	Targeting the catalytic function of PB1 to block RNA chain synthesis	Favipiravir, Ribavirin
RNA polymerase basic protein 2 inhibitors	Targeting the cap-binding domain of PB2 and blocking the transcription of viral mRNAs	ZSP1273, Pimodivir
Hemagglutinin inhibitors	Prevents viral release by selectively inhibiting steps such as HA maturation, intracellular trafficking, and embedding in the host cell membrane	Arbidol, Monoclonal antibodies (CR6261, VIS410,MHAA4549A,MEDI8852,CT-P27)

existing influenza antiviral treatment strategies, explore combined treatment regimens, and develop drugs targeting novel targets.These measures will help effectively address the challenges posed by influenza virus drug resistance.

Recommendation 1: Influenza viruses are prone to developing drug-resistant strains. Monotherapy is likely to induce the selection of drug-resistant strains. Particular attention should be paid to influenza virus resistance in patients with severe influenza, children, and immunocompromised patients (Evidence Level:4, Recommendation Strength: C).

4.2. The influence of drug resistance

4.2.1. Enhancement of virus spread ability

Some drug-resistant mutations of influenza virus may enhance the virus's transmission capacity. This enables the virus to spread rapidly in populations, especially among immunosuppressed patients. Seibert CW *et al.* (*18*) conducted a study using a guinea pig transmission model. They found that influenza viruses carrying S247N and H275Y mutations had high resistance to oseltamivir. These viruses also showed enhanced effective transmission ability. Hickerson *et al.* (*19*) noted that influenza viruses may develop drug-resistant mutations against baloxavir. These mutations include I38L and I38T. Additionally, IAV has emerged with the E199D mutation, and IBV has emerged with the I38T mutation. These initial mutations slightly impaired the virus's replication capacity. However, during continuous viral passage, IAV acquired the compensatory mutation D394N, while IBV evolved the E329G mutation. These subsequent mutations can enhance replication capacity of drug-resistant viruses. They also promote fixation of antiviral resistance in viral populations. Moreover, they facilitate further spread of such resistance. This poses a potential public health threat.

4.2.2. Increased risk of drug resistance gene spread

Influenza viruses (*e.g.*, avian Influenza H5N1) may infect humans *via* cross-species transmission if they accumulate drug-resistant mutations in animal hosts. From 2003 to 2024, the WHO recorded 954 confirmed cases of human infection with highly pathogenic avian Influenza A(H5N1) virus across 24 countries. These cases resulted in 464 deaths, corresponding to a mortality rate of 48.64% (*20*). The highly pathogenic avian Influenza A(H5N1) virus of the 2.3.4.4b evolutionary branch was isolated from severe human cases in Chile. This virus showed high-titer replication ability in the respiratory and extrapulmonary tissues of ferrets (*21*). After the emergence of the self-evolved 2.3.4.4b branch, the highly pathogenic avian Influenza A(H5N1) virus has become a new recombinant virus with stronger cross-species transmission ability, capable of spreading widely among multiple mammalian species, including dairy cows, cats, and raccoons (*22*). The H5N1 virus of the 2.3.4.4b evolutionary branch has developed a new mutation through reassortment events. It possesses dual-receptor binding ability, enabling it to bind to both avian and human receptors. Through molecular adaptation, the H5N1 virus has enhanced its cross-species spread ability. This has led to its transmission in cattle, humans, and other mammals. It is recommended to adopt a multi-target antiviral regimen to reduce the risk of drug resistance (*23*).

4.2.3. Increased risk of clinical treatment failure and death

With development of drug resistance in influenza viruses, amantane drugs (such as amantadine and rimantadine) have become ineffective against most prevalent strains. Neuraminidase inhibitors (such as oseltamivir and zanamivir) were once the main treatment options. However, under drug selection pressure, influenza strains have also developed resistance to these drugs. Influenza drug-resistant strains can reduce the efficacy of monotherapy for influenza and may even lead to the failure of treatment (*24*).

4.2.4. Increased burden of public health

Patients infected with drug-resistant strains require longer hospital stays and more intensive supportive care (such as mechanical ventilation and Extracorporeal Membrane Oxygenation (ECMO)), which increases the pressure on the healthcare system. Patients with drug-resistant infections need to use high-cost alternative drugs (such as new polymerase inhibitors or combination therapies). The per capita treatment cost can increase by 5 to 10 times, leading to a squeeze of medical resources. Drug resistance reduces the effectiveness of antiviral drugs such as neuraminidase inhibitors; Large-scale drug reserves prepared in the early stage may fail to play their expected role, resulting in the waste of drug reserves.

Recommendation 2: Drug resistance of influenza viruses may lead to increased viral transmission ability and a high risk of drug-resistant gene spread (Level of evidence: 4); it may also result in the failure of clinical antiviral treatment, elevate the mortality rate among patients with severe influenza, and increase the burden on public health (Evidence Level: 4, Recommendation Strength: C).

4.3. The theoretical basis of combined antiviral therapy

Influenza virus has high genetic variability, making it prone to resistance to single drugs. To prevent this, strategies of combination therapy or drug enhancement are optional (*25*). Antiviral combination therapy acts on different viral replication links and exerts synergistic effects, reducing single-drug pressure to boost efficacy and lower resistance risk. The WHO's 2024 guidelines (*26*) do not recommend routine combination therapy; single drugs (*e.g.*, oseltamivir, baloxavir marboxil) remain preferred. However, for severe influenza patients (*e.g.*, requiring mechanical ventilation/ECMO) or immunodeficient patients (*e.g.*, post-hematopoietic stem cell transplantation), if viral load does not drop significantly 48 hours after monotherapy, combination therapy (*e.g.*, oseltamivir + baloxavir marboxil) may be considered, subject to individual evaluation. According to *the Diagnosis and Treatment Protocol for Influenza*

(2020 Edition) (*27*) and *(2025 Edition)* (*28*), severe/critical cases may have extended treatment courses based on etiological results. Combining drugs with the same mechanism or increasing dosages is not recommended, but combining those with different mechanisms is not ruled out.

Recommendation 3: For patients with severe influenza or suspected drug-resistant strain infection, after individualized assessment, combined antiviral treatment with drugs of different mechanisms of action and different targets can be considered (Evidence Level: 5, Recommendation Strength:D).

5. Combination antiviral therapy regimen

To date, compared with single-drug treatment, combination therapy with virus-targeted drugs and host-targeted drugs has achieved more positive clinical outcomes. These outcomes include reducing viral shedding, shortening the duration of influenza-related symptoms, and decreasing the selection of drug-resistant variants. Notably, the combination of a virus-targeted drug with anti-inflammatory/immunomodulatory agents has become one of the most promising treatment approaches. A brief introduction to the combination therapy regimens is provided below.

5.1. Sequential monotherapy

Early studies have identified the possibility of single-drug sequential therapy for immunocompromised patients (*29*). Five patients who received allogeneic hematopoietic stem cell transplantation still had symptoms and shed influenza viruses after one or more oseltamivir courses, and were then given sequential baloxavir therapy. Among the three patients with wild-type influenza virus infection, two achieved viral clearance after baloxavir treatment, while another developed a baloxavir-resistant polymerase variant (I38T). Subsequent studies further validated this approach (*30*) : in severe Influenza A (H5N6) cases where oseltamivir was ineffective, baloxavir marboxil rapidly reduced patients' viral load and cytokine levels. In recent years, clinicians observed that some immunocompromised patients or elderly patients with chronic comorbidities still had high influenza virus nucleic acid load 5 days after single oseltamivir treatment or single baloxavir marboxil treatment, with no obvious improvement in pneumonia. Sequential use of these two drugs promoted viral nucleic acid negativity and prevented disease progression. Additionally, sequential therapy is safe with no drug-drug interactions, though verification *via* multicenter large-cohort studies is still required. It should be noted that for sequential treatment with baloxavir marboxil, the single adult dose must not exceed 40 mg. For elderly patients (≥65 years old), adjust the dose based on renal function, and use with caution if creatinine clearance is < 30 mL/min.

Recommendation 4: For immunocompromised patients or elderly patients with chronic underlying diseases, if their condition shows no significant improvement after standard antiviral treatment and they remain persistently positive for Influenza virus nucleic acid, sequential antiviral therapy is recommended. The recommended regimens include oseltamivir followed by baloxavir marboxil, or baloxavir marboxil followed by oseltamivir (Evidence Level: 4, Recommendation Strength:C).

5.2. The combination of virus-targeted drugs with different mechanisms

5.2.1. The combination of different NAIs

In mouse models, for A(H3N2) and wild-type A(H1N1)pdm09 viruses, zanamivir monotherapy was more effective than oseltamivir monotherapy or the oseltamivir-zanamivir combination; however, for the oseltamivir-resistant A(H1N1)pdm09 H275Y virus variant, combination therapy was comparable to zanamivir monotherapy, and both were superior to oseltamivir monotherapy (*31*). In the hollow fiber infection model (HFIM) system, combined treatment with oseltamivir (75 mg Q12h, $t_{1/2}$: 8 h) and zanamivir (600 mg Q12h, $t_{1/2}$: 2.5 h) remained effective against viruses resistant to both agents (*32*). In randomized controlled trials of adult seasonal influenza (mainly H3N2), oseltamivir-zanamivir combination therapy was not more effective than oseltamivir monotherapy, nor was it significantly better than zanamivir monotherapy (*33*); retrospective studies on adult H7N9 infection also showed that oseltamivir-peramivir combination therapy was not superior to oseltamivir monotherapy (*34*). A case report (*35*) indicated that in critically ill Influenza A patients receiving invasive ventilation and ECMO support, the combined regimen of oral oseltamivir and inhaled zanamivir failed to prevent disease deterioration. Existing evidence shows that for wild-type influenza viruses, NAIs combination therapy does not consistently outperform monotherapy. Its potential value may be limited to specific scenarios, such as when NAI-resistant strain infection is confirmed or highly suspected (*e.g.*, in areas with prevalent resistant strains) and no better alternatives (such as baloxavir) are available, and it can be used as a tentative strategy.

Recommendation 5: Routine use of NAIs combination therapy is not recommended for treating seasonal influenza or avian influenza (such as H7N9) infections. Examples of such combination therapy include oseltamivir combined with zanamivir or peramivir (Evidence Level: 1b, Recommendation Strength: A).

5.2.2. The combination of NAIs and RNA polymerase acid protein inhibitors

An *in vitro* study found that combining baloxavir with neuraminidase inhibitors (*e.g.*, oseltamivir, laninamivir) exerted a significant synergistic effect. This effect enhanced the inhibitory activity against influenza virus (*36*). In ferret model experiments, therapeutic effects of baloxavir and oseltamivir were tested separately and in combination. Results showed that compared with monotherapy, combination therapy significantly reduced the upper respiratory tract virus titer in ferrets. It also significantly lowered the rate of drug-resistant virus generation. In ferrets treated with oseltamivir alone, a new oseltamivir-resistant mutation (NA/H275Y) was observed. This phenomenon was not detected in the combination therapy group (*37*). Clinically, combination of baloxavir and oseltamivir has shown relatively favorable effects in treating two patients after hematopoietic stem cell transplantation. For one patient, flu symptoms were rapidly relieved after receiving this combination therapy, and the virus test result turned negative. The other patient also showed a good early response to the same treatment but experienced virus recurrence in the later stage (*38*). Subsequently, international reports indicated that a 10-day regimen of zanamivir combined with baloxavir could effectively control the persistent replication of influenza virus in patients after hematopoietic stem cell transplantation (*39*).

5.2.3. The combination of NAIs and RNA polymerase basic protein inhibitors

A prospective study on adult influenza (*40*) showed that combining favipiravir with oseltamivir accelerated clinical recovery in patients with severe influenza. This effect was more significant than that of oseltamivir monotherapy. This treatment strategy deserves further evaluation in randomized controlled trials. A randomized double-blind trial (*41*) compared the pharmacokinetics and efficacy of pimodivir combined with oseltamivir. The trial included elderly and non-elderly hospitalized patients. Results showed the combination therapy group was safe and effective: its viral load was significantly lower than the placebo group, and symptom relief time was shorter (72.45 hours *vs* 94.15 hours). The incidence of influenza-related complications was also lower (7.9% *vs* 15.6%). Finberg RW *et al.* (*42*) found that compared with the placebo group, the pimodivir-oseltamivir combination group had a significantly lower viral load titer over time. The symptom relief time of the combination group also tended to be shorter than that of the placebo group. The early Phase II study showed positive results. Two subsequent key Phase III clinical trials were conducted in inpatients and high-risk outpatients. These trials failed to reach the primary endpoint. The research and development of this drug has been terminated. It should no longer be considered for clinical treatment.

5.2.4. The combination of NAIs and Envelope glycoprotein hemagglutinin inhibitors

MEDI8852 is a novel monoclonal antibody. In mouse and ferret models, the combination of MEDI8852 and oseltamivir significantly enhances therapeutic efficacy when treatment is delayed. Additionally, combining MEDI8852 with oseltamivir shows notable effects in preventing and treating Influenza A virus (H5N1 and H7N9) infections (*43*). A randomized, double-blind, placebo-controlled clinical trial found that the combination of oseltamivir and MEDI8852 is similar to oseltamivir monotherapy in reducing viral shedding. The combination treatment does not induce viral drug resistance changes and demonstrates good safety (*44*). Yi *et al.* (*45*) developed a new antibody mixture named CT-P27. In mouse models of influenza virus infection, CT-P27 exhibits *in vivo* therapeutic efficacy and preventive potential. It also shows a synergistic effect when used in combination with oseltamivir. In immunodeficient nude mouse models, researchers evaluated the triple therapy of favipiravir combined with two monoclonal antibodies (targeting the HA stem and HA receptor-binding sites). They found that single-drug or dual-drug combinations could inhibit viral replication but not completely eliminate the virus. However, the triple combination therapy successfully cleared the virus, enabling nude mice to survive for 188 days without any recurrence signs. No drug-resistant mutations were detected in this study, and the virus's adaptability was not affected either. This triple combination therapy includes favipiravir, anti-HA stem monoclonal antibody and anti-HA receptor-binding site monoclonal antibody. It provides the possibility of eradicating influenza virus in immunodeficient hosts, thereby offering a new treatment strategy for patients with severe influenza or immunodeficiency (*46*). Gaisina I *et al.* (*47*) found that combining the small-molecule IAV entry inhibitor ING-1466 with oseltamivir or baloxavir marboxil can synergistically enhance therapeutic efficacy.

Recommendation 6: Oseltamivir combined with baloxavir can effectively control influenza virus replication (Evidence Level: 2c, Recommendation Strength:B); Oseltamivir combined with favipiravir is superior to monotherapy in reducing influenza virus load for influenza treatment (Evidence Level: 2a, Recommendation Strength:B); Oseltamivir combined with hemagglutinin inhibitors (e.g., MEDI8852) helps reduce viral shedding and enhance therapeutic efficacy (Evidence Level: 1b, Recommendation Strength: A).

5.3. The combination of host-targeted drugs and antiviral drugs

5.3.1. The combination of nonsteroidal anti-inflammatory drug and Oseltamivir phosphate

In Phase III clinical trials, combining oseltamivir with celecoxib significantly reduced patient mortality compared with oseltamivir monotherapy (*48*). Similarly, in Phase IIB/III clinical trials, the combination of clarithromycin-naproxen and oseltamivir produced two key effects: it significantly reduced the 30-day and 90-day mortality of hospitalized patients infected with H3N2 influenza, and shortened the overall hospital stay (*49*). In addition, a study on hospitalized children with influenza showed results: children treated with the combination of clarithromycin, naproxen and oseltamivir had a shorter fever resolution time than those treated with oseltamivir alone. Their influenza virus titer also decreased significantly faster(*50*). These studies suggest that the treatment regimen of non-steroidal anti-inflammatory drugs combined with oseltamivir has greater potential for influenza treatment.

5.3.2. The combination of immunomodulatory drugs and Oseltamivir phosphate

Long JS *et al.* (*51*) evaluated the effect of oseltamivir combined with human interferon λ on the drug resistance barrier of pandemic H1N1 virus strains A/Netherlands/602/2009 (H1N1pdm09) *via* an *in vitro* infection model. Results showed oseltamivir monotherapy led to rapid viral drug resistance *via* a single neuraminidase gene mutation, while combining with interferon λ significantly delayed the emergence of drug-resistant variants. Some literature has explored new drug development strategies, including targeting viral polymerase complexes (*e.g.*, PB1, PB2, PA) and leveraging host factors such as combining NAIs, polymerase inhibitors and immunomodulators like interferon λ. However, these strategies still need more clinical data to verify their broad applicability and safety (*52*).

Allotern is an immunomodulatory drug with antiviral activity against multiple viruses, including influenza virus. According to studies, when Allotern is used in combination with zanamivir, it can inhibit the production of inflammatory mediators and the migration of inflammatory cells to lung tissue. This effect effectively alleviates progression of lung inflammation induced by H1N1 Influenza virus (*53*).

Nitazoxanide (NTZ) belongs to the class of thiazole antibiotics, and it enhances the host's antiviral resistance by regulating the host's immune response. *In vitro* experiments have demonstrated that compared with oseltamivir or nitazoxanide monotherapy, the combination of these two drugs shows greater efficacy in preventing infection and shortening duration of viral shedding. Moreover, in animal models, this combined regimen not only significantly boosts the antiviral effect of oseltamivir but also successfully blocks the virus from spreading to the lower respiratory tract (*54*).

5.3.3. The combination of host-targeted drugs and baloxavir or Oseltamivir phosphate

The antiviral activity of the MEK inhibitor ATR-002 was evaluated in A549 cells. Both its monotherapy and combination with baloxavir marboxil against wild-type influenza strains and drug-resistant strains (with PA-I38T mutation) were tested *via* virus titer reduction assay and co-analysis. Results showed that ATR-002 exerted significant inhibitory effects on both wild-type and PA-I38T mutant strains. When used in combination with baloxavir marboxil, it exhibited a synergistic effect: combination therapy reduced viral load more effectively, especially when targeting drug-resistant strains, and its inhibitory effect was significantly better than that of either single drug used alone. The combination of ATR-002 and baloxavir marboxil provides a new therapeutic strategy for overcoming baloxavir marboxil resistance. It is also expected to open up new avenues for the treatment of drug-resistant influenza (*55*).

The combination of four MEK inhibitors (PD-0325901, AZD-6244, AZD-8330 and RDEA-119) with oseltamivir significantly enhanced oseltamivir's antiviral activity (*56*). This combination therapy demonstrates the potential of MEK inhibitors and deserves further verification through preclinical *in vitro* and *in vivo* experiments.

Combination treatment with CXCR2 antagonists and antiviral drugs can significantly reduce the incidence and mortality of toxic and sublethal influenza infections (*57,58*). Hanlon *et al.* (*59*) demonstrated that M85, a novel antiviral compound, effectively inhibits influenza virus entry in mouse influenza models. It exerts this effect by targeting the host kinase PIK3C2β. In addition, M85 shows a synergistic effect when combined with oseltamivir.

Recommendation 7: Combining host-targeted drugs with baloxavir marboxil and/or oseltamivir can exert a synergistic effect. It can rapidly reduce viral load and the incidence of drug-resistant influenza virus strains (Evidence Level: 2b, Recommendation Strength: B). The mentioned host-targeted drugs include non-steroidal anti-inflammatory drugs (e.g., celecoxib, naproxen), immunomodulatory drugs (e.g., interferon λ, nitazoxanide), and other host-targeted drugs (e.g., MEK inhibitors).

6. Population applicable for combined antiviral therapy

Combination antiviral therapy may be required for patients with resistance to current anti-influenza viral agents/poor efficacy of antiviral therapy, as well as patients with severe influenza, immunocompromised patients, and other critically ill high-risk patients who may require combination antiviral therapy due to persistent viral replication.

6.1. Patients infected with ineffective/resistant strains of antiviral therapy

The poor efficacy of anti-influenza virus treatment is defined as follows: after standardized use of anti-influenza virus drugs, the patient's symptoms do not improve as expected (*e.g.*, fever [≥38℃] lasting more than three days, and persistent or aggravated symptoms such as cough). Another sign is the continuous replication of the virus, which can be observed through positive nucleic acid testing indicating active viral replication. The poor efficacy of anti-Influenza virus treatment is often closely associated with the "drug resistance" of influenza viruses and infection with "drug-resistant strains". Drug resistance is defined as a functional state. In this state, influenza viruses lose or weaken their sensitivity to drugs through genetic mutations and other means under drug pressure. Drug-resistant strains, by contrast, refer to individual viruses or virus populations. They carry specific drug-resistant mutations and can stably exhibit this "drug-resistant state", serving as specific carriers of the drug-resistant state. According to the WHO definition, for IAV, a strain is determined to be drug-resistant if the concentration (IC_{50}) required for a drug to inhibit 50% of viral replication is more than 100 times higher than the normal value. If the IC_{50} is 10 to 100 times higher than the normal value, it indicates reduced sensitivity, which may affect therapeutic efficacy (*60*). To accurately identify drug resistance, current methods for detecting influenza virus drug resistance mainly include phenotypic analysis and genotypic analysis. Phenotypic analysis includes plaque reduction experiments, chemiluminescence methods, and fluorescence methods. Genotypic analysis includes real-time fluorescence quantitative PCR, digital PCR and other techniques. Technologies such as gene chips, CRISPR detection, and next-generation sequencing are still in the research stage (*61*). In clinical practice, the more common types of drug-resistant strains mainly include oseltamivir-resistant strains and baloxavir-resistant strains. The existence of such drug-resistant strains often directly leads to reduced efficacy or failure of the corresponding drugs. In clinical settings, these factors are of paramount importance when modifying treatment plans.

6.1.1. Oseltamivir resistant strains

For oseltamivir-resistant strains, combining favipiravir can restore the sensitivity of resistant viruses to antiviral drugs (*62*). Favipiravir can effectively inhibit the activity of the PB1 subunit of influenza viruses. It has inhibitory activity against influenza strains resistant to neuraminidase inhibitors and amantadine drugs. Meanwhile, it almost does not inhibit human DNA synthesis and has good safety(*63,64*). *In vitro* experiments have shown that the PB2 inhibitor pimodivir has a synergistic antiviral effect with oseltamivir (*65*). This drug is effective against IAV, including neuraminidase inhibitor-resistant and amantadine-resistant strains. However, it is ineffective against IBV (*66*). In terms of clinical research, results from the TOPAZ trial (*42*) indicated that when treating patients with acute, uncomplicated seasonal influenza A, pimodivir monotherapy could reduce viral load in a dose-dependent manner. The efficacy was more significant when pimodivir was used in combination with oseltamivir. Another set of clinical research data shows that in high-risk outpatients, the combined treatment of pimodivir and oseltamivir can also shorten the duration of influenza symptoms (*67*).

6.1.2. Baloxavir resistant strains

For baloxavir-resistant strains (with PA/I38T or PA/E23K mutation), combination therapy has shown potential to delay the occurrence of drug resistance. Koszalka P *et al.* (*37*) reported that in ferret models, the combination of baloxavir and oseltamivir could reduce the selection pressure on viruses with reduced drug sensitivity. This in turn lowers the risk of drug resistance. Park *et al.* (*68*) further verified the effect of baloxavir marboxil/oseltamivir monotherapy or combination therapy on the drug-resistant substitution of A(H1N1) pdm09 virus during continuous passage in mice. Deep sequencing analysis showed that the PA-I38X amino acid substitution variant emerged in 67% (n=4/6) of the mouse virus populations treated with baloxavir marboxil monotherapy. The combination of baloxavir marboxil and oseltamivir could inhibit the production of this variant, providing a therapeutic strategy to reduce influenza virus drug resistance. Guo X *et al.* (*36*) evaluated the antiviral effect of combining baloxavir with neuraminidase inhibitors on wild-type influenza viruses and drug-resistant mutant influenza viruses. The results showed that this combination had a significant synergistic effect. Given the rapid emergence of baloxavir resistance, these results are believed to provide a useful reference for influenza combination therapy.

Recommendation 8: For influenza patients infected with oseltamivir-resistant strains or with poor antiviral response to oseltamivir, combination of favipiravir and pimodivir is recommended for influenza virus antiviral treatment (Evidence Level: 2b, Recommendation Strength: B); For influenza patients infected with baloxavir-resistant strains or with poor antiviral response to baloxavir, combination with oseltamivir is recommended for influenza virus antiviral treatment (Evidence Level: 3a, Recommendation Strength: B); It is also recommended to select an individualized combination treatment regimen of antiviral drugs and host-targeted drugs.

6.2. Severe/critical influenza patients

According to *the Diagnosis and Treatment Plan for Influenza (2025)* (*28*), adult influenza is defined as severe if any of the following criteria are met: 1.The respiratory rate is ≥30 breaths per minute; 2. Oxygen saturation is ≤93% during resting room air inhalation; 3. The ratio of arterial partial pressure of oxygen to fractional inspired oxygen (PaO_2/FiO_2) is ≤300 mmHg; 4. Lung imaging shows that lesions progress by more than 50% within 24–48 hours. Childhood nfluenza is defined as severe if any of the following criteria are met: 1. Persistent high fever lasting more than 3 days; 2. Shortness of breath (≥30–60 breaths per minute, depending on age); 3. Oxygen saturation is ≤93%; 4. Presence of symptoms such as drowsiness or convulsions; 5. Severe dehydration; 6. Exacerbation of underlying diseases. On the basis of severe influenza, a case is considered critical if any life-threatening manifestation occurs, including respiratory failure requiring mechanical ventilation, septic shock requiring vasoactive drugs, and organ failure (*e.g.*, acute kidney injury or acute necrotizing encephalopathy).

Combination therapy may shorten the course of illness in patients with severe influenza, but the supporting evidence is limited (*69*). A prospective study on adults found that the combination of favipiravir and oseltamivir promotes clinical recovery in patients with severe influenza more quickly than oseltamivir monotherapy (*40*). Fukao K *et al.* (*70*) compared the efficacy of baloxavir marboxil monotherapy, oseltamivir monotherapy, and the combination of the two in mouse models infected with influenza virus. *In vitro* experiments showed that baloxavir marboxil and neuraminidase inhibitors could synergistically inhibit viral replication. In animal experiments, combination therapy was superior to monotherapy in reducing viral titers, mortality, and inflammatory responses. A post hoc analysis was conducted on the FLAGSTONE study (*71*). A total of 143 patients with severe nfluenza were included in the efficacy analysis, including those with immunosuppression, diabetes, or chronic lung disease. Among them, 92 patients received baloxavir combined with neuraminidase inhibitors (dual antiviral group), and 51 patients received neuraminidase inhibitors alone (single antiviral group). Compared with neuraminidase inhibitor monotherapy, the combination of baloxavir and neuraminidase inhibitors showed a better effect in reducing mortality. In the future, multicenter prospective cohort studies and randomized controlled trials need to be conducted to clarify the efficacy and safety of combination therapy in various critically ill patient groups.

Recommendation 9: For patients with severe or critical influenza, antiviral treatment is recommended as follows: one option is oseltamivir combined with favipiravir (Evidence Level: 2b, Recommendation Strength: B). The other option is oseltamivir combined with baloxavir (Evidence Level: 1b, Recommendation Strength: A).

6.3. Immunosuppressed/compromised patients

For influenza patients with weakened immune systems, their immune systems cannot effectively clear the virus, so they often need long-term treatment with neuraminidase inhibitors. Such patients excrete the virus for a long time, which is highly likely to induce drug-resistant mutations—these mutations seriously affect antiviral efficacy and prolong infections. Thus, there is an urgent clinical need for strategies to rapidly and strongly inhibit viral replication, and sequential or combined antiviral therapy is particularly important. Mhamdi Z *et al.* (*72*) studied immunosuppressed mice infected with H3N2 virus, which received 10-day monotherapy or combination therapy with oseltamivir, favipiravir, or baloxavir. Results showed oseltamivir and favipiravir monotherapy only delayed mortality (average death days: 21.4, 24 *vs.* 11.4 in the untreated group). The combination of oseltamivir and favipiravir increased the survival rate to 80% and reduced lung viral titer; the combination of oseltamivir and baloxavir provided complete protection (100% survival) and significantly lowered lung viral titer. Oseltamivir and baloxavir monotherapy induced E119V (NA) and I38T (PA) substitutions respectively, but no resistance mutations were detected in the combination group—indicating combination therapy reduces drug resistance.

Clinical research on combined anti-influenza virus therapy in immunosuppressed populations has also made certain progress. Two patients with severe influenza pneumonia on immunosuppressive drugs had no virus clearance after 18 and 5 days of oseltamivir monotherapy respectively. After adding zanamivir and amantadine to their regimens, their throat swabs and plasma samples turned PCR-negative in 3 and 4 days respectively (*73*). In conclusion, existing evidence shows that for influenza patients with weakened immune function, although combined antiviral therapy can prolong survival or reduce viral load to some extent, a more potent, multi-target combination (*e.g.*, triple combination of polymerase inhibitors, neuraminidase inhibitors, and monoclonal antibodies) may be needed to achieve complete clearance and avoid drug resistance. Future priority should be given to prospective clinical studies to verify the effectiveness and safety of such strategies in severely immunosuppressed populations.

Recommendation 10: For patients with suppressed or weakened immune function, sequential or combined treatment with oseltamivir, baloxavir, favipiravir, etc. can be selected (Evidence Level: 2c, Recommendation Strength: B).

6.4. Elderly patients aged ≥65 years

Elderly individuals, especially those over 65 years old, often have multiple underlying diseases. This makes them prone to worsening existing conditions

after influenza infection and may even trigger severe complications, that threaten their lives. For the elderly, the harm of influenza goes far beyond respiratory symptoms. Within a few weeks after acute infection, it may also induce extrapulmonary complications such as myocardial infarction or stroke, further increasing the medical burden. Studies have shown that elderly patients over 75 years old stay in the hospital for about two more days on average due to flu-related complications than those aged 50 to 64 (*74*). In a Phase 2b clinical study (*41*), O'Neil B *et al.* compared the antiviral effects of pimodivir combined with oseltamivir versus oseltamivir monotherapy in non-elderly adults (18–64 years old) and elderly patients (65–85 years old). The results showed that the combination group significantly shortened the time to relief of influenza symptoms: 72.45 hours for elderly patients and 94.15 hours for non-elderly patients. Moreover, the incidence of influenza-related complications in the combination group was also significantly lower than that in the monotherapy group, at 7.9% and 15.6% respectively. However, this evidence only comes from a single exploratory study and has not been fully validated in large-scale elderly populations. In addition, there is a lack of systematic assessment on the safety of combination treatment for this population.

Recommendation 11: For elderly patients aged ≥65 years, individualized combined antiviral treatment can be formulated based on the patient's immune status, underlying diseases, and condition severity. Relevant recommendations for severe or critical cases and patients with suppressed or weakened immune function can be referred to (Evidence Level: 4, Recommendation Strength: C).

6.5. Pregnant women

Pregnant women and those within two weeks after childbirth are at high risk of influenza. Influenza may cause a series of complications in pregnant women, such as increased risks of premature birth, miscarriage, cesarean section, maternal respiratory failure, and death. Therefore, during the influenza season, it is recommended that pregnant women and women within two weeks after childbirth undergo influenza testing. Once diagnosed or suspected of having influenza, antiviral treatment should be initiated as soon as possible (*75*). For pregnant women, the preferred antiviral drug is oseltamivir. Small cohort studies have shown that inhaled zanamivir is safe for both pregnant women and exposed infants. However, relevant research data on baloxavir and peramivir in pregnant women are still insufficient. Favipiravir is contraindicated for pregnant women due to its reproductive toxicity (*74*). Therefore, the safety of antiviral drugs for pregnant women with influenza still requires further research, and combination antiviral therapy is not recommended at present.

Recommendation 12: For pregnant women with influenza, their condition changes should be closely monitored. Routine combined antiviral treatment for influenza is not recommended. (Evidence Level: 2a, Recommendation Strength: B).

6.6. Children

According to *Practical Guidelines for Influenza Vaccination and Antiviral Drug Use in Children (2024 Edition)* (*76*), for children with severe influenza and those infected with drug-resistant mutant strains, if their condition does not improve and continues to deteriorate 48 hours after initiating antiviral drug treatment, combination therapy of neuraminidase inhibitors and baloxavir or sequential therapy can be considered. The dosage and administration method should refer to the single-drug treatment standards. Baloxavir is only used for children aged 5 years and above; it is not recommended for children under 5 years old due to insufficient safety data. In addition, the course of combination treatment should not exceed 7 days.

Recommendation 13: Routine combination of antiviral drugs for the treatment of childhood influenza is not recommended. However, for children over 5 years old with severe conditions and weakened immune function, if the viral nucleic acid level is ≤30, sequential use or combination of baloxavir and oseltamivir is recommended (Evidence Level: 1a, Recommendation Strength: A).

7. Considerations for combined antiviral therapy for influenza

7.1. Drug interactions

In studies on drug interactions in influenza antiviral combination therapy, the *in vitro* and *in vivo* safety as well as synergistic effects of different drug combinations have been preliminarily verified. *In vitro* studies have shown that the synergistic index and antagonistic index of ZSP1273 combined with oseltamivir are 852.41 and -0.19 respectively. This indicates a strong synergistic effect between the two drugs (*77*). At present, research on drug interactions in special populations is still relatively limited. In the future, further targeted studies are needed to improve medication guidance for different populations.

7.2. Overlapping risk of drug resistance

MU *et al.* (*62*)demonstrated that the combination of famciclovir and oseltamivir may promote the emergence of oseltamivir-resistant variants, thereby accelerating the evolution of resistance mutations. For instance, this combination could lead to the occurrence of PA/I38T + H274Y double mutant strains. Thus, this antiviral combination regimen is not recommended for all

influenza patients. Instead, it should be customized for specific populations, and the use of combination therapy requires individual assessment before decision-making. This approach enables more effective management of therapeutic risks and optimization of treatment outcomes.

7.3. Adverse effects and safety

Combination therapy of naproxen with oseltamivir was associated with a low incidence of adverse events (AEs) in one study (*49*). Another study demonstrated no statistically significant differences in AEs (including vomiting, diarrhea, and abdominal pain) when compared with oseltamivir monotherapy (*50*). In subjects receiving combination therapy with the monoclonal antibody MEDI8852 and oseltamivir, the incidence of AEs was relatively elevated. Nevertheless, the majority of these events were classified as mild or moderate, with bronchitis identified as the most frequent adverse event (*44*).By contrast, the combination of ZSP1273 and oseltamivir exhibited a favorable safety and tolerability profile, and no clinically significant drug-drug interactions were detected (*78*). A randomized controlled trial (RCT) observed that co-administration of baloxavir with a neuraminidase inhibitor did not increase the risk of AEs (*71*).

These studies indicate that although antiviral combination regimens are linked to AEs, their overall safety profile remains acceptable. This finding provides a scientific basis for clinicians to select appropriate drug combinations according to patients' specific conditions in clinical practice. Future studies could further explore the safety and efficacy of these regimens across different disease stages and drug doses, with the aim of continuously optimizing treatment strategies.

7.4. Cost-effectiveness

Jiang Y *et al.* constructed a linked dynamic communication economic evaluation model to assess the cost-effectiveness of oseltamivir combined with baloxavir marboxil in the context of an influenza pandemic in China. The study results showed that adding baloxavir marboxil to the treatment regimen could reduce the cumulative incidence of influenza infection from 49.49% to 43.26% and increase quality-adjusted life years (QALYs). Compared with oseltamivir monotherapy, the intervention regimen combined with baloxavir marboxil achieved a net monetary benefit of 77.85 yuan per person, with a willingness-to-pay (WTP) threshold of 80,976 yuan per QALY (*79*).

From the perspective of Japanese healthcare costs, baloxavir (used for post-exposure prophylaxis) and ranimivir (used for treatment) showed high cost-effectiveness. This means combining these two drugs for influenza prevention and treatment can achieve better therapeutic effects at lower costs. When using the EuroQol-5 Dimension-5 Level (EQ-5D-5L) to measure health-related quality of life, the combination of baloxavir and ranimivir also significantly improved patients' quality of life (*80*).

Baloxavir and ranimivir are not only cost-effective in healthcare but also have significant value in social and public health dimensions. Thus, this drug combination deserves further promotion and application in future influenza pandemic preparedness and response strategies.

7.5. Monitor

7.5.1. Monitoring of antiviral efficacy

Based on pharmacokinetic (PK) and pharmacodynamic (PD) data, anti-influenza drugs typically reach a plasma concentration plateau after 5–6 half-lives. Specifically, oseltamivir has a half-life of 6–10 hours, while zanamivir has a half-life of 2.5–5.1 hours. The efficacy of anti-influenza drugs can be assessed 48 hours after initiating the recommended treatment (*81*). It is recommended to recheck influenza nucleic acid 5 days after treatment initiation. For combined antiviral therapy, influenza virus nucleic acid changes can also be monitored at the above time points. For certain patients, the interval for influenza nucleic acid monitoring can be shortened appropriately, including those with risk factors for severe influenza, influenza patients with immunosuppression or impaired immune function, patients with severe or critical influenza, and patients whose condition worsens during treatment.

7.5.2. Monitoring of antiviral efficacy

From global surveillance data, the resistance rate of influenza viruses to neuraminidase inhibitors (NAIs, *e.g.*, oseltamivir, peramivir) showed a slight upward trend (0.09%–0.23%) globally from 2020 to 2023. The incidence of baloxavir susceptibility reduction events also remained relatively low (0.07%–0.12%) (*82*). Although the current overall resistance rate is low, vigilance is needed regarding the epidemiological changes of drug-resistant strains in long-term monitoring. These changes directly determine clinical treatment efficacy and the success of public health prevention and control strategies, so risks must be managed through systematic monitoring and targeted responses.

According to *the China Influenza Surveillance Weekly Report*, the Influenza A (H1N1)pdm09 strain in China has remained generally sensitive to oseltamivir since 2009. However, local transmission of the H275Y mutant strain has been detected in some regions, and the resistance of this subtype to NAIs still requires close attention (*83*). In clinical practice, regular monitoring of drug-resistant mutations is essential, especially for severe patients with persistent viral replication. If the main cause of disease progression is confirmed to be persistent viral positivity

leading to elevated inflammatory factors, sequential or combined antiviral therapy should be adopted. Alternatively, antiviral drugs can be combined with host-targeting monoclonal antibodies or immunomodulators. Meanwhile, the turnaround time for drug resistance testing should be optimized, and rapid PCR technology should be used to detect specific mutations, facilitating timely adjustment of treatment strategies. Additionally, when evaluating new drugs or formulating combination strategies for immunosuppressed or critically ill patients, emphasis should be placed on analyzing drug resistance. Medical institutions with appropriate testing capabilities are recommended to perform drug resistance gene testing before initiating combined antiviral therapy. They should also conduct such testing if the influenza virus nucleic acid CT value is <30 five days after the start of antiviral treatment (*74*).

Recommendation 14: The overall safety of combined anti-influenza virus therapy is favorable. However, attention should still be paid to adverse drug reactions and drug interactions (Evidence Level: 2a, Recommendation Strength: B). During combined therapy, monitoring of influenza virus nucleic acid load is recommended. Medical institutions with testing capabilities may conduct drug resistance gene testing (Evidence Level: 5, Recommendation Strength: D).

8. Future research directions

The rapid evolution of influenza viruses and the spread of drug resistance have become major threats to global public health. To address this challenge, researchers are conducting in-depth explorations from multiple dimensions, including molecular mechanisms, model prediction, and immune mechanisms, with the aim of innovating existing prevention, control, and treatment strategies. Researchers identified novel allosteric drug-resistant mutations of neuraminidase *via* deep mutational scanning. This study revealed a new mechanism: these mutations do not directly act on the drug-binding pocket but cause resistance by affecting protein tetramerization (*84*). A site-dynamics-based evolutionary model and a machine learning method were developed in two studies, respectively. These tools can more accurately predict the antigenic evolution of influenza viruses, especially H3N2, and provide powerful computational support for vaccine strain selection (*85,86*). Yang B *et al.* found that the breadth of influenza antibody cross-reactivity is affected by viral subtypes and exposure history. Repeated exposure to H3N2 virus can shape and expand the scope of human antibody responses, which lays a framework for understanding immune imprinting and vaccine design (*87*).

Looking ahead, future research directions mainly include the following: developing novel broad-spectrum antiviral drugs and new influenza vaccines; establishing a national influenza virus drug resistance monitoring network that integrates real-time sequencing data and develops an artificial intelligence (AI)-based model for predicting viral evolution and drug resistance to provide early warning of drug-resistant mutations; developing individualized precision treatment strategies based on machine learning and AI algorithms to automatically recommend optimal single-drug or combination therapy regimens; and conducting multicenter RCTs to evaluate the safety and long-term efficacy of combination therapy in preventing severe cases and in populations such as immunocompromised patients and children.

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References

1. GBD 2017 Influenza Collaborators. Mortality, morbidity, and hospitalisations due to Influenza lower respiratory tract infections, 2017: an analysis for the Global Burden of Disease Study 2017. Lancet Respir Med. 2019; 7:69-89.
2. Li L, Liu Y, Wu P, *et al.* Influenza-associated excess respiratory mortality in China, 2010-15: a population-based study. Lancet Public Health. 2019; 4:e473-e481.
3. World Health Organization. Global Influenza strategy 2019-2030.[2019-03-11] *https://iris.who.int/handle/10665/311184*. (accessed September 10, 2025).
4. Świerczyńska M, Mirowska-Guzel DM, Pindelska E. Antiviral Drugs in Influenza. Int J Environ Res Public Health. 2022; 19:3018.
5. Wang Y, Guo Q, Yan Z, *et al.* Factors Associated With Prolonged Viral Shedding in Patients With Avian Influenza A(H7N9) Virus Infection. J Infect Dis. 2018; 217:1708-1717.
6. Chow EJ, Doyle JD, Uyeki TM. Influenza virus-related critical illness: prevention, diagnosis, treatment. Crit Care. 2019; 23:214.
7. Zou QD, Bao JQ, Zheng SF, Chen Y. Research on the Mechanisms of Severe Influenza and Advances in Treatment. Journal of Medical Research. 2019; 48:5-8. (in Chinese)
8. Song RR, Xu JY, Liu HY, Xu YT, Chang K, Cao B. Advances in Antiviral Treatment for Influenza. Chinese Medical Journal. 2023; 103:293-299. (in Chinese)
9. Han J, Perez J, Schafer A, Cheng H, Peet N, Rong L, Manicassamy B. Influenza Virus: Small Molecule Therapeutics and Mechanisms of Antiviral Resistance. Curr Med Chem. 2018; 25:5115-5127.
10. Cao B, Hayden FG. Antiviral monotherapy for hospitalised patients with COVID-19 is not enough. Lancet. 2020; 396:1310-1311.

11. OCEBM Levels of Evidence Working Group. The Oxford Levels of Evidence. [2010-01-07] *https://www.cebm.ox.ac.uk/resources/levels-of-evidence/ocebm-levels-of-evidence* (accessed September 10, 2025).
12. Bonomini A, Mercorelli B, Loregian A. Antiviral strategies against Influenza virus: an update on approved and innovative therapeutic approaches. Cell Mol Life Sci. 2025; 82:75.
13. Batool S, Chokkakula S, Song MS. Influenza Treatment: Limitations of Antiviral Therapy and Advantages of Drug Combination Therapy. Microorganisms. 2023; 11:183.
14. Xu J, Luo Q, Huang Y, Li J, Ye W, Yan R, Zhou X, He Z, Liu G, Zhu Q. Influenza neuraminidase mutations and resistance to neuraminidase inhibitors. Emerg Microbes Infect. 2024; 13:2429627.
15. Tramontana AR, George B, Hurt AC, *et al.* Oseltamivir resistance in adult oncology and hematology patients infected with pandemic (H1N1) 2009 virus, Australia. Emerg Infect Dis. 2010; 16:1068-1075.
16. Lee N, Hurt AC. Neuraminidase inhibitor resistance in Influenza: a clinical perspective. Curr Opin Infect Dis. 2018; 31:520-526.
17. Wang X, Kim KW, Walker G, Stelzer-Braid S, Scotch M, Rawlinson WD. Genome characterization of Influenza A and B viruses in New South Wales, Australia, in 2019: A retrospective study using high-throughput whole genome sequencing. Influenza Other Respir Viruses. 2024; 18:e13252.
18. Seibert CW, Rahmat S, Krammer F, Palese P, Bouvier NM. Efficient transmission of pandemic H1N1 Influenza viruses with high-level oseltamivir resistance. J Virol. 2012; 86:5386-5389.
19. Hickerson BT, Petrovskaya SN, Dickensheets H, Donnelly RP, Ince WL, Ilyushina NA. Impact of Baloxavir Resistance-Associated Substitutions on Influenza Virus Growth and Drug Susceptibility. J Virol. 2023; 97:e0015423.
20. Xie Z, Yang J, Jiao W, Li X, Iqbal M, Liao M, Dai M. Clade 2.3.4.4b highly pathogenic avian Influenza H5N1 viruses: knowns, unknowns, and challenges. J Virol. 2025; 99:e0042425.
21. Pulit-Penaloza JA, Brock N, Belser JA, Sun X, Pappas C, Kieran TJ, Basu Thakur P, Zeng H, Cui D, Frederick J, Fasce R, Tumpey TM, Maines TR. Highly pathogenic avian Influenza A(H5N1) virus of clade 2.3.4.4b isolated from a human case in Chile causes fatal disease and transmits between co-housed ferrets. Emerg Microbes Infect. 2024; 13:2332667.
22. Mostafa A, Naguib MM, Nogales A, Barre RS, Stewart JP, García-Sastre A, Martinez-Sobrido L. Avian Influenza A (H5N1) virus in dairy cattle: origin, evolution, and cross-species transmission. mBio. 2024; 15:e0254224.
23. Azeem RM, Yang YS, Sehrish S, Shi CW, Yang GL, Kumar ST, Yang WT, Wang CF. Emerging threats of H5N1 clade 2.3.4.4b: cross-species transmission, pathogenesis, and pandemic risk. Front Cell Infect Microbiol. 2025; 15:1625665.
24. Abed Y, Boivin G. A Review of Clinical Influenza A and B Infections With Reduced Susceptibility to Both Oseltamivir and Zanamivir. Open Forum Infect Dis. 2017; 4:ofx105.
25. Aw DZH, Zhang DX, Vignuzzi M. Strategies and efforts in circumventing the emergence of antiviral resistance against conventional antivirals. NPJ Antimicrob Resist. 2025; 3:54.
26. World Health Organization. Clinical practice guidelines for Influenza. [2024-09-12] *https://iris.who.int/handle/10665/378872* (accessed September 10, 2025).
27. National Health Commission. Diagnosis and Treatment Protocol for Influenza (2020 Edition). Infectious Disease Information. 2020; 33:385-390. (in Chinese)
28. National Health Commission. Diagnosis and Treatment Protocol for Influenza (2025 Edition). Chinese Journal of Viral Diseases. 2025; 15:101-106. (in Chinese)
29. Salvatore M, Laplante JM, Soave R, Orfali N, Plate M, van Besien K, St George K. Baloxavir for the treatment of Influenza in allogeneic hematopoietic stem cell transplant recipients previously treated with oseltamivir. Transpl Infect Dis. 2020; 22:e13336.
30. Guan W, Qu R, Shen L, *et al.* Baloxavir marboxil use for critical human infection of avian Influenza A H5N6 virus. Med. 2024; 5:32-41.e5.
31. Pizzorno A, Abed Y, Rhéaume C, Boivin G. Oseltamivir-zanamivir combination therapy is not superior to zanamivir monotherapy in mice infected with Influenza A(H3N2) and A(H1N1)pdm09 viruses. Antiviral Res. 2014; 105:54-58.
32. Pires de Mello CP, Drusano GL, Adams JR, Shudt M, Kulawy R, Brown AN. Oseltamivir-zanamivir combination therapy suppresses drug-resistant H1N1 Influenza A viruses in the hollow fiber infection model (HFIM) system. Eur J Pharm Sci. 2018; 111:443-449.
33. Duval X, van der Werf S, Blanchon T, Mosnier A, Bouscambert-Duchamp M, Tibi A, Enouf V, Charlois-Ou C, Vincent C, Andreoletti L, Tubach F, Lina B, Mentré F, Leport C. Efficacy of oseltamivir-zanamivir combination compared to each monotherapy for seasonal Influenza: a randomized placebo-controlled trial. PLoS Med. 2010; 7:e1000362.
34. Zhang Y, Gao H, Liang W, Tang L, Yang Y, Wu X, Yu L, Chen P, Zheng S, Ou H, Li L. Efficacy of oseltamivir-peramivir combination therapy compared to oseltamivir monotherapy for Influenza A (H7N9) infection: a retrospective study. BMC Infect Dis. 2016; 16:76.
35. Petersen E, Keld DB, Ellermann-Eriksen S, Gubbels S, Ilkjær S, Jensen-Fangel S, Lindskov C. Failure of combination oral oseltamivir and inhaled zanamivir antiviral treatment in ventilator- and ECMO-treated critically ill patients with pandemic Influenza A (H1N1)v. Scand J Infect Dis. 2011; 43:495-503.
36. Guo X, Zhao L, Li W, Cao R, Zhong W. The Synergistic Effect of Baloxavir and Neuraminidase Inhibitors against Influenza Viruses *In Vitro*. Viruses. 2024; 16:1467.
37. Koszalka P, George A, Dhanasekaran V, Hurt AC, Subbarao K. Effect of Baloxavir and Oseltamivir in Combination on Infection with Influenza Viruses with PA/I38T or PA/E23K Substitutions in the Ferret Model. mBio. 2022; 13:e0105622.
38. Angelidakis G, Khawaja F, Mulanovich VE, Dailey-Garnes N, Ariza-Heredia E, Chemaly RF. Combination of baloxavir and oseltamivir for treatment of severe Influenza infection in hematopoietic cell transplant recipients: a novel treatment strategy for a high-risk population. Microbes Infect. 2022; 24:104895.
39. Euzen V, Xhaard A, Berreira-Ibraim S, Deville L, Quentin A, De Lima Prata PH, Gournay V, Prot M, Rahou Y, Barbet M, Mercier-Delarue S, Peffault De La Tour R, Simon-Loriere E, Legoff J. Zanamivir and baloxavir combination to cure persistent Influenza and coronavirus infections after hematopoietic stem cell transplant. Int J Antimicrob Agents. 2024; 64:107281.
40. Wang Y, Fan G, Salam A, Horby P, Hayden FG, Chen C, Pan J, Zheng J, Lu B, Guo L, Wang C, Cao B. Comparative

Effectiveness of Combined Favipiravir and Oseltamivir Therapy Versus Oseltamivir Monotherapy in Critically Ill Patients With Influenza Virus Infection. J Infect Dis. 2020; 221:1688-1698.
41. O'Neil B, Ison MG, Hallouin-Bernard MC, Nilsson AC, Torres A, Wilburn JM, van Duijnhoven W, Van Dromme I, Anderson D, Deleu S, Kosoglou T, Vingerhoets J, Rossenu S, Leopold L. A Phase 2 Study of Pimodivir (JNJ-63623872) in Combination With Oseltamivir in Elderly and Nonelderly Adults Hospitalized With Influenza A Infection: OPAL Study. J Infect Dis. 2022; 226:109-118.
42. Finberg RW, Lanno R, Anderson D, Fleischhackl R, van Duijnhoven W, Kauffman RS, Kosoglou T, Vingerhoets J, Leopold L. Phase 2b Study of Pimodivir (JNJ-63623872) as Monotherapy or in Combination With Oseltamivir for Treatment of Acute Uncomplicated Seasonal Influenza A: TOPAZ Trial. J Infect Dis. 2019; 219:1026-1034.
43. Paules CI, Lakdawala S, McAuliffe JM, Paskel M, Vogel L, Kallewaard NL, Zhu Q, Subbarao K. The Hemagglutinin A Stem Antibody MEDI8852 Prevents and Controls Disease and Limits Transmission of Pandemic Influenza Viruses. J Infect Dis. 2017; 216:356-365.
44. Ali SO, Takas T, Nyborg A, Shoemaker K, Kallewaard NL, Chiong R, Dubovsky F, Mallory RM. Evaluation of MEDI8852, an Anti-Influenza A Monoclonal Antibody, in Treating Acute Uncomplicated Influenza. Antimicrob Agents Chemother. 2018; 62:e00694-18.
45. Yi KS, Choi JA, Kim P, *et al.* Broader neutralization of CT-P27 against Influenza A subtypes by combining two human monoclonal antibodies. PLoS One. 2020; 15:e0236172.
46. Kiso M, Yamayoshi S, Kawaoka Y. Triple combination therapy of favipiravir plus two monoclonal antibodies eradicates Influenza virus from nude mice. Commun Biol. 2020; 3:219.
47. Gaisina I, Li P, Du R, Cui Q, Dong M, Zhang C, Manicassamy B, Caffrey M, Moore T, Cooper L, Rong L. An orally active entry inhibitor of Influenza A viruses protects mice and synergizes with oseltamivir and baloxavir marboxil. Sci Adv. 2024; 10:eadk9004.
48. Koszalka P, Subbarao K, Baz M. Preclinical and clinical developments for combination treatment of Influenza. PLoS Pathog. 2022; 18:e1010481.
49. Hung IFN, To KKW, Chan JFW, *et al.* Efficacy of Clarithromycin-Naproxen-Oseltamivir Combination in the Treatment of Patients Hospitalized for Influenza A(H3N2) Infection: An Open-label Randomized, Controlled, Phase IIb/III Trial. Chest. 2017; 151:1069-1080.
50. Lee CW, Tai YL, Huang LM, Chi H, Huang FY, Chiu NC, Huang CY, Tu YH, Wang JY, Huang DT. Efficacy of clarithromycin-naproxen-oseltamivir combination therapy versus oseltamivir alone in hospitalized pediatric Influenza patients. J Microbiol Immunol Infect. 2021; 54:876-884.
51. Long JS, Mistry B, Haslam SM, Barclay WS. Host and viral determinants of Influenza A virus species specificity. Nat Rev Microbiol. 2019; 17:67-81.
52. Shin WJ, Seong BL. Novel antiviral drug discovery strategies to tackle drug-resistant mutants of Influenza virus strains. Expert Opin Drug Discov. 2019; 14:153-168.
53. Lee D, Jo H, Jang Y, Bae S, Agura T, Kang D, Kang M, Kim Y, Cho NH, Kim Y, Kang JS. Alloferon and Zanamivir Show Effective Antiviral Activity against Influenza A Virus (H1N1) Infection *In Vitro* and *In Vivo*. Int J Mol Sci. 2022; 24:678.
54. Mifsud EJ, Tilmanis D, Oh DY, Ming-Kay Tai C, Rossignol JF, Hurt AC. Prophylaxis of ferrets with nitazoxanide and oseltamivir combinations is more effective at reducing the impact of Influenza a virus infection compared to oseltamivir monotherapy. Antiviral Res. 2020; 176:104751.
55. Hamza H, Shehata MM, Mostafa A, Pleschka S, Planz O. Improved *in vitro* Efficacy of Baloxavir Marboxil Against Influenza A Virus Infection by Combination Treatment With the MEK Inhibitor ATR-002. Front Microbiol. 2021; 12:611958.
56. Haasbach E, Hartmayer C, Planz O. Combination of MEK inhibitors and oseltamivir leads to synergistic antiviral effects after Influenza A virus infection *in vitro*. Antiviral Res. 2013; 98:319-324.
57. Ashar HK, Pulavendran S, Rudd JM, Maram P, Achanta M, Chow VTK, Malayer JR, Snider TA, Teluguakula N. Administration of a CXC Chemokine Receptor 2 (CXCR2) Antagonist, SCH527123, Together with Oseltamivir Suppresses NETosis and Protects Mice from Lethal Influenza and Piglets from Swine-Influenza Infection. Am J Pathol. 2021; 191:669-685.
58. Washburn ML, Crosby R, Remlinger K, Wang F, Creech D. Therapeutically Attenuating Neutrophil Recruitment With a CXCR2 Antagonist in Combination With Oseltamivir Ameliorates Influenza-Induced Lung Injury and Disease. Open Forum Infect Dis. 2019; 6:ofz106.
59. O'Hanlon R, Leyva-Grado VH, Sourisseau M, Evans MJ, Shaw ML. An Influenza Virus Entry Inhibitor Targets Class II PI3 Kinase and Synergizes with Oseltamivir. ACS Infect Dis. 2019; 5:1779-1793.
60. Meetings of the WHO working group on surveillance of Influenza antiviral susceptibility – Geneva, November 2011 and June 2012. Wkly Epidemiol Rec. 2012; 87:369-374.
61. Van Poelvoorde LAE, Saelens X, Thomas I, Roosens NH. Next-Generation Sequencing: An Eye-Opener for the Surveillance of Antiviral Resistance in Influenza. Trends Biotechnol. 2020; 38:360-367.
62. Mu S, Zou X, Wang Y, Deng X, Cui D, Liu S, Cao B. The combined effect of oseltamivir and favipiravir on Influenza A virus evolution in patients hospitalized with severe Influenza. Antiviral Res. 2023; 216:105657.
63. Furuta Y, Takahashi K, Fukuda Y, Kuno M, Kamiyama T, Kozaki K, Nomura N, Egawa H, Minami S, Watanabe Y, Narita H, Shiraki K. *In vitro* and *in vivo* activities of anti-Influenza virus compound T-705. Antimicrob Agents Chemother. 2002; 46:977-981.
64. Kiso M, Takahashi K, Sakai-Tagawa Y, Shinya K, Sakabe S, Le QM, Ozawa M, Furuta Y, Kawaoka Y. T-705 (favipiravir) activity against lethal H5N1 Influenza A viruses. Proc Natl Acad Sci U S A. 2010; 107:882-887.
65. Smee DF, Barnard DL, Jones SM. Activities of JNJ63623872 and oseltamivir against Influenza A H1N1pdm and H3N2 virus infections in mice. Antiviral Res. 2016; 136:45-50.
66. Clark MP, Ledeboer MW, Davies I, *et al.* Discovery of a novel, first-in-class, orally bioavailable azaindole inhibitor (VX-787) of Influenza PB2. J Med Chem. 2014; 57:6668-6678.
67. Janssen Research & Development, LLC. A study to evaluate the efficacy and safety of pimodivir in combination with the standard-of-care treatment in adolescent, adult, and elderly non-hospitalized participants with Influenza a infection who are at risk of developing complications [2025-02-03] *https://clinicaltrials.gov/ct2/show/results/nct03381196?Cond=pimodivir&draw=2&rank=6&view=results* (accessed September 15, 2025).
68. Park JH, Kim B, Antigua KJC, Jeong JH, Kim CI, Choi

WS, Oh S, Kim CH, Kim EG, Choi YK, Baek YH, Song MS. Baloxavir-oseltamivir combination therapy inhibits the emergence of resistant substitutions in Influenza A virus PA gene in a mouse model. Antiviral Res. 2021; 193:105126.
69. Bay P, Martin-Loeches I, Haudebourg AF, Lê MP, Peytavin G, Rameix-Welti MA, Fourati S, de Prost N. How to manage antivirals in critically ill patients with Influenza? Clin Microbiol Infect. 2025; 31:1157-1165.
70. Fukao K, Noshi T, Yamamoto A, Kitano M, Ando Y, Noda T, Baba K, Matsumoto K, Higuchi N, Ikeda M, Shishido T, Naito A. Combination treatment with the cap-dependent endonuclease inhibitor baloxavir marboxil and a neuraminidase inhibitor in a mouse model of Influenza A virus infection. J Antimicrob Chemother. 2019; 74:654-662.
71. Yan M, Gu X, Wang Y, Cao B. Effects of Baloxavir Marboxil Plus Neuraminidase Inhibitor vs Neuraminidase Inhibitor in High-risk Patients Hospitalized With Severe Influenza: A Post Hoc Analysis of the Flagstone Trial. Open Forum Infect Dis. 2025; 12:ofaf439.
72. Mhamdi Z, Fausther-Bovendo H, Uyar O, Carbonneau J, Venable MC, Abed Y, Kobinger G, Boivin G, Baz M. Effects of Different Drug Combinations in Immunodeficient Mice Infected with an Influenza A/H3N2 Virus. Microorganisms. 2020; 8:1968.
73. Meijer WJ, Kromdijk W, van den Broek MP, Haas PJ, Minnema MC, Boucher CA, de Lange DW, Wensing AM. Treatment of Immunocompromised, Critically Ill Patients with Influenza A H1N1 Infection with a Combination of Oseltamivir, Amantadine, and Zanamivir. Case Rep Infect Dis. 2015; e504975.
74. Consensus Expert Group on Antiviral Treatment for Adult Influenza. Expert Consensus on Antiviral Treatment for Influenza in Adults. Chinese Journal of Infectious Diseases. 2022; 40:641-655. (in Chinese)
75. Uyeki TM, Bernstein HH, Bradley JS, *et al.* Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 Update on Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenzaa. Clin Infect Dis. 2019; 68:e1-e47.
76. Pediatric Infectious Diseases Working Group IDS, Pediatric Committee, National Health Commission Capacity Building and Continuing Education Commission, Chinese Clinical Practice Guidelines Alliance Methodology Subcommittee. Practical Guidelines for Influenza Vaccination and Antiviral Drug Use in Children (2024 Edition). Chinese Medical Journal. 2024; 104:3705-3725. (in Chinese)
77. Chen X, Ma Q, Zhao M, Yao Y, Zhang Q, Liu M, Yang Z, Deng W. Preclinical Study of ZSP1273, a Potent Antiviral Inhibitor of Cap Binding to the PB2 Subunit of Influenza A Polymerase. Pharmaceuticals (Basel). 2023; 16:365.
78. Pang Y, Li H, Chen X, Cao Y, Jiang H, Huang J, Liu Y. A phase I, single-center, randomized, open-label, three-period crossover study to evaluate the drug-drug interaction between ZSP1273 and oseltamivir in healthy Chinese subjects. Antimicrob Agents Chemother. 2025; 69:e0172924.
79. Jiang Y, Wen J, Sun J, Shu Y. Evaluating the Public Health and Health Economic Impacts of Baloxavir Marboxil and Oseltamivir for Influenza Pandemic Control in China: A Cost-Effectiveness Analysis Using a Linked Dynamic Transmission-Economic Evaluation Model. Pharmacoeconomics. 2024; 42:1111-1125.
80. Nakagawa N, Ono R, Odanaka K, Ohara H, Kisara S, Ito K. A Pharmacoeconomic Study of Post-Exposure Prophylaxis Strategies for Influenza Virus Infections in Japan. Adv Ther. 2025; 42:772-787.
81. Pediatric Committee of the Chinese Medical Education Association, Respiratory Subspecialty Group of the Pediatrics Branch CMA, Pediatric Respiratory Working Committee of the Respiratory Physicians Branch CMDA, Pediatric Committee of the Chinese Research Hospital Association, Pediatric Committee of the China Non-public Medical Institutions Association, Pediatric Health and Drug Research Committee of the China Association of Traditional Chinese Medicine, Pediatric Drug Safety Branch of the China Medical News and Information Association, Pediatric Expert Committee of the China Primary Health Care Foundation, Global Pediatric Respiratory Alliance, Beijing Yao Dun Public Welfare Foundation. Guidelines for Diagnosis, Treatment, and Prevention of Influenza in Children (2024 Physician Edition). Chinese Journal of Practical Pediatrics. 2024; 39:881-895. (in Chinese)
82. Hussain S, Meijer A, Govorkova EA, *et al.* Global update on the susceptibilities of Influenza viruses to neuraminidase inhibitors and the cap-dependent endonuclease inhibitor baloxavir, 2020-2023. Antiviral Res. 2025; 241:106217.
83. China Centers for Disease Control and Prevention. China Influenza Surveillance Weekly Report 2025, Week 35, Issue 872. [2025-09-03] *https://www.chinacdc.cn/jksj/jksj04_14249/202509/t20250903_310160.html* (accessed September 15, 2025). (in Chinese)
84. Wang S, Zhang Th, Hu M, *et al.* Deep mutational scanning of Influenza A virus neuraminidase facilitates the identification of drug resistance mutations *in vivo*. mSystems. 2023; 8:e0067023.
85. Shah SAW, Palomar DP, Barr I, Poon LLM, Quadeer AA, McKay MR. Seasonal antigenic prediction of Influenza A H3N2 using machine learning. Nat Commun. 2024; 15:3833.
86. Lou J, Liang W, Cao L, *et al.* Predictive evolutionary modelling for Influenza virus by site-based dynamics of mutations. Nat Commun. 2024; 15:2546.
87. Yang B, Gostic KM, Adam DC, Zhang R, Einav T, Peng L, Wong SS, Tsang TK, Cummings DAT, Sullivan SG, Cobey S, Cowling BJ. Breadth of Influenza A antibody cross-reactivity varies by virus isolation interval and subtype. Nat Microbiol. 2025; 10:1711-1722.

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[§]These authors contributed equally to this work.
**Address correspondence to:*
Hongzhou Lu, National Clinical Research Center for Infectious Diseases, Shenzhen Third People's Hospital, The Second Affiliated Hospital Southern University of Science and Technology, Shenzhen, Guangdong, China;
E-mail: luhongzhou@szsy.sustech.edu.cn

Guangbin Chen, Department of Pharmacy, The Third People's Hospital of Shenzhen, Shenzhen, Guangdong, China;
E-mail: pts666666@126.com

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