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Viral Infections (N Malavige, Section Editor)

Antiviral Drugs for the Treatment and Prevention of Influenza

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Abstract

Purpose of review This paper provides an overview of the currently available treatment options for influenza infections. Currently, the options are limited to only one class of drugs known as the neuraminidase inhibitors (NAIs) (oseltamivir, zanamivir, laninamivir and peramivir) as there is widespread resistance against the adamantanes, an older class of antivirals. This review therefore discusses the mode of action, dosing, summary of clinical trial data and resistance within the context of NAIs. Newer antiviral therapies in late-phase clinical trials are also summarized in this review.

Recent findings Oseltamivir is the most commonly used NAI amongst the four different types available. The most recent meta-analysis of placebo-controlled trials demonstrates that for uncomplicated seasonal influenza, oseltamivir reduces symptoms by 16–24 h, while observational studies cumulatively suggest that oseltamivir treatment reduces mortality in severely ill patients. NAIs also play an important role in the treatment and control of avian influenza infections in humans, which is a public health concern due to their high case fatality rate. The latest analysis of data suggests that early treatment with oseltamivir can be attributed to reducing mortality in patients with avian A(H5N1) infections; data regarding oseltamivir effectiveness against A(H7N9) infections is however more limited. During the 2014–2015 influenza season, the frequency of resistance to the NAIs in all circulating viruses was below 1%, but immunocompromised patients infected with influenza are often at higher risk of shedding resistant viruses due to slow viral clearance and extended treatment regimens. Favipiravir, a polymerase inhibitor, has received limited approval for use in Japan, but its use is restricted to novel viruses that are resistant to other antiviral therapies. Antivirals such as thiazolide, nitazoxanide and

endonuclease inhibitor, S-033188, are currently in phase III clinical trials and other influenza antivirals are in early or mid-phase clinical trials.

Summary This review highlights a lack of different treatment options for influenza infections. While there are four different types of NAIs, in many countries, oseltamivir is the only available option. New therapies are being rapidly developed to meet the need for a greater variety of antivirals, and as such, it is likely that over the next decade, a broader range of influenza therapeutics will become available for treatment.

Introduction

Antivirals play an important role in the treatment of influenza, particularly for hospitalized and severely ill infected patients [1]. Although vaccinations remain the most appropriate method for preventing influenza infection, vaccine effectiveness is typically only 50–60% and can be lower during years of vaccine mismatch [2]. For example, during the 2014–2015 influenza season, the mismatch of the H3 component of the vaccine in a largely A(H3N2)-dominated influenza season in the USA resulted in an overall effectiveness of only 23% [3]. Antivirals will also play a central role in the treatment and prophylaxis of influenza infections in a pandemic situation, as specific vaccines will take many months to produce.

Currently, two classes of influenza antivirals have received widespread licensure around the world: the M2 ion channel blockers and the neuraminidase inhibitors (NAIs). In addition, a compound from the polymerase inhibitor class of antivirals has received limited licensure in Japan. The adamantanes, which are M2 ion channel blockers, were the first class of drugs licenced for influenza treatment. However, these compounds are typically only effective against influenza A viruses (not influenza B viruses) and can result in adverse side effects [4]. The other downside is that these compounds rapidly select for resistant viruses in patients undergoing treatment [5]. Because adamantane-resistant viruses are not typically diminished in their replication or transmissibility [5, 6], the risk existed that resistant strains could spread amongst circulating viruses. This came to fruition from 2005 onwards when adamantane-resistant A(H3N2) viruses with predominantly the S31N amino acid mutation in the M2 protein began circulating worldwide [7]. The S31N amino acid mutation was also present in the A(H1N1)pdm09 virus when it emerged in humans in 2009 and has been retained in the A(H1N1)pdm09 viruses that are still circulating. As such, all currently circulating influenza A viruses are resistant to the adamantanes [8–10]. Adamantanes are therefore not currently recommended for influenza treatment and will not be discussed further in this review.

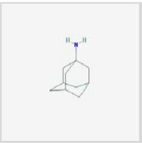
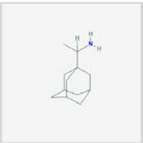
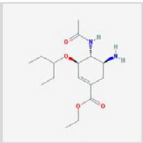
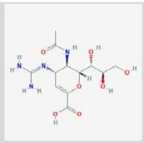
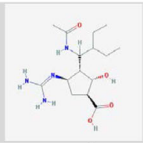
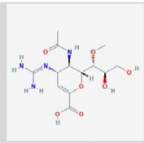
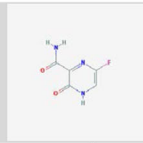
The neuraminidase inhibitors, the second class of drugs approved for influenza, are currently the most widely used antivirals for influenza treatment and prophylaxis [11, 12]. Currently, there are four NAIs available in certain countries around the world: zanamivir (Relenza®), oseltamivir (Tamiflu®), peramivir (Rapivab®/Rapiacta®/Peramiflu®) and laninamivir (Inavir®) (Fig. 1). Oseltamivir is delivered orally as a tablet, while zanamivir and laninamivir are inhaled as a dry powder and peramivir is administered intravenously [12]. The convenience of oral administration and widespread approval in many countries around the world have meant that oseltamivir has the largest global usage amongst the four NAIs [13].

The polymerase inhibitor favipiravir (T705) received limited licensure for the treatment of influenza in Japan in 2014 [12]. However, the drug can only be used for cases of severe influenza with novel viruses that are resistant to current available therapies [12].

Neuraminidase inhibitors

Mode of action

The NAIs target the active site of the neuraminidase (NA) protein of influenza A and B viruses [14]. The NA protein binds to sialic acid moieties in the epithelial

Class of drugs	M2 ion channel blockers		Neuraminidase inhibitors				Polymerase inhibitors
Name of drug	Amantadine	Rimantadine	Oseltamivir	Zanamivir	Peramivir	Laninamivir	Favipiravir
Trade name	Symmetrel®	Flumadine®	Tamiflu®	Relenza ®	Rapivab® Rapiacta ® Peramiflu ®	Inavir ®	Avigan®
Chemical structure							
Effective against both influenza A and B	X	X	✓	✓	✓	✓	✓
Approved in most countries	✓	✓	✓	✓	X[1]	X[2]	X[2]
Level of Resistance	Widespread	Widespread	Low	Negligible	Low	Negligible	Negligible
Administration via oral tablet	✓	✓	✓	X	X	X	✓
Side effects	Insomnia, light headedness, hallucinations, dizziness, head aches		Gastrointestinal- nausea, vomiting and diarrhoea Zanamivir may lead to respiratory distress				Potential embryotoxicity and teratogenicity
Recommended for use and availability in most countries	X	X	✓	X	X	X	X

[1] Approved in Japan, South Korea, USA and China
[2] Approved only in Japan. Favipiravir has very limited approval and can be only used for treatment of NAI resistant novel viral strains.

Fig. 1. Summary of the different antivirals currently available for treatment and prophylaxis of influenza. As depicted, drugs within the same class have structural similarities with each other, though there is more variation between the NAI side groups than the adamantane side groups. These structural similarities have basis in the shared functionality of these compounds, as drugs grouped within the same class target the same influenza protein. A lack of diversity is highlighted in options available for effective influenza treatment. For many countries, oseltamivir is the only available option for treatment. However, there is potential risk of widespread resistance against oseltamivir as was seen in 2008. PubChem CIDs for structures: 2130, 5071, 65028, 60855, 151164, 502272, 492405.

lining of the human respiratory tract and aids in the release of progeny viruses [14]. Inhibition of the NA protein therefore prevents effective spread of influenza viruses from infected host cells to other cells.

Types of drug

There are four different types of NAI available, and as shown in Fig. 1, they not only have structural similarities to each other as they are all analogous to sialic acid, the natural substrate for NA, but also have some distinctive features of their own [14]. For example, while all four NAIs have a carboxylate group similar to sialic acid, oseltamivir and peramivir have a hydrophobic side group which is absent in laninamivir and zanamivir [14].

Dosage

Oseltamivir (Tamiflu®) is an orally available prodrug compound of oseltamivir phosphate that is converted to oseltamivir carboxylate by endogenous esterases [14]. It was first licenced for use in 2000 and has approval for use in most countries [12]. The standard recommended treatment dosage for adults is

75 mg twice daily for 5 days and weight dependent for children under the age of 12 [11, 15]. Oseltamivir usage is restricted for teenagers between the ages of 10–19 in Japan due to concerns of neuropsychiatric side effects [16].

Zanamivir (Relenza®) was first licenced in 1999 and is delivered as a powder by inhalation. It is not recommended for patients with asthma or other underlying airway diseases [11]. Zanamivir has been licenced in several countries, but unlike oseltamivir, it is not approved for children under the age of 7 [11, 12]. The typical dose of zanamivir is 10 mg inhalations administered twice daily for 5 days [11]. During the 2009 pandemic, intravenous zanamivir was used for investigational treatment of critically ill patients under Emergency Investigational New Drug applications [17]. Typical doses used were 600 mg administered 12-hourly for 5 days [17]. It is still not currently FDA approved, even though recent studies suggest its effectiveness in treating severely ill patients [18, 19].

Peramivir (Rapivab®) was approved for intravenous use in Japan and South Korea in 2010 [20]. During the 2009 pandemic, peramivir was temporarily approved under an Emergency Use Authorization in the USA and received full FDA approval in 2015 [20]. It is also currently used for the treatment of some A(H7N9) infections in China [20]. While a 600 mg infusion for 15–30 min is approved as a dosage for adults in the USA, in Japan, a 10 mg/kg dosage is also approved for children [12].

Laninamivir (Inavir®) was licenced for use in Japan in September 2010. It is a long-acting drug, such that a single 40 mg administration by inhalation in adults and 20 mg administration for children under 10 is sufficient to promote antiviral activity for at least 5 days [21]. Laninamivir is very popular in Japan, with its use during the 2014–2015 influenza season exceeding that of oseltamivir [12].

Oseltamivir, zanamivir and laninamivir can also be used for prophylactic purposes; a 75 mg once-daily dose is recommended for oseltamivir while a 10 mg once-daily dose can be used for zanamivir, for a duration of 7–10 days for both drugs [11]. For laninamivir, a 20 mg single inhalation once daily for 2 days is recommended as a prophylactic dosage in Japan [12]. Pharmacokinetic studies show that doses of oseltamivir, peramivir and laninamivir need to be adjusted for patients with reduced renal function [20, 22, 23].

Side effects

Side effects of the four NAIs are similar and generally involve gastrointestinal effects such as nausea, vomiting and diarrhoea [11, 24•]. Zanamivir can also cause some respiratory distress (sinusitis, nasal symptoms) [11].

In 2007 in Japan, a small number of teenagers experienced neuropsychiatric episodes that were linked with oseltamivir use, and resulted in the individuals committing suicide [25]. This initiated the Japanese government to restrict oseltamivir use for patients aged 10–19 years, although follow-up studies have not conclusively linked the episodes with oseltamivir use [16, 25, 26].

Evidence from clinical trials (efficacy and safety)

Oseltamivir and zanamivir

A meta-analysis of all published and unpublished data from randomized placebo-controlled trials on the effectiveness of both zanamivir and

oseltamivir found both drugs reduced symptom duration in otherwise healthy patients with uncomplicated influenza by 16–24 h [24•]. However, different meta-analyses report varying effects of oseltamivir on reducing hospitalizations or secondary complications [24•, 27•]. This led to considerable debate regarding the effectiveness of the NAIs and more specifically the role of oseltamivir in treating severely ill patients [28]. Due to ethical reasons, there is a paucity of placebo-controlled trials evaluating the effect of oseltamivir on the treatment of severe influenza; and therefore, conclusions need to be drawn from observational studies, of which the quality of the evidence is weaker than a placebo-controlled study. By attempting to control for confounding biases with data from observational studies, meta-analyses have found both zanamivir and oseltamivir to have a net benefit in reducing mortality and hospitalization [29] and reducing the probability of influenza-related complications [30]. Analysis of data from the 2009 pandemic also attributes the use of oseltamivir to reducing mortality in adults, critically ill patients and pregnant women infected with influenza [31]. Zanamivir and oseltamivir are also shown to have a significant benefit as a prophylactic, when evaluated in meta-analyses of randomized control trials [24•, 27•, 32].

Peramivir and laninamivir

Peramivir has similar clinical effectiveness to oseltamivir and zanamivir for uncomplicated influenza [20, 33, 34]. However, the intravenous delivery is ideal for severely ill hospitalized patients where oral administration is challenging. Two observational studies reported on the use of investigational intravenous peramivir in severely ill hospitalized patients during the 2009 pandemic and while one study found the drug use to be associated with increased survival in patients, the other did not [35, 36]. Comparative studies have found that peramivir has similar efficacy to oseltamivir in treating influenza in severely ill hospitalized patients [37–40]. A clinical trial in high-risk patients found that the therapeutic efficacy of peramivir increased with repeated dosing, with a 600 mg dose being more effective than a 300 mg dose [40]. However, a different study found no effect of peramivir treatment compared to placebo in hospitalized patients, despite 5 days of treatment with a 600 mg dose [41].

Post-marketing surveillance and observational studies in Japan have found laninamivir to be effective in resolving influenza symptoms and to have similar clinical effectiveness to that of oseltamivir and zanamivir [33, 42, 43]. Laninamivir has also been shown to provide significant prophylactic effect in randomized placebo-controlled trials [44, 45].

General observations from clinical trials

It has been repeatedly found that administration of NAIs within the first 48 h of symptom onset correlates with improved clinical outcomes, and that delayed treatment is associated with reduced effectiveness [1, 29, 31, 46]. However, in cases of severe infections with A(H5N1) or A(H1N1)pdm09 viruses, even late treatment has been shown to have some benefit compared to no treatment [47–49]. There are also reports that

show that the drug effectiveness of both oseltamivir and laninamivir is reduced against influenza B virus infections compared to that against influenza A virus infections [43, 50, 51]. Although these observations fit with in vitro IC_{50} (50% inhibitory concentration) data, which show that a greater concentration of drug is needed to inhibit influenza B viruses compared with influenza A viruses [52], further clinical studies are necessary to clarify this issue.

In cases of severe infection, prolonged therapy and higher dosage regimens are often a consideration. Double doses of oseltamivir (150 mg twice daily) have been previously tested in clinical trials and found to be well tolerated [53–55], but two recent studies have found no added virological or clinical benefit compared to single doses [56, 57].

Clinical efficacy of NAIs against avian influenza

Human infections with avian influenza viruses such as A(H5N1) and A(H7N9) are often severe and have a high case fatality rate (52 and 38%, respectively, as of January 2017) [58–62]. Limited information is available about the effectiveness of the NAIs against avian influenza infections in humans, although studies in animal models indicate treatment benefit and improved responses to higher doses [63]. Analysis of a global patient registry of A(H5N1) human infections by Adisasmito et al. in 2010 found that oseltamivir treatment was associated with 49% reduction in mortality across 308 cases [47]. Clinical findings of A(H7N9) human infections found that the severity of infection remained high despite the vast majority of patients (108/111) receiving oseltamivir therapy [64]. However, it should be noted that only 9.9% of the patients in this study received oseltamivir therapy within 48 h of symptom onset, the period in which the drug would be expected to have maximum benefit [64]. Combination therapy of oseltamivir and peramivir has also been used for the treatment of A(H7N9)-infected patients, but was not superior to oseltamivir monotherapy [65]. There is only limited evidence of the effectiveness of NAI prophylaxis for avian influenza virus infections due to a lack of studies [66].

Resistance

Resistance in circulating strains

The susceptibility of viruses to the NAIs can be reduced due to mutations in the viral NA protein, often in or near the enzyme active site [67, 68]. The prevalence of these mutations differs across NA types and subtypes [67]. While some NA mutations, such as H275Y in A(H1N1)pdm09 viruses confer resistance to oseltamivir and peramivir and not to zanamivir and laninamivir, other NA mutations such as D197N in influenza B viruses lead to resistance to both oseltamivir and zanamivir [67]. This is observed because mutations abrogate binding interactions of the NA active site with the side groups of the NAIs, which can differ between the four NAIs (illustrated in Fig. 1) [68].

A global surveillance study conducted between 2008 and 2013 found that the frequency of oseltamivir resistance in otherwise healthy patients undergoing antiviral treatment was low (2.2%), and mostly developed in children aged 1–5 years amongst whom prevalence was 7.9% [69]. Other studies in paediatric

populations have also found frequency of oseltamivir resistance post-treatment to be 5.5–8.4% [70, 71]. Immunocompromised patients are at a high risk for the development of resistant viruses due to prolonged viral shedding and longer treatment periods [72]. The most commonly described NA mutations that confer NAI resistance from case studies of immunocompromised patients have been E119V in A(H3N2) viruses and H275Y in seasonal A(H1N1) and A(H1N1)pdm09 viruses [72–80].

Mutations in amino acid residues of the NA active site, especially those directly involved with enzyme activity, will typically confer a fitness 'cost' on the virus, compromising viral replication and transmissibility [67]. As such, it was first thought that a NAI-resistant virus was unlikely to be 'fit' enough to spread amongst the community in the absence of drug pressure [67, 68]. However, some resistant viruses have been able to replicate and transmit with equivalent (or greater) intensity than NAI-sensitive strains. The most outstanding example of a fit NAI-resistant virus was the global spread of the oseltamivir-resistant A/Brisbane/59/2007-like seasonal A(H1N1) virus containing the H275Y NA mutation in 2008 [81, 82]. This was surprising at the time, as previous studies had indicated that the H275Y NA mutation reduced viral fitness [83–85]. However, retrospective studies identified 'permissive' mutations (R222Q, V234M and possibly D354G) in the NA of A/Brisbane-like viruses, which arose between 2006 and 2008 during natural virus evolution but created a viral 'backbone' that could acquire the H275Y mutation without fitness loss [86–90]. Though the oseltamivir-resistant seasonal A(H1N1) virus was replaced in 2009 with the A(H1N1)pdm09 virus (which was oseltamivir-sensitive) [91], the episode serves as a cautionary tale for the potential global spread of an oseltamivir-resistant virus in the future. Clusters of oseltamivir resistance in localised communities have been described more recently, with A(H1N1)pdm09 viruses containing the H275Y NA mutation in Australia in 2011 [92] and in Japan in 2014 [93] and influenza B viruses containing the I221V NA mutation in the USA (North Carolina) in 2011 [94]. Despite these clusters of oseltamivir-resistant viruses in the past 5 years, overall levels of NAI resistance in currently circulating viruses remain low (<1%) [10, 95].

Resistance in avian strains

In patients infected with avian A(H5N1) viruses, oseltamivir treatment has led to the selection of viruses with the H275Y NA mutation [96, 97], the same mutation seen in seasonal A(H1N1) and A(H1N1)pdm09 viruses. In addition, a virus with a N294S NA mutation, conferring resistance to oseltamivir and peramivir, was detected in a patient from Egypt prior to treatment [98]. For the human cases of A(H7N9) infection in China since 2013, several viruses with the R292K NA mutation have been observed in oseltamivir-treated patients [99–104]. Of concern was a recent report on the fifth A(H7N9) epidemic wave in China, which stated that 7–9% of viruses analysed had molecular markers in the NA gene for reduced NAI susceptibility [105••]. Given the high case fatality rates observed in patients infected with either A(H5N1) or A(H7N9) viruses, and the lack of availability of a suitable vaccine, the development of NAI resistance in these strains presents a public health concern. Fortunately, there

has been no evidence of sustained person-to-person transmission with either NAI-resistant or NAI-sensitive H5 or H7 viruses to date.

Favipiravir (T705)

Favipiravir (T705) is a competitive inhibitor of the RNA-dependent RNA polymerase and has been shown to have antiviral activity against a broad range of viruses, including influenza [106]. In vitro and in vivo data suggest that favipiravir has antiviral activity against influenza A, B and C viruses, including avian A(H5N1) and A(H7N9) strains [107, 108]. Cell culture-based susceptibility assays have also shown favipiravir to have in vitro activity against NAI-resistant viruses with H275Y, R292K, E119V and D197E NA mutations [109]. Clinical trial results from Japan in 2009 showed favipiravir to have similar effectiveness as oseltamivir, although the primary results are not yet published [12]. Following the 2009 clinical trials, favipiravir (Avigan®) received only limited licensure in Japan due to concerns of side effects. The limitations state that it can only be manufactured following a request from the Ministry of Health, Labour and Welfare and can only be used to treat infections with novel strains (i.e. non-seasonal influenza virus infections) that are resistant to other available antiviral therapies [110]. The approved regimen includes a 1600 mg twice daily administration as an initial dose, followed by 600 mg twice daily administrations for 5 days [110]. Studies in animal models have shown that there is a risk of teratogenicity and embryotoxicity with favipiravir, which may have been the reason for restricting its use in humans [111]. However, ongoing clinical trials and safety studies are being conducted and a phase III clinical trial was recently completed in America and Europe, but there are no reports yet regarding the outcome of these studies [112•].

Serial passaging of influenza seasonal A(H1N1) and A(H1N1) pdm09 viruses in favipiravir has generated high rates of mutations which have rendered the viruses non-viable, with this lethal mutagenesis being proposed as the mechanism of antiviral action of the drug [113]. An analysis of viruses isolated from patients pre- and post-treatment with favipiravir in phase III clinical trials in Japan found no substantial changes in susceptibility, although three amino acid substitutions in PB1, PB2 and PA proteins were identified in viruses isolated post-treatment [109]. One of these mutations, L666F in the PA protein, was found to reduce polymerase activity [109].

Therapies in late-phase clinical trials

In an effort to increase the options available for influenza treatment, a number of new therapies are currently being actively evaluated [114]. Nitazoxanide (NTZ) and S-033188 are two orally available antivirals currently in phase III clinical trials [112•, 114]. Nitazoxanide is a repurposed antiprotozoan broad-spectrum drug that also has antiviral activity and is currently in multiple phase II and III clinical trials [112•]. The active metabolite of NTZ, tizoxanide (TIZ), is thought to target the trafficking and maturation of the HA during viral replication [115, 116]. In vitro studies have shown NTZ to have activity against a range of different influenza A viruses and B viruses [116–118], and published results from phase IIb/III clinical trials found that NTZ reduced both viral load and

symptom duration in uncomplicated influenza-infected patients [119]. Combination therapy of nitaxozanide and oseltamivir has shown synergistic effects in vitro and has been evaluated in clinical trials completed in February 2017 (NCT01610245) [120].

S-033188 is a prodrug that inhibits the cap-snatching endonuclease of the PA subunit of influenza A and B viruses and is currently being developed by Shionogi Pharmaceuticals Co. Ltd. [12, 112•]. Following encouraging results from a phase II clinical trial in 2016, where all three doses of the drug (10, 20 and 40 mg) resulted in a significant reduction in symptoms and viral loads compared to placebo, a phase III clinical trial is being conducted in Japan in 2017 [121].

Development of human monoclonal antibodies (mAb) with broad neutralizing anti-HA activity is an exciting avenue of active research. While several mAbs are being studied experimentally, five are being assessed in clinical trials. CR6261 (NCT02371668), MHAA4549A (NCT02293863) and VIS410 (NCT02989194) are currently in the process of recruiting for phase II clinical trials, while CR8020 (NCT01938352) and Medi18852 (NCT02603952) have been assessed in phase II clinical trials; although, no published results are currently available. Promisingly, pre-clinical studies in mice and ferrets suggest good in vivo efficacy of these mAbs against infections with H5 and H7 avian influenza viruses [112•].

Conclusion

Currently, NAIs are the only effective antiviral options available due to widespread resistance to the older adamantane class of antivirals. Accumulated evidence from placebo-controlled trials demonstrates that NAIs have a moderate effect on reducing symptoms in heathy patients. Observational studies suggest that NAIs reduce mortality and secondary complications, but the quality of evidence from observational studies is not as strong as that from placebo-controlled trials. This limitation is difficult to overcome, given the ethical conundrums in designing a placebo-controlled study with severely ill hospitalized patients. Infections due to avian influenza viruses are also an ongoing public health concern, and evidence on the usefulness of NAIs in their treatment and prevention is scarce. Data suggests that early treatment with oseltamivir has had significant benefits on reducing mortality due to A(H5N1) infections in humans, but so far no such data exists for oseltamivir treatment against A(H7N9) infections.

The limited availability of different antivirals in most of the world means that if there is widespread resistance to oseltamivir, very few countries will have alternate treatment options. Although current levels of resistance in circulating seasonal influenza strains is low, there is always a risk that resistant strains may spread, as seen with the global emergence of oseltamivir-resistant seasonal A(H1N1) viruses during 2008. These factors have prompted Japan to approve favipiravir, albeit in a limited capacity, for use against novel viruses that are resistant to the NAIs. It remains of great importance that a broader range of anti-influenza drugs become more widely available. Fortunately, a number of new therapeutic options are being developed and undergoing clinical trials to potentially address this need. Of these, nitaxozanide and S-033188 are in phase III trials and several other molecules and human monoclonal antibodies are in

earlier phases of clinical trials. Therefore, while treatment options are currently limited, the next decade is likely to see an increase in the different types of influenza antivirals available and with this the potential for antiviral treatment to significantly reduce the morbidity and mortality caused by influenza.

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Compliance with Ethical Standards

Conflict of Interest
Rubaiyea Farrukee declares that he has no conflict of interest.
Aeron C. Hurt declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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