Seasonal Human Influenza: Treatment Options

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Opinion statement
Seasonal influenza can be a self-limiting illness in healthy individuals but is associated with short-term morbidity and economic burden. Influenza can cause significant morbidity and mortality in young children, the elderly, pregnant and post-partum women, patients with co-morbidities and the immunocompromised. Neuraminidase inhibitors (NAIs) are the treatment of choice for influenza due to widespread resistance to the adamantanes. NAIs are efficacious for the treatment of influenza in ambulatory patients with mild illness, when initiated within 48 h of symptom onset. Early treatment with NAIs has been shown to reduce otitis media in children, and lower respiratory tract complications, resulting in antibiotic therapy, in adults. Evidence on the efficacy of NAIs for the prevention of influenza-related complications in at-risk populations, based on reviews of data from randomised trials is inconclusive. However, observational studies suggest that in hospitalised patients early treatment with NAIs has been associated with reduced mortality. NAIs should be initiated as soon as possible in patients at high-risk of influenza-related complications, with suspected or proven influenza, hospitalised patients and patients with severe or progressive disease. NAIs can be considered in previously healthy patients when therapy can be initiated within 48 h of symptom onset. In previously healthy patients, the therapeutic efficacy of oseltamivir is time-dependent, with maximal benefit observed when therapy is initiated within 48 h of symptom onset. However, several observational studies suggest therapeutic benefit beyond 48 h, in hospitalised patients, severe disease, and patients
at high risk of complications, including pregnant women. NAIs should be considered in patients at high risk of influenza-related complications who present late. Further studies are needed to define the optimal timing of NAIs. Oseltamivir-resistant virus has been widely reported but is predominantly an issue in H1N1 seasonal influenza. Zanamivir-resistant influenza virus is rare, and inhaled or intravenous (IV) zanamivir is the treatment of choice in proven or suspected oseltamivir-resistant virus. Intubated patients with severe influenza can be treated with oseltamivir (suspension) administered via nasogastric tube. The commercial dry powder formulation of zanamivir should not be administered, via nebulisation, as it has been associated with ventilator malfunction and mortality. In intubated patients, when there are concerns about gastric absorption, IV zanamivir should be obtained under Emergency Investigational New Drug access schemes. Currently available evidence does not support the use of high-dose or extended-duration oseltamivir in patients with severe influenza, but does require further investigation. Extracorporeal membrane oxygenation has not been shown to be superior to conventional management in patients with influenza-associated acute respiratory distress syndrome and should be considered as salvage therapy. Corticosteroids should not be used in the treatment of severe influenza as this has been associated with increased risk of mortality and bacterial superinfection.

Introduction

Influenza is a contagious respiratory virus transmitted via droplets produced by coughing and sneezing. In the majority of individuals, seasonal influenza is a self-limiting disease but is associated with significant economic burden [1]. However, influenza can cause significant morbidity and mortality in high-risk groups, including the elderly, young children and people with co-morbidities [2].

In temperate climates, seasonal influenza causes outbreaks during the winter, while in tropical areas there is year-round transmission. There are three major strains of seasonal influenza: A, B and C, but influenza A and B cause the majority of disease. Influenza A is classified into subtypes according to the combination of haemagglutinin or ‘H’ protein and the neuraminidase or ‘N’ protein on the surface of the virus [3]. New viruses are created through antigenic shift or drift. A pandemic occurs when a new virus emerges and circulates in a population where there is minimal immunity; this can occur outside the normal influenza season [3].

Symptoms in otherwise healthy adults include fever, cough, headache, runny nose, myalgia and malaise. Cough within 48 h of fever onset is highly predictive of influenza during peak times of virus circulation [4]. Influenza can be confirmed by culture of respiratory secretions but this is resource-intensive and turnaround time is slower than polymerase chain reaction (PCR). Culture has been superseded by reverse-transcriptase PCR, which is highly sensitive and provides rapid results [2]. Rapid influenza diagnostic tests that provide results within 30 min are available but sensitivity is only reported to be 40–70% [5].

Influenza vaccine is the first choice for the prevention of influenza and has been shown to be effective in preventing disease in healthy adults and older children [6]. Influenza vaccine has been associated with a reduction in cardiac events in patients with a history of cardiac disease [7] but efficacy is reduced in the elderly [1, 6]. Live attenuated influenza vaccine is efficacious in young children aged between 6 months and 7 years [1]. Antivirals are highly effective for prophylaxis in exposed individuals but use needs to be weighed against cost, side effects and emergence of viral resistance [8].

The two main classes of antivirals for the treatment of influenza are the adamantanes (M2 ion channel inhibitors) and the neuraminidase inhibitors (NAIs).
The NAIs are the first choice for the treatment of seasonal influenza [2•] as the clinical utility of the adamantanes is limited by widespread antiviral resistance [9]. A summary of the currently available influenza antivirals is provided in Table 1. NAIs are efficacious for the treatment of influenza in ambulatory patients with mild illness, when initiated within 48 h of symptom onset [10–12]. This review will focus on the treatment of seasonal influenza. Emerging avian influenza is beyond the scope of this paper.

Table 1. Antivirals for the treatment of influenza

| Neuraminidase inhibitors | Approval status | Administration | Dosing | Contraindications |
|--------------------------|-----------------|----------------|--------|------------------|
| Oseltamivir              | FDA-approved for the treatment of acute, uncomplicated influenza in subjects ≥2 weeks of age [95, 96] | Oral | Adult 75 mg bid for 5 days, Renal impairment CrCl <30 ml/min 75 mg once daily [13] Haemodialysis [27] 30 mg after alternate sessions CAPD [27] 30 mg weekly Paediatric Age <1 year (duration 5 days) [43] 9–11 months: 3.5 mg/kg bid ≤8 months: 3 mg/kg bid Age ≥1 year (duration 5 days) [96] ≤15 kg: 30 mg bid >15 to 30 kg: 45 mg bid >23–40 kg: 60 mg bid >40 mg: 75 mg bid | Airways disease, Inability to operate inhalational device, Lactose allergy |
| Zanamivir                | FDA-approved for treatment of acute, uncomplicated influenza in subjects ≥7 years of age [97] | Oral inhalation Intravenous under clinical investigation Published phase II trials [34] Phase III development [98] | Adult 10 mg bid for 5 days (as two 5-mg inhalations) | |
| Peramivir                | No FDA approval, available via EINDS. Licensed in Japan and South Korea [99] | Intravenous | Adult 300 mg IV in uncomplicated influenza 600 mg IV in complicated influenza, duration unclear [38] | |
| Laninamivir              | No FDA approval | Oral inhalation Phase III development [98] | Adult 40 mg once | |

| Adamantanes              | FDA-approved in subjects ≥1 year of age [100] | Oral | Adult 200 mg daily | Adamantane-resistant virus |
|--------------------------|-----------------------------------------------|------|--------------------|---------------------------|
| Amantadine               |                                               |      |                    |                           |
| Rimantadine              | FDA-approved in subjects ≥1 year of age [100] | Oral | Adult 100 mg bid   |                           |
Treatment

**Drug classes**

**Neuraminidase inhibitors**

- NAIs are effective against all strains of influenza. They act by interfering with viral replication by blocking the release of the progeny virus from infected host cells and spread within respiratory secretions [13].
- The primary NAIs are oseltamivir and zanamivir; newer agents, peramivir and laninamivir, have limited approval and availability (Table 1).
- Oseltamivir and zanamivir are both efficacious for the treatment of influenza. Zanamivir is preferred in patients suspected of having oseltamivir-resistant influenza, while oseltamivir is preferred in patients with underlying airways disorders or who are unable to use an inhalational device [2•].

**Adamantanes**

- The adamantanes are only effective against influenza A and act by interfering with viral uncoating inside the cell [13].
- Amantadine and rimantadine are equally efficacious, but their use should be discouraged as they are ineffective as a result of widespread resistance and are associated with adverse effects [14].

**Polymerase inhibitors**

- Favipiravir (T-705) is a polymerase inhibitor that has been evaluated in phase III studies in Japan and phase II studies in the US. It selectively inhibits RNA-polymerase of the influenza virus. It is active against a broad range of influenza subtypes, including resistant virus, and demonstrates synergism when used with oseltamivir [15•].

**Efficacy and endpoints**

**Neuraminidase inhibitors**

- NAIs are effective for the treatment of influenza in ambulatory patients with mild illness, when treatment is commenced within 48 h [10–12]. In previously healthy patients, NAIs reduce symptom duration and severity, viral shedding, and time taken to return to normal activities [16]. In a meta-analysis, oseltamivir has been shown to reduce lower respiratory complications that lead to antibiotic use by 28 % compared with placebo [17]. Treatment within 12 h of symptom onset has been shown to reduce...
the incidence of otitis media, and treatment within 24 h of symptoms decreased duration of illness by 3.5 days [18]. However, the efficacy of NAIs for the prevention of complications in some high-risk groups is less clear [19].

- In 2012, Jefferson and colleagues published a Cochrane review of NAIs for the treatment and prevention of influenza in healthy adults and children, but the review was hampered by difficulties in obtaining clinical study reports [20]. They analysed data from 25 of 67 randomised controlled trials reviewed, but noted a high risk of reporting and publication biases. The investigators concluded that oseltamivir had a modest benefit in previously healthy patients, reducing duration of symptoms by 21 h, but had no effect on hospitalisation [20].

- In 2013, Michiels and colleagues published a systematic review of systematic reviews to address the value of NAIs for the prevention and treatment of seasonal influenza focusing on data from randomised clinical trials [8]. NAIs can reduce the time to alleviation of symptoms in previously healthy adults and children but the effect in the elderly and at-risk individuals is unclear (Fig. 1a). The use of NAIs was associated with a non-significant reduction in the odds of

![Graphical representation of data from Michiels et al. [8] on the efficacy of oseltamivir (dark grey bars) and zanamivir (light grey bars) for selected outcome measures and study populations. (a) Reduction in time to alleviation of symptoms; (b) pneumonia; (c) hospitalisation. Error bars denote 95% CIs. Data from Michiels et al. [8] are based on a meta-analysis of randomised trials comparing treated subjects with untreated subjects. CI confidence interval, O oseltamivir, Z zanamivir, OR odds ratio.](image-url)

Fig. 1. Graphical representation of data from Michiels et al. [8] on the efficacy of oseltamivir (dark grey bars) and zanamivir (light grey bars) for selected outcome measures and study populations. (a) Reduction in time to alleviation of symptoms; (b) pneumonia; (c) hospitalisation. Error bars denote 95% CIs. Data from Michiels et al. [8] are based on a meta-analysis of randomised trials comparing treated subjects with untreated subjects. CI confidence interval, O oseltamivir, Z zanamivir, OR odds ratio.
pneumonia in most study populations (Fig. 1b), but the meta-
analysis did not find any consistent reductions in the odds of
hospitalisation (Fig. 1c). Therefore, while the review documented
clear benefits in less definitive outcomes such as time-to-alleviation
of symptoms in previously healthy children and adults [8], it was
unable to give conclusive evidence on the efficacy of NAIs in patients
at the highest risk of influenza-related complications, and
highlighted the lack of evidence for the efficacy of NAIs in more
definitive outcomes such as pneumonia and hospitalisation.

- A systematic review and meta-analysis of 74 observational studies in
2012 by Hsu and colleagues attempted to address the benefits and
potential harm of antivirals for the treatment of influenza [21]. The
meta-analysis suggested that in high-risk patients NAIs may reduce
mortality (odds ratio [OR] 0.23], hospitalisation (OR 0.75) and
duration of symptoms when compared with no therapy. These
findings must be interpreted with caution as the quality of evidence
is low, limited by multiple confounders in the original studies and
publication and reporting biases [21].

- A recently published meta-analysis of individual participant data com-
prised of 29,234 hospitalised patients worldwide with pandemic influ-
enza A H1N1(09) demonstrated that treatment of adult patients with
NAIs reduced mortality risk compared with no treatment. The effect is
more pronounced if treated early. A greater benefit was observed with
early NAI treatment. However, no mortality benefit could be established
in children treated with NAIs. The study was unable to adjust for disease
severity but the results suggest that NAIs should be initiated early in
patients with influenza who require hospitalisation [22].

- In summary, there was a lack of conclusive evidence on the efficacy
of NAIs for the prevention of influenza-related complications in at-
risk populations based on reviews of data from randomised trials.
However, observational studies suggest that, in hospitalised patients,
early treatment with NAIs has been associated with reduced mor-
tality. The World Health Organization and Centers for Disease
Control (US) recommend that NAIs should be used for the treatment
of influenza in patients at risk of influenza-related complications,
hospitalised patients and patients with severe or complicated illness
[2, 23]. NAI therapy can be considered in previously healthy
people when it can be initiated within 48 h of symptom onset, but
needs to be weighed against the risk of drug-related adverse effects
and the potential for NAI resistance.

Administration and dosing

Oseltamivir

- Oseltamivir is administered as an oral formulation (tablet or sus-
pension) as it is readily absorbed from the gastrointestinal tract. The
standard treatment dose is 75 mg twice daily for 5 days for healthy adults and children over 12 years of age [24].

- Oseltamivir undergoes hepatic metabolism to its active form but is predominantly cleared by the kidneys. Dose reduction is not required in patients with hepatic impairment but is required in patients with renal impairment (Table 1) [25]. Dose reduction is required in patients receiving concurrent continuous venovenous hemofiltration and extracorporeal membrane oxygenation (ECMO) [26]. Dose-adjusted oseltamivir is efficacious and safe in patients with end-stage renal failure receiving renal replacement therapy [27].

- Intravenous (IV) oseltamivir was shown to have a favourable safety and pharmacokinetic profile in phase I clinical studies [28] but further development has been stopped.

- The suspension formulation (or dispersed capsules) of oseltamivir can be administered via nasogastric tube in mechanically ventilated patients who have reliable gastric absorption [29].

Zanamivir

- Zanamivir has very low oral bioavailability [13] and is therefore administered via oral inhalation of a dry powder or IV. The approved route of administration is oral inhalation, using a purpose-manufactured device. The standard treatment dose of 10 mg 12-hourly is administered as two 5 mg inhalations, for 5 days. Renal dose adjustment is not required in patients receiving inhalational therapy [30].

- Administration of zanamivir in a lactose powder solution via endotracheal nebulisation (of the commercial powder containing lactose) has been reported in intubated patients with severe influenza. This route of administration has resulted in ventilator malfunction, which likely contributed to mortality [31, 32]. The commercial lactose powder formulation of zanamivir should only be used for oral inhalation [33].

- IV zanamivir is in clinical development and has shown promising results in a phase II study [34]; renal dose adjustment is required [34, 35]. IV formulations can be accessed under clinical trial or Emergency Investigational New Drug access schemes in some countries.

Peramivir

- Peramivir is administered IV. One dose is sufficient in outpatients as the drug exhibits prolonged anti-influenza activity [36]. A dose of 600 mg IV daily is recommended in high-risk adult patients [37]. The optimal duration of therapy in complicated disease remains unclear. Dose adjustment is required in renal impairment [38].

- Peramivir was associated with favourable outcomes in patients with severe pandemic influenza treated under an Emergency Investigational New Drug access scheme [38]. However, in a subsequent publication,
peramivir was associated with increased risk of influenza-related complications, and death in patients with severe influenza [39]. These findings may have been influenced by disease severity. Further studies are required to define the role of peramivir in the treatment of severe influenza.

Paediatric considerations

- Young children (<2 years of age), infants and children with chronic medical conditions are at risk of influenza-related complications [2••, 40].
- NAIs have been shown to be effective for the treatment of influenza in healthy children, reducing symptom duration and time to return to normal activities. Oseltamivir has been shown to reduce influenza-related complications. However, there is a paucity of evidence on the efficacy of NAIs in children ‘at risk’ of influenza-related complications. Oseltamivir did not reduce symptom duration in children with asthma [41]. Retrospective data suggests that early initiation of NAIs may reduce mortality in children [42] but further studies are needed to understand the role of NAIs for the treatment of children at risk of influenza-related complications.
- Weight-based dosing of oseltamivir is recommended in children aged 1–12 years of age [13].
- Oseltamivir pharmacokinetics differ in the very young. Oseltamivir should be dosed at 3.5 mg/kg orally twice daily in children aged between 9 and 11 months, and 3 mg/kg orally twice daily in infants less than 8 months of age [43].
- NAI resistance may be an issue in the paediatric population, with higher rates of post-treatment oseltamivir resistance observed in paediatric patients, but this may be the result of under-dosing in young children, and requires further evaluation [25, 44].
- High rates of neuropsychiatric side effects have been observed in children treated with oseltamivir (up to 36 %) and may be the result of ABCB1 polymorphism which increases brain permeability of the drug [45]. Caution should be exercised when prescribing oseltamivir to adolescents due to reports of significant neuropsychiatric events in this age group; symptomatic management should be used in those who are not at high risk of influenza-related complications [46].

Pregnancy considerations

- Pregnant and postpartum women are at risk of influenza-related complications [2••, 47] and should receive prompt antiviral therapy with NAIs [2•, 23••]. Oseltamivir and zanamivir are pregnancy category C drugs, as a result of inadequate safety data. However, use of oseltamivir has not been associated with adverse neonatal outcomes and is recommended in pregnant and post-partum women with proven or suspected influenza [48–50].
- Oseltamivir should be dosed per the recommendations for non-pregnant women [2•].

**Adverse effects and contraindications**

**Oseltamivir**

- Gastrointestinal side effects occur more commonly in patients treated with oseltamivir than zanamivir [12]. Nausea and vomiting occur in approximately 10% of patients treated with oseltamivir [2•]. Drug administration with food reduces gastrointestinal toxicity, and does not interfere with absorption [16, 51].
- Neuropsychiatric effects (including confusion, delirium, hallucinations and self-harm) have been reported in patients treated with oseltamivir [2•]. Japanese authorities raised concerns in 2007 following suicide in two adolescents treated with oseltamivir [46]. However, widespread use of oseltamivir in Japan has not been associated with increased mortality related to self-harm [52]. A review of clinical trial and postmarketing data by the FDA failed to demonstrate a clear link between oseltamivir and neuropsychiatric events. Influenza-related encephalitis may have contributed to the neuropsychiatric events reported from Japan [46]. Patients treated with oseltamivir should be closely monitored for neuropsychiatric symptoms.
- Oseltamivir is contraindicated in patients allergic to any components of the medication.

**Zanamivir**

- Zanamivir is well-tolerated, with minor gastrointestinal upset and respiratory symptoms (sinusitis, bronchitis, cough) occurring in approximately 2% of treated patients. Serious allergic reactions are rare [13].
- Inhaled zanamivir is contraindicated in persons who are unable to use an inhalation device, including young children (<5 years of age), the elderly and patients with functional impairment or impaired conscious level.
- Zanamivir has been associated with bronchospasm and is therefore relatively contraindicated in patients with underlying airways disease [30].
- Zanamivir is contraindicated in patients allergic to lactose as it is delivered with a lactose vehicle [30].

**Unresolved issues with neuraminidase inhibitors**

**High-dose oseltamivir**

- Standard dosing recommendations of oseltamivir are derived from trials conducted in low-risk patients with mild disease [11]. As oseltamivir is well tolerated at doses up to seven times the standard recommendation [53], authorities have suggested the use of double-dose oseltamivir, for
up to 10 days’ duration, for patients with severe disease [54]. However, a multicentre, double-blind, randomised controlled trial did not show improved clinical or virological outcomes in patients with severe influenza treated with double-dose oseltamivir compared with standard dosing [55]. Likewise, in Hong Kong a prospective intervention of high-dose oseltamivir did not show significant difference in clinical or virological outcomes between patients treated with standard-dose versus high-dose oseltamivir. However, in a subanalysis of influenza B patients, higher-dose oseltamivir was associated with improved virologic response [56]. At this stage there is inadequate evidence to recommend the use of high-dose or extended-duration oseltamivir.

### Optimal timing

- The therapeutic efficacy of oseltamivir is time-dependent. Early initiation of therapy (within 48 h of symptom onset) has been shown to decrease symptom duration and severity and time taken to return to normal activities [16]. International guidelines advocate early treatment (ideally within 48 h of symptom onset) in at-risk individuals [2•, 23••]. Early initiation of NAIs has been associated with improved survival in observational studies [57, 58].

- While it is accepted that early treatment provides maximal benefit, the efficacy of delayed treatment remains unclear. Observational data suggests that treatment with NAIs beyond 48 h is clinically beneficial in patients with severe [59] or complicated disease [60] and in pregnant women [61]. A recent randomised controlled trial demonstrated that oseltamivir reduced viral shedding and symptom duration in uncomplicated influenza, even when initiation was delayed beyond 48 h [62]. Survival benefit has been observed in patients with influenza A (H5N1) infections who received oseltamivir up to 8 days after symptom onset, but maximal benefit was observed with early initiation of therapy [63]. At this stage there is insufficient data to recommend treatment beyond 48 h in patients at low-risk of influenza-related complications. In patients at high-risk of influenza-related complications, initiation of therapy beyond 48 h should be considered. Further studies are needed to delineate the optimal timing of NAIs.

### Resistance

- Adamantanes are no longer recommended for the treatment of influenza as a result of widespread resistance. Resistance to oseltamivir has been widely reported [64] and is a problem in seasonal H1N1 [65]. Significant rates of oseltamivir-resistance have not been found in other subtypes of seasonal influenza [65].

- In a systematic review, the overall incidence of oseltamivir resistance
was 2.7 % [66], but varied by subtype, with higher rates observed in influenza A, especially the H1N1 and H3N2 subgroups [66]. Infection with oseltamivir-resistant virus was associated with influenza-related pneumonia [66].

- Resistance to the NAI is a result of neuraminidase mutations. The neuraminidase mutations that confer resistance vary with influenza subtype and NAI [67].
- The H275Y mutation, in the N1 subtype, is the most common mutation and confers resistance to oseltamivir [67]. This mutation is associated with cross-resistance to peramivir but not to zanamivir [67].
- The E119V mutation, in the N2 subtype, confers resistance to oseltamivir but zanamivir usually remains active [67].
- The R292K mutation, also in the N2 subtype, confers resistance to oseltamivir with cross-resistance to zanamivir [67].
- Inhaled or IV zanamivir is currently the treatment of choice for oseltamivir-resistant virus, as resistance is most commonly secondary to the H275Y mutation, to which zanamivir remains active [67].

**Assistive devices**

**Extracorporeal membrane oxygenation**

- ECMO has been shown to improve survival in patients with acute respiratory distress syndrome (ARDS) [68]. However, there is a paucity of evidence for the use of ECMO in patients with influenza and implementation is extrapolated from ARDS trials [69].
- Observational studies of ECMO in patients with influenza-associated ARDS have reported mortality rates between 14 and 41 % [70–73]. In a meta-analysis of ECMO in H1N1-associated ARDS, median treatment duration was 10 days and mortality ranged from 8 % to 65 %. While this treatment is feasible, patients remain at risk of inhospital mortality [74].
- The risks of ECMO include bleeding, complement activation, air embolism, vascular damage, and infection [75].
- ECMO has not been shown to be superior to conventional management in patients with influenza-associated ARDS [76] and should be considered as salvage therapy. A large, randomised control trial, which includes long-term follow-up, is required to further define the role of ECMO in the management of influenza-associated ARDS.

**Other treatments**

**Convalescent plasma and intravenous immunoglobulin preparations**

- Influenza-convalescent human blood products have been used throughout history as a treatment for influenza. A meta-analysis examining the use of convalescent blood products during the 1918 influenza pandemic demonstrated reduced mortality in patients with influenza-associated
pneumonia [77]. Likewise, in Hong Kong, convalescent plasma was shown to significantly reduce mortality in patients with pandemic influenza who required intensive care support [78].

- IV immunoglobulin (IVIG) contains pooled polyvalent immunoglobulin G (IgG) antibodies extracted from plasma. IVIG has been reported to have improved outcome in a patient with influenza-associated ARDS [79]. Hyperimmune IVIG was shown to be superior to IVIG, with reduction in influenza viral load and mortality in patients with severe influenza requiring intensive care unit support [80].

- Complications of convalescent plasma are similar to those for blood transfusion. Hyperimmune IVIG has been associated with thromboembolic phenomenon [81].

**Emerging and investigational therapies**

- The use of systemic corticosteroids in patients with influenza has been associated with increased mortality and risk of bacterial superinfection [82–84]. In a case-control study of patients with severe influenza, requiring ICU support, 90-day mortality was 54% in patients treated with steroids versus 31% in those without steroids [83].

- DAS 181 (Fludase) is a recombinant sialidase fusion protein composed of a sialidase catalytic domain and a cell surface-anchoring domain. The compound has completed its initial preclinical development and entered clinical development to determine its efficacy and safety in humans [85].

- Nitazoxanide is an oral antiparasitic that is FDA-approved for treatment of Giardia and Cryptosporidium infections. The compound recently received contract for advanced development as a treatment for drug-resistant influenza. Its mechanism of action against influenza is yet to be fully described [1].

- Additional emerging therapies for the treatment of influenza are outlined in Table 2.

| Therapy requiring continued investigation | Therapy associated with adverse outcome |
|------------------------------------------|----------------------------------------|
| N-acetylcysteine [101]                   | Systemic corticosteroids [82–84, 108]  |
| Polymyxin B-immobilised fibre column hemoperfusion [102] |                                        |
| Therapeutic plasma exchange [103]        |                                        |
| Statins [104–106]                        |                                        |
| Macrolides [107]                         |                                        |
| Nitazoxanide (phase III) [1]             |                                        |
| DAS 181 (Fludase; phase II) [85]         |                                        |
Seasonal influenza therapy in Japan

Japan is at the forefront of seasonal influenza research and is a world leader in the implementation of new, novel and emerging therapies.

Laninamivir

- The long-acting NAI laninamivir has been approved in Japan since 2010. It is administered as a 40 mg single-dose inhalation, which achieves high intrapulmonary levels for up to 10 days [86]. Laninamivir has been shown to be safe and efficacious for the treatment of influenza, resulting in symptom relief at a median of 4 days [87]. It is active against influenza A and B, but has greatest efficacy against influenza A [88]. Laninamivir has similar efficacy to oseltamivir in patients with underlying respiratory disease and, unlike other inhaled NAIs, has not been shown to cause bronchospasm [89].
- Laninamivir therapy has been shown to be safe in children with influenza. It has similar efficacy to oseltamivir but offers the advantage of a one-time inhalation. It has been shown to be effective against oseltamivir-resistant virus in the paediatric population [90]. In randomised controlled trials, laninamivir has been shown to be safe and efficacious as prophylaxis against influenza [91].
- Laninamivir has shown promising results in Japan and may have an important role in the treatment of oseltamivir-resistant influenza.

Macrolides

- The macrolide class of antibiotics have anti-inflammatory properties and have been investigated in Japan for the treatment of influenza. A retrospective analysis in children treated with NAIs alone or in combination with 5 days of clarithromycin demonstrated higher levels of antiviral secretory IgA and anti-influenza serum IgG in children receiving combination therapy. The re-infection rate over the year post-treatment was reduced in the combination therapy arm [92]. Azithromycin was recently trialled in combination with oseltamivir for the treatment of influenza in adults. Unfortunately, the randomised trial failed to show a reduction in the level of inflammatory cytokines with combination therapy. However, there was a trend towards reduced duration of symptoms in the combination therapy arm [93]. The use of macrolides for the treatment of influenza requires further investigation.

Other therapies

- Vitamin D has been proposed as a therapy for a variety of medical conditions. A randomised controlled trial of vitamin D versus placebo, for the prevention of influenza A in children, demonstrated a significant reduction in the incidence of influenza A in the vitamin D arm [94]. This
therapy requires additional investigation but may be an option for prevention in countries with a defined influenza season.

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Compliance with Ethics Guidelines

Conflict of Interest

Emily Rowe declares that she has no conflicts of interest.
Yee-Sin Leo declares that she has no conflicts of interest.
Mark I. Cheng Chen declares that he has no conflicts of interest.
Pei Yi Ng declares that she has no conflicts of interest.
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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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