Submission for the 21st Expert Committee on the Selection and Use of Essential Medicines: comments on the application to delete Oseltamivir for the essential medicines list (EML) – 2017

This report has been prepared by the Infectious Hazard Management (IHM) expert networks (EXN) technical subunit led by Prof Shindo

We have prepared this report to provide support for the maintenance of oseltamivir on the Essential Medicines List (EML).

We acknowledge the important data contained within the application by the authors of the Acute Respiratory Infections Cochrane Review Group. However, the data provided are not complete and some recent studies are missing. Experts employing different analytic techniques, and using larger or more recent databases for analysis, have reached different conclusions about the efficacy and tolerability oseltamivir.

Importantly, we feel the scope of the Cochrane analysis is too limited with respect to the role oseltamivir plays in the armamentarium of WHO in its range of public health duties; preparing for and managing novel Influenza A virus threats of pandemic potential such as sporadic zoonotic influenza virus infections, recommendations for clinical management of severe illness from seasonal Influenza virus infections, and well as ensuring availability for the next pandemic influenza response.

Oseltamivir is the sole antiviral against influenza virus infections currently on the EML and EMLc, and we advocate for its retention, at least until a more clinically effective alternative is widely available.

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1. **Background**

- Two classes of influenza antiviral medicines, the influenza A virus M2 ion channel inhibitors (amantadine and rimantadine) and influenza A and B virus neuraminidase inhibitors (NAIs), are widely available.
- Mechanism of action of NAIs: Oseltamivir acts as a competitive inhibitor of influenza viral neuraminidase enzyme and prevents new influenza viral particles from being released and spreading within the respiratory tract.
- Currently circulating human influenza A viruses and most animal influenza A viruses that have caused the highest numbers of zoonotic infections (e.g. avian A(H7N9), A(H5N1)) are resistant to the M2 inhibitors, and these agents are not currently recommended for routine clinical use for seasonal Influenza or zoonotic influenza virus infections.
- The majority of seasonal influenza viruses circulating among humans worldwide remain sensitive to inhibition by NAIs.
- The NAIs, oral oseltamivir and inhaled zanamivir, are widely available worldwide while other NAIs, intravenous peramivir and inhaled laninamivir, are available in a small number of countries.
- Oral oseltamivir is licensed in more than 80 countries for antiviral treatment and chemoprophylaxis for seasonal influenza A and B virus infection.
- In part because of its ease of administration, oral oseltamivir is the only specific influenza antiviral treatment suitable for use in all populations including outpatients, hospitalised and critically ill patients, infants and children, pregnant women, and the elderly or infirm, in any clinical setting worldwide. The US FDA lowered the approved age for use for treatment to 2 weeks of age in December 2012. The US CDC recommends oral oseltamivir for treatment of Influenza in all age groups.
- WHO has prequalified oseltamivir formulations from several companies to facilitate equitable access to the medicine. These are Hoffman La Roche (Switzerland), Cipla Ltd (India) and Strides Arcolab Limited (India). On 3 August 2016 the FDA approved a generic version of oseltamivir. Generic oral oseltamivir was first available in mid-December 2016 and has been used widely in the U.S. during the current 2016-17 influenza season. The increased availability of generic oseltamivir is expected to increase global accessibility and reduce its cost.

2. **Relevant epidemiological data**

WHO undertakes global influenza virological surveillance through the Global Influenza Surveillance and Response System (GISRS).

GISRS monitors the evolution of influenza viruses and provides recommendations about laboratory diagnostics, vaccines, antiviral susceptibility and risk assessment.

GISRS also serves as a global alert mechanism for the emergence of novel influenza A viruses with pandemic potential.
Regular updates on seasonal influenza are published at

Seasonal influenza epidemics continue to cause morbidity and mortality worldwide, despite the availability of vaccines.

GISRS and WHO Outbreak Response also collate and publish information on zoonotic influenza A virus infections at the human-animal interface. Some zoonotic infections such as highly pathogenic avian Influenza (HPAI) A(H5N1) and low pathogenic avian influenza (LPAI) A(H7N9) viruses cause high case morbidity and mortality. Outbreaks of zoonotic infections in humans are closely monitored for the potential of pandemic threat.

At present there have been a total of 856 cases of human infection with avian Influenza A (H5N1) virus and 452 fatalities from 2003-2017. (www.who.int/influenza/; accessed 22/02/2017).

China is currently experiencing a 5th wave of sporadic human infections with avian Influenza A(H7N9) virus. To date a total of 1223 laboratory confirmed human infections with avian Influenza A(H7N9) virus have been reported through IHR notification since 2013 (WHO disease outbreak news 22/02/2017). Additional sporadic cases of A(H7N9) virus infection acquired in China have been identified in Taiwan, Malaysia, and Canada since 2013.

3. Current WHO guidance

The current relevant WHO guidance includes


• 2010 WHO Guidelines for Pharmacological Management of Pandemic Influenza A(H1N1) 2009 and other Influenza Viruses http://www.who.int/csr/resources/publications/swineflu/h1n1_use_antivirals_2009_0820/en/

The guidance is being updated and consolidated this year. The planning proposal will be submitted to the Guideline Review Committee on 29 March 2017 ahead of the GRC meeting in April 2017. The steering group members have been identified and the GDC is being arranged. Clearly the role of the GDC and expert panel will be to review the evidence for any guideline recommendations regarding diagnosis, interventional and supportive therapies in human influenza virus infections. The final meeting for the GDC is arranged for November 2017, and we expect the guidance to be published early in 2018.

WHO guidance on the antiviral treatment of Influenza must consider all the important situations in which Influenza virus infections may cause serious illness:
• Seasonal influenza: Vaccination remains the primary preventative measure against seasonal Influenza A and B virus infections. WHO currently recommends NAI therapy, usually oral oseltamivir, for the antiviral treatment of severe, progressive or complicated seasonal influenza and for treatment of influenza in patients at higher risk of developing severe or complicated disease. WHO does not recommend routine antiviral chemoprophylaxis for seasonal influenza, including the recently emerged Influenza A(H1N1)pdm09 virus. WHO does support the use of prophylactic oseltamivir chemoprophylaxis for controlling nosocomial outbreaks to protect very high-risk patient groups such as the immunocompromised (e.g. HSCT, solid organ transplant, haematological malignancies on treatment).

• Pandemic Influenza preparedness: oral oseltamivir was widely used in response to the 2009 A(H1N1)pdm09 pandemic and its subsequent waves. NAlS, and oral oseltamivir in particular, remain the cornerstone of the early outbreak response in the case of a novel Influenza A virus threat. Oral oseltamivir and inhaled zanamivir are part of the PIP Framework benefit package and core components for the response to the emergence of novel Influenza A viruses; both for antiviral treatment of ill patients and for chemoprophylaxis during the containment phase, antiviral chemoprophylaxis of health care workers and individuals at high risk of severe disease. The PIP Framework also supports the use of oral oseltamivir for treatment of cases infected with a novel Influenza A virus. This is particularly relevant while waiting for vaccines for a novel Influenza A virus to be developed, produced and become accessible in the event of a pandemic. The use of oseltamivir in this context is dependent on the Influenza A viruses at the animal-human interface remaining susceptible to NAI therapy; this is currently the case.

• Zoonotic infection in humans with novel Influenza A viruses that present potential pandemic threat: oral oseltamivir is recommended for treatment of human infection by novel Influenza A subtype viruses of avian (e.g. HPAI H5N1, H5N6, H6N1, H7N2, H7N3, H7N7, H7N9; and LPAI H9N2, H10N7, H10N8) and swine (termed variant) origin (e.g. H1N1v, H1N2v, H3N2v). WHO currently recommends early antiviral treatment with an NAI, oral oseltamivir in the first instance, and the prophylactic use of oral oseltamivir for chemoprophylaxis of persons with a high risk of exposure to novel avian influenza A viruses to prevent illness.

Oral oseltamivir is currently also recommended for the treatment of hospitalized seasonal influenza patients in the guidance of several international societies and the national guidance in many countries. Many of these guidelines are in the process of being updated, similar to the WHO guidance as discussed above. This process involves independent expert review of the evidence, including newly published data, regarding the efficacy and effectiveness of oral oseltamivir in the treatment and chemoprophylaxis of Influenza virus infections.

The Infectious Diseases Society of America (IDSA) and the European Centre for Disease Prevention and Control (ECDC) are in the process of guideline update. The Academy of Medical Sciences supported by the Wellcome Trust reported their guidance on the use of NAlS in Influenza virus infections in 2015. This report is the most recent, published expert review of the evidence regarding the efficacy and safety of NAl treatment and
chemoprophylaxis. They did not substantially change the recommendations for oseltamivir use from the preceding UK guidance and their recommendations remain in line with current WHO guidance.

The independent steering group of the Academy of Medical Sciences review acknowledged that although observational data are generally at higher risk of bias than RCTs, they did not support the assumption that observational data are invariably of less use than data from RCTs. They commented that RCTs may be superior at determining efficacy, but observational data may be better at reflecting the effectiveness of an intervention in usual care and identifying infrequent outcomes. They share the viewpoint of WHO, that in formulating policy and guidance, it can be appropriate to use observational data, particularly when data from large, pragmatic RCTs are not available.

The steering group also commented that they did not consider it appropriate to dismiss the studies from the Multiparty Group for Advice on Science (MUGAS) and PRIDE on the basis of their funding source. The authors of these studies and the company that provided financial support had been transparent about the separation of the work from the funding arrangements. The steering group acknowledged that potential biases may also arise from other kinds of pressures that were equally or more pertinent to non-industry-funded research. For example, some authors’ approaches to particular research questions may also be influenced by the desire for prestige, profile and success in grant applications.

It is important to recognise that NAI therapy has become commonplace and can be considered the standard of care (SOC) for some groups of influenza patients in countries like the United States, Japan, China, Australia, Europe and Canada. For example, one recent study of hospitalized patients with laboratory documented seasonal influenza found that the proportion treated with an NAI (>99% oral oseltamivir) increased from 72% in the 2010-11 season to 89% in the 2014-15 season in the United States. Similarly the use of oral oseltamivir has increased in Canadian ICU’s.

A number of ongoing trials of investigational influenza therapeutics in hospitalized patients include oral oseltamivir in both the SOC arm and in the experimental arm combined with the investigational agent; as described further later in this document.

4. Evidence Update:

The effectiveness and tolerability of NAIIs, specifically oral oseltamivir, for the treatment and chemoprophylaxis of seasonal and pandemic influenza has become the subject of increasing debate in the medical literature over the last few years. Hurt and Kelly provide an excellent overview of the key issues of debate.

The debate has been driven in part by differing conclusions reached by groups retrospectively analyzing the data from older randomized controlled trials (RCTs) conducted in influenza outpatients with uncomplicated and clinically mild disease, and from more recent observational studies in hospitalized and/or high-risk influenza patients, most of which included patients with severe illness due to A(H1N1)pdm09 virus infection.
We aim to summarise the important studies of the last four years and to highlight the key points of debate.

We have divided our response to firstly describe systematic reviews of RCTs, then the evidence from observational studies and lastly the evidence from studies of ecological impact. Please consult the studies for details of their analyses.

**a. Evidence from randomised controlled trials (RCTs):**

**i. Evidence from randomised controlled trials of oseltamivir treatment**

There are three large meta-analyses of placebo-controlled RCTs that have been published since the last meeting of the Expert Committee on Selection and Use of Essential Medicines; two of these were mentioned in the application to remove oseltamivir from the EML.

It is important to note that the RCT evidence for the efficacy of oral oseltamivir in the treatment and chemoprophylaxis of seasonal influenza, outside of China, is largely limited to data collected 10-15 years ago (1997 – 2001), and the subjects were either outpatients, such as otherwise healthy children and adults or they had stable, community managed co-morbidities. The subjects received NAI treatment versus placebo for early treatment of uncomplicated clinically mild influenza or influenza-like illness (ILI).

For a number of reasons, the treatment RCTs did not enable reliable analysis of data from sub-groups of the population that are also of interest to public health organisations, such as hospitalised or severely ill patients or patients at high risk for severe disease (e.g., pregnant women, immunocompromised hosts, those with morbid obesity); these RCTs were underpowered and not intended to assess such outcomes.

Placebo-controlled RCTs were not conducted during the 2009 H1N1 pandemic, or during recent zoonotic influenza outbreaks (H5N1, H7N9, H7N7, H9N2), for ethical and logistical reasons.

The three systematic reviews and meta-analyses assessing the efficacy and safety of oral oseltamivir (and inhaled zanamivir) from placebo-controlled RCT data include:

- 2014 Cochrane Collaboration report (Jefferson et al)
- 2014 MUGAS study (Dobson et al)\(^6\)
- 2015 Meta-analysis including Chinese RCT data (Zhang et al)\(^7\)

The 2014 Cochrane report is a systematic review with meta-analyses of clinical study reports from published and unpublished RCTs assessing early treatment with oral oseltamivir (20 trials encompassing 3954 adult and 1329 paediatric outpatients) and inhaled zanamivir (26 trials encompassing 5411 adult and 723 paediatric outpatients) up to July 2013. The study populations were persons in the community that were either otherwise healthy or with stable co-morbidities and who developed uncomplicated, clinically mild influenza-like illness (ILI) during seasonal epidemics. Data from persons with and without laboratory proven...
influenza were aggregated for analysis. Fewer than 90 participants from the cohort were later hospitalised and there were no deaths.

The MUGAS review was a meta-analysis of individual patient data (IPD) from 9 RCTs assessing the early treatment of uncomplicated ILI in adult outpatients with oral oseltamivir; all but one study had been included in the 2014 Cochrane review. Data from 2,893 persons with laboratory proven influenza virus infection were analysed both separately, and together with data from 1,435 persons without proven influenza virus infection.

The review by Zhang et al included 12 published trials of 107,712 patients with proven or presumed influenza and these included 1,686 Chinese participants that would not have been included in the previous systematic reviews detailed above. However, the Zhang review included studies that encompassed individual RCTs, meta-analyses of RCTs, and non-randomized observational studies and did not specifically summarize the outcomes from the subset of RCTs conducted in China. Consequently, due to concerns about the quality of the evidence presented, the review is not considered further in this report.

The Cochrane and MUGAS reviews reach similar conclusions; in adult outpatients with symptoms of influenza-like illness (ILI), early initiation of oral oseltamivir treatment significantly decreases the time to symptom alleviation (16.8 hours (95% CI 8.4–25.1) and 17.8 hours (95% CI 27.1 to 9.3) respectively); the MUGAS review also showed that the time to symptom alleviation was more marked in those with laboratory proven Influenza virus infection; reduced to 25.2 hours (CI 16.0-36.2). The MUGAS study did not find an effect of oral oseltamivir treatment in those with ILI without evidence of influenza virus infection.

The Cochrane review reported the time to symptom alleviation in healthy children was significantly reduced by 29 hours (95CI 12–47 hours) based on the findings from one study; and there was no significant effect on the subgroup of children with asthma.

The groups differed in their interpretation of their similar findings. The MUGAS group concluded that as the time to alleviation of symptoms was greatest in the laboratory confirmed influenza virus-infected group, and that the benefit was likely due to the effect of oral oseltamivir treatment on influenza viruses; while the Cochrane group concluded it was a non-specific antiviral effect.

The mechanism of action of NAIs, and therefore oseltamivir, is to impair viral replication by reducing in the release of viral particles from infected respiratory tract cells. In uncomplicated influenza virus infection in adults, influenza viral replication precedes symptoms by about 1 day, generally peaks at the time of presentation for care, and decreases within 1–2 days. It is possible that in otherwise healthy individuals, the viral load may have already peaked when antiviral therapy starts. This may explain the modest, but nevertheless significant, effect of NAIs in otherwise healthy individuals with uncomplicated clinically mild influenza5.

Additional analyses in the Cochrane and MUGAS reviews were also undertaken (e.g. hospitalisation and pneumonia), but the quality of this evidence is extremely limited as the
original RCTs were not designed or powered to measure these severe clinical outcomes. We have listed the low frequency of these events in the text below to emphasise this point.

Both reviews documented a statistically significant reduction in patient-reported pneumonia (Cochrane: RR 0.55 95% CI 0.33 – 0.9; total of 117 events) or lower respiratory tract disease (including bronchitis and pneumonia) leading to antibiotic use >48 hours after enrolment in adults (MUGAS: RR 0.56 95%CI 0.42-0.75; 175 events in the proven influenza group and 252 events in the whole cohort). In the MUGAS study, the reduction in lower respiratory tract illness was limited to the subset with proven influenza. In the Cochrane review there was no significant effect of oral oseltamivir treatment in children with uncomplicated influenza on the development of pneumonia.

The MUGAS trial showed a decrease in all-cause hospital admissions among the oseltamivir-treated patients with proven influenza compared to placebo (RR 0.37; 95%CI 0.17-0.81; 31 events), but not among those without influenza (60 events). The Cochrane group did not find a difference in hospitalisation rates for the ILI cohort in the treatment studies (88 events).
There was one death in the MUGAS trial of respiratory failure (placebo, non-proven influenza virus infection). There were no deaths reported in the Cochrane review.

ii. Evidence of harm from systematic reviews of RCTs of oseltamivir treatment

Both the Cochrane and MUGAS reviews reported on the potential harmful effects of oseltamivir treatment.

Patients treated with oral oseltamivir had:

- Significantly increased risk of nausea in adults (Cochrane: RD 3.66%, 95% CI 0.90% - 7.39%; MUGAS RR 1.60, 95% CI 1.29–1.99)
- Significantly increased risk of vomiting in adults (Cochrane: RD 4.56%, 95% CI 2.39% - 7.58%; MUGAS RR 2.43, 95% CI 1.83–3.23) and children (RD 5.34%, 95% CI 1.75% - 10.29%)
- Cochrane reported that serious adverse events (SAE) were not significantly different for oral oseltamivir or placebo groups, either on or off treatment, for adults and children. The MUGAS trial did not find any significant difference in reported SAE.
- The MUGAS study recorded no effect on neurological or psychiatric disorders. The Cochrane review did not find a significant difference in psychiatric events in adults on oseltamivir treatment; but report a dose-response effect in 2 of the trials. These events were not reported off treatment. The Cochrane review did not report on psychiatric events in children on treatment; this group are purported to be at higher risk. The MUGAS trial excluded children.
iii. Evidence from systematic reviews of RCTs of oseltamivir chemoprophylaxis

The Cochrane review reported that oral oseltamivir chemoprophylaxis significantly reduced the risk of symptomatic influenza in adults as individuals and as well as households (RD 3.05%, 95% CI 1.83% to 3.88%; and RD 13.6%, 95% CI 9.52% to 15.47% respectively)

The Cochrane review reported that the serious adverse events in the oral oseltamivir chemoprophylaxis studies did not differ significantly between the oseltamivir and placebo arms either on or off treatment.

The Cochrane review reported that oral oseltamivir chemoprophylaxis in adults increased the risk of headaches (RD 3.15%; 95% CI 0.88-5.78), renal events (RD 0.67% 95% CI -2.93 to0.01) and nausea while on treatment (4.15; 95% CI 0.86-9.51). Psychiatric events were increased in the combined on and off treatment periods (RD 1.06%; 95% CI 0.07 – 2.76) but not when the periods were examined separately.


Nine randomised controlled trials (RCTs) and 8 observational studies were included in the analyses. NAIs provided 67-89% protection for individuals following chemoprophylaxis. Meta-analysis of individual protection showed a significantly lower pooled odds of laboratory confirmed seasonal or influenza A(H1N1)pdm09 virus infection following oral oseltamivir usage compared to placebo or no therapy (n=8 studies; OR=0.11; 95% CI=0.06 - 0.20; p <0.001) This result was comparable to the pooled odds ratio for individual protection with inhaled zanamivir (OR=0.23; 95% CI 0.16 to 0.35). Similar point estimates were obtained with widely overlapping 95% CIs for household protection with oral oseltamivir or inhaled zanamivir. They found no population-based studies of NAIs used for chemoprophylaxis to prevent community transmission of influenza viruses. This study was not included in the application for the deletion of oseltamivir.

iv. Evidence from additional NAI RCTs of interest

In addition to the above meta-analyses of RCTs, there have been individual RCTs published in the past four years that have provided relevant data that were not included in the application to delete oseltamivir from the EML.

- In 2014 Fry et al undertook a placebo-controlled RCT of oral oseltamivir treatment of seasonal influenza in a low income, crowded urban community in Bangladesh enrolled 1,190 influenza index outpatients (median age, 5 years; IQR 2–9) 9. They found that the median duration of symptoms was 1 day shorter with oral oseltamivir treatment (3 days, IQR 1–5) compared to placebo (4 days, IQR 1–6; p=0.01); and significant reductions in influenza viral shedding was also noted. Vomiting was more common in oral oseltamivir-treated children, whereas diarrhea was more common in placebo recipients.
In 2015 Fry et al published a secondary analysis of the study population above\textsuperscript{10}. The 1190 index cases were associated with 4694 household members. Household secondary illness was significantly lower in the oral oseltamivir group than in the placebo group (OR 0.77, 95% CI 0.60–0.98). RT-PCR-confirmed influenza virus infection did not differ between the placebo (103 [5%]) and oral oseltamivir groups (92 [4%]; 0.84, 0.59–1.19, p=0.319); however, only 243 (57%) of ill household members gave a specimen for analysis.

Anekthananon et al undertook a parallel group, double blind, 2 (active drug): 1 (placebo) randomized trial of oral oseltamivir (129)/placebo (65) or inhaled zanamivir (131)/placebo (65) daily over 16 weeks in healthy Thai hospital care professionals\textsuperscript{11}. The primary endpoint was study withdrawal due to drug-related serious or adverse events. A total of 102 AEs were reported or detected in 69 subjects: oseltamivir 23/129 (17.8%) versus 15/65 (23.1%); p=0.26; and zanamivir 23/131 (17.6%) versus 8/65 (12.3%); p=0.28. There were no drug-related study withdrawals. Intercurrent infections/fevers (25.5%), abnormal biochemistry (24.5%) and gastrointestinal symptoms (17.6%) were the most frequently reported AEs. Daily use of oral oseltamivir or inhaled zanamivir was well tolerated in healthy hospital professionals for 16 weeks.

A 4-year RCT directly comparing oral oseltamivir to one of 2 doses of intravenous zanamivir in 488 hospitalized adults with proven influenza found that intravenous zanamivir was not superior to oral oseltamivir in clinical outcomes (including mortality or development of pneumonia post-enrollment), or in virologic measures. No differences in serious adverse events were noted between the drug regimens, although the oseltamivir group was reported to have higher proportion with drug-related adverse events (17%) compared to zanamivir (10-11\%)\textsuperscript{12}.

A placebo-controlled RCT of intravenous peramivir in 217 hospitalized, mostly adult influenza patients receiving oral oseltamivir therapy found that adding peramivir to oseltamivir provided no significant differences in clinical outcomes compared to oseltamivir alone\textsuperscript{13}.

b. Evidence from observational trials of NAI treatment

The efficacy of oral oseltamivir in preventing, or treating, severe influenza disease has not been investigated with RCTs. Evidence for the efficacy of oseltamivir in the severely ill and groups at risk of severe disease therefore has to be derived from observational studies with the caveats that such data may be subject to uncontrolled bias.

We recognise that observational studies are subject to uncontrolled bias; for example time from onset to initiation of antiviral treatment, time available to benefit from antiviral treatment prior to outcome, the impact of disease severity or other patient characteristics that affect the likelihood of receiving antiviral treatment and the response to treatment. Some studies may adjust for some of these biases, the propensity for treatment and they may adjust for the effects of immortal time bias.
Despite these shortcomings, WHO nevertheless values observational and ecological studies of antiviral treatment of influenza that show an impact on populations when developing policy for individual and public health needs; in particular for novel Influenza A viruses of pandemic potential (zoonotic influenza) including those with high case fatality proportion or those with increased pandemic potential, because traditional randomised placebo-controlled trials are not ethical or feasible or available.

It is possible that features of the mode of action of NAIs may benefit the severely ill patient with Influenza virus infection because of the characteristics of severe disease. The severely ill patients may have higher viral loads in the respiratory tract and increased duration of viral shedding, and therefore the effective therapeutic window may be longer from symptom onset to initiate antiviral treatment for agents that affect viral replication\(^5,14\). Severe disease is often associated with dysregulated pro-inflammatory cytokine release; and in cases of severe illness due to HPAI A(H5N1), LPAI A(H7N9) or A(H1N1)pdm2009 virus infections, this has been referred to as “cytokine storm.” Oral oseltamivir has been shown to reduce cytokine responses in an RCT of healthy adults. It is unclear if this effect is due to the antiviral effects of oseltamivir or due to an immune modulating effect\(^5\).

There have been a number of publications of observational cohorts since the last meeting of the Expert Committee on Selection and Use of Essential Medicines.

We note that several were not included in the application for the deletion of oseltamivir from the EML. We include them here under two headings; systemic reviews of observational studies and observational studies of interest published in the last 4 years.

v. Evidence from systematic reviews of observational studies of NAIs

Summaries of the findings of the key studies are highlighted below and these are followed by a summary of the findings of the effect of NAI treatment on mortality of hospitalised patients, hospitalisation rates, and rates of complications.

**List of key studies:**

- 2012 Hsu et al: Antivirals for treatment of Influenza\(^15\).
- 2013 Muthuri et al: Impact of neuraminidase inhibitor treatment on outcomes of public health importance during the 2009–2010 Influenza A (H1N1) Pandemic: a systematic review and meta-analysis in hospitalised patients\(^16\).
- 2014 Muthuri on behalf of PRIDE consortium: Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09: A systematic review and meta-analysis in hospitalized patients\(^17\).
- 2016 Muthuri on behalf of PRIDE consortium: Impact of neuraminidase inhibitors on influenza A(H1N1) pdm09-related pneumonia: an individual participant data meta-analysis (this study was not included in the application for the deletion of oseltamivir from the EML)\(^18\).
- 2015 Lee et al: Neuraminidase inhibitors, superinfection and corticosteroids affect survival of influenza patients (this study was not included in the application for the deletion of oseltamivir from the EML)\(^19\).
• 2016 Heneghan et al: Neuraminidase inhibitors for influenza: a systematic review and meta-analysis of regulatory and mortality data\textsuperscript{20}.
• 2016 Wolkewitz et al: Neuraminidase Inhibitors and Hospital Mortality in British Patients with H1N1 Influenza A: A Re-Analysis of Observational Data\textsuperscript{21}.
• 2017 Venkatesan on behalf of the PRIDE consortium: Impact of outpatient neuraminidase inhibitor treatment in patients infected with influenza A(H1N1)pdm09 at high risk of hospitalization: an Individual Participant Data (IPD) meta-analysis. (This study was not included in the application for the deletion of oseltamivir from the EML)\textsuperscript{22}

\textbf{2012 Hsu et al}\textsuperscript{15}
In 2012 Hsu et al published a systematic review of 74 observational studies assessing the evidence for antiviral treatment in patients with influenza. The reviewers only undertook meta-analyses of the studies that adjusted for confounders, limiting the number of studies included. They found that in high-risk populations, oral oseltamivir reduced mortality (odds ratio, 0.23 [95% CI, 0.13 to 0.43]; low-quality evidence), hospitalisation (odds ratio, 0.75 [CI, 0.66 to 0.89]; low-quality evidence), and duration of symptoms (33 hours [CI, 21 to 45 hours]; very low-quality evidence) compared with no treatment. Earlier treatment with oral oseltamivir was generally associated with better outcomes than later treatment. The authors acknowledged that the overall body of evidence was limited by risk for confounding and selection, reporting, and publication bias.

\textbf{2013 Muthuri et al}\textsuperscript{16}
In 2013 Muthuri et al published a systematic review (107 studies published between 2009-2013) and meta-analysis of the treatment effects of NAI on mortality (44 studies), on severe outcomes (death or critical care admission, 52 studies), and pneumonia (13 studies), in patients admitted to hospital with a clinical or laboratory diagnosis of severe illness due to A(H1N1)pdm09 virus infection. There was a non-significant reduction in mortality associated with NAI treatment at any time (OR, 0.72 [95% CI, 0.51–1.01]). However they reported significant reductions in mortality for early initiation of NAI treatment (≤48 hours after symptom onset) versus later initiation of treatment (OR, 0.38 [95% CI, .27–.53]) and for early initiation of treatment versus none (OR, 0.35 [95% CI, .18–.71]). Of note, NAI treatment (at any time) versus none was associated with an elevated risk of severe outcome (OR, 1.76 [95% CI, 1.22–2.54]), but early versus later treatment significantly reduced the likelihood of a severe outcome (OR, 0.41 [95% CI, .30–.56]). Similarly, the likelihood of pneumonia was increased with NAI treatment (OR, 2.29 [95% CI, 1.16–4.53], whereas early versus later treatment significantly reduced the likelihood of pneumonia (OR, 0.35 [95% CI, 0.24–0.50]). As discussed by the authors, the increased risk of a severe outcome or pneumonia compared to no treatment very likely reflects more severe illness and delayed NAI administration in NAI recipients.

\textbf{2014 Muthuri on behalf of PRIDE consortium}\textsuperscript{17}
In 2014 the PRIDE consortium published a systematic review and meta-analysis of individual patient data of patients (all ages) admitted to hospital with severe illness due to laboratory confirmed or clinically diagnosed with influenza A(H1N1)pdm09 virus infection with respect to NAI effects on mortality (92% received oral oseltamivir).
They included data for 29,234 patients from 78 studies of hospitalised patients 2009 - 2011. 29,234 had laboratory confirmed Influenza, 9,218 were younger than 16 years and 2,166 were pregnant females. 25% had Influenza-related pneumonia and 23% were admitted to critical care.

The authors adjusted for propensity to treat, patient co-morbidities and immortal time bias. Compared with no treatment, NAI treatment (irrespective of timing of initiation of treatment) was associated with a reduction in mortality risk (adjusted odds ratio [adjOR] 0.81; 95% CI 0.70–0.93; p=0.0024). Compared with later initiation of treatment, early initiation of NAI treatment (within 2 days of symptom onset) was associated with a reduction in mortality risk (adjOR 0.48; 95% CI 0.41–0.56; p<0.0001). Early initiation of treatment versus no treatment was also associated with a reduction in mortality (adjOR 0.50; 95% CI 0.37–0.67; p<0.0001). Significantly reduced mortality was observed in critically ill adults (adjOR 0.72; 95% CI 0.56–0.94; P=0.0215) and in pregnant women (adjOR 0.46; 95% CI 0.23–0.89; P=0.0155) treated with NAIs, but the associations with reduced mortality risk were less pronounced and not significant in children. Mortality is an uncommon outcome in children hospitalised with Influenza virus infection; this study was likely underpowered to assess this outcome. There was an increase in the mortality hazard rate with each day’s delay in initiation of treatment up to day 5 as compared with treatment initiated within 2 days of symptom onset (adjusted hazard ratio [HR] 1.23; 95% CI 1.18–1.28; p<0.0001 for the increasing HR with each day’s delay).

2016 Muthuri on behalf of PRIDE consortium

In 2015, the PRIDE consortium published a meta-analysis of individual participant data from 20,634 hospitalised patients with clinically diagnosed (n=613) or laboratory-confirmed A(H1N1)pdm09 (n = 20,021) virus infection across the world. Radiologically confirmed influenza-related pneumonia (IRP) was determined at any time after the onset of symptoms. It was present in 29%; while 3,349 (16.2%) did not show radiographic changes. Early initiation of NAI treatment (within 2 days of symptom onset) versus no NAI was not significantly associated with IRP [adjOR 0.83 (95% CI 0.64–1.06; P = 0.136)], but early NAI treatment compared with later was associated with significantly lower odds of developing IRP (adjOR, 0.43; 95% CI, 0.37–0.51). Among the 5,978 patients with IRP, early NAI treatment versus none did not impact on mortality [adj OR = 0.72 (0.44–1.17; P = 0.180)] or likelihood of requiring ventilatory support [adj OR = 1.17 (0.71–1.92; P = 0.537)], but early treatment versus later significantly reduced mortality [adj OR = 0.70 (0.55–0.88; P = 0.003)] and the likelihood of requiring ventilatory support [adj. OR = 0.68 (0.54–0.85; P = 0.001).

2015 Lee et al

In 2015 Lee et al published a meta-analysis of individual patient data from three Asian cohorts (Hong Kong, Singapore and Beijing) of 2,649 prospectively identified adults hospitalised with laboratory-confirmed seasonal or A(H1N1)pdm09 influenza between 2008-2011. The primary outcome was 30- day mortality (106 patients) and secondary outcomes included 60-day mortality (124 patients). Analysis included adjustments for propensity for treatment, immortal time bias and patient characteristics.

The patients had high morbidity (respiratory/non-respiratory complications in 68.4%, respiratory-failure in 48.6%, pneumonia in 40.8%, and bacterial superinfections in 10.8%) and mortality (5.9% at 30 days and 6.9% at 60 days). NAIs were administered in 75.2% (98.1% received oral oseltamivir and 1.9% intravenous peramivir or inhaled zanamivir);
44.5% of patients received NAI \( \leq 2 \) days after symptom onset and 65.5% \( \leq 5 \) days after onset. There were fewer deaths among patients in the NAI-treated group (5.3% versus 7.6%; \( p=0.032 \)). After adjustments for treatment-propensity score and patient characteristics, NAI treatment was independently associated with survival (adjusted hazard ratio (HR) 0.28, 95% CI 0.19–0.43). Time-dependent analysis showed consistent results of NAI treatment (adjusted HR 0.39, 95% CI 0.27–0.57). Early initiation of NAI treatment was associated with shorter length of stay in a sub-analysis.

2016 Heneghan et al

In 2016 Heneghan et al reported a systematic review of observational studies (2009 -2011) to assess the effect of oral oseltamivir on mortality in patients with confirmed A(H1N1)pdm09 virus infection. Thirty studies were included in the analysis encompassing 11,013 patients and 1,301 deaths. The review included a separate analysis of individual patient data from four of the included studies; accounting for 3,071 patients of whom 242 died. Data on the date of discharge was missing for 886 (29%). The overall percentage of participants receiving oral oseltamivir was similar for survivors and non-survivors (82% v 83%) in the summary data. The reviewers reported time-dependent bias in both the summary data and the individual patient data. They report that oral oseltamivir treatment in the individual patient dataset did not reduce the risk of mortality once they had adjusted for time-dependent bias, potential confounding variables, and the competing risk of hospital discharge or death (HR 1.03, 95% CI 0.64 - 1.65).

2016 Wolkewitz et al

In 2016 Wolkewitz et al published a new analysis of the observational data on NAI treatment from the FLU-CIN study that included 1,391 patients with laboratory-confirmed influenza A(H1N1)pdm09 virus infection collected during 2009-2010 in the UK. Eighty patients in this group died in hospital; the time period was not specified (e.g. 30-day or 60 day mortality). The analyses adjusted for immortal time bias, delayed entry and discharge as the end of follow up and patient characteristics. They found NAI treatment had no direct effect on hospital death rate (HR =1.03; 95%-CI: 0.64–1.66) and could be expressed as the daily risk of death. However, the discharge rate was increased for patients treated with NAIs (HR = 1.89 (95%-CI: 1.65–2.16) indicating that NAI-treated patients had a shorter length of stay; on average 3.10 days (95%-CI: 2.07–4.14). Although NAI treated patients had fewer days in hospital exposed to a similar risk of death did not result in a significant reduction in mortality rate. The authors also show that the timing of NAI treatment (early v late initiation) did not have an effect on hospital death or discharge hazard. The authors conclude that the potential beneficial effect of NAI treatment on hospitalized patients in the UK would be as a result of a reduction of the length of hospital stay rather than a reduction of the mortality rate.

2017 Venkatesan, on behalf of the PRIDE consortium

Venkatesan, on behalf of the PRIDE consortium, has recently published (February 2017) a meta-analysis of individual patient data on the effects of outpatient NAI treatment in A(H1N1)pdm09 virus-infected patients at high risk of hospitalization. The study included data from nine clinical centers and included 3,376 patients of whom 3,085 (91.4%) had laboratory-confirmed A(H1N1)pdm09 virus infection. 1747 were less than
16 years old and 64 >65 years. Co-morbidities were present in 28% suggesting the patients were largely young and previously healthy. 928 of 2,395 (38.8%) with available data had dyspnea or respiratory distress. 1,705 (50.5%) were hospitalized. 873 patients (25.8%) received outpatient or community-based NAI treatment. After adjustment for pre-admission antibiotics and NAI treatment propensity, pre-admission NAI treatment was associated with decreased odds of hospital admission compared to no NAI treatment (adjusted OR = 0.24; 95% CI: 0.20 to 0.30).

**Summary of outcomes from systematic reviews of observational studies regarding mortality data and the effect of oseltamivir**

As outlined above, mortality has been included as an outcome in most of the recent systematic reviews of observational studies with varied reported results.

The Cochrane group has criticized the methodology of systematic reviews that have not adjusted for uncontrolled biases such as patient characteristics, immortal time-bias and propensity for treatment.

The meta-analysis of individual patient data by Muthri et al showed that NAI treatment of adult patients hospitalized with A(H1N1)pdm09 virus infection was associated with a significant reduction in mortality when adjusted for the biases considered above (adjOR 0.81; 95% CI 0.70–0.93)\(^\text{17}\). Muthuri et al, in response to additional methodological questions regarding time-dependent bias, published a re-analysis of the data using multiple methods to adjust for immortal time bias, clustering and competing risk of death and discharge. They continued to show a treatment benefit of NAI \(^\text{23}\).

Lee et al showed that NAI treatment of hospitalized adult patients with influenza was associated with a significant reduction in 30 and 60-day mortality using both time fixed and time-dependent analyses (adjusted HR 0.39, 95% CI 0.27–0.57)\(^\text{19}\).

The systematic review by Heneghan et al found that NAI treatment did not have a significant effect on the mortality of laboratory confirmed A(H1N1)pdm09 patients if adjustments were made for time-dependent bias and the competing risk of discharge\(^\text{20}\). They felt that studies that did not take these factors into account in their analyses, were flawed.

The re-analysis of FLU-CIN data done by Wolkewitz et al showed that NAI treatment had no effect on hospital death rate but that the discharge rate was increased for patients treated with NAIs\(^\text{21}\). NAI treatment provided significant clinical benefit for reduction of hospital stay, but this did not result in a significant reduction in mortality.

Older prospective observational studies of hospitalised patients with laboratory confirmed seasonal influenza have shown that oseltamivir treatment decreases the risk of deaths. Lee et al reported one such study in 2010\(^\text{24}\). They reported findings from a cohort of 754 adults, mainly elderly, with laboratory confirmed Influenza. 41 were mechanically ventilated and 39 died. 52% were treated with oral oseltamivir, 77% of them within 2 days and 95% within 4 days. Oral oseltamivir treatment was associated with reduced mortality (adjOR =0.27 (95% CI 0.13 to 0.55; p<0.001).
Summary of outcomes from systematic reviews of observational studies regarding the effect of the timing of initiation of oseltamivir treatment:
The systematic reviews of Hsu, Muthuri et al 2013 and 2014, Lee et al 2015 and Venkatesan et al 2017 all indicate that earlier initiation of treatment with oral oseltamivir (<48 hours after symptom onset) is associated with improved outcomes as compared to later initiation of treatment or no treatment.15-17,19,22 Wolkewitz et al did not show that the timing of NAI treatment (early v late) had an effect on hospital death or discharge hazard21.

Summary of outcomes from systematic reviews of observational studies regarding the effect of oseltamivir therapy on hospitalisation:
Venkatesan, on behalf of the PRIDE consortium, is the only published meta-analysis of observational data assessing the impact of pre-admission initiation of oral oseltamivir treatment of influenza on subsequent hospital admission. Pre-admission NAI treatment was associated with decreased odds of hospital admission (adjOR = 0.24; 95% CI: 0.20 to 0.30)22.

vi. Evidence from additional observational studies of NAIs

2013 Louie et al: Neuraminidase Inhibitors for Critically Ill Children With Influenza25 Louie et al characterized the outcomes of children (0-17 years) with laboratory-confirmed influenza admitted to ICUs during 2009 – 2012. 653 cases were treated with NAIs; 38 (6%) died compared with 11 (8%) of 131 untreated cases (OR = 0.67, 95% CI: 0.34–1.36). In a multivariate model that included other factors associated with disease severity, the estimated risk of death was reduced in NAI-treated cases (OR= 0.36, 95% CI: 0.16–0.83). Treatment started within 48 hours of illness onset was significantly associated with survival (P = .04). Cases with NAI treatment initiated earlier in illness were less likely to die.

2013 Wollenhaupt: The safety of oseltamivir in pregnancy: an updated review of post marketing data26 Wollenhaupt et al explored the Roche Global Safety Database all exposures to oral oseltamivir during pregnancy 1999- 2012. There were 2926 maternal exposures and pregnancy outcomes were known for 2128. Most exposures (>90%) were reported during or after the 2009 H1N1 pandemic. The incidence of adverse pregnancy outcomes in exposed women was: spontaneous abortions, 2.9% (61/2128); therapeutic abortions, 1.8% (39/2128); and pre-term deliveries, 4.2% (84 of 2000 livebirths), values which are lower than background rates in the general population (women with or without influenza). Fetal outcomes were known in 1875 of the 2926 exposures. For the 81 reported birth defect cases, 11 occurred during the sensitive period for the respective defects. A review of these and other case reports of birth defects did not suggest that they resulted from oral oseltamivir exposure.

Zoonotic Influenza A virus infections:
There have been a number of observational studies describing oral oseltamivir treatment in cohorts of patients with severe illness due to HPAI A (H5N1) and LPAI A(H7N9) virus infections in particular.
Some human infections with avian influenza A viruses are associated with severe illness and high mortality. WHO guidance, and the Chinese and Vietnamese national guidance, recommends that suspected and laboratory-proven human cases of avian influenza A(H5N1) and A(H7N9) virus infection are treated early with NAIs, often oral oseltamivir as soon as possible in the first instance.

**HPAI A(H5N1)**

Human infections with highly pathogenic avian influenza (HPAI) A(H5N1) virus tend to be associated with high morbidity and high case fatality proportion (>50%) and in many case series oral oseltamivir treatment has been initiated late after symptom onset when severe lower respiratory tract disease is already present. However the limited data from published case series suggest that early initiation of treatment with oral oseltamivir may improve survival, and that antiviral treatment may still be beneficial, compared with no treatment, even when administered late in the clinical course.

Kandun reported that in a cohort of 122 hospitalised patients with confirmed HPAI A(H5N1) virus infection in Indonesia, those treated with oral oseltamivir within 2 days of illness onset had significant reduction in mortality than those treated at 5–6 days or >7 days (p<0·0001). In China, in a cohort of 26 cases of HPAI A(H5N1) virus infection, receipt of any antiviral medication was associated with survival (p=0.003). Adisasmito reported data for 308 patients with HPAI A(H5N1) virus infection from 12 countries that were prospectively entered on a patient registry (www.avianfluregistry.org). Multivariate modeling showed 49% mortality reduction with oral oseltamivir treatment and the benefit of treatment persisted provided that oseltamivir treatment was initiated within 6–8 days after symptom onset. Oner reported the data for 193 pediatric patients with HPAI A(H5N1) virus infection from 13 countries; delayed initiation of treatment with oral oseltamivir increased the likelihood of death, with an overall with 75% increase in the adjusted odds ratio for death for each day of oseltamivir treatment delay in this cohort.

**A(H7N9)**

Although a low pathogenic avian influenza (LPAI) virus, human infection with LPAI A(H7N9) virus is associated with severe lower respiratory tract disease and high case fatality proportion (approximately 40%) in infections acquired in China. Most human cases of LPAI A(H7N9) virus infection with severe disease have received late initiation of NAI treatment after hospital admission late in the clinical course. For example, only 5% of cases received oral oseltamivir treatment within 48 hours of symptom onset. Wang et al reported on 25 cases of A(H7N9) virus infection in Gangzhou, China during 2014. Patients were more likely to develop ARDS if there was a delay in the initiation of oral oseltamivir treatment (p = 0.024), however there was no effect on mortality in this small cohort.
Goa et al reported the findings from prospectively collected data from a cohort of 111 patients admitted with A(H7N9) in China up until May 2013. They showed that delay in starting oral oseltamivir treatment beyond 3 days from the onset of symptoms was associated with the development of Acute Respiratory Distress Syndrome (ARDS) (p=0.004). Similarly delay in initiating oral oseltamivir treatment beyond 5 days from the onset of symptoms was associated with mortality (p= 0.024).^{34}

c. Evidence from ecological impact studies.
   i. Evidence from Japan.

Japan has a unique approach among nations to the surveillance and clinical management of Influenza, both seasonal and pandemic. We acknowledge that these data are older than 4 years but it remains relevant to this application.

The influenza surveillance network in Japan is robust and features sentinel outpatient surveillance, virological surveillance, and reports on hospitalization, mortality, and influenza-associated encephalopathy. The number of student absences and school closures are also reported. Volunteer doctors provide real-time information via online influenza surveillance portal. Vaccination remains the primary defense for the prevention of seasonal influenza.

Japan is unique among countries in that NAIs are prescribed to any influenza outpatient rather than being limited to those with severe disease or at high risk of developing severe disease. The majority of patients (80-95%) start NAI treatment within 48 hours of symptom onset. Four NAIs are licensed in Japan and are prescribed to seven to eight million patients annually. Oral oseltamivir and inhaled lanamivir account for 70-80% of the NAIs prescribed; oral oseltamivir is not generally prescribed to 10-19 year-olds because of concerns regarding pathologically abnormal behaviours.^{36,37}

The national clinical management approach has had an impact on outcomes for influenza virus infections in Japan.

Sugaya et al report the outcomes of children aged <16 years with influenza A(H1N1)pdm09 virus infection during the 2009 H1N1 pandemic.^{38} 59% of the patients were children (12.2 million/20.7million adults). However, there were only 38 paediatric deaths reported during the pandemic. They retrospectively reviewed 1000 hospitalised children; 65.1% had respiratory complications and 25.5% had neurological complications. 98.4% of the cohort had been treated with NAIs, primarily oseltamivir, and treatment was initiated within 48 hours of onset of symptoms in 88.9%. In the cohort, 12 (1.2%) were mechanically ventilated and one patient died.

Zaraket reports that the hospitalisation rates published by National Epidemiological Surveillance of Infectious Diseases (iNESID) during the pandemic was 5.8 cases per 100,000 population in Japan; one quarter of the rate in the USA and Australia.^{37} The mortality rate in Japan during the 2009 H1N1 pandemic was estimated at 0.16 per 100,000 persons and is
much lower than that reported in other countries, such as the USA (3.96 per 100,000), Canada (1.32 per 100,000), Mexico (0.93 per 100,000), Australia (0.93 per 100,000), the UK (0.76 per 100,000), Singapore (0.57 per 100,000), Korea (0.53 per 100,000), and France (0.51 per 100,000)\textsuperscript{37}.

Similar ecologic data were observed in Japan among pregnant women with influenza A(H1N1)pdm09 virus infection; a group of patients at high risk for hospitalization and death\textsuperscript{39,40}. Pregnant Japanese women were administered NAI chemoprophylaxis after close contact with an infected person; and if infected and hospitalized, >90% were given NAIs within 48 hours of symptom onset. In comparison to the high mortality rates among pregnant women in many countries around the world, no maternal deaths occurred in Japan during the 2009 H1N1 pandemic.

ii. Other studies of the ecological impact of oseltamivir treatment in influenza virus infections.

Several ecologic studies during the 2009 H1N1 pandemic response reported reduced mortality and healthcare utilization in relationship to deployment of NAI treatment, most commonly oral oseltamivir.

One country-level analysis assessed the relationship between quantitative NAI supplies and predicted A(H1N1)pdm09 mortality from July 2009 to August 2010 in 42 WHO Member States\textsuperscript{41}. After adjustment for economic, demographic, and health-related confounders, it found that each 10% increase in kilograms of oseltamivir, per 100,000 people, was associated with a 1.6% reduction in A(H1N1)pdm09 mortality over the pandemic period (relative rate (RR) = 0.84 per log increase in oseltamivir supply). While the supply of inhaled zanamivir was considerably less than that of oral oseltamivir, each 10% increase in kilogram of active zanamivir, per 100,000, was associated with a 0.3% reduction in mortality (RR = 0.97 per log increase).

Individual reports from countries like Mexico\textsuperscript{42}, Chile\textsuperscript{43}, and Canada\textsuperscript{44} temporal associations were reported between increases in timely NAI use and reductions in severe outcomes (mortality, hospitalizations, ICU admissions) at the population level.

5. Trials of oseltamivir registered with Clinicaltrials.gov.

There are 88 trials involving oseltamivir registered on the clinicaltrials.gov website (accessed 22/02/2017) that are either completed (63), recruiting (16) or not yet recruiting (9). Many of these trials are phase 1 or 2 (31); and many trials use oseltamivir as the SOC for comparison to the intervention. Of the completed trials, 43 have no results (14 industry-funded) and 20 have results (16 industry funded). Of the actively recruiting trials, 6 are phase 3 or 4 and most are due to complete in 2017. Of the trials not yet recruiting, 4 are phase 3 or 4 trials.
6. Conclusion:

The global impact of both seasonal influenza viruses (now including the A(H1N1)pdm09 virus that caused the 2009 H1N1 pandemic) that continue to cause severe illness and death, and sporadic cases of human infections with avian influenza A viruses that continue to cause high mortality and represent potential pandemic threats; provides an argument for wider access to effective antiviral medicines.

In short, there are very few options available for the treatment of severe or complicated influenza virus infections. Oral oseltamivir is the only widely available medicine that is effective against infections with currently circulating seasonal influenza A and B virus strains. It can be used in all age groups, including neonates and infants, and it can be used across the spectrum of disease severity because of the oral route of administration.

Review of the totality of the available evidence from RCTs and observational studies of seasonal influenza and pandemic influenza suggest that oral oseltamivir treatment and chemoprophylaxis provides benefit for public health as well as clinical benefit for individual outpatients and hospitalised patients. Furthermore, review of the available evidence from the 2009 H1N1 pandemic supports a role for influenza antiviral use in future influenza pandemics against a susceptible pandemic virus.\(^45\)

WHO currently recommends oral oseltamivir for treatment of patients with progressive or severe illness due to influenza virus infection and of those with less severe illness who are at higher risk of developing severe or complicated disease, including pregnant women. WHO recommends the use of NAIs, primarily oral oseltamivir, as part of the early outbreak response to novel Influenza A virus infections with pandemic threat potential.

The WHO antiviral guidance for influenza dates to 2010 and is in the process of being updated and consolidated with an anticipated publication date of early 2018. The guideline development process includes a rigorous review of the literature and a transparent framework for the translation of evidence into recommendations. We agree that important data has been published since the last guideline review in 2010; this will be incorporated into the new guideline.

We acknowledge that some international societies, including IDSA and the European CDC are undertaking similar processes; their publication dates are planned for 2017.

It is important to note that the Academy of Medical Sciences has undertaken the most recent expert review of the evidence for the use of NAIs in Influenza virus infections, published in October 2015. They included the Cochrane review, the MUGAS study and the PRIDE study in their evidence review. Their recommendations remain in line with current WHO guidance.

The inclusion of oral oseltamivir in the EML and EMLc has enabled WHO to take measures to ensure equitable access to oseltamivir worldwide. Oseltamivir’s recent transition to a generic medicine should further improve access and lower its cost.
At present the bulk of the available data on oral oseltamivir’s therapeutic and chemoprophylactic efficacy and effectiveness, pharmacologic properties, and tolerability profile indicate that it is currently the most useful anti-influenza antiviral with respect to global public health applicability, and WHO continues to consider oral oseltamivir to be an essential medicine for influenza worldwide. At this time, oral oseltamivir is the only available NAI that can be utilized easily worldwide. There are no other antiviral options with different mechanisms of action currently available for the treatment and chemoprophylaxis of seasonal influenza and novel influenza A viruses of pandemic potential.

Possible changes in NAI susceptibility patterns, new data emerging from further analyses of observational data, and advances in developing new influenza antivirals with non-NAI mechanisms of action may change this perspective in the future.

We advocate strongly that oral oseltamivir remains on the EML and EMLc at this time.
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