

# Managing Seasonal Influenza: Oseltamivir Treatment Policy in Indonesia?

*Herman Kosasih*<sup>1</sup>, *Arie Bratasena*<sup>2</sup>, *Krisna Pangesti*<sup>3</sup>, *Kanti Laras*<sup>1</sup>,  
*Gina Samaan*<sup>4</sup>

<sup>1</sup> INA-RESPOND Secretariat, Jakarta, Indonesia.

<sup>2</sup> Directorate General Disease Control and Environmental Health, Ministry of Health, Jakarta, Indonesia.

<sup>3</sup> National Institute Health Research and Development, Ministry of Health, Jakarta, Indonesia.

<sup>4</sup> Australian National University, Canberra, Australia.

## **Correspondence mail:**

INA-RESPOND Secretariat, Gd. Laboratorium Terpadu Lt 5. Badan Penelitian dan Pengembangan Kesehatan, Kementerian Kesehatan Republik Indonesia. Jl. Percetakan Negara no 29, Jakarta 10560, Indonesia.

email: herman\_kosasih@yahoo.com.

## **ABSTRAK**

Untuk menangani kasus Avian Influenza A/H5N1 serta mengantisipasi potensi terjadinya pandemi yang diakibatkan oleh virus tersebut, Indonesia telah membeli dan mendistribusikan Oseltamivir ke sarana kesehatan yang dimiliki pemerintah. Oseltamivir adalah obat antivirus untuk pengobatan infeksi influenza. Surveilans penyakit dan penelitian menunjukkan bahwa influenza musiman (A/H1N1, A/H3N2 atau B) mengakibatkan angka morbiditas dan mortalitas yang tinggi di Indonesia. Lebih dari 15% pasien dengan penyakit yang menyerupai influenza dan penyakit saluran pernapasan akut yang berat, positif terhadap virus influenza. Indonesia saat ini membatasi penggunaan oseltamivir untuk penanganan kasus avian influenza A/H5N1 dan antisipasi pandemi yang dipicu oleh virus A/H5N1. Kami menjabarkan hal-hal yang mendukung penggunaan oseltamivir dalam pengobatan infeksi influenza musiman sehingga para dokter mempunyai pilihan untuk memberikan obat ini. Kami berpendapat bahwa manfaat kebijakan ini lebih besar dibandingkan dengan risiko terjadinya resistensi terhadap obat antivirus. Kami merekomendasikan ketersediaan oseltamivir sehingga dapat diberikan pada pasien dengan infeksi influenza musiman, terutama bagi mereka yang dirawat di rumah sakit dan mereka yang beresiko tinggi terhadap komplikasi serta hasil pengobatan yang buruk. Secara keseluruhan, diharapkan kebijakan ini akan menurunkan angka morbiditas dan mortalitas akibat influenza musiman.

**Kata kunci:** antivirus, kebijakan, Indonesia, influenza, pengobatan.

## **ABSTRACT**

To manage cases of avian influenza A/H5N1 virus infection and in anticipation of a pandemic triggered by this virus, Indonesia purchased and distributed oseltamivir to the government health facilities. Oseltamivir is an antiviral drug that was developed for the treatment of influenza infections. Disease surveillance and research suggests that seasonal influenza (A/H1N1, A/H3N2 or B) results in considerable morbidity and mortality in Indonesia, where over 15% of influenza-like illness and severe acute respiratory illness patients test positive for the influenza virus. Indonesia currently limits oseltamivir for the management of avian influenza A/H5N1 cases and in anticipation of a pandemic triggered by the A/H5N1 virus. We present the evidence for the use of oseltamivir in the treatment of seasonal influenza infections so that doctors have the option to prescribe the drug. We propose that the benefits of this approach will largely outweigh the risk of antiviral resistance. We recommend that oseltamivir be available for administration to patients with seasonal influenza infections,

*especially for those hospitalized and for groups with high risk of complications and adverse outcomes. Overall, this will reduce morbidity and mortality of seasonal influenza.*

**Key words:** *antiviral, policy, Indonesia, influenza, treatment.*

## INTRODUCTION

Influenza is perceived as a mild infectious disease that could be managed with symptomatic medications, vitamins and rest. However, with the emergence of the avian influenza H5N1 virus, awareness among clinicians about the broader spectrum of influenza illness has increased. The World Health Organization (WHO) recommends the use of oseltamivir and other antivirals for seasonal influenza and avian influenza H5N1 patient management.<sup>1</sup> In Indonesia, the Ministry of Health rapidly purchased and distributed several million doses of oseltamivir to all health centers and hospitals, reserving the drug for the management of avian influenza H5N1 cases.<sup>2</sup> Yet, with the increasing data about the burden of influenza in Indonesia and globally,<sup>3-5</sup> the drug also has the potential to be used in the management of seasonal influenza. As it is undistinguishable from acute bacterial respiratory infections, seasonal influenza is often treated with symptomatic medications or antibiotics.

This paper asks the question: Is it time to use antivirals in the management of seasonal influenza in Indonesia? We present the supporting evidence including findings from Indonesia, and discuss common concerns. We describe the magnitude of influenza disease burden, the groups at risk of complications and adverse outcomes, and then discuss the various options available for disease control and treatment with a specific focus on oseltamivir since it is already available in Indonesia. We aim to stimulate policy update in Indonesia, and suggest the use of antivirals for the clinical management of seasonal influenza cases, especially amongst hospitalized patients and patients from groups known to be at high risk of adverse outcomes.

## BURDEN OF SEASONAL INFLUENZA INFECTION

Recent studies in South-East Asia show that seasonal influenza causes severe disease and has

similar or even higher disease burden compared to temperate countries.<sup>6,7</sup> In a multi-country study, influenza was associated with 10.6, 13.4 and 8.3 deaths per 100,000 population in Guangzhou (China), Hong Kong and Singapore, respectively.<sup>8</sup> In Thailand, the average annual incidence of influenza pneumonia was greatest in children less than 5 years of age (236 per 100,000) and in those age 75 or older (375 per 100,000), and influenza pneumonia resulted in an estimated annual average of 36,413 hospital admissions and 322 in-hospital pneumonia deaths.<sup>9</sup>

In Indonesia, during 2003-2007, influenza viruses were identified in 20.1% (4.236/21.030) of influenza-like illness (ILI) patients, including 20.1% (4.015/20.012) of outpatients, and 21.7% (221/1.018) of hospitalized patients.<sup>3</sup> Influenza was also found to contribute to a high proportion of hospitalized cases: 6% of those with SARI (Severe Acute Respiratory Illness).<sup>10</sup> These data highlight that the perception of influenza as a mild self-limiting disease is misled. Influenza can and does lead to severe disease and fatalities, and results in decreased productivity and significant economic losses. Even though Indonesian data on the economic impact of influenza are not available, Thailand has estimated that economic losses due to influenza amount to 23.4-62.9 million US dollars each year.<sup>11</sup>

## AT-RISK GROUPS

High risk groups for severe illness and death due to influenza infection include infants, persons over 65 years of age, pregnant women, immune-compromised people including transplant recipients and patients with HIV, and those with chronic illnesses such as diabetes mellitus and tuberculosis (TB).<sup>12</sup>

Infants are generally not able to mount an adequate immune response when infected with the influenza virus, resulting in prolonged levels of viral replication. Clinical symptoms can

range from brief episodes of moderate fever<sup>13</sup> to severe complications such as shock, acute glomerulonephritis, pericardial effusion, and encephalitis.<sup>14</sup> It is estimated that about 500 out of 100,000 children under 4 years would require hospitalization due to influenza, whilst in children with comorbidities such as asthma and immune disorders, the hospitalization rate is seven-fold at 3,562/100,000 children.<sup>15</sup> In Thailand, the average annual incidence of influenza pneumonia in children less than 5 years of age was 236 per 100,000 children.<sup>9</sup> Currently, rates of infant influenza-related hospitalizations and mortality are not known in Indonesia, but they likely mirror those found in other South-East Asian countries such as Thailand.

In pregnant women, decreased cellular immunity and changes in lung structure are known to increase susceptibility to influenza infection.<sup>16</sup> Pregnant women in their second and third trimester have a higher risk for hospitalization due to cardiac or respiratory complications associated with influenza infection.<sup>17</sup> Pregnant women with comorbid conditions such as chronic cardiac disease, chronic pulmonary disease, diabetes mellitus, chronic renal disease, malignancies, and immunosuppressive disorders are more than three times more likely to be hospitalized for respiratory illness during the influenza season than women without these comorbidity.<sup>17</sup>

In the elderly, the declining condition of the immune system, the deteriorating function of respiratory tract cilia, the weakening cough reflex, and the presence of comorbid diseases contribute to the risk of infection and severe illness.<sup>18</sup> Complications include pneumonia due to secondary bacterial infections with *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Haemophilus influenzae*.<sup>18</sup> Immuno-compromised persons with HIV/AIDS, solid organ or haemopoietic stem-cell transplant, hemodialysis, cancer, or steroid treatment are known to have severe and prolonged influenza infections as the immune systems that play a crucial part in virus clearance are altered.<sup>19</sup>

TB infection is a risk factor for severe influenza disease. In 2012, WHO reported that Indonesia is a country with high TB burden and

cases of multiple drug resistant (MDR) TB.<sup>20</sup> A mathematical analysis has shown a significant association between tuberculosis and influenza mortality during the 1918 A/H1N1 pandemic<sup>21</sup> and in lower rates during the subsequent A/H2N2 pandemic in 1957 and A/H3N2 pandemic in 1968.<sup>22</sup> However, data describing this association are not available in Indonesia.

## OPTIONS FOR DISEASE CONTROL

There are a number of options for influenza case management and disease control. This includes non-pharmaceutical interventions such as social distancing and hand hygiene measures, as well as pharmaceutical interventions such as vaccines and antivirals. We present these options to highlight that management of influenza is feasible through a variety of methods but the use of oseltamivir is likely to be the most implementable.

## NON-PHARMACEUTICAL INTERVENTIONS

Measures such as school closures and cancellation of large gatherings, as well as hygiene measures such as hand hygiene and face masks may impact the course of influenza disease outbreaks. In particular, since school age students have highest influenza disease prevalence compared to other groups<sup>3</sup> and have high contact rates and viral shedding. Prevention of disease transmission in this cohort can be used to reduce excess morbidity and mortality in other groups.<sup>23</sup> The use of facemasks and hand hygiene have been found to reduce household disease transmission if implemented early and intensively.<sup>24</sup> However, the proportion of cases averted by these social distancing measures remains uncertain.<sup>23</sup> Furthermore, these population-based interventions may minimize disease spread but would not limit the severity of illness or outcome for individuals ultimately infected by the virus. Therefore, non-pharmaceutical interventions cannot stand alone as disease control measures against influenza.

## PHARMACEUTICAL INTERVENTIONS

The two key pharmaceutical interventions available for case management and public health

disease control of influenza are vaccination and antiviral administration.

### **Vaccination**

Increased vaccination coverage in the community is correlated with a lower incidence of influenza.<sup>25</sup> In children, vaccination is recommended starting at 6 months of age.<sup>13</sup> Although the efficacy of vaccines in the elderly and the immune-compromised is lower than the young and healthy adult populations,<sup>18</sup> vaccination is still recommended to reduce their risk of serious complications and adverse outcomes. Undoubtedly, influenza disease trends and burden in Indonesia and other countries demonstrates the importance of vaccination as a public health disease control measure. However, introduction and funding of vaccination requires long term planning and assurance that the immunization program will reach its target audience cost-effectively. Currently, Indonesia recommends that hajj pilgrims receive influenza vaccine but this program is not funded. To develop and implement the policy that expands this recommendation to broader risk groups and/or funds the vaccination in Indonesia is likely to be a protracted process requiring high level political commitment. In the interim, the availability of antiviral drugs offers an attractive alternative to reducing the morbidity and mortality associated with influenza.

### **Antivirals**

Anti-influenza drugs include the M2 channel blockers, amantadine and rimantadine, and the neuraminidase enzyme inhibitors, zanamivir and oseltamivir. These drugs interfere with several stages in the viral replication cycle: entry, viral assembly virus, or release.<sup>26</sup> Due to the high levels of resistance to M2 channel blockers,<sup>26</sup> they will not be discussed further here.

Zanamivir and oseltamivir are analogues of sialic acid that can inhibit this enzyme for viral particle release, thereby inhibiting replication of both influenza A and B viruses.<sup>27</sup> Oseltamivir is taken orally, while zanamivir is administered by oral inhalation. Zanamivir may cause spasms in some patients and may require the use of a bronchodilator.<sup>28</sup> Since oseltamivir is already available in Indonesia, the focus below

is regarding its utility for seasonal influenza treatment.

Oseltamivir is reported to be most effective if given within 48 hours of symptom onset,<sup>14</sup> but it is still beneficial even when given after 48 hours.<sup>28-31</sup> Parameters commonly used to demonstrate the efficacy of oseltamivir include: duration of illness, fever, length of time that the virus is detectable in the respiratory tract, length of time needed to return to normal activities, duration of treatment, clinical severity, and the ability to prevent complications such as otitis media, pneumonia, and death.<sup>14,29-31</sup> A study in Thailand reported that oseltamivir is associated with survival in hospitalized human influenza pneumonia patients.<sup>32</sup>

Various studies have been conducted in children, adults, and groups of high risk patients. A study in 1-12 year old children with influenza showed that the duration of illness was shorter in patients treated with oseltamivir within 48 hours than those not treated (4.2 vs. 5.7 days), the time required to return to daily activities was reduced by 45 hours, and the incidence of otitis media decreased by 40%, thus, automatically reducing the use of antibiotics.<sup>14</sup> As similar findings are reported, oseltamivir is also recommended in infants.<sup>33</sup>

Currently, there is a paucity of data on the use of oseltamivir in pregnant women. Administration of oseltamivir to hospitalized pregnant women infected with the pandemic A/H1N1pdm09 virus in the UK reduced intensive care admissions by 84%.<sup>34</sup>

Studies in patients with chronic lung or heart disease showed that oseltamivir significantly reduced the duration of symptoms by 36.8% ( $p=0.048$ ), duration of fever by 45.2% ( $p<0.001$ ), severity by 43.1% ( $p<0.001$ ), complications by 45% ( $p<0.001$ ) and antibiotic use by 69% ( $p=0.02$ ).<sup>35</sup> The use of oseltamivir in geriatric patients demonstrated lower incidence of serious complications, less antibiotic use, lower hospitalization and mortality rates in those treated within 48 hours.<sup>29,36</sup>

The effectiveness of oseltamivir in healthy adults has recently come into question as a Cochrane review showed that oseltamivir significantly reduces the time to first alleviation

of symptoms by 21 hours in influenza patients receiving oseltamivir compared to placebo, but that the effect of oseltamivir on complications and viral transmission could not be credibly assessed as available data lacked sufficient detail.<sup>37</sup> This does warrant further investigation globally but one must acknowledge that answering such questions may take a long time. Further, the finding relates specifically to health adults rather than groups at high risk of complications and severe illness. Despite the Cochrane review, a recent report using country-level data from forty-two WHO Member States from July 2009 to August 2010 demonstrated evidence of a protective relationship between antiviral drug supply and influenza mortality<sup>38</sup> and the Cochrane review did not impact WHO's recommendations on oseltamivir usage for the management of Influenza (**Table 1**).

**Table 1.** World Health Organization guideline for the pharmaceutical management of Influenza<sup>39</sup>

Population	Pandemic influenza A (H1N1) 2009 and other seasonal influenza viruses
<b>Uncomplicated clinical presentation</b>	
Patients in higher risk groups	Treat with oseltamivir or zanamivir as soon as possible
<b>Severe or progressive clinical presentation</b>	
All patients (including children and adolescents)	Treat with oseltamivir as soon as possible (zanamivir should be used if oseltamivir unavailable)
Patients with severe immunosuppression	Treat with oseltamivir as soon as possible. Consider higher doses and longer duration of treatment

## RESISTANCE TO OSELTAMIVIR

A common concern in using oseltamivir in the treatment of influenza is antiviral resistance. The cause of resistance is mutations that cause three-dimensional changes in the neuraminidase protein that affects the ability of the drug to bind to it.<sup>40</sup> Mutation is inherent to the influenza virus because of the absence of repair mechanism during RNA replication, which is then compounded by environmental factors, such as the use of antiviral drugs or the immune status of the patient. Drug concentrations that

are inadequate to kill the virus prompt the virus to mutate in order to survive.

For influenza B and influenza A/H3N2, oseltamivir resistance is not as widely reported in literature or from routine surveillance systems. The only reports were from a study in patients with cancer from 2002-2008 where resistance to influenza B and A/H3N2 was identified,<sup>41</sup> and a study in Japan in 2002-2003 that identified influenza A/H3N2 resistance in 9 of 50 (18%) children who had been treated by too a low dose of oseltamivir.<sup>38</sup>

Oseltamivir resistance among influenza A/H1N1 viruses is more frequently reported. The first report was from a 2000-2001 study in Japan where the percentage of resistance in children treated with oseltamivir was 16% (7/43).<sup>42</sup> However, the percentage of resistant viruses from routine surveillance from 1996-2007 was very low.<sup>43</sup> Resistance was widespread starting in 2007 in several countries in Europe, where oseltamivir was rarely used (0-68%)<sup>44</sup>, in 2007-2008 in the US (10.9%)<sup>45</sup> and in 2008-2009 in Japan (99.7%).<sup>46</sup> In Indonesia, where oseltamivir is rarely used, resistance rates of 13% were found in isolates tested in 2007-2008.<sup>47</sup>

So far, there is no evidence that suggests resistance is brought about by the widespread but appropriate use of antivirals.<sup>48</sup> For example, the over-the-counter prescription of oseltamivir in New Zealand did not trigger higher resistance rates.<sup>49</sup> Interestingly, the resistant A/H1N1 viruses are no longer circulating in most parts of the world, as they have been replaced by A/H1N1pdm09, which highlights the dynamic nature of influenza viruses despite the pharmaceutical interventions applied.<sup>50,51</sup>

A commonly cited argument against the use of oseltamivir in Indonesia is the possible emergence of a resistant A/H5N1 influenza virus, as a result of re-assortment of the virus with resistant seasonal influenza viruses. In theory, this re-assortment is possible but the probability is very low as it requires the same person to be infected with the two viruses at the same time. Such co-infections have never been reported in the literature. Therefore, this remote possibility does not seem to warrant withholding antivirals from seasonal influenza patients.

## ANTIVIRAL POLICY

Many developed countries use oseltamivir for the treatment and prophylaxis for seasonal influenza. Since 2007, New Zealand provides oseltamivir to patients meeting a clinical case definition for influenza at pharmacies without prescription.<sup>49</sup> One rationale for this is to familiarize clinicians with the use of oseltamivir for the management of influenza infections in anticipation of an influenza pandemic during which clinicians are encouraged to prescribe antivirals. In England, the Netherlands and Australia, oseltamivir is prescribed to patients with influenza symptoms that belong to high-risk groups for complications.<sup>52</sup> In the United States and Japan, oseltamivir is prescribed to influenza-confirmed patients.

Tropical and subtropical countries have differing policy. In India, oseltamivir has been available under physician's prescription since 2009.<sup>53</sup> In Singapore, physicians prescribe oseltamivir, for immune-compromised patients as well as those with hospitalized, laboratory-confirmed influenza illness presenting within 48 hour of onset. Singapore also provides oseltamivir for prophylaxis of contacts of influenza cases in military barracks.<sup>54</sup> In Malaysia, physicians may prescribe oseltamivir to both treat patients and prevent influenza in institutional outbreaks.<sup>55</sup> Other countries such as Laos and Cambodia underutilize oseltamivir, where even during the A/H1N1pdm09 pandemic, clinicians were hesitant to prescribe it to their patients. Despite the varying policies including highly liberal use of oseltamivir, resistance rates among currently circulating influenza viruses remain low.

## OSELTAMIVIR APPROACH FOR SEASONAL INFLUENZA IN INDONESIA

Based on the disease burden evidence, the availability of oseltamivir and the experience of oseltamivir usage in other countries, it may be the time to develop an approach for the use of oseltamivir for seasonal influenza in Indonesia. One potential starting point is allowing doctors to prescribe and administer oseltamivir to influenza-confirmed patients, especially those hospitalized and for those groups at high risk of

adverse outcomes. Oseltamivir use will have two key impacts: (1) clinically reduce the severity of illness, complications and mortality, and (2) epidemiologically reduce the transmission of the virus in healthcare settings. We do not necessarily advocate for government-funded procurement and administration of oseltamivir for these groups since this is a decision that needs to be based on economic analyses. However, we do advocate for a policy which would enable doctors to prescribe oseltamivir at patients cost if indicated.

Policy development requires a combination of evidence and decision-maker commitment. The evidence currently available shows that influenza disease activity is considerable in Indonesia. Further virological and epidemiological surveillance, as well as specific research that assesses disease burden and cost of influenza to society, may help grip decision-maker attention. We recognize that our perspective has some limitations. These include limited discussion about the cost-benefit of oseltamivir in Indonesia and mechanisms to operationalize our suggested approach. There are currently no studies that assess cost-benefit of oseltamivir in Indonesia, but these should be considered priority to build the evidence for an influenza disease control program. We did not elaborate on mechanisms to operationalize our recommendation since Government authorities and Medical Associations are better places to consider these issues in line with regulatory requirements.

## CONCLUSION

The time has come to think about use of oseltamivir for seasonal influenza disease control in Indonesia. The rational use of oseltamivir in managing influenza patients, especially high risk groups may bridge the gap and serve as an interim solution to longer term options such as vaccination. This paper has discussed the available evidence and encourages clinicians, public health practitioners as well as decision-makers to further discuss and develop the relevant policies in Indonesia. We call on researchers and policy-makers to work together in addressing this public health problem.

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