Chapter 7

Therapeutic Approach for Seasonal Influenza and Pandemic

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Additional information is available at the end of the chapter

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Abstract

Influenza infection is usually a self-limiting and suddenly life-threatening disease. Seasonal influenza causes severe clinical symptoms and almost subsides within 7 days in patients without severe illness, following no complications of pneumonia and encephalitis. Influenza A (H1N1) pdm09 brought the disaster including many deaths. We cannot make differential diagnosis between seasonal and pandemic influenza adequately in a pre-pandemic state. Seasonal influenza displaces suddenly pandemic, and we necessarily establish a standard treatment for influenza viral infection in routine work. If antiviral therapy would not be effective for patients with influenza viruses in an early period of illness, further investigations would be proceeded concerning three points: mutations of influenza viruses resistant to neuraminidase inhibitors (NAIs), concomitant diseases of patients, and a new pandemic virus. If the systemic procedure would be functioned, we are able to reduce individually burden of patients with severe clinical symptoms and leading complications and socially delay widespread of pandemic and plan for the streamline management of pandemic documents.

Keywords: antiviral therapy, seasonal epidemic, pandemic, streamline surveillance, the systemic procedure

1. Introduction

Influenza viruses spread seasonally and cause infection of the airway tract in humans following severe symptoms. Influenza viruses grow and multiply among in human, swine, and avian bodies. Influenza viruses escape human immunological protective system against influenza viruses by changing their epitope detected by human immune cells. Annual seasonal influenza epidemic often happened under no antiviral procedure by easy infection of influenza viruses.

Seasonal influenza viruses affect 10–20% of human population in epidemics each year [1] and worldwide, cause an estimated 3.5 million cases of severe illness and 250,000–500,000 death each year [2]. Although almost infected patients with seasonal influenza viruses recover from the disease in less than 2 weeks. On the other hand, some group of people containing young children, adults being elder than 65 years old and compromised hosts with severe illness had complications of influenza infection leading hospital admission [3]. Influenza viruses mutate and change the disease severity in host when transferring from avian to swine or from avian to human or from swine to human. A new mutant of influenza viruses is defined at the site of a mutation and called as influenza A (H5N1), A (H7N9), and A (H1N1) pdm09 each, causing severe affected people following many deaths [4]. Three influenza pandemics happened in the twentieth century: in 1918–1919, 1957, and 1968 and were called as Spanish flu, Asian flu, and Hong-Kong flu each and caused the severe disaster [4]. Especially Spanish flu brought estimated 20–50 million mortality [4]. We have the inability to predict and testify the appearance of dangerous influenza viruses to human health by the lack of rapid, affordable, highly sensitive, and specific diagnostic tests. The appearance of a new mutation of influenza viruses was noticed as unsuccessful treatment cases leading to life-threatening complications of influenza infection in the treatment of seasonal influenza [4]. The expansion of disaster by both the delayed use and little sharing of pre-pandemic information makes difficult in minimizing a widespread of a new mutant infection of influenza virus [4]. So it is necessary to establish a systemic procedure of diagnosis and treatment for patients with seasonal influenza and pandemic viruses in early phase of pandemic. In a first step of diagnosis of influenza virus infection, we can use rapid diagnostic kits for influenza A/B virus and we diagnose easily seasonal influenza infection in the outpatients. But rapid immune-chromatographic kits cannot show the mutation of influenza virus subtypes, we cannot make a differential diagnosis between seasonal and pandemic influenza virus by it [5]. A mutation of influenza virus subtypes is evaluated by reverse-transcriptase polymerase chain reaction (RT-PCR) and direct sequence of a recognition site of influenza virus subtypes [5]. This method is expensive and time-consuming. We cannot apply this method to all outpatients with influenza virus. On the course of clinical treatment, we need to discriminate patients with suspicious pandemic influenza virus from the other patients with seasonal influenza effectively and economically. We would discuss the feasibility and execution of this trial in the following chapters.

2. Prevention

It is not too enough to exaggerate that prevention is the most effective therapy for infectious disease. It is desirable to establish universal most effective vaccine against influenza virus. Vaccine effectiveness (VE) is influenced by viral subtype/lineage as well as the timing of vaccination (early or late epidemic in a season). VE of trivalent influenza vaccine (TIV) is assessed as from 20 to 50% in vaccine programs of several countries [6, 7]. The population rate of people was over 80% in the Korean national immunization program but VE remains low in the elderly adults [8]. They addressed the improvement of influenza vaccine including the adoption of quadrivalent influenza vaccine (QIV), adjuvanted influenza vaccine, and high-dose

influenza vaccine. Recently, WHO has been recommending QIV in 2013 and QIV has been adopted in several countries. QIV is estimated cost-effective and cost saving to reduce the burden of outpatient visit for influenza but 1.62 hospitalizations and 0.078 deaths per 100,000 individuals were estimated in Japan [9]. VE is often influenced by the timing between vaccination and influenza epidemic. Early epidemic occurs seasonally before administration of vaccine against seasonal influenza infection in people and VE is low. A mismatch of influenza viral strains between vaccination and epidemic makes VE low. It is very difficult to overcome influenza infection only by vaccination because of current VE and variability of influenza virus. We need the adequate diagnosis and treatment systematically after the procedure of adequate vaccination.

3. Therapy for patients with influenza viruses

3.1. Antiviral therapy

Adoption of neuraminidase inhibitors (NAIs) for treating patients with influenza virus improves clinical incidences of outpatients leading hospitalization. Influenza infection is typical symptoms such as fever, headache, sore throat, cough, joints lasting, and sometimes diarrhea and nausea. On the first step of the treatment for influenza, concomitant use of antipyretic and mild analgesic drugs such as acetaminophen, are applied to the patients with influenza viruses as symptomatic treatment. It is very difficult to suppress widespread of influenza viruses without the isolation of patients within 1 or 2 weeks. On the next step of the treatment for influenza, amantadine and rimantadine were administered to patients with influenza A, and ribavirin was used to treat immunosuppressed patients with severe influenza conditions [10]. These are limited in operating only against influenza A viruses and adverse effect and resistance of virus to drugs lead to less use. On the use of these drugs, antiviral effectiveness for alleviation of severe symptoms of patients with seasonal influenza viruses was limited and not enough to suppress the widespread of those? On the third step of the treatment for influenza, NAIs are administered to the patients with influenza viruses. The NA protein is a homotetrameric glycoprotein with a stalk region and enzymatically active head. The NA active site cleaves sialic acid at the glycol-sialic bond on the host cell as well as in respiratory mucus, leading to spread of the virus [11–13]. NAIs act to inhibit the release of progeny viral particles from infected host cells and have more effectiveness and less adverse effects than amantadine and rimantadine when administered to patients with influenza viral infection [14]. Administration of NAIs to patients is recommended within 48 h from the onset of infection [14]. NAIs alleviate symptoms and shorten its duration bothered from typical symptoms of influenza, especially high fever and headache without using antipyretic agents. Four NAIs, namely oseltamivir, zanamivir, laninavir, and peramivir are available in various countries and three measures of administration, namely oral intake, inhalation, and infusion to vein are used [14]. Zanamivir was the first NAI to be developed and was licensed in 1999. Its feature is poor absorption and an inhaled agent and is available in an intravenous form for compassionate use [15]. Oseltamivir is a prodrug being developed on the basis of the structure

of the active site of zanamivir and is activated in the liver [16]. Oseltamivir is administered orally and sometimes intravenously in the patients not being tolerable in oral dose [17]. Peramivir is administered only as an intravenous formulation and show low oral bioavailability [17]. It achieves very high concentration in the bloodstream and its half maximal inhibitory concentration (IC_{50}) for influenza viruses is lower than that of both oseltamivir and zanamivir [18]. Laninamivir is another inhaled prodrug which is activated in the respiratory tract. One inhalation of laninamivir is effective for patients with influenza virus because of long half-life and high concentration within tissue [17]. Now the adequate measure for administration of NAIs can be selected following as the patients' condition and ages. If patients are children and cannot intake NAIs orally or inhaler NAIs, intravenous infusion of peramivir would be recommended [19].

3.2. Necessity of monitoring body temperature in patients without antipyretic and analgesic drugs

Patients with seasonal influenza viruses almost have recovered from high-fever state within 1 or 2 days on the condition of no use of antipyretic drugs (**Figure 1**). So monitoring a patient's body temperature is useful to evaluate whether antiviral treatment is successful or not. We showed the typical monitor of successful treatment of NAIs in body temperature measured by

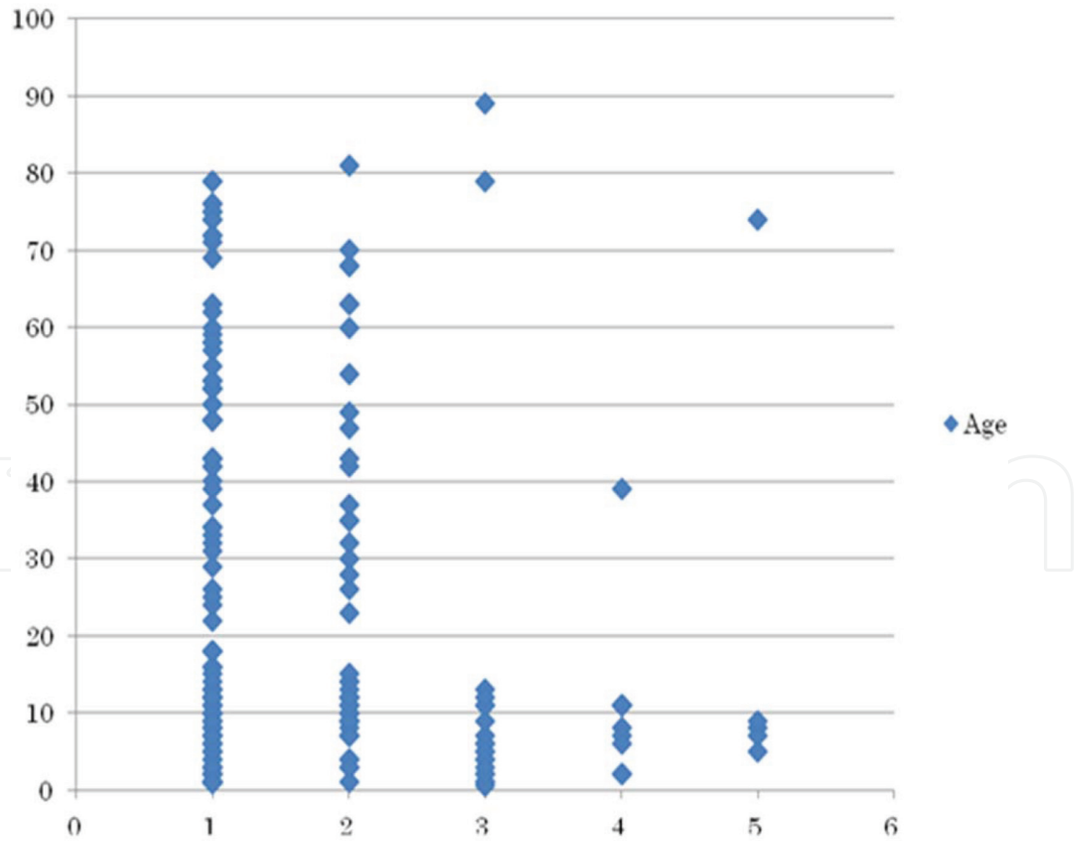

Figure 1. Correlation between age and amount of time required to alleviate fever. Almost cases with NAIs treatment have normal temperature within 3 days. This figure is cited from clinical effects of Oseltamivir, Zanamivir, Laninamivir, and Peramivir on seasonal influenza infection on outpatients in Japan during the winter of 2012–2013. Takemoto et al. [57].

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the patient own (**Figure 2**). If treatment of NAIs fails to alleviate typical symptoms of patients with influenza viruses within 2–3 days, complications of influenza viral infection; influenza-associated pneumonia and encephalopathy would have to be investigated. The patient with influenza virus type A detected by a rapid test for influenza viruses had been annoyed over 4 days from onset of the disease on the condition of administration of zanamivir (**Figure 3**), and was diagnosed as influenza associated pneumonia by a close examination for further diseases (**Figure 4**). The antibiotic drugs were additionally administered to the patient (10-year-old girl) at the outpatient without antipyretic and analgesic drugs and pneumonia was treated successfully at home as the diagnosis of pneumonia categorized as mild severity and bacterial pneumonia following influenza viral infection. No new mutation of influenza virus A derived from this patient was detected. Hospitalization would be recommended for the severe pneumonia with any danger sign according to classification of pneumonia because pneumonia is the significant cause of death in the world [20, 21]. We had experienced one case of influenza-associated encephalopathy which had uncontrolled high fever and mild neuro-psychiatric disorder despite of administration of oseltamivir. We sent the 6-year-old boy to the hospital for diagnosis and treatment of influenza-associated encephalopathy and had good information of a full recovery without death or neurologic sequela. In all, 200–300 cases of influenza encephalopathy are reported as the result of 7% death, 17% survive with neurologic sequel, and 76% full recovery of patients in a year in Japan [22]. If high fever and other typical

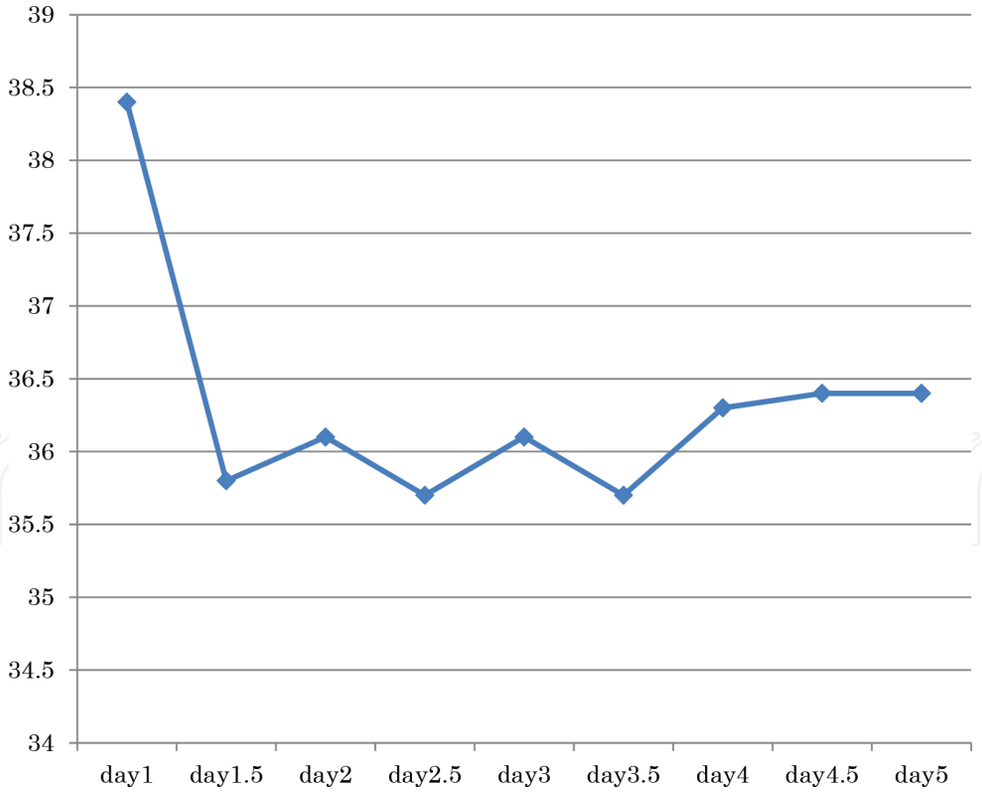

Figure 2. A pattern of body temperature of the patient with influenza virus A in the winter of 2017 is shown in a graph. The NAI is effective for alleviation of high fever and no relapse of fever in the effective clinical course of NAI treatment is shown. Patients with no complications and no resistant influenza viruses to NAIs show this pattern on the administration of NAIs.

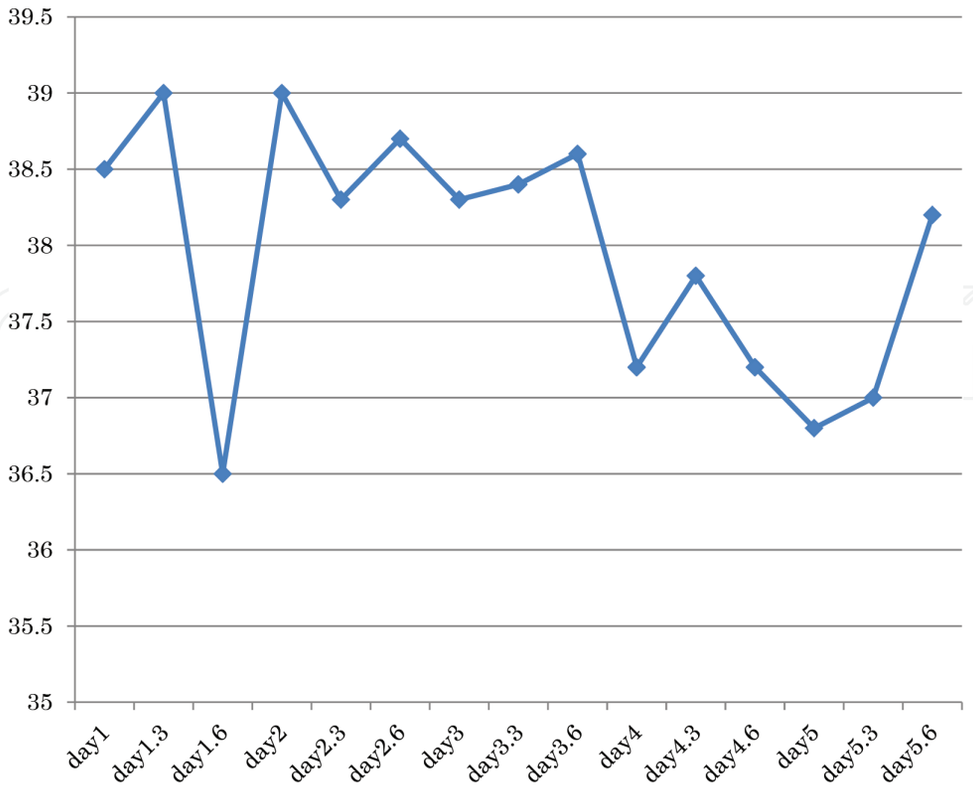

Figure 3. A pattern of body temperature of the patient with influenza virus A in the winter of 2017 is shown. High-grade fever is prolonged and relapsed over 3 days from the onset of influenza infection. Usually NAI treatment does not need the use of antipyretic agent for alleviation of high fever. Complications and/or viral mutations of resistant to NAIs cause the prolongation of high fever.

symptoms in patients with influenza viruses continue over 3–4 days under the administration of a NAI and no remarkable complications of influenza in patients, resistance of viruses to antiviral drugs or new mutations for pandemic should be investigated. It is very important to follow up patients in taking view of their body temperature from the beginning of NAI treatment and inform reconsultation with the doctors to patients on the condition of little amelioration from high fever of influenza infection within a few days.

3.3. NAIs were effective for influenza A (H1N1) pdm09

Pandemic of influenza A (H1N1) pdm09 was disseminated worldwide in 2009 –2010 and in many countries severe complications of its infection, hospitalization, and death from it were reported [23]. On the other hand, the incidence of such phenomenon was lower in a few countries than in the other countries. WHO overviewed pandemic 2009 on October in 2009 and defined the difficulty of comparison for evaluating the difference factors between countries due to the different age classes used to present data and the use of crude number of cases rather than rates [4]. The most burdened population of disease was occurred in younger age group as a striking difference between pandemic (H1N1) 2009 and seasonal epidemic [24]. This difference is hypothesized the population difference exposed to 1918–1919 epidemic like H1N1 influenza viruses between the elder generation over 65 years old and the younger

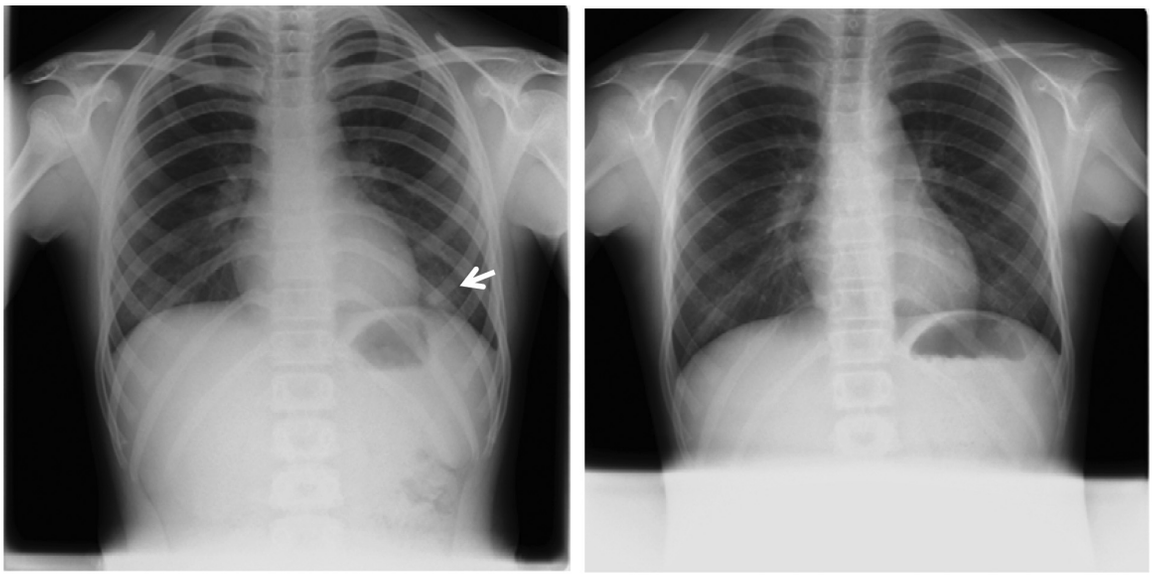

Figure 4. Chest X-ray films shows the influenza-associated pneumonia in the left lobe of the lung in the phase of pre- and post-treatment with antibiotics. Close examination for prolongation of high fever after treatment of NAI clarified the pneumonia in the patient with influenza virus infection in the early phase of pneumonia. A clinical treatment and follow up the patient with influenza virus with NAI and no antipyretic agents is useful for evaluation and findings of complications and viral mutations.

generation under 20. Compared with the rest of the population to develop severe disease, in countries of Americas and the Pacific, disproportionate affection by influenza A (H1N1) pdm 09 might be influenced by the prevalence of underlying medical conditions and limited access to medical care living conditions in addition to a social component and crowded living conditions [25]. Therefore, it is necessary to establish the medical conditions against viral infection and easy access to medical care in the worldwide for pandemic before administrating antiviral drugs. Adequate diagnosis of influenza infection and the early intervention with antiviral drugs (NAIs, etc.) to influenza viral infection among healthy little immunized population are desirable. On the other hand, effectiveness of NAI treatment is suggested for reducing mortality when given to hospitalized patients with influenza A (H1N1) pdm09 and the likelihood of requiring of hospital admission when given to population with confirmed or suspected influenza A (H1N1) pdm09 at high risk of hospitalization [26, 27]. NAI treatment following to rapid positive tests for influenza viruses might be effective for pandemic and reduce mortality rate of pandemic [27]. Additionally, influenza-like illness (ILI) in pandemic without laboratory confirmation among community patients with relatively severe influenza infection and patients with underlying comorbidities would be recommended to be treated by NAIs for reducing hospitalization and prevention of severity in early time (<48 h) after the onset of illness [26, 27].

3.4. Resistance to antiviral drug among influenza viruses

Influenza virus is a negative-sense RNA virus and contains eight gene segments that encode eleven proteins, including hemagglutinin (HA) and neuraminidase (NA) glycoprotein.

Influenza virus initiates the infection using HA to attach to sialic acid residues on the host cells and entries the host cells using M2 to initial receptor mediated endocytosis and releases progeny and propagate infection to other host cells using NA to cleave sialic acid residues on the host cells [28]. Each year influenza virus develops mutations within these genes leading antigenic drift and antigenic shift. Antigenic drift is represented by the little changed nature of virus and causes epidemics. Antigenic shift means change of major variant of virus and initiates a severe pandemic followed at intervals of a year or two by successive epidemics by antigenic drift [13]. Different from antigenic drift in transmission between interspecies by viruses, antigenic shift is the reassortment of gene segments between two different parental viruses within the same host [29]. The most recent pandemic; influenza A (H1N1) pdm09 was caused by a swine-origin H1N1 subtype, which originated from the sequential reassortment events between human H3N2, swine H1N1 subtype, and avian H1N2 subtypes of North America and Eurasian lineages [30]. Concerning to the nature of virus, many mutants of viruses are reported. It is not completely understood in mechanism to produce the resistance to antiviral drugs among influenza viruses. But many types of viruses being resistant to antiviral drugs are reported [31]. Adamantanes were the first approved class of antiviral drugs by binding M2 channel pore and blocking conductance either directly or allosterically. Consequently, adamantanes inhibits the virus RNA release and influenza virus replication [32]. Mutated amino acids (L26F, V27A, A30T/V, S31N, G34E, and L38F) in M2 membrane domain that line the channel pore (V27, A30, and G34) or are involved in the tetramer helix–helix packing (L26, S31, and L38), lead to increase in pore size with hydrophilicity of the channel or lead to narrow of the pore size with destabilization of helix–helix assembly. Consequently, influenza viruses reduced susceptibility to adamantanes [33]. In 1980 epidemics, the first detection of the resistance of influenza to adamantanes was reported [34]. The resistance of influenza viruses to adamantanes was rare with 1–2% frequently until 2000 [35] but the rate of resistance has dramatically risen to 27% since then [36]. From 2005 onward, the rate of the resistance to adamantanes started to increase almost exponentially to 90.6% of the H3N2 and the 15.2% of H1N1 global isolates [37]. Similar rates were confirmed in isolated viruses in the USA and the resistance conferring mutation was S31N in the 90–98% of isolated H1N1 and H3N2 subtypes [38]. Vast majority of adamantanes-resistant influenza virus subtypes (95%) contained the S31N mutation [39, 40]. Similar to M2, influenza virus has mutated several amino acids in or around neuraminidase active site to acquire the resistance to NAIs [41, 42]. Several in vitro and preclinical studies have found some mutations in neuraminidase; E119G/A/D/V, R292K, and H274Y [43]. Therefore, a global Neuraminidase Inhibitor Susceptibility Network (NISN) was established to monitor influenza virus to NAIs [44]. Unlike adamantanes resistance, which initially emerged and was predominant in H3N2 subtypes, NAI resistance first isolated and was spread in H1N1 subtypes [40, 45]. During the first 3 years of using NAI from 1999 to 2002, no resistance basically was detected [43, 44]. But from 2008 to April 2009 [before the emergence of influenza A (H1N1) pdm 09], over 99% influenza viruses of the H1N1 isolated were resistant to oseltamivir but were sensitive to zanamivir and none of the H3N2 isolates were resistant to oseltamivir in the report of the Centers for Disease Control and Prevention (CDC) in the USA [45]. Similarly in 2008–2009 season, more than 90% of the circulating H1N1 subtypes globally were oseltamivir resistant [46, 47]. H274Y mutant was predominantly circulating during 2008–2009 and rapid transmission of H274Y mutation in influenza (H1N1) pdm 09 has been detected in communities with little or no previous expose

to oseltamivir [48, 49]. Fortunately, almost of the pandemic H1N1 global isolates collected between April 2009 and January 2010 were sensitive to NAIs, except an odd 0.7% and other few H1N1 isolated local cases [50–54]. The NAI sensitive 2009 pandemic H1N1 subtypes displaced the-pre-pandemic oseltamivir resistant H1N1 lineage and remains largely NAI sensitive and is predominantly circulating at present [54, 55]. Sequential investigation of influenza virus mutation following impairment of NAI treatment for seasonal epidemics is useful for early detection of pandemic. There is no rapid diagnostic test for the detection of mutation or strains available in clinical laboratories. Systemic reviews of influenza resistance to NAIs did not reveal any difference in time for alleviate symptoms between oseltamivir-resistant and oseltamivir-sensitive patients [56]. This conclusion is different from our data and this difference might be dependent on the different analysis between the monitor for fever isolated from symptoms and the monitor for all symptoms of patients including estimate difference [57]. On the course of NAI treatment, an alleviation time for fever is not over 2–3 days in the group of patients with seasonal influenza viruses susceptible to NAIs. Treatments for patients with influenza viruses resistant to NAIs are considered to switch to other NAI: oseltamivir to zanamivir or other NAIs or to combine two NAIs: oseltamivir and zanamivir or three antiviral drugs; oseltamivir, adamantanes, and ribavirin [58]. Evaluated by the outcome of influenza viral copy numbers at 48 h after treatment, dual therapy; zanamivir/oseltamivir is less effectiveness than oseltamivir monotherapy [59]. Triple combination antiviral drugs (TCAD) composed of oseltamivir, amantadine, and ribavirin impedes the selection of the influenza virus A in vitro and clinical trials have been completed for the treatment with immunocompromised hosts with influenza in the United States [60, 61]. For preparedness to emergence and widespread of influenza virus variants resistant to antiviral drugs, new antiviral agents targeting viral particles and mechanism of viral replication are desired. Polymerase inhibitors; T-705, VX-787, and S-033188 concerning to suppressing of replication, are undergoing phase 2/3 clinical trials and favipiravir (T-705) is approved for the treatment of pandemic in Japan [62] when NAIs are ineffective to pandemic and the government permit to use. In addition to new antiviral agents, pandemic vaccine is necessary for pandemic preparedness [5]. Genotypic and phenotypic assays are available in the surveillance laboratories. Genotypic assays are rapid and can be done without viral culture otherwise genetic resistance does not always correlate phenotypic resistance [63]. Phenotypic assays are able to the effect of both known and unknown resistant mutations coupled with genetic assays and provide susceptibilities to antiviral drugs [64]. World Health Organization (WHO) category based for NA inhibition assay is showed as follows: normal inhibition or susceptibility (S) (<10-fold increase in IC_{50} for influenza A, <5-fold increase for influenza B), reduced inhibition (RI) (between 10- and 100-fold increase for influenza A, between 5- and 50-fold increase for influenza B) and highly reduced inhibition (HRI) (>100-fold increase for influenza A, and >50-fold increase for influenza B [65]. All mutations were not definitely associated phenotypic resistance, but it is important to assess the relevance between clinical and phenotypic resistance to NAIs.

3.5. Strategy for treatment and survey

Nevertheless of clinical effectiveness and little adverse effects of NAI treatment for seasonal influenza infection, concerning about cost effectiveness of NAI treatment, conventional treatment was adopted for influenza infection in healthy populations without rapid tests for

influenza viruses [66]. Effectiveness on NAIs in reducing mortality and hospitalization in patients with influenza A (H1N1) pdm09 was clarified [67]. Compared with no antiviral treatment, diagnostic testing and oseltamivir treatment when positive in children with seasonal influenza viruses is more effective and cost between $25,900 and $71,200 per quality-adjusted life year gained (QALY), depending on the prevalence of oseltamivir resistance in circulating viruses [68]. Oseltamivir treatment for influenza is less cost-effective than conventional treatment, considering the productivity loss by the analysis of the incremental cost-effective ratio (ICER) of oseltamivir in Japan [69]. Pandemic is consequent of unpredictable mutations of seasonal influenza and the only measure of the first information about pandemic is surveillance of an avian suspicious single death following cluster deaths or a report of clinical worsening cases of fevers unknown origin following severe complications in medication. The case of family cluster of a highly pathogenic avian influenza A (H5N1) virus might suggest for the hint of suppressing a widespread of viral infection to pandemic in Thailand in 2004 [70]. The index patient contacted with dying household chickens and 4 days later became ill and was presented to clinic with fever, cough, and a sore throat. The 11-year-old girl got worse in symptoms including fever and dyspnea within 5 days and was admitted for viral pneumonia and died in a day despite of intensive care. Her mother and aunt provided bedside care for her in the hospital for 18 h in 2 days and for 13 h in 1 day each. Her mother began to have high fever after 3 days of unprotected nursing care for her and was admitted to a hospital and died from pneumonia and progressive respiratory failure. Her aunt noted high fever, myalgia, and chills after 9 days of unprotected nursing care for her and was admitted to the distinct hospital. On the day of admission, the patient was suspected as pneumonia due to avian influenza and received treatment with oseltamivir and instituted full isolation precautions by an investigating team. Despite moderate dyspnea and hypoxia, she gradually ameliorated and was discharged a month later. First, a nasopharyngeal swab from the aunt was weakly positive for influenza nucleoprotein gene and no evidence of influenza infection in the laboratory data on tissue culture or egg inoculation. Specimens of lung obtained from the mother's body embalmed were positive for influenza A (H5N1) by RT-PCR at the Siriraj hospital laboratory in Thailand and at CDC in the United States. This study suggests that the systemic procedure of treatment for seasonal influenza is sequent to the systemic procedure of preparedness and response for the following pandemics and is desirable. The desirable systemic procedure for epidemic and pandemic is described as follow; [1] application of rapid tests for influenza virus in diagnosis, [2] early administration of NAIs within 48 h from a onset of influenza infection, [3] monitor for patients without antipyretic, [4] further investigation of complications and mutations of influenza viruses under late time of alleviation for fever, [5] adoption of other treatments for complications or hospitalization in the progression of illness, [6] check of family member or cluster by surveillance system if possible and consultation to public health center for the further investigation. After a new mutated influenza virus is confirmed, the isolation of the patients and the contacts are given antiviral prophylaxis and exposed persons are put under active surveillance and poultry in the surrounding area is culled under the control of government. This procedure would be helpful for treatment of seasonal influenza and the following pandemic. WHO recommend for development and application of measures to assess the severity of every influenza epidemic [5] and this procedure might be one of those? Addiction to measures to assess severity, strengthen surveillance

technology is necessary to detect pandemic, too. There are four types of surveillance for seasonal influenza epidemic in Japan and one of those? is (Nursery) School Absenteeism Surveillance System ((N)SASSy) which enables real-time surveillance and informs its result to school officials including school lengths and teachers by websites [71]. This is one of tools for preparedness for epidemics: noticing each condition of the numbers of infected students with influenza virus, both inter-schools and inter-cities on the closed website and sharing real-time information for spread of epidemics around them. Open access to the website is available for spread of epidemics except personal information, names of schools, and so on. This surveillance system will be applied in pandemic as streamline surveillance in local. WHO suggests the Global Influenza Surveillance Network (GISN) and mobilize the Global Outbreak and Alert Response Network (GROAN) teams for information sharing [72]. WHO recommends a close relationship and partnership with International Health Regulations 2005 (IHR) to prevent and respond to acute public health risks worldwide [5]. Real-time surveillance and sharing of its information are useful in domestics and international.

4. Conclusions

Seasonal influenza virus mutates in transmission of interspecies and suddenly changes both highly lethal and transmissible from person to person. Prevention of influenza infection by universal vaccine is desirable but are undergoing in development. Confirmation for the emergence of pandemic influenza virus is only the detection of cluster infection with severe complications by the new mutated virus. Surveillance in local and global is the effective measure for it. We can add the procedure of clinical diagnosis and treatment for seasonal influenza infection to one of useful surveillance systems for pandemic. Adoption of NAIs and evaluation of clinical effectiveness monitoring body temperature is the first step of surveillance of clinical treatment. Assessment of NAI treatment insufficiency to influenza infection leads to the close examination for the factors of patients and viral mutations as the second step. In third step, antigenic drift and/or antigenic shift are examined on the condition of no patient's factors and information sharing for drug resistance and/or pandemic is necessary for administration of new antiviral drugs and combination therapy of antiviral drugs and/or the management against pandemic. It is difficult to predict when NAIs will not be ineffective to influenza infection due to viral resistance to those? New antiviral drugs for influenza virus are under development and they would change the treatment of influenza infection as NAIs changed it. If the new convenient and rapid diagnostic test for influenza viral infection of seasonal influenza virus and pandemic virus would be developed, it would be more useful than the clinical procedure. At present, the systemic procedure of treatment and taking measure for seasonal influenza infection in usual would lead to the preparedness and taking management against pandemic.

5. Future perspectives

Trial of antiviral therapy in influenza infection is progressed as in the treatment of hepatitis C viral infection and HIV infection, too. Now in influenza virus infection, the three mechanical

points for viral inhibition in cells are applied and new drugs are developed. New NAIs and RNA polymerase inhibitor and the cap-dependent endonuclease inhibitor are in developed. Recently, baloxavir marboxil (trade name Xofluza) may be used within a few months in Japan and prevent viral replication by inhibiting the cap-dependent endonuclease activity of the viral polymerase instead of inhibition for viral release from host cells as NAIs act [73]. It inhibits influenza RNA viruses from hijacking the host mRNA transcription system to allow synthesis of viral RNA. Only oral one dose is effective for amelioration from symptoms of influenza viral infection with less adverse effects. New drugs and combinations for administration of antiviral drugs against influenza virus would be defined following to the appearance of new mutations concerning to drug resistance in the future. Seasonal influenza infection and pandemic would be under controlled by the application of antiviral drugs, vaccination, and surveillance.

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Conflict of interests

The author has no competing of interests to declare.

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