Clinical effectiveness of four neuraminidase inhibitors (oseltamivir, zanamivir, laninamivir, and peramivir) for children with influenza A and B in the 2014-2015 to 2016-2017 influenza seasons in Japan

Nobuhisa Ishiguro [a,*], Naoko Koseki [a,b], Miki Kaiho [a], Tadashi Ariga [a], Hideaki Kikuta [c], Koji Oba [d,e], Takehiro Togashi [f], Keisuke Morita [g], Akira Inagawa [h], Akiko Okamura [i], Shigeru Yamazaki [j], Satoru Shida [k], Mutsuko Konno [l], Nobuaki Kawamura [m], Akihito Ishizaka [n], Kimihiko Takada [o], Keiji Tsubakihara [p], Naoko Nagano [q], Mutsuo Shibata [r], Hideto Furuyama [s], Yoshihiro Matsuzono [t], Akemi Koike [u], Mari Murashita [v], Yoshio Hatae [w], Hideki Arioka [x], Tatsuru Yamanaka [y], Toru Watanabe [z], Yuuichi Tabata [aa], Yoshihiro Kumita [ab], Kyosuke Hazama [ac], Yasushi Akutsu [ad], Hayato Aoyagi [ae], Chie Tobise [af], Katsuki Azuma [ag], Kohichi Yasoshima [ah], Yoko Sawada [ai], Kazuyuki Uetsuji [aj], Akira Tsuchida [ak], Akira Tsuchiyama [al], Kazue Yasuda [am], Yasuhisa Odagawa [an], Mikio Yoshioka [ao]

[a] Department of Pediatrics, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan

[b] Department of Pediatrics, Hokkaido Medical Center for Child Health and Rehabilitation, Sapporo, Japan

[c] Pediatric Clinic, Touei Hospital, Sapporo, Japan

[d] Department of Biostatistics, School of Public Health, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

[e] Interfaculty Initiative in Information Studies, The University of Tokyo, Tokyo, Japan

[f] Hokkaido Anti–Tuberculosis Association Sapporo Fukujuji Clinic, Sapporo, Japan

[g] Department of Pediatrics, Asahikawa Red Cross Hospital, Asahikawa, Japan

[h] Inagawa Pediatric Clinic, Muroran, Japan

[i] Umetsu Pediatric Clinic, Sapporo, Japan

[j] Ultra Pediatric Clinic, Ebetsu, Japan

[k] Department of Pediatrics, Ebetsu City Hospital, Ebetsu, Japan

[l] Department of Pediatrics, Sapporo-Kosei General Hospital, Sapporo, Japan

[m] Department of Pediatrics, Sapporo City General Hospital, Sapporo, Japan

[n] Sumiyoshi Pediatric Clinic, Chitose, Japan

[o] Takada Children's Clinic, Sapporo, Japan

[p] Tsubakibara Pediatric Clinic, Sapporo, Japan

[q] Nagano Pediatric Clinic, Asahikawa, Japan

[r] Department of Pediatrics, Health Sciences University of Hokkaido, Sapporo, Japan

[s] Department of Pediatrics, Japan Community Healthcare Organization Hokkaido Hospital, Sapporo, Japan

[t] Matsuzono Pediatric Clinic, Sapporo, Japan

[u] Koike Children's Hospital, Sapporo, Japan

[v] Murashita Children's Clinic, Sapporo, Japan

[w] Department of Pediatrics, Megumino Hospital, Eniwa, Japan

[x] Mebae Pediatric Clinic, Sapporo, Japan

[y] Yamanaka Tatsuru Pediatric Clinic, Sapporo, Japan

[z] Watanabe Pediatric Allergy Clinic, Sapporo, Hokkaido, Japan

[aa] Iwamizawa Pediatric and Gynecology Clinic, Iwamizawa, Hokkaido, Japan

[ab] Kumita Pediatric Clinic, Chitose, Japan

[ac] Hazama Pediatric Clinic, Muroran, Japan

[ad] Akutsu Pediatric Clinic, Iwamizawa, Japan

[ae] Department of Pediatrics, Obihiro Kyokai Hospital, Obihiro, Japan

[af] Tobise Pediatric Clinic, Asahikawa, Japan

[ag] Azuma Kodomo-Katei Clinic, Ebetsu, Japan

[ah] Makomanai Kids Clinic, Sapporo, Japan

[ai] Ikuai Pediatric Clinic, Sapporo, Japan

[aj] Nishioka Pediatric Clinic, Sapporo, Japan

[ak] Tsuchida Pediatric Clinic, Asahikawa, Japan

[al] Shiroishi Pediatric Clinic, Sapporo, Japan

[am] Department of Pediatrics, Sapporo Hokuyu Hospital, Sapporo, Japan

[an] Department of Pediatrics, Otaru General Hospital, Otaru, Japan

[ao] Department of Pediatrics, KKR Sapporo Medical Center, Sapporo, Japan

* Corresponding author: Department of Pediatrics, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, N-15, W-7, Kita-ku, Sapporo 060-8638, Japan.
E-mail address: nishigur@med.hokudai.ac.jp (N. Ishiguro)

All authors meet the ICMJE authorship criteria.

Abstract

The clinical effectiveness of four neuraminidase inhibitors (NAIs) (oseltamivir, zanamivir, laninamivir, and peramivir) for children aged 0 months to 18 years with influenza A and B were investigated in the 2014-2015 to 2016-2017 influenza seasons in Japan. A total of 1207 patients (747 with influenza A and 460 with influenza B) were enrolled. The Cox proportional-hazards model using all of the patients showed that the duration of fever after administration of the first dose of the NAI was shorter in older patients (hazard ratio = 1.06 per 1 year of age, $p<0.001$) and that the duration of fever after administration of the first dose of the NAI was shorter in patients with influenza A infection than in patients with influenza B infection (hazard ratio = 2.21, $p<0.001$). A logistic regression model showed that the number of biphasic fever episodes was 2.99-times greater for influenza B-infected patients than for influenza A-infected patients ($p<0.001$). The number of biphasic fever episodes in influenza A- or B-infected patients aged 0-4 years was 2.89-times greater than that in patients aged 10-18 years ($p = 0.010$), and the number of episodes in influenza A- or B-infected patients aged 5-9 years was 2.13-times greater than that in patients aged 10-18 years ($p = 0.012$). (207 words)

Keywords

oseltamivir, zanamivir, laninamivir, peramivir, influenza A, influenza B

Introduction

It has been shown that neuraminidase inhibitors (NAIs) can alleviate the major symptoms of uncomplicated influenza A and B and reduce the duration by approximately 1 to 1.5 days when administered within 48 hours of onset of illness compared with the effect of a placebo [1-4]. NAIs reduce the incidence of acute otitis media in children aged one to five years who are suffering from seasonal influenza [5] and contribute to survival benefit in patients infected with influenza A(H1N1)pdm09 virus [6]. In Japan, almost all patients with an influenza-like illness are tested with rapid antigen tests, and they are treated with one of the NAIs when positive; this has become standard practice in clinics nationwide [7]. The clinical effectiveness of zanamivir, laninamivir, and peramivir has been tested mainly in clinical trials compared to the effect of either a placebo or oseltamivir [1, 8-14], and there have been few studies in which the clinical effectiveness of four NAIs (oseltamivir, zanamivir, laninamivir, and peramivir) was compared [15, 16]. In the present study, we evaluated the clinical effectiveness of the four NAIs for children with influenza A and B by comparing the durations of fever after administration of the first doses of NAIs.

PATIENTS AND METHODS

Patients

Outpatients aged 0 months to 18 years who had an axillary temperature of 37.5°C or higher were diagnosed as having influenza virus infection based on results obtained by a rapid antigen test. Patients were excluded from this study if the time from onset of fever to initiating administration was 48 hours or more or if body temperature fell to less than 37.5°C before starting administration. Patients who had

bacterial infections (pneumonia, otitis media) were excluded. Patients diagnosed as having influenza were treated with one of the NAIs (oseltamivir, zanamivir, laninamivir, and peramivir)-after obtaining informed consent from the children's parents. The decision regarding administration of NAIs was left to the discretion of the physician. Oseltamivir was administered at 2 mg/kg/dose (to a maximum of 75 mg/dose) twice daily for 5 days, zanamivir was administered by inhalation at 10 mg/dose twice daily for 5 days, laninamivir was administered as a single inhalation (20 mg for patients less than 10 years of age and 40 mg for patients 10 years of age or more) and peramivir was administered intravenously at 10 mg/kg once daily (to a maximum of 600 mg/dose).

Study procedures

A prospective, multicenter observational study was conducted in the 2014-2015, 2015-2016 and 2016-2017 influenza seasons at 25 pediatric clinics and in departments of pediatrics in 11 hospitals in Hokkaido, Japan.

The age and sex of each patient and the date and results of the rapid diagnostic test were recorded by physicians. The time of onset (the first time that the patient had a fever of more than 37.5°C), vaccination status, selection of NAIs, date and time of first administration of NAIs, and total number of administrations of NAIs were recorded by the parents of children. The parents were also instructed to take their children's axillary body temperatures at least four times daily and to plot the body temperatures on a graph with temperature on the vertical axis and time on the horizontal axis. The time at which a temperature of less than 37.5°C was attained and maintained for more than 48 hours was defined as the time when the patient became afebrile. If a patient's temperature decreased to less than 37.5°C and

remained less than 37.5°C for more than 24 hours but later increased to more than 37.5°C, the patient was considered to have biphasic fever. All ethical approval for this study was obtained from the Institutional Review Board of Hokkaido University Hospital for Clinical Research (014-0172).

Real-time reverse transcription PCR

Real-time reverse transcription PCR for detection of influenza A and B viruses was performed according to the referenced protocol [17].

Power calculation and statistical analysis

To detect a difference of 10% (from 50% to 40%) in the proportions of patients receiving NAIs whose temperature was less than 37.5°C at 24 hours after onset, 70% of the statistical power would be obtained with a two-sided alpha of 5% and the log-rank test of a pair-wise comparison without multiplicity adjustment if 300 patients (1200 patients in total) could be enrolled for each NAI group.

In the primary analysis, the distributions of fever duration were depicted by the Kaplan-Meier method and the log-rank test was used for comparisons of estimated fever duration in each NAI group. To adjust for confounding, we set the duration of fever as a dependent variable and set the following factors as clinically relevant independent variables in multivariate Cox regression analysis: type of NAI, age, sex, vaccination status, and time from onset to first dose of the NAI. The Wald test was performed on statistical significance testing for the adjusted hazard ratio in the Cox regression analysis. For the analysis of episodes of biphasic fever, a logistic regression model was used to determine factors (age, sex, anti-influenza drug, type of influenza, vaccination, and time from onset to administration) influencing the episodes of biphasic

fever with Firth's method [18]. No multiplicity adjustment was performed in the analyses.

In this study, the selection of NAIs was unbalanced among age groups (Table 1, supplemental Table 1). There are at least three reasons for the unbalanced selection of NAIs. First, the two inhalation NAIs, zanamivir and laninamivir, are mainly prescribed for teenagers [19]. Second, in March 2007, Japan's Ministry of Health, Labor and Welfare (MHLW) issued a warning against the use of oseltamivir in teenagers, except for those at high risks, after reports of two suicides by teenagers shortly after ingestion of oseltamivir [20]. Third, peramivir is mainly administered to adult and elderly patients who are admitted to a hospital and are able to tolerate intravenous administration [19]. For these reasons, the results were analyzed separately by three age groups (0-4 years, 5-9 years and 10-18 years) to avoid a selection bias in addition to analysis of the results for all patients without stratification by age group.

A two-sided p value of <0.05 was considered statistically significant. All statistical analyses were performed using JMP software version 13.0.0 (SAS Institute, Cary, NC, USA).

RESULTS

Study population

A total of 1207 patients who were otherwise healthy were enrolled in this study. A total of 747 patients were infected with influenza A: 541, 138 and 68 patients in the 2014-15, 2015-2016 and 2016-2017 influenza seasons, respectively. A total of 460 patients were infected with influenza B: 18, 422 and 20 patients in the 2014-15, 2015-

2016 and 2016-2017 influenza seasons, respectively. Patients under 5 years of age who were treated with either zanamivir or laninamivir were excluded due to uncertainty of inhalation. The demographic characteristics of the patients are shown in Table 1. The NAIs used in patients with influenza A and B in the three age groups are summarized in supplemental Table 1.

Influenza virus typing

Of the 747 influenza A-positive and 460 B-positive samples by the rapid antigen test, 658 and 420 samples were tested by real-time reverse transcription PCR using type-specific primers, respectively, and were confirmed to be influenza A and B viruses, respectively.

Durations of fever after administration of the first doses of NAIs in all patients without stratification by age group

Kaplan–Meier estimates for duration of fever after administration of the first dose of the NAI were stratified by age groups (Fig. 1). Log-rank tests demonstrated statistically significant differences in duration of fever after administration of the first dose of the NAI among age groups ($p = 0.012$ for influenza A and $p<0.001$ for influenza B). Kaplan–Meier estimates for duration of fever after administration of the first dose of each of the four NAIs stratified by age groups are shown in supplemental Fig. 1.

The Cox proportional-hazards model showed that the duration of fever after administration of the first dose of the NAI was shorter in older patients (hazard ratio = 1.06 per 1 year of age, $p<0.001$) and that the duration of fever after administration of the first dose of the NAI was shorter in patients with influenza A infection than in patients with influenza B infection (hazard ratio = 2.21, $p<0.001$) (Table 2).

Durations of fever after administration of the first doses of NAIs in all patients stratified by age group

As explained in the statistical methods, the results were analyzed separately by three age groups to avoid a selection bias. In the 0-4 years of age group, Kaplan-Meier curves showed that the duration of fever after administration of the first dose of the NAI was shorter in patients with influenza A infection than in patients with influenza B infection (Figs. 2A and 2B). This association was similar in the multivariate Cox regression model (hazard ratio = 2.60, $p<0.001$; Table 3). The duration of fever after administration of the first dose of the NAI in patients whose time from onset of influenza virus infection to administration of NAIs was more than 24 hours was shorter than that in patients whose time from onset of influenza virus infection to administration of NAIs was less than 12 hours (hazard ratio = 1.40, $p = 0.046$). There was no statistically significant association between duration of fever following commencement of treatment and choice of NAI (oseltamivir or peramivir), sex or vaccination status (Table 3). There was no statistically significant difference between oseltamivir and peramivir in the Kaplan-Meier curves for the duration of fever after administration of the first dose of the NAI in all of the patients with influenza A or B (Fig. 3A), in patients with influenza A (Fig. 3B) or in patients with influenza B (Fig. 3C).

In the 5-9 years of age group, Kaplan-Meier curves showed that the duration of fever after administration of the first dose of the NAI was shorter in patients with influenza A infection than in patients with influenza B infection (Figs. 2C, 2D, 2E and 2F). This association was similar in the multivariate Cox regression model (hazard ratio = 2.32, $p<0.001$; Table 3). There was no statistically significant difference

between NAIs in the Kaplan-Meier curves for the duration of fever after administration of the first dose of the NAI in all of the patients with influenza A or B (Fig. 3D), in patients with influenza A (Fig. 3E) or in patients with influenza B (Fig. 3F). However, multivariate Cox regression analysis showed that the duration of fever after administration of the first dose of the NAI was shorter in patients treated with oseltamivir (hazard ratio = 1.27, $p = 0.048$), peramivir (hazard ratio = 1.35, $p = 0.049$) or zanamivir (hazard ratio = 1.33, $p = 0.023$) than in patients treated with laninanivir (Table 3). The duration of fever after administration of the first dose of laninamivir showed no statistically significant difference between 106 patients (90.6%) who inhaled laninamivir at a pharmacy and 11 patients (9.4%) who inhaled laninamivir at home in the 5-9 years of age group (log-rank test: $\chi^2 = 0.40$, d.f. = 1, $p = 0.525$). There was no statistically significant association between duration of fever following commencement of treatment and time from onset of influenza virus infection to administration of NAIs, sex ($p = 0.597$) or vaccination status ($p = 0.089$).

In the 10-18 years of age group, Kaplan-Meier curves showed that the duration of fever after administration of the first dose of the NAI was shorter in patients with influenza A infection than in patients with influenza B infection (Figs. 2H and 2I) except for the patients administered oseltamivir or peramivir (Figs. 2G and 2J). These statistically non-significant results were considered to be due to the small number of influenza B-infected patients aged 10-18 years who were administered oseltamivir (n=2) or peramivir (n=7). In the multivariate Cox regression model, the duration of fever after administration of the first dose of the NAI was shorter in patients with influenza A infection than in patients with influenza B infection (hazard ratio = 1.75, $p<0.001$; Table 3). The durations of fever after administration of the first dose of each of the four NAIs in influenza A-infected patients and influenza B-infected patients aged

10-18 years were shown separately by Kaplan–Meier estimates (Figs. 3G, 3H and 3I). Multivariate Cox regression analysis showed that the duration of fever after administration of the first dose of the NAI was shorter in patients treated with oseltamivir than in patients treated with zanamivir (hazard ratio = 1.91, $p = 0.031$; Table 3). There was no statistically significant association between duration of fever following commencement of treatment and time from onset of influenza virus infection to administration of NAIs, sex ($p = 0.672$) or vaccination status ($p = 0.147$).

Episodes of biphasic fever

Biphasic fever occurred in 9 (4.6%) of the 197 influenza A-infected patients and 16 (17.8%) of the 90 influenza B-infected patients in the 0-4 years of age group, in 11 (3.6%) of the 304 influenza A-infected patients and 36 (15.0%) of the 240 influenza B-infected patients in the 5-9 years of age group, and in 12 (4.9%) of the 246 influenza A-infected patients and 4 (3.1%) of the 130 influenza B-infected patients in the 10-18 years of age group (Table 4). These patients did not have infectious complications such as pneumonia or acute otitis media.

The logistic regression model showed that the number of biphasic fever episodes was 2.99-times greater for influenza B-infected patients than for influenza A-infected patients ($p<0.001$) (Supplemental table 3). The number of biphasic fever episodes in influenza A- or B-infected patients aged 0-4 years was 2.89-times greater than that in patients aged 10-18 years ($p = 0.010$), and the number of episodes in influenza A- or B-infected patients aged 5-9 years was 2.13-times greater than that in patients aged 10-18 years ($p = 0.012$). The choice of NAIs was weakly correlated with the number of biphasic fever episodes in influenza A-infected patients. The logistic regression model for factors influencing episodes of biphasic fever showed no statistically significant

differences in time from onset to administration of NAIs, sex and vaccination. The frequencies of biphasic fever in influenza A- and influenza B-infected patients in each age group were evaluated separately by the logistic regression model (Supplemental table 4).

DISCUSSION

In the present study, we evaluated the clinical effectiveness of four NAIs for influenza A and B virus infections by comparing the durations of fever after administration of the first doses of NAIs. In the 0-4 years of age group, the duration of fever after administration of the first dose of the NAI showed no statistically significant difference between patients administered oseltamivir and those administered peramivir (Table 3). Although there have been several clinical studies concerning oseltamivir and peramivir [15, 16, 21, 22], the present study is the first study in which the clinical effectiveness of oseltamivir and that of peramivir were compared in influenza-infected patients aged 0-4 years. In the 5-9 years of age group, the duration of fever after administration of the first dose of the NAI was shorter in patients treated with oseltamivir, zanamivir or peramivir than in patients treated with laninamivir. In patients infected with influenza A virus, the duration of fever after administration of the first dose of either oseltamivir or peramivir was shorter than that in patients treated with laninamivir. Contrary to our results, the clinical effectiveness of laninamivir has been reported to be almost the same as that of oseltamivir in pediatric patients infected with influenza A(H3N2) and influenza B viruses [11, 16] and in adult patients infected with influenza A(H3N2) and influenza A(H1N1) viruses carrying the H274Y mutation [12]. Incomplete delivery of laninamivir might partially explain the

delay of defervescence in the 5-9 years of age group. In the 10-18 years of age group, the duration of fever after administration of the first dose of the NAI was shorter in influenza A-infected patients treated with oseltamivir than in those treated with zanamivir. It has been reported that the mean duration of fever was significantly shorter in influenza A(H3N2)-infected patients treated with oseltamivir than in those treated with zanamivir [23].

According to influenza surveillance by the National Institute of Infectious Diseases (NIID) in Japan, 98.8% and 95.5% of influenza A viruses were subtyped into influenza A(H3N2) in the 2014-2015 and 2016-2017 influenza seasons, respectively [24], indicating that more than 95% of influenza A viruses are expected to be influenza A(H3N2) virus. The results of subanalysis in the 2014-2015 and 2016-2017 influenza seasons are summarized in supplemental Table 2 and supplemental Fig. 2. Since oseltamivir- and peramivir-resistant influenza A viruses have rarely been detected (0.3% of influenza A(H3N2) viruses in the 2014-2015 season, 1.9% and 1.2% of influenza A(H1N1)pdm09 viruses in the 2015-2016 and 2016-2017 seasons, respectively)[24], there seemed to be no necessity to consider the oseltamivir resistance and peramivir resistance of influenza A viruses in this study.

The durations of fever after administration of the first doses of the NAIs in both influenza A-infected and influenza B-infected patients were shorter in older patients (Tables 2, 3, Fig. 1, supplemental Fig. 1). It has been reported that duration of fever in patients with influenza tended to be shorter in old children than in young children when they were treated with oseltamivir, zanamivir or laninamivir [25-28]. These results might be explained partially by immaturity of the immune system against influenza viruses in younger children [29].

The duration of fever after administration of the first dose of the NAI was

shorter in patients with influenza A infection than in patients with influenza B infection at all ages (Tables 2, 3). It has been reported that oseltamivir was less effective against influenza B virus infection than against influenza A virus infection [30, 31] and that zanamivir and laninamivir were less effective against influenza B virus infection than against influenza A(H3N2) virus infection [28, 32]. The 50% inhibitory concentrations (IC50s) of the four NAIs for influenza B virus were higher than those for influenza A(H1N1) and influenza A(H3N2) viruses [33, 34]. These results could account for the reduced clinical effectiveness of NAIs against influenza B virus.

The duration of fever after administration of the first dose of the NAI was only slightly affected by the time from onset to administration in the 0-4 years of age group (Table 3). The same result has been obtained in patients with influenza A and influenza B who were treated with oseltamivir [30].

Biphasic fever in influenza has been observed in patients with influenza A(H3N2), A(H1N1) and B virus infections who were not administered NAIs [35] and in patients with influenza A(H3N2) and B virus infections who were administered NAIs [27, 28]. In this study, biphasic fever episodes were more frequently observed in influenza B-infected patients than in influenza A-infected patients and in patients younger than 10 years of age than in patients over 10 years of age (Tables 4, 5). Immaturity of the immune system against influenza viruses or little chance of prior exposure to influenza might be associated with the high frequency of biphasic fever in young persons.

Limitations of this study should be recognized. This study was an observational, not a randomized, study. The selection of NAIs was left to the discretion of the physician, introducing unmeasured selection bias. Another limitation

is the lack of virological follow-up.

In this study, we evaluated the clinical effectiveness of four NAIs for children with influenza A and B by comparing the durations of fever after administration of the first doses of NAIs. Although the four NAIs were effective for treatment of influenza, the duration of fever in patients with influenza was shorter in old children than in young children and was shorter in patients with influenza A infection than in patients with influenza B infection.

Conflict of interest

This research was supported in part by a Grant-in-Aid for Scientific Research (C), 2010 (25461577), from the Ministry of Education, Science, Sports and Culture of Japan, by a grant from Shionogi & Co., Ltd. and by a grant from Chugai Pharmaceutical Co., Ltd.

Acknowledgement

We thank Stewart Chisholm for proofreading the manuscript.

References

[1] Hayden FG, Osterhaus AD, Treanor JJ, Fleming DM, Aoki FY, Nicholson KG, et al. **Efficacy and safety of the neuraminidase inhibitor zanamivir in the treatment of influenzavirus infections. Gg167 influenza study group**. *N Engl J Med* 1997;337:874-80.

[2] Treanor JJ, Hayden FG, Vrooman PS, Barbarash R, Bettis R, Riff D, et al. **Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza: A randomized controlled trial. Us oral neuraminidase study group**. *JAMA* 2000;283:1016-24.

[3] Whitley RJ, Hayden FG, Reisinger KS, Young N, Dutkowski R, Ipe D, et al. **Oral oseltamivir treatment of influenza in children**. *Pediatr Infect Dis J* 2001;20:127-33.

[4] Harper SA, Bradley JS, Englund JA, File TM, Gravenstein S, Hayden FG, et al. **Seasonal influenza in adults and children--diagnosis, treatment, chemoprophylaxis, and institutional outbreak management: Clinical practice guidelines of the infectious diseases society of america**. *Clin Infect Dis* 2009;48:1003-32.

[5] Winther B, Block SL, Reisinger KDutkowski R. **Impact of oseltamivir treatment on the incidence and course of acute otitis media in children with influenza**. *Int J Pediatr Otorhinolaryngol* 2010;74:684-8.

[6] Lee EH, Wu C, Lee EU, Stoute A, Hanson H, Cook HA, et al. **Fatalities associated with the 2009 h1n1 influenza a virus in new york city**. *Clin Infect Dis* 2010;50:1498-504.

[7] Sugaya N. **Widespread use of neuraminidase inhibitors in japan**. *J Infect Chemother* 2011;17:595-601.

[8] Kohno S, Kida H, Mizuguchi M, Hirotsu N, Ishida T, Kadota J, et al. **Intravenous peramivir for treatment of influenza a and b virus infection in high-risk patients**. *Antimicrob Agents Chemother* 2011;55:2803-12.

[9] Kohno S, Kida H, Mizuguchi M, Shimada JGroup SCS. **Efficacy and safety of intravenous peramivir for treatment of seasonal influenza virus infection**. *Antimicrob Agents Chemother* 2010;54:4568-74.

[10] Kohno S, Yen MY, Cheong HJ, Hirotsu N, Ishida T, Kadota J, et al. **Phase iii randomized, double-blind study comparing single-dose intravenous peramivir with oral oseltamivir in patients with seasonal influenza virus infection**. *Antimicrob Agents Chemother* 2011;55:5267-76.

[11] Sugaya NOhashi Y. **Long-acting neuraminidase inhibitor laninamivir octanoate (cs-8958) versus oseltamivir as treatment for children with influenza virus infection**. *Antimicrob Agents Chemother* 2010;54:2575-82.

[12] Watanabe A, Chang SC, Kim MJ, Chu DW, Ohashi YGroup MS. **Long-acting neuraminidase inhibitor laninamivir octanoate versus oseltamivir for treatment of influenza: A double-blind, randomized, noninferiority clinical trial**. *Clin Infect Dis* 2010;51:1167-75.

[13] Watanabe A. **A randomized double-blind controlled study of laninamivir compared with oseltamivir for the treatment of influenza in patients with chronic respiratory diseases**. *J Infect Chemother* 2013;19:89-97.

[14] Hedrick JA, Barzilai A, Behre U, Henderson FW, Hammond J, Reilly L, et al. **Zanamivir for treatment of symptomatic influenza a and b infection in children five to twelve years of age: A randomized controlled trial**. *Pediatr Infect Dis J* 2000;19:410-7.

[15] Takemoto Y, Asai T, Ikezoe I, Yano T, Ichikawa M, Miyagawa S, et al. **Clinical**

effects of oseltamivir, zanamivir, laninamivir and peramivir on seasonal influenza infection in outpatients in japan during the winter of 2012-2013. *Chemotherapy* 2013;59:373-8.

[16] Shobugawa Y, Saito R, Sato I, Kawashima T, Dapat C, Dapat IC, et al. **Clinical effectiveness of neuraminidase inhibitors--oseltamivir, zanamivir, laninamivir, and peramivir--for treatment of influenza a(h3n2) and a(h1n1)pdm09 infection: An observational study in the 2010-2011 influenza season in japan**. *J Infect Chemother* 2012;18:858-64.

[17] **Who information for molecular diagnosis of influenza virus in humans – update. Available:** Http://www.Who.Int/influenza/gisrs_laboratory/molecular_diagnosis/en/ **accessed 2017 aug 20**.

[18] Firth D. **Bias reduction of maximum likelihood estimates**. *Biometrika* 1993;80:27-38.

[19] Zaraket HSaito R. **Japanese surveillance systems and treatment for influenza**. *Curr Treat Options Infect Dis* 2016;8:311-28.

[20] Okamoto E. **Is oseltamivir (tamiflu) safe? Re-examining the tamiflu 'ado' from japan**. *Expert Rev Pharmacoecon Outcomes Res* 2010;10:17-24.

[21] Sugaya N, Kohno S, Ishibashi T, Wajima TTakahashi T. **Efficacy, safety, and pharmacokinetics of intravenous peramivir in children with 2009 pandemic h1n1 influenza a virus infection**. *Antimicrob Agents Chemother* 2012;56:369-77.

[22] Hikita T, Hikita H, Hikita F, Hikita NHikita S. **Clinical effectiveness of peramivir in comparison with other neuraminidase inhibitors in pediatric influenza patients**. *Int J Pediatr* 2012;2012:834181.

[23] Kawai N, Ikematsu H, Iwaki N, Maeda T, Kawashima T, Hirotsu N, et al.

Comparison of the effectiveness of zanamivir and oseltamivir against influenza a/h1n1, a/h3n2, and b. *Clin Infect Dis* 2009;48:996-7.

[24] **Influenza surveillance by the national institute of infectious diseases (niid) in japan. Available:** Https://www.Niid.Go.Jp/niid/en/ **accessed 2017 aug 20.**

[25] Kawai N, Ikematsu H, Iwaki N, Satoh I, Kawashima T, Maeda T, et al. **Factors influencing the effectiveness of oseltamivir and amantadine for the treatment of influenza: A multicenter study from japan of the 2002-2003 influenza season**. *Clin Infect Dis* 2005;40:1309-16.

[26] Sato M, Saito R, Sato I, Tanabe N, Shobugawa Y, Sasaki A, et al. **Effectiveness of oseltamivir treatment among children with influenza a or b virus infections during four successive winters in niigata city, japan**. *Tohoku J Exp Med* 2008;214:113-20.

[27] Suzuki EIchihara K. **The course of fever following influenza virus infection in children treated with oseltamivir**. *J Med Virol* 2008;80:1065-71.

[28] Koseki N, Kaiho M, Kikuta H, Oba K, Togashi T, Ariga T, et al. **Comparison of the clinical effectiveness of zanamivir and laninamivir octanoate for children with influenza a(h3n2) and b in the 2011-2012 season**. *Influenza Other Respir Viruses* 2014;8:151-8.

[29] Munoz FM. **Influenza virus infection in infancy and early childhood**. *Paediatric respiratory reviews* 2003;4:99-104.

[30] Kawai N, Ikematsu H, Iwaki N, Maeda T, Satoh I, Hirotsu N, et al. **A comparison of the effectiveness of oseltamivir for the treatment of influenza a and influenza b: A japanese multicenter study of the 2003-2004 and 2004-2005 influenza seasons**. *Clin Infect Dis* 2006;43:439-44.

[31] Sugaya N, Mitamura K, Yamazaki M, Tamura D, Ichikawa M, Kimura K, et al. **Lower clinical effectiveness of oseltamivir against influenza b contrasted with**

influenza a infection in children. *Clin Infect Dis* 2007;44:197-202.

[32] Sugaya N, Tamura D, Yamazaki M, Ichikawa M, Kawakami C, Kawaoka Y, et al. **Comparison of the clinical effectiveness of oseltamivir and zanamivir against influenza virus infection in children**. *Clin Infect Dis* 2008;47:339-45.

[33] Dapat C, Kondo H, Dapat IC, Baranovich T, Suzuki Y, Shobugawa Y, et al. **Neuraminidase inhibitor susceptibility profile of pandemic and seasonal influenza viruses during the 2009-2010 and 2010-2011 influenza seasons in japan**. *Antiviral Res* 2013;99:261-9.

[34] Ikematsu H, Kawai N, Iwaki NKashiwagi S. **In vitro neuraminidase inhibitory concentration (ic50) of four neuraminidase inhibitors against clinical isolates of the influenza viruses circulating in the 2010-2011 to 2014-2015 japanese influenza seasons**. *J Infect Chemother* 2016;22:599-604.

[35] Suzuki E, Ichihara KJohnson AM. **Natural course of fever during influenza virus infection in children**. *Clin Pediatr (Phila)* 2007;46:76-9.

Figure legends

Figure 1. Kaplan-Meier curves showing a comparison of times taken for body temperature to return to <37.5°C in different age groups of (A) influenza A-infected patients and (B) influenza B-infected patients. The median times were 24.0, 22.4, and 19.0 hours for influenza A-infected patients aged 0-4, 5-9 and 10-18 years, respectively. The median times were 52.7, 40.2 and 33.5 hours for influenza B-infected patients aged 0-4, 5-9 and 10-18 years, respectively.

Figure 2. Kaplan–Meier curves showing a comparison of times taken for body temperature to return to <37.5°C in patients with influenza A and influenza B aged 0-4 years who were treated with oseltamivir (A) and peramivir (B); in patients with influenza A and influenza B aged 5-9 years who were treated with oseltamivir (C), zanamivir (D), laninamivir (E) and peramivir (F); and in patients with influenza A and influenza B aged 10-18 years who were treated with oseltamivir (G), zanamivir (H), laninamivir (I) and peramivir (J).

Figure 3. Kaplan–Meier curves showing a comparison of times taken for body temperature to return to <37.5°C in patients with influenza A or B aged 0-4 years (A), 5-9 years (D) and 10-18 years (G), in patients with influenza A aged 0-4 years (B), 5-9 years (E) and 10-18 years (H), and in patients with influenza B aged 0-4 years (C), 5-9 years (F) and 10-18 years (I).

Supplemental figure 1. Kaplan–Meier curves showing a comparison of times taken for body temperature to return to <37.5°C in patients with influenza A (A, C, E, G) and influenza B (B, D, F, H) who were treated with oseltamivir (A, B), zanamivir (C, D),

laninamivir (E, F) and peramivir (G, H).

Supplemental figure 2. Kaplan–Meier curves showing a comparison of times taken for body temperature to return to <37.5°C in patients with influenza A aged 0-4 years (A), 5-9 years (B) and 10-18 years (C) in 2014-2015 and 2016-2017.

Figure 1

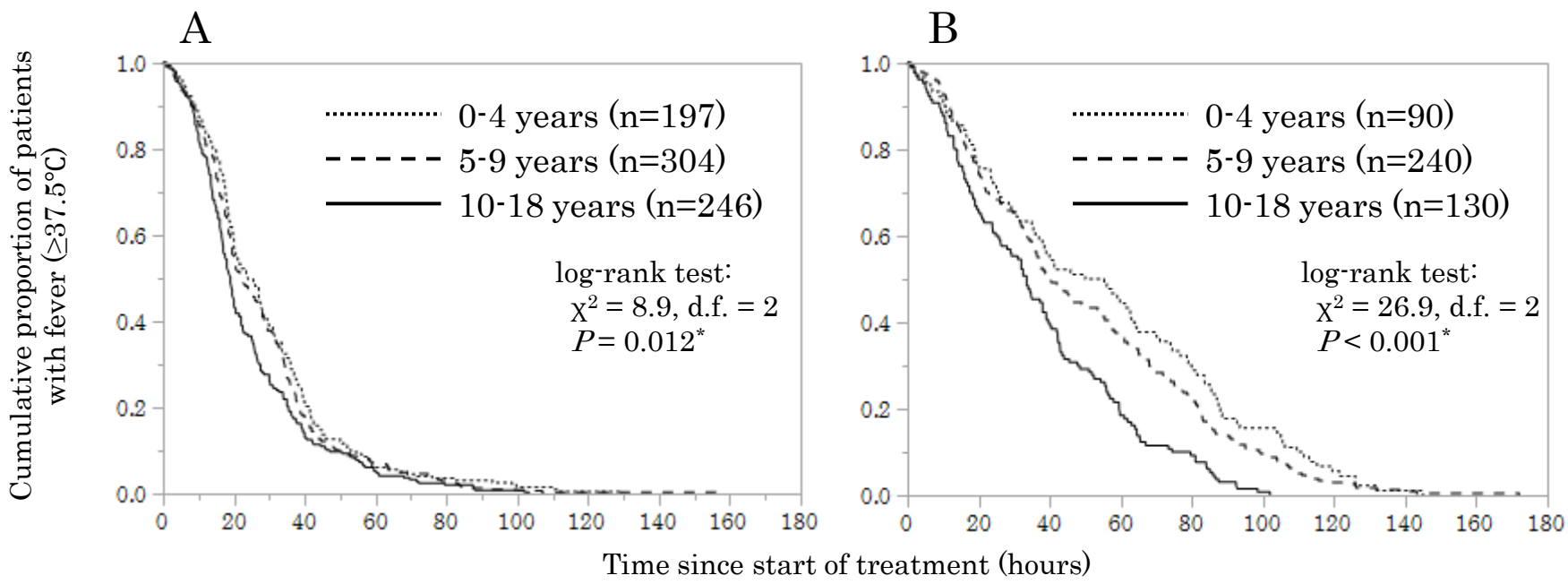

A
B
Cumulative proportion of patients with fever (≥37.5°C)
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
80
100
120
140
160
180
0-4 years (n=197)
5-9 years (n=304)
10-18 years (n=246)
log-rank test:
χ2 = 8.9, d.f. = 2
P = 0.012*
0-4 years (n=90)
5-9 years (n=240)
10-18 years (n=130)
log-rank test:
χ2 = 26.9, d.f. = 2
P < 0.001*
Time since start of treatment (hours)

Figure 2

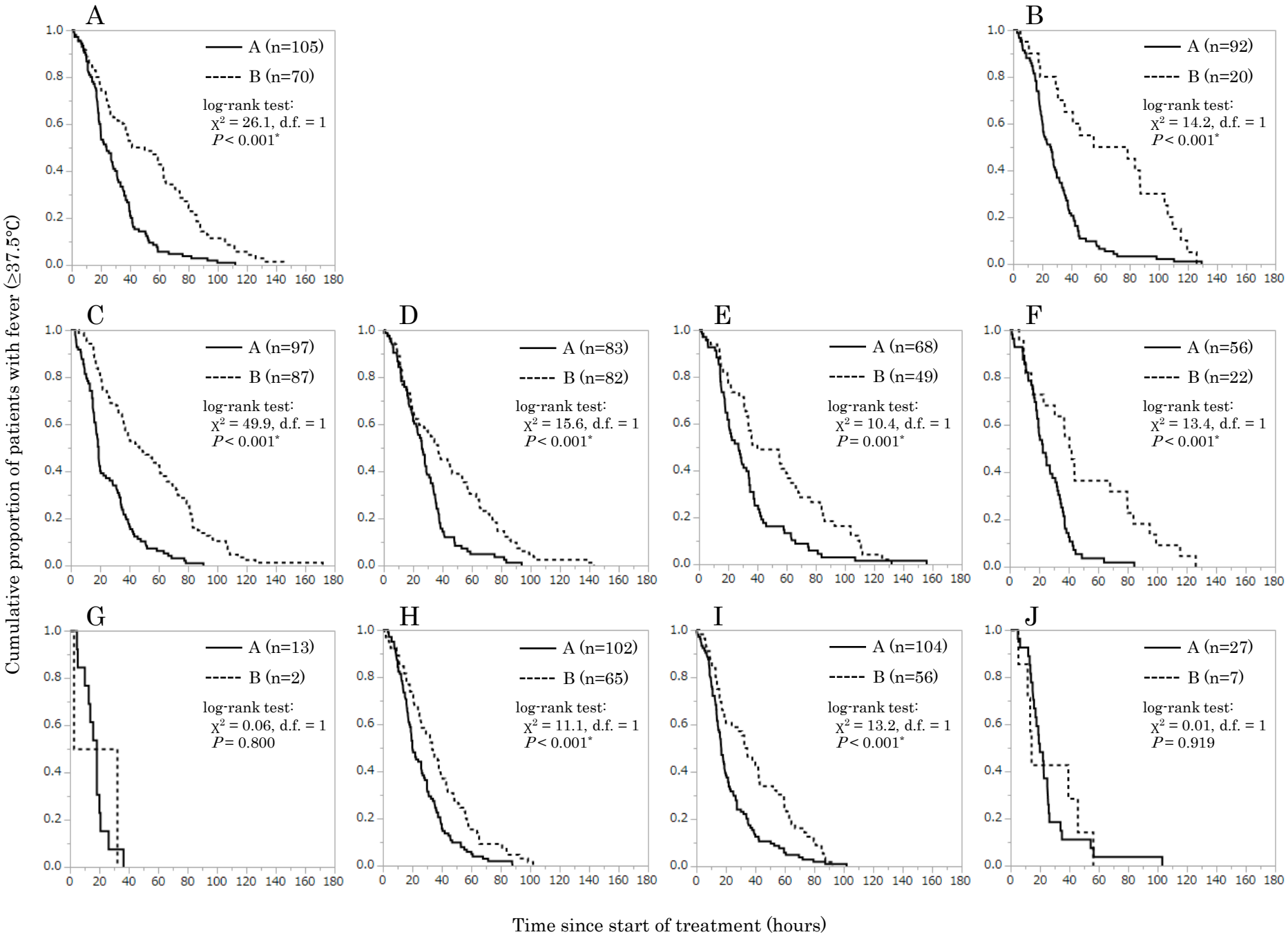
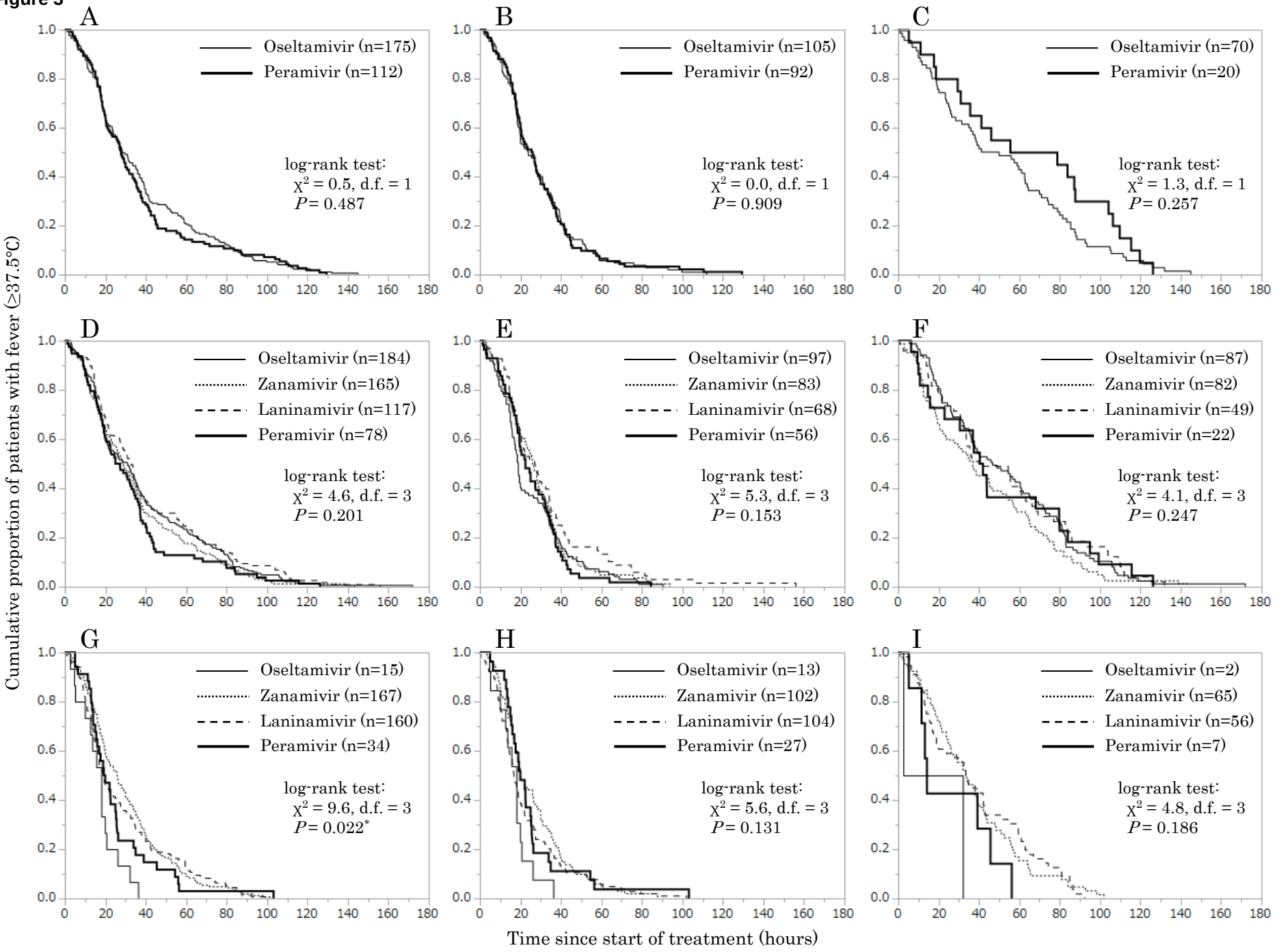
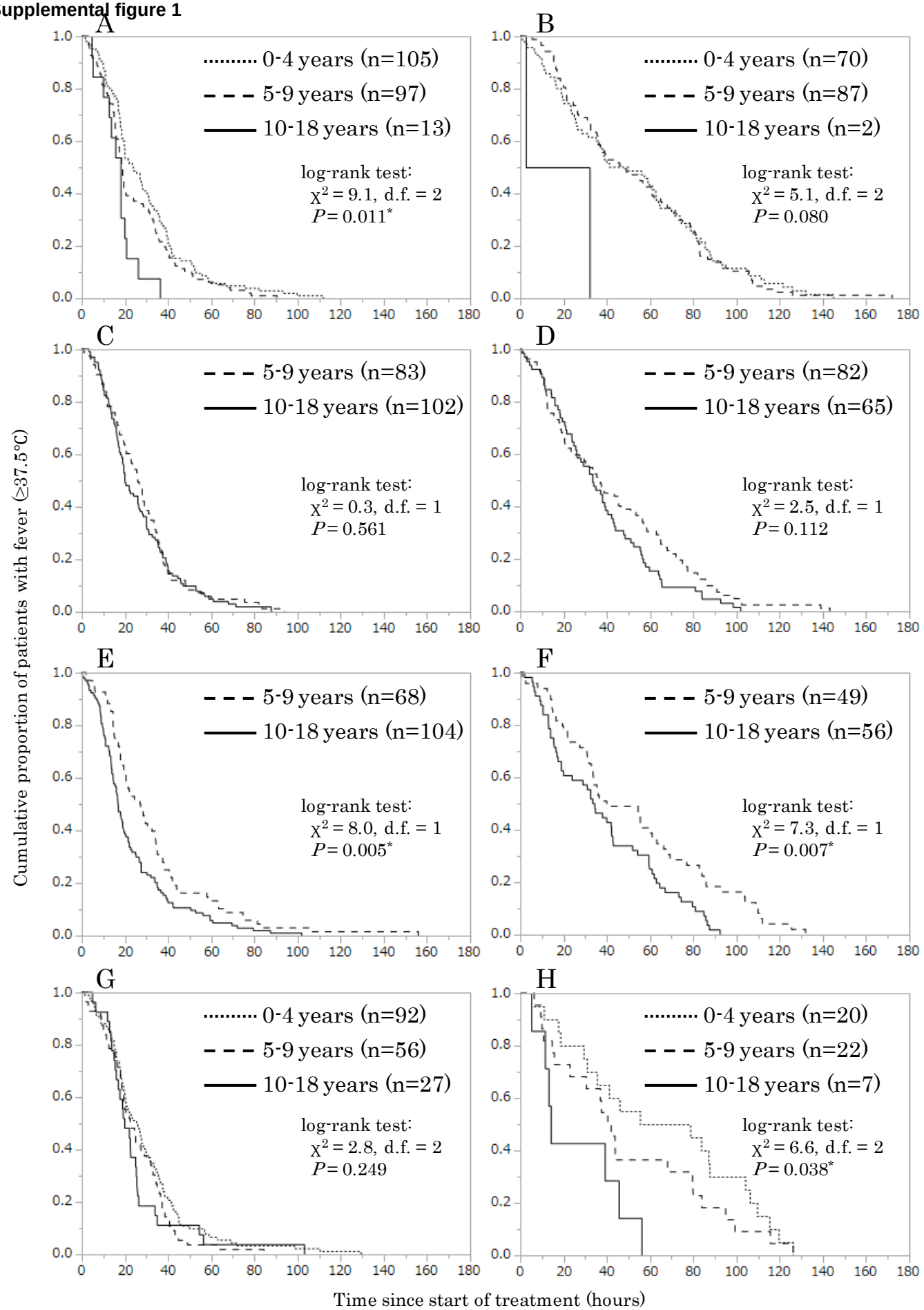

A
A (n=105)
B (n=70)
log-rank test:
X² = 26.1, d.f. = 1
P< 0.001*
B
A (n=92)
B (n=20)
log-rank test:
X² = 14.2, d.f. = 1
P< 0.001*
C
A (n=97)
B (n=87)
log-rank test:
X² = 49.9, d.f. = 1
P< 0.001*
D
A (n=83)
B (n=82)
log-rank test:
X² = 15.6, d.f. = 1
P< 0.001*
E
A (n=68)
B (n=49)
log-rank test:
X² = 10.4, d.f. = 1
P= 0.001*
F
A (n=56)
B (n=22)
log-rank test:
X² = 13.4, d.f. = 1
P< 0.001*
G
A (n=13)
B (n=2)
log-rank test:
X² = 0.06, d.f. = 1
P= 0.800
H
A (n=102)
B (n=65)
log-rank test:
X² = 11.1, d.f. = 1
P< 0.001*
I
A (n=104)
B (n=56)
log-rank test:
X² = 13.2, d.f. = 1
P< 0.001*
J
A (n=27)
B (n=7)
log-rank test:
X² = 0.01, d.f. = 1
P= 0.919
Cumulative proportion of patients with fever (≥37.5°C)
Time since start of treatment (hours)

Figure 3


A
Oseltamivir (n=175)
Peramivir (n=112)
log-rank test:
χ^2 = 0.5, d.f. = 1
P = 0.487
B
Oseltamivir (n=105)
Peramivir (n=92)
log-rank test:
χ^2 = 0.0, d.f. = 1
P = 0.909
C
Oseltamivir (n=70)
Peramivir (n=20)
log-rank test:
χ^2 = 1.3, d.f. = 1
P = 0.257
D
Oseltamivir (n=184)
Zanamivir (n=165)
Laninamivir (n=117)
Peramivir (n=78)
log-rank test:
χ^2 = 4.6, d.f. = 3
P = 0.201
E
Oseltamivir (n=97)
Zanamivir (n=83)
Laninamivir (n=68)
Peramivir (n=56)
log-rank test:
χ^2 = 5.3, d.f. = 3
P = 0.153
F
Oseltamivir (n=87)
Zanamivir (n=82)
Laninamivir (n=49)
Peramivir (n=22)
log-rank test:
χ^2 = 4.1, d.f. = 3
P = 0.247
G
Oseltamivir (n=15)
Zanamivir (n=167)
Laninamivir (n=160)
Peramivir (n=34)
log-rank test:
χ^2 = 9.6, d.f. = 3
P = 0.022*
H
Oseltamivir (n=13)
Zanamivir (n=102)
Laninamivir (n=104)
Peramivir (n=27)
log-rank test:
χ^2 = 5.6, d.f. = 3
P = 0.131
I
Oseltamivir (n=2)
Zanamivir (n=65)
Laninamivir (n=56)
Peramivir (n=7)
log-rank test:
χ^2 = 4.8, d.f. = 3
P = 0.186
Cumulative proportion of patients with fever (≥37.5°C)
Time since start of treatment (hours)

Supplemental figure 1



Supplemental figure 2

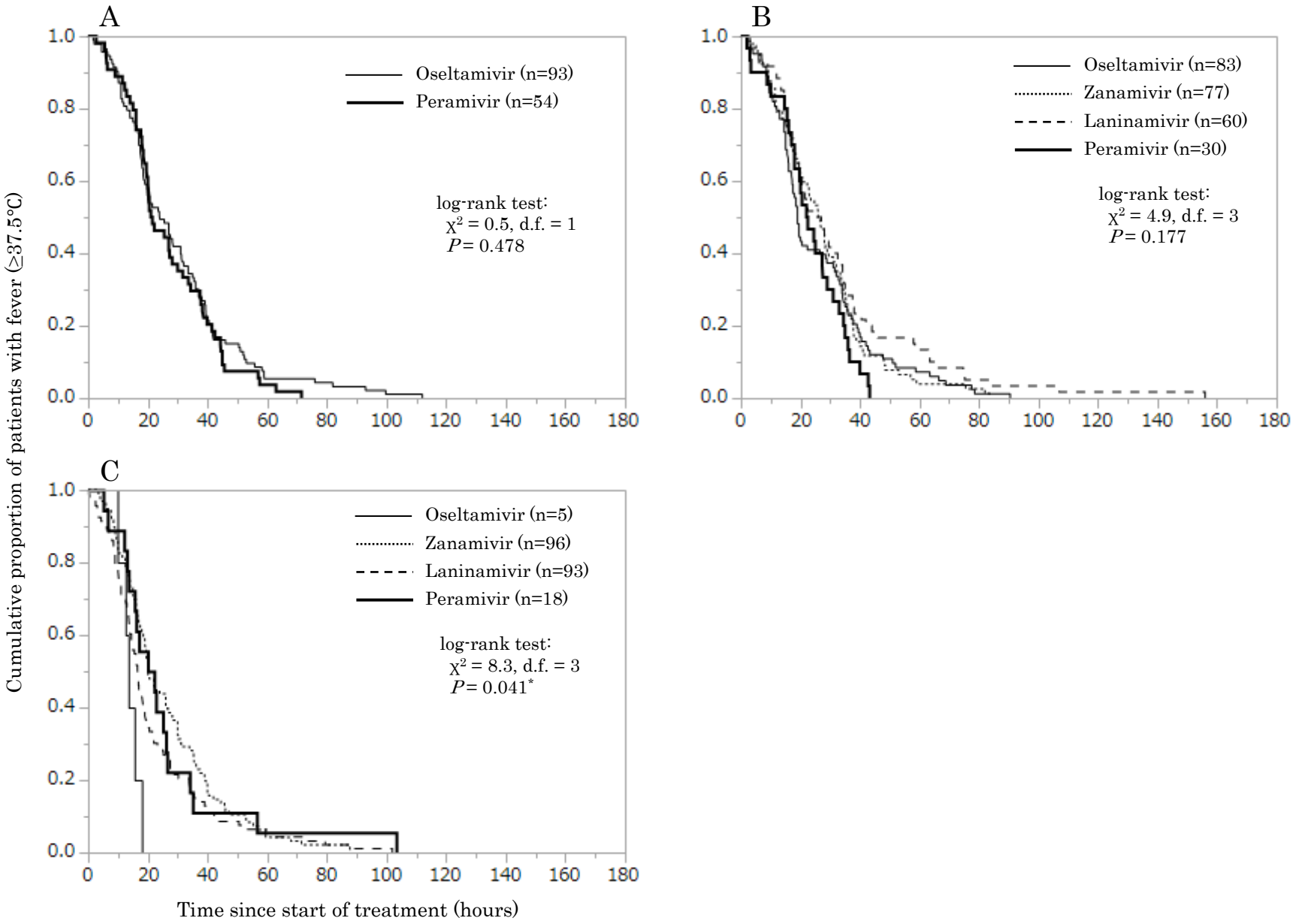


Table 1

Table 1. Background characteristics of patients infected with influenza A and B viruses

	Oseltamivir	Zanamivir	Laninamivir	Peramivir	*p* value
No. of patients	374	332	277	224	
Age (yr)					
Mean ± SD	4.8 ± 2.7	9.6 ± 2.4	10.2 ± 2.8	5.3 ± 3.7	<0.001
Range	0 - 18	5 - 17	5 - 17	0 - 16	
Age groups					
0–4 years	175 (46.8%)	0 (0.0%)	0 (0.0%)	112 (50.0%)	
5–9 years	184 (49.2%)	165 (49.7%)	117 (42.2%)	78 (34.8%)	<0.001
10–18 years	15 (4.0%)	167 (50.3%)	160 (57.8%)	34 (15.2%)	
Sex					
No. (%) of male	197 (52.7%)	172 (51.8%)	143 (51.6%)	121 (54.0%)	0.950
No. (%) of female	177 (47.3%)	160 (48.2%)	134 (48.4%)	103 (46.0%)	
Vaccinated against influenza					
No. (%) vaccinated	177 (47.3%)	153 (46.1%)	130 (46.9%)	92 (41.1%)	0.469
No (%) not vaccinated	197 (52.7%)	179 (53.9%)	147 (53.1%)	132 (58.9%)	
Results of rapid antigen test					
No. (%) of A	215 (57.5%)	185 (55.7%)	172 (62.1%)	175 (78.1%)	<0.001
No. (%) of B	159 (42.5%)	147 (44.3%)	105 (37.9%)	49 (21.9%)	
Mean duration (hr) of illness before treatment ± SD	19.2 ± 10.0	18.0 ± 10.4	17.3 ± 9.8	16.4 ± 11.3	0.008

Table 2

Table 2. Results of Cox's proportional hazards model to determine factors influencing duration of fever after administration of the first dose of the NAI

Independent factors	Unit/Control	Patients infected with either influenza A or B (n=1207)		Patients infected with influenza A (n=747)		Patients infected with influenza B (n=460)	
		Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
Age *	Per one year	1.06 (1.04-1.09)	<0.001	1.06 (1.04-1.09)	<0.001	1.07 (1.03-1.11)	<0.001
Type of influenza **	B	2.21 (1.95-2.51)	<0.001	-	-	-	-
NAI chosen							
Oseltamivir ***	Laninamivir	1.26 (1.05-1.52)	0.014	1.38 (1.09-1.75)	0.008	1.09 (0.80-1.49)	0.601
Peramivir ***	Laninamivir	1.24 (1.01-1.51)	0.039	1.32 (1.03-1.68)	0.027	1.01 (0.68-1.48)	0.953
Peramivir	Oseltamivir	0.98 (0.83-1.16)	0.813	0.96 (0.78-1.17)	0.659	0.93 (0.67-1.28)	0.661
Zanamivir	Laninamivir	1.09 (0.93-1.28)	0.297	0.99 (0.80-1.22)	0.925	1.20 (0.93-1.54)	0.167
Oseltamivir ***	Zanamivir	1.16 (0.97-1.38)	0.099	1.39 (1.11-1.75)	0.005	0.91 (0.68-1.21)	0.516
Peramivir	Zanamivir	1.14 (0.94-1.38)	0.197	1.33 (1.05-1.68)	0.018	0.85 (0.58-1.21)	0.366
Time from onset to administration of NAIs							
≥ 12 hrs and < 24 hrs	< 12 hrs	1.07 (0.94-1.23)	0.303	1.13 (0.96-1.34)	0.151	0.94 (0.74-1.21)	0.639

≥ 24 hrs ****	< 12 hrs	1.24 (1.06-1.46)	0.007	1.31 (1.07-1.60)	0.010	1.20 (0.92-1.57)	0.183
≥ 24 hrs ****	≥ 12 hrs and < 24 hrs	1.16 (1.00-1.33)	0.044	1.16 (0.95-1.39)	0.139	1.27 (1.02-1.58)	0.033
Sex	Female	1.01 (0.90-1.13)	0.903	1.02 (0.89-1.19)	0.746	0.97 (0.81-1.17)	0.766
Vaccination	None	1.08 (0.96-1.21)	0.178	1.07 (0.92-1.24)	0.387	1.13 (0.94-1.36)	0.196

* The duration of fever after administration of the first dose of the NAI was shorter in older patients.

** The duration of fever after administration of the first dose of the NAI was shorter in patients with influenza A infection than in patients with influenza B infection.

*** The duration of fever after administration of the first dose of oseltamivir was shorter than that after administration of the first dose of either laninamivir or zanamivir in patients with influenza A infection. The duration of fever after administration of the first dose of peramivir was shorter than that after administration of the first dose of laninamivir in patients with influenza A infection.

**** The duration of fever after administration of the first dose of the NAI was shorter in patients whose time from onset of influenza virus infection to administration of the NAI was longer.

Table 3

Table 3. Results of Cox's proportional hazards model to determine factors influencing duration of fever after administration of the first dose of the NAI in children aged 0 to 4 years, 5 to 9 years, and 10 to 18 years

Independent factors	Unit/Control	Patients infected with either influenza A or B		Patients infected with influenza A		Patients infected with influenza B	
		Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
(A) 0–4 years							
Type of influenza *	B	2.60 (1.97-3.46)	<0.001	-	-	-	-
NAI chosen							
Peramivir	Oseltamivir	0.92 (0.72-1.17)	0.505	0.96 (0.72-1.27)	0.766	0.80 (0.46-1.31)	0.382
Time from onset to administration of NAIs							
≥ 12 hrs and < 24 hrs	< 12 hrs	1.18 (0.89-1.57)	0.242	1.14 (0.83-1.59)	0.414	1.62 (0.89-3.07)	0.116
≥ 24 hrs **	< 12 hrs	1.40 (1.01-1.94)	0.046	1.53 (1.02-2.28)	0.041	1.81 (0.94-3.62)	0.075
≥ 24 hrs	≥ 12 hrs and < 24 hrs	1.18 (0.88-1.59)	0.265	1.34 (0.91-1.95)	0.140	1.12 (0.68-1.83)	0.655
Sex	Female	0.89 (0.70-1.13)	0.342	0.92 (0.69-1.24)	0.592	0.81 (0.52-1.26)	0.353
Vaccination	None	0.88 (0.69-1.11)	0.282	0.86 (0.64-1.15)	0.304	0.97 (0.63-1.49)	0.890
(B) 5–9 years							
Type of influenza *	B	2.32 (1.93-2.79)	<0.001	-	-	-	-
NAI chosen							
Oseltamivir ***	Laninamivir	1.27 (1.00-1.62)	0.048*	1.45 (1.06-2.01)	0.021*	1.01 (0.71-1.46)	0.945

Peramivir ***	Laninamivir	1.35 (1.00-1.80)	0.049*	1.50 (1.02-2.18)	0.037*	0.97 (0.58-1.60)	0.920
Peramivir	Oseltamivir	1.06 (0.80-1.39)	0.690	1.03 (0.73-1.44)	0.874	0.96 (0.58-1.53)	0.875
Zanamivir ***	Laninamivir	1.33 (1.04-1.70)	0.023*	1.23 (0.88-1.73)	0.218	1.33 (0.93-1.93)	0.125
Oseltamivir	Zanamivir	0.96 (0.78-1.19)	0.703	1.18 (0.88-1.59)	0.274	0.76 (0.56-1.04)	0.084
Peramivir	Zanamivir	1.01 (0.76-1.34)	0.918	1.21 (0.85-1.73)	0.291	0.73 (0.44-1.17)	0.198
Time from onset to administration of NAIs							
≥ 12 hrs and < 24 hrs	< 12 hrs	0.98 (0.79-1.21)	0.827	1.07 (0.82-1.40)	0.627	0.81 (0.58-1.13)	0.210
≥ 24 hrs	< 12 hrs	1.20 (0.94-1.53)	0.139	1.18 (0.85-1.63)	0.327	1.20 (0.84-1.74)	0.314
≥ 24 hrs	≥ 12 hrs and < 24 hrs	1.23 (0.99-1.51)	0.058	1.10 (0.82-1.48)	0.518	1.50 (1.09-2.03)	0.012*
Sex	Female	1.05 (0.88-1.24)	0.597	1.10 (0.88-1.39)	0.407	1.02 (0.79-1.32)	0.881
Vaccination	None	1.16 (0.98-1.38)	0.089	1.19 (0.94-1.51)	0.144	1.19 (0.91-1.54)	0.201
(C) 10–18 years							
Type of influenza *	B	1.75 (1.40-2.20)	<0.001	-	-	-	-
NAI chosen							
Oseltamivir	Laninamivir	1.76 (0.98-2.95)	0.057	1.58 (0.83-2.77)	0.153	2.71 (0.43-9.42)	0.241
Peramivir	Laninamivir	1.04 (0.69-1.53)	0.838	0.96 (0.60-1.51)	0.875	2.16 (0.86-4.69)	0.095
Peramivir	Oseltamivir	0.59 (0.32-1.13)	0.111	0.61 (0.31-1.24)	0.166	0.80 (0.17-5.71)	0.793
Zanamivir	Laninamivir	0.92 (0.74-1.15)	0.468	0.83 (0.63-1.10)	0.191	1.05 (0.73-1.52)	0.790
Oseltamivir ****	Zanamivir	1.91 (1.07-3.18)	0.031*	1.90 (1.01-3.32)	0.048*	2.58 (0.41-8.86)	0.261

Peramivir	Zanamivir	1.13 (0.75-1.65)	0.545	1.16 (0.72-1.80)	0.529	2.06 (0.83-4.41)	0.113
Time from onset to administration of NAIs							
≥ 12 hrs and < 24 hrs	< 12 hrs	1.11 (0.86-1.43)	0.422	1.13 (0.85-1.53)	0.400	0.89 (0.56-1.47)	0.647
≥ 24 hrs	< 12 hrs	1.18 (0.88-1.58)	0.262	1.38 (0.96-1.96)	0.083	0.82 (0.48-1.41)	0.461
≥ 24 hrs	≥ 12 hrs and < 24 hrs	1.07 (0.82-1.38)	0.618	1.21 (0.86-1.69)	0.267	0.91 (0.60-1.37)	0.670
Sex	Female	1.05 (0.85-1.29)	0.672	1.00 (0.77-1.30)	0.993	1.09 (0.75-1.58)	0.658
Vaccination	None	1.17 (0.94-1.46)	0.147	1.18 (0.90-1.55)	0.225	1.29 (0.88-1.89)	0.186

* The duration of fever after administration of the first dose of the NAI was shorter in patients with influenza A infection than in patients with influenza B infection.

** The duration of fever after administration of the first dose of the NAI was shorter in patients whose time from onset of influenza virus infection to administration of the NAI was longer.

*** In the 5-9 years of age group, the duration of fever after administration of the first dose of oseltamivir was shorter than that after administration of the first dose of laninamivir in patients with influenza A infection. The duration of fever after administration of the first dose of peramivir was shorter than that after administration of the first dose of laninamivir in patients with influenza A infection. The duration of fever after administration of the first dose of zanamivir was shorter than that after administration of the first dose of laninamivir in patients with influenza A or B infection.

**** In the 10-18 years of age group, the duration of fever after administration of the first dose of oseltamivir was shorter than that after administration of the first dose of zanamivir in patients with influenza A infection.

Table 4

Table 4. Episodes of biphasic fever in patients with influenza A and B who were treated with the NAIs by age groups

Age group	Virus type	Total	NAIs used			
			Oseltamivir	Zanamivir	Laninamivir	Peramivir
0–4 years	A	9/197 (4.6%)	5/105 (4.8%)	-	-	4/92 (4.4%)
	B	16/90 (17.8%)	11/70 (15.7%)	-	-	5/20 (25.0%)
5–9 years	A	11/304 (3.6%)	2/97 (2.1%)	3/83 (3.6%)	5/68 (7.4%)	1/56 (1.8%)
	B	36/240 (15.0%)	14/87 (16.1%)	12/82 (14.6%)	6/49 (12.2%)	4/22 (18.2%)
10–18 years	A	12/246 (4.9%)	0/13 (0.0%)	7/102 (6.9%)	5/104 (4.8%)	0/27 (0.0%)
	B	4/130 (3.1%)	0/2 (0.0%)	2/65 (3.1%)	2/56 (3.6%)	0/7 (0.0%)

Supplemental table 1

Supplemental table 1. Selection of NAIs in patients with influenza A and B by age groups

Age group	Virus type	Total	NAIs used			
			Oseltamivir	Zanamivir	Laninamivir	Peramivir
0–4 years	A	197	105	-	-	92
	B	90	70	-	-	20
5–9 years	A	304	97	83	68	56
	B	240	87	82	49	22
10–18 years	A	246	13	102	104	27
	B	130	2	65	56	7

Supplemental table 2

Supplemental Table 2. Results of Cox's proportional hazards model to determine factors influencing duration of fever after administration of the first dose of the NAI in influenza A-infected children aged 0 to 4 years, 5 to 9 years, and 10 to 18 years in 2014-2015 and 2016-2017.

Independent factors	Unit/Control	Patients infected with influenza A	
		Hazard ratio (95% CI)	*p* value
(A) 0–4 years			
NAI chosen			
Peramivir	Oseltamivir	1.16 (0.82-1.63)	0.407
Time from onset to administration of NAIs			
≥ 12 hrs and < 24 hrs	< 12 hrs	1.20 (0.83-1.77)	0.334
≥ 24 hrs *	< 12 hrs	2.17 (1.31-3.51)	0.003
≥ 24 hrs *	≥ 12 hrs and < 24 hrs	1.80 (1.12-2.83)	0.017
Sex	Female	1.15 (0.82-1.60)	0.427
Vaccination	None	0.86 (0.61-1.21)	0.387
(B) 5–9 years			
NAI chosen			
Oseltamivir	Laninamivir	1.33 (0.95-1.89)	0.101
Peramivir **	Laninamivir	1.67 (1.04-2.63)	0.034
Peramivir	Oseltamivir	1.25 (0.80-1.91)	0.313
Zanamivir	Laninamivir	1.25 (0.88-1.79)	0.218
Oseltamivir	Zanamivir	1.07 (0.78-1.46)	0.690
Peramivir	Zanamivir	1.34 (0.85-2.05)	0.204
Time from onset to administration of NAIs			
≥ 12 hrs and < 24 hrs	< 12 hrs	1.05 (0.79-1.42)	0.723
≥ 24 hrs	< 12 hrs	1.09 (0.75-1.57)	0.637
≥ 24 hrs	≥ 12 hrs and < 24 hrs	1.04 (0.73-1.44)	0.839
Sex	Female	1.05 (0.82-1.36)	0.680
Vaccination	None	1.08 (0.83-1.39)	0.572
(C) 10–18 years			

NAI chosen			
Oseltamivir	Laninamivir	2.13 (0.74-4.88)	0.147
Peramivir	Laninamivir	0.81 (0.45-1.39)	0.454
Peramivir	Oseltamivir	0.38 (0.14-1.21)	0.096
Zanamivir	Laninamivir	0.77 (0.58-1.03)	0.081
Oseltamivir	Zanamivir	2.76 (0.95-6.35)	0.060
Peramivir	Zanamivir	1.05 (0.59-1.77)	0.862
Time from onset to administration of NAIs			
≥ 12 hrs and < 24 hrs	< 12 hrs	1.03 (0.75-1.43)	0.844
≥ 24 hrs	< 12 hrs	1.20 (0.81-1.75)	0.365
≥ 24 hrs	≥ 12 hrs and < 24 hrs	1.16 (0.80-1.66)	0.435
Sex	Female	1.00 (0.76-1.32)	0.997
Vaccination	None	1.09 (0.81-1.46)	0.553

* The duration of fever after administration of the first dose of the NAI was shorter in patients whose time from onset of influenza virus infection to administration of the NAI was longer.

** In the 5-9 years of age group, the duration of fever after administration of the first dose of peramivir was shorter than that after administration of the first dose of laninamivir in patients with influenza A infection.

Supplemental table 3

Supplemental table 3. Results of logistic regression model to determine factors influencing episodes of biphasic fever

Independent factors	Unit/Control	Patients infected with either influenza A or B (n=1207)		Patients infected with influenza A (n=747)		Patients infected with influenza B (n=460)	
		Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value
Type of influenza *	A	2.99 (1.90-4.80)	<0.001	-	-	-	-
Age group							
0-4 years **	10-18 years	2.89 (1.27-6.77)	0.010	3.00 (0.78-14.13)	0.102	5.83 (1.78-22.40)	0.002
5-9 years ***	10-18 years	2.13 (1.17-4.04)	0.012	1.10 (0.46-2.59)	1.000	5.11 (1.97-16.58)	<0.001
0-4 years	5-9 years	1.36 (0.74-2.51)	0.329	2.73 (0.84-11.15)	0.085	1.14 (0.54-2.37)	0.768
NAI chosen							
Laninamivir	Zanamivir	1.01 (0.53-1.90)	1.000	1.11 (0.45-2.72)	1.000	0.87 (0.34-2.13)	0.817
Laninamivir ****	Peramivir	1.30 (0.57-3.02)	0.538	4.19 (1.10-20.50)	0.027	0.53 (0.18-1.60)	0.276
Oseltamivir	Peramivir	1.01 (0.53-2.01)	1.000	1.23 (0.40-4.03)	0.866	0.61 (0.27-1.47)	0.291
Zanamivir ****	Peramivir	1.29 (0.60-2.89)	0.519	3.77 (1.01-18.20)	0.039	0.62 (0.23-1.69)	0.374
Laninamivir	Oseltamivir	1.28 (0.62-2.63)	0.516	3.40 (0.94-15.28)	0.053	0.88 (0.34-2.18)	0.832

Zanamivir	Oseltamivir	1.27 (0.66-2.49)	0.483	3.06 (0.87-13.56)	0.073	1.01 (0.45-2.24)	1.000
Time from onset to administration of NAIs							
≥ 12 hrs and < 24 hrs	< 12 hrs	1.07 (0.63-1.87)	0.854	0.72 (0.33-1.57)	0.445	1.71 (0.80-3.99)	0.155
≥ 24 hrs	< 12 hrs	1.00 (0.54-1.86)	1.000	0.70 (0.25-1.78)	0.471	1.44 (0.62-3.53)	0.389
≥ 24 hrs	≥ 12 hrs and < 24 hrs	0.93 (0.54-1.57)	0.831	0.98 (0.35-2.48)	1.000	0.84 (0.44-1.59)	0.611
Sex	Female	1.24 (0.80-1.94)	0.342	1.23 (0.61-2.53)	0.623	1.41 (0.80-2.52)	0.232
Vaccination	None	0.73 (0.46-1.13)	0.159	0.66 (0.31-1.35)	0.260	0.76 (0.42-1.34)	0.344

* The number of biphasic fever episodes in patients infected with influenza B virus was 2.99-times greater than that in patients infected with influenza A virus.

** The number of biphasic fever episodes in influenza A- or B-infected patients aged 0-4 years was 2.89-times greater than that in patients aged 10-18 years, and the number of biphasic fever episodes in influenza B-infected patients aged 0-4 years was 5.83-times greater than that in patients aged 10-18 years.

*** The number of biphasic fever episodes in influenza A- or B-infected patients aged 5-9 years was 2.13-times greater than that in patients aged 10-18 years, and the number of biphasic fever episodes in influenza B-infected patients aged 5-9 years was 5.11-times greater than that in patients aged 10-18 years.

**** The number of biphasic fever episodes in influenza A-infected patients treated with laninamivir was 4.19-times greater than that in patients treated with peramivir, and the number of biphasic fever episodes in influenza A-infected patients treated with zanamivir was 3.77-times greater than that in patients treated with peramivir.

Supplemental table 4

Supplemental table 4. Results of logistic regression model to determine factors influencing episodes of biphasic fever in children aged 0 to 4 years, 5 to 9 years, and 10 to 18 years

Independent factors	Unit/Control	Odds ratio (95% CI)	*p* value
(A) 0 – 4 years			
Type of influenza *	A	4.73 (2.00-11.8)	<0.001
NAI chosen			
Oseltamivir	Peramivir	0.77 (0.32-1.96)	0.662
Time from onset to administration of NAIs			
≥ 12 hrs and < 24 hrs	< 12 hrs	0.89 (0.33-2.54)	1.000
≥ 24 hrs	< 12 hrs	0.84 (0.27-2.64)	0.914
≥ 24 hrs	≥ 12 hrs and < 24 hrs	0.94 (0.33-2.51)	1.000
Sex	Female	1.48 (0.65-3.51)	0.358
Vaccination	None	1.30 (0.57-3.03)	0.557
(B) 5 – 9 years			
Type of influenza **	A	4.34 (2.24-9.06)	<0.001
NAI chosen			
Laninamivir	Zanamivir	1.14 (0.49-2.59)	0.867
Laninamivir	Peramivir	1.08 (0.37-3.47)	1.000
Oseltamivir	Peramivir	0.86 (0.32-2.67)	1.000
Zanamivir	Peramivir	0.95 (0.35-2.95)	1.000
Laninamivir	Oseltamivir	1.25 (0.54-2.81)	0.650
Zanamivir	Oseltamivir	1.10 (0.52-2.33)	0.916
Time from onset to administration of NAIs			
≥ 12 hrs and < 24 hrs	< 12 hrs	1.55 (0.72-3.60)	0.254
≥ 24 hrs	< 12 hrs	1.29 (0.53-3.25)	0.611
≥ 24 hrs	≥ 12 hrs and < 24 hrs	0.83 (0.39-1.69)	0.620
Sex	Female	1.10 (0.60-2.02)	0.840
Vaccination	None	0.63 (0.33-1.16)	0.134

(C) 10 – 18 years			
Type of influenza	A	0.60 (0.17-1.71)	0.337
NAI chosen			
Laninamivir	Zanamivir	0.85 (0.31-2.28)	1.000
Laninamivir	Peramivir	5.23 (0.58-692.95)	0.089
Oseltamivir	Peramivir	2.83 (0.01-539.95)	1.000
Zanamivir	Peramivir	6.17 (0.72-809.80)	0.055
Laninamivir	Oseltamivir	1.85 (0.20-246.05)	0.488
Zanamivir	Oseltamivir	2.18 (0.24-288.47)	0.382
Time from onset to administration of NAIs			
≥ 12 hrs and < 24 hrs	< 12 hrs	0.60 (0.19-1.90)	0.428
≥ 24 hrs	< 12 hrs	0.80 (0.21-2.76)	1.000
≥ 24 hrs	≥ 12 hrs and < 24 hrs	1.34 (0.36-4.57)	1.000
Sex	Female	1.70 (0.63-4.94)	0.310
Vaccination	None	0.46 (0.14-1.32)	0.141

* In the 0-4 years of age group, the number of biphasic fever episodes in patients infected with influenza B virus was 4.73-times greater than that in patients infected with influenza A virus.

** In the 5-9 years of age group, the number of biphasic fever episodes in patients infected with influenza B virus was 4.34-times greater than that in patients infected with influenza A virus.