Comparison of Hospitalization Incidence in Influenza Outpatients Treated With Baloxavir Marboxil or Neuraminidase Inhibitors: A Health Insurance Claims Database Study

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SUMMARY

Baloxavir marboxil is a single-dose oral anti-influenza drug with a novel mechanism of action. This real-world data study indicated that baloxavir marboxil may reduce hospitalization after influenza outpatient treatment compared with neuraminidase inhibitor treatment.
ABSTRACT

Background. Baloxavir marboxil (baloxavir) is a single-dose, oral anti-influenza drug with a novel mechanism of action. We compared the incidence of hospitalization in patients treated with baloxavir versus neuraminidase inhibitors.

Methods. This was a retrospective observational cohort study using real-world patient data extracted from a Japanese health insurance claims database. The enrollment period was October 1, 2018 to April 17, 2019. On day 1, eligible patients \( (N = 339,007) \) received baloxavir, oseltamivir, zanamivir, or laninamivir. Baseline characteristics were standardized using the inverse probability of treatment weighting method. Primary end point was the incidence of hospitalization (days 2–14). Secondary end points included antibacterial use, secondary pneumonia, and additional anti-influenza drug use.

Results. Compared with the baloxavir group, the incidence of hospitalization was greater in the oseltamivir group (risk ratio [RR] and 95% confidence interval [CI], 1.41 [1.00–2.00]; risk difference [RD] and 95% CI, 0.06 [0.01–0.12]) and zanamivir group (RR, 1.85 [1.23–2.78]; RD, 0.11 [0.02–0.20]). Oseltamivir-treated patients were less likely to require antibacterials than baloxavir-treated patients (RR, 0.87 [0.82–0.91]). However, oseltamivir-treated patients were more likely to be hospitalized with antibacterials (RR, 1.70 [1.21–2.38]) or antibacterial injection (RR, 1.67 [1.17–2.38]) than baloxavir-treated patients (post hoc analysis). Compared with baloxavir-treated patients, additional anti-influenza drug use was greater in oseltamivir-, zanamivir-, and laninamivir-treated patients (RR, 1.51 [1.05–2.18], 2.84 [2.04–3.96], and 1.68 [1.35–2.10], respectively).

Conclusions. Baloxavir is an efficacious anti-influenza treatment that may reduce hospitalization compared with oseltamivir and zanamivir.

KEYWORDS

baloxavir; human influenza; hospitalization; Japan; neuraminidase inhibitor.
Clinical Trials Registration. This study was registered at the UMIN-CTR Clinical Trials Registry (https://www.umin.ac.jp/ctr/index.htm; UMIN000038159).
INTRODUCTION

Influenza is a contagious respiratory illness that ranges from mild to severe, and although most influenza infections resolve without treatment, they can lead to complications and result in hospitalization [1]. In Japan, 4 neuraminidase inhibitors (NAIs; oseltamivir, zanamivir, laninamivir, and peramivir) are approved for the treatment of influenza [1].

Baloxavir marboxil (baloxavir), an anti-influenza drug with a novel mechanism of action (cap-dependent endonuclease inhibitor), was first approved in Japan [2]. In the trials in adults and adolescents with uncomplicated influenza, 1 day after trial regimen initiation, a single dose of baloxavir significantly reduced the viral load compared with oseltamivir and placebo [3]. In a recent observational study of patients with influenza A, the duration of fever was significantly shorter for baloxavir-treated patients compared with NAI-treated patients [4]. In the phase 3 trial in high-risk influenza patients, baloxavir significantly reduced the incidence of influenza-related complications compared with placebo [5]. Given the ability of baloxavir to significantly reduce the viral load compared with oseltamivir, and reduce the time to alleviation of fever compared with NAI treatment, baloxavir treatment in the real-world setting may provide a superior alternative for alleviating influenza symptoms and thus prevent the onset of complications leading to hospitalization.

The aim of this retrospective observational cohort study, using data extracted from a health insurance claims database, was to examine the effect of baloxavir treatment in the real-world setting on the incidence of hospitalization, antibacterial use, secondary pneumonia, and additional anti-influenza drug use compared with NAI treatment in the 2018/2019 influenza season in Japan.
MATERIALS AND METHODS

Study Design

This was a population-based, active comparator, retrospective cohort study using data from the JMDC health insurance claims database (JMDC Inc., Tokyo, Japan). The JMDC database is an epidemiological receipt database containing inpatient, outpatient, and dispensing receipts received from health insurance associations, allowing for individual patient data to be tracked across multiple facilities. By April 2020, the cumulative dataset consisted of 7.3 million individuals. The data extraction period was April 1, 2018 to April 30, 2019, which included the 2018/2019 influenza season. The study was conducted in accordance with Ethical Guidelines for Medical and Health Research Involving Human Subjects. Informed written consent was not required because the study utilized de-identified data. The study was registered at the UMIN-CTR Clinical Trials Registry (https://www.umin.ac.jp/ctr/index.htm: UMIN000038159).

Study Population

The study consisted of 4 influenza outpatient populations: those treated with baloxavir, oseltamivir, zanamivir, or laninamivir. The oseltamivir group was predefined as the primary comparator group. Peramivir was not included as a comparator in this study as it is administered intravenously and would likely be selected under different circumstances from oral and inhalant anti-influenza drugs.

For the study population, eligible patients were those whose first influenza diagnosis date (day 1: starting date of influenza medical care) was within the enrollment period (October 1, 2018 to April 17, 2019), who were continuously registered in the database ≥6 months before day 1, and who received baloxavir, oseltamivir, zanamivir, or laninamivir on day 1. Influenza virus infection was defined by International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) codes J09–J11. Patients were excluded if they were hospitalized in the last 90 days before day 1, or received antibacterials (European
Pharmaceutical Market Research Association [EphMRA] Anatomical Therapeutic Chemical [ATC] codes: J01) on day 1 or in the last 90 days before day 1, or were diagnosed with pneumonia (ICD-10 codes: J12–J18) within 3 months before day 1 (including day 1). This was to exclude the possibility that hospitalization, antibacterial administration, or pneumonia was due to a chronic illness (or disease other than influenza) as much as possible. Less than 1 years old patients were excluded because baloxavir is not indicated for patients weighing less than 10 kgs. Patients who died on day 1 were also excluded. To ensure that the outcomes measured in this study were attributable to a single agent, patients who received >1 anti-influenza drug (baloxavir, oseltamivir, zanamivir, laninamivir, or peramivir) on day 1 were excluded.

Outcome Measures
The primary end point was the incidence of hospitalization during days 2–14. Secondary end points included the occurrence of antibacterial (oral and/or injectable) administration (EphMRA-ATC codes: J01), antibacterial injection (EphMRA-ATC codes: J01; dosage form: injection drug), pneumonia (ICD-10 codes: J12–J18), and additional anti-influenza drug use (any anti-influenza drug different from the one received on day 1) during days 2–14. The overall incidence of the secondary end points (prespecified analysis) and the incidence of secondary end points with hospitalization (post hoc analysis) were determined.

Statistical Analysis
The analysis population included all patients who met the eligibility criteria and excluded those who were hospitalized on day 1 (Figure 1). The comparison groups were the baloxavir group (patients who received oral baloxavir on day 1) and each NAI group (patients who received oral oseltamivir, inhaled zanamivir, or inhaled laninamivir on day 1). Comparisons were made between the standardized baloxavir group and the standardized NAI groups (oseltamivir [main comparison group], zanamivir, or laninamivir). Risk ratios (RR) and risk differences (RD) were calculated as the incidence of the severity end point in the NAI group divided by, or minus, the incidence in the baloxavir group, respectively. The 95% confidence
intervals (CI) for both the RR and RD after standardization of each group in the comparison pair were determined. When the RR and RD 95% CIs did not contain 1 and 0, respectively, differences between groups were considered statistically significant (2-sided significance level 0.05).

To standardize the patient baseline demographic and clinical characteristics between the baloxavir group and each NAI group, the propensity score was calculated and the inverse probability of treatment weighting (IPTW) method was applied. To calculate propensity score, a logistic regression analysis was performed using the baloxavir group as the response variable (1 for the baloxavir group, 0 otherwise) and the patient baseline characteristics (covariates) as the explanatory variable. The propensity score calculated as the predicted probability (P) from logistic regression analysis for the baloxavir group for each patient was used as the weight (ie, 1/P for the baloxavir group, 1/(1-P) for each NAI group).

Covariates (patient baseline characteristics) used to calculate the propensity score were those considered related to influenza severity [6]. Patient age was categorized as following; 1 to <2, ≥2 to <5, ≥5 to <18, ≥18 to <65, and ≥65 years. The age categories were consistent with those most widely used [7]. Comorbidities were diagnosed by ICD-10 code (a receipt corresponding to the ICD-10 code was required within the 6 months prior to the month of day 1, or if the receipt occurred in the month of day 1, then on a day prior to day 1) or by the administration of disease-related medication (corresponding drug was administered within 180 days before day 1). Covariates included age, gender, influenza virus type (ICD-10 codes: J09–J11), and the presence or absence of the following (disease diagnosis was defined by the administration of disease-related medication; corresponding drug was administered within 180 days before day 1 [excluding day 1]): steroid administration (World Health Organization [WHO] ATC code: H02), dialysis (defined by the presence/absence of a dialysis-related medical care activity), respiratory coinfection (ICD-10 codes: J00–J06, J2) excluding pneumonia, asthma (corresponding drug WHO-ATC code: R03), diabetes (corresponding drug WHO-ATC code: A10), chronic obstructive lung disease (ICD-10 codes:
J41–J44), cardiovascular disease (ICD-10 codes: I20–I25, Q20–Q28), cerebrovascular disease (ICD-10 codes: I60–I69), mental illness including dementia (ICD-10 codes: F00–F99), neurological disease (ICD-10 codes: G00–G99), anemia (ICD-10 codes: D50–D59, D60–D64), immune deficiency (ICD-10 codes: D80–D89), liver disease (ICD-10 codes: K70–K77), and malignant tumor (ICD-10 codes: D00–D09, C00–C97).

The standardized mean difference (SMD) between the comparison groups was calculated for each patient baseline characteristic (by giving 1 if appropriate for the category, 0 for otherwise). Sensitivity analyses of the primary and secondary end points were conducted for the comparison of 2 treatment groups and included patients with an influenza virus diagnostic test on day 1 (data not shown).

Missing values were not replaced and multiplicity was not adjusted for repeated tests. All analyses were conducted using SAS® version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Demographic and Baseline Clinical Characteristics

During the 2018/2019 influenza season, 7 320 512 individuals were recorded in the JMDC claims database; of these, 339 007 patients met the eligibility criteria for the study analysis population (Figure 1). The most common anti-influenza drug was baloxavir (N = 146 192), followed by oseltamivir (N = 92 700), laninamivir (N = 81 438), and zanamivir (N = 18 677). Table 1 summarizes the unadjusted patient baseline demographic and clinical characteristics for the study population.

The proportion of <5 years old patients was higher in the oseltamivir group compared with the other 3 treatment cohorts. For those patients whose influenza type could be determined, most were infected with influenza A. Approximately half the patients in the study population had a respiratory coinfection, and the proportion of patients with asthma in the oseltamivir group was approximately twice that in the baloxavir group. Baseline demographic and clinical characteristics of patients after standardization using the IPTW method were well balanced across the treatment groups (SMD were all <0.1) (Table 2).
Hospitalization Incidence

The incidence of hospitalization was greater in the oseltamivir group than in the baloxavir group, with no statistically significant RR of 1.41 (95% CI, 1.00–2.00) and a statistically significant RD of 0.06 (95% CI, 0.01–0.12) (Figure 2). The incidence of hospitalization was statistically significantly greater in the zanamivir group than in the baloxavir group, with a significant RR of 1.85 (95% CI, 1.23–2.78) and significant RD of 0.11 (95% CI, 0.02–0.20). No significant difference in the incidence of hospitalization between the laninamivir and baloxavir groups was observed.

Antibacterial Administration, Pneumonia, and Additional Anti-influenza Drug Use

Overall, patients in the oseltamivir group had a reduced risk of requiring antibacterial administration than patients in the baloxavir group (Figure 3A). In contrast, patients in the oseltamivir group had a greater risk of requiring additional anti-influenza drugs than patients in the baloxavir group (Figure 3A). Patients in the zanamivir group had a reduced risk of pneumonia compared with patients in the baloxavir group (Figure 3B). In the zanamivir and laninamivir groups, patients were more likely to require additional anti-influenza drugs compared with patients in the baloxavir group (Figure 3B and 3C). Details of additional anti-influenza drug use and antibacterial administration were shown in supplementary tables 1 and 2. Baloxavir and peramivir were most frequently used as additional anti-influenza drugs, while macrolides and cephalosporins were most frequently used as antibacterial drugs.

As post hoc analysis, the incidence of secondary end points with hospitalization were assessed. Patients treated with oseltamivir had a significantly greater risk of requiring hospitalization with antibacterial administration and hospitalization with antibacterial injection compared with baloxavir-treated patients (Figure 4A). Patients treated with zanamivir had a significantly greater risk of requiring hospitalization with antibacterial administration compared with baloxavir-treated patients (Figure 4B). Patients in the laninamivir group were 1.38 times more likely to require hospitalization with antibacterial administration than the
baloxavir group, although this risk was not significantly different (95% CI, 1.00–1.91) (Figure 4C).

**DISCUSSION**

To our knowledge, this is the first study using population-based, real-world patient data to investigate the incidence of hospitalization after outpatient influenza treatment with baloxavir compared with NAIs. The incidence of hospitalization was lower in baloxavir-treated patients than in oseltamivir-treated patients with no statistically significant RR and a statistically significant RD while that was statistically significantly lower compared with zanamivir-treated patients. These results suggest that baloxavir reduces the risk of hospitalization compared with oseltamivir or zanamivir.

In this study, the administration of antibacterial treatment (both oral and injectable) upon hospitalization was significantly reduced for baloxavir-treated patients compared with oseltamivir-treated patients. However, the incidence of antibacterial administration regardless of hospitalization was significantly higher with baloxavir than with oseltamivir. One possible explanation for this discrepancy is that the outpatient administration of antibacterial drugs may have contributed to the reduced incidence of hospitalization in the baloxavir group. However, for all cohorts, the incidence of hospitalization was increased in those patients who received outpatient antibacterials (Supplementary Table 3). This is not surprising as the requirement for antibacterials indicates that a patient may be experiencing a secondary infection, which can lead to complications requiring hospitalization. These results suggest that the lower hospitalization incidence for baloxavir-treated patients compared with oseltamivir-treated patients was not due to the higher antibacterial administration rate. Studies have shown that ≥16 years old patients hospitalized with influenza have a high and persistent viral load [8, 9]. Although the study results from ≥16 years old patients may not always be applicable to all age groups, the lower incidence of hospitalization observed for the baloxavir group in this study compared with the oseltamivir group may be attributable to baloxavir’s ability to reduce the viral load more rapidly than
oseltamivir [3]. This is also consistent with our observation that the incidence of additional administration of anti-influenza drugs was significantly lower for the baloxavir group compared with the oseltamivir group (Figure 3A). The reason why the baloxavir group had a higher incidence of antibacterial administration is not known and is a limitation. As possible reasons, since diphasic fever is often observed in young children with influenza [10, 11], oral antibacterials, which might be prescribed for inadequate reasons in Japan [12], might have been more frequently prescribed for baloxavir-treated outpatients due to its single dose administration and concerns about development of secondary infections such as bacterial infection or baloxavir-insensitive strains in pediatric patients [13].

Baloxavir compared favorably with both inhaled NAIs (zanamivir and laninamivir), although direct comparisons are limited because of possible confounding due to the different routes of administration. In comparison with the zanamivir group, baloxavir-treated outpatients had a reduced incidence of hospitalization and hospitalization requiring antibacterials (oral/injectable). However, the baloxavir group had an increased risk of pneumonia compared with the zanamivir group. Physicians may have been less likely to prescribe zanamivir, which requires 10 inhalations over 5 days, to patients with compromised lung function; such patients are also more likely to develop pneumonia. Although we adjusted for underlying patient baseline characteristics, including chronic respiratory diseases, the condition of some patients with compromised lung function may not have been captured in the database. Therefore, we have not adjusted for this condition in those patients, and it was possible that those patients were less likely to be prescribed zanamivir. Nevertheless, we are unable to determine the reason for the difference in pneumonia incidence. Both zanamivir- and laninamivir-treated patients in this study were more likely to require additional anti-influenza drugs than baloxavir-treated patients. The additional anti-influenza treatments may have been prescribed if the attending physician had concerns that the inhaled formulation was not properly inhaled, for example in children [14, 15], or if a patient’s symptoms had not improved [16]. Analysis of data from a double-blind randomized clinical
trial indicated that non-persistence with influenza medication was greater for inhaled medication compared with oral medication (hazard ratio, 1.23; \( P = .043 \)) [17]. In Japan, a survey of adherence to oseltamivir therapy revealed that 21% of patients discontinued oseltamivir, with patients revealing that a shorter treatment plan would be preferred [18]. In the current study, treatment adherence was not examined, which is a limitation of the study; however, baloxavir treatment consists of a single oral dose, and therefore concerns of non-adherence to this anti-influenza therapy, in particular in response to adverse side effects, are not relevant.

Extracting data from the health insurance claims database allowed us to compare the incidence of hospitalization associated with multiple anti-influenza drugs in real-world patient data with a sample size >330 000. However, we acknowledge that oseltamivir, given its oral route of administration, was the only true active comparator for baloxavir. This study was further strengthened by using the IPTW method as we were able to adjust for the differences in treatment choice between patients based on demographics, influenza type, and the presence of other factors related to influenza severity.

Several limitations arose from using data from the health insurance claims database. The proportion of elderly patients (\( \geq 65 \) years) in the database is low (approximately 1% [19]) because retired individuals no longer belong to an employer-based health insurance association; therefore, the database is not representative of the aging population (28% are \( \geq 65 \) years [20]). In addition, the number of <5 years old patients treated with baloxavir, laninamivir, or zanamivir is also limited compared with those treated with oseltamivir. Therefore, our study results may not be applicable to these population. Receipt information in the database does not include information on the period from the onset of influenza to the start of treatment, temperature data, and findings on influenza symptoms, so severity of influenza symptoms at the start of treatment is unknown. The accuracy and the severity of the diagnosis of the covariates used to calculate the propensity score is unknown. Similarly,
the accuracy and the severity of the diagnosis of pneumonia, a secondary outcome measure, was also unknown. As this was an observational study, other unmeasured confounding factors may have existed, and although significant differences can be identified in observational studies of large datasets, it is very difficult to verify causal relationships. Additional studies to determine why hospitalization incidence was lower in the baloxavir group are required. Finally, the observational period for this study covered the 2018/2019 influenza season, when both influenza A/H1N1 and A/H3N2 were the major influenza types, and therefore data for influenza B were limited.

In conclusion, the results of this study using real-world influenza patient data indicate that a single oral dose of baloxavir may reduce hospitalization compared with NAI treatment and provides an alternative anti-influenza treatment option.
Notes

Role of contributors
All authors participated in the interpretation of study results, and in the drafting, critical revision, and approval of the final version of the manuscript. T. Komeda, H. Miyauchi, K. Honda, M. Fujiwara, H. Watanabe, and Y. Kitanishi were involved in the study design and data analyses. M. Fujiwara, Y. Ajisawa, and H. Watanabe conducted the statistical analysis.

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Potential conflicts of interest
E. Ogura, M. Fujiwara, Y. Ajisawa, H. Watanabe, Y. Kitanishi, and K. Hara are employees of Shionogi & Co., Ltd. M. Fujiwara, Y. Ajisawa, Y. Kitanishi, and K. Hara report company stock in Shionogi & Co. T. Komeda, S. Iwata, H. Miyachi, and K. Honda are employees of Shionogi Pharmacovigilance Center Co., Ltd and report company stock in Shionogi & Co. H. Mukae has received honoraria for lecturing and research grants from Shionogi & Co., Ltd and Chugai Pharmaceutical Co, Ltd and grants and honoraria for lecturing from Daiichi Sankyo Co, Ltd. H. Mukae also reports personal fees from AbbVie GK, Asahi Kasei Pharma Corporation, Astellas Pharma, AstraZeneca K.K., Bristol-Myers Squibb, Eli Lilly Japan K.K.,
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### Table 1. Unadjusted Baseline Demographic and Clinical Characteristics of Study Population

| Characteristic                        | Baloxavir N=146 192 | Oseltamivir N=92 700 | Laninamivir N=81 438 | Zanamivir N=18 677 |
|---------------------------------------|----------------------|----------------------|----------------------|-------------------|
| Age, years                            |                      |                      |                      |                   |
| 1 to <2                               | 104 (0.1)            | 3948 (4.3)           | 4 (<0.1)             | 3 (<0.1)          |
| ≥2 to <5                              | 1758 (1.2)           | 17 789 (19.2)        | 213 (0.3)            | 53 (0.3)          |
| ≥5 to <18                             | 45 220 (30.9)        | 27 556 (29.7)        | 29 907 (36.7)        | 12 048 (64.5)     |
| ≥18 to <65                            | 97 215 (66.5)        | 42 426 (45.8)        | 50 464 (62.0)        | 6513 (34.9)       |
| ≥65                                   | 1895 (1.3)           | 981 (1.1)            | 850 (1.0)            | 60 (0.3)          |
| Sex                                   |                      |                      |                      |                   |
| Male                                  | 82 906 (56.7)        | 50 628 (54.6)        | 44 604 (54.8)        | 9522 (51.0)       |
| Female                                | 63 286 (43.3)        | 42 072 (45.4)        | 36 834 (45.2)        | 9155 (49.0)       |
| Type of influenza                     |                      |                      |                      |                   |
| A virus                               | 106 340 (72.7)       | 62 436 (67.4)        | 57 119 (70.1)        | 12 043 (64.5)     |
| B virus                               | 991 (0.7)            | 662 (0.7)            | 701 (0.9)            | 191 (1.0)         |
| A and B                               | 30 (<0.1)            | 17 (<0.1)            | 19 (<0.1)            | 1 (<0.1)          |
| Unknown                               | 38 831 (26.6)        | 29 585 (31.9)        | 23 599 (29.0)        | 6442 (34.5)       |
| Steroid use                           | 472 (0.3)            | 270 (0.3)            | 302 (0.4)            | 47 (0.3)          |
| Dialysis use                          | 17 (<0.1)            | 113 (0.1)            | 21 (<0.1)            | 4 (<0.1)          |
| Presence of the following comorbidities: |                      |                      |                      |                   |
| Respiratory coinfection\(^a\)        | 85 168 (58.3)        | 50 204 (54.2)        | 46 935 (57.6)        | 10 495 (56.2)     |
| Asthma\(^b\)                          | 16 382 (11.2)        | 22 918 (24.7)        | 9078 (11.1)          | 2947 (15.8)       |
| Diabetes mellitus\(^c\)               | 2448 (1.7)           | 1206 (1.3)           | 1264 (1.6)           | 96 (0.5)          |
| COPD                                  | 918 (0.6)            | 642 (0.7)            | 490 (0.6)            | 71 (0.4)          |
| Cardiovascular disease                | 1694 (1.2)           | 1064 (1.1)           | 917 (1.1)            | 121 (0.6)         |
| Cerebrovascular disease               | 1338 (0.9)           | 668 (0.7)            | 676 (0.8)            | 71 (0.4)          |
| Mental disease including dementia     | 8509 (5.8)           | 5542 (6.0)           | 4475 (5.5)           | 974 (5.2)         |
| Neurological disease                  | 10 676 (7.3)         | 5461 (5.9)           | 5695 (7.0)           | 919 (4.9)         |
| Anemia                                | 3171 (2.2)           | 1982 (2.1)           | 2013 (2.5)           | 366 (2.0)         |
| Immune deficiency                     | 150 (0.1)            | 119 (0.1)            | 112 (0.1)            | 27 (0.1)          |
| Hepatic disease                       | 4569 (3.1)           | 2331 (2.5)           | 2508 (3.1)           | 281 (1.5)         |
| Malignant tumor                       | 1636 (1.1)           | 804 (0.9)            | 890 (1.1)            | 107 (0.6)         |

Data are n (%).

Abbreviations: ATC, Anatomical Therapeutic Chemical Classification System; COPD, chronic obstructive pulmonary disease; WHO, World Health Organization.

\(^a\)Excluding pneumonia.

\(^b\)Diagnosis based on administration of disease-related medication WHO-ATC code R03.

\(^c\)Diagnosis based on administration of disease-related medication WHO-ATC code A10.
Table 2. Adjusted* Baseline Demographic and Clinical Characteristics of Study Population

| Characteristic                      | Baloxavir N=240 341.4 | Oseltamivir N=238 657.8 | SMD | Baloxavir N=227 633.9 | Laninamivir N=227 618.3 | SMD | Baloxavir N=164 892.3 | Zanamivir N=163 701.7 | SMD |
|-------------------------------------|------------------------|-------------------------|-----|-----------------------|-------------------------|-----|-----------------------|-----------------------|-----|
| **Age, years**                      |                        |                         |     |                       |                         |     |                       |                       |     |
| 1 to <2                             | 4524.3 (1.9)           | 4052.3 (1.7)            | 0.01| 108.0 (0.0)           | 105.5 (<0.1)            | <0.01| 107.0 (0.1)           | 119.9 (0.1)            | <0.01|
| ≥2 to <5                            | 20 581.4 (8.6)         | 19 556.6 (8.2)          | 0.01| 1971.1 (0.9)          | 1973.8 (0.9)            | <0.01| 1811.0 (1.1)          | 1816.1 (1.1)            | <0.01|
| ≥5 to <18                           | 72 693.4 (30.2)        | 72 636.0 (30.4)         | <0.01| 75 151.6 (33.0)       | 75 181.2 (33.0)         | <0.01| 57 299.9 (34.7)       | 57 692.9                | 0.01 |
| ≥18 to <65                          |                        |                         |     |                       |                         |     |                       |                       |     |
| ≥65                                 | 139 660.2 (58.1)       | 139 521.4 (58.5)        | <0.01| 127 490.0 (56.0)      | 127 395.1 (56.0)        | <0.01| 92 370.5 (53.9)       | 92 112.3                | 0.01 |
| Sex                                 |                        |                         |     |                       |                         |     |                       |                       |     |
| Male                                | 134 618.5 (56.0)       | 133 537.5 (56.0)        | <0.01| 127 490.0 (56.0)      | 127 395.1 (56.0)        | <0.01| 92 370.5 (53.9)       | 92 112.3                | 0.01 |
| Female                              | 105 702.9 (44.0)       | 105 120.3 (44.0)        | <0.01| 100 143.9 (44.0)      | 100 223.2 (44.0)        | <0.01| 72 521.7 (46.1)       | 75 526.3                | 0.04 |
| **Type of influenza**               |                        |                         |     |                       |                         |     |                       |                       |     |
| A virus                             | 169 211.8 (70.4)       | 168 300.2 (70.5)        | <0.01| 163 433.2 (71.8)      | 163 420.6 (71.8)        | <0.01| 118 370.3 (71.1)      | 116 356.6                | 0.02 |
| B virus                             | 1683.5 (0.7)           | 1657.8 (0.7)            | <0.01| 1693.1 (0.7)          | 1686.2 (0.7)            | <0.01| 1182.8 (0.7)          | 1203.3                   | <0.01|
| A and B                             | 43.2 (<0.1)            | 45.2 (<0.1)             | <0.01| 49.4 (<0.1)           | 50.0 (<0.1)             | <0.01| 31.0 (<0.1)           | 60.7                    | <0.01|
| Unknown                             | 69 402.8 (28.9)        | 68 654.6 (28.8)         | <0.01| 62 458.2 (27.4)       | 62 461.5 (27.4)         | <0.01| 45 308.2 (27.5)       | 46 081.2                 | 0.01 |
| **Steroid use**                     | 758.1 (0.3)            | 748.3 (0.3)             | <0.01| 771.1 (0.3)           | 767.5 (0.3)             | <0.01| 517.5 (0.3)           | 459.4                   | <0.01|
| Dialysis use                        | 127.8 (0.1)            | 129.9 (0.1)             | <0.01| 37.1 (<1.0)           | 37.4 (<1.0)             | <0.01| 20.7 (<1.1)           | 16.6                    | <0.01|
| Presence of the following comorbidities: |                       |                         |     |                       |                         |     |                       |                       |     |
| Respiratory coinfectionb            | 134 428.5 (55.9)       | 134 519.8 (56.4)        | <0.01| 132 074.8 (58.0)      | 131 973.9 (58.0)        | <0.01| 95 659.9 (57.6)       | 94 354.7                 | <0.01|
| Asthmac                             | 3660.1 (1.5)           | 3648.3 (1.5)            | <0.01| 3714.1 (1.6)          | 3717.2 (1.6)            | <0.01| 2543.5 (1.5)          | 2475.8                   | <0.01|
| Diabetes mellitusd                 |                        |                         |     |                       |                         |     |                       |                       |     |
| COPD                                | 1645.8 (0.7)           | 1592.2 (0.7)            | <0.01| 1408.1 (0.6)          | 1407.1 (0.6)            | <0.01| 989.6 (0.6)           | 998.5                   | <0.01|
|                          | Baloxavir | Oseltamivir | SMD | Baloxavir | Laninamivir | SMD | Baloxavir | Zanamivir | SMD |
|--------------------------|-----------|-------------|-----|-----------|-------------|-----|-----------|-----------|-----|
| Cardiovascular disease   | 2729.8 (1.1) | 2731.1 (1.1) | <0.01 | 2612.2 (1.1) | 2623.8 (1.2) | <0.01 | 1815.4 (1.1) | 1868.2 (1.1) | <0.01 |
| Cerebrovascular disease  | 1997.8 (0.8) | 1995.6 (0.8) | <0.01 | 2017.1 (0.9) | 2023.2 (0.9) | <0.01 | 1409.6 (0.9) | 1446.4 (0.9) | <0.01 |
| Mental disease including dementia | 14 138.7 (5.9) | 14 021.8 (5.9) | <0.01 | 12 997.4 (5.7) | 13 009.7 (5.7) | <0.01 | 9484.1 (5.8) | 9453.6 (5.8) | <0.01 |
| Neurological disease     | 16 233.3 (6.8) | 16 174.1 (6.8) | <0.01 | 16 372.8 (7.2) | 16 372.9 (7.2) | <0.01 | 11 597.8 (7.0) | 11 652.8 (7.1) | <0.01 |
| Anemia                   | 5062.0 (2.1) | 5154.8 (2.2) | <0.01 | 5179.3 (2.3) | 5170.0 (2.3) | <0.01 | 3538.4 (2.1) | 3549.1 (2.2) | <0.01 |
| Immune deficiency        | 277.7 (0.1) | 268.6 (0.1) | <0.01 | 261.2 (0.1) | 259.2 (0.1) | <0.01 | 177.8 (0.1) | 198.1 (0.1) | <0.01 |
| Hepatic disease          | 6912.4 (2.9) | 6930.9 (2.9) | <0.01 | 7078.3 (3.1) | 7081.3 (3.1) | <0.01 | 4849.3 (2.9) | 4781.4 (2.9) | <0.01 |
| Malignant tumor          | 2446.5 (1.0) | 2423.1 (1.0) | <0.01 | 2526.7 (1.1) | 2529.7 (1.1) | <0.01 | 1742.1 (1.1) | 1638.3 (1.0) | <0.01 |

Data are n (%). SMD <0.1 indicated the characteristics were balanced between the comparison pairs.

Abbreviations: ATC, Anatomical Therapeutic Chemical Classification; COPD, chronic obstructive pulmonary disease; IPTW, inverse probability of treatment weighting; SMD, standardized mean difference; WHO, World Health Organization.

a Adjustment (standardization) was performed according to the IPTW method using a propensity score with each item as a covariate.

b Excluding pneumonia

c Diagnosis based on administration of disease-related medication WHO-ATC code R03.

d Diagnosis based on administration of disease-related medication WHO-ATC code A10.
FIGURE LEGENDS

Figure 1. Flow chart of the study cohort. Abbreviations: BXM, baloxavir marboxil; LNV, laninamivir; OTV, oseltamivir; PRV, peramivir; ZNV, zanamivir. aPatients could be excluded for ≥1 reason. bDate of earliest diagnosis of influenza virus infection.

Figure 2. Risk ratio and risk difference of hospitalization. Abbreviations: CI, confidence interval; IPTW, inverse probability of treatment weighting; NAI, neuraminidase inhibitor. aData were standardized using the IPTW method; the risk ratio was calculated using the exposed (baloxavir) group as the denominator and the NAI group (oseltamivir, zanamivir, or laninamivir) as the numerator. Risk difference was the incidence of the outcome end point in the NAI group minus the incidence in the baloxavir group.

Figure 3. Risk ratio and risk difference of antibacterial administration (oral and/or injectable), injectable antibacterial use, pneumonia, and additional anti-influenza drug use regardless of hospitalization. (A) Oseltamivir versus baloxavir. (B) Zanamivir versus baloxavir. (C) Laninamivir versus baloxavir. Abbreviations: CI, confidence interval; IPTW, inverse probability of treatment weighting; NAI, neuraminidase inhibitor. aData were standardized using the IPTW method; the risk ratio was calculated using the exposed (baloxavir) group as the denominator and the NAI group (oseltamivir, zanamivir, or laninamivir) as the numerator. Risk difference was the incidence of the outcome end point in the NAI group minus the incidence in the baloxavir group.

bBaloxavir, N = 146 192; oseltamivir, N = 92 700. cBaloxavir, N = 240 341.4; oseltamivir, N = 238 657.8. dBaloxavir, N = 146 192; zanamivir, N = 18 677. eBaloxavir, N = 164 892.3; zanamivir, N = 163 701.7. fBaloxavir, N = 146 192; laninamivir, N = 81 438. gBaloxavir, N = 227 633.9; laninamivir, N = 227 618.3.
Figure 4. Risk ratio and risk difference of antibacterial administration (oral and/or injectable), injectable antibacterial use, pneumonia, and additional anti-influenza drug use with hospitalization. (A) Oseltamivir versus baloxavir. (B) Zanamivir versus baloxavir. (C) Laninamivir versus baloxavir. Abbreviations: CI, confidence interval; IPTW, inverse probability of treatment weighting; NAI, neuraminidase inhibitor. aData were standardized using the IPTW method; the risk ratio was calculated using the exposed (baloxavir) group as the denominator and the NAI group (oseltamivir, zanamivir, or laninamivir) as the numerator. Risk difference was the incidence of the outcome end point in the NAI group minus the incidence in the baloxavir group.

bBaloxavir, N = 146 192; oseltamivir, N = 92 700. cBaloxavir, N = 240 341.4; oseltamivir, N = 238 657.8. dBaloxavir, N = 146 192; zanamivir, N = 18 677. eBaloxavir, N = 164 892.3; zanamivir, N = 163 701.7. fBaloxavir, N = 146 192; laninamivir, N = 81 438. gBaloxavir, N = 227 633.9; laninamivir, N = 227 618.3.
Figure 1

Study population for analysis, N = 339,007

- BMN: N = 140,192 (41.3%)
- OTN: N = 63,101 (18.6%)
- ZMN: N = 43,002 (12.7%)

Excluded, N = 481,431 (46.6%)

- Died on day 1, N = 475 (0.1%)
- History of antibiotic treatment within 30 days before day 1, N = 5725 (0.1%)
- Hospitalized within 60 days before day 1 (including day 1), N = 60,699 (18.3%)
- History of pneumonia within 3 months before day 1 (including day 1), N = 5209 (0.1%)
- Died on day 1, N = 50 (0.1%)
- Multiple amphotericin B use (BMN, OTN, ZMN) on day 1, N = 3417 (0.3%)

MDC data set from the 2018-2019 influenza season (Apr. 1, 2018 to Apr. 17, 2019), N = 130,512

Study population, N = 339,007

- BMN: N = 140,192 (41.3%)
- OTN: N = 63,101 (18.6%)
- ZMN: N = 43,002 (12.7%)

Excluded, N = 399,423 (46.6%)

- Died on day 1, N = 475 (0.1%)
- History of antibiotic treatment within 30 days before day 1, N = 5725 (0.1%)
- Hospitalized within 60 days before day 1 (including day 1), N = 60,699 (18.3%)
- History of pneumonia within 3 months before day 1 (including day 1), N = 5209 (0.1%)
- Died on day 1, N = 50 (0.1%)
- Multiple amphotericin B use (BMN, OTN, ZMN) on day 1, N = 3417 (0.3%)
### Figure 2

| Comparison   | Not adjusted | Adjusted$^a$ | Adjusted$^a$ |
|--------------|-------------|-------------|-------------|
|              | n/N (%)     | n/N (%)     | Risk ratio (95% CI) | Risk difference (95% CI) |
| Oseltamivir  | 223/92 700 (0.24) | 524.3/238 657.8 (0.22) | 1.41 (1.00–2.00) | 0.06 (0.01–0.12) |
| vs baloxavir | 189/146 192 (0.13) | 373.6/240 341.4 (0.16) |           |                         |
| Zanamivir    | 38/18 677 (0.20) | 388.7/163 701.7 (0.24) | 1.85 (1.23–2.78) | 0.11 (0.02–0.20) |
| vs baloxavir | 189/146 192 (0.13) | 211.3/164 892.3 (0.13) |           |                         |
| Laninamivir  | 125/81 438 (0.15) | 352.3/227 618.3 (0.15) | 1.20 (0.96–1.51) | 0.03 (–0.01 to 0.06) |
| vs baloxavir | 189/146 192 (0.13) | 293.0/227 633.9 (0.13) |           |                         |

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NAI superior    Baloxavir superior    NAI superior    Baloxavir superior
### Figure 3

#### A

| Outcome               | Comparison      | Not adjusted | Adjusted* |
|-----------------------|-----------------|--------------|-----------|
|                       | n/N (%)         | n/N (%)      | Risk ratio (95% CI) | Risk difference (95% CI) |
| Antibacterial         | Oseltamivir     | 8992 (3.77)  | 0.87 (0.82–0.91)    | –0.58 (–0.80 to –0.37)   |
| administration        | vs baloxavir    | 10 454 (4.35)|                       |                         |
| Antibacterial         | Oseltamivir     | 965 (0.41)   | 0.98 (0.85–1.13)    | –0.01 (–0.07 to 0.05)    |
| injection             | vs baloxavir    | 1012 (0.42)  |                       |                         |
| Diagnosed             | Oseltamivir     | 482 (0.20)   | 0.92 (0.74–1.13)    | –0.02 (–0.06 to 0.03)    |
| pneumonia             | vs baloxavir    | 530 (0.22)   |                       |                         |
| Additional            | Oseltamivir     | 887 (0.37)   | 1.51 (1.05–2.18)    | 0.13 (0.03–0.22)         |
| anti-influenza drugs  | vs baloxavir    | 590 (0.25)   |                       |                         |

#### B

| Outcome               | Comparison      | Not adjusted | Adjusted* |
|-----------------------|-----------------|--------------|-----------|
|                       | n/N (%)         | n/N (%)      | Risk ratio (95% CI) | Risk difference (95% CI) |
| Antibacterial         | Zanamivir       | 633 (4.46)   | 1.11 (1.02–1.21)    | 0.46 (0.08–0.84)         |
| administration        | vs baloxavir    | 678 (4.05)   |                       |                         |
| Antibacterial         | Zanamivir       | 677 (0.41)   | 0.97 (0.73–1.26)    | –0.01 (–0.13 to 0.11)    |
| injection             | vs baloxavir    | 702 (0.43)   |                       |                         |
| Diagnosed             | Zanamivir       | 195 (0.12)   | 0.57 (0.36–0.88)    | –0.09 (–0.15 to –0.03)   |
| pneumonia             | vs baloxavir    | 346 (0.21)   |                       |                         |
| Additional            | Zanamivir       | 638 (0.39)   | 2.94 (2.04–3.96)    | 0.25 (0.13–0.37)         |
| anti-influenza drugs  | vs baloxavir    | 226 (0.14)   |                       |                         |

#### C

| Outcome               | Comparison      | Not adjusted | Adjusted* |
|-----------------------|-----------------|--------------|-----------|
|                       | n/N (%)         | n/N (%)      | Risk ratio (95% CI) | Risk difference (95% CI) |
| Antibacterial         | Laninamivir     | 10 405 (4.57)| 1.13 (1.09–1.18)    | 0.53 (0.35–0.71)         |
| administration        | vs baloxavir    | 9205 (4.05)  |                       |                         |
| Antibacterial         | Laninamivir     | 1038 (0.45)  | 1.06 (0.93–1.21)    | 0.03 (–0.03 to 0.05)     |
| injection             | vs baloxavir    | 977 (0.43)   |                       |                         |
| Diagnosed             | Laninamivir     | 486 (0.21)   | 1.01 (0.83–1.22)    | 0.0 (–0.04 to 0.04)      |
| pneumonia             | vs baloxavir    | 481 (0.21)   |                       |                         |
| Additional            | Laninamivir     | 513 (0.23)   | 1.68 (1.35–2.10)    | 0.09 (0.05–0.13)         |
| anti-influenza drugs  | vs baloxavir    | 305 (0.13)   |                       |                         |
Figure 4

A

| Outcome with hospitalization | Comparison          | Not adjusted | Adjusted a |
|------------------------------|---------------------|--------------|------------|
|                              | n/N (%)             |              | Risk ratio (95% CI) | Risk difference (95% CI) |
| Antibacterial administration | Oseltamivir vs baloxavir | 95 (0.10)   | 245.6 (0.10) | 1.70 (1.21-2.38) | 0.04 (0.02-0.07) |
| Antibacterial injection      | Oseltamivir vs baloxavir | 88 (0.09)   | 226.1 (0.09) | 1.67 (1.17-2.38) | 0.04 (0.01-0.06) |
| Diagnosed pneumonia          | Oseltamivir vs baloxavir | 29 (0.03)   | 65.8 (0.03)  | 1.16 (0.59-2.22) | 0.00 (-0.01 to 0.02) |
| Additional anti-influenza drugs | Oseltamivir vs baloxavir | 38 (0.04)   | 69.3 (0.03)  | 0.75 (0.22-2.40) | -0.01 (-0.03 to 0.04) |

B

| Outcome with hospitalization | Comparison          | Not adjusted | Adjusted a |
|------------------------------|---------------------|--------------|------------|
|                              | n/N (%)             |              | Risk ratio (95% CI) | Risk difference (95% CI) |
| Antibacterial administration | Zanamivir vs baloxavir | 17 (0.09)    | 199.4 (0.12) | 2.11 (1.21-3.69) | 0.06 (0.03-0.13) |
| Antibacterial injection      | Zanamivir vs baloxavir | 13 (0.07)    | 161.0 (0.10) | 1.84 (0.99-3.43) | 0.06 (-0.01 to 0.10) |
| Diagnosed pneumonia          | Zanamivir vs baloxavir | 1 (0.01)     | 14.1 (0.01)  | 0.46 (0.08-3.36) | -0.01 (-0.03 to 0.01) |
| Additional anti-influenza drugs | Zanamivir vs baloxavir | 8 (0.04)     | 37.5 (0.02)  | 1.74 (0.76-4.01) | 0.01 (-0.01 to 0.03) |

C

| Outcome with hospitalization | Comparison          | Not adjusted | Adjusted a |
|------------------------------|---------------------|--------------|------------|
|                              | n/N (%)             |              | Risk ratio (95% CI) | Risk difference (95% CI) |
| Antibacterial administration | Laninamivir vs baloxavir | 64 (0.08)   | 184.2 (0.08) | 1.38 (1.00-1.91) | 0.02 (0.00-0.05) |
| Antibacterial injection      | Laninamivir vs baloxavir | 52 (0.06)   | 149.8 (0.07) | 1.21 (0.85-1.71) | 0.01 (-0.01 to 0.03) |
| Diagnosed pneumonia          | Laninamivir vs baloxavir | 9 (0.01)     | 26.1 (0.1)   | 0.60 (0.28-1.27) | -0.01 (-0.02 to 0.00) |
| Additional anti-influenza drugs | Laninamivir vs baloxavir | 5 (0.01)     | 12.9 (0.01)  | 0.43 (0.16-1.17) | -0.01 (-0.02 to 0.00) |