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Comparison of Household Transmission of Influenza Virus From Index Patients Treated With Baloxavir Marboxil or Neuraminidase Inhibitors: A Health Insurance Claims Database Study

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Background. Baloxavir marboxil (baloxavir) is expected to reduce influenza transmission by rapid reduction of viral load. The incidence of household transmission was compared between index patients (IPs) treated with baloxavir and those treated with neuraminidase inhibitors.

Methods. Using a Japanese claims database, the first family members with influenza diagnosis during the 2018–2019 influenza season were identified as IPs, and the diagnosis date was designated day 1. According to the anti-influenza drug dispensed to the IP, their families were classified into the oral baloxavir group and 3 controls: oral oseltamivir group (a primary control), inhaled zanamivir group, and inhaled laninamivir group. A household transmission was defined as influenza diagnosed for any non-IP family members during days 3–8. The incidence of household transmission was compared between groups using a logistic regression model adjusting backgrounds of IPs.

Results. The proportion of families with household transmission was 17.98% (15 226 of 84 672) in the baloxavir group and 24.16% (14 983 of 62 004) in the oseltamivir group. The covariate-adjusted odds ratio (oseltamivir/baloxavir) was 1.09 (95% confidence interval [95% CI], 1.05–1.12), which indicated significantly lower incidence in the baloxavir group. The adjusted odds ratios (controls/baloxavir) against zanamivir and laninamivir were 0.93 (95% CI, .89–.97) and 0.99 (95% CI, .96–1.02), respectively.

Conclusions. Baloxavir may contribute to reduction in household transmission compared with oseltamivir. In comparison between baloxavir and inhalants, a similar reduction was not shown and it might be due to unmeasured confounding by administration route differences.

Keywords. influenza virus; baloxavir marboxil; neuraminidase inhibitors; oseltamivir; Japan.

Seasonal influenza is a global health threat, with 1 billion cases, 3–5 million severe cases, and 290 000–650 000 respiratory deaths per year worldwide [1]. In Japan, seasonal influenza begins in November to December and ends in April to May and affects more than 10 million people each year [2]. From a public health perspective, it is important not only to obtain early alleviation of influenza symptoms but also to inhibit transmission of influenza virus from infected individuals to surrounding people, including family members. Several studies have suggested that treatment of primarily infected patients with an anti-influenza drug may reduce household transmission [3–11]. Baloxavir marboxil (BXM), an anti-influenza drug with a novel mechanism of action (cap-dependent endonuclease inhibitor), was approved in February 2018 in Japan. In a clinical study of patients with uncomplicated influenza, BXM rapidly reduced the viral load compared with oseltamivir (OTV), a neuraminidase inhibitor (NAI) [12]. BXM is expected to help reduce influenza transmission by reducing viral shedding.

Health insurance claims data can be used in extensive research without burdening medical institutions, patients, and patients' families. A previous study of household transmission used a health insurance claims database to compare the incidence of household transmission among users of NAIs [3]. In this study, we used the same database to compare the incidence of household transmission in the 2018–2019 influenza season when index patients (IPs) were treated with either BXM or a NAI.

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METHODS

Database

The data source of this study was the JMDC Claims Database (JMDC-DB) provided by JMDC Inc. The JMDC-DB comprises Japanese health insurance claims data of insured members and contains medical claims, diagnosis procedure combination claims, and dispense claims in a cumulative population of approximately 7.3 million people from January 2005 through April 2019. Family relationships among the insured members can be identified by a unique family code contained in the JMDC-DB. This study used data from October 2018 through April 2019, which includes most patients in the 2018–2019 influenza season. All data in the database are anonymized in such a manner that no single patient can be identified.

Study Design and Definitions of Exposure and Outcome

This study used a cohort design with active comparators to reduce confounding by unmeasured patient characteristics [13]. This study was registered at University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) as UMIN000038155 and then conducted.

The first family members with a diagnosis of influenza (*International Classification of Diseases, Tenth Revision, Clinical Modification*: J09, J10, and J11) were identified as IPs, and the date of diagnosis was designated day 1.

The families were grouped based on the anti-influenza drug dispensed to the IP on day 1. The exposed group was the families of IPs dispensed BXM on day 1, and the primary control group was the families of IPs dispensed oseltamivir (OTV), an oral NAI. Other control groups consisted of zanamivir (ZNV) and laninamivir (LNV), which are inhaled NAIs. Peramivir (PRV), another NAI that requires intravenous infusion and can be administered for consecutive days according to symptoms or when patients are not amenable to oral or inhaled treatment, was not included in the control group because of presumable differences in patient characteristics between PRV and BXM.

Household transmission of influenza virus was defined as influenza diagnosed for any non-IP family member during days 3–8.

Definitions of Study Population and Primary Analysis Population

The study population was extracted according to the study inclusion criteria (families for which day 1 was from 1 October 2018 through 23 April 2019; families that included an IP who was diagnosed with influenza on day 1 on an outpatient basis; and families that included an IP to whom BXM, OTV, ZNV, or LNV was dispensed on day 1 and the study exclusion criteria (families containing no family member other than an IP as of the month of day 1 and families containing ≥2 IPs).

The primary analysis population was the study population that met the analysis inclusion criterion (all family members as of day 1 had been insured since October 2018) and none of the analysis exclusion criteria (families that included an IP who was hospitalized on days 1–2 and families that included an IP to whom multiple anti-influenza drugs [BXM, OTV, ZNV, LNV, or PRV] were dispensed on days 1–2).

Statistical Analyses

The primary end point was the onset of household transmission. Using a logistic regression model with the presence or absence of household transmission as the response, the odds ratios (ORs; controls/BXM) and its confidence interval (CI) were calculated after adjusting covariates (family size after excluding the IP, age category of the IP, sex, family role, scale of medical facility, month of onset, type of influenza virus) to compare the incidence of household transmission between the BXM group and the control group.

Sensitivity analyses were performed by changing the evaluation period for household transmission to days 3–6, days 3–7, days 2–6, days 2–7, and days 2–8 by incorporating testing in the definition of onset of influenza, by incorporating the prescribed anti-influenza drug in the definition of onset of influenza in a family member, and by changing the analysis inclusion criterion/analysis exclusion criteria (the analysis inclusion criterion was not applied, the exclusion period based on hospitalization was not applied/changed to days 1–8, and the exclusion period based on treatment with multiple anti-influenza drugs was changed to days 1–8 and day 1).

Subgroup analyses by the type of influenza virus, month of onset, and age group of the IP were also performed.

SAS 9.4 (SAS Institute, Cary, NC) was used for the statistical analyses. Missing data were not imputed. A 2-sided significance level of 5% was used, and no adjustment for multiplicity due to repeated testing was performed.

RESULTS

Analysis Population

In total, 208 225 families were identified as the primary analysis population in the JMDC-DB (Figure 1). In the primary analysis population, the BXM group was the largest (84 672 families), followed by the OTV group (62 004 families). In IPs, the most common age group was 19–64 years (47.5%) in the BXM group and ≤6 years (52.1%) in the OTV group (Table 1). Influenza type A was predominant in the IPs with an identified virus type. The most common month of onset was January, which accounted for 65.8% of all IPs.

Incidence of Household Transmission

The proportion of families with household transmission was 17.98% (15 226 of 84 672) in the BXM group and 24.16% (14 983 of 62 004) in the OTV group, which was the primary control group (Figure 2). The covariate-adjusted odds ratio (aOR, control/BXM) was calculated using a logistic regression model. In the comparison between the OTV group and the BXM group, the aOR was 1.09 (95% CI, 1.05–1.12), which

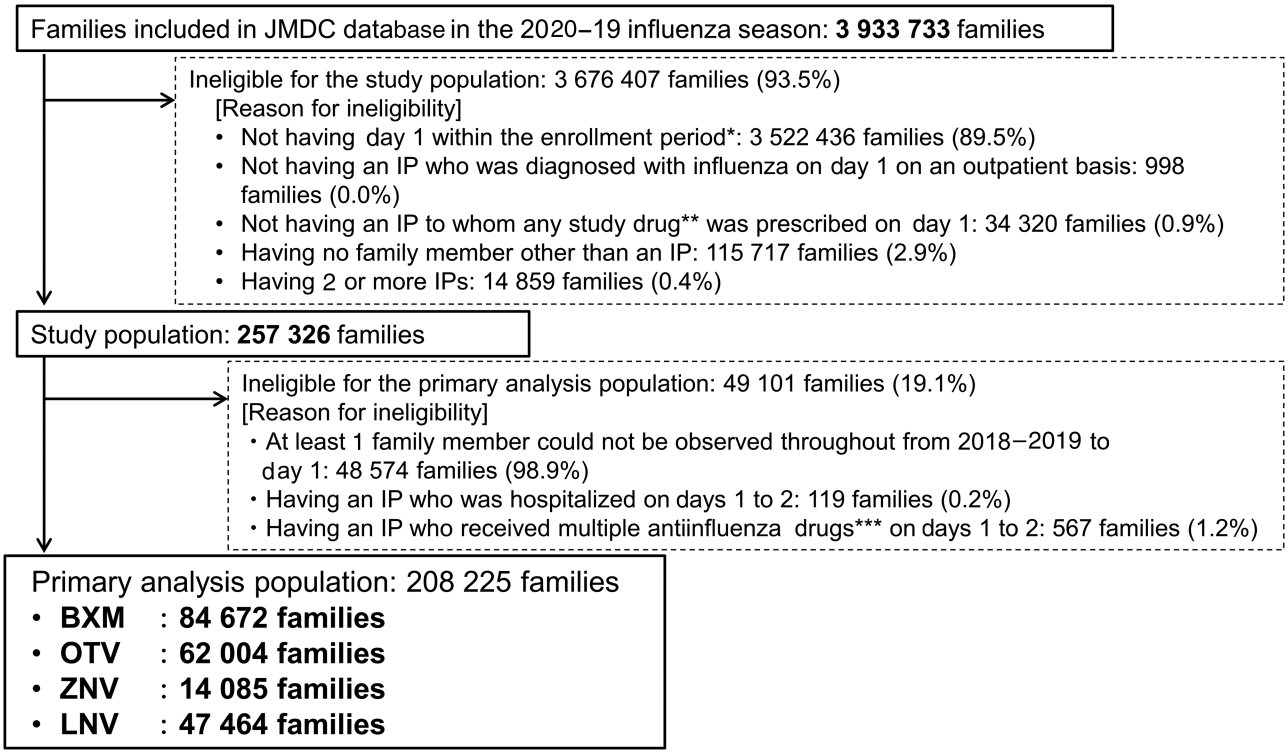

Figure 1. Flow of identification of families included in the study population and analysis population. *1 October 2018 to 23 April 2019. **BXM, OTV, ZNV, LNV. ***Anti-influenza drugs: BXM, OTV, ZNV, LNV, or peramivir hydrate. Abbreviations: BXM, baloxavir marboxil; IP, index patient; LNV, laninamivir octanoate hydrate; OTV, oseltamivir; ZNV, zanamivir hydrate.

indicates a significantly lower odds of household transmission in the BXM group.

The proportion of families with household transmission was 18.41% (2593 of 14 085) and 17.43% (8272 of 47 464) in the inhalation ZNV and LNV groups, respectively. The aOR for ZNV and LNV groups vs BXM group were 0.93 (95% CI, .89–.97) and 0.99 (95% CI, .96–1.02), respectively, which shows that the BXM group had a significantly higher odds of household transmission than the ZNV group but odds that were similar to those of the LNV group.

The ORs of household transmission for each covariate included in the analysis are presented in Table 2. The OR relative to the population aged 19–64 years was 3.63 (95% CI, 3.42–3.86) and 2.53 (95% CI, 2.39–2.68) in the populations aged ≤6 years and 7–12 years, respectively, which indicates that the incidence of household transmission was especially high when the IP was aged ≤12 years.

The sensitivity analyses yielded similar results (data not shown).

Subgroup Analysis by Viral Type in the IPs

A subgroup analysis by viral type in the IPs showed that the proportion of families with household transmission tended to be lower in type B in all drug groups (Figure 3). The aOR (OTV/BXM) was 1.11 (95% CI, 1.07–1.15) in influenza type A, which was similar to that in the overall analysis, and 1.06 (95% CI, .71–1.56) in influenza type B, which represented a wider 95% CI but revealed no clear viral type–related difference.

Subgroup Analysis by Month of Onset in the IP

A subgroup analysis by month of onset showed that the proportion of families with household transmission was highest in January, during which time more IPs were identified than in the other months (Figure 4). The aOR (OTV/BXM) was 1.05 to 1.08 in December to March, which was similar to that in the overall analysis, but was higher in October to November (aOR, 1.42; 95% CI, 1.01–2.01) and April (aOR, 1.24; 95% CI, .93–1.65), when fewer IPs were identified, than in the overall analysis. The aOR (ZNV/BXM) was 0.88 to 0.97 in December to March, which was <1.00 as in the overall analysis but >1.00 in October to November (aOR, 1.17; 95% CI, .76–1.81) and April (aOR, 1.27; 95% CI, .86–1.88). The aOR (LNV/BXM) was 0.96 to 1.08, which was almost identical to that in the overall analysis in all periods.

Subgroup Analysis by Age Category

A subgroup analysis by age category in the IPs showed that the proportion of families with household transmission tended to be higher in lower age groups of ≤6 years and 7–12 years in all drug groups (Figure 5). The aOR (OTV/BXM) was >1.00 (95% CI, 1.01–1.22) in all age groups, although the range was wide.

Table 1. Background Factors of Index Patients

Background Factors	BXM (N = 84 672) n (%)	OTV (N = 62 004) n (%)	ZNV (N = 14 085) n (%)	LNV (N = 47 464) n (%)	Overall (N = 208 225) n (%)
Age, years					
≤6	5493 (6.5)	32 278 (52.1)	745 (5.3)	1916 (4.0)	40 432 (19.4)
7–12	22 293 (26.3)	10 280 (16.6)	7111 (50.5)	14 617 (30.8)	54 301 (26.1)
13–18	15 280 (18.0)	2674 (4.3)	3575 (25.4)	10 499 (22.1)	32 028 (15.4)
19–64	40 254 (47.5)	16 082 (25.9)	2590 (18.4)	19 811 (41.7)	78 737 (37.8)
≥65	1352 (1.6)	690 (1.1)	64 (0.5)	621 (1.3)	2727 (1.3)
Sex					
Male	48 399 (57.2)	34 202 (55.2)	7476 (53.1)	26 522 (55.9)	116 599 (56.0)
Female	36 273 (42.8)	27 802 (44.8)	6609 (46.9)	20 942 (44.1)	91 626 (44.0)
Type of influenza virus					
A	61 246 (72.3)	42 883 (69.2)	9188 (65.2)	33 353 (70.3)	146 670 (70.4)
B	818 (1.0)	570 (0.9)	193 (1.4)	594 (1.3)	2175 (1.0)
A and B	24 (0.0)	15 (0.0)	3 (0.0)	6 (0.0)	48 (0.0)
Unknown	22 584 (26.7)	18 536 (29.9)	4701 (33.4)	13 511 (28.5)	59 332 (28.5)
Number of family members excluding the IP					
<3	40 121 (47.4)	32 636 (52.6)	5378 (38.2)	21 967 (46.3)	100 102 (48.1)
≥3	44 551 (52.6)	29 368 (47.4)	8707 (61.8)	25 497 (53.7)	108 123 (51.9)
Family role					
Insured person	22 300 (26.3)	9439 (15.2)	1113 (7.9)	10 684 (22.5)	43 536 (20.9)
Insured person's spouse	11 497 (13.6)	4705 (7.6)	757 (5.4)	5740 (12.1)	22 699 (10.9)
Child	46 272 (54.6)	45 015 (72.6)	11 490 (81.6)	28 937 (61.0)	131 714 (63.3)
Other (including "unknown")	4603 (5.4)	2845 (4.6)	725 (5.1)	2103 (4.4)	10 276 (4.9)
Month of onset					
October 2018	146 (0.2)	172 (0.3)	59 (0.4)	181 (0.4)	558 (0.3)
November 2018	613 (0.7)	421 (0.7)	165 (1.2)	467 (1.0)	1666 (0.8)
December 2018	11 167 (13.2)	6165 (9.9)	1910 (13.6)	5891 (12.4)	25 133 (12.1)
January 2019	58 548 (69.1)	40 211 (64.9)	8738 (62.0)	29 515 (62.2)	137 012 (65.8)
February 2019	11 248 (13.3)	12 165 (19.6)	2519 (17.9)	8977 (18.9)	34 909 (16.8)
March 2019	1952 (2.3)	1889 (3.0)	409 (2.9)	1470 (3.1)	5720 (2.7)
April 2019	998 (1.2)	981 (1.6)	285 (2.0)	963 (2.0)	3227 (1.5)
Scale of medical facility that the IP visited					
≥100 beds	4030 (4.8)	6772 (10.9)	569 (4.0)	4993 (10.5)	16 364 (7.9)
≤99 beds	80 642 (95.2)	55 201 (89.0)	13 514 (95.9)	42 460 (89.5)	191 817 (92.1)
Unknown	0 (0.0)	31 (0.0)	2 (0.0)	11 (0.0)	44 (0.0)

Abbreviations: BXM, baloxavir marboxil; IP, index patient; LNV, laninamivir octanoate hydrate; OTV, oseltamivir; ZNV, zanamivir hydrate.

DISCUSSION

In comparison with the OTV group (predefined as the primary control group), the aOR (OTV/BXM) was 1.09 (95% CI, 1.05–1.12), which indicates a significantly lower odds of household transmission in the BXM group. OTV-resistant strains were detected in only 1.0% of all AH1pdm strains isolated in

Figure 2. Comparison of incidence of household transmission among drug groups. *The odds in the BXM group are in the denominator, and the odds in the control group are the numerator. **Covariates for the adjustment: index patient (IP) age (≤6, 7–12, 13–18, 19–64, and ≥65 years), IP sex, family role of IP, scale of medical facility where IP was diagnosed, number of family members (continuous variable), month of onset for IP, type of influenza virus. Abbreviations: BXM, baloxavir marboxil; CI, confidence interval; LNV, laninamivir octanoate hydrate; OR, odds ratio; OTV, oseltamivir; ZNV, zanamivir hydrate.

Table 2. Odds Ratios of Household Transmission by Covariates Included in Multivariate Logistic Regression Analysis

Covariate	Reference Category	Test Category	Odds Ratio (95% Confidence Interval)
Number of family members excluding the index patient	–[a]	–	1.48 (1.46–1.50)
Age, years	19–64	≤6	3.63 (3.42–3.86)
		7–12	2.53 (2.39–2.68)
		13–18	1.29 (1.21–1.37)
		≥65	1.21 (1.08–1.36)
Sex	Male	Female	0.82 (.80–.84)
Type of influenza virus	A	B	0.62 (.54–.72)
		A and B	0.68 (.29–1.63)
		Unknown	0.92 (.90–.95)
Family role	Insured person	Insured person's spouse	1.19 (1.13–1.25)
		Child	0.56 (.52–.59)
		Other (including "unknown")	0.63 (.59–.68)
Month of onset	January 2019	October 2018	0.49 (.38–.63)
		November 2018	0.65 (.56–.74)
		December 2018	0.85 (.82–.88)
		February 2019	0.72 (.69–.74)
		March 2019	0.75 (.70–.81)
		April 2019	0.80 (.72–.89)
Scale of medical facility	≥100 beds	≤99 beds	0.91 (.87–.95)
		Unknown	0.47 (.17–1.33)

[a]Because the number of family members is a continuous variable, the odds ratio per increment was calculated.

Japan in the 2018–2019 season [2]. Furthermore, a randomized clinical trial [4] suggested the efficacy of OTV in preventing household transmission. These results support that BXM may more strongly contribute to prevention of household transmission than OTV. BXM has shown superior antiviral activity against OTV, especially on H3N2 and B [14]. The result of

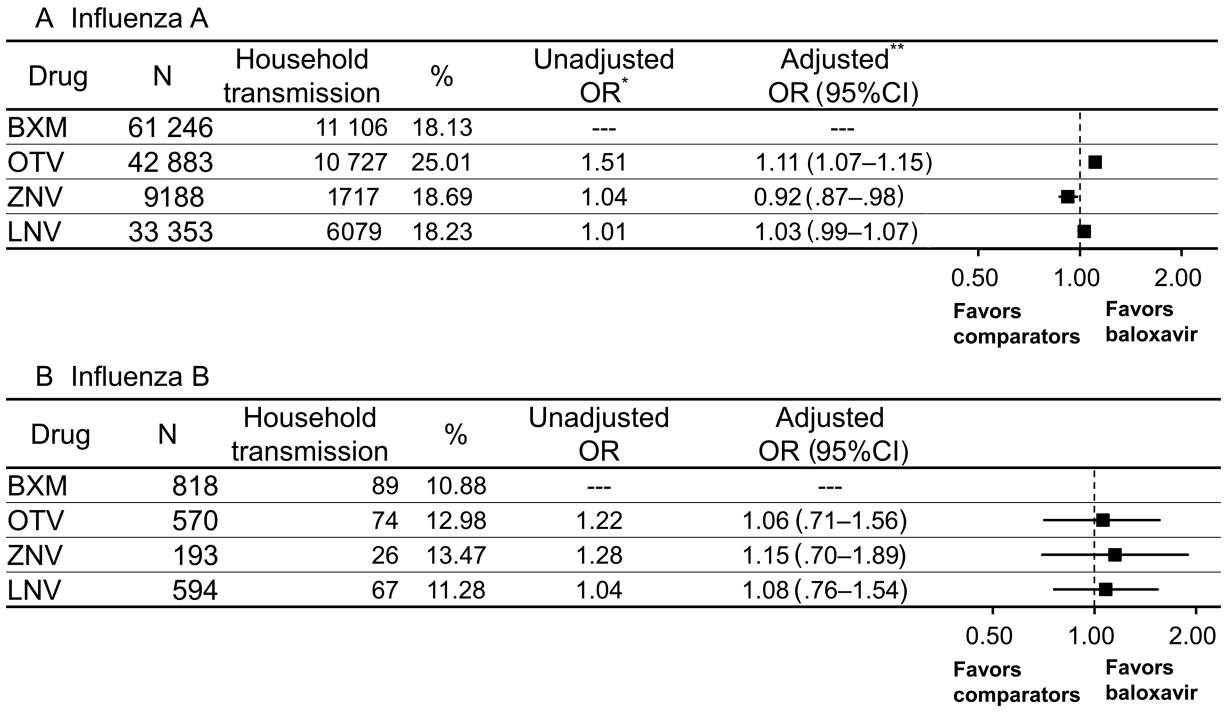

Figure 3. Subgroup analysis by viral type: (*A*) type A and (*B*) type B. *The odds in the BXM group are in the denominator, and the odds in the control group are the numerator. **Covariates for the adjustment: index patient (IP) age (≤6, 7–12, 13–18, 19–64, and ≥65 years), IP sex, family role of IP, scale of medical facility where IP was diagnosed, number of family members (continuous variable), month of onset for IP. Abbreviations: BXM, baloxavir marboxil; CI, confidence interval; LNV, laninamivir octanoate hydrate; OR, odds ratio; OTV, oseltamivir; ZNV, zanamivir hydrate.

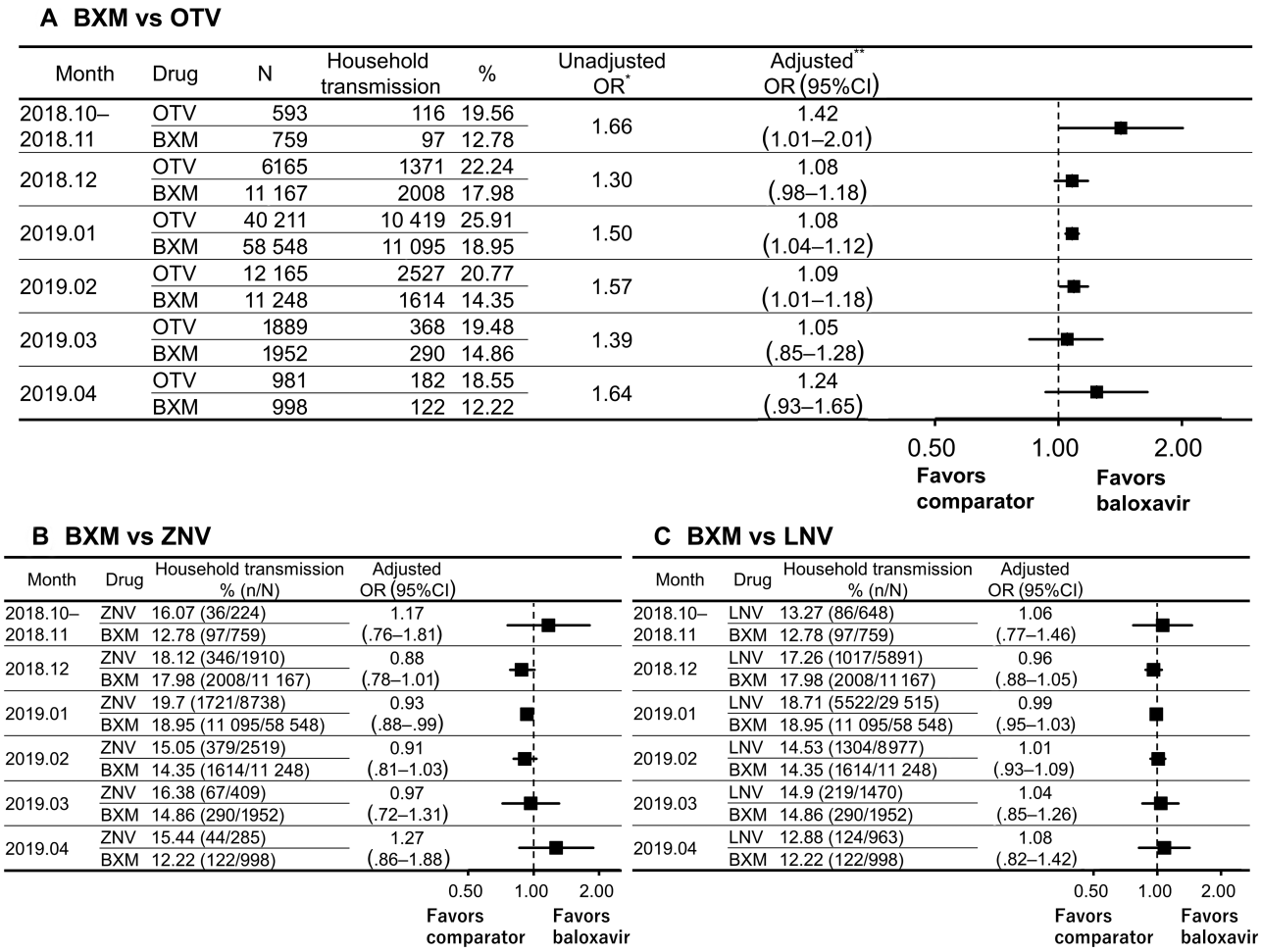

Figure 4. Subgroup analysis by month of onset: (*A*) BXM vs OTV, (*B*) BXM vs ZNV, and (*C*) BXM vs LNV. *The odds in the BXM group are in the denominator, and the odds in the control group are the numerator. **Covariates for the adjustment: index patient (IP) age (≤6, 7–12, 13–18, 19–64, and ≥65 years), IP sex, family role of IP, scale of medical facility where IP was diagnosed, number of family members (continuous variable), type of influenza virus. Abbreviations: BXM, baloxavir marboxil; CI, confidence interval; LNV, laninamivir octanoate hydrate; OR, odds ratio; OTV, oseltamivir; ZNV, zanamivir hydrate.

this study may reflect the stronger antiviral activity of BXM than OTV.

The results of the subgroup analysis by month of onset in the IPs (Figure 4) indicate that the proportion of families with household transmission may be affected by the extent of the spread of influenza, in addition to the drugs used. Since IPs are infected from nonfamily members, the monthly number of IPs is generally proportional to the risk of extrafamilial transmission in the relevant month. In this study, the aOR (OTV/BXM) was higher in October to November (aOR, 1.42; 95% CI, 1.01–2.01) and April (aOR, 1.24; 95% CI, .93–1.65) when a smaller number of IPs was identified (a nonepidemic period) than in the overall analysis. These higher ORs during the nonepidemic periods may be more reflective of the influence of each drug on the incidence of household transmission due to the low risk of extrafamilial transmission.

The ORs by covariates included in the logistic regression analysis (Table 2) and the proportion of families with household transmission in the subgroup analysis by age group (Figure 5) showed that the incidence of household transmission was higher in lower IP age groups of ≤6 years and 7–12 years than in the other groups. This higher risk of household transmission affecting children is consistent with the results of another study [7].

In a clinical study of pediatric patients aged <12 years, BXM-insensitive strains were detected in 23.4% (18/77) of patients after treatment [15]. In our study, which could not determine whether insensitive strains or relevant household transmission occurred, the incidence of household transmission in the age groups of ≤6 years and 7–12 years was significantly lower in the BXM group than in the OTV group (Figure 5). Moreover, in the population aged ≤12 years, the aOR (OTV/BXM) in the nonepidemic period was as high as 1.67 (95% CI, 1.15–2.41) in October to November and 1.42 (95% CI, .96–2.10) in April (Supplementary Figure 1), not raising concerns that household transmission may increase

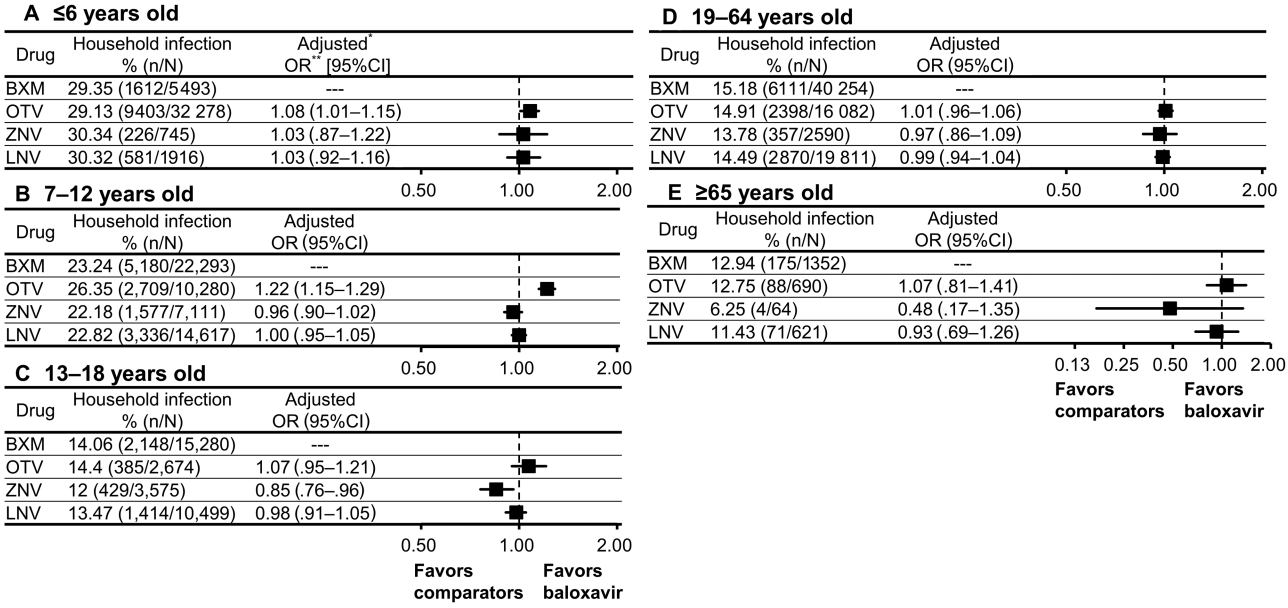

Figure 5. Subgroup analysis by age group: (*A*) ≤6 years, (*B*) 7–12 years, (*C*) 13–18 years, (*D*) 19–64 years, and (*E*) ≥65 years. *Covariates for the adjustment: index patient (IP_ sex, family role of IP, scale of medical facility where IP was diagnosed, number of family members (continuous variable), month of onset for IP, type of influenza virus. **The odds in the BXM group are in the denominator, and the odds in the control group are the numerator. Abbreviations: BXM, baloxavir marboxil; CI, confidence interval; LNV, laninamivir octanoate hydrate; OR, odds ratio; OTV, oseltamivir; ZNV, zanamivir hydrate.

because of the development of insensitive strains in patients aged ≤12 years.

In addition to OTV, inhaled ZNV and LNV were included in the control groups. The aOR (ZNV/BXM) was 0.93 (95% CI, .89–.97), indicating a significantly higher odds of household transmission in the BXM group. However, by month of onset, the odds of household transmission tended to be lower in the BXM group, although not consistently, with an OR of 1.17 (95% CI, .76–1.81) in October to November and 1.27 (95% CI, .86–1.88) in April, which suggests the potential superiority of BXM over ZNV as well as OTV. The aOR (LNV/BXM) was 0.99 (95% CI, .96–1.02) with no significant difference. The incidence of household transmission did not differ markedly between BXM and inhaled ZNV or LNV. Although the superior antiviral activity on H1N1 by LNV compared with OTV was suggested in clinical trials [16, 17], there are no clinical trials that can be used for comparison with BXM and inhalants (LNV, ZNV). For this reason, it is difficult to discuss the comparability of results of the antiviral activity in the clinical setting vs the results of this study. Additionally, because inhaled medications are used in patients who can inhale, confounding may have occurred by the severity of respiratory symptoms and other factors, which differ from those of oral drugs; therefore, there may be limitations in comparisons between BXM and these inhaled medications.

Types of influenza in the IPs and the non-IP family members were not always clear as it is not required to report the influenza type for insurance claims purposes in Japan. For this reason, we did not define household transmission as being of the same influenza type as the IP. However, we confirmed that the non-IP family members were predominantly type B when IPs had type B (Supplementary Table 1). This data would support the prediction that the majority of the events were household transmissions.

In addition to the presence or absence of BXM, there are some differences between this study and a study conducted by Nakano and Shiosakai [3], who evaluated the incidence of household transmission using the JMDC-DB. Nakano and Shiosakai [3] defined the onset of influenza based on treatment with an anti-influenza drug, but we defined the onset based on the diagnosis of influenza. The diagnostic information used in our study allowed for adjustment and subgroup analysis by viral type in the IPs. The lower odds of household transmission in type B than in type A (Table 2) indicates that the viral type should be taken into consideration. Another difference lies in the influenza season analyzed. The number of influenza cases per fixed point over several years in Japan [18] showed that influenza occurred more frequently during a shorter period of time in the 2018–2019 season, which we analyzed, than in the 2010–2011 season, which Nakano and Shiosakai [3] analyzed. In our study, the estimated proportion of families with household transmission was higher and varied more markedly according to month of onset than in the study by Nakano and Shiosakai [3], which indicates that extrafamilial transmission may have been more influential in our study because of the more concentrated occurrence of influenza.

Our study has several limitations. First, because family members covered by the same health insurance were identified as a family, the study results may not have reflected the actual family composition or shared household living, as exemplified by a lack of data for older patients covered by the national health insurance whose claims data JMDC Inc. did not collect. As a result, the estimated proportion of families with household transmission may differ from that in families living together. Second, although active comparators were included to reduce confounding by unmeasured patient characteristics [13] and although ORs were adjusted for various background factors of IPs, unadjusted confounding or bias may have still affected the study results. In particular, confounding by the time from onset of influenza to the hospital visit, body temperature, and severity of each influenza symptom, which are difficult to collect from claims data, cannot be ruled out. Third, the possibility exists for the presence of preexisting infection in a non-IP family member prior to IP treatment. However, because the importance of early treatment with anti-influenza drugs is well known in Japan [19], it is considered that most occurrences of influenza have been confirmed in a timely manner. Fourth, the prescription of anti-influenza drugs recorded in the JMDC-DB may have been generally intended for treatment covered by insurance, but records of prescriptions for prophylaxis not covered by insurance might have still been included. Because OTV, ZNV, and LNV were approved for prophylactic use during the study period, prescription for prophylaxis may have resulted in underestimation of the incidence of household transmission in these drug groups. Finally, the study results were based on the data in only 1 season (2018–2019). Given the limited number of type B in this study as well as the yearly differences in type A subtypes and time course of the number of patients, multiseason studies may be required. A phase 3 study to assess the efficacy of BXM to reduce onward transmission of influenza in households is ongoing (ClinicalTrials.gov identifier NCT03969212). The effect of BXM on household transmission suggested by this study will be evaluated.

CONCLUSIONS

Treatment of IPs with BXM results in a significantly lower incidence of household transmission compared with those treated with OTV. BXM, which has strong antiviral activity, may contribute to reduction in the risk of household transmission compared with OTV, the most widely used influenza antiviral worldwide. In comparison between BXM and inhaled medications, a similar reduction in the risk was not shown and it might be due to unmeasured confounding by administration route differences. Because this study has several limitations, further studies may be required.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Potential conflicts of interest. T. K., H. Miyauchi, S. I., and K. Honda are employees of Shionogi Pharmacovigilance Center Co, Ltd. E. O., M. F., Y. A., H. W., Y. K., and K. Hara are employees of Shionogi & Co, Ltd. Y. A., Y. K., M. F., K. Honda, S. I., K. Hara, T. K., and H. Miyauchi report company stock in Shionogi & Co, Ltd. H. Mukae has received honoraria for lecturing and research grants from Shionogi 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 Inc, AstraZeneca K.K., Bristol-Myers Squibb, Eli Lilly Japan K.K., FUJIFILM Toyama Chemical Co, Ltd, Gilead Sciences Inc, Insmed Incorporated, Janssen Pharmaceutical K.K., Kyorin Pharmaceutical Co, Ltd, Meiji Seika Pharma Co, Ltd, Mitsubishi Tanabe Pharma Corporation, MSD Co, Ltd, Nihon Pharmaceutical Co, Ltd, Nippon Boehringer Ingelheim Co, Ltd, Novartis Pharma K.K, Pfizer Inc, Sumitomo Dainippon Pharma Co, Ltd, Taiho Pharmaceutical Co, Ltd, Taisho Pharma Co, Ltd, Teijin Home Healthcare Ltd, and Toa Shinyaku Co, Ltd and grants from Asahi Kasei Pharma Corporation, Astellas Pharma Inc, FUJIFILM Toyama Chemical Co, Ltd, Kyorin Pharmaceutical Co, Ltd, Meiji Seika Pharma Co, Ltd, Pfizer Inc, Taiho Pharmaceutical Co, Ltd, Taisho Pharma Co, Ltd, Teijin Pharma Ltd, Toa Shinyaku Co, Ltd, and Torii Pharmaceutical Co, Ltd outside the submitted work. T. T. reports grants and personal fees from MSD Co Ltd and Sumitomo Dainippon Pharma Co, Ltd and personal fees from Pfizer Inc outside the submitted work. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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