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Report

Differential Recovery of Anti-Influenza Agent Utilization in Japan After the COVID-19 Pandemic: A Nationwide Analysis Using NDB Open Data (2019–2024)

Atsushi Ishimura*

Laboratory of Clinical Pharmacy Assessment, Hoshi University, 2-4-41 Ebara, Shinagawa-ku, Tokyo 142-8501, Japan
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The coronavirus disease 2019 (COVID-19) pandemic substantially altered the epidemiology of seasonal influenza and markedly reduced the utilization of anti-influenza agents. Although influenza activity resumed following the relaxation of public health interventions, it remains unclear whether the utilization patterns of anti-influenza agents returned to the pre-pandemic state or changed after the pandemic. Prescription volumes of anti-influenza agents were extracted from the National Database of Health Insurance Claims and Specific Health Checkups Open Data (NDB Open Data) for fiscal years (FY) 2019–2024. Oseltamivir, baloxavir, zanamivir, and laninamivir were evaluated. To compare temporal changes among antiviral agents, prescription volumes were normalized using FY2019 as the reference (index = 100). Utilization of all evaluated anti-influenza agents declined markedly during FY2020 and FY2021. However, the recovery patterns differed substantially among antiviral agents following the resumption of influenza activity. In FY2024, the prescription index reached 297.0 for baloxavir 20-mg tablets and 191.6 for oseltamivir capsules/tablets, whereas zanamivir remained at 57.2. Laninamivir recovered to nearly the pre-pandemic level. These findings indicate that post-pandemic drug utilization differed substantially among antiviral agents. In conclusion, utilization patterns of anti-influenza agents in Japan changed following the COVID-19 pandemic. The heterogeneous recovery observed among antiviral agents suggests that post-pandemic utilization patterns may have been influenced by drug-specific characteristics in addition to the resurgence of influenza activity.

Key words Anti-influenza agents, Drug utilization, Baloxavir, NDB Open Data

INTRODUCTION

Seasonal influenza remains a major public health concern worldwide and is associated with substantial morbidity, mortality, and healthcare burden.[1] In Japan, several antiviral agents are available for the treatment of influenza, including neuraminidase inhibitors (oseltamivir, zanamivir, and laninamivir) and the cap-dependent endonuclease inhibitor baloxavir marboxil. These agents differ considerably in their route of administration, dosing frequency, and target patient populations, all of which may influence treatment selection in routine clinical practice.

The COVID-19 pandemic profoundly altered the epidemiology of seasonal influenza. Widespread implementation of non-pharmaceutical interventions, including mask wearing, hand hygiene, physical distancing, school closures, and restrictions on social activities, resulted in an unprecedented decline in influenza transmission worldwide. Consequently, utilization of anti-influenza agents also declined markedly during the pandemic.[2]

Following the relaxation of pandemic-related restrictions, seasonal influenza epidemics re-emerged in Japan. However, restoration of influenza activity does not necessarily imply that the utilization of anti-influenza agents returned to the FY2019 level, because prescribing patterns had already varied across agents before the pandemic. Clinical practice also changed substantially during the pandemic because of changes in healthcare delivery, infection control measures, and antiviral prescribing. In addition, currently available anti-influenza agents differ considerably in their routes of administration and dosing schedules, factors that may influence treatment selection in routine clinical practice.

A previous nationwide study using NDB Open Data described utilization of anti-influenza agents in Japan during FY2014–2020, including the early phase of the COVID-19 pandemic.[3] That study showed that the composition of antiviral use had already changed substantially before the pandemic: laninamivir was the most frequently prescribed agent in 2017, whereas baloxavir accounted for 40.8% of prescriptions in 2018 after its introduction but declined to 15.9% in 2019.

*To whom correspondence should be addressed. e-mail: ishimura.atsushi@hoshi.ac.jp

However, whether utilization patterns after the resumption of seasonal influenza activity differed among individual agents has remained unclear. Because NDB Open Data provides comprehensive nationwide prescription data covering almost the entire Japanese population, it offers a valuable opportunity to evaluate long-term changes in drug utilization.

Therefore, the present study investigated nationwide changes in the utilization of anti-influenza agents during and after the COVID-19 pandemic using NDB Open Data from FY2019 to FY2024, with particular emphasis on differences in post-pandemic recovery among individual agents. FY2019 was used as the reference year for quantitative comparison, while previously reported pre-pandemic trends were considered in the interpretation of the findings.

MATERIALS AND METHODS

Data Source Prescription data were obtained from the National Database of Health Insurance Claims and Specific Health Checkups Open Data (NDB Open Data),[4] which is publicly released by the Ministry of Health, Labour and Welfare of Japan. NDB Open Data contains aggregated health insurance claims data and enables nationwide evaluation of prescription trends in Japan. The database covers almost the entire Japanese population and is widely used for nationwide pharmacoepidemiological research.

Study Drugs The following anti-influenza agents were evaluated: oseltamivir, baloxavir, zanamivir, and laninamivir. Oseltamivir was analyzed separately as capsules/tablets and powder formulations. Baloxavir was analyzed separately as 20-mg and 10-mg tablets. Zanamivir was evaluated as blister formulations, and laninamivir as inhalation kits. Amantadine was not included because prescriptions for influenza could not be distinguished from those for other indications, such as Parkinsonian syndromes, in the aggregated dataset.

Study Period and Analysis Prescription volumes were extracted for fiscal years (FY) 2019 to 2024. Because the units differed among formulations (capsules/tablets, grams of powder, blisters, and inhalation kits), actual prescription volumes were presented together with normalized indices. To compare temporal changes among agents, prescription volumes were normalized using FY2019 as the reference value.

$$\text{Prescription index} = \text{prescription volume in each fiscal year} / \text{prescription volume in FY2019} \times 100.$$

For baloxavir 10-mg tablets, FY2023 was used as the reference because the FY2019 value was not available in the dataset. This study was descriptive, and no inferential statistical analyses were performed because NDB Open Data provides aggregated nationwide prescription counts rather than patient-level observations.

Ethical Considerations Ethical approval and informed consent were not required because this study used publicly available, aggregated, and anonymized open data.

RESULTS

Actual prescription volumes and prescription indices of anti-influenza agents from FY2019 to FY2024 are summarized in Table 1. In FY2019, the prescription volumes were 13.31 million capsules/tablets for oseltamivir capsules/tablets, 14.70 million g for oseltamivir powder, 2.00 million tablets for baloxavir 20-mg tablets, 9.04 million blisters for zanamivir, and 4.50 million kits for laninamivir. Utilization of all evaluated agents declined markedly during FY2020 and FY2021. Oseltamivir capsules/tablets, oseltamivir powder, and baloxavir 20-mg tablets were reported as 0 in NDB Open Data during FY2020 and FY2021 because values fewer than 1,000 units are masked according to the data release policy.

From FY2022 onward, utilization of anti-influenza agents recovered; however, the extent of recovery differed substantially among agents. In FY2023, baloxavir 20-mg tablets showed the highest prescription index (351.9), followed by oseltamivir capsules/tablets (242.3) and oseltamivir powder (197.7).

In FY2024, differences in utilization patterns became more evident. Baloxavir 20-mg tablets maintained the highest prescription index (297.0), followed by oseltamivir capsules/tablets (191.6). In contrast, laninamivir recovered to levels comparable with FY2019 (100.3), whereas zanamivir remained substantially below the pre-pandemic level (57.2). Baloxavir 10-mg tablets decreased to an index of 72.2 compared with the FY2023 reference.

DISCUSSION

The present nationwide analysis demonstrated that utilization of anti-influenza agents in Japan changed following the COVID-19 pandemic. Although prescriptions of all antiviral agents markedly decreased during FY2020 and FY2021, recovery after the resumption of influenza activity differed substantially among agents. Notably, baloxavir 20-mg tablets remained nearly three times higher than the FY2019 level in FY2024, whereas zanamivir remained well below the pre-pandemic level. These findings indicate that the post-pandemic recovery of anti-influenza agent utilization differed substantially among antiviral agents.

Table 1. Prescription Volumes and Indices of Anti-Influenza Agents in Japan from FY2019 to FY2024

Drug	FY2019	FY2020	FY2021	FY2022	FY2023	FY2024
Oseltamivir (caps/tab)	13.31 (100)	0	0	6.25 (47.0)	32.24 (242.3)	25.49 (191.6)
Oseltamivir (powder)	14.70 (100)	0	0	10.66 (72.5)	29.07 (197.7)	13.77 (93.7)
Baloxavir 20-mg (tab)	2.00 (100)	0	0	0.86 (42.8)	7.04 (351.9)	5.94 (297.0)
Baloxavir 10-mg (tab)	-	-	-	-	0.09 (100)	0.06 (72.2)
Zanamivir (blister)	9.04 (100)	0.05 (0.6)	0.01 (0.2)	3.13 (34.6)	14.66 (162.0)	5.17 (57.2)
Laninamivir (kit)	4.50 (100)	0.02 (0.4)	0.01 (0.1)	1.49 (33.1)	7.91 (175.9)	4.51 (100.3)

Values are shown as actual prescription volume in millions, followed by the prescription index in parentheses. The units for actual volume are capsules/tablets for oseltamivir capsules/tablets, g for oseltamivir powder, tablets for baloxavir, blisters for zanamivir, and kits for laninamivir. Prescription indices were normalized to FY2019 (FY2019 = 100). For baloxavir 10-mg tablets, FY2023 was used as the reference (index = 100) because the FY2019 value was not available in the dataset. Values fewer than 1,000 units are masked in NDB Open Data and are shown as 0.00 (0).

The heterogeneous recovery observed among antiviral agents may reflect differences in their pharmaceutical characteristics and clinical use. Among the available antiviral agents, baloxavir is unique in that it is administered as a single oral dose and has demonstrated clinical efficacy in both otherwise healthy patients and those at high risk of influenza-related complications.[5,6] The convenience of single-dose oral administration may have contributed to its sustained utilization. In contrast, zanamivir and laninamivir require inhalation, which may limit their use in patients who have difficulty using inhalation devices. However, convenience alone is unlikely to explain the observed differences. Annual variation in circulating influenza virus types and subtypes, antiviral susceptibility, recommendations issued by professional societies, and accumulated clinical experience may also have influenced antiviral selection. In particular, recommendations concerning the cautious use of baloxavir in some pediatric populations and ongoing nationwide surveillance for antiviral-resistant viruses may have affected prescribing decisions. Nevertheless, because the present study analyzed aggregated nationwide prescription data, the contribution of each factor could not be directly evaluated.

An important strength of the present study is the inclusion of FY2024 data. Previous nationwide analyses using NDB Open Data primarily described anti-influenza utilization through FY2020, including the early phase of the COVID-19 pandemic.[3] The previous study also demonstrated that antiviral selection was not stable before the pandemic: laninamivir predominated in 2017, baloxavir rapidly became the most frequently used agent in 2018, and its share subsequently decreased in 2019. Therefore, FY2019 should be regarded as a practical reference year rather than a fixed representation of a stable pre-pandemic trend. By extending the observation period through FY2024, the present study demonstrated that post-pandemic recovery was not uniform across antiviral agents and that prescribing patterns continued to evolve beyond the initial recovery period.

The present findings have implications for understanding drug utilization in routine clinical practice. Nationwide prescription databases provide valuable opportunities to monitor long-term changes in therapeutic selection that may not be apparent from single-season surveillance. Continued monitoring will be important to determine whether the post-pandemic utilization patterns observed in FY2024 persist in future influenza seasons.

Several limitations should be acknowledged. First, NDB Open Data provides aggregated prescription data and does not include patient-level clinical information such as age, diagnosis, disease severity, vaccination status, or treatment outcomes. Second, values fewer than 1,000 units are masked in the public dataset, limiting detailed subgroup analyses. Third, annual influenza incidence was not incorporated into the present analysis. Therefore, observed changes in antiviral utilization likely reflect both fluctuations in influenza activity and changes in therapeutic selection. Fourth, information on circulating influenza virus types and subtypes, antiviral susceptibility, recommendations followed by individual prescribers, and the clinical rationale for drug selection was unavailable. Finally, because this study was descriptive, causal relationships between the COVID-19 pandemic and subsequent changes in antiviral utilization cannot be established.

Future studies integrating annual influenza surveillance, antiviral susceptibility data, and patient-level prescription information are warranted to clarify the relative contribution of epidemiological, virological, and clinical factors to post-pandemic changes in antiviral utilization.

Conflict of interest The authors declare no conflict of interest.

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