



# Comparison of Inconvenience Costs Between Influenza Antivirals for Japanese Pediatric Patients: A Conjoint Analysis of Parental Responses

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## ABSTRACT

**Introduction:** Certain drug characteristics, including dosage and form, are associated with either convenience or inconvenience for the patients taking them, and any inconvenience can be considered as a “cost” in disease treatment. Multiple antivirals are available for influenza in Japan, with various dosages and forms. This study evaluated the inconvenience costs associated with influenza antivirals for pediatric patients by using conjoint analysis on responses from their parents.

**Methods:** An online survey (May 2021) was conducted for parents whose child took antivirals for influenza at 6–11 years during the 3 years until March 2021. Attributes of the

conjoint analysis were administration routes and formulation (tablet, capsule, dry syrup, or inhalant), duration of administration, frequency of administration per day, and out-of-pocket expenses. We assumed the efficacy and safety to be equivalent among the antivirals. A logistic regression model was applied to the analysis. We also asked parents about their recent experiences with antiviral treatment for their child.

**Results:** We collected responses from 3161 eligible individuals. The mean age (standard deviation) of the children when taking the antivirals and percentage of female children were 8.27 (1.63) years old and 53.2%, respectively. The tablet was the most preferred formulation; the inconvenience costs for each administration route and formulation, relative to the tablet as zero, were Japanese yen (JPY) 515 (US dollar 4.61, as of October 2021) for the inhalant, JPY 775 for the capsule, and JPY 804 for the dry syrup. The inconvenience costs for 5 days relative to 1 day and for twice a day relative to once a day were JPY 2150 and JPY 399, respectively.

**Conclusion:** Based on the conjoint analysis, a single-dose tablet antiviral was suggested to have the lowest inconvenience cost for pediatric patients.

**Trial Registration:** UMIN000044243.

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**Keywords:** Administration route; Antivirals; Baloxavir; Conjoint analysis; Formulation; Influenza; Neuraminidase inhibitors; Online survey; Pediatric patients; Patient preference

### Key Summary Points

#### Why carry out this study?

In Japan, approximately 10 million people are infected by influenza viruses annually, including patients aged below 15 years (40–50% of all patients), and multiple antivirals with various dosages and forms are available for the treatment.

Certain drug characteristics, including dosage and form, are associated with either convenience or inconvenience for the patients taking them, and any inconvenience can be considered as a “cost” in disease treatment.

This study evaluated the inconvenience costs associated with influenza antivirals for pediatric patients among available treatments in Japan using a conjoint analysis on responses from their parents.

#### What was learned from the study?

Longer durations of administration resulted in the highest costs compared with the other attributes, and the tablet was the most preferred formulation, followed by the inhalant, the capsule, and dry syrup; a single-dose tablet antiviral was identified to have the lowest inconvenience cost for pediatric patients.

In patient-centered care, it is necessary to consider the patients’ preferences and convenience when deciding on a course of treatment; we believe these results could be helpful when choosing treatments for children with influenza.

## INTRODUCTION

Influenza viruses cause seasonal epidemics with infection rates of 10–20% worldwide [1]. These viruses often spread through coughing or sneezing and are rapidly transmitted in crowded places, including schools and nursing homes. In Japan, approximately 10 million people are infected annually, including patients aged below 15 years (40–50% of all patients) [2, 3]. Treatment with antivirals is recommended for influenza patients in Japan. Multiple antivirals, with various dosages and forms available, include neuraminidase inhibitors: oseltamivir (a capsule or dry syrup, twice daily for 5 days, hereafter called the “5-day treatment”), zanamivir (a 5-day inhalant), peramivir (intravenous for once or repeated treatment), and laninamivir (a single-dose inhalant); and a cap-dependent endonuclease inhibitor: baloxavir (a single-dose tablet) [4].

Certain drug characteristics, including dosage and form, are associated with either convenience or inconvenience for the patients taking them, and any inconvenience can be considered as a “cost” in disease treatment. The monetary value of the inconvenience costs associated with influenza antivirals, in terms of administration route and dosage, have previously been evaluated for Japanese adult patients [5]. However, the costs for pediatric patients remain unknown. Although similar antivirals are used in pediatric patients as in adult patients, there are some differences in treatment between adults and children. That is, the dosages of some antivirals vary depending on the patient’s weight and age [6, 7]. Other differences include the importance of administration route and dosage form that are associated with acceptability including palatability and affect adherence [6, 7]. A powdered drug called “dry syrup” is frequently used among children, but not adults. The fact that guardians must be involved when administering medicine to children is also an important difference. Thus, the inconvenience costs of the different types of antivirals could differ between pediatric and adult patients. Considering the possibility of such differences and the high proportion of

pediatric influenza patients, the inconvenience costs of administering antivirals to pediatric patients should be considered separately from those in adults when promoting patient-centered care.

In this study, we employed conjoint analysis to evaluate the inconvenience costs of the antivirals approved in Japan for influenza treatment in pediatric patients (6–11 years old) from the perspective of patients and their guardians. The reason for limiting the target age to 6–11 years old is that this is the age for elementary school in Japan, and that inhalation is thought to be difficult for children aged 4 years or younger [8]. We performed an online survey of patient guardians for the analysis.

## METHODS

### Study Design

We applied conjoint analysis to estimate the inconvenience costs of antivirals for influenza treatment in pediatric patients. Data for the analysis were collected through an online survey of patients' parents. Conjoint analysis is an established research method originally used in marketing research, and is increasingly utilized in the medical field to assess value from the patient's perspective [5, 9]. Moreover, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) has developed a checklist of good research practices for conjoint analysis in healthcare [10]. We assumed efficacy and safety to be equivalent among the antivirals in this study. In addition to the survey for the conjoint analysis, we surveyed the parents about their recent experiences with antiviral treatment.

### Data Source and Participants

We performed an online survey (May 20–24, 2021) using an online panel managed by INTAGE (Tokyo, Japan). The panel consisted of individuals who had registered in advance to participate in online surveys. We planned to include at least 3000 individuals as respondents,

based on a previous study [5]. Participants with children aged 6–13 years were divided into 16 blocks by their child's age and gender, and 1875 people from each block (30,000 people in total) were randomly invited to take the survey. Among those who responded, eligible respondents for the survey were selected through screening questions [questions (Q) 1–5 in Supplementary Material Table S1], as follows: individuals had to have at least one child living with them in Japan from April 2018 to March 2021, and at least one child in the household (6–11 years old) had to have taken oral (tablets, capsules, or dry syrup) or inhalant antivirals for influenza treatment during the period they lived with respondents from April 2018 to March 2021. If the respondents had multiple children meeting the above criteria, they were limited to answering only for the child who had most recently taken antivirals. Intravenous infusion antivirals, which are also available for influenza treatment, were excluded from the target antivirals. This is because intravenous infusion antivirals may be used in patients with different characteristics from those prescribed oral or inhalant antivirals, such as hospitalized patients and those with difficulty ingesting oral medication. We also excluded antivirals for prophylaxis from this study.

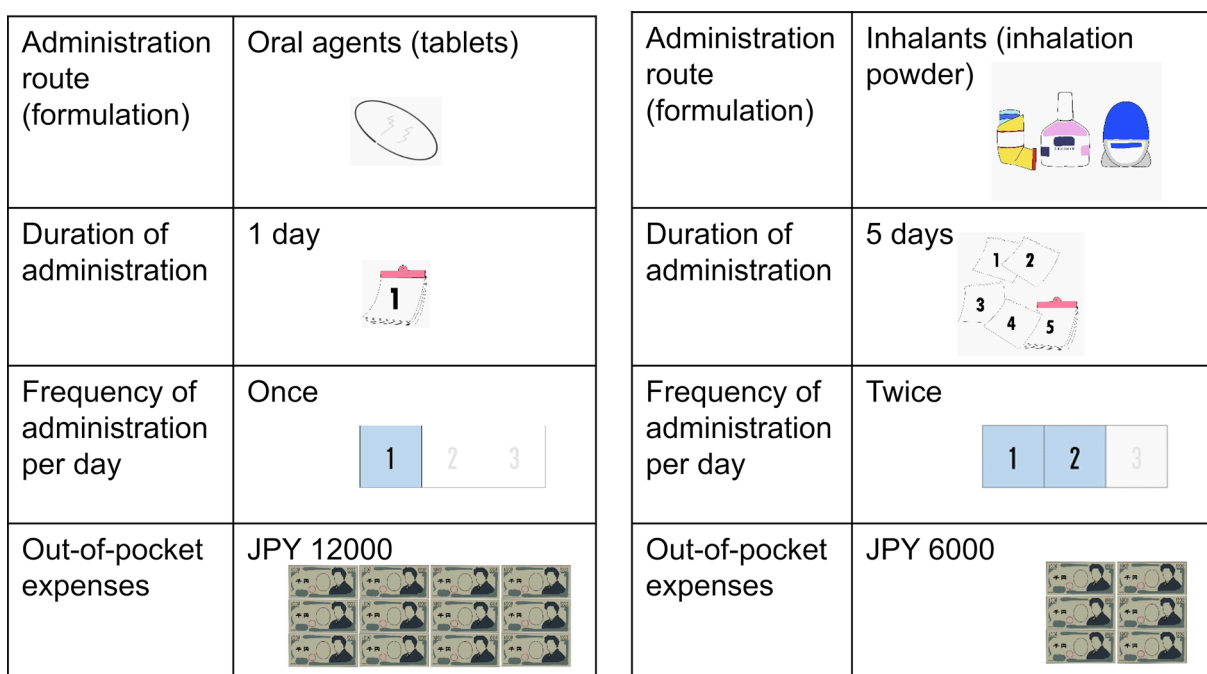
### Survey for the Conjoint Analysis

The questionnaire for the conjoint analysis used to estimate the inconvenience costs of antivirals consisted of dosage forms (administration route and formulation, duration of administration, and frequency of administration per day) and out-of-pocket expenses as attributes (Table 1). The attributes and levels were determined through a discussion between the authors, including a physician who specializes in infectious diseases and pediatrics, referring to a previous conjoint analysis of adult patients [5]. Twenty-one combinations of the attributes and levels were created from 180 possible combinations for choice tasks based on an orthogonal design (see Fig. 1 for a representative example of the choice task questions). The dosage forms including administration method and size of

**Table 1** Attributes and attribute levels in the survey for the conjoint analysis

Attribute	Level
Administration route (formulation)	Oral agents (tablet)/oral agents (capsule)/oral agents (dry syrup)/inhalants (inhalation powder)
Duration of administration	1 day/5 days/10 days
Frequency of administration per day	Once/twice/thrice
Out-of-pocket expenses	JPY 1000/JPY 3000/JPY 6000/JPY 9000/JPY 12,000

JPY Japanese yen (\$1.00 corresponded to approximately JPY 111.65 as of October 2021)



**Fig. 1** Example of the choice task questions in the discrete choice experience survey. Respondents were provided choice task questions including two treatment options in

each task and required to choose their preferred one. Each respondent completed 20 choice tasks

drug for tablets (8.5 mm long) and capsules (16 mm long) on the basis of the available antivirals were explained using pictures and text (Supplementary Material Figure S1).

Assuming that all antivirals have the same efficacy and that no financial support or health insurance is available to cover out-of-pocket medical expenses (Supplementary Material Fig-

ure S1), respondents were randomly provided with two treatment options and asked, “If your child is prescribed antiviral drugs for influenza, which drug do you think is preferable?” Respondents were required to choose which option they preferred. Respondents were each given 20 choice tasks.

## Survey of Drug Administration Status

Respondents were then asked about their experiences the last time their children were given antiviral treatment, including the child's age at the time of treatment, drug type and dosage, adherence, difficulty respondents had making their children take the drugs, number of days until the fever resolved, number of days until normal activities were resumed (e.g., attending school), number of days respondents took off work to take care for their child (or if respondents did not work outside the home, the number of days in which housework was disrupted), presence or absence of transmission within the household, presence or absence of financial support for health expenditure, experience of using inhalant agents for asthma or other diseases, and family composition. The options for type and dosage were based on the available antivirals in Japan. These include five types: (1) a single-dose tablet, (2) a 5-day capsule treatment, (3) a 5-day dry syrup treatment, (4) a 5-day inhalant, and (5) a single-dose inhalant treatment. The actual questions are listed in Supplementary Material Table S1.

## Statistical Analysis

The utility of each level for each attribute was estimated using a logistic regression model in the conjoint analysis. This model reveals the hidden utility behind each level of each attribute through inverse estimation based on each choice made in the choice task. The utility was assumed to be the same among the respondents in this model. Non-monetary utility was converted to a monetary equivalent by comparing the same utility of the linearly interpolated level of the monetary attribute (out-of-pocket expenses). The costs were estimated using 95% confidence intervals (CIs).

The answers to the questions about respondents' most recent experiences giving antiviral medicine to their children were tabulated by the type of antiviral used. We calculated the mean and 95% CIs for each question, and compared the mean values of the different types of antivirals. As we assumed that there were no

confounding effects among the antiviral choices and answers to the questions, we did not adjust for confounding factors.

We further calculated the per-patient total drug and inconvenience costs of influenza treatment for each antiviral available in Japan to support an interpretation of the results. The dosage of some drugs depend on patient age or weight, so the drug costs were calculated considering patient age and body weight, which was calculated by age and gender in our survey, based on government statistics [11]. A detailed description of the method used to calculate the drug costs is described in Supplementary Material Method S1. The inconvenience costs for each antiviral were calculated based on the estimated cost by conjoint analysis for each level of each attribute corresponding to each antiviral. No confounding factors were assumed for treatment choice among the respondents in this calculation. We additionally calculated the total costs including guardian productivity loss, which was calculated based on the number of days off the respondents took. The productivity loss was calculated by applying an average wage of JPY 10,116 per day across all industries, all ages, and both genders in Japan [12] to the number of days off, which is according to the Japanese Guideline for Cost Effective Evaluation [13].

MS Excel 2016 (Microsoft, Redmond, WA, USA) and SAS v.9.4 (SAS Institute, Cary, NC, USA) were used for the analyses.

## Ethics Statement

We performed the study in accordance with the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects by the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare [14], as well as the checklist of good research practices for conjoint analysis by the ISPOR [10]. Informed consent was obtained from all respondents online. The study was approved by the Ethics Committee of the Research Institute of Healthcare Data Science (RI2020032) and registered with the University Hospital Medical

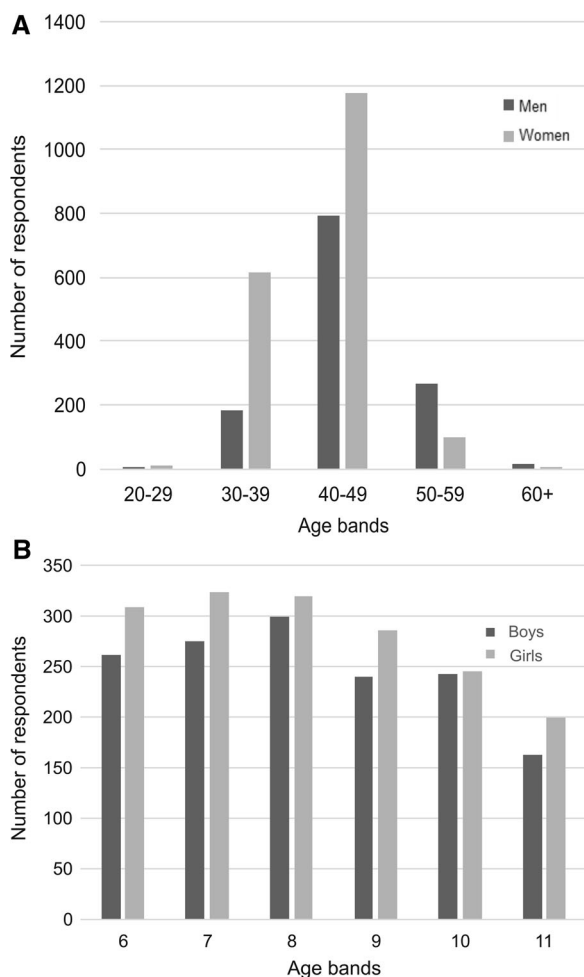


Information Network Clinical Trial Registry (UMIN000044243).

## RESULTS

### Respondents

We collected answers from 3161 eligible individuals. The attributes of the respondents are shown in Fig. 2A (age and gender distribution) and Supplementary Material Table S2 (other information). The mean age [standard deviation (SD)] of the children when taking the antivirals and percentage of female children were 8.27



**Fig. 2** Age and gender distribution of **A** respondents and **B** their children who took antiviral drugs (age when taking the drugs)

(1.63) years old and 53.2%, respectively (Table 2; see Fig. 2B for the distribution by age–gender bands). Table 2 shows the number of children taking each type of medicine. Most respondents’ children took the single-dose inhalant, followed by the single-dose tablet, 5-day inhalant treatment, 5-day dry syrup treatment, and 5-day capsule treatment (Table 2). The treatment with the youngest mean (SD) age was the 5-day dry syrup at 7.38 (1.47) years and the treatment with the oldest mean age was the 5-day inhalant at 8.56 (1.59) years (Table 2).

Despite the availability of financial support for children’s health expenditure in all prefectures and local governments in Japan [15], only 41.1% of the respondents answered that they received support for the full price of the treatment and 32.2% answered that they received no support (Supplementary Material Table S3).

### Utility Costs of Antivirals Based on the Conjoint Analysis

Higher out-of-pocket expenses, a longer duration of administration, and more frequent administration per day contributed to a larger negative utility in the conjoint analysis (Table 3; Fig. 3). The largest difference in utility between the attributes, aside from out-of-pocket expenses, was shown in the duration of administration. Among the administration routes and formulations, tablets were the most preferred, followed by inhalant, capsule, and dry syrup. The costs of each administration route and formulation in Japanese yen (JPY), with reference to the tablet as JPY 0, were calculated as JPY 515 for the inhalant, JPY 775 for the capsule, and JPY 804 for dry syrup (Table 3).

### Administration Status Based on the Survey

The mean percentage of adherence was more than 90% for all the types of antivirals (Supplementary Material Table S4). The percentage was the lowest (94.4%) for the 5-day dry syrup treatment and the highest for the single-dose inhalant (99.4%). The percentage of the respondents who answered “No” to the

**Table 2** Demographics of the respondents' children who took antiviral medication by drug type and dosage

	Total	Oral tablet Single dose	Oral capsule 5-day dose	Oral dry syrup 5-day dose	Inhalant 5-day dose	Inhalant Single dose	Not sure
Total ( <i>n</i> )	3161	486	346	366	425	897	641
Age at taking antivirals (mean)	8.27	8.33	8.43	7.38	8.56	8.54	8.06
Age at taking antivirals (SD)	1.63	1.66	1.62	1.47	1.59	1.57	1.60
Female (%)	53.2%	50.2%	52.0%	49.7%	51.8%	56.2%	54.8%

*SD* standard deviation

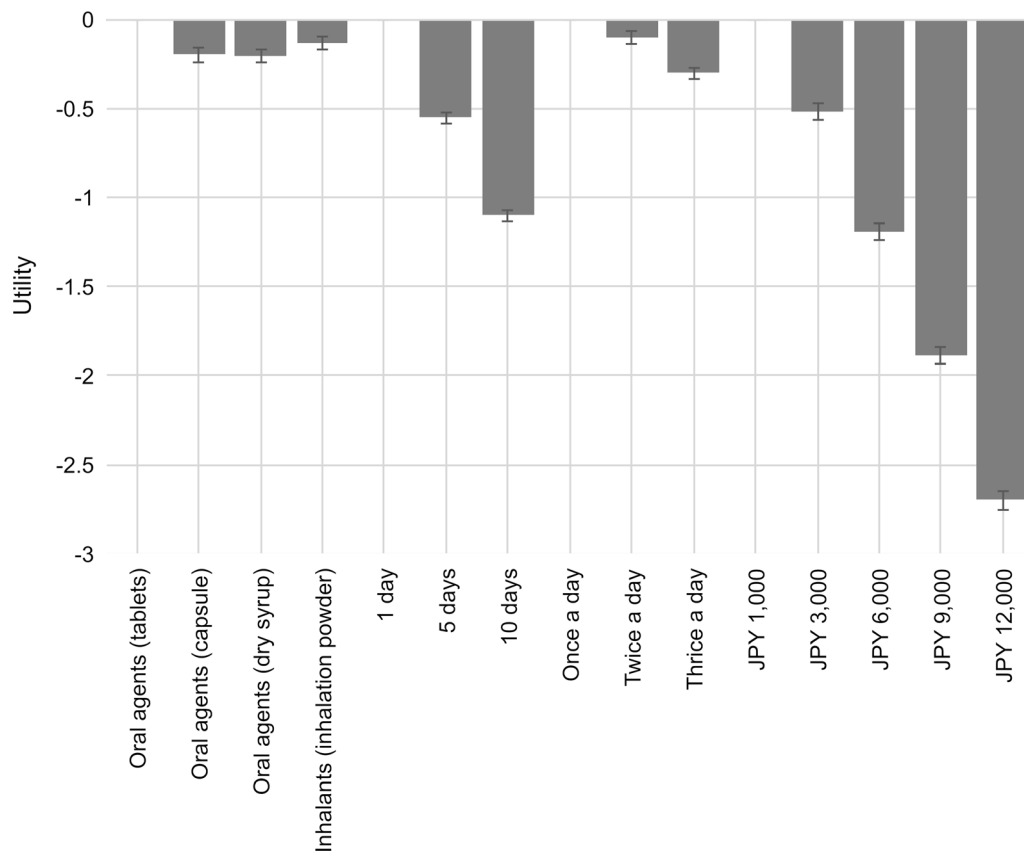
**Table 3** Utility and cost of each level for each attribute

Attribute	Level	Utility			Cost		
		95% CI			95% CI		
Administration route (formulation)	Oral agents (tablet)	0.000	0.000	0.000	¥0	¥0	¥0
	Oral agents (capsule)	− 0.201	− 0.163	− 0.238	¥775	¥630	¥919
	Oral agents (dry syrup)	− 0.208	− 0.172	− 0.244	¥804	¥666	¥943
	Inhalants (inhalation powder)	− 0.133	− 0.097	− 0.169	¥515	¥376	¥653
Duration of administration	1 day	0.000	0.000	0.000	¥0	¥0	¥0
	5 days	− 0.552	− 0.519	− 0.584	¥2150	¥2004	¥2296
	10 days	− 1.104	− 1.068	− 1.140	¥4615	¥4455	¥4775
Frequency of administration per day	Once	0.000	0.000	0.000	¥0	¥0	¥0
	Twice	− 0.103	− 0.070	− 0.137	¥399	¥270	¥529
	Thrice	− 0.304	− 0.271	− 0.337	¥1173	¥1045	¥1300
Out-of-pocket expenses	¥1000	0.000	0.000	0.000			
	¥3000	− 0.518	− 0.475	− 0.561			
	¥6000	− 1.190	− 1.146	− 1.235			
	¥9000	− 1.888	− 1.843	− 1.933			
	¥12,000	− 2.696	− 2.644	− 2.748			

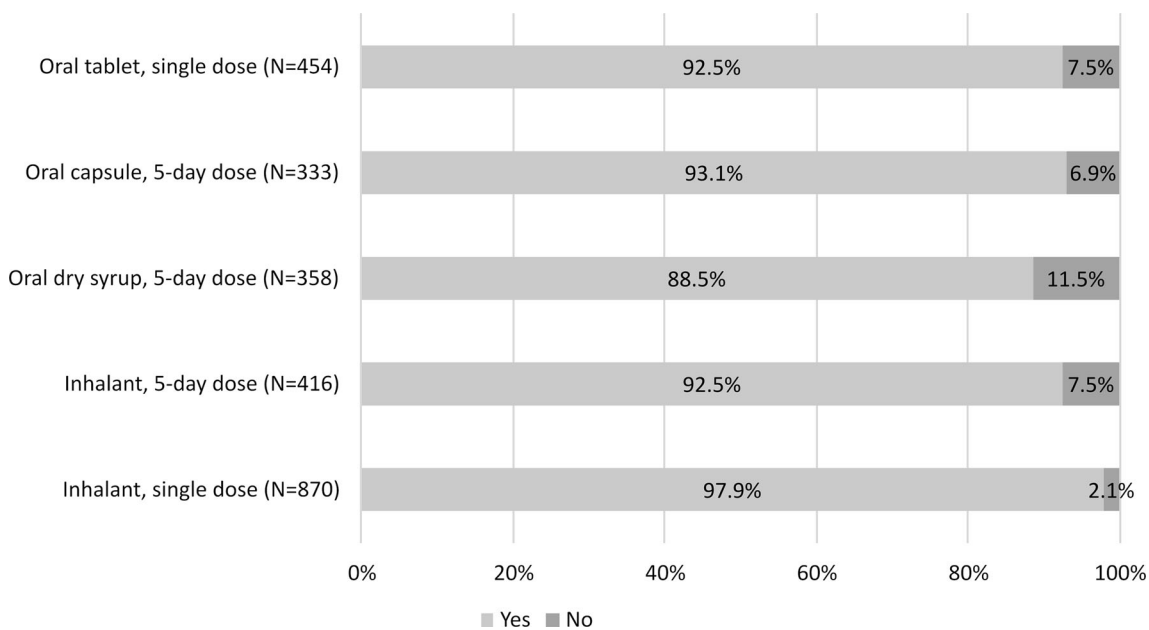
*CI* confidential interval

question of whether the child took all medicine as instructed was the largest for the 5-day dry syrup treatment (11.5%) (Fig. 4). Among the respondents who answered “No” to the above question, dry syrup had a larger percentage of

the respondents whose children took less than 20% of the drugs compared with the other 5-day antiviral treatments (Supplementary Material Figure S2).

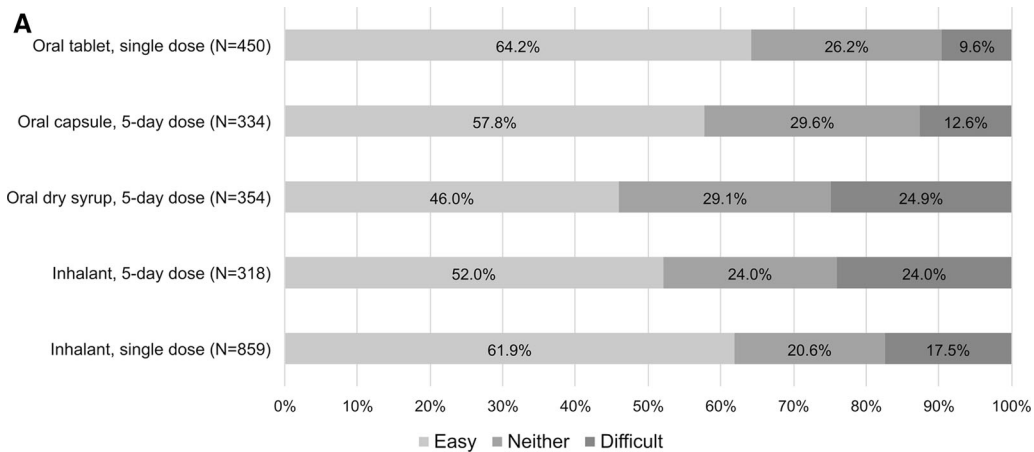


**Fig. 3** Utility of each variable. Error bars represent the 95% confidence intervals



**Fig. 4** Whether the child took all drugs as instructed (answer to Q8: “Did your child take all of her/his medicine as instructed?”) by drug type and dosage





**Fig. 5** Difficulty in taking the drug (answer to Q10: “Was it easy for your child to take the antiviral last time?”) (A) and the reasons for the difficulty (answer to Q11: “Why did you answer ‘Neither’ or ‘No’ to Q10 regarding

whether it was easy for your child to take the antiviral last time?”) (B) by drug type and dosage. Multiple choices were allowed. Denominator: all respondents, according to drug type and dosage

Regarding the difficulty in making their children take the antivirals, the respondents who used the 5-day dry syrup treatment had the highest percentage (46.0%) of those who answered that it was difficult, and the lowest percentage (24.9%) of those who answered that it was easy (Fig. 5A). Inhalants had the second highest rate of those who answered that it was difficult, and the percentage was higher for the 5-day treatment (24.0%) than the single dose (17.5%). We further investigated whether the difficulty in making children take inhalants was different for children who had previously experienced inhalant use due to asthma or other diseases (Supplementary Material Figure S3). Almost no difference was observed in the percentage of the respondents who answered that the single-dose inhalant was easy to take (63.6% vs. 61.9%); however, the percentage of those who answered that it was difficult was lower for children with experience (10.9%) than for those in the entire group (17.5%). In the 5-day inhalant treatment, the percentages of the respondents who answered that it was easy or difficult were almost the same between the subgroups, including those with experience and the entire group: 50.0% for the subgroup with experience vs. 52.0% for the entire group for easy and 25.0% vs. 24.0% for difficult.

The reasons the respondents had difficulty making their children take the antivirals are

shown in Fig. 5B. Among the oral drugs, the most common reason was that it was hard for the child to swallow the tablet (16.3%) or capsule (21.7%), whereas the children disliked the taste of dry syrup (38.3%). For the 5-day inhalant, coughing or choking was the most common problem (17.9%), followed by the taste being disliked (16.2%), and some found that it was difficult for the child to use the inhalant kit (13.2%). For the single dose, the most common problem was that the child had difficulty using the inhalant kit (15.5%), followed by coughing or choking (13.6%).

The mean (95% CIs) and median number of days until fever resolution after the initiation of the antiviral treatment was 2.18 (2.15–2.22) (Supplementary Material Table S5) and 2, respectively. By type of antiviral, the single-dose antivirals showed a smaller mean number of days, 2.07 (1.98–2.16) for the tablet and 2.06 (1.99–2.12) for the inhalant, than the 5-day antiviral treatments, 2.34 (2.24–2.45) for the capsule, 2.33 (2.23–2.42) for the inhalant, and 2.24 (2.14–2.34) for dry syrup (Supplementary Material Table S5). The percentage of the respondents who said that their child’s fever resolved within 1 day was approximately 30% for the single-dose drugs (both the tablet and the inhalant), which was higher than that for the 5-day drug treatments (approximately 20%;

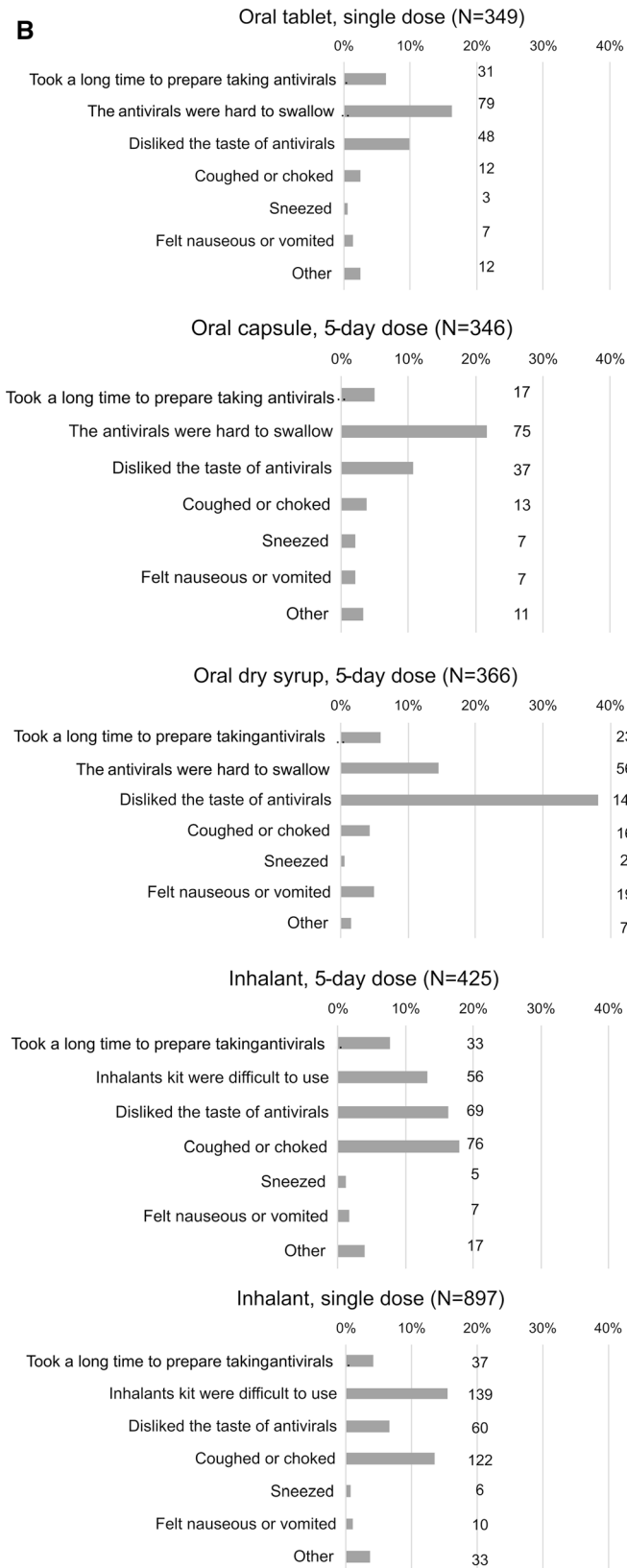
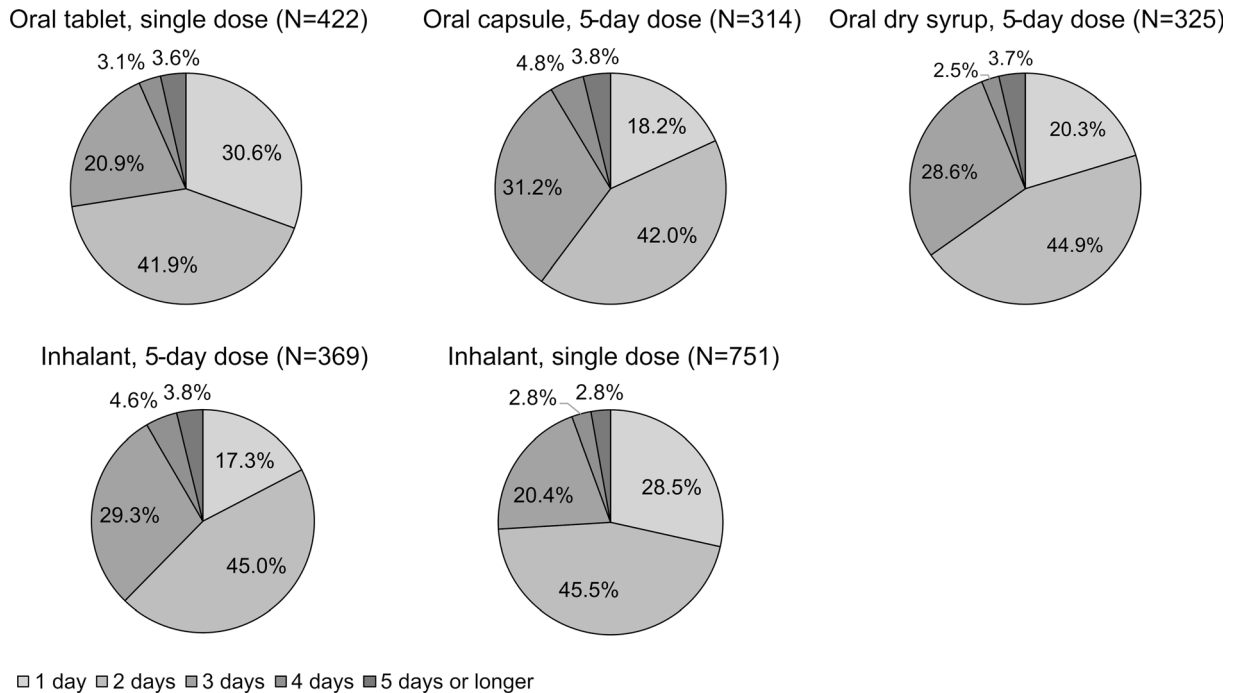


Fig. 5 continued



**Fig. 6** Number of days before fever resolved after beginning antivirals (answer to Q12: “The last time your child took antiviral medication for influenza, how long did

it take for your child’s fever to break after the first dose?”) by drug type and dosage

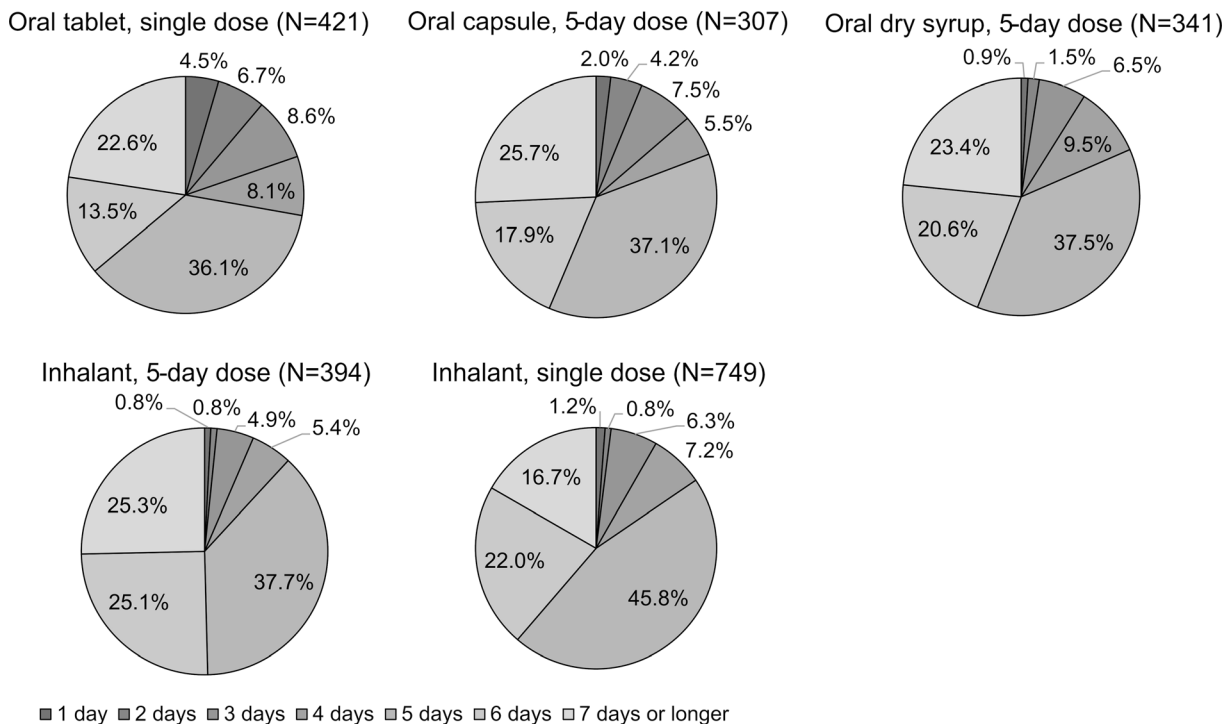
Fig. 6). Regarding the time until returning to normal life, the mean (95% CIs) and median number of days were 5.29 (5.23–5.34) (Supplementary Material Table S6) and 5, respectively. The mean number of days was the lowest for the single-dose tablet, 4.95 (4.80–5.11), compared with the single-dose inhalants, 5.28 (5.20–5.37), and 5-day drug treatments, 5.28 (5.12–5.45) for the capsule, 5.55 (5.43–5.67) for the inhalant, and 5.37 (5.23–5.51) for dry syrup (Supplementary Material Table S6). In addition, the single-dose tablet had the highest percentage of the respondents who answered that it took 1–4 days to return to normal life compared with the other types of drugs (Fig. 7).

For the respondents themselves, the mean (95% CIs) and median numbers of days taken off to care for their children were 2.56 (2.47–2.65) (Supplementary Material Table S7) and 2, respectively. By type of drug, the mean number of days was the shortest for the single-dose inhalant, 2.43 (2.27–2.59), and the longest for the 5-day dry syrup treatment, 2.93 (2.68–3.19). The inhalant treatments had

higher percentage of the respondents who answered that they did not take off to take care for their children than oral treatments (Fig. 8). We also asked the respondents whether the transmission of influenza occurred in their household. Those who answered “Yes” accounted for 34.9% of all the respondents. This number was the smallest for the 5-day inhalant (32.2%) followed by the 5-day capsule (33.7%), single-dose tablet (33.8%), 5-day dry syrup (38.0%), and single-dose inhalant treatments (38.1%) (Supplementary Material Table S8).

### Estimated Total Costs of Treatment for Each Antiviral

We compared the estimated total costs of treatment for available antivirals (Table 4). It is noted that the inconvenience costs were calculated from the estimated costs for each level of each attribute using the conjoint analysis, and the cost of each level was calculated as the difference in value from that of tablets for administration route and formulation: 1 day for



**Fig. 7** Number of days to return to normal life after beginning antivirals (answer to Q13: “The last time your child took antiviral medication for influenza, how long did

it take to return to your child’s normal life (attending school) after the first dose?”) by drug type and dosage

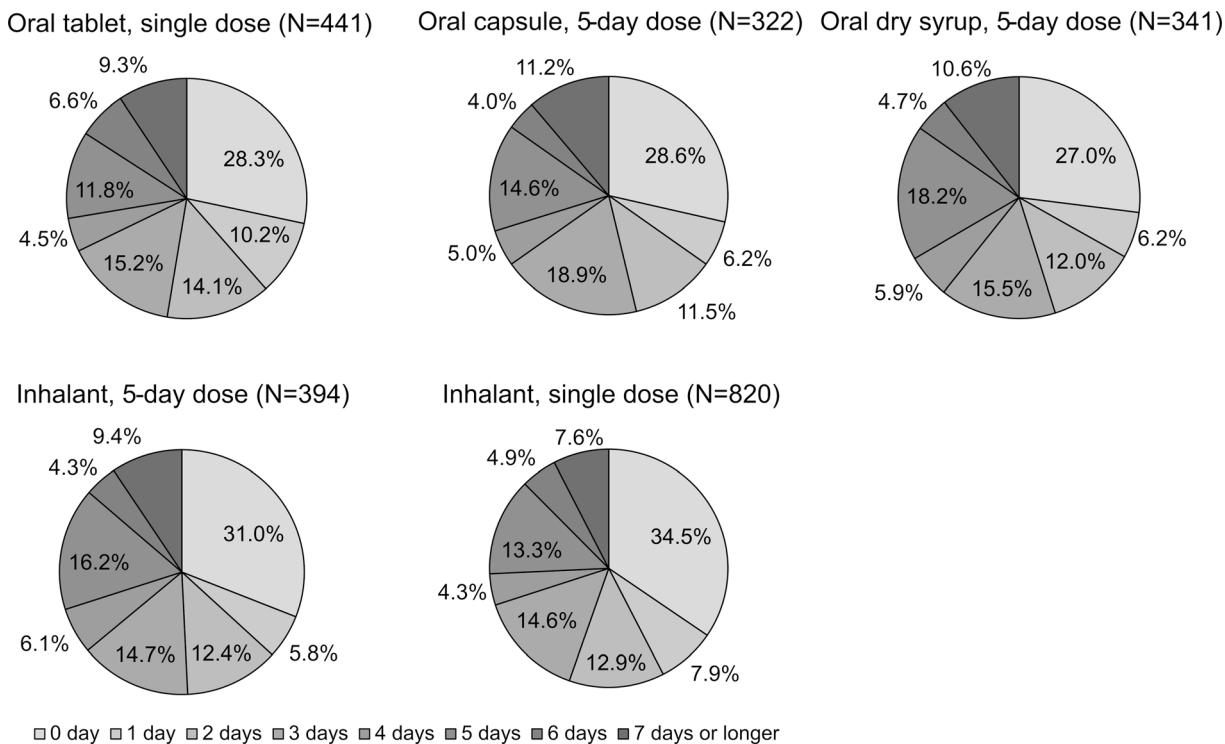
duration of administration, or once a day for frequency of administration per day as shown in Table 3. Therefore, the inconvenience costs for baloxavir (oral tablet, 1 day and once a day) were calculated to be JPY 0, and the costs for each drug were calculated as the difference from those for baloxavir. The total costs were the lowest for baloxavir, although the drug costs were the lowest for the generic drugs, oseltamivir capsule and dry syrup (Table 4, see Supplementary Material Table S9 for the costs by age group). When adding guardian productivity loss, the costs were the lowest for laninamivir followed by baloxavir, and the costs of these drugs were lower than those of the generic drugs (Supplementary Material Tables S10 and S11).

## DISCUSSION

We estimated the inconvenience costs associated with treating pediatric influenza patients

with antivirals by dosage and form using conjoint analysis. Longer durations of administration resulted in the highest costs compared with the other attributes. The tablet was the most preferred formulation, followed by the inhalant, the capsule, and dry syrup. To the best of our knowledge, this is the first study to evaluate the preferences and inconvenience costs of antivirals, by dosage and treatment form, for pediatric patients.

Different preferences were observed among the oral drugs; capsules and dry syrup were less preferred, whereas tablets were preferred over inhalants. While the administration route, oral and inhalant, has been compared in a previous study for adults [5], the current study also looked at the type of formulation in addition to administration route, because formulation is considered an important factor affecting acceptability in pediatric patients [6, 7, 16–18]. One of the reasons for the higher preference for tablets than capsules may be associated with its size, which was set smaller for the tablet than



**Fig. 8** Number of days taken off work to care for a child with influenza (answer to Q14: “How many days did you have to take off work to take care of your child with

influenza? If you do not work outside the home, how many days was your housework affected by taking care of your child?”) by drug type and dosage

the capsule in this survey based on available antivirals in market. The size of oral drugs is reportedly an important factor when choosing treatments for children [7, 17, 18], which is associated with higher preference for tablet in previous reports from Japan [18] and the United Kingdom [17]. Our survey results indicate that difficulty swallowing the drug was the most frequent reason children had trouble taking both capsules and tablets and the percentage was larger for capsules than for tablets (21.7% vs. 16.3%). Other than the size, we speculate, based on an author’s clinical experience, that the preference for tablets might be related to their resemblance to a type of candy (“ramune candy”) common in Japan, a resemblance that can be referred to when introducing the medicine to children, making them feel familiar with the tablets. We also speculate that capsules may be difficult for children to become comfortable with because of their taste, which returns to bitter when held in the mouth. Contrary to

our assumption prior to the survey, dry syrup was the least preferred alternative in this study. Notably, the results from the conjoint analysis, which were based on choice tasks, were consistent with the experiences of difficulty in making children take the antiviral reported in the questionnaire survey: dry syrup had the highest number of being reported as difficult to administer and the lowest for being reported as easy. The top reason for the difficulty was the taste, which was reported by almost 40% of the respondents who used dry syrup in our survey. Although dry syrup itself can be used as a liquid preparation regardless of age [6, 7, 16], taste is also a crucial factor that impacts adherence [6, 7, 16]. While flavoring is often added to dry syrup to mask the original taste, the flavor might still be unacceptable or unpleasant to some patients.

The higher impact of a longer treatment duration than frequent administration per day for pediatric patients is the same as that seen in

**Table 4** Estimated total drug and inconvenience costs per patient for the treatment of influenza with the available antivirals in Japan

	<b>Baloxavir Oral tablet, single dose</b>	<b>Oseltamivir Oral capsule, 5-day dose</b>	<b>Oseltamivir (generic) Oral capsule, 5-day dose</b>	<b>Oseltamivir Oral dry syrup, 5-day dose</b>	<b>Oseltamivir (generic) Oral dry syrup, 5-day dose</b>	<b>Zanamivir Inhalant, 5-day dose</b>	<b>Laninamivir Inhalant, single dose</b>
1) Drug cost	¥2442	¥2557	¥1196	¥2827	¥1381	¥2806	¥2887
2) Total inconvenience costs	¥0	¥3324	¥3324	¥3353	¥3353	¥3064	¥515
Administration route (formulation)	¥0	¥775	¥775	¥804	¥804	¥515	¥515
Duration of administration	¥0	¥2150	¥2150	¥2150	¥2150	¥2150	¥0
Frequency of administration per day	¥0	¥399	¥399	¥399	¥399	¥399	¥0
1 + 2	¥2442	¥5881	¥4520	¥6180	¥4735	¥5870	¥3401
Difference from baloxavir	¥0	¥3438	¥2077	¥3738	¥2292	¥3427	¥959

Inconvenience costs were calculated based on the estimated inconvenience cost for each level of each attribute (Table 3) corresponding to each antiviral. The estimated inconvenience cost was calculated as the difference in value from reference level

adult patients in a previous study (Table 5) [5]. The value of costs was also similar between adult and pediatric patients for all the attributes: that is, the costs for 10 days compared with 1 day were JPY 4615 for children and JPY 4172 for adults, and those for the thrice a day compared with once a day were JPY 1173 and JPY 1129, respectively. Although the preference for administration route was different, the range of costs was similar: JPY 804 for children and JPY 741 for adults. These results suggest that the respondents evaluated the inconvenience costs of antivirals equally for their children and for themselves.

Regarding administration status, adherence was high (approximately 90%), regardless of the dosage form. Dry syrup showed the lowest adherence and had many respondents who

answered that below 20% of the prescribed drugs were taken compared with the other types of drugs. These results correspond to the lowest preference shown in the conjoint analysis as well as the difficulty respondents had making their children take it. Moreover, dry syrup had the lowest mean patient age, probably due to its acceptability of form for children with younger age [6, 7, 16], which may have contributed to the lowest adherence.

Inhalants had the second highest percentage of answers stating it was difficult to make the child take the medicine. This answer was more frequently given for the 5-day dose than for the single dose, and there were few difference in the reasons for difficulty between the two treatment lengths. The difference in difficulty might be associated not only with the differences in



**Table 5** Utility and cost of each level of each attribute for adult patients [5]

Attribute	Level	Cost	95% CI	
Administration route (formulation)	Oral	¥0	¥0	¥0
	Inhalants	¥741	¥652	¥830
Duration of administration	1 day	¥0	¥0	¥0
	5 days	¥2072	¥1967	¥2177
	10 days	¥4172	¥4056	¥4288
Frequency of administration per day	Once	¥0	¥0	¥0
	Twice	¥574	¥462	¥686
	Thrice	¥1129	¥1021	¥1237

CI confidential interval

dosage but also with the differences in the inhalant kit; taste might also be associated with the difference. The suitability of the device to inhale the drug as well as palatability, including smell, taste, aftertaste, and texture, are mentioned as important elements that affect preference for inhalants [7]. In addition, we speculate, based on an author's clinical experience, that pediatricians may usually assume that their patients will not be able to inhale the drug properly the first time. Consequently, they tend to prescribe a 5-day treatment over the single dose when prescribing inhalants to patients without inhaler experience to minimize the risk of losing the drugs. Thus, less experienced patients taking inhalants might be more likely to be prescribed a 5-day treatment than a single-dose inhalant. Another possibility related to the higher adherence and lower difficulty with single-dose inhalants is that the single-dose drug is often inhaled at the pharmacy. Considering these reasons, the differences in adherence and difficulty between single-dose and 5-day inhalants seem reasonable. Previous experience using inhalants to treat other diseases might contribute to reducing the difficulty in taking inhalant antivirals, which was observed in those who took single-dose inhalants.

The mean numbers of days until fever resolution (approximately 2 days) and until

returning to normal life (approximately 5 days) from the initiation of the antivirals are reasonable when considering previous reports as well as regulation in Japan. Although a significant difference was observed among types of influenza viruses, the number of days until fever resolution is reportedly within 2 days from treatment initiation for Japanese pediatric patients, regardless of the type of antiviral [19–21]. Students developing influenza are suspended from school for 5 days after the onset of influenza and 2 days (or 3 days for infants) after fever resolution [22, 23]. Although no adjustments were made for confounding factors, and the difference was not very large, the period until fever resolution was shorter for the single-dose antivirals (both the tablet and the inhalant), while for the single-dose tablet, the time taken to return to normal life was the shortest. A similar tendency was observed in a survey of adult patients [5]. The administration period itself might cause recall bias; the respondents associated with the shorter administration period might recall the recovery length to be shorter. Patients may also tend to make their child stay home from school while taking the prescribed medicine, regardless of the symptoms. Even so, the time it took to return to normal life was similar between the single-dose and 5-day inhalants.

The mean number of days off respondents had to take to care for their children was 2.56 days, indicating that parents took time off work until their children's fevers resolved, but not until their children returned to normal life, including attending school. This duration might be associated with various factors such as patient age, the number of guardians living together, and the existence of infections within the household in addition to treatment effects.

When calculating the inconvenience costs of each available antiviral based on the estimated cost for each level of each attribute and level by the conjoint analysis, the difference in inconvenience costs was greater than the difference in drug costs in some comparisons (Table 4). As the results, although the drug costs were the lowest for the generic drugs, oseltamivir (capsule or dry syrup), the total costs by adding the inconvenience costs to the drug costs were the lowest for baloxavir among the available antivirals. The costs including guardian productivity loss was the lowest for laninamivir followed by baloxavir. Notably, no confounding factors were assumed for treatment choice among the respondents.

This study has several limitations. First, it is based on an online survey using an online panel, so the respondents were limited to those within the panel, which affects the generalizability of the results. Notably, the panel includes a nationwide sample of people with a variety of attributes, and the respondents in this study included people with various occupations and from all prefectures in Japan, as shown in Supplementary Material Table S2. Second, the reliability of the results depends on whether the respondents accurately understood the questions and to what extent they answered the questions truthfully. In particular, the survey about administration status asked about their past experience, so the respondents may not have accurately recalled the experience when answering. For example, they might have remembered a treatment used for a separate illness or combined multiple experiences, including different types of antivirals or experiences with another child, although the survey was limited to only the most recent experience with one child. The results could also be

affected by recall bias, as mentioned above, when discussing the duration and dosage of antivirals. Moreover, the relatively high percentage of the respondents who answered that they did not receive any financial support for health expenditure suggests that respondents misunderstood the question or remembered incorrectly. Third, although respondents in the conjoint analysis should be chosen regardless of experience to secure generalizability, only those who had a child who had taken antivirals for influenza treatment were included in this study. Even so, influenza is a common disease and most patients with influenza, including pediatric patients, are prescribed antivirals for treatment in Japan [2, 24]; therefore, we consider the impact of limiting the respondents to be small. Finally, we aggregated the data about experiences with antiviral intake by dosage and drug form and compared the results assuming no confounding effects among the choice of antiviral and answers to the questions. Consequently, confounding factors were not adjusted for in this analysis.

## CONCLUSIONS

From our comparison of different formulations and dosages, we found that the treatment with the lowest inconvenience cost for pediatric patients was the single-dose tablet. The amount of inconvenience costs was similar to that in a previous study of adult patients. Baloxavir had the lowest cost among the antivirals available in Japan in terms of drug and inconvenience costs combined. In patient-centered care, it is necessary to consider the patients' preferences and convenience, including those of pediatric patients, when deciding on a course of treatment. We believe these results could be helpful when choosing treatments for children with influenza.

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**Compliance with Ethics Guidelines.** This study was performed in accordance with the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects by the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare. The study was approved by the Ethics Committee of the Research Institute of Healthcare Data Science (RI2020032) and registered with the University Hospital Medical Information Network Clinical Trial Registry (UMIN000044243). Informed consent was obtained from all respondents online.

**Data Availability.** The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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