Annals of Clinical Epidemiology 2022;4(4):120–128

Annals of Clinical Epidemiology

ORIGINAL ARTICLE

Maoto plus neuraminidase inhibitor versus neuraminidase inhibitor alone for reducing hospitalization in older adults with seasonal influenza

Hayato Yamana[1], Yusuke Sasabuchi[2], Hiroki Matsui[2,3], Nobuaki Michihata[1], Taisuke Jo[1], Hideo Yasunaga[2,3]

ABSTRACT

BACKGROUND

Maoto is a Japanese Kampo formula used for treating febrile illnesses. However, researchers have not yet clarified its effect in preventing severe influenza among older adults. We evaluated the association between the addition of maoto to a neuraminidase inhibitor in older adults and reduced hospitalization following influenza.

METHODS

Using a prefecture-wide health insurance claims database, we identified outpatients aged ≥60 years who were diagnosed with influenza between September 2012 and August 2017. We performed one-to-one propensity score matching between patients who received maoto in addition to a neuraminidase inhibitor and those who received a neuraminidase inhibitor alone. Hospitalization within 7 days of influenza diagnosis was compared using the McNemar's test. We performed subgroup analyses based on sex, age, and other characteristics.

RESULTS

We identified 57,366 eligible patients with influenza. Maoto was used in 8.1% of these patients. In 4,630 matched pairs, the 7-day hospitalization rate was 1.77% (n = 82) and 1.62% (n = 75) for patients with and without maoto, respectively; the difference between the groups was insignificant (P = 0.569). Subgroup analysis showed a tendency toward more hospitalizations within 7 days among patients aged 90 years or older who were prescribed maoto than those who were not (9.7% vs. 6.6%, P = 0.257).

CONCLUSIONS

Maoto use was not associated with decreased hospitalization rates in older adults with influenza. This warrants further research to evaluate the safety and effectiveness of maoto in different patient groups, particularly the oldest-old population.

KEY WORDS

complementary therapies, database, human influenza, Kampo medicine

[1] Department of Health Services Research, Graduate School of Medicine, The University of Tokyo
[2] Data Science Center, Jichi Medical University
[3] Department of Clinical Epidemiology and Health Economics, School of Public Health, The University of Tokyo

Corresponding author: Hayato Yamana
Department of Health Services Research, Graduate School of Medicine, The University of Tokyo. 7-3-1 Hongo, Bunkyo, Tokyo 113-0033, Japan
E-mail: yamana@m.u-tokyo.ac.jp

Received: March 1, 2022
Accepted: April 25, 2022
J-STAGE Advance published date: July 8, 2022

No. 22015

INTRODUCTION

One billion cases of influenza were estimated to occur annually worldwide before the coronavirus disease 2019 pandemic [1, 2]. There were 3–5 million severe influenza cases and 290,000–650,000 influenza-associated deaths annually [2, 3]. Non-pharmaceutical health measures for coronavirus disease 2019 may have exceptionally decreased influenza epidemics in recent times [4–7]. However, the threat of influenza persists. According to a simulation study, outbreaks larger than those during the pre-pandemic period can occur after relaxing the non-pharmaceutical interventions, depending on the transmission rate and susceptibility dynamics [8].

Maoto is a traditional Japanese Kampo formula used for treating febrile illnesses. It is prepared from ephedra herb, glycyrrhiza root, apricot kernel, and cinnamon bark, and is approved for prescription under the Japanese health insurance system. In vitro and in vivo studies have reported the effects of maoto's components in inhibiting the growth of influenza virus [9–14]. In addition, several small-scale clinical studies have evaluated the effect of maoto in alleviating influenza symptoms [15–18]. Researchers have reported an association between the addition of maoto to a neuraminidase inhibitor (NAI) and a reduction in the duration of fever [19].

However, there is limited evidence for the prevention of severe influenza by maoto. Previous studies were underpowered to detect complications or hospitalizations. According to a large-scale study using a health insurance claims database, the addition of maoto to an NAI was not associated with decreased hospitalization among patients younger than 60 years [20]. Nevertheless, the effect of maoto in older adults remains unclear. Maoto may be effective in older patients at an increased risk of severe influenza. Conversely, the cardiovascular effects of ephedrine and glycyrrhizin in maoto may harm older adults.

This study aimed to evaluate the association between the addition of maoto to an NAI and hospitalization among older adults following influenza. We utilized a population-based database of the health insurance claims data in Japan and conducted a propensity score-matched analysis.

METHODS

DATA SOURCE

We conducted a retrospective observational study using the database of anonymized health insurance claims data of the Kumamoto Prefecture's residents. Kumamoto is located in the southwestern region of Japan, and has a population of approximately 1.8 million. Data were obtained from the National Health Insurance and Late Elders' Health Insurance. The National Health Insurance is a community-based health insurance plan for residents aged <75 years, which covers the self-employed, irregularly employed, or pensioners. The Late Elders' Health Insurance is for people aged ≥75 years. We obtained data of all enrollees of the two health insurances in Kumamoto Prefecture to construct a database of approximately 800,000 residents.

The database contains the years and months of birth. All medical claims data on health insurance-covered outpatient, inpatient, and pharmacy services are recorded in it. Diagnoses are based on the International Classification of Diseases, 10th Revision codes and Japanese standardized diagnosis codes. Whether the diagnosis was suspected or confirmed and the date of treatment commencement for each diagnosis are also recorded. Drugs are classified according to the Anatomical Therapeutic Chemical Classification System codes and Japanese codes for reimbursement. Moreover, the type and amount of drugs and the date and institution of prescription are recorded. The database also records the procedures and their provision dates according to the Japanese codes for reimbursement.

PARTICIPANTS

We identified outpatient diagnosis records of confirmed influenza cases (International Classification of Diseases, 10th Revision codes J10 or J11) between September 2012 and August 2017. We included patients aged ≥60 years. For each patient, the earliest day within each 1-year period (September to August) that treatment for influenza started was considered the index date. We excluded second or later episodes for each patient within a 1-year period from the analysis, whereas multiple reports of a single patient in different years were separately recorded. Following a previous study [20], we required the patients to undergo an antigen test for influenza on the index date. Patients who were hospitalized on the index date were excluded. We divided the patients into two groups, namely one that received maoto in addition to an NAI and another that received an NAI only. We excluded those who did not receive NAIs or received multiple types of NAIs.

VARIABLES AND OUTCOMES

Patient age was categorized into four types, namely 60–69, 70–79, 80–89, and ≥90 years. Using outpatient data of the index date, we identified prescriptions of maoto, NAIs (oseltamivir, zanamivir, or laninamivir), acetaminophen (oral or suppository), and antibiotics (Anatomical Therapeutic Chemical Classification System code, J01). The influenza type (A or B) was determined using the Japanese standardized diagnosis codes. Diagnostic codes that did not indicate a specific influenza type or recordings of both types A and B were categorized as missing. We used all confirmed diagnosis records from 1–3 months prior to the influenza diagnosis to identify the following comorbidities: chronic heart failure, myocardial infarction, chronic pulmonary diseases, liver diseases, diabetes mellitus, and renal diseases. The codes used for their identification were based on Quan et al.'s algorithm [21]. Furthermore, we identified hospitalization for any reason during the month preceding the influenza diagnosis.

Hospitalization for any cause within 7 days of influenza diagnosis was the primary outcome. Additionally, we evaluated hospitalization within 14 days of the diagnosis.

STATISTICAL ANALYSIS

We performed the chi-squared tests for univariate analyses of patient characteristics and hospitalization rates. Subsequently, we conducted propensity score matching between patients who received maoto in addition to an NAI and patients who received an NAI alone. Propensity scores were estimated using logistic regression with maoto use as the dependent variable and the following independent variables: sex, age, year, the type of influenza, the type of NAI, acetaminophen use, antibiotic use, comorbidities (congestive heart failure, chronic pulmonary disease, liver disease, diabetes, and renal disease), and hospitalization during the previous month. Using the estimated propensity scores, we conducted nearest-neighbor one-to-one matching without replacement. The caliper for matching was set at 0.2 times the standard deviation of the estimated propensity scores. We used standardized difference to evaluate the balance in covariates following matching, and an absolute value of the standardized difference exceeding 10% was considered indicative of imbalance [22].

We used the McNemar's test to compare hospitalization within 7 days of influenza diagnosis in the matched pairs of patients with and without maoto. We compared 14-day admission rates in the same manner. Subgroup analyses were conducted by performing propensity score matching in each subgroup of sex, age group, type of influenza, type of NAI, and acetaminophen use. We conducted three sensitivity analyses. First, we used the updated Charlson comorbidity index instead of individual comorbidities [21, 23]. The index was categorized into 0, 1, 2, and ≥3. Second, we included patients hospitalized on the index date and analyzed 7-day and 14-day admission rates, including the index date. Finally, we excluded patients who underwent antigen tests in multiple institutions and analyzed using outpatient data from the same day and institution wherein a patient underwent an antigen test. $P < 0.05$ was considered statistically significant for all analyses. Secondary and subgroup analyses were conducted for exploratory purposes; we did not adjust the P values for multiple comparisons. Statistical analyses were performed using the Stata SE, Version 16.0 (StataCorp, College Station, TX, USA).

ETHICAL CONSIDERATIONS

The study was approved by Clinical Research Ethics Committee, Jichi Medical University. The requirement for informed consent was waived because of the anonymous nature of the data.

RESULTS

We identified 65,802 patients with influenza aged ≥60 years. We excluded 4,200 patients without antigen tests. Following the exclusion of 590 patients hospitalized on the index date, 3,580 patients not receiving NAIs, and 66 receiving multiple types of NAIs, 57,366 patients were eligible for the analysis. Of these, 1,334 (2.3%) and 1,922 (3.4%) patients were hospitalized within 7 and 14 days of influenza diagnosis, respectively.

Table 1 summarizes the patient characteristics and results of the univariate analyses. Maoto was used in 4,630 (8.1%) of the 57,366 eligible patients. The crude 7-day hospitalization rates in patients with and without maoto were 1.8% (n = 82) and 2.4% (n = 1,252), respectively ($P = 0.009$). The crude 14-day hospitalization rates in patients with and without maoto were 2.5% (n = 115) and 3.4% (n = 1,807), respectively ($P = 0.001$).

Table 2 compares the characteristics of patients with and without maoto. Before propensity matching, patients with maoto were younger than those without. Laninamivir was most frequently administered in both the groups; nonetheless, more patients with maoto received laninamivir (66%), compared with those without (54%). The proportion of patients receiving acetaminophen and antibiotics was similar between the groups.

Table 1 Patient characteristics and results of univariate analyses (N = 57,366)

Characteristic	Total, n	Hospitalization within 7 days, n (%)	*P*-value	Hospitalization within 14 days, n (%)	*P*-value
Sex					
Male	22,797	544 (2.39)	0.432	794 (3.48)	0.152
Female	34,569	790 (2.29)		1,128 (3.26)	
Age, years					
60–69	21,428	156 (0.73)	<0.001	245 (1.14)	<0.001
70–79	18,090	273 (1.51)		424 (2.34)	
80–89	13,835	566 (4.09)		801 (5.79)	
90–	4,013	339 (8.45)		452 (11.26)	
Year					
2012–13	7,810	192 (2.46)	0.044	280 (3.59)	0.016
2013–14	8,212	205 (2.50)		294 (3.58)	
2014–15	18,589	460 (2.47)		654 (3.52)	
2015–16	9,714	215 (2.21)		313 (3.22)	
2016–17	13,041	262 (2.01)		381 (2.92)	
Type of influenza					
A	38,477	888 (2.31)	0.238	1,275 (3.31)	0.235
B	7,526	161 (2.14)		239 (3.18)	
Missing	11,363	285 (2.51)		408 (3.59)	
Neuraminidase inhibitor					
Oseltamivir	24,722	673 (2.72)	<0.001	981 (3.97)	<0.001
Zanamivir	1,087	14 (1.29)		19 (1.75)	
Laninamivir	31,557	647 (2.05)		922 (2.92)	
Acetaminophen use					
Yes	37,611	914 (2.43)	0.022	1,294 (3.44)	0.098
No	19,755	420 (2.13)		628 (3.18)	
Antibiotic use					
Yes	14,330	335 (2.34)	0.910	476 (3.32)	0.825
No	43,036	999 (2.32)		1,446 (3.36)	
Congestive heart failure					
Yes	7,561	417 (5.52)	<0.001	573 (7.58)	<0.001
No	49,805	917 (1.84)		1,349 (2.71)	
Chronic pulmonary disease					
Yes	11,427	440 (3.85)	<0.001	597 (5.22)	<0.001
No	45,939	894 (1.95)		1,325 (2.88)	
Liver disease					
Yes	8,892	232 (2.61)	0.054	319 (3.59)	0.177
No	48,474	1,102 (2.27)		1,603 (3.31)	
Diabetes					
Yes	3,001	94 (3.13)	0.003	135 (4.50)	<0.001
No	54,365	1,240 (2.28)		1,787 (3.29)	
Renal disease					
Yes	2,000	128 (6.40)	<0.001	176 (8.80)	<0.001
No	55,366	1,206 (2.18)		1,746 (3.15)	
Hospitalization in previous month					
Yes	605	47 (7.77)	<0.001	76 (12.56)	<0.001
No	56,761	1,287 (2.27)		1,846 (3.25)	

Table 2 Patient characteristics before and after propensity score matching

Characteristic	Patients with maoto, N = 4,630 n (%)	Patients without maoto (all), N = 52,736 n (%)	Standardized difference[a)]	Patients without maoto (matched), N = 4,630 n (%)	Standardized difference[b)]
Male	1,969 (42.5)	20,828 (39.5)	6.17	1,963 (42.4)	0.26
Age, years					
60–69	2,007 (43.3)	19,421 (36.8)	13.34	2,015 (43.5)	−0.35
70–79	1,465 (31.6)	16,625 (31.5)	0.25	1,457 (31.5)	0.37
80–89	959 (20.7)	12,876 (24.4)	−8.87	973 (21.0)	−0.74
90–	199 (4.3)	3,814 (7.2)	−12.61	185 (4.0)	1.52
Year					
2012–13	576 (12.4)	7,234 (13.7)	−3.79	575 (12.4)	0.07
2013–14	651 (14.1)	7,561 (14.3)	−0.79	626 (13.5)	1.57
2014–15	1,320 (28.5)	17,269 (32.7)	−9.20	1,348 (29.1)	−1.34
2015–16	886 (19.1)	8,828 (16.7)	6.25	895 (19.3)	−0.49
2016–17	1,197 (25.9)	11,844 (22.5)	7.94	1,186 (25.6)	0.54
Type of influenza					
A	3,311 (71.5)	35,166 (66.7)	10.46	3,335 (72.0)	−1.15
B	677 (14.6)	6,849 (13.0)	4.74	665 (14.4)	0.74
Missing	642 (13.9)	10,721 (20.3)	−17.23	630 (13.6)	0.75
Neuraminidase inhibitor					
Oseltamivir	1,464 (31.6)	23,258 (44.1)	−25.95	1,474 (31.8)	−0.46
Zanamivir	92 (2.0)	995 (1.9)	0.73	82 (1.8)	1.59
Laninamivir	3,074 (66.4)	28,483 (54.0)	25.50	3,074 (66.4)	0.00
Acetaminophen use	3,190 (68.9)	34,421 (65.3)	7.73	3,160 (68.3)	1.40
Antibiotic use	1,268 (27.4)	13,062 (24.8)	5.97	1,242 (26.8)	1.26
Congestive heart failure	537 (11.6)	7,024 (13.3)	−5.21	507 (11.0)	2.05
Chronic pulmonary disease	849 (18.3)	10,578 (20.1)	−4.37	845 (18.3)	0.22
Liver disease	780 (16.8)	8,112 (15.4)	3.98	765 (16.5)	0.87
Diabetes	236 (5.1)	2,765 (5.2)	−0.66	202 (4.4)	3.46
Renal disease	146 (3.2)	1,854 (3.5)	−2.02	100 (2.2)	6.18
Hospitalization in previous month	24 (0.5)	581 (1.1)	−6.51	14 (0.3)	3.38

Every patient in the maoto group was matched with one without maoto.
[a)] Between patients with maoto and those without maoto.
[b)] Between patients with maoto and their matched counterparts without maoto.

Propensity score matching selected 4,630 patients from those without maoto as matched counterparts for patients with maoto. **Table 2** outlines the characteristics of the matched patients. The characteristics were balanced between those with and without maoto. Among the 4,630 pairs, 82 (1.77%) and 75 (1.62%) patients with and without maoto, respectively, were hospitalized within 7 days. The risk difference was 0.15%, and the McNemar's

test did not reveal significant difference between the groups (P = 0.569). The 14-day hospitalization rate was 2.48% (n = 115) and 2.51% (n = 116) for patients with and without maoto, respectively, with a risk difference of 0.02%. The difference between the groups was also insignificant (P = 0.946).

Table 3 summarizes the results of subgroup analyses. Frequency of hospitalization within 7 days tended to be higher among patients aged 90 years or older who were prescribed maoto than those who were not (9.7% vs. 6.6%, P = 0.257). **Table 4** summarizes the results of main analysis and three sensitivity analyses. All sensitivity analyses showed results that were similar to those of the main analysis.

DISCUSSION

Using a health insurance claims database, we evaluated the association between the addition of maoto to an NAI and hospitalization among older adults following influenza. Maoto was used in 8% of patients aged 60 years or older. Overall, there was no significant association between the use of maoto and hospitalization rates.

We used a prefecture-wide claims database of the National Health Insurance and Late Elders' Health Insurance. According to government-issued statistics in 2015, the population coverage of the two insurance schemes in Kumamoto Prefecture were 66% and 99% for those aged 60–74 years and ≥75 years, respectively [24–26]. Using this representative sample, we analyzed 57,563 older adults with influenza. Maoto was used by 8% of the patients who received NAI. This proportion was higher

Table 3 Result of subgroup analyses

Subgroup	Number of matched pairs	Hospitalization within 7 days			Hospitalization within 14 days		
		Patients with maoto, n (%)	Patients without maoto, n (%)	*P*-value	Patients with maoto, n (%)	Patients without maoto, n (%)	*P*-value
Sex							
Male	1,969	41 (2.08)	31 (1.57)	0.225	56 (2.84)	57 (2.89)	0.922
Female	2,660	41 (1.54)	42 (1.58)	0.909	59 (2.22)	58 (2.18)	0.924
Age group, years							
60–69	2,007	15 (0.75)	17 (0.85)	0.715	20 (1.00)	27 (1.35)	0.286
70–79	1,463	18 (1.23)	18 (1.23)	1.000	29 (1.98)	34 (2.32)	0.529
80–89	959	28 (2.92)	31 (3.23)	0.696	41 (4.28)	49 (5.11)	0.394
90–	196	19 (9.69)	13 (6.63)	0.257	23 (11.73)	17 (8.67)	0.317
Type of influenza							
A	3,311	64 (1.93)	53 (1.60)	0.292	85 (2.57)	83 (2.51)	0.872
B	677	12 (1.77)	16 (2.36)	0.450	19 (2.81)	22 (3.25)	0.639
Missing	642	6 (0.93)	15 (2.34)	0.050	11 (1.71)	19 (2.96)	0.144
Type of neuraminidase inhibitor							
Oseltamivir	1,464	25 (1.71)	25 (1.71)	1.000	36 (2.46)	39 (2.66)	0.710
Zanamivir	92	4 (4.35)	1 (1.09)	0.180	4 (4.35)	2 (2.17)	0.414
Laninamivir	3,074	53 (1.72)	64 (2.08)	0.305	75 (2.44)	94 (3.06)	0.139
Acetaminophen use							
Yes	3,190	61 (1.91)	66 (2.07)	0.649	87 (2.73)	93 (2.92)	0.641
No	1,439	21 (1.46)	18 (1.25)	0.631	28 (1.95)	29 (2.02)	0.893

Table 4 Summary of results from the main analysis and sensitivity analyses

Analysis	Number of patients with maoto before matching	Number of patients without maoto before matching	Number of matched pairs	7-day hospitalization after matching			14-day hospitalization after matching		
				Patients with maoto, n (%)	Patients without maoto, n (%)	*P*-value	Patients with maoto, n (%)	Patients without maoto, n (%)	*P*-value
Main analysis	4,630	52,736	4,630	82 (1.77)	75 (1.62)	0.569	115 (2.48)	116 (2.51)	0.946
Sensitivity analysis —Charlson comorbidity index[a)]	4,630	52,736	4,630	82 (1.77)	90 (1.94)	0.527	115 (2.48)	134 (2.89)	0.217
Sensitivity analysis —include same day-hospitalization[b)]	4,646	53,115	4,646	98 (2.11)	95 (2.04)	0.824	131 (2.82)	137 (2.95)	0.706
Sensitivity analysis —single institution[c)]	4,625	52,627	4,625	82 (1.77)	74 (1.60)	0.514	115 (2.49)	116 (2.51)	0.946

[a)] Used the updated Charlson comorbidity index (categorized into 0, 1, 2, and ≥3) instead of individual comorbidities.
[b)] Included patients hospitalized on the index date and analyzed 7-day and 14-day admission rates, including the index date.
[c)] Excluded patients who underwent antigen tests in multiple institutions and analyzed using outpatient data from the same day and institution wherein a patient underwent an antigen test.

than the previously reported rates in influenza patients younger than 60 years (4%) [20]. This difference may be attributable to the inclusion of children in the previous study. Maoto use was uncommon (1%) in patients aged ≤10 years [20]. The hospitalization rate was high in the present study; 2% patients were hospitalized within 7 days. The 7-day hospitalization rate was 8% in those aged ≥90 years.

We observed differences in patient characteristics before the propensity score matching between patients who received maoto and those who did not. Patients who received maoto were relatively young, and revealed a slightly lower proportion of congestive heart failure than in those without. The prescribing physicians may have been more likely to avoid maoto use in the oldest-old or those with risk factors, considering the cardiovascular effects of ephedrine and glycyrrhizin. The measured patient characteristics were well-balanced following the propensity score matching.

Overall, the addition of maoto to an NAI was not associated with an increase or decrease in hospitalization rates in the propensity score-matched patients. A previous study of patients aged <60 years also reported no significant association between maoto use and hospitalization [20], consistent with our findings in older adults with more frequent hospitalization. According to previous studies, the addition of maoto to an NAI may be effective in alleviating symptoms [19]. However, in this study, this possible effect of maoto did not result in preventing severe influenza.

We conducted exploratory subgroup analyses based on different patient characteristics. The results of most analyses were consistent with the primary analysis; maoto use was not associated with an increase or decrease in hospitalization rate. However, there was a tendency toward more hospitalizations among patients aged 90 years or older who were prescribed maoto than those who were not. The limited number of variables to describe patient conditions may have resulted in residual confounding. In addition, some subgroups had fewer patients. Nevertheless, our findings highlight the importance of identifying the correct indications for maoto. There has been a concern that physicians may be using Kampo products without the consideration of traditional diagnoses [27]. This necessitates detailed research using traditional diagnoses to evaluate the safety and effectiveness of maoto in patients with different conditions. Safety in the oldest-old population may deserve particular attention.

This study had several limitations. First, we conducted a retrospective observational study. Despite performing propensity score matching to balance the characteristics between patients with and without maoto, we did not randomize the patients. Confounding might have occurred owing to unmeasured factors. Second, we used a health insurance claims database. We could not obtain detailed information regarding the examination results, severity or underlying risk factors. For example, we could not obtain data on influenza vaccines. This is because

vaccinations are not covered by the insurance. The results of antigen tests were also unavailable. We were therefore unable to identify patients who were diagnosed clinically, and there may be misclassification of influenza cases. In addition, we selected all-cause hospitalization as the outcome of this study because detailed information of hospitalization could not be obtained. Further research on the cause of hospitalization, such as pneumonia and heart failure, is important. Third, we excluded patients who did not receive NAIs. Effectiveness of maoto when used alone requires further assessment. Finally, the study population consisted of enrollees of the National Health Insurance and Late Elders' Health Insurance. The results may not be generalizable to those aged <75 years who are enrolled in other types of health insurance.

CONCLUSIONS

An analysis of population-representative regional health insurance claims databases revealed that the use of maoto in addition to an NAI was not associated with decreased hospitalization rates in older adults with influenza. Further research is required to identify the indications for maoto and to evaluate its safety and effectiveness, particularly in the oldest-old population.

CONFLICTS OF INTEREST STATEMENT

Yamana, Michihata, and Jo have academic affiliations with the Department of Health Services Research, Graduate School of Medicine, The University of Tokyo, which is supported by Tsumura & Company. Tsumura & Company played no role in the design of the study; the collection, analysis, or interpretation of the data; writing of the manuscript; or the decision to publish the results. The other authors have nothing to disclose.

ACKNOWLEDGMENTS

This work was supported by grants from the Ministry of Health, Labour and Welfare, Japan (21AA2007) and the Ministry of Education, Culture, Sports, Science and Technology, Japan (20H03907).

REFERENCES

1. Ghebrehewet S, MacPherson P, Ho A. Influenza. *BMJ* 2016;355:i6258.
2. World Health Organization. Global Influenza Strategy 2019–2030. Available from: https://apps.who.int/iris/handle/10665/311184, Accessed 2022 Mar 7.
3. Iuliano AD, Roguski KM, Chang HH, Muscatello DJ, Palekar R, Tempia S, et al. Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. *Lancet* 2018;391:1285–300.
4. Olsen SJ, Azziz-Baumgartner E, Budd AP, Brammer L, Sullivan S, Pineda RF, et al. Decreased influenza activity during the COVID-19 pandemic—United States, Australia, Chile, and South Africa, 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:1305–9.
5. Lee L, Butt K, Buckrell S, Nwosu A, Sevenhuysen C, Bancej C. National influenza mid-season report, 2020–2021. *Can Commun Dis Rep* 2021;47:1–4.
6. Huang QS, Wood T, Jelley L, Jennings T, Jefferies S, Daniells K, et al. Impact of the COVID-19 nonpharmaceutical interventions on influenza and other respiratory viral infections in New Zealand. *Nat Commun* 2021;12:1001.
7. Adlhoch C, Mook P, Lamb F, Ferland L, Melidou A, Amato-Gauci AJ, et al. Very little influenza in the WHO European Region during the 2020/21 season, weeks 40 2020 to 8 2021. *Euro Surveill* 2021;26:2100221.
8. Baker RE, Park SW, Yang W, Vecchi GA, Metcalf CJE, Grenfell BT. The impact of COVID-19 nonpharmaceutical interventions on the future dynamics of endemic infections. *Proc Natl Acad Sci U S A* 2020;117:30547–53.
9. Mantani N, Andoh T, Kawamata H, Terasawa K, Ochiai H. Inhibitory effect of Ephedrae herba, an oriental traditional medicine, on the growth of influenza A/PR/8 virus in MDCK cells. *Antiviral Res* 1999;44:193–200.
10. Hayashi K, Imanishi N, Kashiwayama Y, Kawano A, Terasawa K, Shimada Y, et al. Inhibitory effect of cinnamaldehyde, derived from Cinnamomi cortex, on the growth of influenza A/PR/8 virus in vitro and in vivo. *Antiviral Res* 2007;74:1–8.
11. Wolkerstorfer A, Kurz H, Bachhofner N, Szolar OHJ. Glycyrrhizin inhibits influenza A virus uptake into the cell. *Antiviral Res* 2009;83:171–8.
12. Nagai T, Kataoka E, Aoki Y, Hokari R, Kiyohara H, Yamada H. Alleviative effects of a Kampo (a Japanese herbal) medicine "maoto (Ma-Huang-Tang)" on the early phase of influenza virus infection and its possible mode of action. *Evid Based Complement Alternat Med* 2014;2014:187036.
13. Masui S, Nabeshima S, Ajisaka K, Yamauchi K, Itoh R, Ishii K, et al. Maoto, a traditional Japanese herbal medicine, inhibits uncoating of influenza virus. *Evid Based Complement Alternat Med* 2017;2017:1062065.
14. Nishi A, Ohbuchi K, Kushida H, Matsumoto T, Lee K, Kuroki H, et al. Deconstructing the traditional Japanese medicine "Kampo": compounds, metabolites and pharmacological profile of maoto, a remedy for flu-like symptoms. *NPJ Syst Biol Appl* 2017;3:32.
15. Kubo T, Nishimura H. Antipyretic effect of Mao-to, a Japanese herbal medicine, for treatment of type A influenza infection in children. *Phytomedicine* 2007;14:96–101.
16. Nabeshima S, Kashiwagi K, Ajisaka K, Kitajima K, Masui S, Ikematsu H, et al. A comparison of oseltamivir with maoto, a traditional herbal medicine, for the treatment of adult seasonal influenza A. *J Tradit Med* 2010;27:148–56.
17. Nabeshima S, Kashiwagi K, Ajisaka K, Masui S, Takeoka H, Ikematsu H, et al. A randomized, controlled trial comparing traditional herbal medicine and neuraminidase inhibitors in the treatment of seasonal influenza. *J Infect Chemother* 2012;18:534–43.
18. Toriumi Y, Kamei T, Murata K, Takahashi I, Suzuki N, Mazda O. Utility of Maoto in an influenza season where reduced effectiveness of oseltamivir was observed—a clinical, non-randomized study in children. *Forsch Komplementmed* 2012;19:179–86.
19. Yoshino T, Arita R, Horiba Y, Watanabe K. The use of maoto (Ma-Huang-Tang), a traditional Japanese Kampo medicine, to alleviate flu symptoms: a systematic review and meta-analysis. *BMC Complement Altern Med* 2019;19:68.
20. Yamana H, Ono S, Michihata N, Jo T, Yasunaga H. Association between maoto use and hospitalization for seasonal influenza in a nonelderly cohort in Japan. *Intern Med* 2021;60:3401–8.
21. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med*

Care 2005;43:1130–9.
22. Austin PC. Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. *Commun Stat Simul Comput* 2009;38:1228–34.
23. Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol* 2011;173:676–82.
24. Statistics Bureau of Japan. 2015 Population Census (in Japanese). Available from: http://www.stat.go.jp/data/kokusei/2015/kekka.html, Accessed 2022 Mar 7.
25. Ministry of Health, Labour and Welfare. Survey on the National Health Insurance (in Japanese). Available from: https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/iryouhoken/database/seido/kokumin_jitai.html, Accessed 2022 Mar 7.
26. Ministry of Health, Labour and Welfare. Survey on the Late Elders' Health Insurance (in Japanese). Available from: https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/iryouhoken/database/seido/kouki_jittai.html, Accessed 2022 Mar 7.
27. Yakubo S, Ito M, Ueda Y, Okamoto H, Kimura Y, Amano Y, et al. Pattern classification in kampo medicine. *Evid Based Complement Alternat Med* 2014;2014:535146.