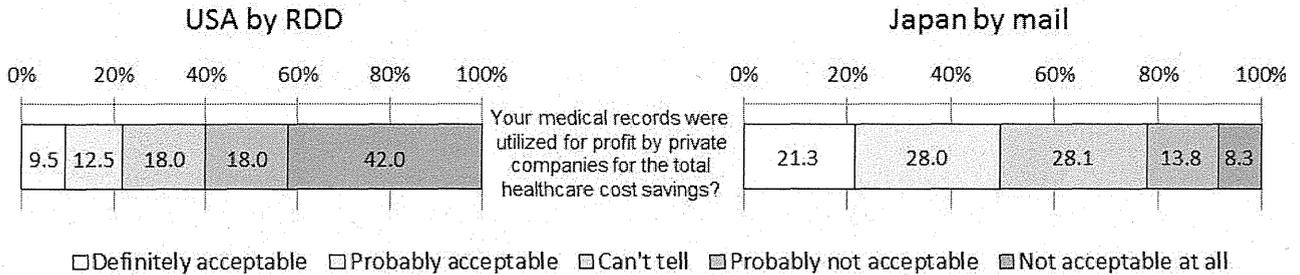


**Figure 3.** Findings related to secondary usage of information.

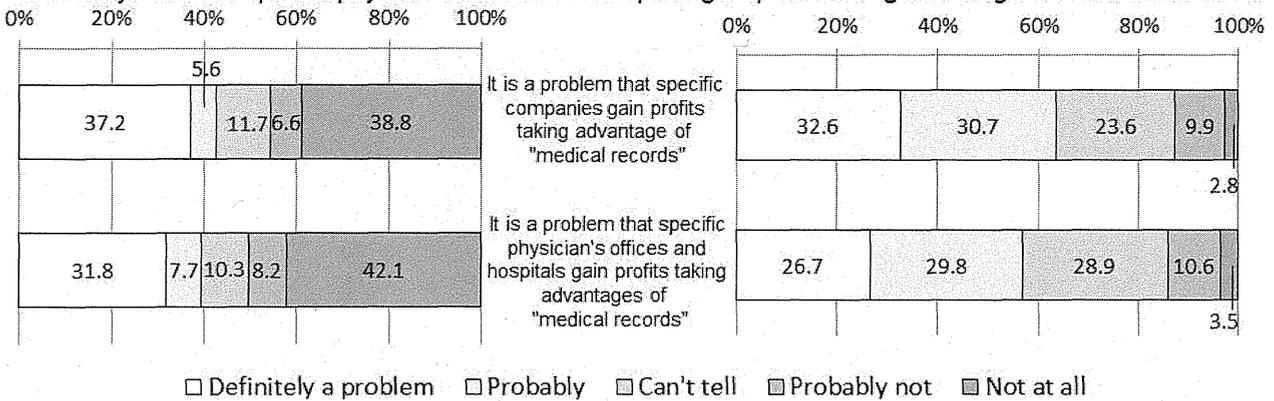
**Question 4**

“What do you think if an unidentifiable form of your medical records were utilized for profit by private companies (e.g., pharmaceutical companies and medical device manufacturers), which would likely lead to the establishment of a social system in which total healthcare cost savings can be attained?”



**Question 5;**

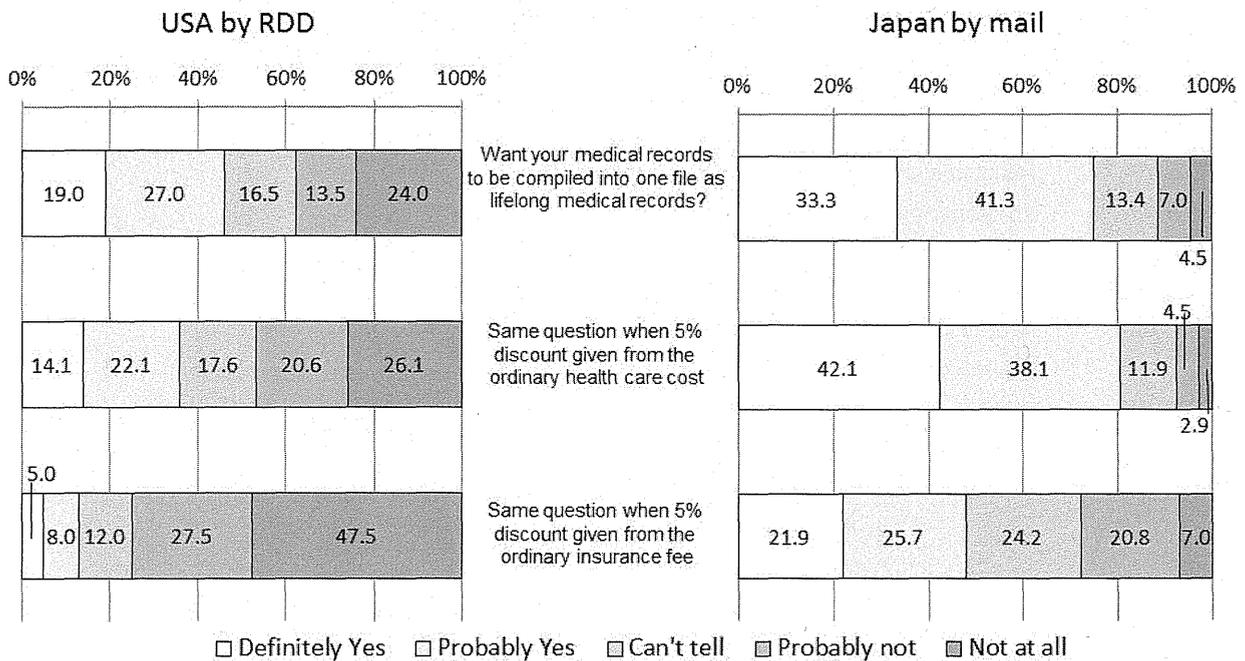
“What do you think if specific companies gain profits taking advantage of medical records?” and “What do you think if specific physician's offices and hospitals gain profits taking advantages of medical records?”



**Figure 4.** Do you want your medical records to be compiled into one file as lifelong medical records? How about with 5% off on medical cost? with 5% insurance discount?

**Question 6 and 7**

“Do you want your medical records to be compiled into one file as lifelong medical records?”

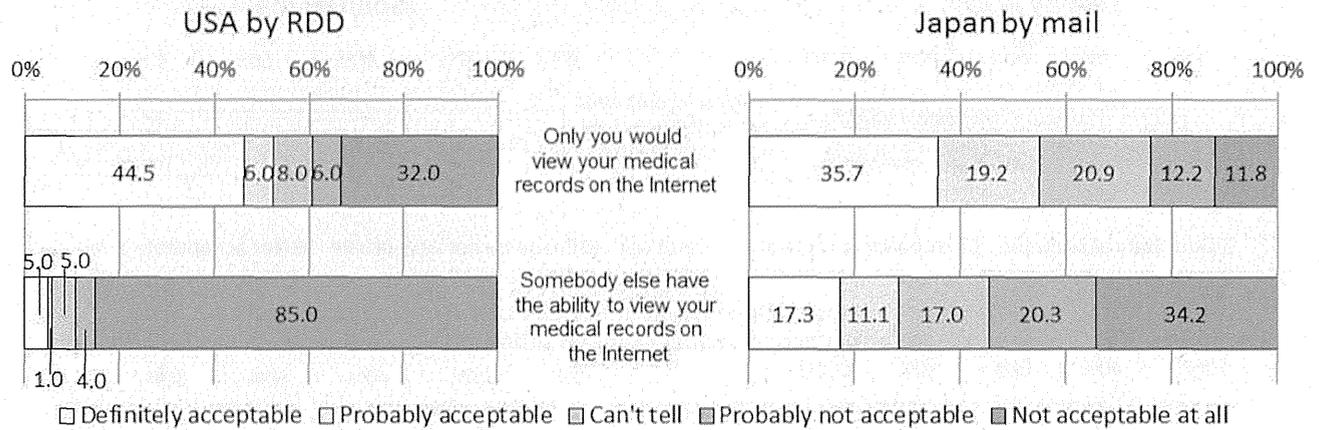


**Figure 5.** Findings related to access to medical records on the internet.

Question 8;

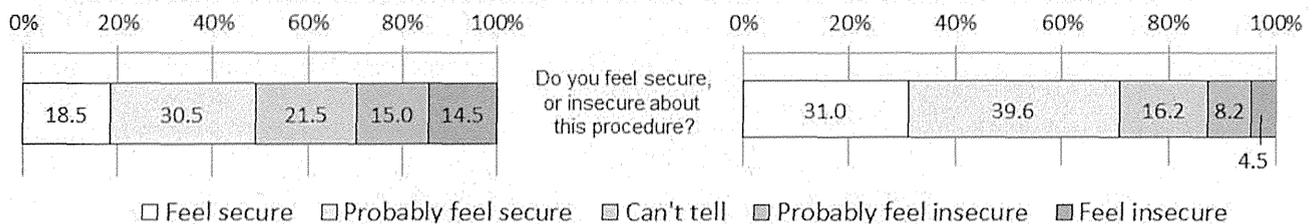
“How do you feel when only you would view your medical records on the Internet”

“How do you feel when somebody who you do not know would have the ability to view your unidentifiable medical records on the Internet”



Question 9

“Do you feel secure, or insecure about the given procedure to access your records?”



**Table 2.** Expected benefits of healthcare IT innovation (in the US survey only) explored by the item, “Please let me know which, if any, of the following you would expect to be achieved by the digitization of medical records and accessing these records online?” The responders were asked to choose one of the following options.

Percentage	Single choice answers
21.0%	Being able to receive treatment of the same quality at any physician’s office or hospital
18.0%	Avoiding duplicated tests and prescriptions
9.0%	Healthcare cost savings
5.0%	Receiving an adequate explanation for your disease
4.0%	Promotion of collaborative community healthcare
4.0%	Provision of a lifelong medical record system
4.0%	Contribution to future medical progress
1.5%	Access to health care at a nearby hospital
1.0%	Establishment of a team-based healthcare environment in various medical facilities
32.5%	Other

## 4. Discussion

### 4.1. Q1 about the Handling of Medical Records

In the US survey, in the identifiable situation, except for the case with referral doctors, almost half or more US people have a negative attitude defined as a cumulative response of “Probably not acceptable” and “Not acceptable at all” (hereafter referred to as negative). This indicates that sharing of their medical records without consent to doctors other than the doctors in charge or a referral doctor is not acceptable.

There is a significant difference ( $p < 0.01$ ) between “referred doctors” (negative: 25.5%) and “doctors not in charge but in the same department of the same hospital” (44.5%) whereas no significant difference is seen between “doctors in the same department of the same hospital” and “doctors in a different department of the same hospital”. There is a barrier between people’s attitudes to “referred doctors” and “doctors in the same department of the same hospital”

Note that there is a significant difference between “referred doctors” and “doctors in the same community,” which indicates people think that the range of the medical record sharing should be limited to referral doctors determined by their own doctors and think it should not be assigned regionally. In a questionnaire survey conducted in five clinics in Australia and New Zealand [13], patients’ attitudes toward sharing their electronic health records (EHR) were found to be influenced by three factors which were identity of recipient: level of anonymity: and type of information: In this survey, we obtained similar results.

As for the survey conducted in Japan which is shown to the right of Figure 1, negative attitude is significantly less than that of the US survey for all items.

In the Japanese survey, there is no significant difference between “referred doctors (negative 16.1%)” and “doctors in the same department of the same hospital (negative 11.4%)” whereas a significant difference ( $p < 0.01$ ) is observed between each of those two recipients and doctors in a different department of the same hospital (21.2%). This indicates that the Japanese participants had a tendency to believe, “I am treated in the department of the hospital,” whereas Americans had a tendency to believe, “I am treated by the doctor.”

As for any difference between men and women (not shown in the figures), for example, in the US there is no significant difference between men (48.2%) and women (44.4%) who have negative attitudes toward the sharing of their information with a regional core hospital whereas a significant difference ( $p < 0.01$ ) is seen between Japanese men (28.3%) and women (39.2%) who answered negatively to the same question.

### 4.2. Q2 and 3 Disclosure of the Name of the Disease

Although notifiable infectious diseases must be reported, more than half the US responders felt negative not only about sharing just the name of the disease in an identifiable manner for profit-oriented research as a matter of course, but also for official and non-profit purposes. When the usage of information contains both the individual’s name and the name of the disease, it is a strict requirement that it should be for the public good and under the control (such as punitive measures taken against those allowing an information leak) of a reliable administrator.

In information given in an unidentifiable form, 39.0%, 32.0%, 35.0% of the US responders answered negatively for the public/research purposes and 55.0% and 59.0% for commercial usages, showing a significant difference ( $p < 0.05$ ) between any pairs, one each from the two groups. However, no significant difference was observed in the negative attitudes within the public, academic, and industry-academia research collaboration.

In Japan, 11.5%, 10.3%, 10.9% of the responders have negative attitudes to information usage for the purposes of public interest and 22.2%, 19.5% for the purposes for profit of business respectively. As long as there is such a substantial negative attitude in both countries, an opt-out consent approach is not considered to be acceptable, not only in the US, but also in Japan. In other words, an opt-in approach should be required when considering the possibility of commercial secondary usage. As indicated in a study about possible forms of consent in an electronic environment [10], blanket consent cannot always serve the needs of each subject and the content of consent should be designed on a case-by-case basis, although this could be time consuming.

#### 4.3. Q4 and 5 Secondary Usage of Information

Figure 3 shows people's attitudes toward the proposal that patients would provide their medical records in unidentifiable form to a profit-oriented private company for attaining healthcare cost savings. To this, 22.0% of the US responders have favorable attitudes and 60.0% have negative attitudes. Willison's survey [19] of the Canadian public, concerning consent of secondary use of unidentified data in 2007 showed that 11% felt no need for notification or consent, 24% supported notification and opt-out, while 32% needed consent for each use. 22% favorable attitude of our study is considered almost similar to sum of 11 and 24 of the Canadian survey.

The last two segments of Figure 3 show the results of the question on how they would feel if specific companies or hospitals gained profits from such a business model. About 40% of the US responders and more of the Japanese responders answer negatively, suggesting people in both countries think the profits should be returned to the public or patients

#### 4.4. Q6 and 7 Lifelong Medical Records

In this survey, Electronic Medical Record (EMR) refers to the individual lifelong medical electronic records. Based on this definition, we presented both the advantages and disadvantages briefly and then asked whether respondents wanted their medical records to be compiled into one (without asking how they would be used). As shown in Figure 4, in the US survey, positive answers were 46.0% and negative answers were 37.5%, which yielded no significant difference. In Japan, positive answers were 74.6% and negative answers were 11.5%. The US answer of 46.0% positive was lower than expected. This could be because the questionnaire wording "compiled in one file" caused more fear of privacy risk.

Hoerbst's survey for EHR among Austrian and German citizens [20] showed that between 80% and 90% were supportive of the idea of exchanging health related data between health care providers. Also, Perera's survey citizens of Ontario, Canada [21] showed that most (>90%) supported the computerized sharing of the patient's health record among their health care providers. Thinking that our questionnaire is clearly stating "compiling as one file", these Austrian/German and Ontario answers are nearer to Japanese 74.6% positive answers.

When asked whether they were interested in compiling their medical records into one lifelong medical record if they were given a 5% discount from the ordinary health care cost as a result, US negative answers increased (46.7%) the difference of which was however not significant. However, when asked whether they would be interested if they were to receive a 5% discount from the ordinary insurance fee if their lifelong medical records were disclosed, US positive answers further dropped off and negative answers significantly increased to 75.0% ( $p < 0.01$ ). No significant differences between answers of healthy (negative 74.9%) and non-healthy (75.9%) responders and between answers of people aged 39 and under (67.5%) and those aged 40 and over (78.9%). This suggests such discount incentives do not have much efficacy.

In Japan, favorable attitudes towards savings of healthcare cost are relatively higher but people react negatively to the suggestion of an insurance fee discount.

Little change is observed in attitudes of the responders either in the US or Japan when proposed healthcare cost savings. The result, however, indicates that people in both countries may fear the possibilities of cherry picking by insurance companies (trying to contract only with low risk people). In the US, people can choose insurance, and at the same time, insurance companies can choose the people to whom they offer the policy. This discount is thought to be an invitation for people with lower health risks, while those with high risk may lose a chance to avail a moderate price. In Japan however, healthcare insurance coverage is universal. This resulted in lesser change in the unfavorable response of the participants. This is in contrast to the perceived health condition of the respondents, as presented in Table 1 on respondent attributes. Note that 60.0% of the American respondents rated themselves as "Healthy," while the same was rated by only 30.0% of the Japanese respondents. This may indicate that Japanese people have a tendency to avoid choosing extreme (definite) options, which is clear from the minor difference in the combined numbers of "Healthy" and "Rather healthy" (85.5% to 79.2%).

#### 4.5. Q8 and 9 Access to Medical Records on the Internet

As regards to reference of their own medical records on the Internet, 50.5% of US responders answered favorably while 38.0% had negative attitudes. It is interesting to note that a substantial number of responders (44.5%) answered that they thought it was acceptable in a positive manner whilst a considerable number of the responders were negative. In order to serve the needs of people with a positive attitude at the same time as maintaining trust in the healthcare information system in relation to the people with negative attitudes, it would be desirable that only the data of those in agreement should be placed in access servers with outside access and that the data in such servers should be clearly distinguished from the database of the hospital information system.

Note that as many as 89.0% of the US responders are against access from unidentified people even in unidentifiable form. This suggests that the system in which anyone can have unlimited access to medical records as public property even in an unidentifiable form would lead to heavy criticism.

A study evaluated patients' attitudes towards access to computerized patient records, which resulted that this may compromise safety [27]. This US-Japan survey aimed at citizens revealed the pros and cons are still weighted equally about the public confidence in the internet communication of medical records in technical terms.

#### 4.6. Q10 Expectation for Healthcare IT Innovation

We explored the respondents' expectations regarding healthcare IT innovation, which was asked as a single-choice question (refer to Table 2). High expectations were placed on options such as avoiding duplicated tests or receiving above a certain level of healthcare, while low expectations were given for collaborative community healthcare, access to health care at a nearby hospital and provision of a lifelong medical record system. After all, the latter three expectations have been produced from the viewpoint of healthcare providers whereas the former two represents actual public opinions. We consider that the reason for the lumbering healthcare collaboration via IT could be attributed to the discrepancy between what are expected and what can be achieved.

The same options concerning expectation for healthcare innovation were used in the questionnaire conducted by the Fukuoka City Medical Association in Japan in 2002, targeting patients who participated in a regional network of electronic medical records project [28]. In the Japanese surveys, the responders were allowed to mark all that apply. When comparing the Japanese 2008 survey (which has been reported) (hereafter referred to as the Shizuoka survey) with the Fukuoka 2002 survey, the responders in both cities selected some options at similar rates including "receiving above a certain level of healthcare (Shizuoka: 61%, Fukuoka: 65%)", "receiving an adequate explanation (Shizuoka: 59%, Fukuoka: 56%)" and "provision of a lifelong medical record system (Shizuoka: 28%, Fukuoka: 27%)". On the other hand, Shizuoka showed a higher percentage for other options such as "avoiding duplicated tests and prescriptions (Shizuoka: 69%, Fukuoka: 56%)" and "access to health care at a nearby hospital (Shizuoka: 41%, Fukuoka: 32%)" while Fukuoka had a higher percentage in "promotion of collaborative healthcare (Shizuoka: 35%, Fukuoka: 55%)". As regard to healthcare cost saving, 22% of the responders of the Fukuoka survey selected the option while 63% of the Shizuoka responders marked the option this time, which suggests a deteriorating medical situation has pervaded society during this period. The option "Contribution to future medical progress" was newly introduced in this survey, which accounted for a rather high percentage of 44%

#### 4.7. Limitations of This Survey

The sample size (200 and 457 for US and Japan, respectively) was not very large to exhibit the phenomenon tested by the hypotheses sufficiently. Further, different methods were applied in the two surveys (RDD and by mail). As in Table 1, female responders were dominant over male in US survey, while most responders were male in Japan, though we requested answers by a family member whose birthday is the nearest. In addition, RDD is known to involve a significant level of bias [29].

Respondents of these surveys were living in their house, either contacted through the RDD in the US, or mail in Japan. Consequently, patients suffering from severe diseases may have been eliminated from this survey. Such patients may have a higher motivation to compile their medical records into one.

The 2012 Commonwealth Fund survey [30] revealed that the percentage of doctors who used electronic patient medical records in their practice varied among countries. In this context, more than 90% of the doctors in the Netherlands, UK, Norway, New Zealand, and Australia used such electronic records, while the same was found to be 69% in the US. Japan has not joined this survey; however, a Japan Association of Healthcare Information System Industry survey in 2012 shows this figure to be

18.7% [31]. The surveyed countries were found to exhibit a low use of EMR as compared to other countries of Commonwealth survey. As a result, doctors are less accustomed to using digital medical records and the internet for healthcare. This is in contrast to the fact that Taiwan started IC chip card identification for healthcare professionals since 2007 [5].

It is important to note the difference between the healthcare systems of the two countries surveyed in the present study. A universal coverage policy is maintained in Japan, while citizens have the choices to select their insurance provider (including none) in the US. Further, the consumption tax is rather low in these two countries (US less than 10%, Japan 5%), which is generally high, especially in the northern European countries, which cover healthcare mainly by tax budget. This may have affected the participants' responses to Q6 and 7.

## 5. Conclusions

US people think that the range of the sharing of their identifiable medical records should be limited to the doctors in charge and specified referred doctors referred to by their own doctors. About 50% of the responders felt negatively about the sharing of medical data to other doctors of the hospital where they are treated or the regional core hospital. Japanese people think that their medical records may be shared by other doctors of the same hospital. More US responders have negative attitudes to information disclosure to unspecified healthcare institutes. This result highlights the importance of a clear indication of the identity of recipient in terms of public perception.

Even in an unidentifiable manner, US people feel profit-oriented usage of medical data without specific consent is not acceptable. There is a significant difference between usage of unidentifiable medical data for profit (about 50% feel negatively) and for official/research purposes (about 30% feel negatively). About 60% of the US responders have a negative view on the proposal that unidentifiable medical information is utilized for profit by private companies to attain healthcare cost savings.

As regards compiling a lifelong medical record, positive answers and negative answers are equally divided in the US, while more positive attitudes are seen in Japan. However, any incentive measures aimed at changing attitudes to such a compiling including the discount of healthcare costs or insurance fees are unwelcomed by both US and Japan people, regardless of their age or health condition.

Regarding the access to their own medical records via the Internet, 38% of the US responders feel this is unacceptable, while 50.5% were willing to accept it. On the other hand, there is strong opposition toward unlimited access to their medical records from unknown or unidentified people on the Internet even in unidentifiable form.

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## Author Contributions

Michio Kimura: Research director

Jun Nakaya: Listing up questionnaire

Hiroshi Watanabe, Toshiro Shimizu: Data processing

Kazuyuki Nakayasu: Privacy concern advisory

## Conflicts of Interest

The authors declare no conflict of interest.

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## **Appendix**

### **Questionnaires**

Q1. Assuming that you are needed to visit the hospital or physician's office, please rate how you'd feel if, without your consent, but for the purpose of treating your illness, your medical records were disclosed in an identifiable manner to the following recipients?

For this item, respondents were asked to choose any one from the following options that best described his/her feelings: "Definitely acceptable", "Probably acceptable", "Can't tell", "Probably not acceptable" and "Not acceptable at all".

The information regarding the recipient of the medical records was as follows: "Doctors who are not in charge of you, but are in the same department of the same hospital", "Doctors in a different department in the same hospital", "Doctors in another hospital which you were referred to", "Assuming that you are treated in the regional core hospital, doctors in another hospital or clinic in the same community".

Q2. Assuming that you have a disease, how would you feel if the name of your disease was disclosed in an identifiable manner to the following entities other than medical institutes (hospitals or clinics): the US Department of Health and Human Services (Japan Ministry of Health), an academic lab for the purpose of its unique research, an academic lab for the purpose of an industry-academia research collaboration, health insurance companies, and pharmaceutical companies?

The response options were the same as those for Q1.

Q3. The same question was asked again by replacing the expression "in an identifiable manner" by "in an unidentifiable manner".

Q4. What would you think if an unidentifiable form of your medical records were utilized for profit by private companies (e.g., pharmaceutical companies and medical device manufacturers), which would likely lead to the establishment of a social system in which savings on total healthcare costs can be attained?

The respondents were not presented any specific model capable of bringing about cost by using the information.

The response options were the same as those for Q1.

Q5. What would you think about specific companies gaining profits by taking advantage of medical records? What would you think about specific physician's offices and hospitals gaining profits by taking advantages of medical records?

The response options were: "Definitely a problem", "Probably", "Can't tell", "Probably not" and "Not at all".

Q6. Lifelong medical records refer to individual medical records that include one's lifelong history of diseases, medical care, and administration of drugs, all of which are compiled into one file, instead of being managed by each hospital or physician's office. The advantages and disadvantages of lifelong medical records are as follows:

Advantage: Duplication of the same tests or drugs is avoided when you are treated by another physician.

Disadvantage: Your medical history cannot be concealed even if you do not want to disclose any part of it when you are treated by another physician.

Now, do you want your medical records to be compiled into one file as a lifelong medical record?

Q7. Would you be interested in compiling your medical records into one lifelong medical record if you were given a 5% discount on regular health care cost as a result? How would you respond if a special contract were proposed by a life insurance salesman saying that you would receive a 5% discount on the regular insurance fee if you showed him your lifelong medical records?

The response options for Q6 and 7 were "Definitely yes", "Probably yes", "Can't tell", "Probably not" and "Not at all".

Q8. How would you feel if only you could view your medical records on the Internet? How would you feel when somebody else has the ability to view your unidentifiable medical records on the Internet?

The response options were the same as those for Q1.

Q9. Assuming that your doctor wouldn't be allowed to see your lifelong medical records in his/her practice unless you present him/her the IC-enabled key card for your lifelong medical records and enter your PIN by yourself, would you feel secure or insecure about this procedure?

The response options were "Feel secure", "Probably feel secure", "Can't tell", "Probably feel insecure" and "Feel insecure".

Q10. (Only in the US survey) Please let me know which if any of the following you would expect to be achieved by the digitization of medical records and accessing these records online?

The respondents were asked to choose any **one** of the following options:

- Being able to receive treatment of the same quality at any physician's office or hospital
- Avoiding duplicated tests and prescriptions<sup>01</sup>
- Healthcare cost savings
- Receiving an adequate explanation for your disease
- Promotion of collaborative community healthcare
- Provision of a lifelong medical record system
- Contribution to future medical progress
- Access to health care at a nearby hospital
- Establishment of team-based healthcare environment in various medical facilities
- Other

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## Evaluation of two Japanese regulatory actions using medical information databases: a 'Dear Doctor' letter to restrict oseltamivir use in teenagers, and label change caution against co-administration of omeprazole with clopidogrel

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### SUMMARY

**What is known and objective:** The implementation of appropriate epidemiological methodology using medical information databases (MIDs) to evaluate the effects of regulatory actions has been highly anticipated. To assess scientific methods for active pharmacovigilance using MIDs, we conducted a quantitative assessment of the impact of two regulatory actions by the Japanese government: (i) restriction of use of oseltamivir in teenagers in March 2007 and (ii) caution against the co-administration of omeprazole (OPZ) with clopidogrel (CPG) in April 2010.

**Methods:** Data were obtained from four hub hospitals in Japan. We measured the seasonal proportion of patients prescribed oseltamivir to those prescribed neuraminidase inhibitors for the 2002/2003 to 2010/2011 seasons. The monthly proportion of patients co-administered OPZ and CPG (OPZ+CPG) to those prescribed CPG was measured from May 2009 to April 2011. We evaluated the changes observed with implementation of the regulatory actions. To estimate the impact of the actions, we conducted segmented regression analysis using interrupted time series data. The impact was assessed by two parameter estimates of the regression model: the change in level for short-term effects and change in trend for long-term effects.

**Results and discussion:** The use of oseltamivir in the target 10–19 years age group showed a significant and large decline (63.16%) immediately after the intervention ( $P = 0.0008$ ). No change was observed in OPZ+CPG, although there was a relative inhibitory trend for OPZ+CPG compared with co-administration of lansoprazole or rabeprazole with CPG as the control group. When restricted to new users of CPG, the stratified results were consistent with the overall results.

**What is new and conclusion:** The current analysis demonstrates the effectiveness of two regulatory actions. The results of the current study indicate that MID research can contribute to assessing and improving pharmacovigilance activities.

### WHAT IS KNOWN AND OBJECTIVE

Drug regulatory authorities regularly furnish healthcare providers with drug information and conduct regulatory actions to protect patients from avoidable risks when an adverse drug event (ADE) or other drug-related safety concern is identified.<sup>1</sup> A revision to drug labelling is one of the most common regulatory mechanisms for disseminating updated safety information. The *Dear Doctor* letter (also called a *yellow letter*), in the U.S. and Japan, and the direct healthcare professional communication, in the EU, are written communications for highlighting urgent or serious problems.<sup>2</sup> However, these safety warnings are known to have weaknesses.<sup>3,4</sup> To minimize risk, it is important that both the short- and long-term effects of regulatory actions are measured and assessed in a timely and appropriate manner. If a regulatory action is not effective, additional safety measures should be considered.

Oseltamivir is a neuraminidase inhibitor shown to be effective in the treatment and prophylaxis of influenza A and B viral infections.<sup>5,6</sup> Its use has spread worldwide from its successful launch in 1999.<sup>7</sup> Seventy-five per cent of the total production of oseltamivir was used in Japan through March 2007.<sup>8</sup> However, a number of case reports of delirium and abnormal behaviour after treatment with oseltamivir, especially in teenagers, led to public concern about its safety.<sup>9</sup> In March 2007, the Japanese Ministry of Health, Labour, and Welfare (MHLW) ordered the holder of marketing approval to issue a *Dear Doctor* letter, essentially restricting the use of oseltamivir in children and adolescents aged 10–19 years.<sup>10</sup>

Clopidogrel (CPG) is an antiplatelet drug used for the prevention of recurrent ischaemic cerebrovascular disease and the treatment for ischaemic heart disease after percutaneous coronary intervention.<sup>11</sup> CPG is a pro-drug requiring activation by cytochrome P450 enzymes, including CYP 2C19.<sup>12,13</sup> Proton pump inhibitors (PPIs) are occasionally co-administered to reduce the risk of gastrointestinal bleeding associated with CPG.<sup>14</sup> Because certain PPIs are considered to have inhibitory effects on CYP2C19,<sup>15,16</sup> the U.S. Food and Drug Administration (FDA)<sup>17</sup> and the European Medicines Agency<sup>18</sup> have warned against the co-administration of omeprazole (OPZ) or esomeprazole with CPG, to prevent cardiovascular events caused by loss of

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effectiveness of CPG. However, this issue remains controversial,<sup>19–23</sup> and there are some differences in the intensity of regulatory actions among regulatory authorities. In Japan, the MHLW did not issue the highest level warning, similar to the FDA black-box warning. Instead, they cautioned against the concurrent use of OPZ and CPG (OPZ+CPG) in April 2010 through changes to the conventional label. Esomeprazole was not approved by the MHLW at the time. This caution was not applied to the co-administration of CPG with lansoprazole or rabeprazole (LPZ/RPZ+CPG) because of the difference in the inhibitory effects on CYP2C19.

Recently, there has been considerable anticipation of the effective use of medical information databases (MIDs) for pharmacovigilance. To this end, many countries have directed large efforts towards establishing nationwide MID systems and the scientific methodologies to exploit them for active drug surveillance. In May 2008, the FDA announced the Sentinel Initiative with a Sentinel System for performing active nationwide surveillance using the electronic health data of a minimum of 100 million people.<sup>24,25</sup> In Japan, the MHLW launched its Sentinel Project in Japan (J-Sentinel) in 2010 for more accurate and comprehensive benefit-risk assessment.<sup>26</sup> An extensive MID covering 10 million individuals by 2015 is to be established under its J-sentinel plan.

To achieve the aims of the J-Sentinel project, we initiated collaborative research with four hub hospitals in Japan with the goal of establishing appropriate epidemiological methodology for pharmacovigilance using MIDs. In our research project, we used the four MIDs to conduct a quantitative assessment of the direct impact of the two regulatory actions on the prescribing of the target drugs in a timely and effective manner.

## METHODS

### Data source and study organization

We used MIDs of the University of Tokyo Hospital (Tokyo, Japan), Hamamatsu University Hospital (Shizuoka, Japan),<sup>27</sup> Kagawa University Hospital (Kagawa, Japan) and Kyushu University Hospital (Fukuoka, Japan), which covered nearly one million individuals. The average numbers of outpatients and inpatients per day in the four hospitals were more than 7200 and 3100, respectively. In each hospital, the number of target patients per defined period was counted using their local MID, and the summary data without personally identifiable information were submitted to the National Institute of Health Sciences (Tokyo, Japan). The summary data from the four hospitals were combined and used for the current analysis. The study was approved by the ethics committees of the Hamamatsu University Hospital and the National Institute of Health Sciences together with other pharmacoepidemiological studies. For the other three university hospitals, such approval was not necessary according to current ethical regulations in Japan.

### Study design for oseltamivir

The outcome and intervention were defined as the proportion of patients prescribed oseltamivir relative to those prescribed neuraminidase inhibitors, and the *Dear Doctor* letter for oseltamivir issued on 20 March 2007, respectively. We used the number of patients taking any neuraminidase inhibitors as the denominator assuming that these patients in our four hospitals were

representative of influenza cases in Japan (Figure S1). Period from the beginning of April of one year to the end of March of the following year was defined as a season, and the number of patients in each season was measured during the observation period from the 2002/2003 season to the 2010/2011 season. The seasons of 2007/2008 and later were assigned to the post-intervention period. Patients were classified into two different age groups: 10–19 years as the target group and 20 years or over as the control group. Children aged 0–9 years were not included in the study, because oseltamivir in dry syrup formulation was used preferentially for this age group, regardless of the regulatory action. The neuraminidase inhibitors examined in this study included oseltamivir, zanamivir, peramivir and laninamivir. As peramivir and laninamivir were approved in Japan in January 2010 and September 2010, respectively, the patient number for these two prescriptions was counted over two seasons (2009/2010 to 2010/2011) and one season (2010/2011), respectively. Oseltamivir and zanamivir were approved in December 2000 and December 1999 in Japan, respectively, and were in clinical use before the observation period.

### Study design for OPZ+CPG

The outcome and intervention were defined as the proportion of patients prescribed OPZ+CPG relative to those prescribed CPG, and the label revision issued on 27 April 2010, respectively. The number of patients prescribed CPG per month was counted during the study period from the beginning of May 2009 to the end of April 2011. The period from beginning of May 2010 and later was assigned to the post-intervention period. PPIs examined in this study included oral OPZ, lansoprazole and rabeprazole, but PPI-antibiotic combination products for the treatment of *Helicobacter pylori* only were excluded because of the different indications. A prescription including one of the PPIs and CPG within the same day was defined as co-administration. Patients were classified into two different treatment groups: OPZ+CPG as the target group and LPZ/RPZ+CPG as the control group. *New users* were defined as patients who had not received CPG within six months prior to the month in which CPG was prescribed.

### Statistical analysis

To estimate the effects of the two regulatory interventions, we conducted segmented regression analysis using interrupted time series data.<sup>28</sup> The effect was assessed using two parameters, level ( $\beta_2$ ) and trend ( $\beta_3$ ), according to the following linear regression model:

$$Y_t = \beta_0 + \beta_1 \times \text{time}_t + \beta_2 \times \text{intervention}_t + \beta_3 \times \text{time after intervention}_t + e_t$$

where  $Y_t$  is the proportion of patients prescribed the target drug in regularly spaced intervals at time  $t$ ;  $\text{time}$  is a continuous variable indicating time from the start of the observation period;  $\text{intervention}$  is a binary variable for pre ( $\text{intervention}_t = 0$ )- or post-intervention ( $\text{intervention}_t = 1$ );  $\text{time after intervention}$  is a continuous variable indicating time from the intervention;  $\beta_2$  represents the change in the level at the intervention, from the last point before intervention to the first point after intervention, indicating the short-term effect;  $\beta_3$  represents the trend change in the slope in the post-intervention period compared with that in the preintervention period, indicating the long-term effect.

Ordinary least squares regression analysis assumes that the error terms associated with each observation are independent.<sup>28,29</sup>

As autocorrelation was detected in some linear regression models, the autoregressive error model using the Yule-Walker estimation method for first-order autoregression was applied as appropriate.<sup>30</sup> After adjusting for autocorrelation, the Durbin-Watson statistics for the final model indicated no autocorrelation. Values of  $P < 0.05$  (two-sided) were considered statistically significant. All statistical analyses were conducted using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

**RESULTS**

*Results of action against oseltamivir use*

Mean seasonal numbers of the patients prescribed neuraminidase inhibitors prior to and after the regulatory action in the four hospitals are shown in Table 1. There was no significant difference in the total number of patients prescribed neuraminidase inhibitors between pre- and post-intervention periods (686 vs. 647,  $P = 0.858$ , Student's *t*-test), although the numbers varied from year to year due to variability in the prevalence of influenza.

The time series plots and results of the segmented regression analysis of mean seasonal proportions of patients prescribed oseltamivir to the total number of patients prescribed any neuraminidase inhibitor between different age groups using data

from the four hospitals are shown in Fig. 1 and Table 2, respectively. There were significant reductions in prescription levels after the intervention ( $\beta_2$ ): 63.16% for ages 10 to 19 years ( $P = 0.0008$ ) and 16.50% for ages  $\geq 20$  years ( $P = 0.0354$ ), respectively. The trends ( $\beta_3$ ) for ages 10–19 years and ages  $\geq 20$  years were  $-1.37$  ( $P = 0.6948$ ) and  $2.47$  ( $P = 0.2380$ ), respectively, indicating an insignificant 1.37% decrease per season for the target group, and an insignificant 2.47% increase by per season for the control group compared with the baseline trends.

*Results of action against OPZ+CPG*

The average monthly numbers of patients prescribed the study drugs prior to and after the regulatory action in the four hospitals are summarized in Table 3. After the regulatory action, the mean number of individuals prescribed PPIs, CPG and co-administration increased significantly and to the same extent, 9.7% (8 070 vs. 8 856,  $P = 0.0017$ ; Mann-Whitney *U*-test), 13.2% (903 vs. 1 022,  $P = 0.0020$ ) and 13.2% (342 vs. 387,  $P = 0.0029$ ), respectively.

The time series plots for mean proportions of the numbers of OPZ+CPG and LPZ/RPZ+CPG prescribed to patients prescribed CPG per month in the four hospitals are shown in Fig. 2, and the results of the segmented regression analysis are summarized in Table 4. The number of individuals prescribed OPZ+CPG did not

**Table 1.** Mean seasonal numbers of patients prescribed neuraminidase inhibitors prior to and after the regulatory action (20 March 2007) in four hospitals, by age group

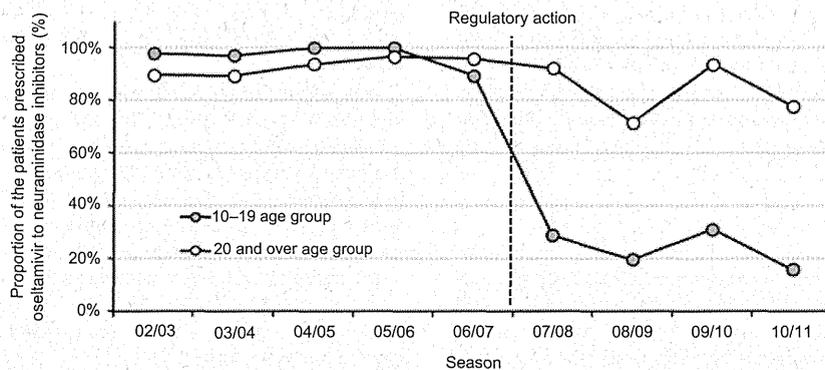
Drug group	Age group Period	Total ( $\geq 10$ )		10–19		$\geq 20$	
		Pre <sup>a</sup>	Post <sup>b</sup>	Pre <sup>a</sup>	Post <sup>b</sup>	Pre <sup>a</sup>	Post <sup>b</sup>
Total		686(201)	647(411)	109(50)	145(161)	576(189)	502(252)
Oseltamivir		641(185)	470(312)	106(49)	40(54)	535(175)	430(259)
Zanamivir		44(23)	159(120)	3(4)	100(111)	41(24)	59(35)
Peramivir <sup>c</sup>		–	4(4)	–	0.5(0.7)	–	4(4)
Laninamivir <sup>d</sup>		–	65	–	20	–	45

<sup>a</sup>From 2002/2003 to 2006/2007 season (5 seasons).

<sup>b</sup>From 2007/2008 to 2010/2011 season (4 seasons).

<sup>c</sup>Counted for 2009/2010 and 2010/2011 seasons (2 seasons) after approval of peramivir in January 2010.

<sup>d</sup>Counted for 2010/2011 season after approval of laninamivir in September 2010. Data in parentheses indicate SD.



**Fig. 1.** Time series plots of seasonal change in the proportion of patients prescribed oseltamivir to neuraminidase inhibitors, by age group.

**Table 2.** Interrupted time series regression analysis of seasonal change in the proportion of the patients prescribed oseltamivir to neuraminidase inhibitors, by age group<sup>a</sup>

Group	Parameter	Coefficient	Standard error	P-value
10–19	Level change after action $\beta_2$	-63.16	8.69	0.0008
	Trend change after action $\beta_3$	-1.37	3.28	0.6948
≥20	Level change after action $\beta_2$	-16.50	5.28	0.0354
	Trend change after action $\beta_3$	2.47	1.78	0.2380

<sup>a</sup>Each model is adjusted for first-order autocorrelation as appropriate.

change significantly in level ( $P = 0.9250$ ) or trend ( $P = 0.8040$ ). In contrast, a slight but significant change in trend (a 0.60% increase per month compared with the preintervention trend,  $P = 0.0017$ ) was observed in the LPZ/RPZ+CPG group.

For higher sensitivity in the detection of the intervention effect, we conducted a subanalysis of new users of CPG. Figure 3 shows the time series plots of mean proportions for OPZ+CPG and LPZ/RPZ+CPG among new CPG users. OPZ+CPG prescriptions did

not show any change in level ( $P = 0.2814$ ) or trend ( $P = 0.9945$ ) in the new-user study. Prescriptions for LPZ/RPZ+CPG did not show any significant decline in level (4.99%,  $P = 0.1183$ ), but there was an evident increase in trend (2.06% per month,  $P = 0.0001$ ).

**DISCUSSION**

The interrupted time series is the strongest, quasi-experimental design for the evaluation of the longitudinal effects of an intervention that occurs at a particular time-point.<sup>28,31–33</sup> In addition, this design is recommended as a method with strong internal validity in a FDA-sponsored Mini-Sentinel project, the aim of which is to facilitate the Sentinel Initiative and to identify appropriate designs for evaluating FDA regulatory actions.<sup>34</sup> The interrupted time series design also allows analysis of aggregate data without identifiable personal information, which is suitable for a multicenter study. The analysis has the advantage of presenting the results in a graphical and intuitive way. Therefore, we adopted the interrupted time series analysis to evaluate the impact of regulatory actions in this study.

The regulatory action on oseltamivir had immediate effects, not only for the 10–19 years target age group, but also for the ≥20 years age group in our study. However, a steep decline was more prominent in the target group (63.16%) than in the control

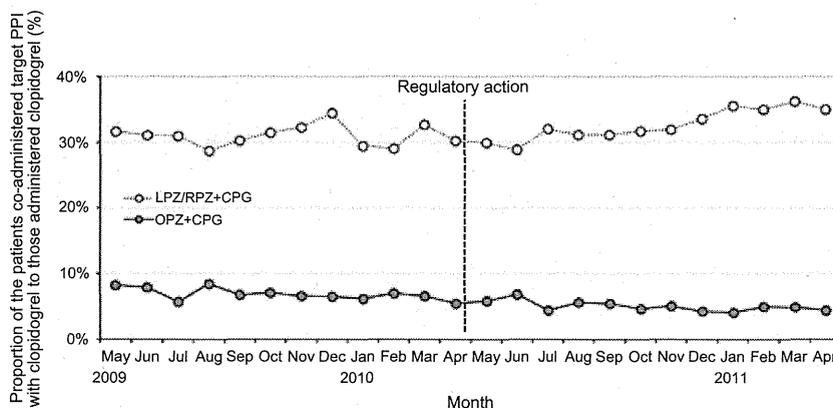
**Table 3.** Mean monthly numbers of patients prescribed proton pump inhibitors, clopidogrel, or both prior to and after the regulatory action (27 April 2010) in four hospitals

Group	Period	CPG total		PPIs total		OPZ subgroup		LPZ/RPZ subgroup	
		Pre <sup>a</sup>	Post <sup>b</sup>						
PPIs				8 070(487)	8 856(454)	1 701(81)	1 708(54)	6 369(418)	7 147(432)
Co-administration of PPI with CPG									
CPG		903(78)	1 022(52)	342(31)	387(36)	62(6)	51(7)	281(31)	335(38)

PPIs, proton pump inhibitors; OPZ, omeprazole; LPZ/RPZ, lansoprazole or rabeprazole; CPG, clopidogrel.

<sup>a</sup>From May 2009 to April 2010 (12 months).

<sup>b</sup>From May 2010 to April 2011 (12 months). Data in parentheses indicate SD.



**Fig. 2.** Time series plots of monthly change in the proportion of patients co-administered proton pump inhibitors with clopidogrel to those administered clopidogrel, by treatment group.

**Table 4.** Interrupted time series regression analysis of monthly change in the proportion of patients co-administered proton pump inhibitors with clopidogrel, by treatment group<sup>a</sup>

Group	Parameter	Coefficient	Standard error	P-value
<b>OPZ+CPG</b>				
Total				
	Level change after action $\beta_2$	-0.06	0.58	0.9250
	Trend change after action $\beta_3$	0.02	0.08	0.8040
New-user subgroup <sup>b</sup>				
	Level change after action $\beta_2$	-1.90	1.71	0.2814
	Trend change after action $\beta_3$	0.001	0.25	0.9945
<b>LPZ/RPZ+CPG</b>				
Total				
	Level change after action $\beta_2$	-2.33	1.14	0.0550
	Trend change after action $\beta_3$	0.60	0.16	0.0017
New-user subgroup <sup>b</sup>				
	Level change after action $\beta_2$	-4.99	3.06	0.1183
	Trend change after action $\beta_3$	2.06	0.44	0.0001

OPZ+CPG, co-administration of omeprazole with clopidogrel; LPZ/RPZ+CPG, co-administration of lansoprazole or rabeprazole with clopidogrel.

<sup>a</sup>Each model is adjusted for first-order autocorrelation as appropriate.

<sup>b</sup>Patients who had not received clopidogrel within six months prior to the month in which clopidogrel was prescribed.

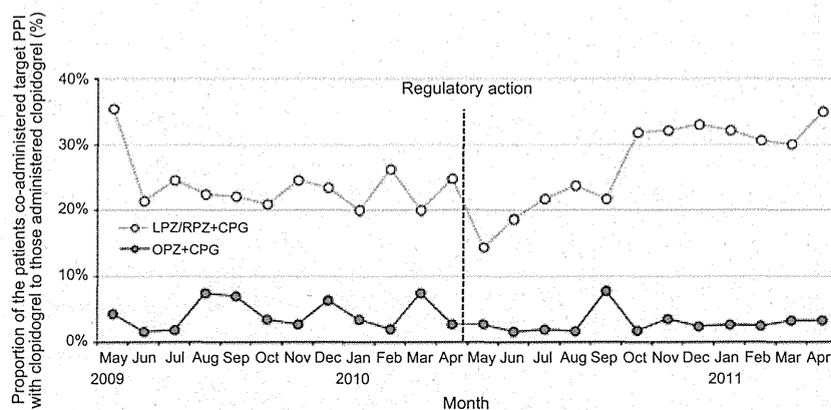
group (16.50%). The change in the control group was assumed to be due to external influences such as media publicity. The lower proportion of oseltamivir users after the intervention in the target group remained until the end of the follow-up period, suggesting a prolonged inhibitory effect for the regulatory action. Although a small but significant number of teenage patients were still prescribed oseltamivir after the action, this was considered reasonable because the restriction was not applied to patients at

high risk of influenza<sup>10</sup>. Therefore, the current results indicate that the regulatory action against oseltamivir use was effective both in the short-term and long-term.

To evaluate the generalizability of the current result to a larger population, our data were compared with those of two other Japanese studies, the MIHARI project conducted by the Pharmaceuticals and Medical Devices Agency, and Urushihara's report.<sup>35,36</sup> A comparison of the three data sets showed that our data were graphically consistent with both the MIHARI and Urushihara's results (Figure S2). In addition, a comparison of data from each hospital in this study revealed that the influence of the two regulatory actions was essentially identical among the four hospitals (data not shown). All our hospitals are equipped with a drug information (DI) room, the installation of which is encouraged by the MHLW to disseminate drug safety information. We estimated based on the MHLW documents<sup>37</sup> that approximately 65% of all hospitals in Japan already had a DI room in 2010, and therefore, our study hospitals were not considered to be special cases in terms of their response capability to regulatory actions. These findings indicate our four-hospital database is representative of the general population in Japan and is appropriate for use in a preliminary survey for pharmacovigilance purposes.

Regarding regulatory action against the use of OPZ+CPG, the target group showed no significant changes in prescription status after the regulatory action, but the control LPZ/RPZ+CPG group had a slight increase in trend. A comparison of the two groups indicates that this regulatory action might have a relatively small inhibitory effect in the target group.

To further examine the impact of this regulatory action, the data were stratified by selecting new users (i.e. patients without a medical history of CPG in the preceding six months) because continuous users of CPG were likely to continue receiving the same medication regardless of the regulatory action unless they experienced some problem. The results of the new-user study showed a significant increase in LPZ/RPZ+CPG prescriptions, which was consistent with the results from the complete data set. The difference between the two PPI groups, that is, no long-term change in OPZ+CPG prescriptions and gradual increase of LPZ/RPZ+CPG prescriptions, may reflect the response to the label change, suggesting that the intention of the regulatory action (label addition in drug-interaction section) is not communicated



**Fig. 3.** Time series plots of monthly change in the proportion of patients co-administered proton pump inhibitors with clopidogrel to those administered clopidogrel only in the clopidogrel new-user population, by treatment group.

immediately, but leading to slower translation to the clinical setting. In addition, stratification by new users would be useful for eliminating bias due to the possible hangover effects in continuous users.

Drug regulatory authorities implement different levels of safety measures depending on the type of adverse reactions involved. In this study, we analysed the impact of two different levels of regulatory action, the *Dear Doctor* letter advisory for oseltamivir and a label change for OPZ+CPG. It was difficult to judge, based on our results, whether the *Dear Doctor* letter was more effective than the conventional label change. Moreover, the difference in time units of the two regulatory actions should be taken into account, especially when comparing their short-term effects. Additional evidence from future studies will be required to more accurately assess the impact of these regulatory actions. In particular, a comparative analysis of the impact of different levels of regulatory action for the same or related drugs would be beneficial.

### Limitations

There are some limitations to this study. First, when using interrupted time series analysis to investigate the use of medications, it is generally recommended that 12 data points be used before and after the intervention.<sup>28</sup> However, in the current analysis of oseltamivir, fewer data points were available because data were collected only once annually to incorporate the influenza epidemic season. In addition, the impact of other sources, for example, media publicity and other regulatory notices, could not be distinguished from the effect of the regulatory action because of the annual intervals. Thus, this design may be better suited for the analysis of regulatory actions whose outcomes can be measured over shorter time intervals, for example monthly or weekly. Second, we examined a limited data set from only four hospitals. Although this analysis suggests generalizability of the

method, a further large-scale study will be required to provide a more accurate and reliable assessment of the methodology for evaluating the impact of regulatory action.

### WHAT IS NEW AND CONCLUSION

We have used analysis of interrupted time series with segmented regression of data from hospital MIDs to investigate the safe use of drugs and demonstrated the effectiveness of regulatory actions on the use of oseltamivir and OPZ+CPG. The results of the current study indicate that MID research can contribute to assessing and improving pharmacovigilance activities.

### CONFLICT OF INTEREST

No conflict of interests have been declared.

### SOURCE OF FUNDING

This study was supported by the Program for the Promotion of Studies in Health Science of the Ministry of Health, Labour and Welfare (Tokyo, Japan). The research was conducted independently of the funding organization.

### SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

**Figure S1** Seasonal changes in average number of patients prescribed any neuraminidase inhibitors in our four hospitals and infected with Flu per sentinel in Japan.

**Figure S2** Time series plots of seasonal change in the proportion of patients prescribed oseltamivir to neuraminidase inhibitors, by age groups compared to other Japanese reported studies.

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