Drug lag—delayed approval or reimbursement—is a major barrier to accessing cutting-edge drugs. Unlike approval lag, reimbursement lag is under-researched. We investigated the key determinants of reimbursement lag under Taiwan National Health Insurance (NHI), and compared this lag with those in the United Kingdom, Canada, Australia, Japan, and South Korea. Using retrospective data on 190 new NHI-reimbursed drugs from 2007 to 2014, we studied reimbursement lag in Taiwan vs. other countries, and investigated associated factors using generalized linear models (GLMs). The median reimbursement lags during before (“first-generation”) and after (“second-generation”) NHI drug reimbursement scheme in Taiwan were 378 and 458 days, respectively. The “first-generation” lag was shorter only than that in South Korea, whereas the “second-generation” lag only exceeded those of the United Kingdom and Japan. In GLM models, higher drug expenditure and the introduction of the “second-generation” NHI were two statistically significant parameters associated with reimbursement lag among antineoplastic and immunomodulating agents. For other drug classes, the reimbursement price proposed by pharmaceutical companies and use of price-volume agreements were two statistically significant parameters associated with longer reimbursement lags. The current reimbursement lag in Taiwan is longer than 1 year, but only longer than those of the United Kingdom and Japan. The determinants differ between drug categories. A specific review process for antineoplastic and immunomodulating drugs may expedite reimbursement. There is a clear need for systematic data collection and analysis to ascertain factors associated with reimbursement lag and thereby inform future policy making.

With burgeoning development of innovative medicines, ever more new drugs are commercially available. Medical innovations undoubtedly improve clinical outcomes and/or safety, and potentially increase survival rates, longevity, and quality of life. However, most patients cannot benefit until a new drug becomes available in routine clinical practice, and several barriers to pharmaceutical access, including safety, efficacy, pricing, and reimbursement, must first be overcome. Drug lag, defined as delay in approval (“marketing lag”) and/or reimbursement (“reimbursement lag”) of new drugs, is a potentially significant barrier to patient access. Therefore, marketing authorization and drug reimbursement are key hurdles to overcome in expediting patient access to new medicines. Reimbursement is an especially important determinant of patient access to new drugs in universal national health insurance (NHI) systems. However, published
studies have largely focused on marketing lag rather than reimbursement lag.\textsuperscript{5-14}

In Taiwan, all new drugs are evaluated and get approved by the Taiwan Food and Drug Administration (TFDA). Subsequently, the reimbursement of a new drug is decided by the National Health Insurance Administration (NHIA).\textsuperscript{8}

In 2007, Taiwan started to conduct health technology assessments,\textsuperscript{15} to support decision making and provide evidence in clinical effectiveness and economic impacts.\textsuperscript{16,17} Up until 2013, the Drug Benefit Committee (DBC) provided professional evaluations to new drug applications for decisions of listing new drugs. On January, 1, 2013, the Taiwan NHIA system transitioned from its first-generation incarnation to the current second-generation.\textsuperscript{16} After 2013, the Pharmaceutical Benefit and Reimbursement Scheme (PBRS) Joint Committee, a 29-member panel comprising government officials, health professionals, manufacturers, and members of the public, as the final arbiter of suitability for NH insurance reimbursement.\textsuperscript{2} Besides reimbursement decisions, the PBRS also sets the final NH insurance reimbursement price.\textsuperscript{18} However, subsequent to these substantial changes to Taiwan NHIA, it has remained unknown whether the reimbursement lag has improved or worsened, and what its determining factors are.

The NHIA drug list status and reimbursement lag substantially influence drug accessibility. In a study of drug lag in Taiwan during 1996–2002, the average reimbursement lag was 11.7 months\textsuperscript{6}; that study also found that the NH insurance reimbursement price had a negligible effect on reimbursement lag. Regrettably, no more recent studies have updated the reimbursement lag duration and its important determinants in Taiwan.

Hence, we conducted this study to investigate the key determinants of reimbursement lag for new drugs in Taiwan, and to compare it with lags in the United Kingdom, Canada, Australia, Japan, and South Korea.

**METHODS**

**Sample selection and inclusion criteria**

We first identified new drugs reimbursed by the Taiwan NHIA between January 1, 2007 and December 31, 2014, with inclusion criteria of: a new active ingredient; a new strength; a new administration route; or a new combination with different efficacy. Drugs also reimbursed in the United Kingdom, Canada, Australia, Japan, and/or South Korea, which have NH schemes similar to Taiwan’s, were selected to compare reimbursement lags between different countries. Finally, we conducted two adjusted generalized linear model (GLM) analyses to explore factors contributing to reimbursement lag in 40 new antineoplastic or immunomodulating drugs and in 82 new drugs of other classes (alimentary tract and metabolism, blood and blood-forming organs, nervous system, and systemic anti-infectives).

### Table 1 Exploratory variables included in the generalized linear model

| Variable                                                                 | Data type                        | Definition                                                                                                                                 |
|-------------------------------------------------------------------------|----------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|
| **Drug characteristics**                                                |                                  |                                                                                                                                           |
| Type of pharmaceutical company                                         | Categorical (domestic/multinational) | Type of pharmaceutical company, categorized based on domestic or multinational ownership                                              |
| New drug innovation attribute                                           | Categorical (categories 1, 2A, 2B) | New drug innovation attribute was classified into three categories after 2010: category 1 (breakthrough drug); category 2A (drugs with moderately improved efficacy vs. existing therapy); category 2B (me-too drugs) |
| Number of alternative drugs                                            | Categorical (few/more)           | Alternative drugs defined as drugs with the same ATC codes. “Few” indicates only one alternative, “more” indicates ≥ 2 alternatives.     |
| Listing status in five other countries                                  | Categorical (yes/no)             | Whether or not the new drug is already listed in the United Kingdom, Canada, Australia, Japan, or South Korea                             |
| **Evaluation criteria for new drug reimbursement**                      |                                  |                                                                                                                                           |
| Number of candidate patients                                           | Categorical (few/more)           | Number of patients eligible to use the new drug when it is reimbursed. The thresholds were 208 patients for ATC group L drugs and 1,419 for non-L group drugs. |
| Budgetary impact                                                       | Categorical (small/large)        | Predicted budgetary impact based on the pharmaceutical company projection                                                               |
| NH insurance reimbursement price                                        | Numeric                           | The initial NH insurance reimbursement price suggested by the pharmaceutical company                                                    |
| Pricing method (the lowest price of 10 reference countries)             | Categorical (yes/no)             | “Yes” indicates that the final price of the new drug was determined based on the lowest price of 10 reference countries. “No” indicates that the final price was determined by other pricing methods. |
| **PBRS policies**                                                      |                                  |                                                                                                                                           |
| Under second-generation NHI                                            | Categorical (yes/no)             | Whether or not the new drug was reimbursed under the second-generation NH implemented in 2013. As Taiwan’s NH is a mandatory, single payer, national health insurance program. Patients can only pay out-of-pocket if a new drug is not reimbursed by the (second generation) NH. |
| Price-volume agreement                                                  | Categorical (yes/no)             | Whether or not the new drug was reimbursed with confidential price-volume agreement\textsuperscript{a} between the NHIA and the pharmaceutical company. |

ATC, World Health Organization, Anatomical Therapeutic Chemical classification; ATC group L, antineoplastic and immunomodulating agents; NHIA, National Health Insurance (Administration); PBRS, Pharmaceutical Benefit and Reimbursement Scheme.
Data source and study design
Drug information was obtained from Taiwan NHIA and from publicly available data sets in other countries (Table S1). The main outcome, reimbursement lag, was defined as the period elapsed between drug approval and drug reimbursement.

Study drugs were classified by therapeutic area, based on their first-level World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classifications, reimbursement years, reimbursement schemes (first or second generation), and innovatory attributes. New drugs in Taiwan were further categorized, according to innovativeness and efficacy vs. existing therapy: category 1 (breakthrough drugs), category 2A (drugs with moderately improved efficacy), and category 2B (“me-too” drugs). Table 1 summarizes the 10 explanatory variables incorporated into model analyses to identify factors associated with the continuous dependent variable of reimbursement lag; these were selected based on perceived relevance to the reimbursement listing process in Taiwan, and according to previous studies and expert opinion. They comprise three main groups: drug characteristics, evaluation criteria for new drug reimbursement, and PBRS policies.

Statistical analyses
All analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC), with a statistical significance level set at 5%. Continuous variables were expressed as mean ± SD, and median (range); categorical variables were expressed as number and percentage. Wilcoxon rank-sum test, Kruskal–Wallis test, and Spearman’s rank correlation coefficient were used to assess the association between each of the dependent and independent variables. GLM analyses were used to investigate factors associated with the reimbursement lag of new drugs, and the variance inflation factor calculated to diagnose collinearity between multiple variables. GLM is a flexible generalization of ordinary linear regression that allows for response variables that have error distribution models other than a normal distribution. GLM analyses included new drugs without any missing variables in ATC groups A (alimentary tract and metabolism), B (blood and blood forming organs), N (nervous system), J (anti-infective for systemic use), and L (antineoplastic and immunomodulating agents). Because L group drugs have distinct characteristics, such as being especially innovative and expensive, we analyzed these separately from pooled non-L group drugs (groups A + B + N + J).

RESULTS
Drug characteristics
The analytic sample comprised 190 new drugs, among which 171 were reimbursed in the first-generation NHI, and 19 in the second-generation scheme; moderate improvement drugs (category 2A) predominated (55.3%), while breakthrough drugs accounted for < 10% (Table 2). ATC pharmacological groups with > 20 new drugs were: alimentary tract and metabolism (group A); blood and blood forming organs (group B); general anti-infectives for systemic use (group J); antineoplastic and immunomodulating agents (group L); and nervous system (group N).

Reimbursement lag in Taiwan
The median reimbursement lag of new drugs in the first-generation Taiwan NHI was 378 (range 128–11,070) days, which increased to 458 (range 274–2,189) days under the second-generation NHI (Table 3).

Analyses of reimbursement lag by therapeutic area, reimbursement year and scheme, and new drug innovation attribute (Tables S2–S5) revealed differences between first-generation and second-generation NHI, and between group L and other ATC groups. Disregarding groups with only one drug (H and J), group S had the longest (median 642 days) reimbursement lag under first-generation NHI (Table S2), but group L had the longest reimbursement lag (median 853 days) in second-generation NHI (Table S3).

Comparison of the reimbursement lag between Taiwan vs. other countries
Table 4 summarizes the reimbursement lag in Taiwan vs. the United Kingdom, Canada, Australia, Japan, and South Korea. Of the 190 drugs listed in Taiwan, 120, 49, 78, 81, and 105, respectively, were also listed in the United Kingdom, Canada, Australia, Japan, and South Korea. The median reimbursement lag under first-generation NHI in Taiwan was longer than lags in all countries except South

| Variables | Number (%) |
|-----------|------------|
| New drug innovation attribute | |
| Category 1 (breakthrough drugs) | 16 (8.4) |
| Category 2A (moderate improvement drugs) | 105 (55.3) |
| Category 2B (me-too drugs) | 65 (34.2) |
| Others* | 4 (2.1) |
| Year listed | |
| 2007 | 42 (22.1) |
| 2008 | 28 (14.7) |
| 2009 | 44 (23.2) |
| 2010 | 20 (10.5) |
| 2011 | 14 (7.4) |
| 2012 | 19 (10.0) |
| 2013 | 8 (4.2) |
| 2014 | 15 (7.9) |
| World Health Organization Anatomical Therapeutic Chemical group | |
| A: Alimentary tract and metabolism | 29 (15.3) |
| B: Blood and blood forming organs | 24 (12.6) |
| C: Cardiovascular system | 15 (7.9) |
| D: Dermatologicals | 3 (1.6) |
| G: Genito-urinary system and sex hormones | 4 (2.1) |
| H: Systemic hormonal preparations, excluding sex hormones and insulins | 4 (2.1) |
| J: Anti-infective for systemic use | 20 (10.5) |
| L: Antineoplastic and immunomodulating agents | 41 (21.6) |
| M: Musculoskeletal system | 7 (3.7) |
| N: Nervous system | 30 (15.8) |
| R: Respiratory system | 4 (2.1) |
| S: Sensory organs | 7 (3.7) |
| V: Various | 2 (1.1) |

*New drug innovation attributes of some new drugs were unavailable.
Factors affecting the reimbursement lag in Taiwan
Most new ATC group L drugs were moderate improvement drugs (category 2A) manufactured by multinational pharmaceutical companies (Table S5); these had high NHI reimbursement prices suggested by the manufacturer and few alternatives.

Collinearity diagnosis were tested for all variables in the GLM model. The variance inflation factor were all < 10, which indicated no collinearity between our variables.

Adjusted GLM models showed that a higher budget impact ($P = 0.005$) and the introduction of the second-generation NHI ($P < 0.001$) significantly increased the reimbursement lag of new ATC group L drugs (Table 5), with a proportion of variance explained ($R^2$) equal to 0.58. For non-L group drugs, prolonged reimbursement lag was significantly associated with a high NHI reimbursement price suggested by the pharmaceutical company and the adoption of price-volume agreements, with a $R^2 = 0.68$ (Table 6).

Analyses of how different procedural stages contribute to reimbursement lag showed that the longest median lag under both first-generation and second-generation NHI was between initial pharmaceutical company submission of reimbursement dossiers and subsequent drug reimbursement appraisal listing for the DBC meeting (Tables S6, S7 and Figure S1).

DISCUSSION
We believe this to be the first study to have investigated the reimbursement lag of new drugs before and after the NHI drug reimbursement scheme in Taiwan was reorganized in 2013; the median reimbursement lag increased under the second-generation NHI system and we report key contributory factors.

The average reimbursement lag in Taiwan from 1996 to 2002 was 11.7 months (~ 355 days), lower than 378,458 days (median) in first-generation NHI and days (median) under second-generation NHI in this study (Table 3). Although the reimbursement lag in Taiwan seems not to have improved over time, much has changed between these two study periods, including the introduction of health technology assessments in 2007, and the introduction of PBRS in 2013. Although the current appraisal process is certainly more comprehensive, we are concerned that it may also be cumbersome and lengthy, thereby delaying reimbursement...
and patient access to innovative drugs. We discovered that the main determinant of reimbursement lag was waiting time to be listed in the DBC meeting after submission of the pharmaceutical company dossier, which may be because some dossiers are incomplete or due to lacking human resources. Facilitating communication between pharmaceutical companies and the NHIA and increasing human resources could help to address this problem.

We also found that the reimbursement lag of antineoplastic and immunomodulating agents under first-generation NHI differed little from that of all new drugs; whereas under second-generation NHI, it was considerably longer (Tables S2 and S3). There was also a significant correlation between prolonged reimbursement lag and the introduction of the second-generation NHI (Table 5). These results suggest that the second-generation NHI has not conduced to listing new antineoplastic and immunomodulating agents, and that patient access to such drugs can be improved; a specific review process for antineoplastic and immunomodulating drugs could potentially expedite their reimbursement.

In the United Kingdom, virtually all approved drugs are covered by state insurance through the National Health Service, which refers drugs with both high clinical and economic impacts for health technology assessment by The National Institute for Health and Care Excellence (NICE), which makes recommendations on each drug’s reimbursement and use.21,22 Unlike Taiwan, the United Kingdom drug reimbursement scheme does not have a national list. The mean reimbursement lag between drug authorization and NICE recommendation in our study was 385–520 days. An earlier study, in 2007, reported a mean of 976 days between marketing approval and first issuance of NICE guidance.21 A 2016 IMS Consulting Group report estimated an average of 447 days from marketing authorization to pricing and market access in the United Kingdom,23 commensurate with our results.

The average time between marketing authorization and initiation of reimbursement in Japan was 66 days,24 which was also similar to our estimate. Potential factors

| Table 5 Determinants associated with the reimbursement lag of 40 new drugs in the ATC L groups |
|---------------------------------|-----------------|-----------------|
| Type of pharmaceutical company | β               | Standard error  | P value |
| Domestic (reference)            |                 |                 |
| Multinational                   | -308.63         | 168.03          | 0.077   |
| New drug innovation attribute   |                 |                 |
| Me-too drugs (reference)        |                 |                 |
| Breakthrough drugs              | 214.54          | 230.08          | 0.359   |
| Moderate improvement drugs      | 203.73          | 153.89          | 0.196   |
| Number of alternative drugs     |                 |                 |
| Few (≤ 2 drugs) (reference)     |                 |                 |
| More (> 2 drugs)                | 55.98           | 192.93          | 0.774   |
| Listing status in five countries |                 |                 |
| No (reference)                  |                 |                 |
| Yes                            | -204.43         | 166.25          | 0.229   |
| Number of candidate patients    |                 |                 |
| Few (≤ 208 patients) (reference) |                 |                 |
| More (> 208 patients)           | -155.31         | 139.91          | 0.276   |
| Budgetary impact                |                 |                 |
| ≤ 20 million New Taiwan Dollars (reference) | 468.89 | 154.96 | 0.005 |
| > 20 million New Taiwan Dollars | -0.0002         | 0.0012          | 0.844   |
| NH1 reimbursement price         |                 |                 |
| Yes (reference)                 |                 |                 |
| No                             | 199.85          | 161.18          | 0.225   |
| Under second-generation NHI     |                 |                 |
| No (reference)                  |                 |                 |
| Yes                            | 635.67          | 170.33          | < 0.001 |
| Price-volume agreement          |                 |                 |
| Yes (reference)                 |                 |                 |
| No                             | 55.64           | 131.16          | 0.675   |

ATC, World Health Organization Anatomical Therapeutic Chemical; NHI, National Health Insurance.

| Table 6 Determinants associated with the reimbursement lag of 82 new drugs in the ATC non-L groups |
|---------------------------------|-----------------|-----------------|
| Type of pharmaceutical company | β               | Standard error  | P value |
| Domestic (reference)            |                 |                 |
| Multinational                   | -24.82          | 75.78           | 0.744   |
| New drug innovation attribute   |                 |                 |
| Me-too drugs (reference)        |                 |                 |
| Breakthrough drugs              | -84.32          | 222.98          | 0.707   |
| Moderate improvement drugs      | -107.67         | 83.53           | 0.202   |
| Number of alternative drugs     |                 |                 |
| Few (≤ 2 drugs) (reference)     |                 |                 |
| More (> 2 drugs)                | -10.07          | 67.52           | 0.882   |
| Listing status in five countries |                 |                 |
| No (reference)                  |                 |                 |
| Yes                            | -33.52          | 74.82           | 0.656   |
| Number of candidate patients    |                 |                 |
| Few (≤ 1,419 patients) (reference) |                 |                 |
| More (> 1,419 patients)         | -46.50          | 71.25           | 0.516   |
| Budgetary impact                |                 |                 |
| ≤ 20 million New Taiwan Dollars (reference) | -117.52 | 93.35 | 0.212 |
| > 20 million New Taiwan Dollars |                 |                 |
| NH1 reimbursement price          | 0.047           | 0.005           | < 0.001 |
| Pricing method (the lowest price of 10 reference countries) | Yes (reference) |                 |
| No                             | 34.58           | 111.57          | 0.758   |
| Under second-generation NHI     |                 |                 |
| No (reference)                  |                 |                 |
| Yes                            | 42.51           | 145.41          | 0.771   |
| Price-volume agreement          |                 |                 |
| No (reference)                  |                 |                 |
| Yes                            | 294.91          | 117.71          | 0.015   |

ATC, World Health Organization Anatomical Therapeutic Chemical; NHI, National Health Insurance.

*United Kingdom, Canada, Australia, Japan, and South Korea.
contributing to the shorter reimbursement lag in Japan than other countries implies that reimbursement decisions are prompt, probably due to the Japanese NHI listing scheme not requiring cost-effectiveness evidence prior to April 2016. Furthermore, Japan’s Ministry of Health, Labour, and Welfare stipulates that the NHI price listing procedure should be completed within 60 days, 90 days at longest, to ensure rapid patient access to cutting-edge drugs.

Studies of reimbursement lag of new drugs in other countries have also been reported. In Canada, the delay from approval by Health Canada to provincial reimbursement was 538 days in 2009 and 358 days in 2010; however, as data on provincial reimbursement are not publicly available, we were only able to calculate the lag between drug approval and issuance of a recommendation by the Canadian Agency for Drugs and Technologies in Health (CADTH). In Australia, the time between Australia Drug Evaluation Committee recommendation and Pharmaceutical Benefits Scheme listing was 1,026 days in 2009.

In contrast to Chung, who reported in 2006 that the NHI reimbursement price does not noticeably influence reimbursement lag in Taiwan, we found the pharma-proposed NHI reimbursement price to be significantly associated with prolonged reimbursement lag of new drugs in the non-L group (Table 6); higher budget impact significantly influenced the reimbursement lag of new drugs in the ATC group L (Table 5). These findings reflect current practice. In the last decade, marketing of expensive, innovative anticancer drugs and immunomodulating drugs has increased, imposing a heavier financial burden upon payers; consequently, the budget implications of covering them under NHI has become a crucial issue for decision makers. Some new drugs with high budget impact may not be listed, despite having significant clinical benefits.

Our study had several limitations. First, information on the date of drug reimbursement in the United Kingdom, Canada, and Australia was limited to publicly available data. Second, the study sample of new drugs under second-generation NHI was small; therefore, the results on second-generation NHI should be interpreted cautiously. Nevertheless, our analysis provides a general idea of the reimbursement lag under the current NHI scheme. Third, due to missing data on some drugs, the GLM analyses included only 122 drugs without any missing variables. Fourth, we could not fully capture changes in the healthcare/insurance systems in the United Kingdom, Australia, Canada, Japan, or South Korea over the time period studied here. The impact on these changes on reimbursement lag time in these countries may be a confounding factor we could not account for.

CONCLUSIONS

The reimbursement lag for new drugs in Taiwan is longer under the current NHI scheme than it was under the first-generation NHI. Compared with other countries, it is only longer than lags in the United Kingdom and Japan. The determinants of reimbursement lag differ among WHO ATC categories. We advocate implementing a specific review process for antineoplastic and immunomodulating drugs to expedite their reimbursement. However, future studies are warranted as the small study sample of new drugs under second-generation NHI may limit the interpretation of these findings. Moreover, there is an evident need to establish a system for continuous collection and analysis of the factors associated with reimbursement lag to provide valuable information for policy making.

Supporting Information. Supplementary information accompanies this paper on the Clinical and Translational Science website (www.cts-journal.com).

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