Drug Saf
DOI 10.1007/s40264-017-0524-3

ORIGINAL RESEARCH ARTICLE

Impact of Safety-Related Regulations on Codeine Use in Children: A Quasi-Experimental Study Using Taiwan's National Health Insurance Research Database

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Abstract

Introduction Safety concerns regarding potential life-threatening adverse events associated with codeine have resulted in policy decisions to restrict its use in pediatrics. However, whether these drug safety communications have had an immediate and strong impact on codeine use remains in question.

Objective We aimed to investigate the impact of the two implemented safety-related regulations (label changes and reimbursement regulations) on the use of codeine for upper respiratory infection (URI) or cough.

Methods A quasi-experimental study was performed using Taiwan's National Health Insurance Research Database. Quarterly data of codeine prescription rates for URI/cough visits were reported, and an interrupted time series design was used to assess the impact of the safety regulations on the uses of codeine among children with URI/cough visits. Multivariable logistic regression models were used to explore patient and provider characteristics associated with the use of codeine.

Results The safety-related regulations were associated with a significant reduction in codeine prescription rates of −4.24% (95% confidence interval [CI] −4.78 to −3.70), and the relative reduction compared with predicted rates based on preregulation projections was 60.4, 56.6, and 53.2% in the first, second, and third year after the regulations began, respectively. In the postregulation period, physicians specializing in otolaryngology (odds ratio [OR] 1.47, 95% CI 1.45–1.49), practicing in district hospitals (OR 6.84, 95% CI 5.82–8.04) or clinics (OR 6.50, 95% CI 5.54–7.62), and practicing in the least urbanized areas (OR 1.60, 95% CI 1.55–1.64) were more likely to prescribe codeine to children than their counterparts.

Conclusions Our study provides a successful example of how to effectively reduce the codeine prescriptions in children in the 'real-world' settings, and highlights areas where future effort could be made to improve the safety use of codeine. Future research is warranted to explore whether there was a simultaneous decrease in the incidence rates of codeine-related adverse events following the safety-related regulations.

Electronic supplementary material The online version of this article (doi:10.1007/s40264-017-0524-3) contains supplementary material, which is available to authorized users.

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Published online: 30 March 2017

Key Points

The prescription rates of codeine in children were reduced by more than half after the two implemented safety-related regulations (label changes and reimbursement regulations) took effect. The greatest impact of the regulations was found in children aged <2 years, followed by children aged 2–5, 6–11, and 12–18 years.

After safety regulations began, physicians specializing in otolaryngology, practicing in district hospitals or clinics, and practicing in the least urbanized areas prescribed codeine more frequently than their counterparts.

This study provides a successful example of how to effectively reduce codeine prescriptions in children in the 'real-world' settings, and also highlights areas where future effort could be made to improve the safety use of codeine.

1 Introduction

Codeine-containing products have been widely prescribed to pediatric patients as both analgesics and antitussive agents for many decades [1–3]; however, the benefit of codeine in pediatric patients remains unclear as there is very little evidence supporting its use for cough management in children [4, 5]. Moreover, severe adverse events, such as unanticipated respiratory depression and death [6–10], have been reported in pediatric patients, particularly in infants whose hepatic metabolism system and blood–brain barrier are incompletely developed. These cases are further complicated by unpredictability due to genetic polymorphisms of the hepatic enzymes that metabolize codeine into morphine, a powerful analgesic and respiratory depressant [11].

Growing concern of the potential life-threatening adverse events associated with codeine use in pediatrics has fueled recent safety warnings promulgated by professional organizations and regulatory bodies. The US Food and Drug Administration (FDA) [12], the European Medicines Agency (EMA) [13, 14], Health Canada [15], the American Academy of Pediatrics (AAP) [4, 16], and the American College of Chest Physicians (ACCP) [17] all recommend the restriction of codeine use in children, especially those younger than 12 years of age. However, whether these 'drug safety communications' have had an immediate and strong impact on codeine use remains in question. For example, a previous study in the US has shown that national guidelines did not impact overall prescription rates of codeine, and suggested that more effective interventions should be adopted [1].

In Taiwan, the Taiwan FDA (TFDA) added a new warning to the drug label of codeine-containing products in September 2006 [18]. The warning states that codeine is not recommended for children under 2 years of age and should be used with decreased doses in children between 2 and 12 years of age. In February 2007, in response to the TFDA's labeling regulation, a reimbursement regulation was introduced by Taiwan's National Health Insurance Administration (NHIA) to all its contracted medical institutions [19]. For any physician who prescribes codeine to children under 2 years of age, a penalty is exacted by the NHIA that deducts all reimbursement for healthcare services provided to children <2 years of age in the institution that physician practices in.

The objective of this study was thus to investigate the impact of the two safety-related regulations (i.e. the label changes and reimbursement regulations) on the uses of codeine for upper respiratory infection (URI) or cough using both a 'before and after' and 'interrupted time series' study design. The two safety-related regulations were applied to codeine-containing products regardless of their indications, but children using codeine for URI or cough were the main focus in this study. The rationale for using the URI/cough cohort was that since the trials conducted in children have shown that codeine is not superior to placebo in alleviating acute cough due to URI, and guidelines have recommended against its use as a cough suppressant [4, 5, 17], we hypothesized that the safety-related regulations would have significant impacts in this patient population. Specifically, we also investigated the characteristics of children who use codeine, and the doctors who prescribe it to them, to help highlight areas in which clinicians and policy makers can exert more effort in order to more effectively reduce or eliminate codeine use among young children.

2 Methods

2.1 Data Source

This was a retrospective, population-based study using data from Taiwan's National Health Insurance Research Database (NHIRD), a nationwide database composed of outpatient and inpatient claims for 99% of Taiwan's population of more than 23 million [20]. Comprehensive data, including patient demographics, diagnosis, prescriptions, and healthcare utilization are well-documented in the

database. We used a subset of the NHIRD, the Longitudinal Health Insurance Database, which contains one million beneficiaries randomly selected from the NHIRD in 2010, as our data source. Claims data from 2003 to 2010 for the one million beneficiaries were extracted to compose an 8-year panel of claims for analysis. This study was approved by the Institutional Review Board of the National Taiwan University Hospital (201601018RIND). Informed consent was waived since the identification information in the NHIRD are encrypted to ensure privacy.

2.2 Study Population

Patients aged under 18 years who had experienced an outpatient visit for URI (defined as a visit with a principle diagnosis of International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] codes 460.x–466.x, 487.x) or cough (ICD-9-CM code 786.2) were included as the study population and were divided into four age groups: infants (aged <2 years), preschool children (aged 2–5 years), school-age children (aged 6–11 years), and adolescents (aged 12–18 years). The 'primary target group' was children aged <2 years targeted by both the label changes and reimbursement regulations, and the 'secondary target group' was preschool children and school-age children targeted by the label changes. Adolescents were not targeted by the two safety-related regulations but were included as a 'reference group' and to examine whether any spillover effect occurred.

2.3 Measures of Codeine and Other Antitussive Use

We used the prescribing records in the outpatient visit database of the NHIRD to capture codeine prescriptions in our study. The quarterly prescription rates of codeine were calculated by dividing the number of URI/cough visits with prescription of oral codeine-containing medication (numerator) by the number of URI/cough visits (denominator). Details about the codeine prescriptions were further extracted, including product formulation, dosage form, and the most frequently used substances. In addition, URI/-cough visits with prescriptions of other antitussives were identified to assess the rate of therapeutic duplication, which was defined as a physician prescribing codeine and other antitussives on the same visit. Oral antitussives available in Taiwan were included in the analyses, including opium antitussives (dextromethorphan, dimemorfan, noscapine, and opium) and non-opium antitussives (benproperine, benzonatate, butamirate, carbetapentane, chlophedianol, cloperastine, dibunate, hydropropizine, oxeladin, oxolamine, and tipepidine).

2.4 Statistical Analysis

The study employed a before–after design with a preregulation period consisting of a 4-year control phase from the first quarter (Q1) of 2003 to the second quarter (Q2) of 2006, and a postregulation period from the third quarter (Q3) of 2007 to the fourth quarter (Q4) of 2010. Because the safety warning was issued in September 2006 and was followed by the reimbursement regulation in February 2007, we considered the third quarter of 2006 to the second quarter of 2007 as a transition period to account for the lagged effects of policy interventions.

For each URI/cough visit, patient characteristics (sex, age, and principle diagnosis) and provider characteristics (physician specialties, hospital accreditation level, and urbanization level of hospital location) were collected. Urbanization level was classified into seven categories (1 indicating the most urbanized area, and 7 indicating the least urbanized area) according to the definition established by Taiwan's National Health Research Institutes (NHRI) based on the population density, the proportion of people with a college or higher educational level, the proportion of people aged over 65 years, the proportion of the agricultural population, and the number of physicians per 100,000 people in each township in Taiwan [21, 22]. Data regarding patient and provider characteristics, as well as codeine prescriptions, were examined for the pre- and postregulation periods. Multivariable logistic regression models were conducted separately for the pre- and postregulation period to explore significant patient and provider characteristics associated with the use of codeine. The associations are presented as odds ratios (ORs) with 95% confidence intervals (CIs).

An interrupted time series design was further used to assess the impact of the safety regulations on quarterly prescription rates of codeine among children with URI/-cough visits. This study design is among the most robust quasi-experimental designs that can control for pre-existing trends of codeine prescription rates to estimate changes attributable to the safety-related regulations [23]. Segmented regression models were used to estimate changes in both the level and trend of quarterly codeine prescription rates. A total of 14 data points before regulations (2003 Q1–2006 Q2) and 14 data points after regulations (2007 Q3–2010 Q4) were included in the segmented regression models, while the four data points in the transition period (2006 Q3–2007 Q2) were excluded.

The basic segmented regression model contained terms to estimate the level of the codeine prescription rates at the beginning of the preregulation period (the intercept), the trend in the preregulation period (the slope), a change in the level (an immediate change at the beginning of the postregulation period), and a change in the trend

(difference between the pre- and postregulation slopes) [23]. To adjust for seasonal variation, a term indicating each season was further added. In addition, autocorrelation was tested using the Durbin–Watson test and, if significant, was included in the models [24]. Electronic supplementary material 1 provides more information about the segmented regression model we used. To express the impact of the safety regulations, we compared the estimated postregulation codeine prescription rates with the predicted codeine prescription rates (rates estimated using the baseline level and baseline trend as if the safety regulations had not occurred), and the absolute changes and relative changes were reported in 2008 Q3 (1 year later), 2009 Q3 (2 years later), and 2010 Q3 (3 years later) to assess the long-term effect of the regulations [23, 25]. Finally, stratified analyses were performed according to patient and provider characteristics.

All of the analyses were performed using SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA). A two-sided p value was used, with $p < 0.05$ considered statistically significant.

3 Results

3.1 Upper Respiratory Infection (URI) or Cough Visits in Children

There were 5,894,062 and 4,441,137 URI/cough visits in children within the pre- and postregulation period, respectively (Table 1). Approximately 40% of URI/cough visits were identified in preschool children (aged 2–5 years), followed by 30% in school-age children (aged 6–11 years), 15% in infants (aged 0–1 years), and 15% in adolescents (aged 12–18 years). The distributions of age, sex, diagnosis, hospital accreditation level, and urbanization level of hospital location were comparable between the pre- and postregulation periods.

3.2 Codeine Prescription for URI/Cough Visits in Children

There were 381,999 and 146,817 URI/cough visits in which codeine was prescribed within the pre- and postregulation period, respectively (Table 2). Among these visits, the co-prescription rates of other antitussives in combination with codeine were 44.6 and 39.6% in the pre- and postregulation period, respectively. In particular, in approximately one-third (37.2% in the preregulation period and 29.9% in the postregulation period) of these visits in which codeine was prescribed, opium antitussives were also prescribed. In both the pre- and postregulation periods, 99% of the codeine prescriptions were multiple-ingredient products. Most of these products contained more than three active ingredients with different pharmacological properties. Products consisting of a combination of codeine and terpin were the most frequently prescribed codeine-containing products during the study period.

3.3 Patient and Provider Characteristics Associated with Codeine Prescriptions

In the preregulation period, children aged 2–5 years (OR 1.68, 95% CI 1.66–1.70) were more likely than other age groups to receive a codeine prescription, but children aged 6–11 years (OR 21.04, 95% CI 19.91–22.23) and 12–18 years (OR 22.68, 95% CI 21.46–23.98) were more likely to receive a codeine prescription in the postregulation period (Table 3). Children with a principle diagnosis of laryngitis and tracheitis, bronchitis and bronchiolitis, or cough were more likely to receive a codeine prescription in both periods compared with those with another principle diagnosis. As for provider characteristics, nonpediatricians were more likely to prescribe codeine than pediatricians in the outpatient department in both periods, and otolaryngologists were the most likely to prescribe codeine to children after safety regulations began (OR 1.47, 95% CI 1.45–1.49). In addition, physicians practicing in district hospitals (OR 6.84, 95% CI 5.82–8.04) and clinics (OR 6.50, 95% CI 5.54–7.62) were six to seven times more likely to prescribe codeine than those practicing in medical centers in the postregulation period. We also found some urban–rural discrepancies in physicians who prescribed codeine.

3.4 Effects of the Safety-Related Regulations on Quarterly Codeine Prescription Rates for URI/Cough Visits

Overall, codeine prescription rates for URI/cough visits in children gradually increased in the preregulation period, from 6.64% in the first quarter of 2003 to 7.35% in the first quarter of 2006. After the safety regulations began, codeine prescription rates suddenly dropped to 2.74% in the third quarter of 2007 and then slightly increased during the 3 years following implementation, up to 3.39% in the third quarter of 2010 (Fig. 1a). The safety-related regulations were associated with a significant reduction in codeine prescription rates of −4.24% (95% CI −4.78 to −3.70), and the relative reduction compared with predicted rates was 60.4% (95% CI 55.8–64.9%), 56.6% (95% CI 50.8–62.5%), and 53.2% (95% CI 44.8–61.6%) in the first, second, and third year after regulations began, respectively (Table 4).

Age-stratified analysis showed that children aged 2–5 years had the highest codeine prescription rates at the

Table 1 Patient and provider characteristics of URI/cough visits

	Preregulation period		Postregulation period	
	N	%	*N*	%
Overall	5,894,062		4,441,137	
Age, years				
0–1 (0 ≤ age <2)	949,659	16.1	658,213	14.8
2–5 (2 ≤ age <6)	2,373,367	40.3	1,682,816	37.9
6–11 (6 ≤ age <12)	1,760,513	29.9	1,328,617	29.9
12–17 (12 ≤ age <18)	810,523	13.8	771,491	17.4
Sex				
Female	2,771,703	47.0	2,069,677	46.6
Male	3,122,359	53.0	2,371,460	53.4
Diagnosis				
Common cold	518,613	8.8	361,816	8.1
Sinusitis	632,026	10.7	641,982	14.5
Pharyngitis	310,624	5.3	240,109	5.4
Tonsillitis	389,709	6.6	411,696	9.3
Laryngitis or tracheitis	317,779	5.4	206,923	4.7
URI of unspecified site	2,711,148	46.0	1,636,053	36.8
Bronchitis or bronchiolitis	857,380	14.5	694,250	15.6
Influenza	108,321	1.8	84,570	1.9
Cough	48,462	0.8	163,738	3.7
Physician specialty				
Outpatient department				
Pediatrics	1,878,636	31.9	1,806,503	40.7
Otolaryngology	1,577,086	26.8	1,242,369	28.0
Family medicine	632,683	10.7	926,826	20.9
Internal medicine	293,431	5.0	373,063	8.4
Others	1,445,971	24.5	38,022	0.9
Emergency department	66,255	1.1	54,354	1.2
Hospital accreditation level				
Medical center	72,485	1.2	56,794	1.3
Regional hospital	159,214	2.7	125,218	2.8
District hospital	205,644	3.5	121,339	2.7
Clinic	5,456,719	92.6	4,137,786	93.2
Urbanization level				
1 (most urbanized)	1,330,517	22.6	1,003,832	22.6
2	2,117,134	35.9	1,602,370	36.1
3	1,145,579	19.4	882,443	19.9
4	960,558	16.3	683,447	15.4
5	32,001	0.6	27,724	0.6
6	129,551	2.2	99,845	2.2
7 (least urbanized)	178,722	3.0	141,476	3.2

URI upper respiratory infection

beginning of the study (7.36%), followed by children aged 6–11 years (6.99%), 12–18 years (6.32%), and <2 years (4.66%). Among all age groups, codeine prescription rates increased during the preregulation period and abruptly decreased after the safety regulations. However, the decline of codeine prescription rates only continued among children aged <2 years and those aged 12–18 years, while an upward trend in codeine prescription rates among children aged 2–5 and 6–11 years was observed in the postregulation period (Fig. 1b–e). The effect of safety regulations at 1 year postregulation was greater in younger children. The greatest relative reduction of codeine

Table 2 Codeine prescription for URI/cough visits

	Pre-regulation period		Post-regulation period	
	N	%	N	%
Visits with codeine prescription	381,999		146,817	
Co-prescribing of other antitussive	170,381	44.6	58,189	39.6
Co-prescribing of other opium antitussive	141,916	37.2	43,950	29.9
Codeine prescriptions	391,808		149,157	
Single drug formulations	261	0.1	162	0.1
Fixed-dose combinations	391,547	99.9	148,995	99.9
Syrup/ Solution	190,828	48.7	79,719	53.5
Tablet/ Capsule/ Granule	200,719	51.3	69,276	46.5
Top 10 frequently used medications (ingredients other than codeine were listed)	Terpin		Terpin	
	Guaiacolsulfonate, platycodon, chlorpheniramine, methylephedrine		Guaiacolsulfonate, chlorpheniramine, methylephedrine	
	Papaverine, phenolphthalein		Guaiacolsulfonate, platycodon, chlorpheniramine, methylephedrine	
	Senega, ammonium chloride, chlorpheniramine, methylephedrine, caffeine		Senega, ammonium chloride, chlorpheniramine, methylephedrine, caffeine	
	Guaiacolsulfonate, chlorpheniramine, methylephedrine		Chlorpheniramine, methylephedrine, caffeine	
	Guaifenesin, ammonium chloride, chlorpheniramine, phenylephrine		Papaverine, phenolphthalein	
	Guaiacolsulfonate, polygala, ammonium chloride, chlorpheniramine, ephedrine		Guaifenesin, ammonium chloride, chlorpheniramine, phenylephrine	
	Chlorpheniramine, methylephedrine, caffeine		Acetaminophen	
	Acetaminophen		Guaiacolsulfonate, polygala, ammonium chloride, chlorpheniramine, ephedrine	
	Guaifenesin, ammonium chloride, sodium citrate, chlorpheniramine, phenylephrine		Guaiacolsulfonate, chlorpheniramine, methylephedrine, acetaminophen, caffeine	

URI upper respiratory infection

prescription rate was observed among children aged <2 years (98.3%, 95% CI 94.3–102.3%), followed by children aged 2–5 years (70.3%, 95% CI 66.7–74.0%), 6–11 years (45.4%, 95% CI 37.3–53.4%), and 12–18 years (28.8%, 95% CI 19.7–37.8%). Nevertheless, when we examined the effect of the safety regulations on a yearly basis, the reduction in the codeine prescription rate revealed a decrease over time in children aged 2–5 years and 6–11 years (Table 4). Furthermore, as shown in the analysis stratified by different patient and provider characteristics, the relative changes in trends during the postregulatory period were numerically smaller in the least urbanized area compared with the other areas (see electronic supplementary material 2 and 3).

4 Discussions

This is the first study examining the utilization of codeine in the pediatric population after the labeling revision announcements and accompanying reimbursement regulations of codeine in Taiwan. We examined the codeine prescribing patterns in children treated for URI or cough from 2003 to 2010 and quantified the effect of the policy

Table 3 Patient and provider characteristics associated with codeine prescriptions

	Preregulation period		Postregulation period	
	OR	95% CI	OR	95% CI
Age, years				
0–1 (0 ≤ age <2)	1.00	–	1.00	–
2–5 (2 ≤ age <6)	1.68	1.66–1.70	13.93	13.18–14.72
6–11 (6 ≤ age <12)	1.53	1.51–1.55	21.04	19.91–22.23
12–17 (12 ≤ age <18)	1.39	1.37–1.41	22.68	21.46–23.98
Sex				
Female	1.00	–	1.00	–
Male	1.01	1.01–1.02	1.02	1.01–1.03
Diagnosis				
Common cold	1.00	–	1.00	–
Sinusitis	1.10	1.08–1.12	1.09	1.06–1.11
Pharyngitis	0.94	0.93–0.96	0.94	0.91–0.97
Tonsillitis	0.81	0.79–0.82	0.87	0.85–0.90
Laryngitis or tracheitis	1.31	1.28–1.33	1.56	1.51–1.60
URI of unspecified site	1.07	1.05–1.08	1.00	0.98–1.02
Bronchitis or bronchiolitis	1.60	1.58–1.62	1.58	1.55–1.62
Influenza	1.16	1.13–1.19	0.82	0.78–0.85
Cough	1.75	1.70–1.81	1.34	1.29–1.38
Physician specialty				
Outpatient department				
Pediatrics	1.00	–	1.00	–
Otolaryngology	1.13	1.12–1.14	1.47	1.45–1.49
Family medicine	1.03	1.02–1.04	1.36	1.34–1.38
Internal medicine	1.25	1.23–1.27	1.20	1.17–1.22
Others	1.07	1.06–1.08	1.32	1.25–1.39
Emergency department	0.63	0.59–0.68	0.88	0.80–0.98
Hospital accreditation level				
Medical center	1.00	–	1.00	–
Regional hospital	1.75	1.62–1.90	1.90	1.60–2.26
District hospital	4.53	4.21–4.88	6.84	5.82–8.04
Clinic	5.13	4.77–5.52	6.50	5.54–7.62
Urbanization level				
1 (most urbanized)	1.00	–	1.00	–
2	1.45	1.44–1.47	1.16	1.14–1.18
3	1.67	1.65–1.69	1.19	1.17–1.21
4	1.23	1.21–1.24	1.04	1.02–1.06
5	1.54	1.48–1.61	1.23	1.16–1.31
6	1.39	1.36–1.42	1.32	1.28–1.37
7 (least urbanized)	1.36	1.33–1.39	1.60	1.55–1.64

OR odds ratio, *CI* confidence interval, *URI* upper respiratory infection

interventions using an interrupted time series design. Overall, the prescription rates of codeine for URI/cough were reduced by more than half after the safety-related regulations took effect, and the greatest impact of the regulations was found in children aged <2 years ('the primary targeted group', targeted by both regulations), followed by children aged 2–12 years ('the secondary targeted group', targeted by the labeling changes). At the same time, a smaller reduction in codeine prescription rates found in adolescents, for whom the regulations do not apply, suggested a spillover effect of the safety-related regulations.

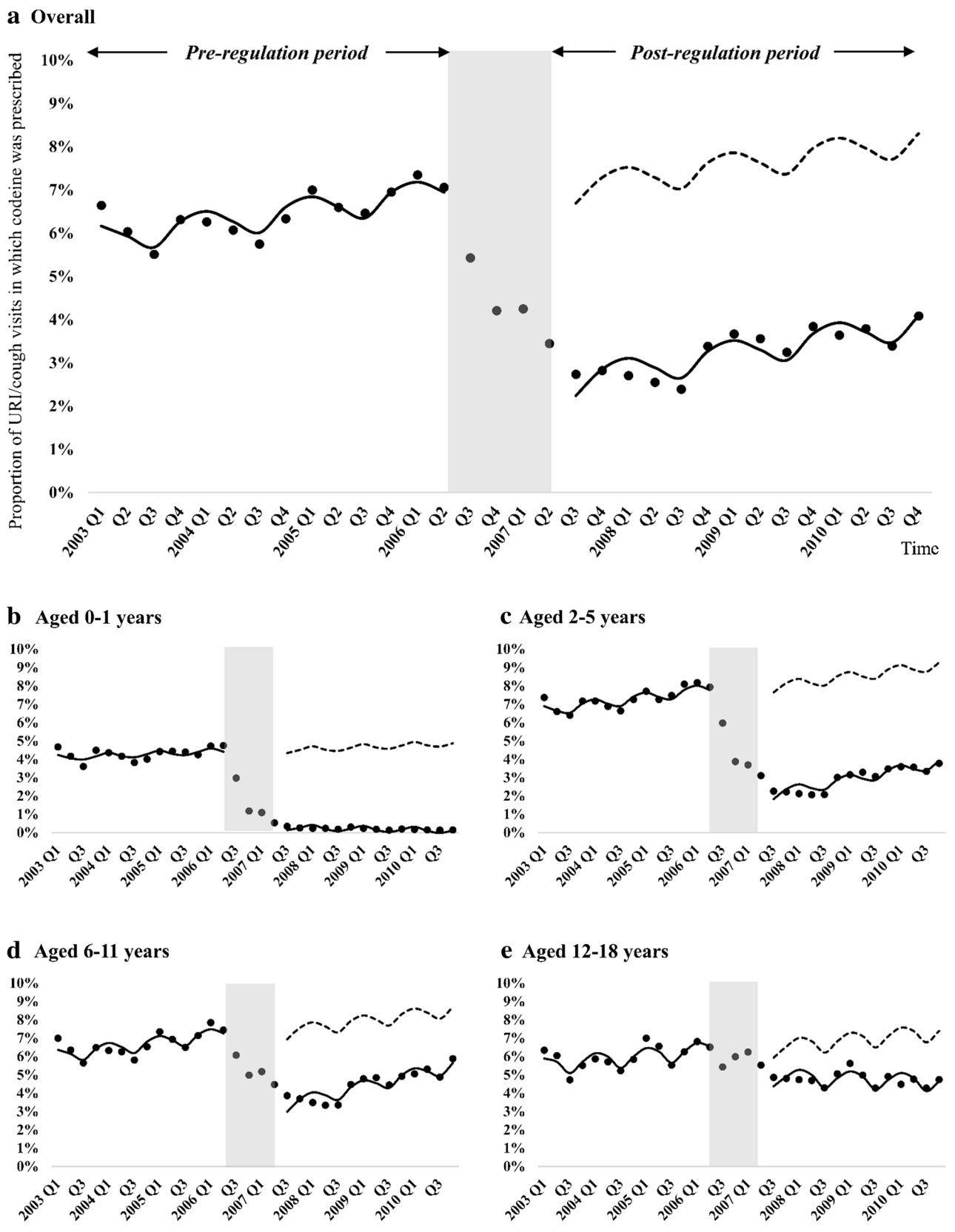

Fig. 1 Quarterly prescription rates of codeine before and after the safety regulations. *URI* upper respiratory infection, *Qx* quarter *x*

Table 4 Estimated changes in prescription rates of codeine following the safety regulations

	Codeine prescription rate									
	Intercept (95% CI)	Baseline trend (95% CI)	Level change (95% CI)	Trend change (95% CI)	1 year postregulation		2 years postregulation		3 years postregulation	
					Absolute change[a] (95% CI)	Relative change[a] (95% CI)	Absolute change[a] (95% CI)	Relative change[a] (95% CI)	Absolute change[a] (95% CI)	Relative change[a] (95% CI)
Overall	6.10 (5.60 to 6.60)[b]	0.07 (0.01 to 0.12)[b]	−4.24 (−4.78 to −3.70)[b]	0.03 (−0.06 to 0.11)	−4.10 (−4.88 to −3.33)	−60.4% (−64.9 to −55.8)	−4.00 (−4.92 to −3.08)	−56.6% (−62.5 to −50.8)	−3.89 (−4.99 to −2.80)	−53.2% (−61.6 to −44.8)
Age, years										
0–1	4.04 (3.75 to 4.33)[b]	0.03 (0.00 to 0.06)[b]	−4.17 (−4.50 to −3.84)[b]	−0.04 (−0.08 to 0.00)[b]	−4.38 (−4.84 to −3.93)	−98.3% (−102.3 to −94.3)	−4.55 (−5.09 to −4.01)	−99.4% (−103.2 to −95.6)	−4.72 (−5.37 to −4.07)	−100.5% (−105.4 to −95.5)
2–5	6.85 (6.33 to 7.37)[b]	0.08 (0.03 to 0.14)[b]	−5.77 (−6.32 to −5.22)[b]	0.04 (−0.05 to 0.13)	−5.57 (−6.38 to −4.77)	−70.3% (−74.0 to −66.7)	−5.41 (−6.36 to −4.47)	−65.6% (−70.2 to −61.1)	−5.26 (−6.39 to −4.12)	−61.3% (−68.0 to −54.6)
6–11	6.34 (5.56 to 7.12)[b]	0.06 (−0.03 to 0.14)	−3.54 (−4.33 to −2.75)[b]	0.09 (−0.04 to 0.22)	−3.10 (−4.32 to −1.88)	−45.4% (−53.4 to −37.3)	−2.75 (−4.16 to −1.33)	−38.9% (−50.5 to −27.3)	−2.39 (−4.07 to −0.71)	−32.8% (−49.7 to −16.0)
12–17	5.52 (4.94 to 6.10)[b]	0.06 (0.00 to 0.12)	−1.31 (−1.98 to −0.64)[b]	−0.09 (−0.18 to 0.00)	−1.74 (−2.63 to −0.86)	−28.8% (−37.8 to −19.7)	−2.09 (−3.15 to −1.03)	−33.2% (−43.7 to −22.7)	−2.43 (−3.72 to −1.14)	−37.3% (−50.1 to −24.5)

CI confidence interval

[a] Absolute changes and relative changes were calculated compared with the predicted codeine prescription rates (rates estimated using the intercept and baseline trend as if the safety regulations had not occurred)

[b] $p < 0.05$

To ensure the safety of medication use after market approval, a variety of strategies such as direct health professional communications (or 'Dear Doctor letters'), public health advisories, and drug label revisions (or 'black-box warnings' for severe adverse effects) have been used to communicate new safety issues regarding drugs with patients and healthcare professionals, and the variation in the effect of different safety-related regulations on drug utilization has been documented in prior studies [26, 27]. In the case of codeine use in Taiwanese children, infants and toddlers (aged <2 years) were the primary focus of the safety-related regulations because they were the group most vulnerable to adverse drug events associated with codeine use [4, 11]. Therefore, in addition to the labeling revision, reimbursement regulation was issued in Taiwan to reinforce the safety warnings. Since Taiwan's National Health Insurance (NHI) is a mandatory enrollment and single-payer health system, physicians' prescribing behaviors are strongly altered by the reimbursement regulation. As expected, our findings revealed that codeine was rarely used in children aged <2 years following the policy interventions.

Children aged 2–12 years account for two-thirds of URI/cough visits among the pediatric population, and codeine prescription rates in this age group also decreased significantly after the safety regulations. However, as shown in Fig. 1, an upturning trend was found in children aged 2–5 and 6–11 years, whereas the decline was maintained in children aged <2 years and 12–18 years over the 3.5 years after the safety regulations began (postregulation trends estimated using only the data points in the postregulation period: aged <2 years, −0.01, 95% CI −0.02 to −0.01; 2–5 years, +0.11, 95% CI +0.14 to +0.19; 6–11 years, +0.15, 95% CI +0.05 to +0.25; and 12–18 years, −0.02, 95% CI −0.07 to +0.03). A possible explanation for the reversal in the decline of codeine prescription rates was that the initial effect of the safety regulations may taper off over time. Another explanation was that the prescription rates of codeine may be influenced by another new policy initiated by Taiwan's NHIA during the study period. In Taiwan, most clinics had chosen the 'fixed fees by days of supply' approach for medication reimbursements rather than the 'fee for service' approach [28]. In September 2008, the NHIA increased the fixed fees for physicians who prescribed pediatric oral formulations to children under 12 years of age to encourage the use of child-suitable preparations (e.g. a 1-day supply without pediatric oral formulation received a reimbursement of US$0.78, while a 1-day supply with pediatric oral formulations received a reimbursement ranging between US$0.97 and US$1.28). Although the prescription rates of codeine in the postregulation period were very low compared with the preregulation period, persistent communication and education may be warranted, especially given recent recommendations from Health Canada [15] and the EMA [13, 14] to avoid codeine use not only in infants but also in children aged <12 years. In addition, the changes we observed over time point out the importance of continued assessments to ensure that the effects of safety-related policy interventions are sustained.

Of note, our results revealed several areas about which special consideration should be given by policy makers and healthcare professionals. First, physicians with different specialties responded differently to the safety regulations. After the safety regulations took effect, pediatricians were found less likely to prescribe codeine, while otolaryngologists were found more likely to prescribe codeine. Prior studies have demonstrated similar results of pediatricians being less likely to prescribe suboptimal medications to children because they may have more expert knowledge about pediatric drug use and may be more sensitive to new medical information about children [29, 30]. Further communication should be made with nonpediatricians to resolve the cross-specialty discrepancy. Moreover, our results suggest that more than one-quarter of the children went to otolaryngologists for URI or cough. Since people in Taiwan are free to choose their physicians without referral, and are accustomed to choosing a specialty based on their symptoms, educating parents to bring their children to a pediatrician is also important for preventing children from potentially harmful medications [30].

Second, although our results did not show a linear relationship within the seven urbanization levels, physicians practicing in the least urbanized area were more likely to prescribe codeine to children than those practicing in areas with more urbanization. A previous study in Taiwan found that off-label antibiotics were also more likely to be prescribed in rural regions [29]. The urban–rural disparity in prescribing behaviors may well be related to inequitable access to up-to-date medical information, including human resources, library resources, and Internet resources of information [29, 31, 32]. Efforts should be made to understand the obstacles preventing physicians practicing in rural areas from changing prescribing behaviors, which might warrant development of area-specific strategies for communicating drug safety issues.

Third, we found that a substantial number of codeine prescriptions were co-prescribed with other antitussives during the same visits. It was unclear whether physicians prescribed codeine as an add-on therapy for more severe cough symptoms or unintentionally prescribed more than one product with the same pharmacological effects. However, there is a clear need to continuously communicate with physicians that therapeutic duplication is dangerous. The risk of overdose and adverse drug events may further increase with concomitant use of codeine and other

antitussives, especially opium antitussives. It has been reported that opium antitussives, such as dextromethorphan [4], have a similar risk profile as codeine.

5 Limitations

Our study provides valuable information for future healthcare policymaking, but, as with any observational study based on claims databases, it has several limitations. First, we were unable to capture variables not recorded in the NHIRD, including the severity of URI or cough and the reason for using codeine (used as an analgesic or antitussive). Although we have conducted stratified analysis according to several patient and provider characteristics, we could not evaluate the impact of these unmeasured factors on our findings. It is also important to recognize that the severity of symptoms may play a role in the relationship between provider characteristics and use of codeine. For example, a potential reason that otolaryngologists were more likely to prescribe codeine to children may be that children with more severe URI or cough symptoms were more likely to visit otolaryngologists. Furthermore, we expected that the dosage of codeine prescriptions may also decrease after the safety warnings, and the safety use of codeine may further lead to the decline in incidence rates of codeine-related adverse events. However, we did not have information on dosages of codeine-containing products in the NHIRD as half of them were prescribed in liquid form (syrup/solution). In addition, codeine-related adverse events, particularly respiratory depression, were not well recorded in the NHIRD as the identification of these adverse events relied on biomedical symptoms. Research using other data sources is warranted to explore the impact of safety-related regulations on the dosage of codeine prescriptions and the incidence rates of codeine-related adverse events. Second, physicians in the clinics adopting the 'fixed fees by days of supply' approach (e.g. 1-day supply of any prescribed drug receives a fixed reimbursement payment) [28] may underreport the medication they prescribe; therefore, codeine prescription rates may be underestimated. Additionally, we were unable to obtain relevant data on over-the-counter medications; therefore, the results may not reflect the whole picture relating to the use of codeine in children. Third, other concurrent interventions or events might have impacts on the reduction in prescription rates of codeine. However, to the best of our knowledge, there were no other co-occurring policy interventions or events during the transition period that could have a significant impact on codeine use found in our study. Fourth, we have evaluated the impact of different patient and provider characteristics on codeine use in children, but we could not include parents' treatment-seeking behaviors. Since physicians may have prescribed symptom relief medication according to parents' requests, and studies have indicated that parents have continued to believe in the safety and efficacy of cough and cold medications even after the FDA advisory recommended against their use [33], future research is needed to understand parental influence on compliance to regulations aimed at restricting the use of codeine by children. Fifth, there were differences in the distribution of physician specialty between the pre- and postregulation periods. The differences were mainly due to the change in the regulation for physicians contracted with Taiwan's NHI. Before 2007, contracted physicians could report their specialty as 'general practice' (specialty categorized as 'others' in our study) while applying for their reimbursement from the NHI, but they were required to report their specialty more specifically after 2007 (i.e. the specialty 'general practice' was no longer recorded in the NHIRD after 2007). Finally, our study was conducted using nationally representative data to ensure generalizability. However, the restriction of our analysis to children with URI or cough may limit the generalizability of our findings to children using codeine for other indications. It would be of interest to undertaken future research on the effect of the safety regulations in other patient populations. Moreover, given the unique national health system in Taiwan, the results may not be directly applicable to other healthcare systems.

6 Conclusions

The prescription rates of codeine were reduced by more than half after the safety-related regulations took effect. The greatest impact of the regulations was found in children aged <2 years, followed by children aged 2–5, 6–11, and 12–18 years. Our study provides a successful example of how to effectively reduce the prescription of codeine for children with URI or cough in 'real-world' settings, and highlights areas where future effort could be made. Continuous monitoring of the use of codeine in pediatrics is warranted to ensure the sustained effects of the regulatory action, and more attention should be paid to the determinants of prescribing codeine identified in our study. Future research is needed to explore whether there was a simultaneous decrease in the incidence rates of codeine-related adverse events following the safety-related regulations.

Acknowledgements The authors thank the NHIA and NHRI for making available the databases for this study; however, the content of this article in no way represents any official position of the NHIA or NHRI.

Compliance with Ethical Standards

Funding This work was supported by a research grant from the Food and Drug Administration, Ministry of Health and Welfare (MOHW), Taiwan (MOHW 105-FDA-D-113-000411). The funding source had no role in the design and conduct of the study; collection, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and the decision to submit the manuscript for publication.

Conflict of interest Chih-Wan Lin, Ching-Huan Wang, Wei-I Huang, Wei-Ming Ke, Pi-Hui Chao, Wen-Wen Chen, and Fei-Yuan Hsiao have no conflicts of interest that are directly relevant to the content of this study.

Ethical approval This study was approved by the Institutional Review Board of the National Taiwan University Hospital (201601018RIND). Informed consent was waived since the identification information in Taiwan's National Health Insurance Research Database is encrypted to ensure privacy.

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