

Background

Safety concerns regarding severe adverse events associated with codeine have resulted in policy decisions to restrict its use in pediatrics in both Taiwan and other countries.

In September 2006, Taiwan Food and Drug Administration (TFDA) required manufacturers to add a new warning to the drug label of codeine-containing products, which stated that codeine is not recommended in children under 2 years old and should be used with decreased doses in children 2 -12 years old.

In February 2007, National Health Insurance Administration (NHIA), Taiwan, further imposed a reimbursement regulation, which stated that payments of health care services will be subtracted for institutions with excessive rates of prescribing codeine in children under 2 years old.

Objective

To investigate the epidemiology and determinants of codeine use in Taiwanese pediatric population.

To assess whether the safety-related regulatory action have an impact on the codeine prescription trends.

Methods

Data source: 2003 -2010 Taiwan’s National Health Insurance Research Database

Study population: Patients under 18 years who experienced an outpatient visit for upper respiratory infection (URI) (defined as a visit with principle diagnosis of ICD-9-CM codes 460.x-466.x, 487.x) or cough (ICD-9-CM code 786.2).

**Interrupted time series design:**

Quarterly data of codeine prescription rates of URI/cough visits were reported.

Segmented regression models were used to estimate changes in both the level and the trend of codeine prescription rates.

Pre-regulation period: 2003/1/1 – 2006/6/30

Transition period: 2006/7/1 – 2007/6/30

Post-regulation period: 2007/7/1 – 2010/12/31

Estimated post-regulation codeine prescription rates were compared to the predicted codeine prescription rates (rates estimated using the baseline level and baseline trend as if the safety-regulation had not occurred), and the absolute and relative changes were reported.

Multivariable logistic regression models were used to explore significant patient and provider characteristics associated with the use of codeine.

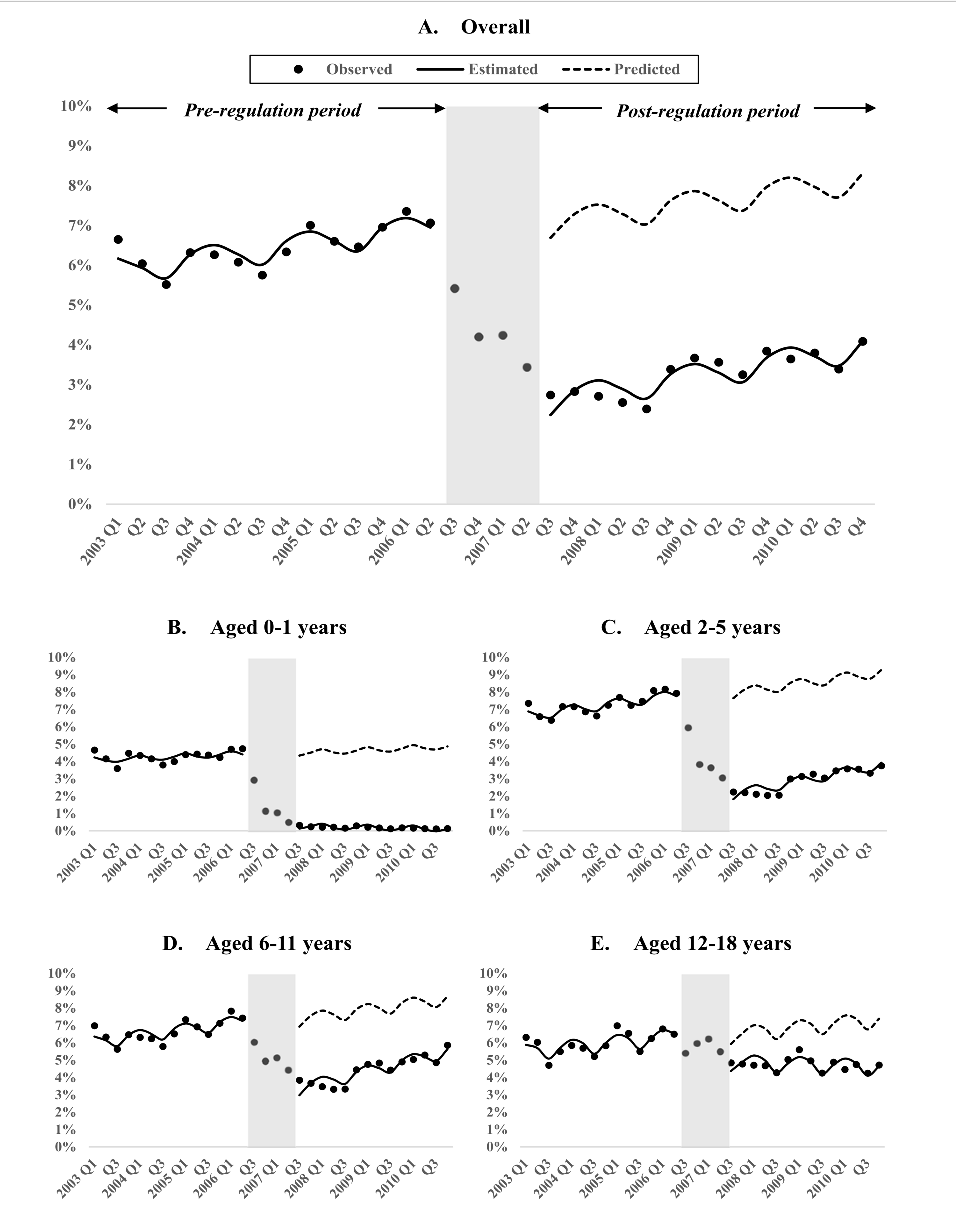
Results

The prescription rates of codeine were reduced by more than one-half following the safety regulation, and the reduction was greater in children with younger age.

Physicians whose specialties were otolaryngology, practicing in district hospitals or clinics, and practicing in rural area prescribed codeine to children more frequently.

Approximately 40% of URI/cough visits with codeine prescriptions were co-prescribed with other antitussives in the same visit.

Codeine prescription rates before and after the safety regulation



Patient and provider characteristics associated with codeine use

	Pre-regulation period			Post-regulation period		
	OR	95%CI	P value	OR	95%CI	P value
<b>Age</b>						
0-1 (0 ≤ age <2)	1.00	-	-	1.00	-	-
2-5 (2 ≤ age <6)	1.68	1.66 - 1.70	<0.0001	13.93	13.18 - 14.72	<0.0001
6-11 (6 ≤ age <12)	1.53	1.51 - 1.55	<0.0001	21.04	19.91 - 22.23	<0.0001
12-17 (12 ≤ age <18)	1.39	1.37 - 1.41	<0.0001	22.68	21.46 - 23.98	<0.0001
<b>Gender</b>						
Female	1.00	-	-	1.00	-	-
Male	1.01	1.01 - 1.02	<0.0001	1.02	1.01 - 1.03	0.0011
<b>Diagnosis</b>						
Common cold	1.00	-	-	1.00	-	-
Sinusitis	1.10	1.08 - 1.12	<0.0001	1.09	1.06 - 1.11	<0.0001
Pharyngitis	0.94	0.93 - 0.96	<0.0001	0.94	0.91 - 0.97	0.0002
Tonsillitis	0.81	0.79 - 0.82	<0.0001	0.87	0.85 - 0.90	<0.0001
Laryngitis or tracheitis	1.31	1.28 - 1.33	<0.0001	1.56	1.51 - 1.60	<0.0001
URI of unspecified site	1.07	1.05 - 1.08	<0.0001	1.00	0.98 - 1.02	0.9942
Bronchitis or bronchiolitis	1.60	1.58 - 1.62	<0.0001	1.58	1.55 - 1.62	<0.0001
Influenza	1.16	1.13 - 1.19	<0.0001	0.82	0.78 - 0.85	<0.0001
Cough	1.75	1.70 - 1.81	<0.0001	1.34	1.29 - 1.38	<0.0001
<b>Physician specialty</b>						
Outpatient Department						
Pediatrics	1.00	-	-	1.00	-	-
Otolaryngology	1.13	1.12 - 1.14	<0.0001	1.47	1.45 - 1.49	<0.0001
Family medicine	1.03	1.02 - 1.04	<0.0001	1.36	1.34 - 1.38	<0.0001
Internal medicine	1.25	1.23 - 1.27	<0.0001	1.20	1.17 - 1.22	<0.0001
Others	1.07	1.06 - 1.08	<0.0001	1.32	1.25 - 1.39	<0.0001
Emergency Department	0.63	0.59 - 0.68	<0.0001	0.88	0.80 - 0.98	0.0189
<b>Hospital accreditation level</b>						
Medical center	1.00	-	-	1.00	-	-
Regional hospital	1.75	1.62 - 1.90	<0.0001	1.90	1.60 - 2.26	<0.0001
District hospital	4.53	4.21 - 4.88	<0.0001	6.84	5.82 - 8.04	<0.0001
Clinic	5.13	4.77 - 5.52	<0.0001	6.50	5.54 - 7.62	<0.0001
<b>Urbanization level</b>						
1 (most urbanized)	1.00	-	-	1.00	-	-
2	1.45	1.44 - 1.47	<0.0001	1.16	1.14 - 1.18	<0.0001
3	1.67	1.65 - 1.69	<0.0001	1.19	1.17 - 1.21	<0.0001
4	1.23	1.21 - 1.24	<0.0001	1.04	1.02 - 1.06	<0.0001
5	1.54	1.48 - 1.61	<0.0001	1.23	1.16 - 1.31	<0.0001
6	1.39	1.36 - 1.42	<0.0001	1.32	1.28 - 1.37	<0.0001
7 (least urbanized)	1.36	1.33 - 1.39	<0.0001	1.60	1.55 - 1.64	<0.0001

Estimated changes in codeine prescription rates

	Codeine prescribing rate (95%CI)				Absolute change (Relative change)	
	Intercept	Baseline trend	Level change	Trend change	1 year later	3 years later
Overall	6.10 (5.60, 6.60)*	0.07 (0.01, 0.12)*	-4.24 (-4.78, -3.70)*	0.03 (-0.06, 0.11)	-4.11 (-60.44%)	-3.90 (-53.27%)
Aged 0-1	4.04 (3.75, 4.33)*	0.03 (0.00, 0.06)	-4.17 (-4.50, -3.84)*	-0.04 (-0.08, 0.00)*	-4.38 (-98.26%)	-4.72 (-100.48%)
Age 2-5	6.85 (6.33, 7.37)*	0.08 (0.03, 0.14)*	-5.77 (-6.32, -5.22)*	0.04 (-0.05, 0.13)	-5.57 (-70.27%)	-5.25 (-61.28%)
Age 6-11	6.34 (5.56, 7.12)*	0.06 (-0.03, 0.14)	-3.54 (-4.33, -2.75)*	0.09 (-0.04, 0.22)	-3.10 (-45.29%)	-2.39 (-32.77%)
Age 12-17	5.52 (4.94, 6.10)*	0.06 (0.00, 0.12)	-1.31 (-1.98, -0.64)*	-0.09 (-0.18, 0.00)	-1.74 (-28.75%)	-2.43 (-37.29%)

\* P<0.05

Codeine prescriptions for URI/cough visits

	Pre-regulation period		Post-regulation period	
	N	%	N	%
<b>Visits with codeine prescription</b>				
Co-prescribing of other antitussive	381,999		146,817	
Co-prescribing of other opium antitussive	170,381	44.6	58,189	39.6
Codeine prescriptions	141,916	37.2	43,950	29.9
Single drug formulations	391,808		149,157	
Fixed-dose combinations	261	0.1	162	0.1
Syrup/ Solution	391,547	99.9	148,995	99.9
Tablet/ Capsule/ Granule	190,828	48.7	79,719	53.5
	200,719	51.3	69,276	46.5

Conclusions

The prescription rate of codeine in Taiwanese children was greatly reduced after the safety-related regulation.

Continuous monitoring of the trends of codeine prescriptions may be warranted, and more attention should be paid to the determinants of prescribing codeine and the high proportion of therapeutic duplication.

Acknowledgement: Funding for this project was provided by Food and Drug Administration, Ministry of Health and Welfare, Taiwan.

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ISPOR 7th Asia-Pacific Conference– Suntec Singapore Convention & Exhibition Center, Singapore – 3-6 September, 2016 (Abstract # PIH28)