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Supporting Information

Supplementary methods and results

This appendix was part of the submitted manuscript and has been peer reviewed.
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Appendix to: Schaffer AL, Cairns R, Brown JA, et al. Changes in sales of analgesics to pharmacies after codeine was rescheduled as a prescription only medicine. *Med J Aust* 2020; doi: 10.5694/mja2.50552.

1. Supplementary methods: statistical analysis

We performed an interrupted time series analysis to quantify changes in monthly sales after the rescheduling of over-the-counter (OTC) codeine to a prescription-only medicine in February 2018. Interrupted time series analysis is one of the strongest observational study designs for evaluating the impact of population-level interventions.[1]

While our data are counts (i.e. number of tablets or packs sold), when the expected counts (λ) are large and the distribution is not bounded by zero, a Poisson distribution can be approximated by a Normal distribution. Thus, we modelled the intervention using a segmented linear regression, which assumes a continuous outcome.

The base segmented regression model can be expressed as:

$$Y_t = \beta_0 + \beta_1 \times months\ since\ start\ of\ study + \beta_2 \times intervention + \beta_3 \times months\ since\ intervention + \epsilon_t$$

In this equation:

- Y_t is the outcome (i.e. sales per 10,000 population);
- β_0 is the intercept, or Y_t at time zero;
- β_1 is the baseline (pre-rescheduling announcement) slope, or change in sales per month;
- $months\ since\ start\ of\ study$ is an integer representing the number of months from the start of the study;
- β_2 represents the step change or level shift post-rescheduling, which is an immediate change that is sustained for the duration of the study period;
- $intervention$ is a dichotomous variable, taking the value of “0” prior to the date of the intervention and “1” otherwise;
- β_3 is the change in slope post-rescheduling;
- $months\ since\ intervention$ is an integer taking the value of “0” prior to the intervention, and increasing by 1 on and after the date of the intervention; and
- ϵ_t is the error.

One of the assumptions of linear regression is that the errors (residuals) are independent, that is, not serially correlated. However, time series often exhibit autocorrelation and seasonality, potentially violating this assumption; therefore, these must be accounted for in time series models to get accurate estimates of the standard errors.

Seasonality

First, based on previous experience we know that medicine dispensing is often seasonal;[2,3]

thus, we expected pharmaceutical sales data to also exhibit seasonality. Additionally, sales of cold/flu products and cough suppressants showed a sinusoidal pattern that mimics trends in respiratory infections and influenza,[4] with sales being higher in the winter months, and lower in the summer months.

We used two different approaches for adjusting for seasonality. For analgesic sales, we included dummy variables representing the months; that is, a variable for each month taking a value of "1" in that month and "0" otherwise. For some outcomes (e.g. number of codeine sales), there was little seasonality and thus these terms were dropped from the model. For sales of cold/flu and cough products, we included Fourier terms,[4] of the form: $\sin\left(\frac{2\pi\times time}{12}\right)$ and $\cos\left(\frac{2\pi\times time}{12}\right)$, as the data were monthly. If necessary, we also created an intervention between the intervention variable and the Fourier terms to allow the sinusoidal pattern to vary before and after the intervention.

Autocorrelation

For each outcome, we constructed a segmented regression model as described above, including the appropriate seasonal terms depending on the outcome. After fitting the initial model, we used a combination of the Durbin-Watson test, the Ljung-Box test for white noise, and the autocorrelation function (ACF)/partial autocorrelation function (PACF) plots to test for the presence of residual autocorrelation in our models. For both the Durbin-Watson test and the Ljung-Box test the null hypothesis of these tests is that there is no autocorrelation of the residuals, and thus $P < 0.05$ indicates the presence of autocorrelation. The ACF plot estimates the correlation of values of a time series and its lagged values, with a significant value ($P < 0.05$) indicating autocorrelation at that lag. Similarly, the PACF plots the correlation between values of a time series and its lagged values that is not explained by correlation at lower order lags.

If autocorrelation was present as indicated by one of these tests, we included autoregressive terms in our model to control for autocorrelation. An autoregressive (AR) model regresses the outcome (Y_t) on its own past values. The number of lags required is the autoregressive "order". For example, an AR(2) model is an autoregressive model of order 2, and includes two lags of Y_t. We used the *arima* function in R to estimate our models; as we were interested in fitting autoregressive (AR) models, we specified the model order as (p,0,0) with p representing the AR order of the model. The ACF/PACF plots can also suggest how many autoregressive terms are needed, based on how many lags have significant autocorrelation. We chose the most appropriate model based on the lowest Akaike Information Criterion (AIC), with a preference for a more parsimonious model (i.e., a smaller number of autoregressive terms). The final model orders for each outcome are in the table below.

Final model

As previous research observed that sales changed in the year between the rescheduling announcement in December 2016 and the date that the rescheduling was implemented in February 2018,[5] we excluded this time period from the model (January 2017 to January 2018) from the modelling.[6] Essentially, we modelled the difference in observed sales post-rescheduling to the expected number of sales had the trend prior to the announcement continued, and estimated the pre-announcement (baseline) monthly slope, the level shift or step change in number of sales post-rescheduling, and the change in slope post-rescheduling. A level shift represents an immediate change sustained for the duration of the study period.

Lastly, we also checked each model to ensure that it met the other assumptions of linear regression; that is, that the residuals were normally distributed, without heteroscedasticity (non-constant variance). We did so by visualising the plot of the residuals against time, the residuals against fitted values, and the normal quantile plot of residuals. Analyses were performed using the *arima* function in R version 3.3.1.

Autoregressive orders for estimated models

Category	Outcome (Y_t)*	Autoregressive order
Overall OTC analgesics	Tablets/capsules	AR(3)
	Packs	AR(3)
Codeine-containing analgesics	Tablets/capsules	AR(3)
	Packs	AR(3)
	Kilograms	AR(1)
OTC analgesics		
Paracetamol	Tablets/capsules	AR(3)
Ibuprofen	Tablets/capsules	AR(3)
Paracetamol/ibuprofen	Tablets/capsules	AR(4)
Other paracetamol combinations	Tablets/capsules	AR(0)
Aspirin	Tablets/capsules	AR(4)
Diclofenac	Tablets/capsules	AR(2)
Prescription analgesics		
Tramadol	Tablets/capsules	AR(2)
Strong opioids	Tablets/capsules	AR(2)
NSAIDs	Tablets/capsules	AR(4)
Antimigraine treatment	Tablets/capsules	AR(1)
Gabapentinoids	Tablets/capsules	AR(2)
OTC cold/flu products		
All non-codeine-containing	Packs	AR(3)
Dextromethorphan-containing	Packs	AR(3)
Non-codeine- and non-dextromethorphan-containing	Packs	AR(4)
OTC cough suppressants		
Dextromethorphan-containing	Packs	AR(1)
Pholcodine-containing	Packs	AR(2)
Dihydrocodeine	Packs	AR(2)
Prescription codeine linctus	Packs	AR(0)

*Sales per 10,000 population

References

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2. Mellish L, Karanges EA, Litchfield MJ, et al. The Australian Pharmaceutical Benefits Scheme data collection: a practical guide for researchers. *BMC Res Notes* 2015; 8: 634.

3. Schaffer AL, Buckley NA, Dobbins TA, et al. The crux of the matter: did the ABC's Catalyst program change statin use in Australia? *Med J Aust* 2015; 202: 591-594.

4. Schaffer A, Muscatello D, Cretikos M, et al. The impact of influenza A(H1N1)pdm09 compared with seasonal influenza on intensive care admissions in New South Wales, Australia, 2007 to 2010: a time series analysis. *BMC Public Health* 2012; 12: 869.

5. Cairns R, Schaffer AL, Brown JA, et al. Codeine use and harms in Australia: evaluating the effects of re-scheduling. *Addiction* 2020; 115: 451-459.

6. Bernal JL, Soumerai S, Gasparrini A. A methodological framework for model selection in interrupted time series studies. *J Clin Epidemiol* 2018;103: 82-91.

2. Supplementary tables and figures

Table 1. Codeine containing products sold during the study period (March 2015 to March 2019)

	Product	Codeine tablet strength (as phosphate salt)	Schedule prior to February 2018
Rescheduled to Schedule 4 (prescription only) medicine	**Analgesics**		
	Codeine/aspirin	≤15 mg	Schedule 3 – Pharmacist only
	Codeine/doxylamine/paracetamol	≤15 mg	Schedule 3 – Pharmacist only
	Codeine/ibuprofen	≤15 mg	Schedule 3 – Pharmacist only
	Codeine/paracetamol	≤15 mg	Schedule 3 – Pharmacist only
	Cold/flu products		
	Codeine/paracetamol/phenylephrine	≤10 mg	Schedule 2 – Pharmacy only
	Codeine/paracetamol/chlorphenamine/phenylephrine	≤10 mg	Schedule 3 – Pharmacist only
	Codeine/paracetamol/phenylephrine/triprolidine	≤10 mg	Schedule 3 – Pharmacist only
	Codeine/paracetamol/chlorphenamine/dextromethorphan	≤10 mg	Schedule 3 – Pharmacist only
	Codeine/paracetamol/chlorphenamine/atropa belladonna/ pseudoephedrine	≤10 mg	Schedule 3 – Pharmacist only
	Codeine/paracetamol/chlorphenamine/pseudoephedrine	≤10 mg	Schedule 3 – Pharmacist only
	Codeine/paracetamol/pseudoephedrine	≤10 mg	Schedule 3 – Pharmacist only
Prescription only medicine for duration of study period	**Analgesics**		
	Codeine	30 mg	Schedule 8 – Controlled drug
	Codeine/doxylamine/paracetamol	30 mg	Schedule 4 – Prescription only
	Codeine/paracetamol	30 mg	Schedule 4 – Prescription only
	Cough suppressants		
	Codeine linctus	5 mg/ml	Schedule 8 – Controlled drug

Table 2. Non-codeine over-the-counter and prescription analgesic tablets/capsules sold during the study period (March 2015 to March 2019)

Over-the-counter	Prescription only
Aspirin*	**Gabapentinoids**
Diclofenac	Pregabalin
Ibuprofen	Gabapentin
Mefenamic acid	**Antimigraine medicines†**
Naproxen	Eletriptan
Paracetamol (immediate release)	Naratriptan
Paracetamol (modified release)	Sumatriptan
Paracetamol/caffeine	Zolmitriptan
Paracetamol/diphenhydramine	**NSAIDs‡**
Paracetamol/ibuprofen	Celecoxib
Paracetamol/metoclopramide	Diclofenac
	Diclofenac/misoprostol
	Etoricoxib
	Ibuprofen
	Indometacin
	Ketoprofen
	Ketorolac
	Mefenamic acid
	Meloxicam
	Naproxen
	Parecoxib
	Piroxicam
	Sulindac
	Opioids
	Dextropropoxyphene/paracetamol
	Hydromorphone
	Methadone§
	Morphine
	Oxycodone/naloxone
	Oxycodone
	Pethidine
	Tapentadol
	Tramadol
	Tramadol/paracetamol

* Low-dose aspirin for prevention of cardiovascular events not included

† Preventive products (i.e. pizotifen, erenumab, flunarizine) not included

‡ High strength and/or large pack sizes of ibuprofen, diclofenac, naproxen, and mefenamic acid are prescription-only

§ Methadone for treatment of opioid dependence not included

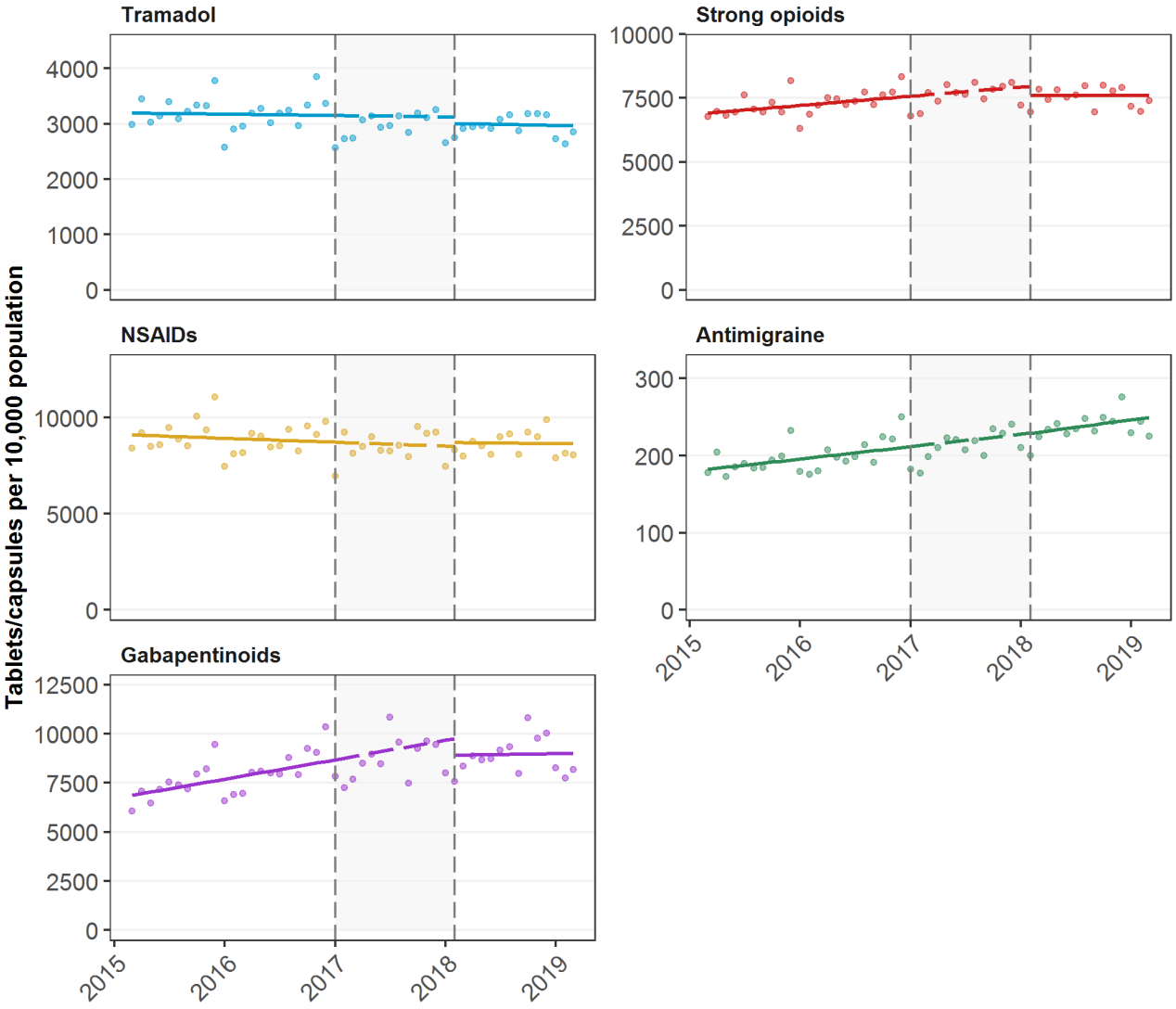
Table 3. Non-codeine over-the-counter and prescription cold/flu products and cough suppressants sold during the study period (March 2015 to March 2019)

Product name
Cold/flu products
Aspirin/pseudoephedrine
Ibuprofen/phenylephrine
Ibuprofen/pseudoephedrine
Paracetamol/chlorphenamine/dextromethorphan
Paracetamol/chlorphenamine/dextromethorphan/pseudoephedrine
Paracetamol/chlorphenamine/dextromethorphan/phenylephrine
Paracetamol/chlorphenamine/phenylephrine
Paracetamol/chlorphenamine/pseudoephedrine
Paracetamol/dextromethorphan
Paracetamol/dextromethorphan/doxylamine
Paracetamol/dextromethorphan/doxylamine/pseudoephedrine
Paracetamol/dextromethorphan/phenylephrine
Paracetamol/dextromethorphan/pseudoephedrine
Paracetamol/guaifenesin/phenylephrine
Paracetamol/phenylephrine
Paracetamol/pseudoephedrine
Cough suppressant-containing products without analgesic
Dextromethorphan
Dextromethorphan/brompheniramine/phenylephrine
Dextromethorphan/guaifenesin
Dextromethorphan/guaifenesin/pseudoephedrine/ammonium
Dextromethorphan/phenylephrine
Dihydrocodeine
Pentoxyverine
Pholcodine
Pholcodine/bromhexine
Pholcodine/chlorphenamine/phenylephrine
Pholcodine/pseudoephedrine

Table 4. Sales of tables/capsules of over-the-counter analgesics

	Year before rescheduling announcement (Jan 2016 to Dec 2016)				Year after rescheduling (Feb 2018 to Jan 2019)			
	Packs		Tablets		Packs		Tablets	
	Sales/10,000 population	%	Sales/10,000 population	%	Sales/10,000 population	%	Sales/10,000 population	%
All OTC analgesics	24 285	100.0	1 396 650	100.0	19 576	100.0	1 291 277	100.0
OTC non-codeine analgesics	16 699	68.8	1 147 523	82.2	19 576	100.0	1 291 277	100.0
Paracetamol	10 895	44.9	935 668	67.0	11 761	60.1	1 022 581	79.2
Ibuprofen	3118	12.8	140 592	10.1	3541	18.1	166 916	12.9
Diclofenac	1341	5.5	34 634	2.5	1513	7.7	39 697	3.1
Aspirin	459	1.9	18 722	1.3	450	2.3	17 490	1.4
Paracetamol/ibuprofen	369	1.5	6448	0.5	1624	8.3	28 330	2.2
Paracetamol/caffeine	129	0.5	4296	0.3	232	1.2	7541	0.6
Paracetamol/metoclopramide	57	0.2	495	0.0	57	0.3	497	0.0
Paracetamol/diphenhydramine	0	0.0	1	0.0	29	0.2	578	0.0
Naproxen	239	1.0	5014	0.4	272	1.4	5697	0.4
Mefenamic acid	83	0.3	1654	0.1	97	0.5	1949	0.2
OTC codeine analgesics	7586	31.2	249 127	17.8				
Codeine/paracetamol	3601	14.8	125 573	9.0				
Codeine/ibuprofen	2497	10.3	73 541	5.3				
Codeine/doxylamine/ paracetamol	1401	5.8	47 551	3.4				
Codeine/aspirin	87	0.4	2462	0.2				

Figure 1. Monthly sales of prescription analgesics per 10 000 population



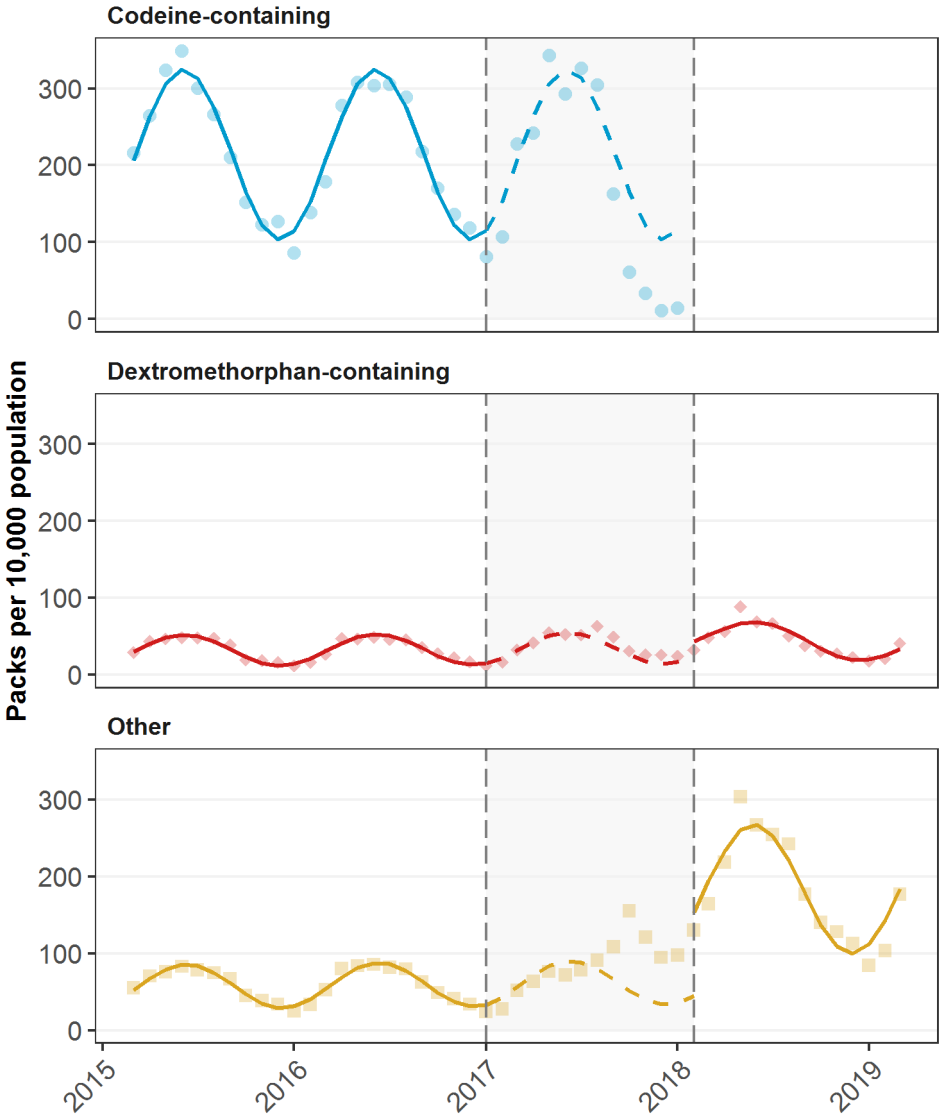
The rescheduling was announced on 20 December 2016 and implemented on 1 February 2018. The shaded area represents the time between the announcement and rescheduling that was excluded from modelling. Dots = observed values; solid line = predicted values; dashed line = predicted values had trends prior to the announcement continued.

Table 5. Change in monthly sales of packs of non-codeine-containing over-the-counter (OTC) cold/flu products after rescheduling of OTC codeine to prescription only

	Monthly gradient prior to announcement		Level shift after rescheduling		Change in gradient after rescheduling	
	Estimate	**95% CI**	**Estimate**	**95% CI**	**Estimate**	**95% CI**
All non-codeine-containing OTC cold/flu products	0.2	–0.3 to 0.7	146.4	128.0 to 164.8	–1.8	–3.5 to –0.2
Dextromethorphan-containing	0.1	–0.1 to 0.3	22.6	15.2 to 30.1	–1.7	–2.2 to –1.2
Non-dextromethorphan-containing	0.2	0.0 to 0.5	123.5	112.9 to 134.0	–0.5	–1.6 to 0.5

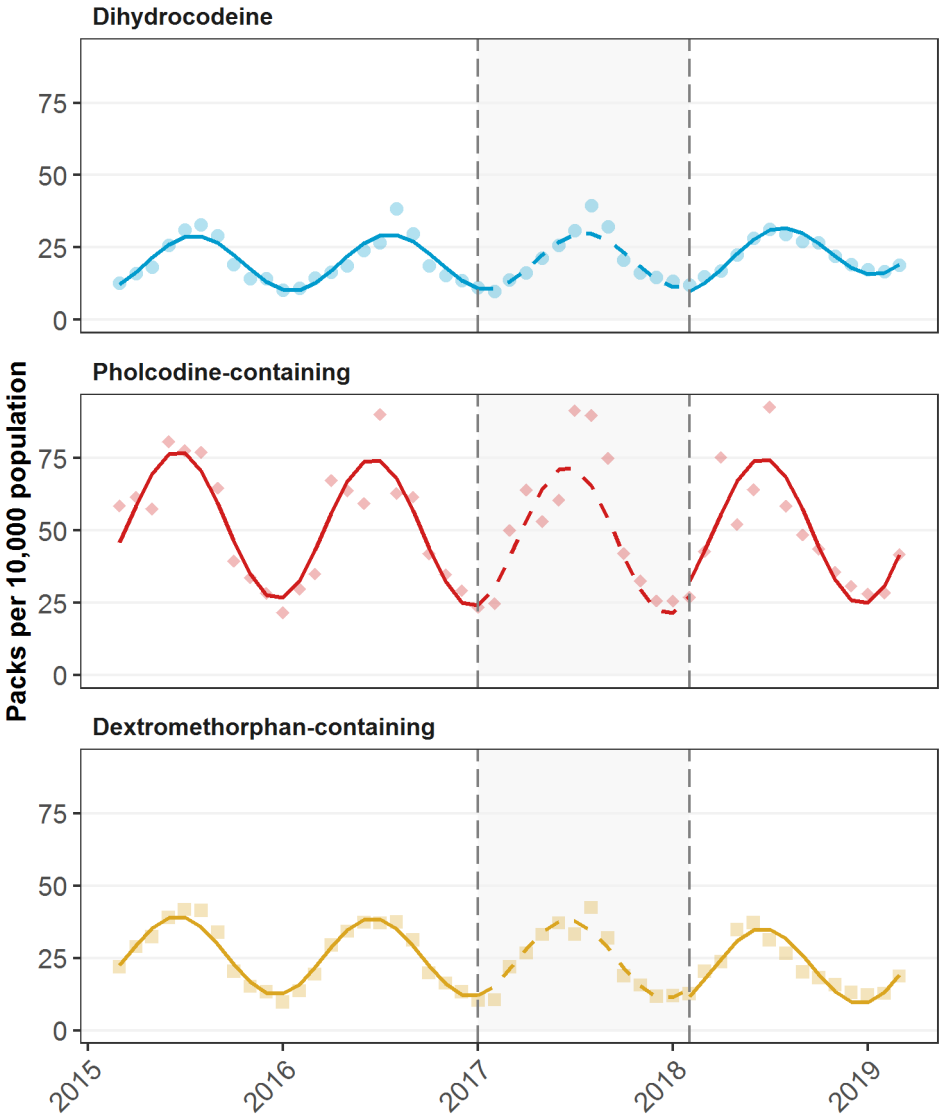
CI = confidence interval.

Figure 2. Monthly sales per 10 000 population of over-the-counter cold/flu products by primary ingredient



The rescheduling was announced on 20 December 2016 and implemented on 1 February 2018. The shaded area represents the time between the announcement and rescheduling that was excluded from modelling. Dots = observed values; solid line = predicted values; dashed line = predicted values had trends prior to the announcement continued. Products containing both dextromethorphan and codeine are included under “codeine-containing”.

Figure 3. Monthly sales per 10 000 population of over-the-counter cough products



The rescheduling was announced on 20 December 2016 and implemented on 1 February 2018. The shaded area represents the time between the announcement and rescheduling that was excluded from modelling. Dots = observed values; solid line = predicted values; dashed line = predicted values had trends prior to the announcement continued.

Table 6. Change in monthly sales per 10 000 population of over-the-counter (OTC) and prescription cough suppressants after rescheduling of OTC codeine to prescription only

	Monthly slope prior to announcement		Level shift after rescheduling		Change in slope after rescheduling	
	Sales per 10 000 population	**95% CI**	**Sales per 10 000 population**	**95% CI**	**Sales per 10 000 population**	**95% CI**
OTC cough suppressant containing products						
Dextromethorphan-containing	–0.06	–0.32 to 0.19	–2.61	–9.56 to 4.33	0.14	-0.40 to 0.68
Dihydrocodeine	0.03	–0.10 to 0.16	–1.92	–6.06 to 2.23	0.51	0.22 to 0.79
Pholocodine-containing	–0.22	–0.46 to 0.02	4.97	–2.72 to 12.66	0.11	-0.41 to 0.63
Prescription cough suppressants						
Codeine linctus	0.03	0.00 to 0.06	–1.12	–1.99 to –0.25	0.01	-0.05 to 0.07