Mandatory labeling requirements and over-the-counter cough and cold medication use in early childhood

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ABSTRACT

OBJECTIVES: Due to rare but severe adverse events, Health Canada in October 2009 required manufacturers to relabel over-the-counter (OTC) cough and cold medication (CCM) to state that the products should not be used in children <6 years of age. The main objective of this study was to determine whether this labeling standard decreased OTC CCM use among young children with a recent cough, cold or flu.

METHODS: An interrupted time series study was conducted using data from the TARGet Kids! practice-based research network. A total of 3,515 healthy children 1–5 years of age were recruited from 2008–2011; of these, 1,072 had a cough, cold or flu in the previous month. Parents completed a standardized survey instrument. For the primary analysis, use of OTC CCMs prior to and after October 1, 2009 was compared using time series analyses. For the secondary analysis, multivariable logistic regression was used to identify predictors of recent OTC CCM use.

RESULTS: OTC CCM use was reported in 222 of 1,072 (20.7%) children with a cough, cold or flu within the previous month. OTC CCM use declined from 22.2% to 17.8% following the October 2009 Health Canada labeling standard ($p = 0.014$). Maternal age <35 years (OR 1.49; 95% CI: 1.05–2.13) and having older siblings (OR 1.65; 95% CI: 1.16–2.35) were independently associated with OTC CCM use.

CONCLUSION: Labeling legislation against OTC CCM use for children <6 years resulted in a small decrease in OTC CCM use. Stronger measures may be needed to curtail OTC CCM use, particularly for younger parents and those with multiple children.

KEY WORDS: Nonprescription drugs; child; preschool; drug legislation; time series analysis

La traduction du résumé se trouve à la fin de l'article.

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There has been much debate about the appropriateness of over-the-counter (OTC) cough and cold medication (CCM) use in young children, such use being a frequent topic of conversation between parents and health care providers. Cough and cold medication use is common among North American children,¹ despite 1) a lack of evidence for effectiveness and 2) evidence of adverse but rare events, including death.^{2–11} CCMs are the leading cause of emergency department visits from adverse drug reactions, including allergic and neurologic complications.¹¹

In 2007, pharmaceutical manufacturers in the United States voluntarily withdrew OTC CCMs labeled for children younger than two years of age.¹² In 2007 and 2008 respectively, public health advisories were issued by Health Canada and the U.S. Food and Drug Administration (FDA) stating that children under the age of 2 years should not use OTC CCMs.^{13,14} In 2008, pharmaceutical manufacturers in the US voluntarily relabeled OTC CCMs to state that the products should not be used in children younger than 4 years of age.¹⁵ In October 2009, Health Canada required manufacturers to relabel OTC CCMs containing antihistamines, antitussives, expectorants and decongestants to indicate that the product should not be used for children younger than 6 years of age; the prohibition “Do not use this cough and cold product in children under 6 years of age” must be included on the inner and outer labels of all products.¹⁶ Health Canada listed four reasons for this labeling requirement: 1) children 2 to 6 years of age sometimes weigh the same as children less than 2 years of age; 2) Canadian and international

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experts indicated risk of harm; 3) children younger than 6 years of age tend to have more colds than older children and therefore have more opportunities to be exposed to OTC CCMs; and 4) children younger than 6 years of age may be less able to communicate side effects to their parents than children 6 years or older.¹⁶

Given current FDA and Health Canada advisories against OTC CCM use in young children, our primary objective was to determine whether the government-mandated labeling standard decreased the proportion of children younger than 6 years of age who used OTC CCMs in a cohort of healthy urban preschoolers. Our secondary objective was to examine the characteristics of children who recently used OTC CCMs to identify opportunities for targeted anticipatory guidance during routine primary health care.

METHODS

Subjects and design

We conducted an interrupted time series study¹⁷ of healthy young children through the TARGet Kids! primary care practice-based research network in Toronto, Canada. TARGet Kids! is a collaboration between child health outcomes researchers in the Faculty of Medicine at the University of Toronto and primary health care providers from the Departments of Pediatrics and of Family and Community Medicine at the University of Toronto.¹⁸ Study participants were recruited by research personnel embedded in seven participating pediatric and family medicine practices between September 2008 and October 2011. All children meeting the eligibility criteria were initially contacted by letter two weeks before the scheduled visit. Parents of all eligible children were then approached by the research assistant when they attended their child's scheduled well-child visit. Approximately 7% were missed due to research assistants being occupied by another patient, and 8% were not approached as they had cancelled or rescheduled their visit; whenever possible, these families were approached for recruitment at their next well-child visit.¹⁸

Children were eligible for inclusion if they received scheduled primary health care at a TARGet Kids! participating clinic, were considered healthy by parent report, and were aged 1 to 5 years (12–71 months). Children were excluded if they had severe developmental delay, health conditions affecting growth, any acute or chronic illness (other than asthma), were born <32 weeks' gestation, or if families were unable to communicate in English. For this analysis, children were only included if they were reported by their parents as having had a cough, cold or flu in the previous month. This study was approved by the Research Ethics Boards at The Hospital for Sick Children and St. Michael's Hospital, and all parents of participating children consented to participation in the study.

Data were collected through a standardized parent-completed survey instrument based on the Canadian Community Health Survey.¹⁹ Children with a cough, cold or flu were defined in response to the following question: "Has your child been ill within the past month? If yes, please describe". If the parent responded that the child had any of the following, the child was defined as having had a cough, cold or flu and was kept in the analysis: cough, cold, flu, fever, ear infection, wheezing, bronchitis, runny nose, strep throat, or throat infection. All data

were uploaded to the central MediData Rave platform (MediData Solutions, New York) housed at the Applied Health Research Centre of the Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto.

Outcome and predictor variables

The primary outcome was use of OTC CCMs in the previous two weeks as determined by response to the following question: "Has your child taken a non-prescription cold or flu medication in the past 2 weeks". The primary exposure variable was date of visit before or after October 1, 2009, which was the date by which manufacturers were required to comply with the Health Canada labeling requirement.

Predictor variables we hypothesized might also be associated with OTC CCM use included: age, sex, ethnicity, daycare attendance, birth order, maternal age, maternal employment, maternal education, income, and winter season (October through March). Child age was dichotomized to children <2 years of age and those ≥2 years of age, since the advisory from Health Canada that children less than 2 years of age should not use OTC CCMs has been in effect since 2007.¹⁴ Income was estimated using Statistics Canada postal code conversion file by linking median after-tax household income in each standard census geographic area to the postal codes provided by the families.²⁰ Income was categorized based on quartiles defined using the full TARGet Kids population.

Statistical analysis

Descriptive statistics were performed on the main outcomes and predictors. For our primary analysis, use of OTC CCMs prior to and after October 1, 2009 was compared using time series intervention analysis, which is a type of discrete time series analysis used for modeling temporal correlation in non-stationary time series data.^{21,22} We specified a step function in the Autoregressive Integrated Moving Average (ARIMA) model to estimate the effect of the labeling standard starting in November 2009.²² The model fitting was examined by testing residual normality, autocorrelations and white noise probability, as well as comparison between model prediction and observed values. All diagnostics indicated adequate model fitting.

For our secondary analysis, multivariable logistic regression was used to identify predictors associated with recent OTC CCM use. All potential predictors (specified above) were identified a priori as important predictors and therefore all were included in the final model regardless of statistical significance. All statistical analyses were performed using SAS software (version 9.3, SAS Institute, Inc., Cary, NC).

RESULTS

Study population

Of the 3,515 children between 1 and 5 years of age who were assessed for eligibility, 2,172 were not reported as having had a cough, cold or flu in the previous month and so did not meet eligibility criteria. Of the remaining 1,343 children, 271 had missing medication use data, leaving 1,072 (80%) children who were included in the analysis. The median child age was 24.2 months and 49.7% were male (see Table 1). Approximately

Table 1. Characteristics of children 1 to 5 years of age in TARGet Kids! by cough, cold or flu status

Subjects	Children who had a cough, cold or flu in the previous month (<i>n</i> = 1072)	Children who did not have a cough, cold or flu in the previous month (<i>n</i> = 2172)
Visit date after October 1, 2009, <i>n</i> (%)	522 (48.7)	1024 (47.2)
Age (months), median (IQR)	24.2 (15.2, 48.0)	36.2 (17.7, 49.5)
Male, <i>n</i> (%)	533 (49.7)	1133 (52.2)
Child birth order, <i>n</i> (%)		
1 st	589 (59.7)	1171 (58.0)
≥2 nd	398 (40.3)	848 (42.0)
Maternal age, mean (SD)	36.0 (4.7)	36.0 (4.9)
Daycare, <i>n</i> (%)	513 (48.5)	943 (44.1)
Maternal working status, <i>n</i> (%)		
Full-time	539 (51.8)	988 (47.4)
Part-time	183 (17.6)	330 (15.8)
Other	93 (8.9)	200 (9.6)
On parental leave	36 (3.5)	64 (3.1)
Unemployed	189 (18.2)	502 (24.0)
Income, <i>n</i> (%)		
>\$71,450	254 (25.3)	517 (24.9)
\$56,194–\$71,450	245 (24.4)	525 (25.3)
\$43,966–\$56,193	270 (26.9)	503 (24.3)
<\$43,966	236 (23.5)	529 (25.5)
Ethnicity, <i>n</i> (%)		
European	817 (77.1)	1493 (69.6)
South East Asian	88 (8.3)	247 (11.5)
East Asian	50 (4.7)	130 (6.1)
African/Caribbean	33 (3.1)	116 (5.4)
Other	72 (6.8)	158 (7.4)

48.5% of children were in daycare, 51.8% of mothers worked full-time, and 77.1% were European. Children who had a cough, cold or flu in the previous month were slightly younger (mean age 30.1 vs. 34.9 months) and were more likely to be in daycare (48.5% vs. 44.1%) than those who had not. Among children who had a cough, cold or flu in the previous month, age, sex, maternal age, income and ethnicity were similar before and after October 2009; however, statistically significant differences were

observed for maternal working status ($p = 0.01$) and child birth order ($p = 0.04$), such that children observed after 2009 were more likely to be first-born and mothers were more likely to be working part-time or on parental leave.

Over-the-counter cough and cold medication use

Of the 1,072 children whose parents reported their child had been sick with a cough, cold or flu during the previous month,

Figure 1. Proportion of children 1 to 5 years of age with a cough, cold or flu, who used cough and cold medications before and after October 2009 Health Canada labeling requirement

Note: Circles and crosses indicate proportion using CCM per month, lines indicate trend.

Figure 2. Next-month forecast of the proportion of OTC CCM users using fitted time series analysis before and after October 2009 Health Canada labeling requirement

222 (20.7%) had received OTC CCMs within the previous 2 weeks. The proportion of children who used OTC CCMs in the previous two weeks over time is shown in Figure 1. In the time series analysis, the estimated intervention effect of the policy change was -0.045 ($p = 0.0014$) from a baseline OTC CCM level of 0.22. The autocorrelation term was significant ($p = 0.0086$) and was included in the model. In other words, there was a small but statistically significant decrease in OTC CCM use before vs. after the October 2009 Health Canada labeling standard (22.2% vs. 17.8%, $p = 0.014$). The forecasted next-month prediction model is shown in Figure 2.

Variables independently associated with OTC CCM use

Results of the multivariable logistic regression model for our secondary analysis are shown in Table 2. Maternal age less than 35 years (OR 1.49; 95% CI: 1.05–2.13), and second or later child in birth order compared to first (OR 1.65; 95% CI: 1.16–2.35) were found to be independently associated with use of OTC CCM. There was a trend towards lower OTC CCM use in children younger than 2 years of age (OR 0.71; 95% CI: 0.49–1.02).

DISCUSSION

In this time series study, we examined the effect of the Health Canada labeling requirement for children younger than 6 years of age on OTC CCM use in early childhood. Twenty percent of children in our cohort who had a cough, cold or flu in the previous month had taken an OTC CCM despite government recommendations against such use. The proportion of children using OTC CCM decreased by 4% after the October 2009 Health Canada labeling standard came into effect.

Studies examining patterns of OTC CCM use in early childhood are relatively rare. Unlike for prescription medications, which may be recorded in insurance databases, OTC CCM use must be

determined from parental report. Our prevalence data compare favourably with previous studies. Data from the 1991 follow-up to the National Maternal and Infant Health Survey indicated that half of American preschoolers had used OTC CCM in the previous month.²³ The Avon Longitudinal Study of Parents and Children identified that two thirds of preschoolers had received an OTC CCM in the previous year.²⁴ The 1999–2006 Slone Survey found that 10% of US children under 18 years of age used a CCM in the previous week.²⁵

To our knowledge, our study is unique in examining OTC CCM use in otherwise healthy children younger than 6 years of age recruited from primary care before and after a mandated labeling standard advising against their use. One US study among children younger than 2 years of age hospitalized with bronchiolitis found a significant decrease in OTC CCMs, from 25% pre-advisory to 7% post-advisory.²⁶ Another US study found no change in the use of OTC CCMs among children less than 2 years of age in emergency departments or ambulatory clinics.²⁷ Our findings suggest that this labeling standard had a relatively minor effect on OTC CCM use in children younger than 6 years of age. Similar to tobacco marketing legislation, stronger deterrents, such as mandated front-of-package labeling advising against use in young children or requiring that CCMs be behind the counter, may be necessary.

The withdrawal of OTC CCMs marketed to children younger than 2 years of age appears to have had an effect in reducing their use.^{8,9} The mean number of therapeutic errors involving OTC CCMs reported to the American Association of Poison Control Centers for children younger than 2 years of age decreased by 46% following the voluntary withdrawal and voluntary relabeling.⁹ Similarly, the estimated number of emergency department visits for OTC CCM-related medication errors decreased by more than half following the withdrawal of infant OTC CCMs from the market.⁸ However, even with the

Table 2. Multivariable logistic regression model for cough and cold medication use in previous two weeks

	Adjusted OR*	95% CI	p-value
Age			
2 to 5 years	Referent		
<2 years	0.71	0.49–1.02	0.06
Sex			
Female	Referent		
Male	1.18	0.84–1.64	0.34
Child birth order			
1 st	Referent		
≥2 nd	1.65	1.16–2.35	0.005
Maternal age			
≥35 years	Referent		
<35 years	1.49	1.05–2.13	0.03
Daycare			
No	Referent		
Yes	0.97	0.68–1.39	0.86
Maternal working status			
Full-time	Referent		
Part-time	0.71	0.44–1.15	0.16
Other	1.04	0.59–1.83	0.91
On parental leave	0.46	0.16–1.38	0.17
Unemployed	0.71	0.44–1.15	0.16
Income			
>\$71,450	Referent		
\$56,194–\$71,450	1.18	0.72–1.93	0.78
\$43,966–\$56,193	1.47	0.92–2.36	0.20
<\$43,966	1.32	0.80–2.17	0.64
Ethnicity			
European	Referent		
African/Caribbean	1.09	0.39–3.09	0.90
East Asian	1.71	0.81–3.65	0.23
South East Asian	1.19	0.66–2.13	0.92
Other	0.92	0.46–1.86	0.46

* Multivariable logistic regression adjusted for all variables in the table.

withdrawal of OTC CCMs for children younger than 2 years of age, rates of therapeutic errors were still 45.2 per 100,000 (95% CI 30.7–66.6), indicating that parents continue to provide these medications to their young children.⁹

Primary care anticipatory guidance may also play a role in reducing OTC CCM use in young children. We have identified that children with younger mothers and children with older siblings appear to have increased odds of receiving OTC CCM, suggesting opportunities for targeted intervention. We speculate that parents with older children may have used OTC CCMs safely in the past and therefore continue to use them with their younger children.

Study limitations

Limitations of this study include limited detail on the specific OTC CCMs taken, including the type of medication used, and the frequency and duration of use. Our finding that 20% of children with a cough, cold or flu had used an OTC CCM is likely an underestimate because parents were asked about OTC CCMs use in the previous two weeks while the child could have had a cough, cold or flu any time in the previous month and thus have taken OTC CCM in the first 2 weeks of the month. Our study may not be generalizable to all children in Canada and our study population could not be compared to the source population due to a lack of data on children under 6 years of age in Toronto or Ontario. Furthermore, our study relied on

parent recall of both child illness and OTC CCM use, which may be subject to measurement error. We are also unable to rule out the possibility that some parents may have used medications purchased prior to the mandated labeling requirements effective October 1, 2009. Finally, as this was an observational study, causation cannot be inferred from the identified associations.

CONCLUSION

A high proportion of young children continue to use OTC CCMs despite the lack of evidence for effectiveness, evidence of harm, public health advisories against such use and mandated labeling requirements. We have identified that a government-mandated labeling standard had a small effect on curtailing OTC CCM use in children younger than 6 years of age. Stronger measures may be needed to curtail their use, such as more pronounced warning labels and keeping such products behind the pharmacy counter, to avoid inadvertent purchasing by parents of young children. Anticipatory guidance around the harms and lack of benefit from OTC CCMs may be helpful, particularly among younger parents and those with multiple children.

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RÉSUMÉ

OBJECTIFS : En raison d'effets secondaires rares mais graves, Santé Canada a exigé en octobre 2009 que les fabricants refassent les étiquettes des médicaments en vente libre contre la toux et le rhume (MEVLCTR) pour indiquer que ces produits ne doivent pas être administrés aux enfants de <6 ans. Le principal objectif de notre étude était de déterminer si cette norme d'étiquetage a réduit l'administration des MEVLCTR aux jeunes enfants ayant récemment eu une toux, un rhume ou une grippe.

MÉTHODE : Nous avons mené une étude des séries chronologiques interrompues à l'aide des données de TARGet Kids!, un réseau de recherche fondée sur la pratique. Entre 2008 et 2011, nous avons recruté 3 515 enfants sains âgés de 1 à 5 ans; de ce nombre, 1 072 avaient eu une toux, un rhume ou une grippe au cours du mois précédent. Les parents ont rempli un instrument de sondage standardisé. Pour l'analyse primaire, nous avons comparé l'administration des MEVLCTR avant et après le 1^{er} octobre 2009 à l'aide d'analyses des séries chronologiques. Pour l'analyse secondaire, nous avons utilisé la régression logistique multivariée pour repérer les variables prédictives de l'utilisation récente de MEVLCTR.

RÉSULTATS : L'utilisation de MEVLCTR a été déclarée pour 222 des 1 072 (20,7 %) enfants ayant eu une toux, un rhume ou une grippe au cours du mois précédent. L'utilisation des MEVLCTR a baissé, passant de 22,2 % à 17,8 %, après l'imposition de la norme d'étiquetage par Santé Canada en octobre 2009 ($p = 0,014$). L'âge maternel <35 ans (RC 1,49; IC de 95 % : 1,05–2,13) et la présence de frères et sœurs plus âgés (RC 1,65; IC de 95 % : 1,16–2,35) étaient indépendamment associés à l'utilisation des MEVLCTR.

CONCLUSION : La loi sur l'étiquetage des MEVLCTR pour en empêcher l'administration aux enfants <6 ans a entraîné une légère diminution de l'utilisation de ces produits. Des mesures plus strictes pourraient être nécessaires pour limiter l'utilisation des MEVLCTR, particulièrement par les jeunes parents et dans les familles de plusieurs enfants.

MOTS CLÉS : médicaments en vente libre; enfant d'âge préscolaire; législation pharmaceutique; analyse des séries chronologiques