

Adverse Events From Cough and Cold Medications After a Market Withdrawal of Products Labeled for Infants



WHAT'S KNOWN ON THIS SUBJECT: A voluntary market withdrawal of orally administered, over-the-counter cough and cold medications (CCMs) labeled for infants was announced in October 2007 because of concerns regarding limited evidence of efficacy and potential harmful effects of these products among young children.



WHAT THIS STUDY ADDS: This study assessed changes in CCM-related harm, as measured with national estimates of emergency department visits for CCM-related adverse events, among children after announcement of the withdrawal of orally administered, over-the-counter, infant CCMs.

abstract

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OBJECTIVE: A voluntary market withdrawal of orally administered, over-the-counter, infant cough and cold medications (CCMs) was announced in October 2007. The goal of this study was to assess CCM-related adverse events (AEs) among children after the withdrawal.

METHODS: Emergency department (ED) visits for CCM-related AEs among children <12 years of age were identified from a nationally representative, stratified, probability sample of 63 US EDs, for the 14 months before and after announcement of withdrawal.

RESULTS: After withdrawal, the number and proportion of estimated ED visits for CCM-related AEs involving children <2 years of age were less than one-half of those in the prewithdrawal period (1248 visits [13.3%] vs 2790 visits [28.7%]; difference: -15.4% [95% confidence interval (CI): -25.9% to -5.0%]), whereas the overall number of estimated ED visits for CCM-related AEs for children <12 years of age remained unchanged (9408 visits [95% CI: 6874-11 941 visits] vs 9727 visits [95% CI: 6649-12 805 visits]). During both periods, two-thirds of estimated ED visits involved unsupervised ingestions (ie, children finding and ingesting medications).

CONCLUSIONS: ED visits for CCM-related AEs among children <2 years of age were substantially reduced after withdrawal of over-the-counter infant CCMs. Further reductions likely will require packaging improvements to reduce harm from unsupervised ingestions and continued education about avoiding CCM use for young children. Monitoring of CCM-related harm should continue because recommendations were updated in October 2008 to avoid the use of CCMs for children <4 years of age. *Pediatrics* 2010;126:1100-1107

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KEY WORDS

adverse events, drug safety, poisoning, medication errors, drug packaging, nasal decongestants, expectorants, antitussive agents, product withdrawals, nonprescription drugs

ABBREVIATIONS

AE—adverse event
CCM—cough and cold medication
CI—confidence interval
ED—emergency department
FDA—Food and Drug Administration
NEISS-CADES—National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance
OTC—over-the-counter

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The use of cough and cold medications (CCMs) for children recently garnered increased attention because of concerns regarding the potential harmful effects of these medications when used inappropriately and limited evidence for their efficacy, particularly for infants and young children.¹⁻⁹ On October 11, 2007, on behalf of the leading makers of over-the-counter (OTC) CCMs, the Consumer Healthcare Products Association announced a voluntary market withdrawal of orally administered CCMs labeled or intended for infants.¹⁰ This was followed by a US Food and Drug Administration (FDA) recommendation on January 17, 2008, to avoid use of these products to treat infants and children <2 years of age, “because serious and potentially life-threatening side effects can occur.”¹¹ Here, we use nationally representative public health surveillance data to assess potential changes in the number of emergency department (ED) visits because of CCM-related adverse events (AEs) after announcement of the withdrawal of OTC products for infants.

METHODS

National estimates of ED visits for AEs were based on surveillance cases from the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance (NEISS-CADES) project, which involves a nationally stratified, probability sample of 63 hospitals in the United States and its territories with a minimum of 6 beds and a 24-hour ED.¹² All hospitals treat pediatric patients, and 5 are pediatric specialty hospitals. The NEISS-CADES project is a collaboration of the Centers for Disease Control and Prevention (CDC), the FDA, and the US Consumer Product Safety Commission and was described previously.^{12,13} In brief, trained coders at each hospital review clinical records of ED visits to identify physician-diagnosed AEs, report up to

2 medications implicated in the AE, and record narrative descriptions of the incidents. Narrative descriptions are coded by using the Medical Dictionary for Regulatory Activities, an international terminology system used to analyze AE reports.

Surveillance cases included any incident ED visit by a patient <12 years of age because of a condition that was attributed to a medication (any prescription or OTC drug product, including vitamins, herbal remedies/dietary supplements, and vaccines) in the ED medical record and that occurred in the 14-month period before announcement of the market withdrawal of orally administered, OTC, infant CCMs (July 22, 2006, to October 11, 2007; referred to here as the prewithdrawal period) or in the 14-month period after announcement of the withdrawal (October 12, 2007, to December 31, 2008; referred to here as the postwithdrawal period). These periods were chosen because, at the time of this evaluation, weighted data enabling national estimates were available only through the end of 2008. CCMs were defined as orally administered prescription or OTC products containing decongestants, antitussive agents/expectorants, or decongestant, antihistamine, antitussive agent, and/or expectorant combinations.

ED visits were classified as attributable to “unsupervised ingestions” when cases involved children accessing medications without adult permission or oversight and as “supervised administrations” when medications were given to children by caregivers. Medication errors were defined as any errors made during the prescribing, dispensing, or administration of the medication, as documented in the ED medical record. ED visits were excluded if they were attributed to drug abuse or harmful intent or if the AE occurred during the ED visit.

Each selected NEISS-CADES case was accompanied by a sample weight based on the inverse probability of selection, with adjustment for nonresponse rate and poststratification to adjust for the number of annual hospital ED visits. National estimates of ED visits and corresponding 95% confidence intervals (CIs) were calculated by using the Surveymeans procedure in SAS 9.2 (SAS Institute, Cary, NC) to account for weighting and complex sample design. National estimates based on <20 cases were considered statistically unstable and are not shown; therefore, some analyses are descriptive and are based on the number of surveillance cases rather than on national estimates. Estimates with a coefficient of variation of >30% are indicated in the tables.

To compare patterns of ED visits for AEs between the prewithdrawal and postwithdrawal periods, we used the Surveymeans procedure to estimate selected proportions (eg, the proportions of CCM-related ED visits involving children <2 years of age) for the 2 periods. The estimated proportions (and variances) were then used to estimate before/after differences and accompanying 95% CIs.¹⁴ Because the prewithdrawal and postwithdrawal periods did not overlap, estimated proportions for the respective periods were treated as statistically independent.

RESULTS

National Estimates

In the 14-month period after announcement of the withdrawal of orally administered, OTC CCMs for infants, the number and proportion of estimated ED visits for CCM-related AEs involving children <2 years of age were less than one-half of those in the prewithdrawal period (1248 visits [13.3%] vs 2790 visits [28.7%]; difference: -15.4% [95% CI: -25.9% to -5.0%]), whereas the overall number of esti-

TABLE 1 Numbers of Cases and National Estimates of AEs from CCMs Among Children <12 Years of Age Treated in EDs Before and After Voluntary Withdrawal of OTC Infant CCMs, According to Case Characteristics: United States, July 22, 2006 to December 31, 2008

Case Characteristics	ED Visits Before Voluntary Withdrawal		ED Visits After Voluntary Withdrawal	
	Cases, <i>n</i>	National Estimate, <i>n</i> (% [95% CI])	Cases, <i>n</i>	National Estimate, <i>n</i> (% [95% CI])
Patient age				
<2 y	54	2790 (28.7 [21.0–36.3])	36	1248 (13.3 [5.8–20.7])
2–5 y	122	5928 (60.9 [52.1–69.8])	155	7154 (76.0 [67.7–84.3])
6–11 y	21	1009 (10.4 [4.7–16.1])	23	1006 ^a (10.7 [4.3–17.1])
Patient gender				
Female	98	4755 (48.9 [39.5–58.3])	94	4076 (43.3 [33.1–53.6])
Male	99	4972 (51.1 [41.7–60.5])	120	5332 (56.7 [46.4–66.9])
Type of ingestion ^b				
Unsupervised ingestion	136	6603 (67.9 [58.0–77.8])	147	6150 (65.4 [57.4–73.3])
Supervised administration without documented medication error	47	2685 (27.6 [18.4–36.9])	48	2323 (24.7 [16.6–32.8])
Supervised administration with documented medication error	14	—	19	—
ED treatment and disposition				
Gastric decontamination	44	2180 (22.4 [14.6–30.3])	35	1623 (17.3 [8.7–25.8])
Treated and released or left against medical advice	164	8754 (90.0 [80.3–99.7])	170	8606 (91.5 [84.9–98.1])
Total	197	9727	214	9408

Case counts and estimates were from the 2006–2008 NEISS-CADES project, Centers for Disease Control and Prevention. CCMs refer to orally administered prescription or OTC drug products that contain decongestant, antihistamine, antitussive, and/or expectorant combinations, as well as single-ingredient decongestants and antitussive agents/expectorants. Voluntary market withdrawal of OTC CCMs labeled for infants was announced on October 11, 2007. The period before withdrawal refers to the 14-month period beginning July 22, 2006, and ending October 11, 2007; the period after withdrawal refers to the 14-month period beginning October 12, 2007, and ending December 31, 2008. Estimates based on <20 cases are not shown (—).

^a Estimate with coefficient of variation of 32.9.

^b Unsupervised ingestion refers to cases in which children accessed the medication without adult permission or oversight. Supervised administration refers to cases in which the medication was administered by a caregiver. Medication errors include errors made during the prescribing, dispensing, or administration of the medication, as documented in the ED record.

mated ED visits for CCM-related AEs for children <12 years of age remained unchanged (9408 visits [95% CI: 6874–11 941 visits] vs 9727 visits [95% CI: 6649–12 805 visits]) (Table 1). During both time periods, most ED visits for CCM-related AEs involved children 2 to 5 years of age, and boys accounted for a nominally greater number of ED visits.

Overall, the type of ingestions most commonly involved in ED visits for CCM-related AEs remained unchanged postwithdrawal (Table 1). Unsupervised ingestions caused approximately two-thirds of estimated ED visits pre- and postwithdrawal with supervised administrations accounting for the remaining one-third in each period. For most ED visits involving supervised administrations, no medication error was documented in the ED record (prewithdrawal: 86.0% [95% CI: 75.9%–96.0%]; postwithdrawal: 71.3% [95% CI: 55.4%–87.3%]).

In the prewithdrawal and postwithdrawal periods, AE-related symptoms

were documented in the ED record for 37.1% (95% CI: 28.5%–45.8%) and 35.7% (95% CI: 26.4%–45.1%), respectively, of estimated ED visits for CCM-related AEs. Among ED visits in which symptoms were documented, symptoms were most commonly described as allergic in nature (eg, rash or urticaria) (prewithdrawal: 57.6% [95% CI: 39.7%–75.4%]; postwithdrawal: 52.8% [95% CI: 35.3%–70.4%]) or as neurologic or behavioral manifestations (eg, somnolence, unsteady gait, irritability, or psychomotor hyperactivity) (prewithdrawal: 42.3% [95% CI: 29.0%–55.6%]; postwithdrawal: 39.8% [95% CI: 22.5%–57.2%]). The prewithdrawal and postwithdrawal periods were similar in the proportions of children who underwent gastric decontamination (eg, receipt of activated charcoal) in the ED (22.4% vs 17.3%; difference: –5.2% [95% CI: –16.5% to 6.2%]) and in the proportions of children who were treated and released from the ED (90.0% vs 91.5%; difference: 1.5% [95% CI: –10.0% to 13.0%]).

For most ED visits for CCM-related AEs in both the prewithdrawal and postwithdrawal periods, no other medication class was implicated concomitantly in the AEs (prewithdrawal: 93.5% [95% CI: 88.9%–98.1%]; postwithdrawal: 94.6% [95% CI: 90.7%–98.4%]). For visits involving only CCMs, a single CCM was nearly always implicated (prewithdrawal: 99.0% [95% CI: 97.1%–100.0%]; postwithdrawal: 99.7% [95% CI: 99.1%–100.0%]). The specific product characteristics of the CCMs implicated in the ED visit were not identifiable for all surveillance cases. Dosage form information was available for 77.5% and 85.6% of all CCM products implicated in the prewithdrawal and postwithdrawal periods, respectively; of those, 78.9% (95% CI: 67.4%–90.4%) and 83.9% (95% CI: 75.6%–92.2%), respectively, were liquids (compared with tablets/capsules or other formulations). Prescription status was identifiable for 89.3% and 92.8% of all CCM products implicated in the prewithdrawal and postwithdrawal periods,

TABLE 2 Numbers of Cases and National Estimates of AEs from CCMs Among Children <12 Years of Age Treated in EDs Before and After Voluntary Withdrawal of OTC Infant CCMs, According to Ingestion Type and Age: United States, July 22, 2006 to December 31, 2008

Patient Age	ED Visits Before Voluntary Withdrawal				ED Visits After Voluntary Withdrawal			
	Unsupervised Ingestions		Supervised Administrations		Unsupervised Ingestions		Supervised Administrations	
	Cases, <i>n</i>	National Estimate, % (95% CI)	Cases, <i>n</i>	National Estimate, % (95% CI)	Cases, <i>n</i>	National Estimate, % (95% CI)	Cases, <i>n</i>	National Estimate, % (95% CI)
<2 y	33	59.5 (38.9–80.1)	21	40.5 (19.9–61.1)	24	52.2 (27.9–76.5)	12	—
2–5 y	101	83.1 (73.2–92.9)	21	16.9 (7.1–26.8)	122	76.7 (67.7–85.7)	33	23.3 (14.3–32.3)
6–11 y	2	—	19	—	1	—	22	99.1 (97.4–100.0)

Case counts and estimates were from the 2006–2008 NEISS-CADES project, Centers for Disease Control and Prevention. CCMs refer to orally administered prescription or OTC drug products that contain decongestant, antihistamine, antitussive, and/or expectorant combinations, as well as single-ingredient decongestants and antitussive agents/expectorants. Voluntary market withdrawal of OTC CCMs labeled for infants was announced on October 11, 2007. The period before withdrawal refers to the 14-month period beginning July 22, 2006, and ending October 11, 2007; the period after withdrawal refers to the 14-month period beginning October 12, 2007, and ending December 31, 2008. Estimates based on <20 cases are not shown (—).

respectively; of those, 87.3% (95% CI: 78.6%–95.9%) and 84.7% (95% CI: 76.8%–92.6%), respectively, were identified as OTC products. Only 1 surveillance case in each of the prewithdrawal and postwithdrawal periods referred to the implicated CCM as an infant product; both cases involved unsupervised ingestions.

When results were examined according to age group, the types of CCM ingestions leading to ED visits for AEs also remained relatively unchanged in the prewithdrawal and postwithdrawal periods (Table 2). Among children <2 years of age, unsupervised ingestions caused 59.5% (95% CI: 38.9%–80.1%) and 52.2% (27.9%–76.5%) of estimated visits in the prewithdrawal and postwithdrawal periods, respectively. Among children 2 to 5 years of age, unsupervised ingestions caused most ED visits for CCM-related AEs in both time periods, that is, an estimated 4924 ED visits, 83.1% (95% CI: 73.2%–92.9%) of the ED visits in this age group, in the prewithdrawal period and an estimated 5490 ED visits, 76.7% (95% CI: 67.7%–85.7%) of the ED visits in this age group, in the postwithdrawal period. Among children 6 to 11 years of age, nearly all cases were after supervised administrations.

Among children <2 years of age, we examined ED visits for AEs resulting from supervised administrations of

other medications that might have been influenced by the withdrawal of OTC infant CCMs (ie, medications that might have been used by caregivers in place of infant CCMs). For children in this age group, the proportions of ED visits for AEs resulting from orally administered nonopioid analgesics (including single-ingredient acetaminophen, other acetaminophen-containing analgesics, and salicylate-containing analgesics), orally administered, single-ingredient antihistamines, orally administered, nonselective, nonsteroidal antiinflammatory drugs, nasal decongestants, ophthalmic decongestants, or topical analgesics were similar in the prewithdrawal and postwithdrawal periods (5.2% vs 4.7%; difference: –0.5% [95% CI: –3.7% to 2.7%]). The proportions of ED visits for antibiotic-related AEs after supervised administrations in this age group also were similar in the prewithdrawal and postwithdrawal periods (53.2% vs 55.4%; difference: 2.2% [95% CI: –8.0% to 12.4%]).

The contribution of CCMs to the ED visit burden for all medication-related AEs was reduced significantly for children <2 years of age (difference: –2.1% [95% CI: –3.8% to –0.4%]) in the postwithdrawal period, relative to the prewithdrawal period, but remained statistically unchanged for children 2 to 11 years of age (difference: 1.1% [95% CI: –1.4% to 3.6%]) (Table 3). Overall,

among children <12 years of age, CCMs accounted for 5.5% (95% CI: 4.1%–6.8%) and 5.3% (95% CI: 4.1%–6.5%) of estimated ED visits for all medication-related AEs in the prewithdrawal and postwithdrawal periods, respectively.

Case-Based Medication Error Analysis

Among surveillance cases in which medication errors were documented in the ED record, more than three-fourths of CCM-related cases (26 of 33 cases) involved excess dosing (eg, administration of 1.5 teaspoons instead of 0.5 teaspoon) by caregivers (9 of 14 cases prewithdrawal and 17 of 19 cases postwithdrawal). The remaining documented medication errors (7 of 33 cases) included inadvertent administration of a CCM or administration of another patient's CCM (eg, one belonging to a parent or sibling). Children <2 years of age accounted for approximately one-third of all cases involving CCM errors in the prewithdrawal period (5 of 14 cases) and approximately one-fifth of these cases in the postwithdrawal period (4 of 19 cases). The medication errors documented in cases involving children <2 years of age all involved excess dosing of a CCM. Children 2 to 5 years of age accounted for approximately two-fifths of all cases involving CCM errors in the prewithdrawal period (6 of 14 cases) and

TABLE 3 National Estimates of Medication-Related AEs Among Children <12 Years of Age Treated in EDs Before and After Voluntary Withdrawal of OTC Infant CCMs: United States, July 22, 2006 to December 31, 2008

Patient Age	ED Visits Before Voluntary Withdrawal			ED Visits After Voluntary Withdrawal			Difference in Proportions (95% CI), %
	No. of CCM-Related Visits	No. of All Medication-Related Visits	Proportion of CCM-Related Visits Among All Medication-Related Visits, %	No. of CCM-Related Visits	No. of All Medication-Related Visits	Proportion of CCM-Related Visits Among All Medication-Related Visits, %	
<2 y	2790	72 717	3.8	1248	71 934	1.7 ^a	-2.1 (-3.8 to -0.4)
2-11 y	6937	105 570	6.6	8160	106 344	7.7	1.1 (-1.4 to 3.6)
Total	9727	178 287	5.5	9408	178 278	5.3	-0.2 (-2.0 to 1.6)

Estimates were from the 2006-2008 NEISS-GADES project, Centers for Disease Control and Prevention. CCMs refer to orally administered prescription or OTC drug products that contain decongestant, antihistamine, antitussive, and/or expectorant combinations, as well as single-ingredient decongestants and antitussive agents/expectorants. All medications refer to prescription or OTC medications including vitamins, herbal preparations/dietary supplements, and vaccines. Voluntary market withdrawal of OTC CCMs labeled for infants was announced on October 11, 2007. The period before withdrawal refers to the 14-month period beginning July 22, 2006, and ending October 11, 2007; the period after withdrawal refers to the 14-month period beginning October 12, 2007, and ending December 31, 2008.

^a Estimate with coefficient of variation of 30.6.

more than one-half of such cases in the postwithdrawal period (11 of 19 cases). During both the prewithdrawal and postwithdrawal periods, among cases involving medication errors for which the product was identified adequately, implicated CCMs were exclusively liquid (13 of 13 cases in the prewithdrawal period and 19 of 19 cases in the postwithdrawal period) and OTC products were involved 45% (5 of 11 cases) and 72% (13 of 18 cases) of the time, respectively.

DISCUSSION

The use of CCMs for children remains an important concern in the medical and public health communities. In the 14-month period after announcement of the withdrawal, the numbers and proportions of estimated ED visits for CCM-related AEs involving children <2 years of age were reduced by more than one-half, compared with the 14-month period before the announcement. Because of the relatively large numbers of unsupervised ingestions of CCMs among children 2 to 5 years of age, however, the overall numbers of ED visits for CCM-related AEs and the contribution of CCMs to the total medication-related ED visit burden remained unchanged for children <12 years of age. A recent study documented a significant reduction in the mean annual rate of calls reported to US poison control centers that in-

involved therapeutic errors with OTC CCMs among children <2 years of age in the 15 months after withdrawal, relative to a 27-month prewithdrawal period. Because calls to poison control centers are voluntary, however, an impact of reporting bias on the findings could not be excluded and the incidence of national exposures could not be calculated.¹⁵ To our knowledge, ours is the first report that, on the basis of active surveillance, assessed the changes in the national burden and scope among children of CCM-related AEs and AEs related to medications potentially substituted for infant CCMs since the announcement of the withdrawal of orally administered OTC products marketed for infants. Although these safety data cannot be used in isolation to dictate clinical or regulatory actions, our findings have important implications for continued efforts to reduce the burden of harm resulting from these medications.

First, the finding of a substantial reduction in estimated ED visits for CCM-related AEs among children <2 years of age after announcement of the market withdrawal is especially important because, after the withdrawal, some caregivers might have maintained belief in the overall safety and efficacy of these products or might have been unaware of or misinterpreted warnings

and either administered infant products still present in the home or substituted products labeled for older children and adults.¹⁶⁻²⁰ A related concern regarding the withdrawal of infant CCMs was that caregivers might have sought other treatments to relieve cough and cold symptoms, which might have resulted in inappropriate use of some medications (eg, antibiotics) or increased the burden of harm from others (eg, analgesics). In a survey of 1265 parents conducted between March and May 2008 at 20 pediatric offices, 27% of parents with children <2 years of age stated that they were more likely to request an antibiotic from the doctor after market withdrawal of infant CCMs.¹⁹ Although we could not account directly for changes in patterns of medication use, we did not identify any significant changes in the estimated numbers or proportions of ED visits for AEs resulting from supervised administrations of antibiotics or other medications that might have been substituted for cough and cold relief for children <2 years of age. Overall, the finding of a reduction in ED visits for children <2 years of age is encouraging, but continued education of clinicians and caregivers and further monitoring likely will be needed to ensure that the burden of CCM-related harm continues to decrease for young children, espe-

cially given recent recommendations to avoid CCMs for children <4 years of age.^{21,22}

Second, although medication errors contributed to few ED visits overall, the errors that did occur were almost exclusively the result of caregivers overdosing liquid formulations of CCMs. This finding is important, because administration-related medication errors constitute a large proportion of drug-related AEs that are considered to be readily preventable in pediatric outpatient settings.^{23,24} For liquid medications intended for children, it has been suggested that administration-related medication errors stem from caregiver misunderstanding of labeling instructions, failure to distinguish between certain volumetric measures (eg, “tsp” versus “tbsp”), or confusion resulting from inconsistency of dosing device markings with the labeled dosage directions²⁵ and that these types of errors can be prevented through the use of more-accurate dosing instruments (eg, droppers, dosing spoons, and syringes versus dosing cups).^{25–28}

One recent development that may prevent these types of medication errors in the future is a shift toward improved industry standards for displaying volumetric measures on liquid medication labels and dosing devices.^{29,30} In collaboration with the “CDC”, the FDA, and other stakeholders, Consumer Healthcare Products Association manufacturers recently adopted voluntary guidance to simplify and to standardize volumetric measures used in the labeling of children’s OTC, orally administered, liquid medications and their respective dosing devices.²⁹ The FDA recently released similar draft guidance for industry, aimed at improving the clarity and consistency of dosage delivery devices packaged with newly approved OTC, orally adminis-

tered, liquid medications.³⁰ Future studies will be required to assess the impact of these new guidelines on harm resulting from CCMs and other liquid medications.

Third, unsupervised ingestions remained the primary cause of harm resulting from CCMs for children <12 years of age, and preschool-aged children (2–5 years) continued to account for most CCM-related AEs. These findings point to the need for continued interventions targeted at reducing the potential for harm when children find and ingest medications. To that end, we previously suggested engineering innovations, including packaging improvements designed to minimize unsupervised ingestions of liquid medications.³¹ Examples of such innovations include incorporation of adaptors on liquid medication bottles, so that the medication could be accessed only with a needleless syringe, or the use of bottle-neck flow restrictors that would limit the amount of liquid that could be ingested if an unsupervised child gained access to the medication. Our findings are subject to a few important limitations. First, surveillance through the NEISS-CADES project likely underestimates the total burden of AEs resulting from CCMs because it does not identify AEs resulting in calls to poison control centers, visits to outpatient physician offices, or deaths; however, the ED is probably the best single setting to identify serious AEs, because it is the location where children with serious symptoms most likely would be brought for treatment. Second, the NEISS-CADES project relies on assessment and documentation by ED physicians; therefore, it is more likely to identify well-recognized AEs (eg, unsupervised ingestions) and is less likely to identify AEs that are rare, previously unreported, or difficult to diagnose in the ED setting.^{12,13} Third, information

on the specific CCM formulation (ie, infant versus pediatric versus adult) implicated in the AE was not available in some cases, which limited our ability to draw conclusions about specific products. Fourth, we cannot comment on whether changes in the number of ED visits differed according to race/ethnicity, socioeconomic status, or caregiver health literacy, because information about these variables is limited or unavailable through the NEISS-CADES project. Fifth, although our findings suggest that removal of infant products from the market likely contributed to the reduction of CCM-related morbidity among children <2 years of age, other factors, including widespread attention in the media to the issue of the safety and efficacy of CCMs, changes in provider attitudes and recommendations, and warnings issued by the FDA, also might have affected use of these medications and ED visits for CCM-related AEs in this age group. Lastly, there may be a seasonality component to CCM use, with less use of these products in the summer months and subsequently fewer ED visits for CCM-related AEs. Therefore, the selection of 14-month periods before and after the announcement of market withdrawal in October 2007 might have favored higher estimates of the number of ED visits for the postwithdrawal period, relative to the pre-withdrawal period of the same duration, however, this further strengthens the finding that ED visits among children <2 years of age were reduced.

Future work will be needed to assess the impact of more-recent labeling changes to avoid the use of CCMs for children <4 years of age^{21,22} and to evaluate whether, as attention to the issue of the safety and efficacy of CCM wanes, caregivers will return to administering CCMs labeled for older

children and adults to infants. Although CCMs constitute a small proportion of all ED visits for AEs among children <12 years of age, the safety concerns they have raised demonstrate how public-private collaborative efforts and a combination of education, engineering, and enforcement

strategies can be used to improve medication safety in the outpatient setting.

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REFERENCES

- Gunn VL, Taha SH, Liebelt EL, Serwint JR. Toxicity of over-the-counter cough and cold medications. *Pediatrics*. 2001;108(3). Available at: www.pediatrics.org/cgi/content/full/108/3/e52
- Sharfstein JM, North M, Serwint JR. Over the counter but no longer under the radar: pediatric cough and cold medications. *N Engl J Med*. 2007;357(23):2321–2324
- US Food and Drug Administration. Nonprescription Drug Advisory Committee Meeting: cold, cough, allergy, bronchodilator, antiasthmatic drug products for over-the-counter human use, October 18 and 19, 2007. Available at: www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4323b1-02-FDA.pdf. Accessed May 3, 2010
- Dolansky G, Rieder M. What is the evidence for the safety and efficacy of over-the-counter cough and cold preparations for children younger than six years of age? *Paediatr Child Health*. 2008;13(2):125–127
- Vassilev ZP, Kabadi S, Villa R. Safety and efficacy of over-the-counter cough and cold medicines for use in children. *Expert Opin Drug Saf*. 2010;9(2):233–242
- Centers for Disease Control and Prevention. Infant deaths associated with cough and cold medications: two states. *MMWR Morb Mortal Wkly Rep*. 2007;56(1):1–4
- Rimsza ME, Newberry S. Unexpected infant deaths associated with use of cough and cold medications. *Pediatrics*. 2008;122(2). Available at: www.pediatrics.org/cgi/content/full/122/2/e318
- Pitetti RD, Whitman E, Zaylor A. Accidental and nonaccidental poisonings as a cause of apparent life-threatening events in infants. *Pediatrics*. 2008;122(2). Available at: www.pediatrics.org/cgi/content/full/122/2/e359
- Dart RC, Paul IM, Bond GR, et al. Pediatric fatalities associated with over the counter (nonprescription) cough and cold medications. *Ann Emerg Med*. 2009;53(4):411–417
- Consumer Healthcare Products Association. Makers of OTC cough and cold medicines announce voluntary withdrawal of oral infant medicines, October 11, 2007. Available at: www.chpa-info.org/10_11_07_OralInfantMedicines.aspx. Accessed May 3, 2010
- US Food and Drug Administration. News & Events. FDA Releases Recommendations Regarding Use of Over-the-Counter Cough and Cold Products. Products should not be used in children under 2 years of age; evaluation continues in older populations. Available at: www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116839.htm. Accessed May 3, 2010
- Budnitz DS, Pollock DA, Weidenbach KN, Mendelsohn AB, Schroeder TJ, Annest JL. National surveillance of emergency department visits for outpatient adverse drug events. *JAMA*. 2006;296(15):1858–1866
- Jhung MA, Budnitz DS, Mendelsohn AB, et al. Evaluation and overview of the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance Project (NEISS-CADES). *Med Care*. 2007;45(10 suppl 2):S96–S102
- Kish L. *Survey Sampling*. New York, NY: Wiley Inter-Science; 1995
- Klein-Schwartz W, Sorkin JD, Doyon S. Impact of the voluntary withdrawal of over-the-counter cough and cold medications on pediatric ingestions reported to poison centers. *Pharmacoepidmiol Drug Saf*. 2010;19(8):819–824
- NPR; Kaiser Family Foundation; Harvard School of Public Health. Children's OTC cold medicines: the public, and parents, weigh in, December 2007. Available at: www.kff.org/kaiserpolls/upload/7726.pdf. Accessed May 3, 2010
- Lokker N, Sanders L, Perrin EM, et al. Parental misinterpretations of over-the-counter pediatric cough and cold medication labels. *Pediatrics*. 2009;123(6):1464–1471
- Yaghai BF, Cordts C, Ahlers-Schmidt CR, Issa BA, Warren RC. One community's perspective on the withdrawal of cough and cold medications for infants and young children. *Clin Pediatr (Phila)*. 2010;49(4):310–315
- Garbutt JM, Sterkel R, Banister C, Walber T, Strunk RC. Physician and parent response to the FDA advisory about use of over-the-counter cough and cold medications. *Acad Pediatr*. 2010;10(1):64–69
- Hanoch Y, Gummerum M, Miron-Shatz T, Himmelstein M. Parents' decision following the Food and Drug Administration recommendation: the case of over-the-counter cough and cold medication. *Child Care Health Dev*. 2010;36(6):795–804
- Consumer Healthcare Products Association. Statement from CHPA on the voluntary label updates to oral OTC children's cough and cold medicines, October 7, 2008. Available at: www.chpa-info.org/10_07_08_PedCC.aspx. Accessed May 3, 2010
- US Food and Drug Administration. FDA statement following CHPA's announcement on nonprescription over-the-counter cough and cold medicines in children. Available at: www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116964.htm. Accessed May 3, 2010
- Kaushal R, Goldmann DA, Keohane CA, et al. Adverse drug events in pediatric outpatients. *Ambul Pediatr*. 2007;7(5):383–389
- Shah K, Barker KA. Out-of-hospital medication errors: a 6-year analysis of the national poison data system. *Pharmacoepidmiol Drug Saf*. 2009;18(11):1080–1085
- Yin HS, Mendelsohn AL, Wolf MS, et al. Parents' medication administration errors: role of dosing instruments and health literacy. *Arch Pediatr Adolesc Med*. 2010;164(2):181–186
- Madlon-Kay DJ, Mosch FS. Liquid medication dosing errors. *J Fam Pract*. 2000;49(8):741–744
- Litovitz T. Implication of dispensing cups in dosing errors and pediatric poisonings: a report from the American Association of Poison Control Centers. *Ann Pharmacother*. 1992;26(7–8):917–918
- Sobhani P, Christopherson J, Ambrose PJ, Corelli RL. Accuracy of oral liquid measuring devices: comparison of dosing cup and

- oral dosing syringe. *Ann Pharmacother*. 2008;42(1):46–52
29. Consumer Healthcare Products Association. Volumetric measures for dosing of over-the-counter oral liquid drug products for children ≤ 12 years of age. Available at: www.chpa-info.org/scienceregulatory/Voluntary_Codes.aspx#volumetricmeasure. Accessed May 3, 2010
30. US Food and Drug Administration. Guidance for industry: dosage delivery devices for OTC liquid drug products. Available at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM188992.pdf. Accessed May 3, 2010
31. Schaefer MK, Shehab N, Cohen AL, Budnitz DS. Adverse events from cough and cold medications in children. *Pediatrics*. 2008;121(4):783–787

Snakes, Eels, and the Mongoose: *Whenever I go hiking in northern California, I am very careful not to put my hands or feet where I can't see them. That is because I have a very healthy respect for the rattlesnake and have no desire to suffer the myriad severe complications of a venomous bite. How is it then that some ground squirrels scamper about unfazed and seemingly immune to the ill effects of rattlesnake bites? According to an article in The New York Times (Carroll S, October 25, 2010), many of the squirrels in northern California survive rattlesnake bites because they have developed serum proteins that neutralize rattlesnake venom. Squirrels, not living in close proximity to rattlesnakes, eg Alaskan squirrels, have not developed these proteins and are extremely susceptible to the toxic effects of rattlesnake venom. This idea—that in order to survive, the prey of venomous animals must develop defense mechanisms—is not unique to squirrels. Eels in the western Pacific, the favorite food of some venomous sea snakes, have developed resistance to the neurotoxin of the snake. Eels in the Caribbean, where there are no venomous sea snakes remain highly susceptible. A good defense can be turned into a good offence. The kingsnake has developed a serum protein that neutralizes rattlesnake venom and so protected preys fearlessly on rattlesnakes. The King Cobra preys on venomous snakes and may itself be bitten. The King Cobra survives because it has developed mutated acetylcholine receptors to which neurotoxins in venom cannot bind. So, a bite from a venomous snake causes no significant problem for the King Cobra. The problem for the King Cobra is the mongoose. In addition to extremely quick reflexes and powerful jaws, the mongoose too may have developed mutated acetylcholine receptors making it less susceptible to the venom of the Cobra. Evolution is amazing.*

Noted by WVR, MD

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