Division of Healthcare Quality Promotion
National Center for Emerging and Zoonotic Infectious Diseases

Unsupervised Ingestions by Young Children:
Monitoring Emergency Department Visits for Opioid Overdoses

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Disclosures

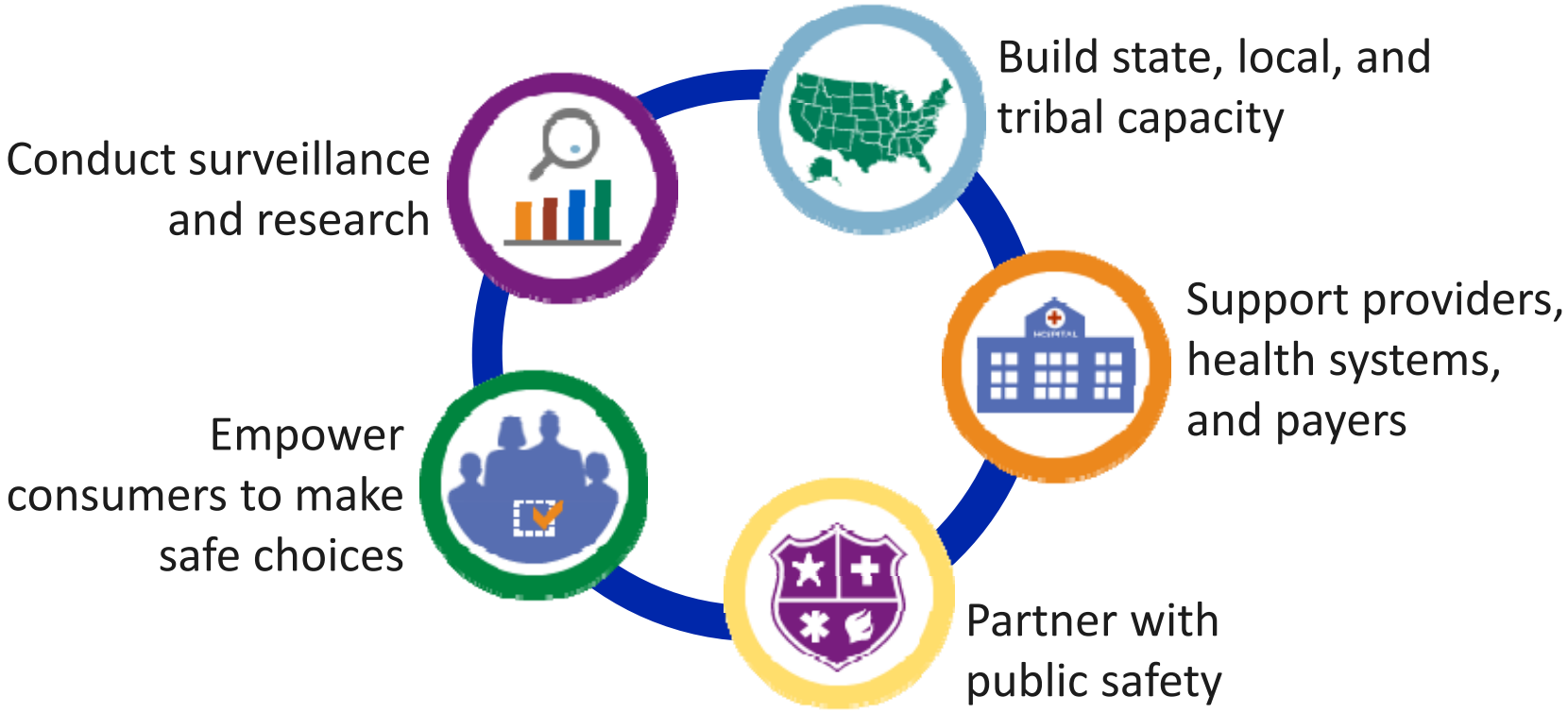
- No financial disclosures to report

- The findings and conclusions in this presentation are those of the author and do not necessarily represent official position of the Centers for Disease Control and Prevention.

Outline

- Brief Background
- Packaging for Prevention
- Post-Market Data
- Lessons from Post-Market Monitoring

Preventing Opioid Overdoses and Opioid-Related Harms



NEISS-CADES: Population Representative Surveillance

- National Electronic Injury Surveillance System (NEISS)
  - Operated by the U.S. Consumer Product Safety Commission (CPSC)
  - Cooperative (with CDC/FDA) Adverse Drug Event Surveillance (CADES)

- National Probability Sample
  - ~60 hospital Emergency Departments (EDs)
  - Stratified by hospital size & children's hospitals
  - Cases weighted by inverse probability of selection

NEISS-CADES: Case Definition (2004-2015)

- **"Injury" from the use of a drug**
  - ED visit
- **Injury "from the use of" a drug**
  - Treating physician explicitly attributes to drug effects
  - Pathognomonic drug-symptom sequence
  - Therapeutic intent
- **Injury from the use of "a drug"** (up to 2 implicated)
  - Prescription product
  - Over-the-counter product
  - Supplement (vitamin, herb, homeopathic)
  - Vaccine

- Allergic Reactions
- Side Effects
- Supra-therapeutic Effects (Therapeutic Overdoses)
- Errors
- Misuse/Abuse
- Self Harm
- Unknown Intent

NEISS-CADES: Case Definition (2016-)

- **"Injury" from the use of a drug**
  - ED visit
- **Injury "from the use of" a drug**
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  - **All "intents"**
- **Injury from the use of "a drug"** (up to 4 implicated)
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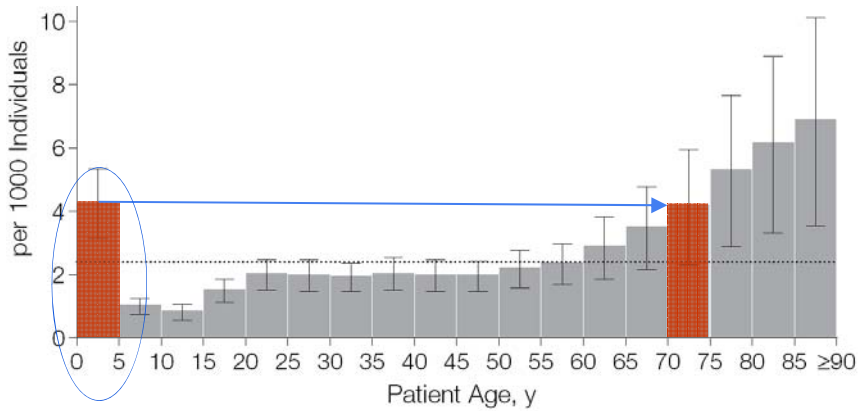
Rate of Emergency Visits for Adverse Drug Events (ADEs) in Children <5 Years Similar to 70-75 Year-olds



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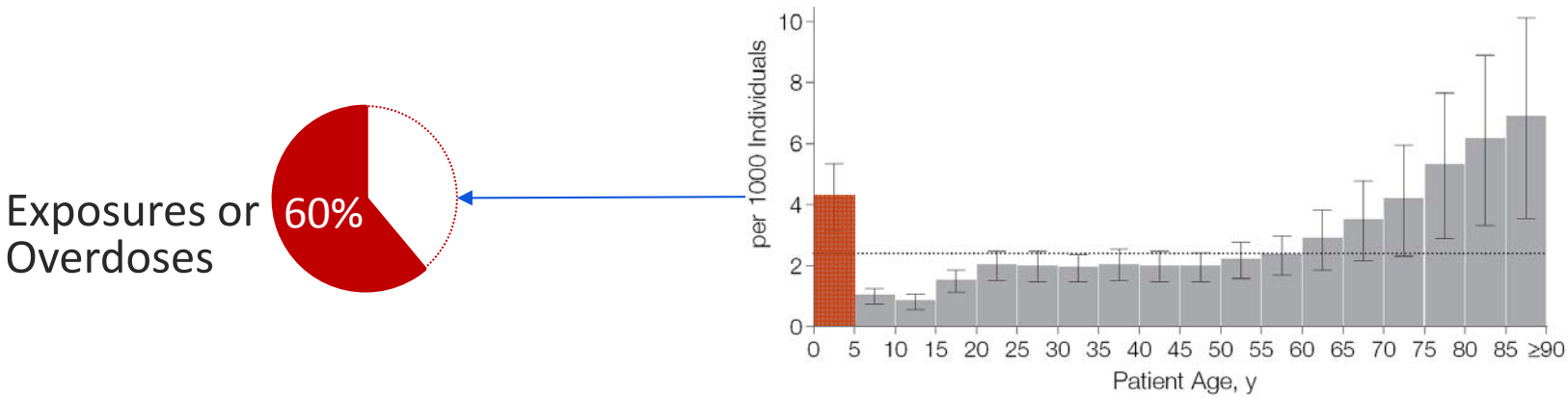
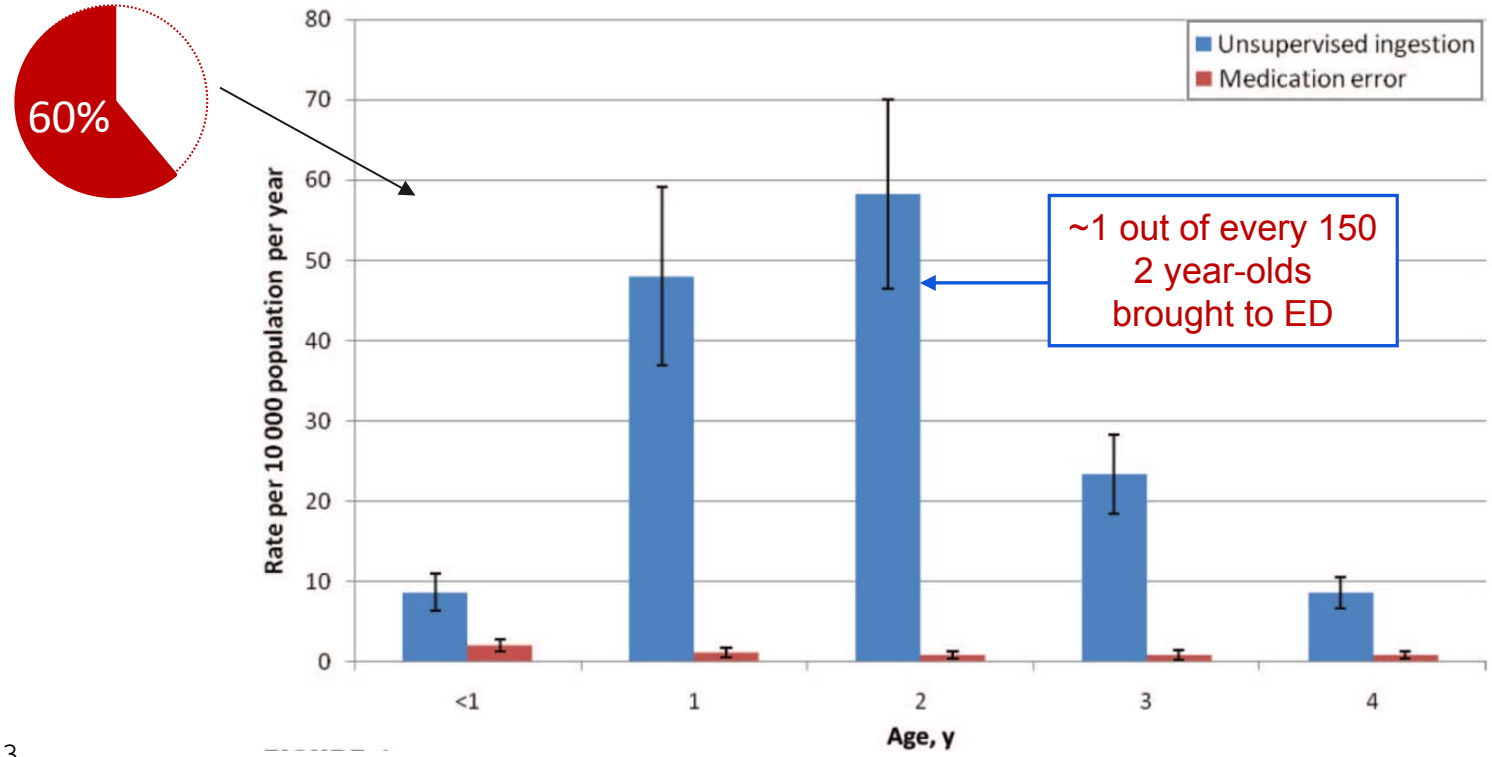
Budnitz DS et al. *JAMA* 2006;296:1858-66

Most Emergency Visits for ADEs in Children <5 years Due to Unintentional Medication Exposures or Overdoses



Cohen AL et al. *J Pediatr* 2008;152: 416-421
Schillie SF et al. *Am J Prev Med* 2009;37:181-7

How do Medication Exposures & Overdoses Happen?
Mostly by Unsupervised Ingestions



Budnitz DS and Salis S. *Pediatrics* 2011;127:1597-9

Which Solid Dosage Form Classes Cause ED Visits for Overdoses in Children ≤5 years?

Most Commonly Implicated Medications	ED Visits: Annual National Estimate		
	No.	%	95% CI
Oral prescription solid medications			
Opioid analgesics	4661	13.8	11.8–15.8
Benzodiazepines	4293	12.7	10.8–14.7
Antidepressants	3594	10.7	8.9–12.4
β-blockers	2080	6.2	5.0–7.4
Amphetamine-related stimulants	1965	5.8	4.5–7.1
Centrally acting antiadrenergics	1847	5.5	4.0–6.9
Anticonvulsants	1715	5.1	4.0–6.2
Oral hypoglycemics	1454	4.3	2.6–6.0
Skeletal muscle relaxants	1437	4.3	3.2–5.3
Calcium channel blockers	1377	4.1	2.6–5.5
Atypical antipsychotics	1318	3.9	2.8–5.0
Angiotensin-converting enzyme inhibitors	1239	3.7	2.8–4.5

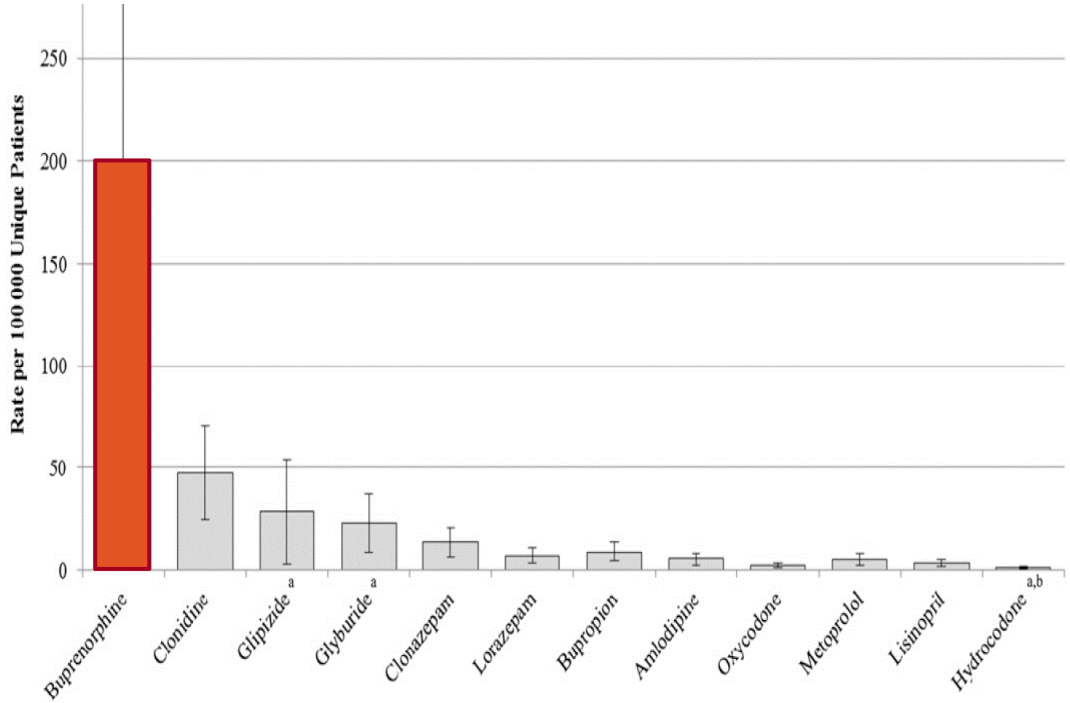
Lovegrove M et al. *Pediatrics* 2014:134;e1009-16

Which Solid Dosage Form Ingredients Cause Hospitalizations in Children ≤5 years

Active Ingredient	Annual National Estimate of Hospitalizations			Proportion of ED Visits Resulting in Hospitalization, %
	Number	Percentage	(95% CI)	
Buprenorphine	734	7.7	(3.9–11.5)	62.4
Clonidine	701	7.4	(4.9–9.8)	56.2
Glipizide	386[a]	4.1[a]	(1.0–7.2)	74.2
Clonazepam	368	3.9	(2.3–5.5)	24.0
Metoprolol	314	3.3	(1.8–4.8)	34.5
Lorazepam	309	3.3	(1.7–4.8)	38.4
Lisinopril	298	3.1	(2.0–4.3)	28.9
Amlodipine	295	3.1	(1.3–4.9)	51.4
Bupropion	265	2.8	(1.5–4.1)	56.2
Glyburide	257[a]	2.7	(1.2–4.2)	75.1
Hydrocodone[b]	252[a]	2.7	(1.4–3.9)	30.5
Oxycodone	249	2.6	(1.5–3.8)	26.1

Lovegrove M et al. *Pediatrics* 2014:134;e1009-16

For every 500 Adults Treated with Buprenorphine, 1 Child Hospitalized, 2007-2011



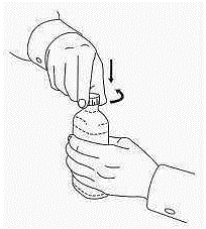
justice.gov/archive/ndic/pubs10/10123/index.htm

Lovegrove M et al. *Pediatrics* 2014:134;e1009-16

Hypothesis: Would Passive Exposure-Limiting Features Reduce Child Ingestions and Overdoses?

Seatbelts

Re-engagement Required



Automatic Protection

Air Bags

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Unit-Dose Packaging

Hypothesis: How Would Passive "Exposure-Limiting" Features Reduce Child Ingestions?

1. Additional passive protection
   - Unit-dose packaging remains in place for remaining doses after one dose is used

2. A little is less harmful than a lot (dose-limiting)
   - incorporates child resistance around every dose

ct.gov/dcp/cwp/view.asp?Q=525232

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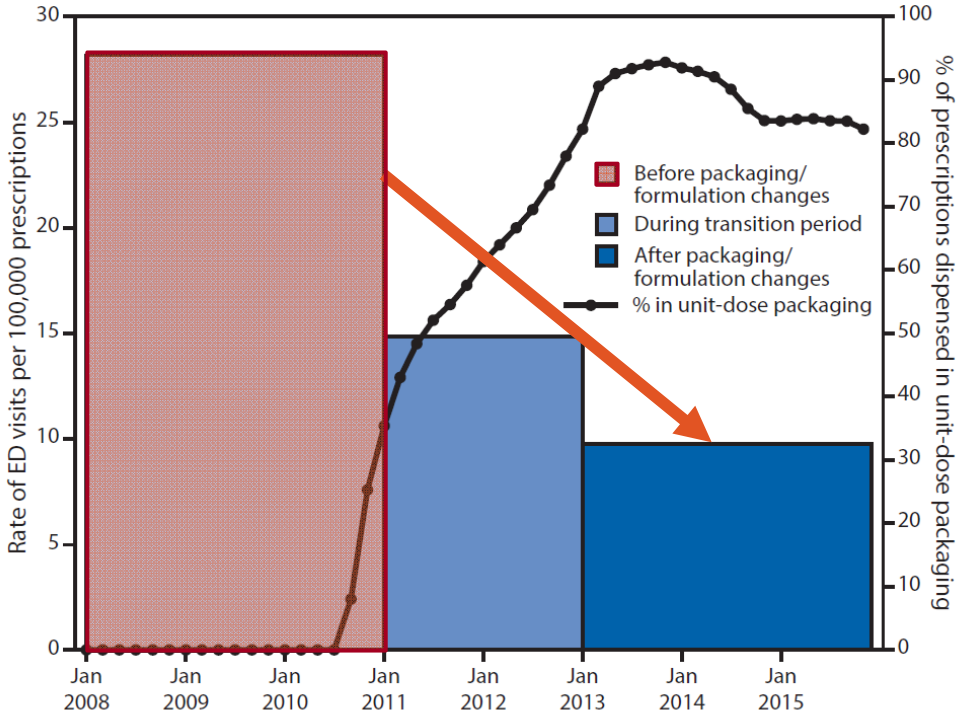
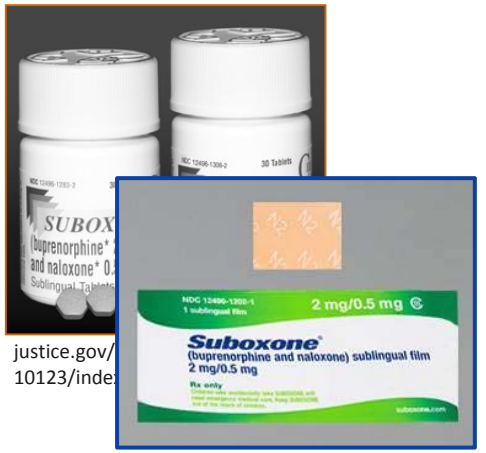
Data: After Unit-Dose Packaging & Re-formulation, ED Visits for Child Ingestions ↓65%





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Budnitz DS et al. *MMWR* 2016; 65:1148-9

Data: After Flow Restrictors Added, Amount Ingested Declines Based on Calls to Poison Centers

- 6 participating Poison Centers (August 2013 – January 2014)
- 289 cases of pediatric acetaminophen ingestions
- Primary Finding:
  - 2.5 higher odds of ingesting >150 mg/kg dose of acetaminophen in "old" packaging vs. "new" packaging with flow restrictors
- Conclusion:
  - More extensive use would likely reduce morbidity and mortality
  - Further implementation packaging should be encouraged

Geller RJ et al. 2015 Annual Meeting of the North American Congress of Clinical Toxicology (NACCT) *Clinical Toxicology*, 53:7, 641-2

93. The impact of repackaging from bottle to blister on paediatric intoxications with the levothyroxine brand Thyrax®

Antoinette J. H. P. van Riel, Tessa E. van Riemsdijk, Claudine C. Hunault and Irma de Vries

University Medical Center Utrecht (UMCU), Utrecht, The Netherlands

Objective: In December 2013, the packaging of levothyroxine with the brand name Thyrax® was changed by the manufacturer from a bottle to a blister pack in order to improve protection against various environmental factors such as light, air, and humidity. We hypothesized that this change also increased child safety, and analysed the telephone inquiries to our Poisons Information Center (PIC) to investigate the influence of this repackaging on intoxications in young children.

Methods: Cases of exposure and acute overdose with Thyrax® in children under 7 years were included from January 2010 to December 2015. A bottle of Thyrax® contained 90 tablets, so it is likely that between January and March 2014 patients were still using the remaining tablets from their bottle. Cases from January to March 2014 were therefore considered not representative for evaluating the effect of repackaging. Trends in the number of cases per month before and after repackaging were compared using Interrupted Time Series analyses. An unknown dose or an ingested dose of more than 0.05 mg/kg of levothyroxine was defined as a toxic dose. The proportional decreases in the number of cases exposed to a toxic versus a non-toxic dose, before and after repackaging were compared, using a *z*-test.

Results: After repackaging, the number of enquiries per month concerning exposures to Thyrax® decreased from a mean of 12.1/month in 2010–2013 to 5.8/month in 2014–2015 ($p = .03$). Furthermore, the decrease in the number of children exposed to a toxic dose of Thyrax® was proportionally larger (−65%) compared to children exposed to a non-toxic dose (−38%; $p = .002$). Remarkably, even two years after repackaging, part of the Thyrax® tablets were still packed in a bottle. It is unclear whether the tablets were still delivered in a bottle. In five cases the parents indicated that they transferred the tablets from a blister to a bottle themselves. In 2015, 50% of the cases with a toxic dose of levothyroxine still came from bottled tablets.

Conclusion: Changing the packaging of Thyrax® from bottle to blister has led to a significant decline in the total number of accidental exposures to Thyrax®. The proportion of decrease was even larger for the number of toxic doses. Clearly, blister packaging of tablets is more child safe than bottle packaging. Users, especially those with small children in their household, should be instructed not to repackage tablets from blisters to bottles.

Post-Market Data Considerations: Numerator

- Definition of harm
  - Exposures, Visits, Toxicity?
- Attribution of harm
  - Are symptoms due to the drug?
  - Are multiple substances involved?
- Intention of administration
  - Documentation limitations?
- Categorization of the product
  - By active ingredient, brand, formulation, packaging, source?

Post-Market Data Considerations: Denominator

- Units of exposure
  - Prescriptions written, prescriptions dispensed, days supply, dose supplied, patient-days, patients?
- Time period
  - Shelf-life, washout?
- Intention of administration
  - Documentation limitations?
- Categorization of the product
  - By active ingredient, brand, formulation, packaging

Post-Market Data Considerations: Time Trends

- Correlation is not causation
  - Assessing secular effects?
- Maturation of monitoring systems
  - Both numerator and denominator drift?
- Timing requirements
  - Availability of baseline?
  - Market penetration of packaging?
- Statistical testing
- Unknowns over time

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov