Evaluation of Liquid Laundry Detergent Packet Exposures Reported to the National Poison Data System (NPDS) Before and After the Implementation of American Society for Testing and Materials (ASTM) Safety Standards

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EXECUTIVE SUMMARY

Key Findings:

A total of 64,532 unintentional-general exposures involving liquid laundry detergent packets in children <6 years of age were reported to the NPDS from 01 July 2012 through 31 December 2017, with 10,229 exposures reported during the baseline period (01 July 2012 to 30 June 2013), 43,507 exposures reported during the transition period (01 July 2013 to 31 December 2016), and 10,796 exposures reported during the post period (01 January 2017 to 31 December 2017). Analysis compared characteristics of exposures in the baseline versus the post period to evaluate the impact of the American Society for Testing and Materials (ASTM) standards to improve liquid laundry detergent packet safety.

- While overall exposure counts increased slightly from the baseline to the post period, the percentage of exposures involving healthcare facility (HCF) treatment decreased from 41.5% to 38.7%, the percentage of exposures involving HCF admission decreased from 4.5% to 1.9%, and the percentage of exposures involving a severe medical outcome decreased from 0.6% to 0.2%.
- Mean age was similar in the baseline (2.1 years) and post periods (2.3 years), but the percentage of exposures involving children <2 years of age decreased from 41.3% to 32.0% and the percentage of exposures involving children 2 to <4 years (48.2% to 54.4%) and children 4 to <6 years of age (10.2% to 13.3%) increased. The overall age distribution changing from the baseline to the post period (p<.001).
- The percentage of exposures involving ingestion decreased from 90.4% in the baseline period to 82.3% in the post period (p<.001), with an increase in ocular exposures from 13.3% to 21.9% i (p<.001), and an increase in dermal exposures from 10.2% to 16.7% (p<.001).
- The distribution of both level of HCF treatment and medical outcome differed when comparing the post period to the baseline period (p<.001). The percentage of exposures involving the recommendation to or receipt of HCF treatment decreased 9.2% from baseline to post period and fewer exposures involving minor effect (8.9% decrease), moderate effect (2.4% decrease), and major effect (0.4% decrease) were reported in the post period.
- As another measure of exposure severity, fewer exposures in the post period (58.7%) resulted in a related clinical effect compared to exposures in the baseline period (69.6%; p<.001).
- When adjusted for the US population of children <6 years of age, all exposures increased 5.9% from the baseline to post period (p<.001), however exposures involving HCF treatment decreased 15.5% (p<.001), exposures involving HCF admission decreased 54.2% (p<.001), and exposures involving severe medical outcomes decreased 70.2% (p<.001).
- When adjusted for sales of liquid laundry detergent packets, all exposures decreased 53.4% from the baseline to post period (p<.001), exposures involving HCF treatment decreased 62.6% (p<.001), exposures involving HCF admission

decreased 79.6% (p<.001), and exposures involving severe medical outcomes decreased 86.4% (p<.001).

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BACKGROUND

In late 2015, voluntary standards were created by the American Society for Testing and Materials (ASTM) to help reduce unintentional exposures to liquid laundry detergent packets in children. These changes included requirements for an aversive agent, opaque packaging, packaging that is difficult to open by children, warning statements about the dangers of putting liquid laundry detergent packets in the mouth, and that liquid laundry detergent packets should be kept away from children[1]. As with all safety interventions, it is important to measure the impact of such changes. A surveillance and evaluation model has been employed to describe characteristics of National Poison Data System (NPDS) exposures to liquid laundry detergent packets in the context of these changes. Surveillance of exposures reported during the period prior to (baseline), during (transition), and after the implementation of ASTM standards (post period) has been completed. This report systematically compares data in the baseline and post periods to describe the impact of the ASTM standards on exposures to liquid laundry detergent packets and describes the overall trends in reported exposures.

OBJECTIVE

The objective of this report is to compare data from the period prior to implementation of the American Society for Testing and Materials (ASTM) safety standards (baseline period) to data for the period after implementation of the safety standards (post period) to determine the impact of the ASTM standards on reducing accidental exposures to liquid laundry detergent packets reported to the National Poison Data System (NPDS) and to describe trends in exposures reported over the study period.

METHODS

Through work with the American Society for Testing and Materials (ASTM) Laundry Packets Data Team, the baseline period was defined as 01 July 2012 to 30 June 2013, the transition period was defined as 01 July 2013 to 31 December 2016, and the post period was defined as 01 January 2017 to 31 December 2017. These periods were determined based on the availability of data and in relation to the period of implementation of the ASTM standards. This report will describe the overall trends in exposures throughout the full study period with additional focused comparison of data reported in the baseline to data reported in the post period.

Data Sources

National Poison Data System (NPDS)
The National Poison Data System (NPDS) is the data repository for the regional poison centers of the American Association of Poison Control Centers (AAPCC). AAPCC member centers offer coverage for the entire United States, providing free medical management services to both healthcare professionals and the general public. Exposure information is collected using a standardized coding system and database. These patient data are auto-uploaded in real time from the member poison centers to the NPDS. An exposure is defined as an actual or suspected contact with any

substance which has been ingested, inhaled, absorbed, applied to, or injected into the body, regardless of toxicity or clinical manifestation. For the purposes of this report an exposure represents one unique case.

The NPDS database consists of categorical variables, which capture patient demographics, exposure details (including exposure reason, chronicity, and products involved), medical outcome, clinical effects, therapies, and scenario information. The NPDS definitions associated with these variables are outlined in Appendix A.

The NPDS was searched to identify human exposures from 01 July 2012 through 31 December 2017 to liquid laundry detergent packets. Cases that were confirmed later to be non-exposures were excluded. Exposures involving children <6 years of age with the NPDS exposure reason of unintentional-general were included. The exposure reason of unintentional-general is the reason code reserved for unintended exposures to substances not for a specific reason[2].

US Census Data
Quarterly population counts for children <6 years of age were obtained to generate population-adjusted rates of exposures[3] for the quarter corresponding to the start of the baseline period. The 2017 model of the US Census Bureau's monthly postcensal resident population estimates were averaged for each quarter to generate estimates. For the cumulative population, the monthly estimates were averaged over the entire time period to generate an overall population estimate.

Nielsen Sales Data
Sales data reported by Nielsen through its Strategic Planner Service for the Liquid Laundry Packs category were obtained in four week intervals and used to generate sales-adjusted exposure rates. Because sales data are received in four week increments, the intervals do not align perfectly with the study period calendar dates (01 July 2012 to 31 December 2017). Sales-adjusted rates of exposure were calculated using exposures and sales starting with the four week interval beginning 22 July 2012 and ending with the four week interval ending 30 December 2017.

Data Analysis

National Poison Data System Summary
Descriptive statistics were used to compare the variables of interest for all unintentional-general exposures in children <6 years of age in the baseline and post periods. Variables compared included age, route of exposures, level of healthcare facility (HCF) treatment, medical outcome, and reported clinical effects. For this summary, related clinical effects were evaluated. When assumptions of normality were met, continuous data were analyzed using analysis of variance. When normality assumptions did not hold, a Mann-Whitney U-test (i.e., Wilcoxon rank sum test) was implemented to compare distributions. For all categorical data analyzed, a Chi-square test was used to compare proportions and changes in distribution between the baseline and post periods. All analyses used a two-sided test with a 0.05 level of significance.

Cumulative and Trends Over Time Rates Summary
US Census data were used to calculate population-adjusted rates of exposures per 100,000 children <6 years of age. Nielsen sales data were used to calculate reported exposure rates per 1 million units (i.e., packets) sold. Exposure rates and corresponding 95% confidence intervals were calculated utilizing a log-linear Poisson regression model.

Rates were calculated cumulatively for the baseline and post period. The log-linear Poisson regression model for the cumulative rates was used to estimate a percent change in rate from the baseline to the post period (with corresponding 95% confidence interval and p-value). For all rate calculations, the average of the monthly population estimates was used and the total of sales was used. For population-adjusted rates, cumulative rates were generated corresponding to the calendar dates of the study period (01 July 2012 to 31 December 2017) in accordance with the availability of US Census data. Sales-adjusted rates were calculated cumulatively for the period of 22 July 2012 to 30 December 2017 in accordance with the availability of the Nielsen sales data. Rates over time during the baseline and post periods were described but not compared statistically due to the limited time points (1 year) included in each period.

Rate analyses were performed for all exposures, exposures involving clinically significant outcomes: exposures involving HCF treatment (level of HCF treatment: treated/evaluated and released, admitted to non-critical care unit, admitted to critical care unit, admitted to psychiatric care facility), exposures involving HCF admission (level of HCF treatment: admitted to non-critical care unit, admitted to critical care unit, admitted to psychiatric care facility), and exposures with severe medical outcomes (medical outcome: major effect and death). Importantly, these stratifications are not mutually exclusive as they are composite groupings of progressing levels of severity of treatment and/or medical outcome, and a single case may exist in all or just one of the stratifications.

All calculations and analyses were done in SAS, version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

National Poison Data System (NPDS) Summary

A total of 64,532 unintentional-general exposures involving liquid laundry detergent packets in children <6 years of age were reported to the NPDS from 01 July 2012 through 31 December 2017. A total of 10,229 exposures were reported during the baseline period (01 July 2012 to 30 June 2013), with 41.5% (n=4,241) of exposures involving HCF treatment, 4.5% (n=458) involving HCF admission, and 0.6% (n=64) involving severe medical outcomes (major effect or death). A total of 43,507 exposures were reported during the transition period (01 July 2013 to 31 December 2016), with 38.7% (n=16,830) of exposures involving HCF treatment, 3.7% (n=1,621) involving HCF admission, and 0.3% (n=130) involving severe medical outcomes (major effect or death). A total of 10,796 exposures were reported during the post period (01 January 2017 to 31 December 2017), with 33.1% (n=3,570) of exposures involving HCF treatment, 1.9% (n=209) involving HCF admission, and 0.2% (n=19) involving severe medical outcomes (major effect or death; Table 1). The remainder of this section of the report will focus on a comparison of the baseline and post periods.

Table 1. Counts of All Unintentional-General Exposures to Liquid Laundry Detergent Packets by Reporting Period[a]

	Baseline Period 01 July 2012 – 30 June 2013	Transition Period 01 July 2013 – 31 December 2016	Post Period 01 January 2017 – 31 December 2017	Total 01 July 2012 – 31 December 2017
All Exposures	10,229 (100%)	43,507 (100%)	10,796 (100%)	64,532 (100%)
Exposures Involving HCF Treatment	4,241 (41.5%)	16,830 (38.7%)	3,570 (33.1%)	24,641 (38.2%)
Exposures Involving HCF Admission	458 (4.5%)	1,621 (3.7%)	209 (1.9%)	2,288 (3.5%)
Exposures with Severe Medical Outcomes	64 (0.6%)	130 (0.3%)	19 (0.2%)	213 (0.3%)

[a]*Level of care and medical outcome categories are not mutually exclusive.*

Comparison of Exposure Characteristics and Outcomes
The mean age of exposures during the baseline period was 2.1 years (SD 1.0), with 41.3% of unintentional-general exposures to liquid laundry detergent packets involving a child <2 years of age and 48.2% involving a child 2 to <4 years of age. During the post period, the mean age of patients was 2.3 years (SD 1.0), with 32.0% of exposures involving a child <2 years of age and 54.4% involving a child 2 to <4 years of age. The distribution of exposure by age group was different in the post period compared to the baseline period (p<.001; Table 2). The largest percentage difference in exposures involved children <2 years of age (9.3% decrease; 2 to <4 years of age 6.2% increase; 4 to <6 years of age 3.1% increase).

Table 2. Demographics of All Unintentional-General Exposures to Liquid Laundry Detergent Packets by Reporting Period

	Baseline Period 01 July 2012 – 30 June 2013 (n=10,229)	**Post Period 01 January 2017 – 31 December 2017 (n=10,796)**	**p-value[a]**
Age			
Mean (SD), years	2.1 (1.0)	2.3 (1.0)	<.001
Median, years	2.0	2.0	
IQR, years	(1.4, 3.0)	(1.6, 3.0)	
Age (categorical)			
<2 years	4,227 (41.3%)	3,457 (32.0%)	<.001
2 to <4 years	4,930 (48.2%)	5,876 (54.4%)	
4 to <6 years	1,047 (10.2%)	1,440 (13.3%)	
≤5 years (estimated age)	25 (0.2%)	23 (0.2%)	

[a]*P-value was calculated by Wilcoxon rank sum for numerical covariates; and chi-square test for categorical covariates, where appropriate.*

The majority of all unintentional-general exposures involving liquid laundry detergent packets in children <6 years of age in the baseline period (90.4%) and the post period (82.3%) involved an ingestion. The percentage of exposures involving ingestion from the baseline period to the post period significantly differed (8.1% decrease; p-value <.001). While aspiration (with ingestion), ocular, and dermal routes of exposures were reported less frequently, the percentage of each was significantly different in the baseline period compared to the post period (aspiration (with ingestion): 0.2% decrease, p=0.006; ocular: 8.6% increase, p<.001; dermal: 6.5% increase, p<.001; Table 3).

Table 3. Route of All Unintentional-General Exposures to Liquid Laundry Detergent Packets by Reporting Period

Route[a]	Baseline Period 01 July 2012 – 30 June 2013 (n=10,229)	Post Period 01 January 2017 – 31 December 2017 (n=10,796)	p-value[b]
Ingestion	9,248 (90.4%)	8,881 (82.3%)	<.001
Aspiration (with ingestion)	45 (0.4%)	24 (0.2%)	0.006
Ocular	1,357 (13.3%)	2,362 (21.9%)	<.001
Dermal	1,047 (10.2%)	1,798 (16.7%)	<.001
Other/ Unknown	33 (0.3%)	47 (0.4%)	0.184

[a] *A single exposure may involve more than one route.*
[b] *P-value was calculated by a chi-square test for categorical covariates.*

Less than half of all unintentional-general exposures involving liquid laundry detergent packets in children <6 years of age in the baseline period (46.9%) and post period (37.7%) were recommended to or received HCF treatment. The distribution of the recommendation to or the receipt of HCF treatment differed by time period (p<.001), with a 9.2% decrease in the percent of exposures that were recommended to or received HCF treatment from the baseline period to the post period (Table 4).

Of those that received HCF treatment, the majority were treated without being admitted in both the baseline (78.9%) and post periods (82.6%), with 9.6% involving admission in the baseline period and 5.1% involving admission in the post period. The distribution of level of treatment received differed by time period (p<.001; Table 4). The percentage of exposures involving admission to a non-critical care unit decreased 1.6% and the percentage of exposures involving admission to a critical care unit decreased 2.8% from baseline period to post period.

Table 4. Level of Healthcare Facility (HCF) Treatment of All Unintentional-General Exposures to Liquid Laundry Detergent Packets by Reporting Period

	Baseline Period 01 July 2012 – 30 June 2013 (n=10,229)	Post Period 01 January 2017 – 31 December 2017 (n=10,796)	p-value[a]
Recommended to or Received HCF Treatment			
Yes	4,795 (46.9%)	4,071 (37.7%)	<.001
No	5,298 (51.8%)	6,596 (61.1%)	
Unknown	136 (1.3%)	129 (1.2%)	
Level of Treatment[b]			
Treated/evaluated and released	3,783 (78.9%)	3,361 (82.6%)	<.001
Admitted to non-critical care unit	251 (5.2%)	148 (3.6%)	
Admitted to critical care unit	207 (4.3%)	61 (1.5%)	
Admitted to psychiatric care facility	0 (0.0%)	0 (0.0%)	
Patient refused referral/did not arrive at HCF	168 (3.5%)	138 (3.4%)	
Patient lost to follow-up/left AMA	386 (8.1%)	363 (8.9%)	

[a]*P-value was calculated by a chi-square test for categorical covariates.*
[b]*Denominator was the number of exposures that were recommended to or received healthcare facility treatment.*

The majority of all unintentional-general exposures involving liquid laundry detergent packets in children <6 years of age were followed to a known outcome in both the baseline (77.3%) and post (69.1%) periods. The distribution of exposures followed to a known outcome (p<.001) and not followed to a known outcome (p=0.006) both differed by time period. The percentage of exposures involving minor effect (8.9% decrease), moderate effect (2.4% decrease), and major effect (0.4% decrease) each decreased from the baseline period to the post period, while the percentage of exposures with no or unrelated effect increased (3.5% increase). One death was reported in the baseline period, while no deaths were reported in the post period (Table 5).

Table 5. Medical Outcome of All Unintentional-General Exposures to Liquid Laundry Detergent Packets by Reporting Period

	Baseline Period 01 July 2012 – 30 June 2013 (n=10,229)	Post Period 01 January 2017 – 31 December 2017 (n=10,796)	p-value[a]
Followed to a Known Outcome	**7,908 (77.3%)**	**7,458 (69.1%)**	<.001
Death	1 (<0.1%)	0 (0.0%)	
Major Effect	63 (0.6%)	19 (0.2%)	
Moderate Effect	740 (7.2%)	515 (4.8%)	
Minor Effect	5,267 (51.5%)	4,602 (42.6%)	
No Effect or Unrelated Effect	1,837 (18.0%)	2,322 (21.5%)	
Not Followed to Known Outcome	**2,321 (22.7%)**	**3,338 (30.9%)**	0.006
Unable to follow, potentially toxic	464 (4.5%)	568 (5.3%)	
Not followed, Non-toxic	147 (1.4%)	252 (2.3%)	
Not followed, minimal clinical effects expected	1,710 (16.7%)	2,518 (23.3%)	

The majority of all unintentional-general exposures involving liquid laundry detergent packets in children <6 years of age reported a related clinical effect in both the baseline (69.6%) and post (58.7%) periods. The percentage of exposures that reported a related clinical effect in the baseline period decreased 10.9% to the post period (p<.001; Table 6).

Table 6. Report of a Related Clinical Effect Among All Unintentional-General Exposures to Liquid Laundry Detergent Packets by Reporting Period

	Baseline Period 01 July 2012 – 30 June 2013 (n=10,229)	**Post Period 01 January 2017 – 31 December 2017 (n=10,796)**	**p-value[a]**
Related Clinical Effect(s) Reported	7,119 (69.6%)	6,337 (58.7%)	<.001
Related Clinical Effect(s) Not Reported	3,110 (30.4%)	4,459 (41.3%)	

[a]*P-value was calculated by a chi-square test for categorical covariates.*

Population-Adjusted Rates

Cumulative Population-Adjusted Rates

The population-adjusted rate of reported unintentional-general exposures involving liquid laundry detergent packets during the baseline period was 42.499 exposures per 100,000 US children <6 years of age. The population-adjusted rate of reported exposures during the post period was 45.024 exposures per 100,000 US children <6 years of age. This equates to one exposure per every 2,353 US children <6 years of age in the baseline period and one exposure per every 2,221 US children <6 years of age in the post period. The population-adjusted rate of exposures to liquid laundry detergent packets in children <6 years of age increased significantly from the baseline period to the post period (5.9% increase; CI 3.1%, 8.8%; p<.001).

When stratified by level of HCF treatment and medical outcome, the population-adjusted rate of exposures decreased significantly from the baseline period to the post period within each stratification (p<.001): 15.5% decrease (CI -19.2%, -11.7%) in the rate of exposures involving HCF treatment; 54.2% decrease (CI -61.1%, -46.1%) in the rate of exposures involving HCF admission; 70.2% decrease (CI -82.1%, -50.3%) in the rate of exposures involving severe medical outcomes (Table 7).

Table 7. Cumulative Population-Adjusted Rates of All Unintentional-General Exposures to Liquid Laundry Detergent Packets by Reporting Period

	Baseline Period Cumulative Rate per 100,000 Children <6 Years of Age	Post Period Cumulative Rate per 100,000 Children <6 Years of Age	% Change (95% CI)	p-value[a]
All Exposures	42.499	45.024	5.9% (3.1%, 8.8%)	<.001
Exposures Involving HCF Treatment	17.620	14.889	-15.5% (-19.2%, -11.7%)	<.001
Exposures Involving HCF Admission	1.903	0.872	-54.2% (-61.1%, -46.1%)	<.001
Exposures with Severe Medical Outcomes	0.266	0.079	-70.2% (-82.1%, -50.3%)	<.001

[a]*P-value was calculated by Poisson regression.*

Population-Adjusted Rates of Exposures Over Time

Over time, counts of unintentional-general exposures involving liquid laundry detergent packets in children <6 years of age fluctuated seasonally with decreases in the fall and winter months (4th and 1st quarters). From the baseline period through the transition period, counts of reported exposures seemed to follow an upward trend with each seasonal peak exceeding the previous seasonal peak. This was followed by a decrease in the post period seasonal peak (2nd quarter 2017), which peaked at a similar frequency as the baseline seasonal peak (2nd quarter 2013). The total population of US children <6 years of age remained consistent during the study period (Table 8; Figure 1).

The population-adjusted rate of reported unintentional-general exposures involving liquid laundry detergent packets in children <6 years of age fluctuated throughout the study period, with a peak in the population-adjusted rate of exposure in 2nd quarter 2016 (15.035 exposures per 100,000 US children <6 years of age (CI 14.548, 15.530)) and a low in 4th quarter 2017 (9.516 exposures per 100,000 US children <6 years of age (CI 9.130, 9.910)). Seasonal peaks of population-adjusted rates were reported during the 2nd and 3rd quarter of each year in alignment with the seasonality in reported exposures. Comparing the first seasonal peak in 2nd quarter 2013 with the last seasonal peak of 2nd quarter 2017, the rates were 12.210 exposures per 100,000 US children <6 years of age (CI 11.772, 12.656) and 12.873 exposures per 100,000 US children <6 years of age (CI 12.423, 13.331), respectively. Comparing the first seasonal low point in 4th quarter 2013 with the last seasonal low point of 1st quarter 2017, the rates were 10.169 exposures per 100,000 US children <6 years of age (CI 9.769, 10.577) and 10.625 exposures per 100,000 US children <6 years of age (CI 10.216, 11.041), respectively (Table 8; Figure 2).

Table 8. Population-Adjusted Rates of All Exposures by Quarter (01 July 2012 to 31 December 2017)

Quarter	Exposure Count	Total Population Count	Rates of All Exposures per 100,000 Children <6 Years of Age (95% CI)
2012Q3 (01 July 2012 to 30 September 2012)	2,319	24,108,094	9.619 (9.232,10.015)
2012Q4 (01 October 2012 to 31 December 2012)	2,514	24,095,846	10.433 (10.029,10.845)
2013Q1 (01 January 2013 to 31 March 2013)	2,465	24,064,871	10.243 (9.843,10.651)
2013Q2 (01 April 2013 to 30 June 2013)	2,931	24,005,552	12.210 (11.772,12.656)
2013Q3 (01 July 2013 to 30 September 2013)	2,906	23,968,981	12.124 (11.687,12.569)
2013Q4 (01 October 2013 to 31 December 2013)	2,436	23,955,652	10.169 (9.769,10.577)
2014Q1 (01 January 2014 to 31 March 2014)	2,633	23,939,357	10.999 (10.582,11.423)
2014Q2 (01 April 2014 to 30 June 2014)	3,199	23,894,773	13.388 (12.928,13.856)
2014Q3 (01 July 2014 to 30 September 2014)	3,419	23,888,650	14.312 (13.836,14.796)
2014Q4 (01 October 2014 to 31 December 2014)	2,914	23,909,828	12.187 (11.749,12.634)
2015Q1 (01 January 2015 to 31 March 2015)	2,828	23,930,320	11.818 (11.386,12.257)

Quarter	Exposure Count	Total Population Count	Rates of All Exposures per 100,000 Children <6 Years of Age (95% CI)
2015Q2 (01 April 2015 to 30 June 2015)	3,451	23,929,371	14.422 (13.944,14.907)
2015Q3 (01 July 2015 to 30 September 2015)	3,507	23,939,980	14.649 (14.168,15.138)
2015Q4 (01 October 2015 to 31 December 2015)	3,266	23,971,382	13.625 (13.161,14.096)
2016Q1 (01 January 2016 to 31 March 2016)	3,019	23,982,978	12.588 (12.143,13.041)
2016Q2 (01 April 2016 to 30 June 2016)	3,603	23,963,893	15.035 (14.548,15.530)
2016Q3 (01 July 2016 to 30 September 2016)	3,540	23,964,050	14.772 (14.289,15.263)
2016Q4 (01 October 2016 to 31 December 2016)	2,786	23,973,356	11.621 (11.194,12.057)
2017Q1 (01 January 2017 to 31 March 2017)	2,547	23,972,176	10.625 (10.216,11.041)
2017Q2 (01 April 2017 to 30 June 2017)	3,086	23,972,540	12.873 (12.423,13.331)
2017Q3 (01 July 2017 to 30 September 2017)	2,880	23,977,281	12.011 (11.577,12.454)
2017Q4 (01 October 2017 to 31 December 2017)	2,283	23,990,865	9.516 (9.130,9.910)

Figure 1. All Exposures and Population Counts by Quarter (01 July 2013 to 31 December 2016)

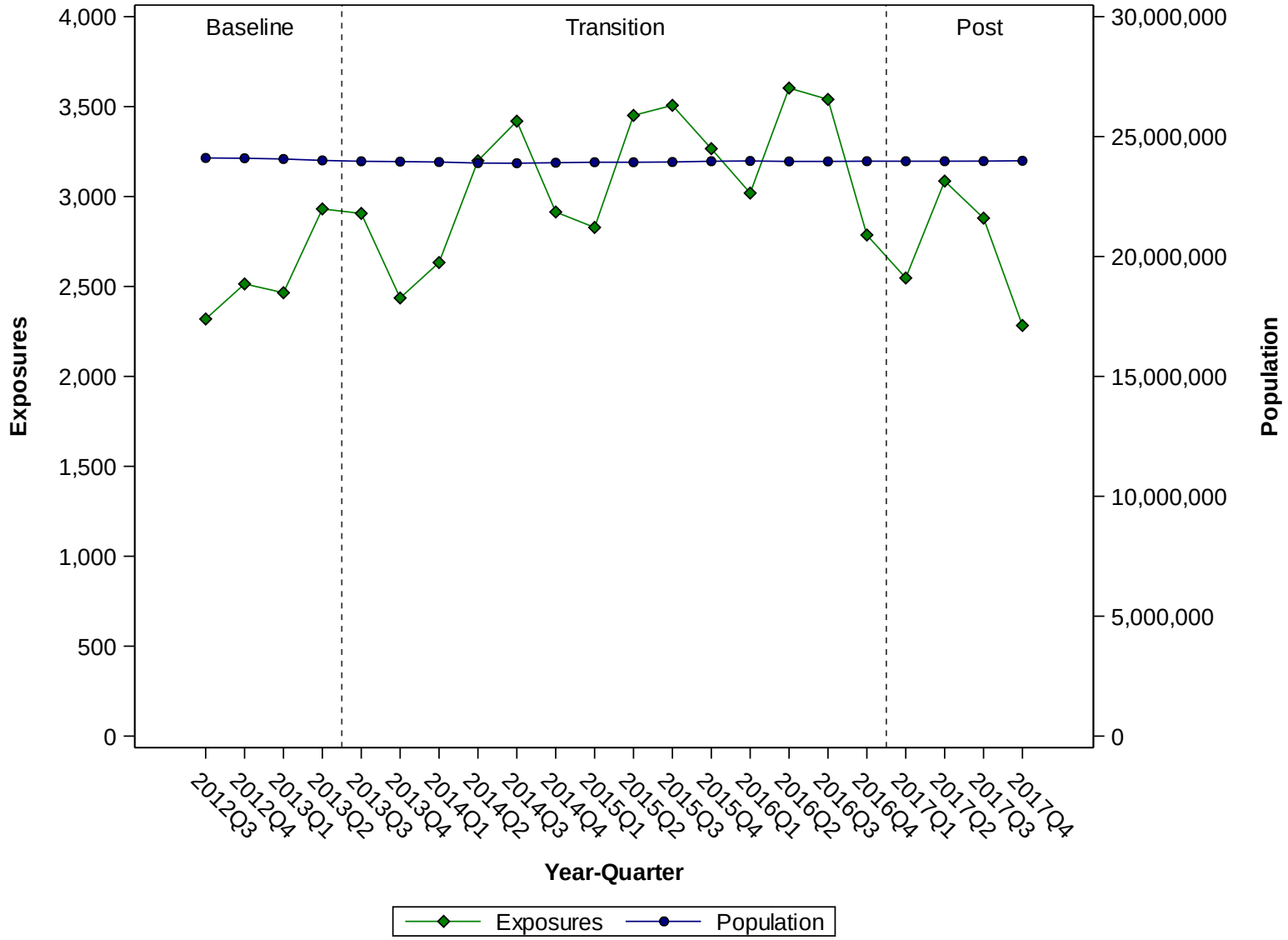
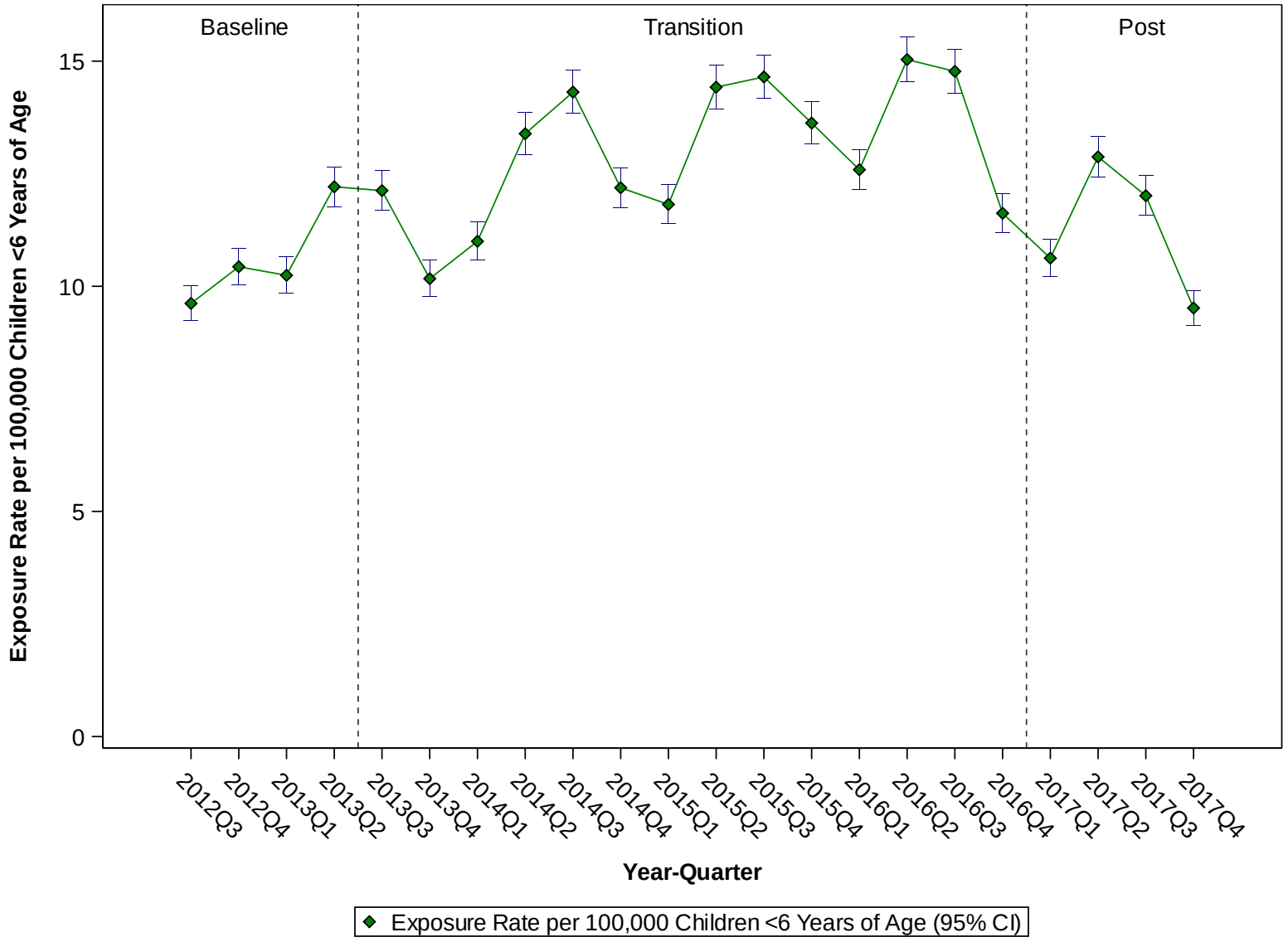


Figure 2. Population-Adjusted Rates of All Exposures by Quarter (01 July 2013 to 31 December 2016)



Over time, counts of exposures involving HCF treatment fluctuated seasonally in the same pattern as all exposures with decreases in the fall and winter months (4th and 1st quarters). There was no apparent increase or decrease in reported exposures during the baseline period and transition period, followed by a decrease in reported exposures during the post period. During the same time period the total population of US children <6 years of age remained consistent (Table 9; Figure 3).

The population-adjusted rate of reported exposures involving treatment in a HCF fluctuated throughout the study period with a peak in the population-adjusted rate of exposure in 3rd quarter 2014 (6.082 exposures per 100,000 US children <6 years of age (CI 5.774, 6.399)) and a low in 4th quarter 2017 (3.072 exposures per 100,000 US children <6 years of age (CI 2.854, 3.298)). Seasonal peaks of population-adjusted rates were reported during the 2nd or 3rd quarter of each year in alignment with the seasonality in reported exposures involving HCF treatment. Comparing the first seasonal peak in 2nd quarter 2013 with the last seasonal peak of 2nd quarter 2017, the rates were 4.957 exposures per 100,000 US children <6 years of age (CI 4.680, 5.243) and 4.171 exposures per 100,000 US children <6 years of age (CI 3.917, 4.434), respectively. Comparing the first seasonal low point in 1st quarter 2013 with the last seasonal low point of 1st quarter 2017, the rates were 4.089 exposures per 100,000 US children <6 years of age (CI 3.837, 4.348) and 3.517 exposures per 100,000 US children <6 years of age (CI 3.283, 3.758), respectively (Table 9; Figure 4).

Table 9. Population-Adjusted Rates of Exposures Involving Healthcare Facility Treatment by Quarter (01 July 2012 to 31 December 2017)

Quarter	Exposure Count	Total Population Count	Rates of All Exposures per 100,000 Children <6 Years of Age (95% CI)
2012Q3 (01 July 2012 to 30 September 2012)	1,042	24,108,094	4.322 (4.064,4.589)
2012Q4 (01 October 2012 to 31 December 2012)	1,025	24,095,846	4.254 (3.997,4.518)
2013Q1 (01 January 2013 to 31 March 2013)	984	24,064,871	4.089 (3.837,4.348)
2013Q2 (01 April 2013 to 30 June 2013)	1,190	24,005,552	4.957 (4.680,5.243)
2013Q3 (01 July 2013 to 30 September 2013)	1,119	23,968,981	4.669 (4.399,4.946)
2013Q4 (01 October 2013 to 31 December 2013)	975	23,955,652	4.070 (3.819,4.329)
2014Q1 (01 January 2014 to 31 March 2014)	1,068	23,939,357	4.461 (4.198,4.733)
2014Q2 (01 April 2014 to 30 June 2014)	1,361	23,894,773	5.696 (5.397,6.002)
2014Q3 (01 July 2014 to 30 September 2014)	1,453	23,888,650	6.082 (5.774,6.399)
2014Q4 (01 October 2014 to 31 December 2014)	1,146	23,909,828	4.793 (4.519,5.074)
2015Q1 (01 January 2015 to 31 March 2015)	1,075	23,930,320	4.492 (4.228,4.765)

Quarter	Exposure Count	Total Population Count	Rates of All Exposures per 100,000 Children <6 Years of Age (95% CI)
2015Q2 (01 April 2015 to 30 June 2015)	1,348	23,929,371	5.633 (5.337,5.938)
2015Q3 (01 July 2015 to 30 September 2015)	1,396	23,939,980	5.831 (5.529,6.141)
2015Q4 (01 October 2015 to 31 December 2015)	1,275	23,971,382	5.319 (5.031,5.615)
2016Q1 (01 January 2016 to 31 March 2016)	1,093	23,982,978	4.557 (4.291,4.832)
2016Q2 (01 April 2016 to 30 June 2016)	1,289	23,963,893	5.379 (5.089,5.676)
2016Q3 (01 July 2016 to 30 September 2016)	1,267	23,964,050	5.287 (5.000,5.582)
2016Q4 (01 October 2016 to 31 December 2016)	965	23,973,356	4.025 (3.775,4.283)
2017Q1 (01 January 2017 to 31 March 2017)	843	23,972,176	3.517 (3.283,3.758)
2017Q2 (01 April 2017 to 30 June 2017)	1,000	23,972,540	4.171 (3.917,4.434)
2017Q3 (01 July 2017 to 30 September 2017)	990	23,977,281	4.129 (3.876,4.390)
2017Q4 (01 October 2017 to 31 December 2017)	737	23,990,865	3.072 (2.854,3.298)

Figure 3. Exposures Involving Healthcare Facility Treatment and Population Counts by Quarter (01 July 2012 to 31 December 2017)

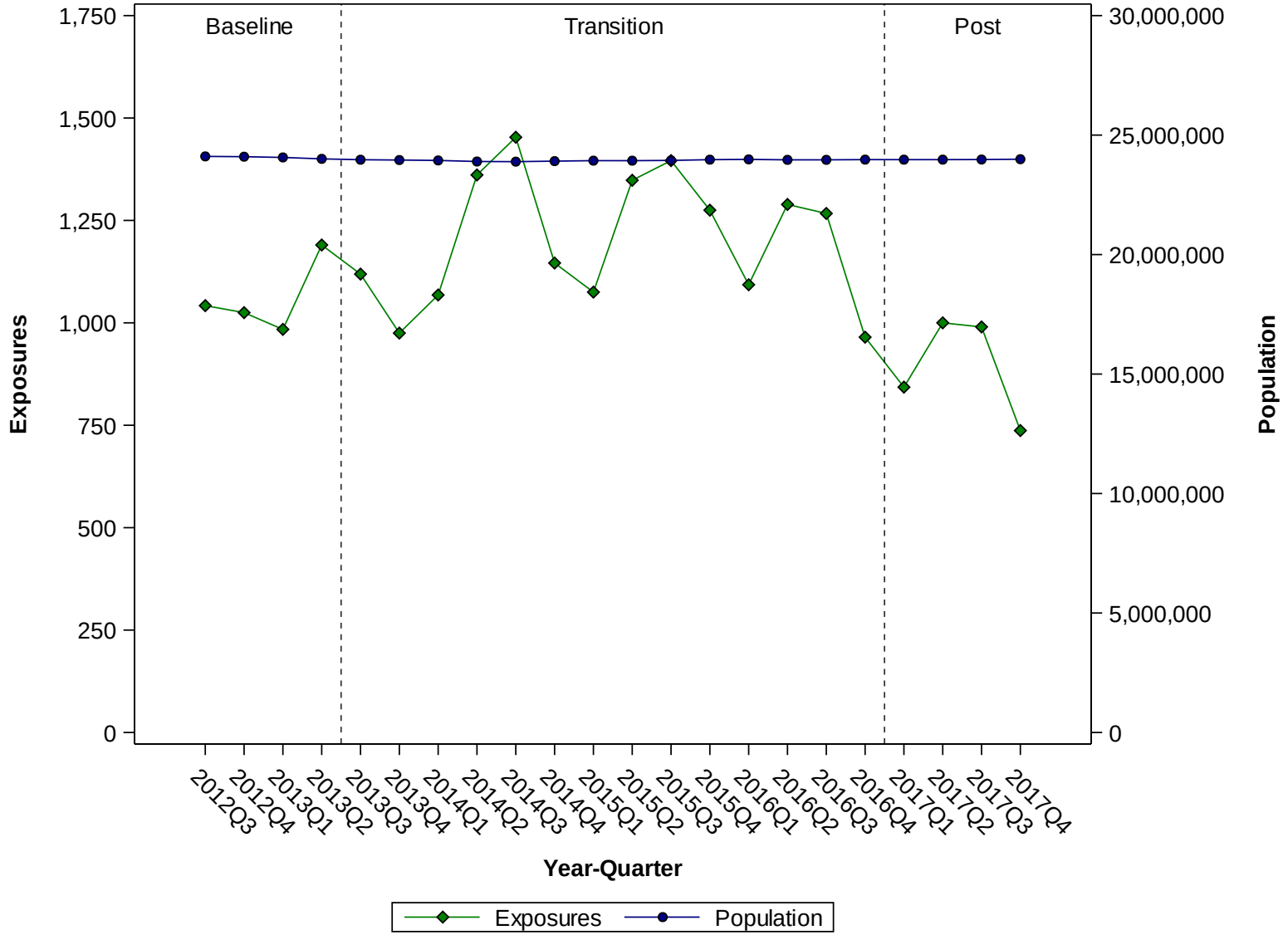
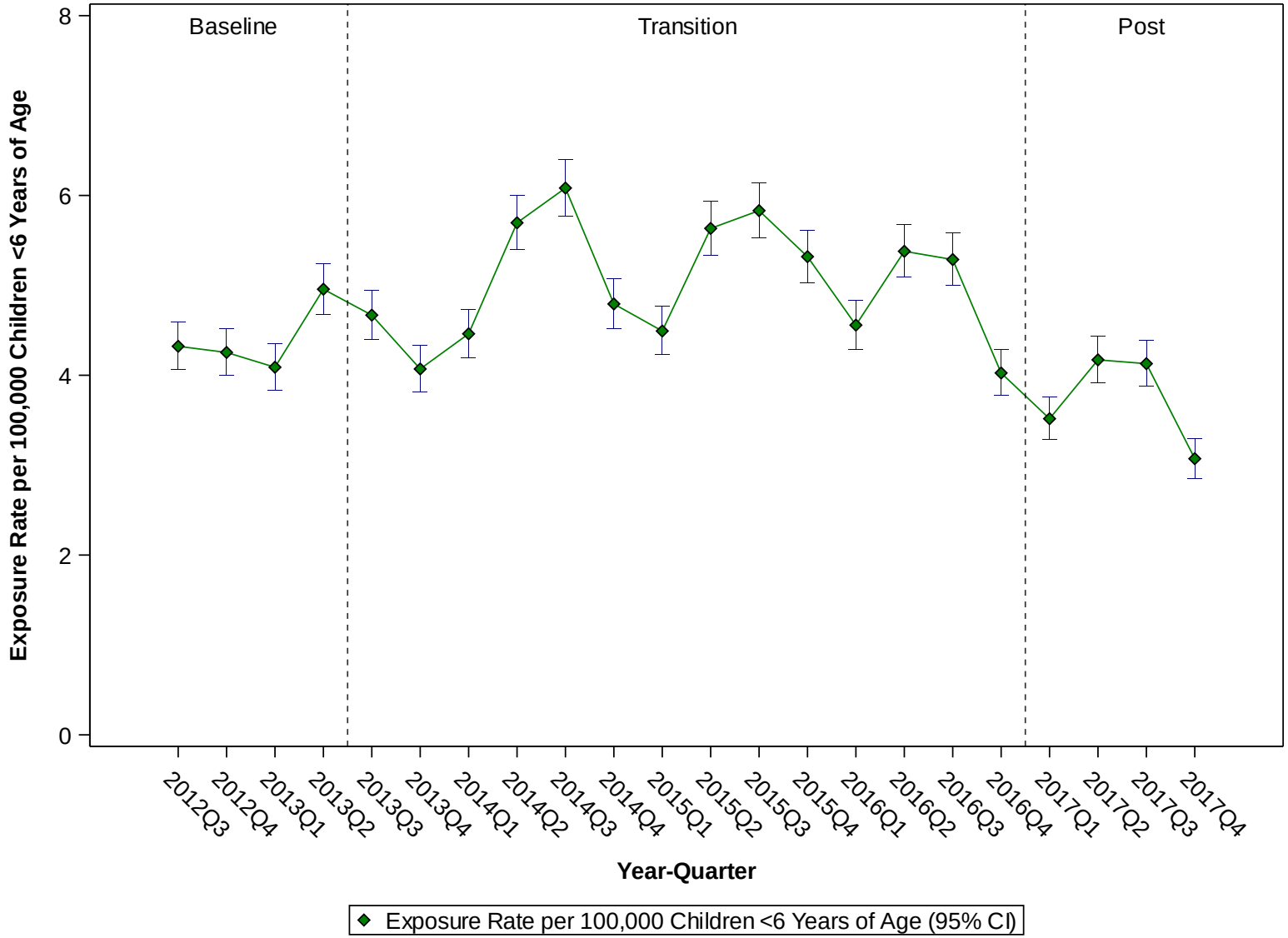


Figure 4. Population-Adjusted Rates of Exposures Involving Healthcare Facility Treatment by Quarter (01 July 2012 to 31 December 2017)



Over time, counts of exposures involving HCF admission fluctuated seasonally in the same pattern as all exposures with decreases in the 4th and 1st quarters but demonstrated a downward trend in reporting frequency over time. During the same time period, the total population of US children <6 years of age remained consistent (Table 10; Figure 5).

The population-adjusted rate of reported exposures involving admission to a HCF fluctuated throughout the study period with a peak in the population-adjusted rate of exposure in 2nd quarter 2014 (0.699 exposures per 100,000 US children <6 years of age (CI 0.597, 0.809)) and a low in 4th quarter 2017 (0.192 exposures per 100,000 US children <6 years of age (CI 0.140, 0.251)). In alignment with the seasonality in reported exposures involving HCF admission, peak population-adjusted rates were reported during the 2nd or 3rd quarters of each year. Comparing the first seasonal peak in 2nd quarter 2013, with the last season peak of 3rd quarter 2017 during the post period, the rates were 0.529 exposures per 100,000 US children <6 years of age (CI 0.441, 0.625) and 0.254 exposures per 100,000 US children <6 years of age (CI 0.195, 0.322), respectively. Comparing the first seasonal low point in 1st quarter 2013 with the last seasonal low point of 1st quarter 2017, the rates were 0.395 exposures per 100,000 US children <6 years of age (CI 0.319, 0.478) and 0.192 exposures per 100,000 US children <6 years of age (CI 0.140, 0.251), respectively (Table 10; Figure 6).

Table 10. Population-Adjusted Rates of Exposures Involving Healthcare Facility Admission by Quarter (01 July 2012 to 31 December 2017)

Quarter	Exposure Count	Total Population Count	Rates of All Exposures per 100,000 Children <6 Years of Age (95% CI)
2012Q3 (01 July 2012 to 30 September 2012)	118	24,108,094	0.489 (0.405,0.582)
2012Q4 (01 October 2012 to 31 December 2012)	118	24,095,846	0.490 (0.405,0.582)
2013Q1 (01 January 2013 to 31 March 2013)	95	24,064,871	0.395 (0.319,0.478)
2013Q2 (01 April 2013 to 30 June 2013)	127	24,005,552	0.529 (0.441,0.625)
2013Q3 (01 July 2013 to 30 September 2013)	117	23,968,981	0.488 (0.404,0.580)
2013Q4 (01 October 2013 to 31 December 2013)	125	23,955,652	0.522 (0.434,0.617)
2014Q1 (01 January 2014 to 31 March 2014)	139	23,939,357	0.581 (0.488,0.681)
2014Q2 (01 April 2014 to 30 June 2014)	167	23,894,773	0.699 (0.597,0.809)
2014Q3 (01 July 2014 to 30 September 2014)	154	23,888,650	0.645 (0.547,0.750)
2014Q4 (01 October 2014 to 31 December 2014)	125	23,909,828	0.523 (0.435,0.618)
2015Q1 (01 January 2015 to 31 March 2015)	101	23,930,320	0.422 (0.344,0.508)

Quarter	Exposure Count	Total Population Count	Rates of All Exposures per 100,000 Children <6 Years of Age (95% CI)
2015Q2 (01 April 2015 to 30 June 2015)	142	23,929,371	0.593 (0.500,0.695)
2015Q3 (01 July 2015 to 30 September 2015)	120	23,939,980	0.501 (0.416,0.595)
2015Q4 (01 October 2015 to 31 December 2015)	105	23,971,382	0.438 (0.358,0.526)
2016Q1 (01 January 2016 to 31 March 2016)	84	23,982,978	0.350 (0.279,0.429)
2016Q2 (01 April 2016 to 30 June 2016)	75	23,963,893	0.313 (0.246,0.388)
2016Q3 (01 July 2016 to 30 September 2016)	99	23,964,050	0.413 (0.336,0.498)
2016Q4 (01 October 2016 to 31 December 2016)	68	23,973,356	0.284 (0.220,0.355)
2017Q1 (01 January 2017 to 31 March 2017)	46	23,972,176	0.192 (0.140,0.251)
2017Q2 (01 April 2017 to 30 June 2017)	56	23,972,540	0.234 (0.176,0.299)
2017Q3 (01 July 2017 to 30 September 2017)	61	23,977,281	0.254 (0.195,0.322)
2017Q4 (01 October 2017 to 31 December 2017)	46	23,990,865	0.192 (0.140,0.251)

Figure 5. Exposures Involving Healthcare Facility Admission and Population Counts by Quarter (01 July 2012 to 31 December 2016)

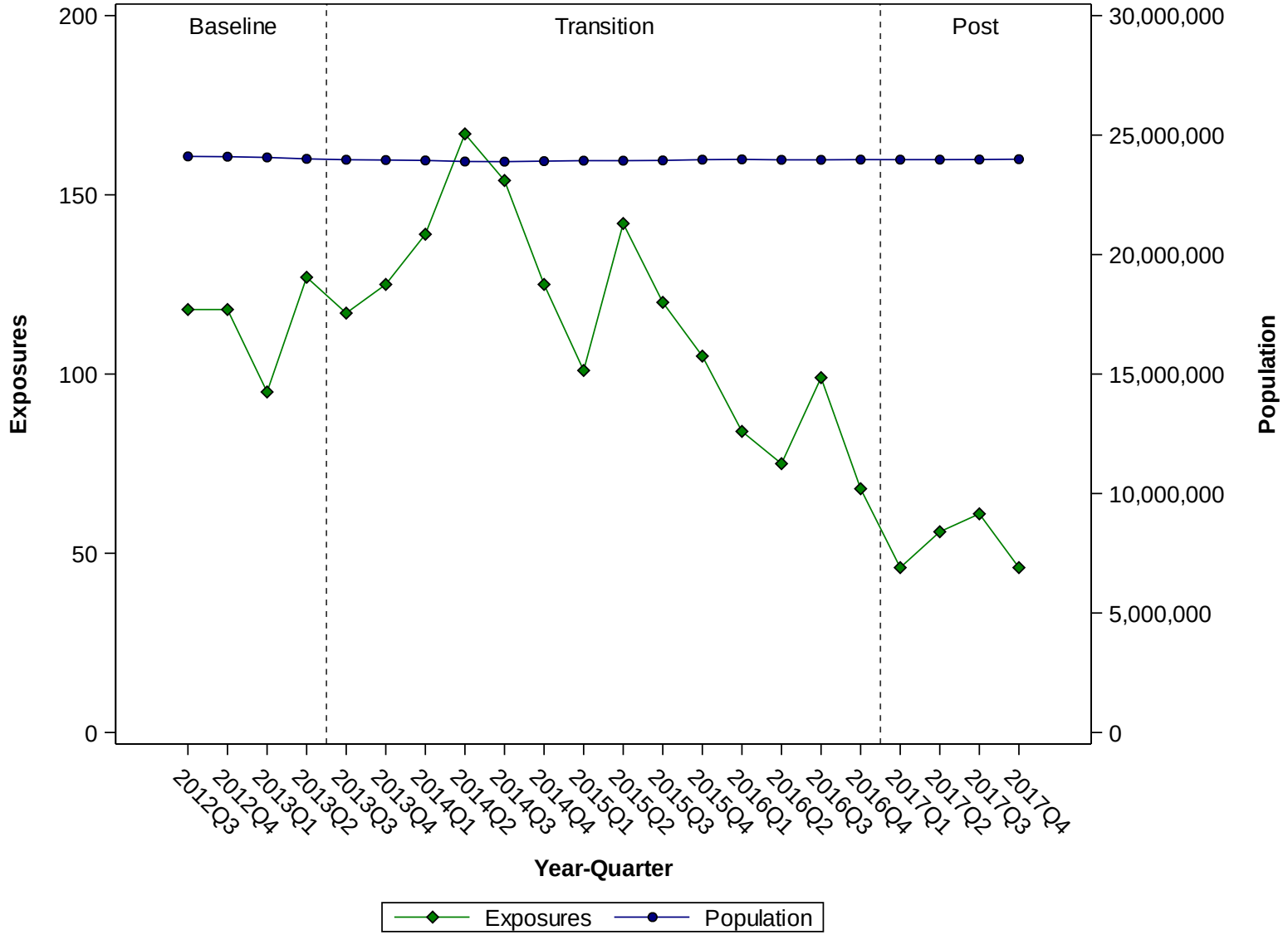
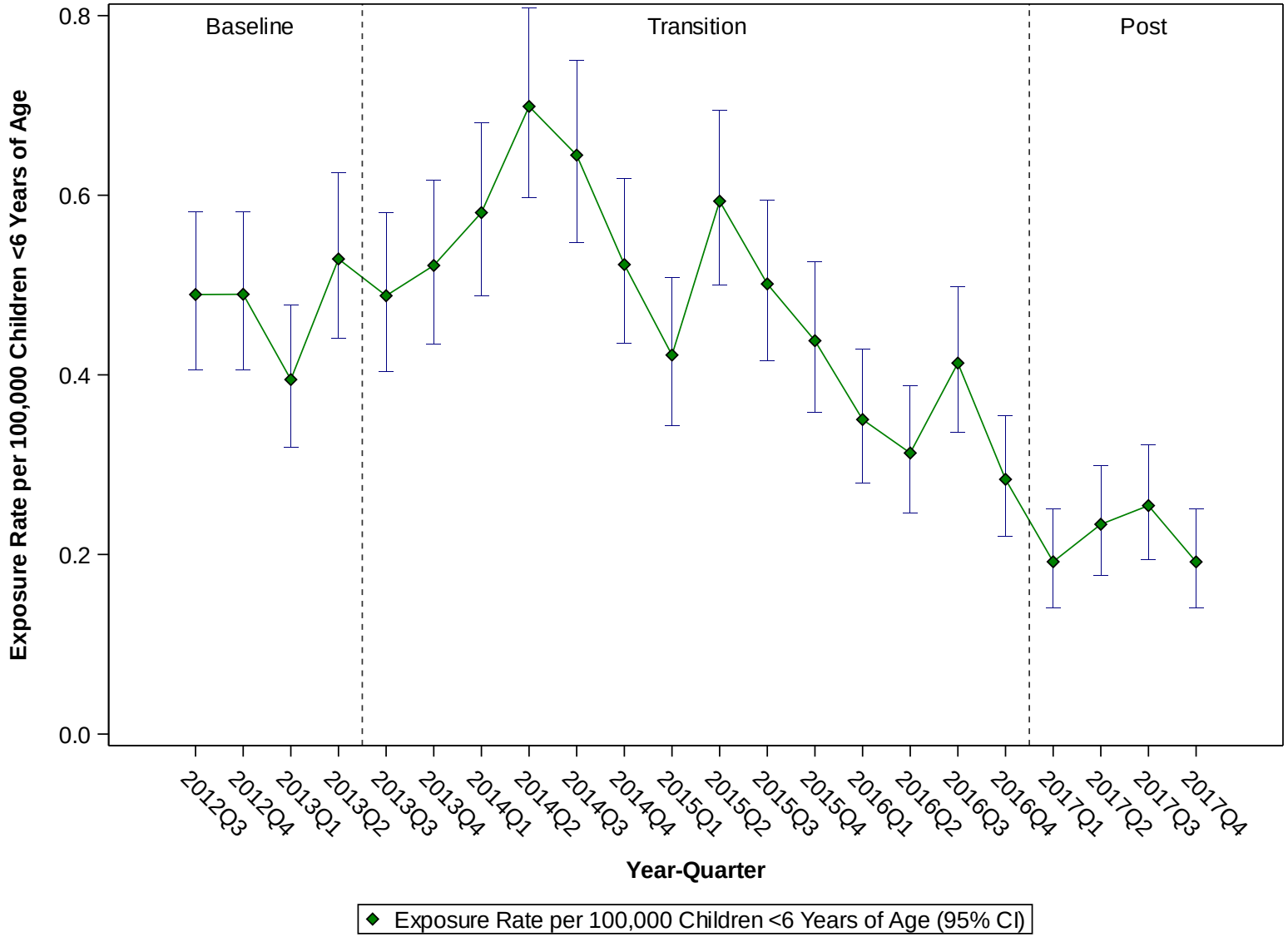


Figure 6. Population-Adjusted Rates of Exposures Involving Healthcare Facility Admission by Quarter (01 July 2012 to 31 December 2017)



Over time, counts of exposures involving severe medical outcomes fluctuated seasonally through 3rd quarter 2015 followed by a marked decrease in exposures without an apparent seasonal trend through 4th quarter 2017. During the same time period the total population of US children <6 years of age remained consistent (Table 11; Figure 7).

The population-adjusted rate of reported exposures involving severe medical outcomes fluctuated throughout the study period with a peak in the population-adjusted rate of exposure in 3rd quarter 2014 (0.075 exposures per 100,000 US children <6 years of age (CI 0.045, 0.114)) and a low in 3rd quarter 2016 and 1st quarter 2017 (0.013 exposures per 100,000 US children <6 years of age (CI 0.003, 0.030)). The population-adjusted rate of reported exposures involving severe medical outcomes ranged from a peak rate of 0.108 exposures per 100,000 US children <6 years of age (CI 0.070, 0.153) in 3rd quarter 2012 to a rate of 0.013 exposures per 100,000 US children <6 years of age (CI 0.003, 0.030) in 3rd quarter 2016 and 1st quarter 2017 (Table 11; Figure 8). Due to the low exposure counts and wide confidence intervals, a comparison of peak and low rates during the baseline and study period is not appropriate.

Table 11. Population-Adjusted Exposure Rates Resulting in Severe Medical Outcomes by Quarter (01 July 2012 to 31 December 2017)

Quarter	Exposure Count	Total Population Count	Rates of All Exposures per 100,000 Children <6 Years of Age (95% CI)
2012Q3 (01 July 2012 to 30 September 2012)	26	24,108,094	0.108 (0.070,0.153)
2012Q4 (01 October 2012 to 31 December 2012)	15	24,095,846	0.062 (0.035,0.097)
2013Q1 (01 January 2013 to 31 March 2013)	8	24,064,871	0.033 (0.014,0.060)
2013Q2 (01 April 2013 to 30 June 2013)	15	24,005,552	0.062 (0.035,0.098)
2013Q3 (01 July 2013 to 30 September 2013)	17	23,968,981	0.071 (0.041,0.108)
2013Q4 (01 October 2013 to 31 December 2013)	10	23,955,652	0.042 (0.020,0.071)
2014Q1 (01 January 2014 to 31 March 2014)	11	23,939,357	0.046 (0.023,0.077)
2014Q2 (01 April 2014 to 30 June 2014)	16	23,894,773	0.067 (0.038,0.104)
2014Q3 (01 July 2014 to 30 September 2014)	18	23,888,650	0.075 (0.045,0.114)
2014Q4 (01 October 2014 to 31 December 2014)	11	23,909,828	0.046 (0.023,0.077)
2015Q1 (01 January 2015 to 31 March 2015)	10	23,930,320	0.042 (0.020,0.071)

Quarter	Exposure Count	Total Population Count	Rates of All Exposures per 100,000 Children <6 Years of Age (95% CI)
2015Q2 (01 April 2015 to 30 June 2015)	8	23,929,371	0.033 (0.014,0.060)
2015Q3 (01 July 2015 to 30 September 2015)	9	23,939,980	0.038 (0.017,0.066)
2015Q4 (01 October 2015 to 31 December 2015)	4	23,971,382	0.017 (0.005,0.037)
2016Q1 (01 January 2016 to 31 March 2016)	4	23,982,978	0.017 (0.005,0.037)
2016Q2 (01 April 2016 to 30 June 2016)	4	23,963,893	0.017 (0.005,0.037)
2016Q3 (01 July 2016 to 30 September 2016)	3	23,964,050	0.013 (0.003,0.030)
2016Q4 (01 October 2016 to 31 December 2016)	5	23,973,356	0.021 (0.007,0.043)
2017Q1 (01 January 2017 to 31 March 2017)	3	23,972,176	0.013 (0.003,0.030)
2017Q2 (01 April 2017 to 30 June 2017)	5	23,972,540	0.021 (0.007,0.043)
2017Q3 (01 July 2017 to 30 September 2017)	5	23,977,281	0.021 (0.007,0.043)
2017Q4 (01 October 2017 to 31 December 2017)	6	23,990,865	0.025 (0.009,0.049)

Figure 7. Exposures Resulting in Severe Medical Outcomes and Population Counts by Quarter (01 July 2012 to 31 December 2017)

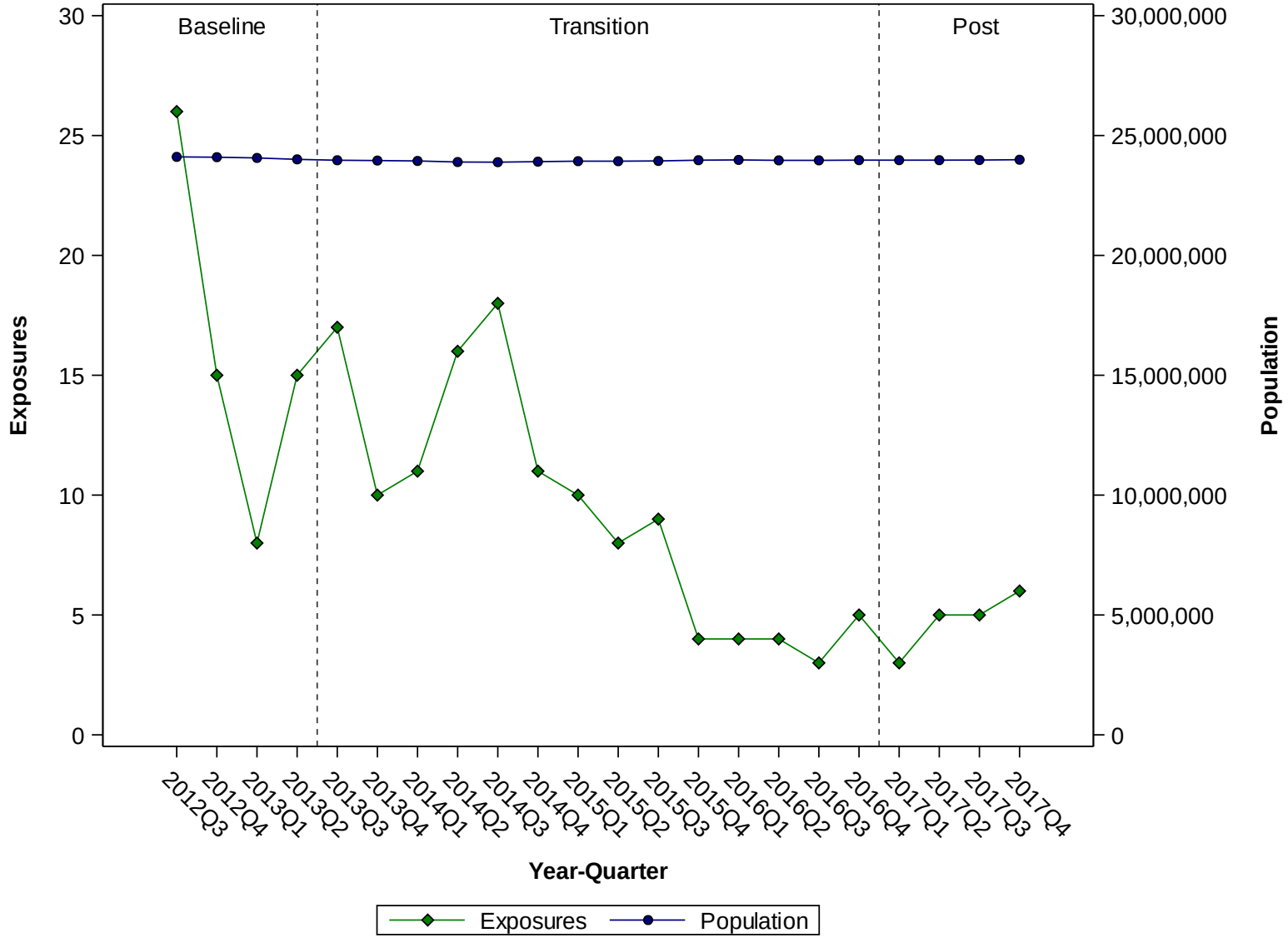
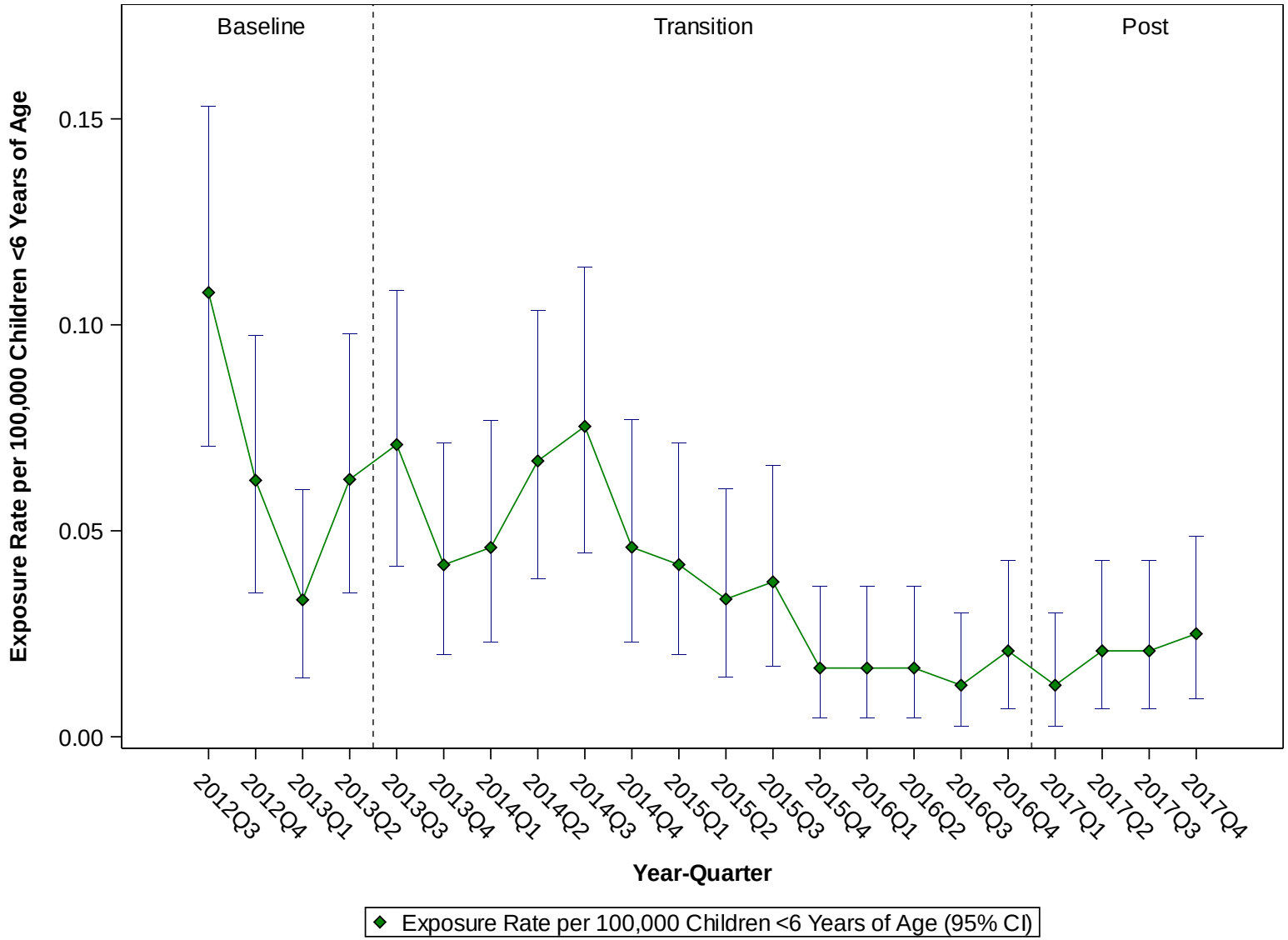


Figure 8. Population-Adjusted Rates of Exposures Resulting in Severe Medical Outcomes by Quarter (01 July 2012 to 31 December 2017)



Sales-Adjusted Rates

Cumulative Sales-Adjusted Rates of Exposures

The sales-adjusted rate of reported unintentional-general exposures involving liquid laundry detergent packets during the baseline period was 4.920 exposures per 1 million packets sold. The sales-adjusted rate of reported exposures during the post period was 2.291 exposures per 1 million packets sold. This equates to one exposure per every 203,252 packets sold in the baseline period and one exposure per every 436,491 packets sold in the post period. The sales-adjusted rate of reported exposures to liquid laundry detergent packets in children <6 years of age decreased significantly from the baseline period to the post period (53.4% decrease, CI -54.7%, -52.1%; p<.001; Table 12). When stratified by level of HCF treatment and medical outcome, the sales-adjusted rate of exposure decreased significantly from the baseline period to the post period within each stratification: 62.6% decrease (CI -64.3%, -60.9%) in the rate of exposures involving HCF treatment; 79.6% decrease (CI -82.8%, -76.0%) in the rate of exposures involving HCF admission; 86.4% decrease (CI -91.9%, -77.1%) in the rate of exposures involving severe medical outcomes (Table 12).

Table 12. Cumulative Sales-Adjusted Rates of All Unintentional-General Exposures to Liquid Laundry Detergent Packets by Reporting Period

	Baseline Period Cumulative Rate per 1,000,000 Packets Sold	Post Period Cumulative Rate per 1,000,000 Packets Sold	% Change (95% CI)	p-value[a]
All Exposures	4.920	2.291	-53.4% (-54.7%, -52.1%)	<.001
Exposures Involving HCF Treatment	2.026	0.758	-62.6% (-64.3%, -60.9%)	<.001
Exposures Involving HCF Admission	0.218	0.044	-79.6% (-82.8%, -76.0%)	<.001
Exposures with Severe Medical Outcomes	0.030	0.004	-86.4% (-91.9%, -77.1%)	<.001

[a]*P-value was calculated by Poisson regression.*

Sales-Adjusted Rates Over Time

When examined by four week intervals corresponding to sales periods, counts of unintentional-general exposures involving liquid laundry detergent packets in children <6 years of age fluctuated seasonally with an increase through the first five to eight months of the year followed by a decrease through the end of the year. From the baseline period through the transition period, counts of reported exposures seemed to follow an upward trend with each seasonal peak exceeding the previous seasonal peak. This was followed by a decrease in the post period seasonal peak (May-June 2017), which peaked at a similar frequency as the baseline seasonal peak (July-August 2013). During the same time period the total sales fluctuated slightly with a steady increase over time (Table 13; Figure 9).

The sales-adjusted rate of reported unintentional-general exposures involving liquid laundry detergent packets in children <6 years of age fluctuated throughout the study period, with a peak in the four week interval ending 27 April 2013 (5.602 exposures per 1 million packets sold (CI 5.242, 5.973)) and a low in the four week interval ending 30 December 2017 (1.640 exposures per 1 million packets sold (CI 1.508, 1.777)). Comparing the seasonal peak in 2013 to the seasonal peak in 2017, the sales-adjusted rates were 5.602 exposures per 1 million packets sold (CI 5.242, 5.973) in the four week interval ending 27 April 2013 and 2.739 exposures per 1 million packets sold (CI 2.573, 2.911) in the four week interval ending 17 June 2017. Comparing the first seasonal low point in 2013 with the last seasonal low point in 2017, the rates were 4.149 exposures per 1 million packets sold (CI 3.871, 4.437) in the four week interval ending 14 September 2013 and 2.029 exposures per 1 million packets sold (CI 1.884, 2.178) in the four week interval ending 28 January 2017 (Table 13; Figure 10).

Table 13. Sales Adjusted Rates of All Exposures by Four Week Interval (22 July 2012 to 30 December 2017)

Four Week Interval Date	Exposure Count	Total Packets Sales Count	Rates of All Exposures per 1,000,000 Packets Sold (95% CI)
22 July 2012 to 18 August 2012	660	138,355,958	4.770 (4.413,5.141)
19 August 2012 to 15 September 2012	721	146,612,045	4.918 (4.565,5.283)
16 September 2012 to 13 October 2012	780	156,369,907	4.988 (4.644,5.344)
14 October 2012 to 10 November 2012	814	160,177,007	5.082 (4.739,5.437)
11 November 2012 to 08 December 2012	815	157,666,057	5.169 (4.820,5.530)
09 December 2012 to 05 January 2013	649	158,606,062	4.092 (3.783,4.413)
06 January 2013 to 02 February 2013	703	171,063,002	4.110 (3.811,4.419)
03 February 2013 to 02 March 2013	788	177,595,380	4.437 (4.133,4.752)
03 March 2013 to 30 March 2013	834	164,788,263	5.061 (4.723,5.410)
31 March 2013 to 27 April 2013	902	161,022,945	5.602 (5.242,5.973)
28 April 2013 to 25 May 2013	893	160,244,796	5.573 (5.213,5.944)
26 May 2013 to 22 June 2013	912	172,357,060	5.291 (4.953,5.640)
23 June 2013 to 20 July 2013	878	176,228,963	4.982 (4.658,5.317)
21 July 2013 to 17 August 2013	935	195,923,666	4.772 (4.471,5.083)
18 August 2013 to 14 September 2013	825	198,831,756	4.149 (3.871,4.437)
15 September 2013 to 12 October 2013	884	189,728,555	4.659 (4.357,4.971)
13 October 2013 to 09 November 2013	759	189,855,974	3.998 (3.718,4.287)
10 November 2013 to 07 December 2013	747	192,893,990	3.873 (3.600,4.155)
08 December 2013 to 04 January 2014	665	185,611,612	3.583 (3.316,3.860)
05 January 2014 to 01 February 2014	721	213,956,221	3.370 (3.128,3.620)
02 February 2014 to 01 March 2014	844	232,885,277	3.624 (3.384,3.873)
02 March 2014 to 29 March 2014	887	243,496,603	3.643 (3.407,3.886)

Four Week Interval Date	Exposure Count	Total Packets Sales Count	Rates of All Exposures per 1,000,000 Packets Sold (95% CI)
30 March 2014 to 26 April 2014	918	230,264,949	3.987 (3.733,4.249)
27 April 2014 to 24 May 2014	924	227,820,254	4.056 (3.798,4.321)
25 May 2014 to 21 June 2014	1,066	232,636,163	4.582 (4.311,4.861)
22 June 2014 to 19 July 2014	1,029	243,531,931	4.225 (3.971,4.487)
20 July 2014 to 16 August 2014	1,076	254,650,805	4.225 (3.977,4.482)
17 August 2014 to 13 September 2014	1,038	260,544,201	3.984 (3.745,4.230)
14 September 2014 to 11 October 2014	1,041	249,220,913	4.177 (3.927,4.435)
12 October 2014 to 08 November 2014	933	259,506,292	3.595 (3.368,3.830)
09 November 2014 to 06 December 2014	873	261,748,236	3.335 (3.118,3.560)
07 December 2014 to 03 January 2015	806	259,951,250	3.101 (2.890,3.318)
04 January 2015 to 31 January 2015	849	283,829,321	2.991 (2.793,3.196)
01 February 2015 to 28 February 2015	857	264,812,881	3.236 (3.023,3.456)
01 March 2015 to 28 March 2015	926	278,942,632	3.320 (3.109,3.537)
29 March 2015 to 25 April 2015	980	266,267,713	3.681 (3.454,3.914)
26 April 2015 to 23 May 2015	1,008	268,069,072	3.760 (3.532,3.996)
24 May 2015 to 20 June 2015	1,160	275,907,638	4.204 (3.966,4.450)
21 June 2015 to 18 July 2015	1,058	268,363,850	3.942 (3.708,4.183)
19 July 2015 to 15 August 2015	1,103	281,773,843	3.914 (3.687,4.149)
16 August 2015 to 12 September 2015	1,066	293,314,307	3.634 (3.419,3.856)
13 September 2015 to 10 October 2015	1,064	266,552,970	3.992 (3.755,4.235)
11 October 2015 to 07 November 2015	986	282,026,373	3.496 (3.281,3.718)
08 November 2015 to 05 December 2015	1,011	297,973,693	3.393 (3.187,3.605)
06 December 2015 to 02 January 2016	940	290,601,182	3.235 (3.031,3.445)

Four Week Interval Date	Exposure Count	Total Packets Sales Count	Rates of All Exposures per 1,000,000 Packets Sold (95% CI)
03 January 2016 to 30 January 2016	948	316,167,331	2.998 (2.811,3.192)
31 January 2016 to 27 February 2016	915	334,235,847	2.738 (2.563,2.918)
28 February 2016 to 26 March 2016	941	315,910,549	2.979 (2.791,3.172)
27 March 2016 to 23 April 2016	1,022	316,651,931	3.228 (3.033,3.428)
24 April 2016 to 21 May 2016	1,176	318,236,039	3.695 (3.487,3.910)
22 May 2016 to 18 June 2016	1,089	316,567,950	3.440 (3.239,3.647)
19 June 2016 to 16 July 2016	1,109	356,018,984	3.115 (2.934,3.301)
17 July 2016 to 13 August 2016	1,125	351,674,468	3.199 (3.015,3.389)
14 August 2016 to 10 September 2016	1,118	356,942,908	3.132 (2.951,3.318)
11 September 2016 to 08 October 2016	933	335,661,035	2.780 (2.604,2.961)
09 October 2016 to 05 November 2016	939	344,522,260	2.726 (2.554,2.903)
06 November 2016 to 03 December 2016	854	346,044,054	2.468 (2.305,2.636)
04 December 2016 to 31 December 2016	726	335,408,265	2.165 (2.010,2.325)
01 January 2017 to 28 January 2017	730	359,862,022	2.029 (1.884,2.178)
29 January 2017 to 25 February 2017	798	386,913,157	2.062 (1.922,2.208)
26 February 2017 to 25 March 2017	821	360,794,539	2.276 (2.123,2.434)
26 March 2017 to 22 April 2017	858	371,856,361	2.307 (2.156,2.464)
23 April 2017 to 20 May 2017	923	351,578,519	2.625 (2.459,2.797)
21 May 2017 to 17 June 2017	1,011	369,080,801	2.739 (2.573,2.911)
18 June 2017 to 15 July 2017	981	365,486,827	2.684 (2.519,2.855)
16 July 2017 to 12 August 2017	841	360,532,691	2.333 (2.178,2.493)
13 August 2017 to 09 September 2017	880	383,751,886	2.293 (2.144,2.447)
10 September 2017 to 07 October 2017	878	356,237,506	2.465 (2.304,2.630)

Four Week Interval Date	Exposure Count	Total Packets Sales Count	Rates of All Exposures per 1,000,000 Packets Sold (95% CI)
08 October 2017 to 04 November 2017	784	347,358,978	2.257 (2.102,2.418)
05 November 2017 to 02 December 2017	706	345,461,141	2.044 (1.896,2.197)
03 December 2017 to 30 December 2017	569	346,944,075	1.640 (1.508,1.777)

Figure 9. All Exposures and Sales Counts by Four Week Interval (22 July 2012 to 30 December 2017)

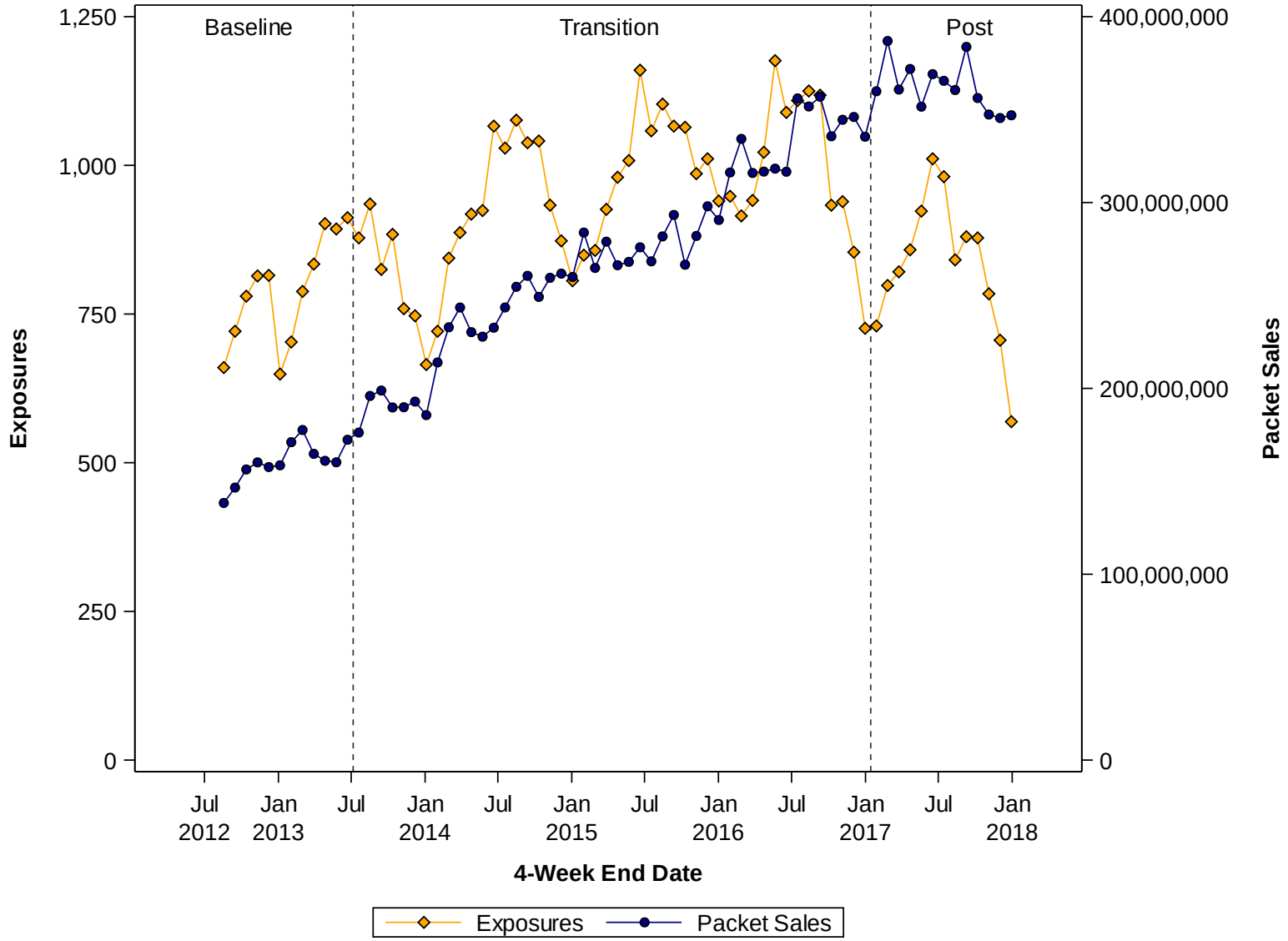
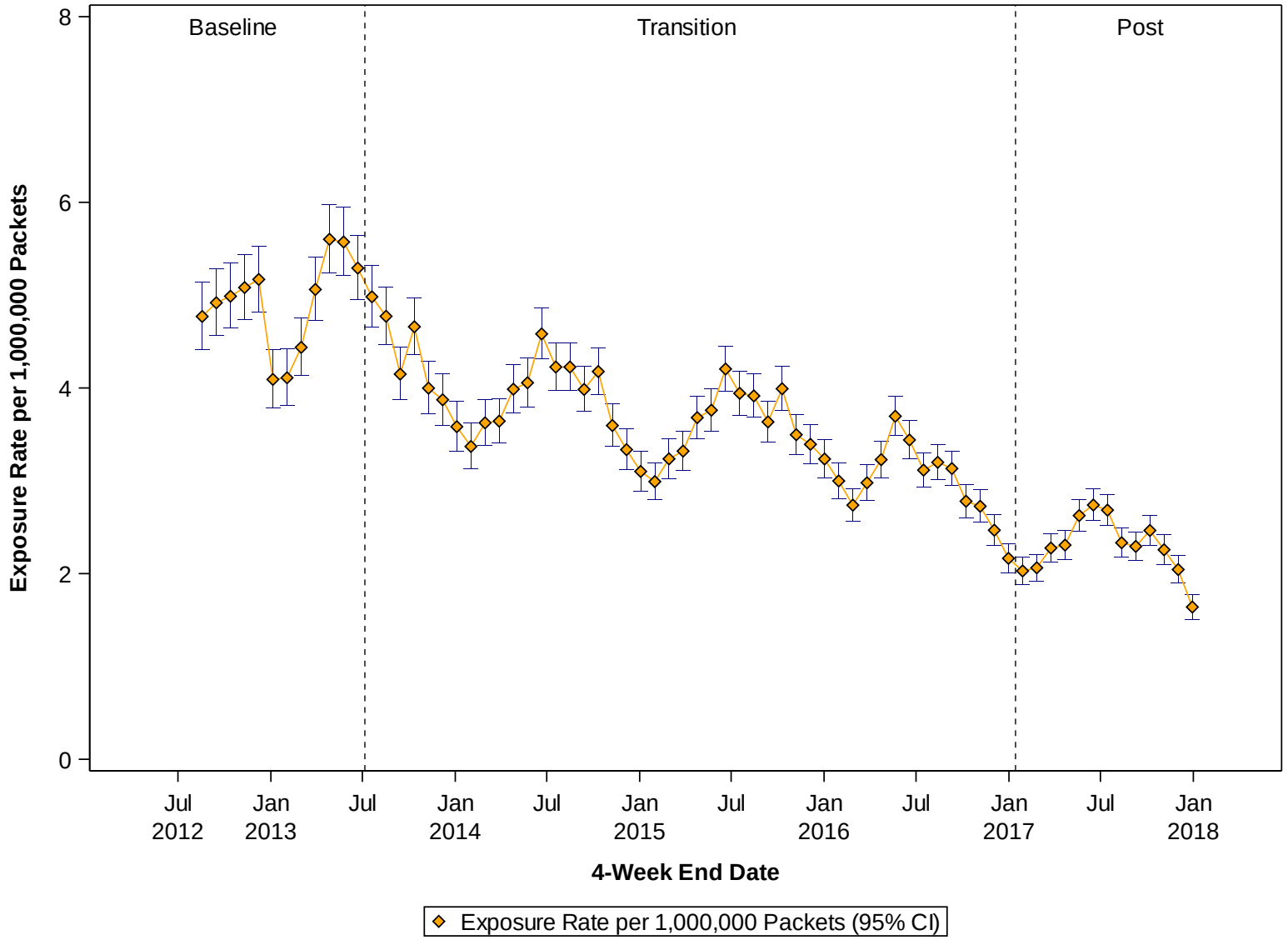


Figure 10. Sales-Adjusted Rates of All Exposures by Four Week Interval (22 July 2012 to 30 December 2017)



When examined by four week intervals corresponding to sales periods, counts of exposures involving HCF treatment fluctuated seasonally in the same pattern as all exposures with increases over the initial part of the year followed by decreases through the end of the year. Over time, the seasonal peaks appeared to be at their highest during the transition period, followed by a decrease in the seasonal peak occurring during the post period (May-June 2017). During the same time period the total sales fluctuated slightly with a steady increase over time (Table 14; Figure 11).

The sales-adjusted rate of reported exposures involving treatment in a HCF fluctuated throughout the study period, with a peak in the sales-adjusted rate of exposure in the four week interval ending 18 August 2012 (2.255 exposures per 1 million packets sold (CI 2.012, 2.512)) and a low in the four week interval ending 30 December 2017 (0.522 exposures per 1 million packets sold (CI 0.448, 0.600)). Comparing the seasonal peak in 2013 to the seasonal peak in 2017, the rates were 2.253 exposures per 1 million packets sold (CI 2.026, 2.491) in the four week interval ending 25 May 2013 and 0.932 exposures per 1 million packets sold (CI 0.836, 1.033) in the four week interval ending 17 June 2017. Comparing the first seasonal low point in 2013 with the last seasonal low point in 2017, the rates were 1.595 exposures per 1 million packets sold (CI 1.405, 1.798) in the four week interval ending 05 January 2013 and 0.644 exposures per 1 million packets sold (CI 0.566, 0.726) in the four week interval ending 25 February 2017 (Table 14; Figure 12).

Table 14. Sales-Adjusted Rates of Exposures Involving Healthcare Facility Treatment by Four Week Interval (22 July 2012 to 30 December 2017)

Four Week Interval Date	Exposure Count	Total Packets Sales Count	Rates of All Exposures per 1,000,000 Children Packets Sold (95% CI)
22 July 2012 to 18 August 2012	312	138,355,958	2.255 (2.012,2.512)
19 August 2012 to 15 September 2012	311	146,612,045	2.121 (1.892,2.363)
16 September 2012 to 13 October 2012	323	156,369,907	2.066 (1.846,2.297)
14 October 2012 to 10 November 2012	339	160,177,007	2.116 (1.897,2.348)
11 November 2012 to 08 December 2012	336	157,666,057	2.131 (1.909,2.365)
09 December 2012 to 05 January 2013	253	158,606,062	1.595 (1.405,1.798)
06 January 2013 to 02 February 2013	276	171,063,002	1.613 (1.429,1.809)
03 February 2013 to 02 March 2013	308	177,595,380	1.734 (1.546,1.933)
03 March 2013 to 30 March 2013	350	164,788,263	2.124 (1.907,2.352)
31 March 2013 to 27 April 2013	344	161,022,945	2.136 (1.917,2.368)
28 April 2013 to 25 May 2013	361	160,244,796	2.253 (2.026,2.491)
26 May 2013 to 22 June 2013	386	172,357,060	2.240 (2.022,2.468)
23 June 2013 to 20 July 2013	349	176,228,963	1.980 (1.778,2.193)
21 July 2013 to 17 August 2013	355	195,923,666	1.812 (1.628,2.005)
18 August 2013 to 14 September 2013	334	198,831,756	1.680 (1.504,1.865)
15 September 2013 to 12 October 2013	340	189,728,555	1.792 (1.607,1.987)
13 October 2013 to 09 November 2013	328	189,855,974	1.728 (1.546,1.920)
10 November 2013 to 07 December 2013	282	192,893,990	1.462 (1.296,1.637)
08 December 2013 to 04 January 2014	261	185,611,612	1.406 (1.241,1.582)
05 January 2014 to 01 February 2014	286	213,956,221	1.337 (1.186,1.496)
02 February 2014 to 01 March 2014	333	232,885,277	1.430 (1.280,1.587)

Four Week Interval Date	Exposure Count	Total Packets Sales Count	Rates of All Exposures per 1,000,000 Children Packets Sold (95% CI)
02 March 2014 to 29 March 2014	369	243,496,603	1.515 (1.365,1.674)
30 March 2014 to 26 April 2014	376	230,264,949	1.633 (1.472,1.802)
27 April 2014 to 24 May 2014	384	227,820,254	1.686 (1.521,1.858)
25 May 2014 to 21 June 2014	463	232,636,163	1.990 (1.813,2.176)
22 June 2014 to 19 July 2014	446	243,531,931	1.831 (1.665,2.005)
20 July 2014 to 16 August 2014	447	254,650,805	1.755 (1.596,1.922)
17 August 2014 to 13 September 2014	463	260,544,201	1.777 (1.619,1.943)
14 September 2014 to 11 October 2014	421	249,220,913	1.689 (1.532,1.854)
12 October 2014 to 08 November 2014	369	259,506,292	1.422 (1.281,1.571)
09 November 2014 to 06 December 2014	347	261,748,236	1.326 (1.190,1.469)
07 December 2014 to 03 January 2015	308	259,951,250	1.185 (1.056,1.321)
04 January 2015 to 31 January 2015	325	283,829,321	1.145 (1.024,1.273)
01 February 2015 to 28 February 2015	311	264,812,881	1.174 (1.048,1.308)
01 March 2015 to 28 March 2015	371	278,942,632	1.330 (1.198,1.469)
29 March 2015 to 25 April 2015	381	266,267,713	1.431 (1.291,1.578)
26 April 2015 to 23 May 2015	411	268,069,072	1.533 (1.389,1.685)
24 May 2015 to 20 June 2015	440	275,907,638	1.595 (1.449,1.747)
21 June 2015 to 18 July 2015	421	268,363,850	1.569 (1.422,1.722)
19 July 2015 to 15 August 2015	425	281,773,843	1.508 (1.368,1.655)
16 August 2015 to 12 September 2015	437	293,314,307	1.490 (1.353,1.633)
13 September 2015 to 10 October 2015	421	266,552,970	1.579 (1.432,1.734)
11 October 2015 to 07 November 2015	377	282,026,373	1.337 (1.205,1.475)
08 November 2015 to 05 December 2015	394	297,973,693	1.322 (1.195,1.456)

Four Week Interval Date	Exposure Count	Total Packets Sales Count	Rates of All Exposures per 1,000,000 Children Packets Sold (95% CI)
06 December 2015 to 02 January 2016	369	290,601,182	1.270 (1.144,1.403)
03 January 2016 to 30 January 2016	350	316,167,331	1.107 (0.994,1.226)
31 January 2016 to 27 February 2016	323	334,235,847	0.966 (0.864,1.075)
28 February 2016 to 26 March 2016	328	315,910,549	1.038 (0.929,1.154)
27 March 2016 to 23 April 2016	374	316,651,931	1.181 (1.064,1.304)
24 April 2016 to 21 May 2016	428	318,236,039	1.345 (1.221,1.475)
22 May 2016 to 18 June 2016	384	316,567,950	1.213 (1.095,1.337)
19 June 2016 to 16 July 2016	390	356,018,984	1.095 (0.989,1.207)
17 July 2016 to 13 August 2016	403	351,674,468	1.146 (1.037,1.260)
14 August 2016 to 10 September 2016	400	356,942,908	1.121 (1.013,1.233)
11 September 2016 to 08 October 2016	338	335,661,035	1.007 (0.902,1.117)
09 October 2016 to 05 November 2016	342	344,522,260	0.993 (0.890,1.101)
06 November 2016 to 03 December 2016	287	346,044,054	0.829 (0.736,0.928)
04 December 2016 to 31 December 2016	245	335,408,265	0.730 (0.642,0.825)
01 January 2017 to 28 January 2017	250	359,862,022	0.695 (0.611,0.783)
29 January 2017 to 25 February 2017	249	386,913,157	0.644 (0.566,0.726)
26 February 2017 to 25 March 2017	268	360,794,539	0.743 (0.657,0.834)
26 March 2017 to 22 April 2017	285	371,856,361	0.766 (0.680,0.858)
23 April 2017 to 20 May 2017	296	351,578,519	0.842 (0.749,0.940)
21 May 2017 to 17 June 2017	344	369,080,801	0.932 (0.836,1.033)
18 June 2017 to 15 July 2017	335	365,486,827	0.917 (0.821,1.017)
16 July 2017 to 12 August 2017	294	360,532,691	0.815 (0.725,0.911)
13 August 2017 to 09 September 2017	293	383,751,886	0.764 (0.679,0.853)

Four Week Interval Date	Exposure Count	Total Packets Sales Count	Rates of All Exposures per 1,000,000 Children Packets Sold (95% CI)
10 September 2017 to 07 October 2017	274	356,237,506	0.769 (0.681,0.863)
08 October 2017 to 04 November 2017	268	347,358,978	0.772 (0.682,0.867)
05 November 2017 to 02 December 2017	228	345,461,141	0.660 (0.577,0.748)
03 December 2017 to 30 December 2017	181	346,944,075	0.522 (0.448,0.600)

Figure 11. Exposures Involving Healthcare Facility Treatment and Sales Counts by Four Week Interval (22 July 2012 to 30 December 2017)

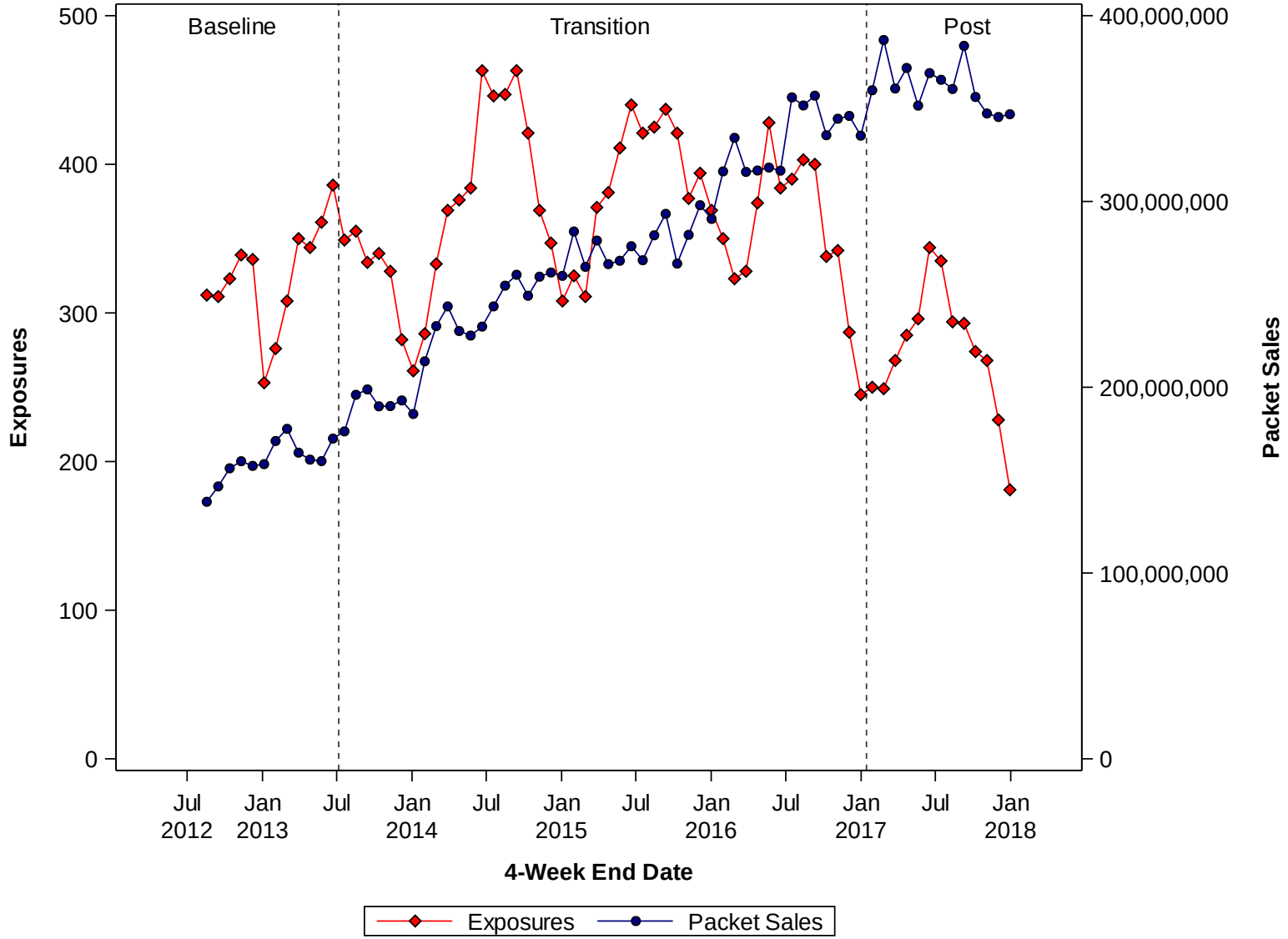
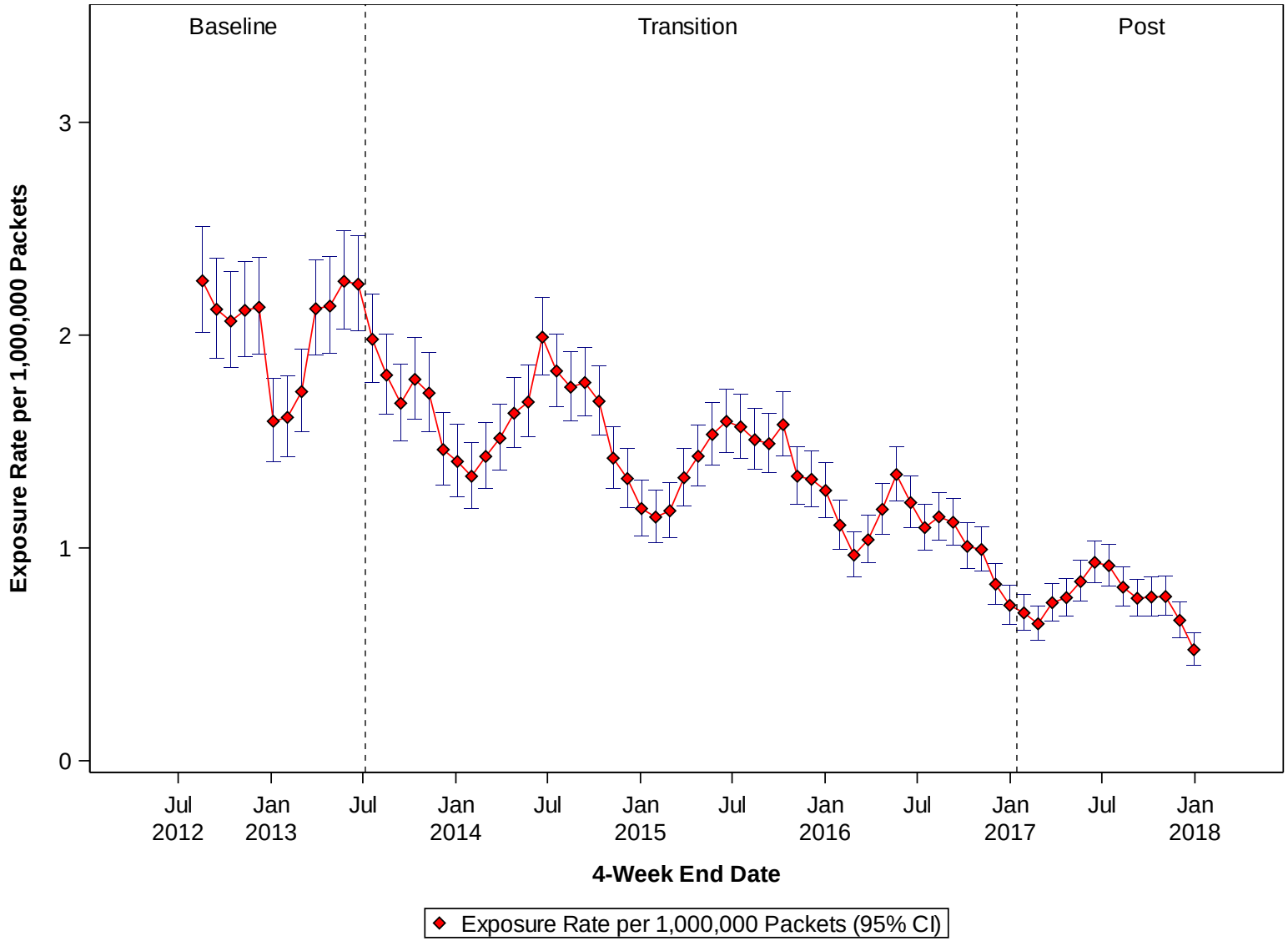


Figure 12. Sales-Adjusted Rates of Exposures Involving Healthcare Facility Treatment by Four Week Interval (22 July 2012 to 30 December 2017)



When examined by four week intervals corresponding to sales periods, counts of exposures involving HCF admission fluctuated without a clear seasonal pattern throughout the study period. A decrease in reported exposures involving HCF admission was observed in the second half of the study period. During the same time period the total sales fluctuated slightly with a steady increase over time (Table 15; Figure 13).

The sales-adjusted rate of reported exposures involving admission to a HCF fluctuated throughout the study period without an apparent seasonal pattern. A peak in the sales-adjusted rate of exposure was observed in the four week interval ending 15 September 2012 (0.293 exposures per 1 million packets sold (CI 0.212, 0.387)) and a low in the sales-adjusted rate of exposure was observed in the four week interval ending 30 December 2017 (0.020 exposures per 1 million packets sold (CI 0.008, 0.038); Table 15; Figure 14). Without a clear seasonal pattern in reported sales-adjusted rates of exposure, seasonal peak and low rates could not be compared.

Table 15. Sales-Adjusted Rates of Exposures Involving Healthcare Facility Admission by Four Week Interval (22 July 2012 to 30 December 2017)

Four Week Interval Date	Exposure Count	Total Packets Sales Count	Rates of All Exposures per 1,000,000 Children Packets Sold (95% CI)
22 July 2012 to 18 August 2012	33	138,355,958	0.239 (0.164,0.327)
19 August 2012 to 15 September 2012	43	146,612,045	0.293 (0.212,0.387)
16 September 2012 to 13 October 2012	35	156,369,907	0.224 (0.156,0.304)
14 October 2012 to 10 November 2012	42	160,177,007	0.262 (0.189,0.347)
11 November 2012 to 08 December 2012	32	157,666,057	0.203 (0.139,0.279)
09 December 2012 to 05 January 2013	28	158,606,062	0.177 (0.117,0.248)
06 January 2013 to 02 February 2013	20	171,063,002	0.117 (0.071,0.173)
03 February 2013 to 02 March 2013	39	177,595,380	0.220 (0.156,0.294)
03 March 2013 to 30 March 2013	33	164,788,263	0.200 (0.138,0.274)
31 March 2013 to 27 April 2013	39	161,022,945	0.242 (0.172,0.324)
28 April 2013 to 25 May 2013	39	160,244,796	0.243 (0.173,0.325)
26 May 2013 to 22 June 2013	37	172,357,060	0.215 (0.151,0.289)
23 June 2013 to 20 July 2013	39	176,228,963	0.221 (0.157,0.296)
21 July 2013 to 17 August 2013	37	195,923,666	0.189 (0.133,0.254)
18 August 2013 to 14 September 2013	28	198,831,756	0.141 (0.094,0.198)
15 September 2013 to 12 October 2013	44	189,728,555	0.232 (0.169,0.305)
13 October 2013 to 09 November 2013	44	189,855,974	0.232 (0.168,0.305)
10 November 2013 to 07 December 2013	37	192,893,990	0.192 (0.135,0.258)
08 December 2013 to 04 January 2014	28	185,611,612	0.151 (0.100,0.212)
05 January 2014 to 01 February 2014	29	213,956,221	0.136 (0.091,0.189)
02 February 2014 to 01 March 2014	43	232,885,277	0.185 (0.134,0.244)

Four Week Interval Date	Exposure Count	Total Packets Sales Count	Rates of All Exposures per 1,000,000 Children Packets Sold (95% CI)
02 March 2014 to 29 March 2014	58	243,496,603	0.238 (0.181,0.303)
30 March 2014 to 26 April 2014	42	230,264,949	0.182 (0.131,0.242)
27 April 2014 to 24 May 2014	45	227,820,254	0.198 (0.144,0.259)
25 May 2014 to 21 June 2014	59	232,636,163	0.254 (0.193,0.322)
22 June 2014 to 19 July 2014	55	243,531,931	0.226 (0.170,0.289)
20 July 2014 to 16 August 2014	45	254,650,805	0.177 (0.129,0.232)
17 August 2014 to 13 September 2014	52	260,544,201	0.200 (0.149,0.257)
14 September 2014 to 11 October 2014	41	249,220,913	0.165 (0.118,0.219)
12 October 2014 to 08 November 2014	37	259,506,292	0.143 (0.100,0.192)
09 November 2014 to 06 December 2014	44	261,748,236	0.168 (0.122,0.221)
07 December 2014 to 03 January 2015	34	259,951,250	0.131 (0.091,0.178)
04 January 2015 to 31 January 2015	26	283,829,321	0.092 (0.060,0.130)
01 February 2015 to 28 February 2015	27	264,812,881	0.102 (0.067,0.144)
01 March 2015 to 28 March 2015	42	278,942,632	0.151 (0.109,0.199)
29 March 2015 to 25 April 2015	40	266,267,713	0.150 (0.107,0.200)
26 April 2015 to 23 May 2015	42	268,069,072	0.157 (0.113,0.207)
24 May 2015 to 20 June 2015	50	275,907,638	0.181 (0.135,0.235)
21 June 2015 to 18 July 2015	40	268,363,850	0.149 (0.106,0.199)
19 July 2015 to 15 August 2015	43	281,773,843	0.153 (0.110,0.201)
16 August 2015 to 12 September 2015	33	293,314,307	0.113 (0.077,0.154)
13 September 2015 to 10 October 2015	29	266,552,970	0.109 (0.073,0.152)
11 October 2015 to 07 November 2015	32	282,026,373	0.113 (0.078,0.156)
08 November 2015 to 05 December 2015	35	297,973,693	0.117 (0.082,0.159)

Four Week Interval Date	Exposure Count	Total Packets Sales Count	Rates of All Exposures per 1,000,000 Children Packets Sold (95% CI)
06 December 2015 to 02 January 2016	28	290,601,182	0.096 (0.064,0.135)
03 January 2016 to 30 January 2016	24	316,167,331	0.076 (0.049,0.109)
31 January 2016 to 27 February 2016	26	334,235,847	0.078 (0.051,0.110)
28 February 2016 to 26 March 2016	26	315,910,549	0.082 (0.054,0.117)
27 March 2016 to 23 April 2016	18	316,651,931	0.057 (0.034,0.086)
24 April 2016 to 21 May 2016	26	318,236,039	0.082 (0.053,0.116)
22 May 2016 to 18 June 2016	22	316,567,950	0.069 (0.044,0.101)
19 June 2016 to 16 July 2016	29	356,018,984	0.081 (0.055,0.114)
17 July 2016 to 13 August 2016	26	351,674,468	0.074 (0.048,0.105)
14 August 2016 to 10 September 2016	38	356,942,908	0.106 (0.075,0.143)
11 September 2016 to 08 October 2016	30	335,661,035	0.089 (0.060,0.124)
09 October 2016 to 05 November 2016	19	344,522,260	0.055 (0.033,0.083)
06 November 2016 to 03 December 2016	24	346,044,054	0.069 (0.044,0.100)
04 December 2016 to 31 December 2016	17	335,408,265	0.051 (0.030,0.077)
01 January 2017 to 28 January 2017	16	359,862,022	0.044 (0.025,0.069)
29 January 2017 to 25 February 2017	17	386,913,157	0.044 (0.026,0.067)
26 February 2017 to 25 March 2017	9	360,794,539	0.025 (0.011,0.044)
26 March 2017 to 22 April 2017	16	371,856,361	0.043 (0.025,0.067)
23 April 2017 to 20 May 2017	17	351,578,519	0.048 (0.028,0.074)
21 May 2017 to 17 June 2017	18	369,080,801	0.049 (0.029,0.074)
18 June 2017 to 15 July 2017	22	365,486,827	0.060 (0.038,0.088)
16 July 2017 to 12 August 2017	17	360,532,691	0.047 (0.027,0.072)
13 August 2017 to 09 September 2017	19	383,751,886	0.050 (0.030,0.074)

Four Week Interval Date	Exposure Count	Total Packets Sales Count	Rates of All Exposures per 1,000,000 Children Packets Sold (95% CI)
10 September 2017 to 07 October 2017	15	356,237,506	0.042 (0.024,0.066)
08 October 2017 to 04 November 2017	26	347,358,978	0.075 (0.049,0.106)
05 November 2017 to 02 December 2017	10	345,461,141	0.029 (0.014,0.049)
03 December 2017 to 30 December 2017	7	346,944,075	0.020 (0.008,0.038)

Figure 13. Exposures Involving Healthcare Facility Admission and Sales Counts by Four Week Interval (22 July 2012 to 30 December 2017)

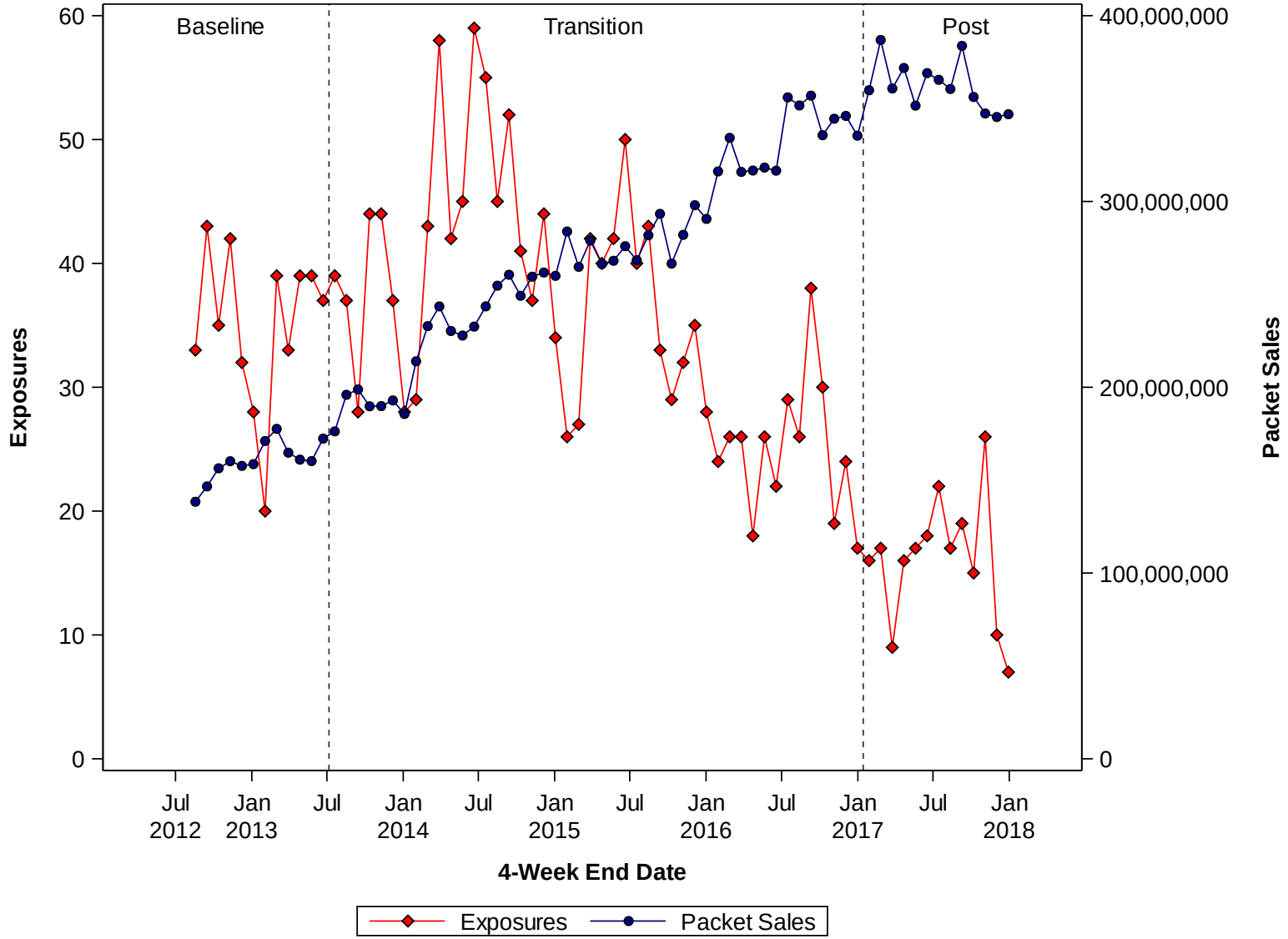
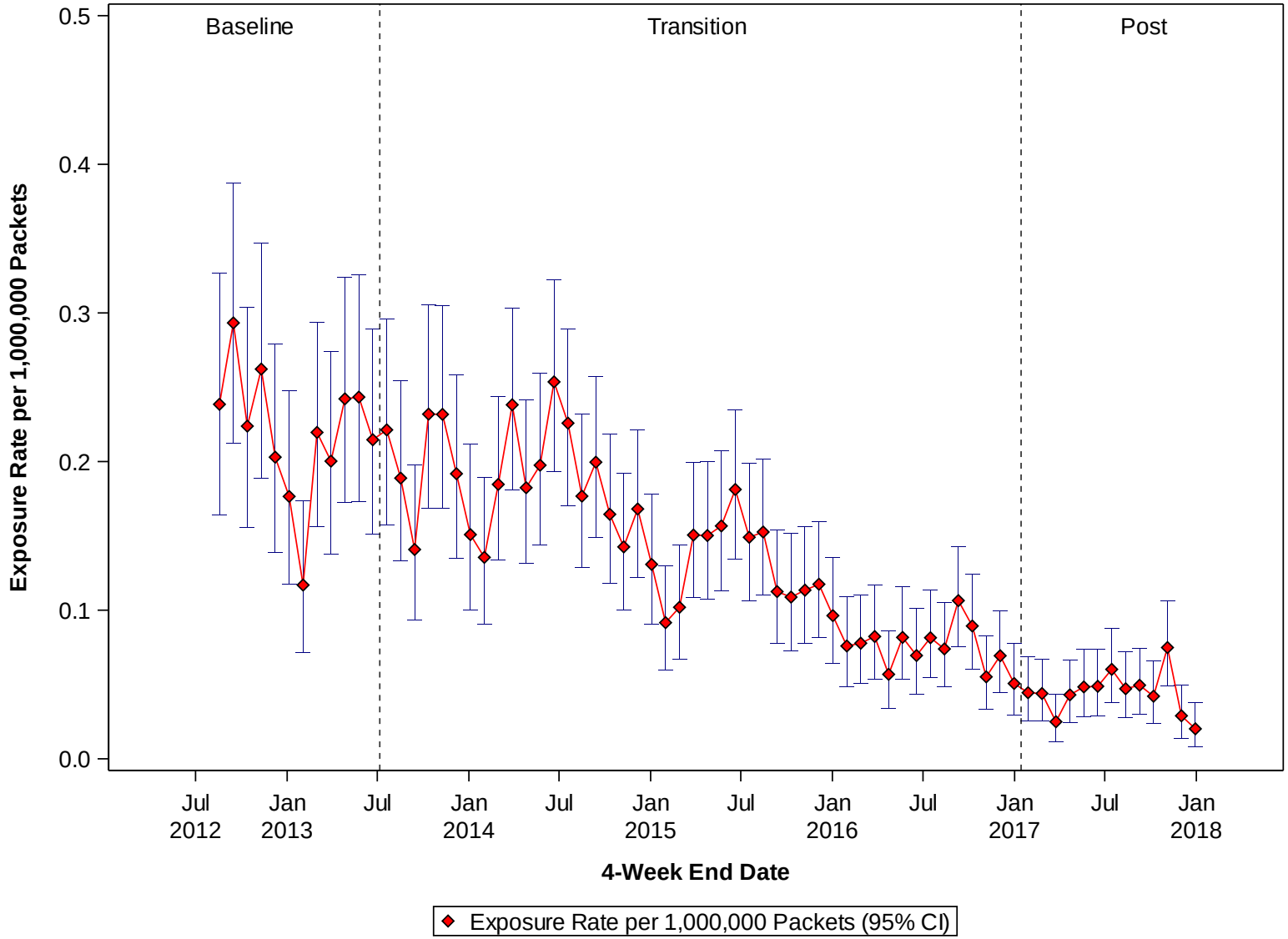


Figure 14. Sales-Adjusted Rates of Exposures Involving Healthcare Facility Admission by Four Week Interval (22 July 2012 to 30 December 2017)



When examined by four week intervals corresponding to sales, counts of exposures involving severe medical outcomes fluctuated from 0 to 11 exposures without an apparent seasonal pattern throughout the study period. An overall decrease in reporting frequency was observed over time with a range of 0 to 3 exposures being reported in the post period. During the same time period the total sales fluctuated slightly with a steady increase over time (Table 16; Figure 15).

The sales-adjusted rate of reported exposures involving severe medical outcomes fluctuated from 22 July 2012 to 30 December 2017 with a rate of 0.000 due to no severe medical outcomes reported in four week intervals ending 01 February 2014, 18 July 2015, 21 May 2016, 13 August 2016, 28 January 2017, and 25 February 2017. The peak rate of 0.070 exposures per 1 million packets sold (CI 0.035, 0.118) was observed in the four week interval ending 13 October 2012 (Table 16; Figure 16). As the number of severe medical outcomes reported during each four week interval remained low, the rate calculations generated wide confidence intervals and were less precise. Thus, further comparison of rates at different time points over the study period was not appropriate.

Table 16. Sales-Adjusted Rates of Exposures Resulting in Severe Medical Outcomes by Four Week Interval (22 July 2012 to 30 December 2017)

Four Week Interval Date	Exposure Count	Total Packets Sales Count	Rates of All Exposures per 1,000,000 Children Packets Sold (95% CI)
22 July 2012 to 18 August 2012	7	138,355,958	0.051 (0.020,0.094)
19 August 2012 to 15 September 2012	6	146,612,045	0.041 (0.015,0.080)
16 September 2012 to 13 October 2012	11	156,369,907	0.070 (0.035,0.118)
14 October 2012 to 10 November 2012	4	160,177,007	0.025 (0.007,0.055)
11 November 2012 to 08 December 2012	3	157,666,057	0.019 (0.004,0.046)
09 December 2012 to 05 January 2013	3	158,606,062	0.019 (0.004,0.046)
06 January 2013 to 02 February 2013	2	171,063,002	0.012 (0.001,0.033)
03 February 2013 to 02 March 2013	4	177,595,380	0.023 (0.006,0.049)
03 March 2013 to 30 March 2013	2	164,788,263	0.012 (0.001,0.034)
31 March 2013 to 27 April 2013	8	161,022,945	0.050 (0.021,0.090)
28 April 2013 to 25 May 2013	2	160,244,796	0.012 (0.002,0.035)
26 May 2013 to 22 June 2013	5	172,357,060	0.029 (0.009,0.059)
23 June 2013 to 20 July 2013	1	176,228,963	0.006 (0.000,0.021)
21 July 2013 to 17 August 2013	8	195,923,666	0.041 (0.018,0.074)
18 August 2013 to 14 September 2013	4	198,831,756	0.020 (0.005,0.044)
15 September 2013 to 12 October 2013	7	189,728,555	0.037 (0.015,0.069)
13 October 2013 to 09 November 2013	3	189,855,974	0.016 (0.003,0.038)
10 November 2013 to 07 December 2013	3	192,893,990	0.016 (0.003,0.037)
08 December 2013 to 04 January 2014	1	185,611,612	0.005 (0.000,0.020)
05 January 2014 to 01 February 2014	0	213,956,221	0.000 (0.000,0.017)
02 February 2014 to 01 March 2014	6	232,885,277	0.026 (0.009,0.050)

Four Week Interval Date	Exposure Count	Total Packets Sales Count	Rates of All Exposures per 1,000,000 Children Packets Sold (95% CI)
02 March 2014 to 29 March 2014	4	243,496,603	0.016 (0.004,0.036)
30 March 2014 to 26 April 2014	7	230,264,949	0.030 (0.012,0.057)
27 April 2014 to 24 May 2014	4	227,820,254	0.018 (0.005,0.038)
25 May 2014 to 21 June 2014	3	232,636,163	0.013 (0.003,0.031)
22 June 2014 to 19 July 2014	6	243,531,931	0.025 (0.009,0.048)
20 July 2014 to 16 August 2014	6	254,650,805	0.024 (0.009,0.046)
17 August 2014 to 13 September 2014	8	260,544,201	0.031 (0.013,0.055)
14 September 2014 to 11 October 2014	2	249,220,913	0.008 (0.001,0.022)
12 October 2014 to 08 November 2014	3	259,506,292	0.012 (0.002,0.028)
09 November 2014 to 06 December 2014	4	261,748,236	0.015 (0.004,0.033)
07 December 2014 to 03 January 2015	3	259,951,250	0.012 (0.002,0.028)
04 January 2015 to 31 January 2015	1	283,829,321	0.004 (0.000,0.013)
01 February 2015 to 28 February 2015	3	264,812,881	0.011 (0.002,0.027)
01 March 2015 to 28 March 2015	5	278,942,632	0.018 (0.006,0.037)
29 March 2015 to 25 April 2015	3	266,267,713	0.011 (0.002,0.027)
26 April 2015 to 23 May 2015	3	268,069,072	0.011 (0.002,0.027)
24 May 2015 to 20 June 2015	3	275,907,638	0.011 (0.002,0.026)
21 June 2015 to 18 July 2015	0	268,363,850	0.000 (0.000,0.014)
19 July 2015 to 15 August 2015	2	281,773,843	0.007 (0.001,0.020)
16 August 2015 to 12 September 2015	2	293,314,307	0.007 (0.001,0.019)
13 September 2015 to 10 October 2015	5	266,552,970	0.019 (0.006,0.038)
11 October 2015 to 07 November 2015	2	282,026,373	0.007 (0.001,0.020)
08 November 2015 to 05 December 2015	1	297,973,693	0.003 (0.000,0.012)

Four Week Interval Date	Exposure Count	Total Packets Sales Count	Rates of All Exposures per 1,000,000 Children Packets Sold (95% CI)
06 December 2015 to 02 January 2016	1	290,601,182	0.003 (0.000,0.013)
03 January 2016 to 30 January 2016	2	316,167,331	0.006 (0.001,0.018)
31 January 2016 to 27 February 2016	1	334,235,847	0.003 (0.000,0.011)
28 February 2016 to 26 March 2016	1	315,910,549	0.003 (0.000,0.012)
27 March 2016 to 23 April 2016	1	316,651,931	0.003 (0.000,0.012)
24 April 2016 to 21 May 2016	0	318,236,039	0.000 (0.000,0.012)
22 May 2016 to 18 June 2016	1	316,567,950	0.003 (0.000,0.012)
19 June 2016 to 16 July 2016	2	356,018,984	0.006 (0.001,0.016)
17 July 2016 to 13 August 2016	0	351,674,468	0.000 (0.000,0.010)
14 August 2016 to 10 September 2016	2	356,942,908	0.006 (0.001,0.016)
11 September 2016 to 08 October 2016	1	335,661,035	0.003 (0.000,0.011)
09 October 2016 to 05 November 2016	3	344,522,260	0.009 (0.002,0.021)
06 November 2016 to 03 December 2016	1	346,044,054	0.003 (0.000,0.011)
04 December 2016 to 31 December 2016	1	335,408,265	0.003 (0.000,0.011)
01 January 2017 to 28 January 2017	0	359,862,022	0.000 (0.000,0.010)
29 January 2017 to 25 February 2017	0	386,913,157	0.000 (0.000,0.010)
26 February 2017 to 25 March 2017	1	360,794,539	0.003 (0.000,0.010)
26 March 2017 to 22 April 2017	2	371,856,361	0.005 (0.001,0.015)
23 April 2017 to 20 May 2017	2	351,578,519	0.006 (0.001,0.016)
21 May 2017 to 17 June 2017	3	369,080,801	0.008 (0.002,0.020)
18 June 2017 to 15 July 2017	1	365,486,827	0.003 (0.000,0.010)
16 July 2017 to 12 August 2017	1	360,532,691	0.003 (0.000,0.010)
13 August 2017 to 09 September 2017	2	383,751,886	0.005 (0.001,0.015)

Four Week Interval Date	Exposure Count	Total Packets Sales Count	Rates of All Exposures per 1,000,000 Children Packets Sold (95% CI)
10 September 2017 to 07 October 2017	1	356,237,506	0.003 (0.000,0.010)
08 October 2017 to 04 November 2017	2	347,358,978	0.006 (0.001,0.016)
05 November 2017 to 02 December 2017	1	345,461,141	0.003 (0.000,0.011)
03 December 2017 to 30 December 2017	3	346,944,075	0.009 (0.002,0.021)

Figure 15. Exposures Resulting in Severe Medical Outcomes and Sales Counts by Four Week Interval (22 July 2012 to 30 December 2017)

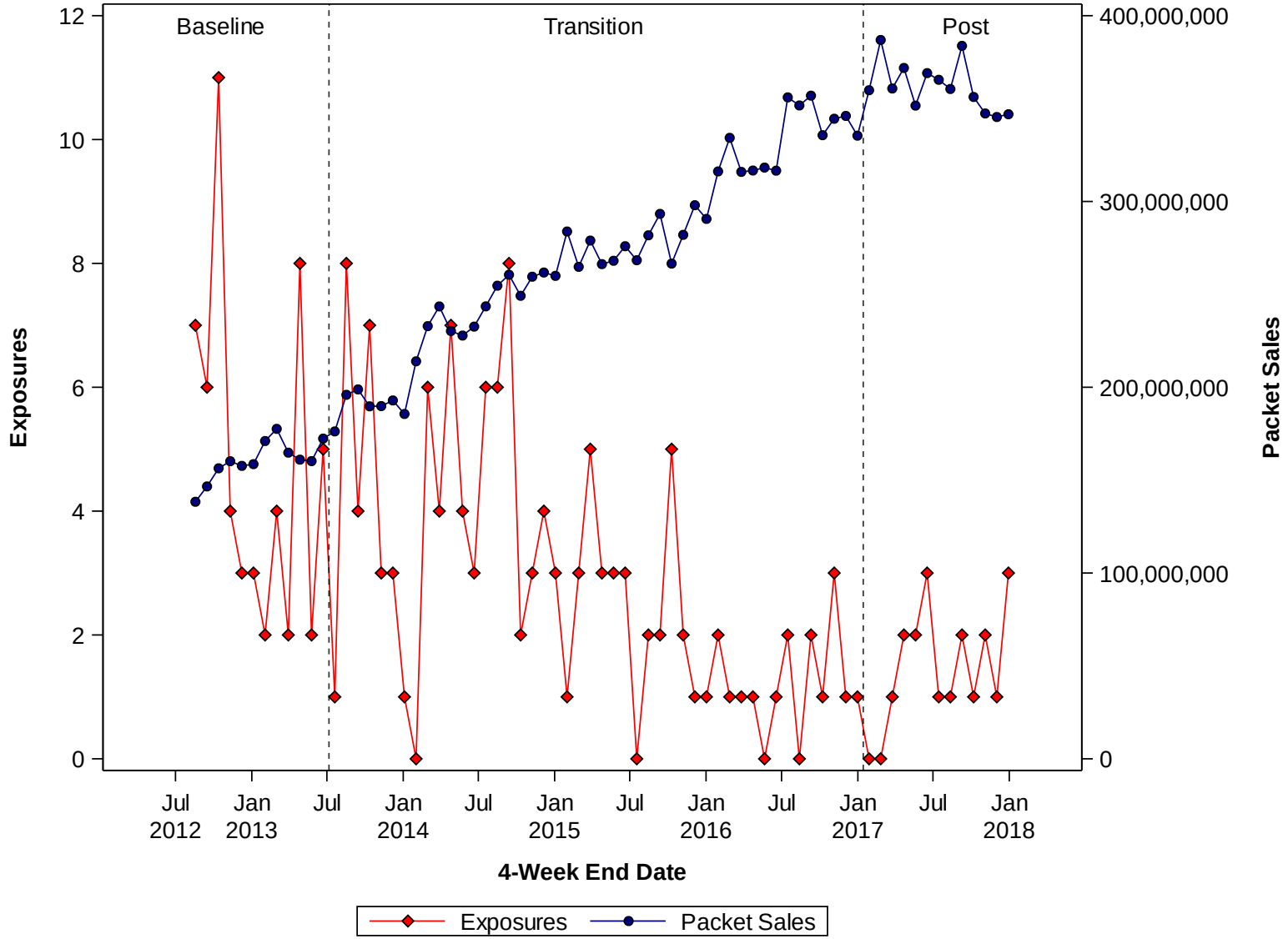
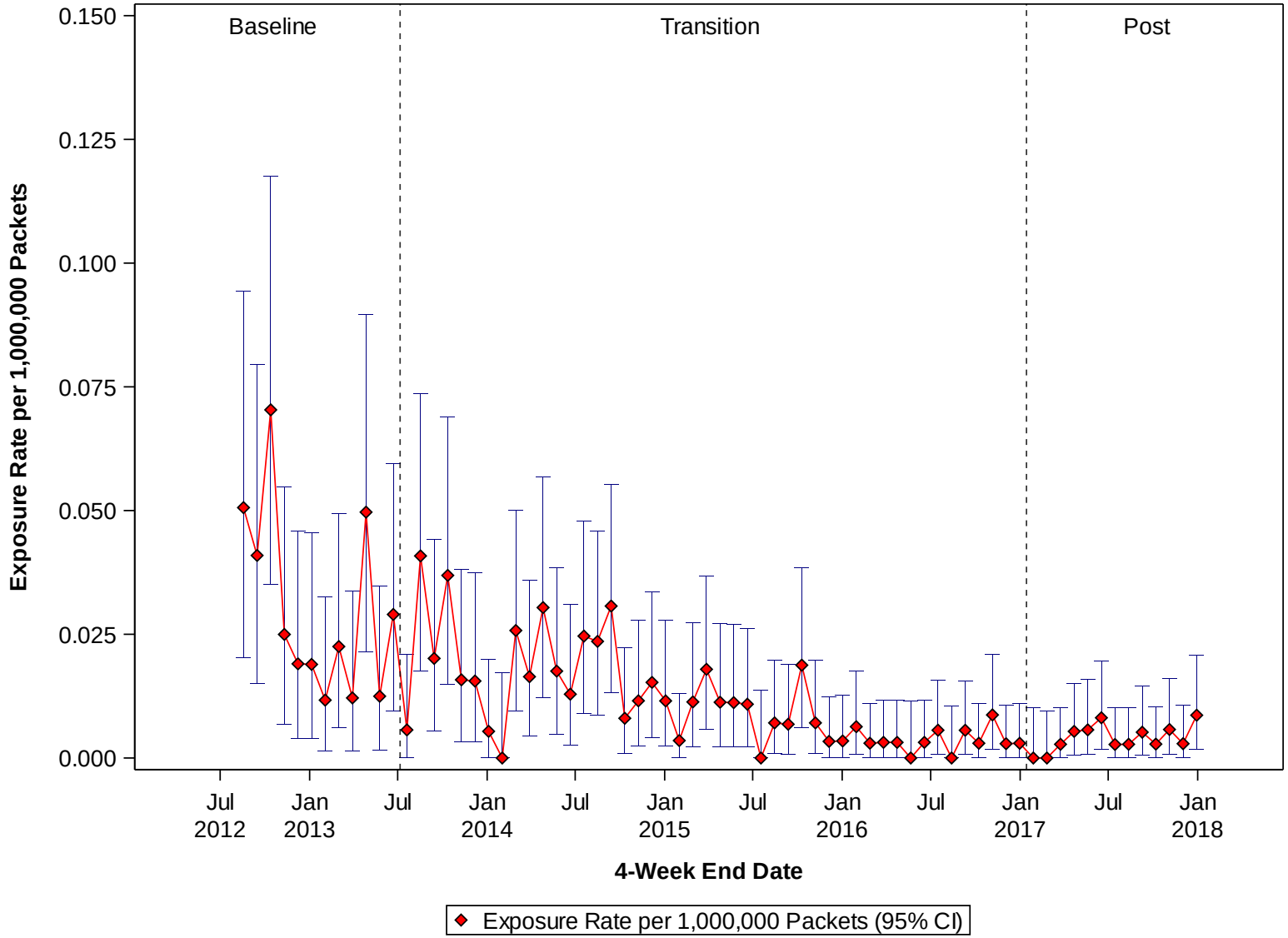


Figure 16. Sales-Adjusted Rates of Exposures Resulting in Severe Medical Outcomes by Four Week Interval (22 July 2012 to 30 December 2017)



SUMMARY

Reporting of unintentional pediatric exposures involving liquid laundry detergent packets to US regional poison centers via the National Poison Data System (NPDS) initially increased from 2012 through 2016, with a marked decrease in the frequency of exposures reported in 2017. The increasing trend in reported exposures from 2012 through 2016 correlates with the introduction (baseline period) of liquid laundry detergent packets in the US through the time period in which ASTM standards to improve liquid laundry detergent packet safety were being implemented (transition period). The subsequent decrease in 2017 correlates with the period at which full adoption of the ASTM safety standards had been achieved (post period), suggesting that the ASTM standards may have prevented some unintentional pediatric exposures to liquid laundry detergent packets.

Comparing the cumulative rate of exposures in the baseline and post periods, adjusted for packet sales, further suggests a significant decrease (53%) in exposures in the context of consistently increasing product availability over the time period. However, when adjusted for the US population of children <6 years of age, the cumulative rate of exposures increased 6% from the baseline to the post period. As the US population fluctuated slightly (within 1%) over the time period, a slightly higher frequency of exposures reported in the post period contributed to the increased population-adjusted rate. Long term monitoring of the apparent downward trend in reported exposures in the post period, including measurement of the annual rate of change, would provide additional context for the association between the ASTM standards and changes in trends in reported exposures.

Regardless of the change in the number of all unintentional pediatric exposures involving liquid laundry detergent packets, exposures involving treatment in a healthcare facility (HCF), admission to a HCF, and clinically significant medical outcomes decreased significantly when adjusted for both product sales and for the US population of children <6 years of age. The largest rate reduction was observed among exposures involving severe medical outcomes, with one severe medical outcome occurring per 375,940 US children <6 years of age or per 33,333,333 packets sold during the baseline period compared to one severe medical outcome occurring per 1,265,823 US children <6 years of age or per 250,000,000 packets sold during the post period. While monitoring changes in exposures is important in understanding the broad safety profile of a product, monitoring changes in exposures with outcomes like admission to a HCF and severe medical outcomes is most valuable in understanding the impact of safety interventions. Many factors can influence a report to a poison center, including perceptions of safety or consumer knowledge about a product, but medically significant exposures tend to be reported regardless of these factors due to the need for medical management provided by poison centers.

The comparison of exposure characteristics provides additional insight into the nature of the impact of the ASTM standards. One key change observed from baseline to post period is the change in the distribution of age with a decrease in the percent of

exposures that involved children <2 years of age. Another change to highlight includes the decrease in exposures involving ingestion and increases in ocular and dermal exposures. Finally, fewer exposures in the post period resulted in a related clinical effect (adverse event), further suggesting decreased severity associated with exposures occurring after ASTM standard implementation. These characteristics should be considered in the context of changes in the packaging, capsule integrity, the addition of an aversive agent, and product labeling to determine if the intended impact has been achieved or if revisions to the standards should be made.

Use of NPDS data has limitations that should be considered in this evaluation. Exposures are self-reported to poison centers for the purposes of medical management and some exposures may be underreported. Furthermore, factors other than safety interventions may affect reporting and limit the interpretation of observed increases or decreases in exposures over time. As such, this evaluation cannot directly measure the impact of the ASTM standards or specific components of the standards and the interpretation of temporal trends should be limited to associations not causality.

Nonetheless, the data presented here demonstrate changes in the pattern of exposures after full adoption of safety standards to improve the safety liquid laundry detergent packets. Importantly the biggest decreases were observed among clinically significant exposures, especially among exposures with severe medical outcomes. Changes in some exposure characteristics further suggest decreased severity of exposures in alignment with the improved safety of these products. However, despite the marked decreases in exposures associated with implementation of the ASTM safety standards, 150 to 350 children received care in a HCF each month due to liquid laundry detergent packet exposure and additional opportunity to ensure safety may be necessary regardless of the improvements seen here. As such, ongoing monitoring of trends is warranted to measure sustainment of observed decreases and to ensure the real-world relevance of changes in reported exposures.

DISCLAIMERS

American Association of Poison Control Centers

The American Association of Poison Control Centers (AAPCC; http://www.aapcc.org) maintains the national database of information logged by the country's regional poison centers (PCs) serving all 50 United States, Puerto Rico, and the District of Columbia. Case records in this database are from self-reported calls: they reflect only information provided when the public or health care professionals report an actual or potential exposure to a substance (e.g., an ingestion, inhalation, or topical exposure), or request information/educational materials. Exposures do not necessarily represent a poisoning or overdose. The AAPCC is not able to completely verify the accuracy of every report made to member centers. Additional exposures may go unreported to PCs and data referenced from the AAPCC should not be construed to represent the complete incidence of national exposures to any substance(s).

Nielsen

The analyses performed in this report are based in part on data reported by Nielsen through its Strategic Planner Service for the Liquid Laundry Packs category for four week intervals from 22 July 2012 through 30 December 2017, for the Total US market for Nielsen's Expanded All Outlets Combined channel which includes Food, Drug, Mass Merchandise, Club, Dollar, and Military/Deca. Conclusions drawn from the use of Nielsen data do not reflect the views of Nielsen.

REFERENCES

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2. Gummin DD, Mowry JB, Spyker DA, Brooks DE, Fraser MO, Banner W. 2016 Annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 34th Annual report. *Clin. Toxicol.* 2017; 55(10): 1072-252. DOI:10.1080/15563650.2017.1388087.
3. 2010 Census Data. U.S. Census Bureau website. https://www.census.gov/2010census/data/. Accessed January 16, 2018.

APPENDICES

Appendix A: National Poison Data System (NPDS) Definitions

EXPOSURE
Actual or suspected contact with any substance which has been ingested, inhaled, absorbed, applied to, or injected into the body, regardless of toxicity or clinical manifestation.

REASON FOR EXPOSURE
Unintentional Exposure
An unintentional exposure results from an unforeseen or unplanned event. Includes all subtypes: unintentional general, environmental, occupational, therapeutic error, misuse, bite/sting, food poisoning and unintentional unknown.

1) **Unintentional-General**: All unintended exposures that are not specifically defined below. Most unintentional exposures in children should be coded here. Never use this code if there is another code that fits the case.
2) **Unintentional-Environmental**: Any passive, non-occupational exposure that results from contamination of air, water, or soil. Environmental exposures are usually, but not always, caused by man-made contaminants.
3) **Unintentional-Occupational**: Any exposure that occurs as a direct result of the person being on the job or in the workplace.
4) **Unintentional-Therapeutic Error**: An unintentional deviation from a proper therapeutic regimen that results in the wrong dose, incorrect route of administration, administration to the wrong person, or administration of the wrong substance. Includes instances in which any type of substance (medications, herbals, non-pharmaceuticals, or other products) is substituted for medications. Drug interactions (or drug/food interactions) resulting from unintentional administration of drugs/foods which are known to interact are also included.
5) **Unintentional-Misuse**: Unintentional improper or incorrect use of a non-pharmaceutical substance. Unintentional Misuse differs from Intentional Misuse in that the exposure was unplanned or not foreseen by the patient.
6) **Unintentional-Bite/Sting**: All animal bites and stings, with or without envenomation.
7) **Unintentional-Food Poisoning**: All suspected or confirmed food poisoning regardless of clinical manifestation. This includes ingestion of any food contaminated with microorganisms. The specific agent involved, if known, is recorded in the substance code area. This reason is used even if the patient develops no symptoms from the contaminated food.
8) **Unintentional-Unknown**: An exposure determined to be unintentional but the exact reason is unknown.

CHRONICITY
Chronicity of the exposure.

Acute: A single, repeated or continuous exposure occurring over a period of eight hours or less.

Acute-on-Chronic: A single exposure that was preceded by a continuous, repeated, or intermittent exposure occurring over a period exceeding eight hours.

Chronic: A continuous, repeated, or intermittent exposure to the same substance lasting longer than eight hours.

Unknown: It is not possible to determine whether the exposure is acute, acute-on-chronic, or chronic.

HEALTHCARE FACILITY (HCF) LEVEL OF CARE

Treated/evaluated and released: The patient is observed, treated and/or evaluated then released to home, work, shelter, jail, or similar site which is not a health care facility. If the patient came from a nursing home or other long-term care facility and went back to that facility from the health care facility, this response is selected. This includes patients treated/observed in a 23-hour observation unit to avoid admission.

Admitted to critical care unit: The patient is admitted to a critical or intensive care unit.

Admitted to noncritical care unit: The patient is observed or treated by a physician and subsequently admitted to a medical unit.

Admitted to psychiatric care facility: The patient is observed or treated by a physician and subsequently admitted primarily to receive psychiatric care or evaluation.

Patient refused referral/did not arrive at healthcare facility: The patient declined to follow the referral recommendation or failed to arrive at the health care facility to which he or she was referred.

Patient lost to follow-up/left AMA: The patient is lost to follow-up or the patient has left the health care facility against medical advice.

MEDICAL OUTCOME

Case followed to known outcome:

A response is appropriate in this area only if follow-up continues until medical outcome can be documented with reasonable certainty.

Unrelated effect: Based upon all the information available, the exposure was probably not responsible for the effect(s).

No effect: The patient developed no symptoms as a result of the exposure. Follow-up is required to make this determination unless the initial poison center

call occurs sufficiently long after the exposure that you are reasonably certain no effects will occur.

Minor effect: The patient exhibited some symptoms as a result of the exposure, but they were minimally bothersome to the patient. The symptoms usually resolve rapidly and usually involve skin or mucous membrane manifestations. The patient has returned to a pre-exposure state of wellbeing and has no residual disability or disfigurement.

Moderate effect: The patient exhibited symptoms as a result of the exposure which are more pronounced, more prolonged or more of a systemic nature than minor symptoms. Usually some form of treatment is or would have been indicated. Symptoms were not life-threatening and the patient has returned to a pre-exposure state of well-being with no residual disability or disfigurement.

Major effect: The patient has exhibited symptoms as a result of the exposure which were life-threatening or resulted in significant residual disability or disfigurement.

Death: The patient died as a result of the exposure or as a direct complication of the exposure where the complication was unlikely to have occurred had the toxic exposure not preceded the complication. Only includes deaths which are probably or undoubtedly related to the exposure.

Case <u>not</u> followed to a known outcome:
In some circumstances it is not appropriate or possible to follow a patient to a reasonably certain medical outcome.

Not followed, judged as nontoxic exposure. The patient was not followed because in the clinical judgment of the specialist in poison information, the exposure was likely to be nontoxic because:

- the agent involved was nontoxic
- the amount implicated in the exposure was insignificant (nontoxic), and/or
- the route of exposure was unlikely to result in a clinical effect

Not followed, minimal clinical effects possible. The patient was not followed because, in the clinical judgment of the specialist in poison information, the exposure was likely to result in only minimal toxicity of a trivial nature. This outcome is selected only when reasonably certain, in a worst case scenario, that the patient will experience no more than a minor effect. This also includes cases that refused follow-up if the exposure would possibly result in minimal clinical effects and would cause no more than a minor effect.

Unable to follow, judged as a potentially toxic exposure. The patient was lost to follow-up (or the poison center neglected to provide follow-up) and in the judgment of the specialist in poison information the exposure was significant and

may have resulted in toxic manifestations with a moderate, major or fatal outcome.

Death, indirect report: A reported fatality is coded as “indirect” if no inquiry was placed to the poison center. For example, if the case was obtained from a medical examiner who sends post mortem reports to the poison center or from a newspaper article. An inquiry to the poison center after the patient died is not necessarily indirect. For example, a medical examiner calling with a question about the cause of death or a family member calling with a question about a toxicology laboratory result is not an indirect report.

CLINICAL EFFECT
Reported signs, symptoms and clinical findings associated with an exposure, recorded by relationship to the exposure.

THERAPIES
Therapies that were recommended and/or performed in relation to the exposure reported.

SCENARIO
A description of the events that led to the reported exposure.