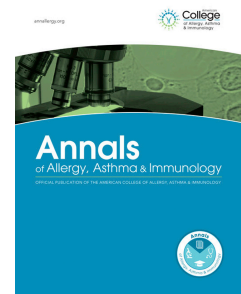


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Trends in U.S. hospitalizations for anaphylaxis among infants and toddlers:
2006-2015

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Title: Trends in U.S. hospitalizations for anaphylaxis among infants and toddlers: 2006-2015

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Keywords: Anaphylaxis, allergy, infant, child, food allergy, hospitalization

Abbreviations:

AAR: acute allergic reaction

AHRQ: Agency for Healthcare Research and Quality

CI: Confidence interval

IQR: Interquartile range

ED: emergency department

FAAR: food-induced acute allergic reaction

FIA: food-induced anaphylaxis

HCUP: Healthcare Cost and Utilization Project

ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification

ICD-10-CM: International Classification of Diseases, Tenth Revision, Clinical Modification

NIS: National (Nationwide) Inpatient Database

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Background: Anaphylaxis is a potentially fatal acute allergic reaction. Its overall prevalence appears to be rising, but little is known about U.S. hospitalization trends among infants and toddlers.

Objective: To identify the trends and predictors of hospitalization for anaphylaxis among infants and toddlers.

Methods: We used the nationally representative National Inpatient Sample (NIS), from 2006-2015, to perform an analysis of trends in U.S. hospitalizations for anaphylaxis among infants and toddlers (age <3 years) and other children (age 3-18 years). For internal consistency, we identified patients with anaphylaxis by ICD-9-CM diagnosis code and excluded those with ICD-10-CM (late 2015). We calculated trends in anaphylaxis hospitalizations over time by age group, then used multivariable logistic regression to describe anaphylaxis hospitalizations among infants and toddlers. **Results:** Among infants and toddlers, there was no significant change in anaphylaxis hospitalizations during the 10-year study period (P trend =0.14). Anaphylaxis hospitalization among infants and toddlers was more likely in males, with private insurance, in the highest income quartile, with chronic pulmonary disease, who presented on a weekend day, to an urban teaching hospital, located in the Northeast. In contrast, anaphylaxis hospitalizations among older children (age 3 to <18 years) rose significantly during the study (P trend <0.001).

Conclusion: Anaphylaxis hospitalizations among infants and toddlers in the US were stable from 2006-2015, while hospitalizations among older children were rising. Future research should focus on the trends in disease prevalence and healthcare utilization in the understudied population of infants and toddlers.

INTRODUCTION

Anaphylaxis is a severe and potentially life-threatening acute allergic reaction (AAR) that can occur at any age.¹ The lifetime prevalence of anaphylaxis is likely rising², though little is known about the trends in healthcare utilization among children with anaphylaxis. Even less is known about the trends for the youngest children - infants and toddlers. Infants and toddlers are an understudied patient population with variable clinical presentation and high rates of food-induced anaphylaxis (FIA).^{3, 4}

The rising prevalence of food allergy and anaphylaxis has a significant impact on patients, families and our health care system.^{5, 6} Children with food allergies, and their parents, have decreased health-related quality of life.⁷ In 2007, the direct medical costs of food-induced acute allergic reactions (FAAR), including FIA, were estimated at \$225 million, with a large portion attributable to hospitalization.⁸ To more fully understand the trends in healthcare utilization for anaphylaxis among infants and toddlers, we used a nationally-representative database of US hospital inpatient stays to investigate the trends and predictors of hospitalization from 2006-2015.

METHODS

We conducted a study of the trends in anaphylaxis hospitalizations among infants and toddlers (age <3 years) in the US from 2006-2015. To maintain internal validity, we excluded data from the last quarter of 2015 after the transition to *International Classification of Diseases, Tenth Revision, Clinical Modification* (ICD-10-CM) coding.

Data Sources

We utilized data from the Healthcare Cost and Utilization Project (HCUP) National (Nationwide) Inpatient Sample (NIS),⁹ a nationally representative US database of hospital inpatient stays, maintained by the Agency for Healthcare Research and Quality (AHRQ). NIS is a large, publicly available, all-payer inpatient healthcare database. It provides US regional and national estimates of inpatient utilization, access, quality and outcomes. With weighting, it estimates more than 35 million hospitalizations annually, comprising more than 95 percent of all discharges in the U.S. This study was approved by the local Institutional Review Board.

Study population

We identified hospitalization diagnoses among infants and toddlers (age <3 years), and older children (age 3 to <18 years) by *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnosis codes as follows:

Anaphylaxis: anaphylactic shock due to unspecified food (995.60), anaphylactic shock due to specified food (995.61-995.69) and other anaphylactic shock (995.00). The anaphylaxis

definition corresponds to Method 1 of the previously validated algorithm by Harduar-Morano.¹⁰

This anaphylaxis definition includes FIA, in addition to other non-food triggers of anaphylaxis.

Acute allergy reaction (AAR): allergy unspecified (995.3), dermatitis due to ingested food (693.1), anaphylactic shock due to unspecified food (995.60), anaphylactic shock due to specified food (995.61-995.69) and other anaphylactic shock (995.00). This is the broadest category of allergic reaction. Overall AAR contains the codes for anaphylaxis, FAAR and FIA as well as additional codes related to allergic reactions.

Food-induced anaphylaxis (FIA): anaphylactic shock due to unspecified food (995.60) and anaphylactic shock due to specified food (995.61-995.69). FIA includes only the anaphylaxis codes directly related to FIA.

Food-induced acute allergic reaction (FAAR): dermatitis due to ingested food (693.1), anaphylactic shock due to unspecified food (995.60), anaphylactic shock due to specified food (995.61-995.69). Overall FAAR includes the codes for FIA and those within AAR that are associated with food-induced allergy.

These 4 categories of allergic reactions (anaphylaxis, AAR, FIA, FAAR) are not mutually exclusive but rather represent 4 groupings of ICD-9-CM codes based on potential reaction severity and trigger.

Outcomes

The primary outcome of the study was to characterize the temporal trend in US hospitalizations for anaphylaxis among infants and toddlers. Secondary outcomes were to characterize the trends in hospitalizations for overall AAR, FIA, and overall FAAR.

Covariates

We evaluated multiple covariates including patient demographics and hospital characteristics. Patient demographics include age, sex, race/ethnicity, primary payer, and median household income quartile.

Hospital characteristics include discharge quarter, hospitalization day (weekday vs. weekend), hospital region, hospital size, hospital status (rural or urban, teaching or non-teaching), endotracheal intubation or mechanical ventilation, number of procedures, length of stay (days), and hospital disposition (home, other medical facility, deceased, other). Use of endotracheal intubation and mechanical ventilation were identified by ICD-9-CM procedure codes 96.7 and 96.04, respectively. Chronic pulmonary disease was identified by the Chronic Condition Indicator (maintained by NIS) which allows for identification of a condition that was chronic and likely present prior to admission. Chronic conditions are then mapped to 18 different body systems, including respiratory diseases. The chronic condition indicator for pulmonary disease includes asthma and other chronic respiratory diseases. Admission to the intensive care unit (ICU) was not available in this dataset.

Statistical Analyses

All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC). Data are presented as proportions with 95% confidence intervals (95% CIs), or medians with interquartile ranges (IQR), as appropriate. We calculated the trends in the number of total hospitalizations per 100,000 visits by age group during the study period using appropriate survey weighting. All 2015 proportions were weighted to account for censoring of ICD-10-CM codes in the last quarter of 2015. To examine anaphylaxis hospitalizations, we performed multivariable logistic regression modeling comparing anaphylaxis hospitalizations to hospitalizations for other causes. We included multiple covariates in the model including year, age, sex, race/ethnicity, primary payer, median household income quartile, discharge quarter, hospitalization day (weekday vs. weekend), hospital region, hospital size, hospital status (rural or urban, teaching or non-teaching), endotracheal intubation or mechanical ventilation, history of chronic pulmonary disease, number of procedures, and length of stay (days). All P values were two-tailed, with $P < 0.05$ considered statistically significant.

RESULTS

Trends in hospitalization

Anaphylaxis hospitalizations among infants and toddlers remained stable at 10 per 100,000 visits in 2006 and 12 per 100,000 visits in 2015 ($P_{\text{trend}} = 0.14$) (**Figure 1**). Infants and toddlers hospitalized for FIA also remained stable at 7 per 100,000 visits in 2006 and in 2015 ($P_{\text{trend}} = 0.70$). A similar, stable trend was seen among infants and toddlers for hospitalized for AAR ($P_{\text{trend}} = 0.89$) and FAAR ($P_{\text{trend}} = 0.49$) (**Table 1, eTable 2**).

Conversely, among older children aged 3 to <6 years, 6 to <12 years, and 12 to <18 years, hospitalizations for anaphylaxis and AAR increased significantly over time (all groups $P_{\text{trend}} < 0.001$) (**Figure 2, eTable 1**). The highest absolute increase in anaphylaxis hospitalizations of 137 per 100,000 visits occurred in those aged 3 years to <6 years ($P_{\text{trend}} < 0.001$). FIA hospitalizations among children aged 6 to <12 years ($P_{\text{trend}} = 0.001$) and 12 to <18 years ($P_{\text{trend}} < 0.001$) also increased, while FIA hospitalizations in children aged 3 to <6 years remained stable ($P_{\text{trend}} = 0.06$).

Patient and Hospital Characteristics

The characteristics of infants and toddlers hospitalized for anaphylaxis changed over time. Anaphylaxis hospitalizations among non-Hispanic Black (NHB), Hispanic, publicly insured and those in the lowest income quartile increased during the 10-year study period (**Table 2**). Similarly, anaphylaxis hospitalization increased in those admitted on a weekend day, those in the

South region of the US, admitted to a large hospital and those with a history of chronic pulmonary disease.

Mechanical Ventilation, Procedures, Length of Stay and Disposition

There was no significant change in the trend of infants and toddlers requiring mechanical ventilation or endotracheal intubation during the study period ($P_{\text{trend}} = 0.09$). The median number of procedures remained stable at 0 throughout the study period ($P=0.44$). The median length of stay remained less than 1 day during the study period but was rising over time from 0.6 days (IQR: 0.2,0.9) in 2006 to 0.7 (IQR: 0.2, 1.3) in 2015 ($P<0.001$) (**Table 2**). The vast majority of patients were discharged home after hospitalization. There were a total of 5 deaths during the entire study period; due to low absolute numbers we were unable to calculate trends over time.

Anaphylaxis Hospitalizations

Among infants and toddlers, anaphylaxis hospitalization was more likely among males, those with private insurance, in the highest income quartile, admitted on a weekend day, in the Northeast, admitted at urban teaching hospitals, requiring mechanical ventilation or endotracheal intubation and with history of chronic pulmonary disease (**Table 3**). The number of procedures, but not the length of stay, was associated with anaphylaxis hospitalization.

DISCUSSION

Using a nationally representative database from 2006-2015, we found no change in anaphylaxis hospitalizations among infants and toddlers (age <3 years). We also found that there was no significant change in the trend of hospitalizations among infants and toddlers for overall AAR, FIA, and overall FAAR. In contrast, anaphylaxis hospitalization significantly increased among older children (age 3 to <18 years).

Trends in hospitalizations

Few studies have specifically focused on the trends in anaphylaxis hospitalization among infants and toddlers. Infants and toddlers with anaphylaxis are a unique and vulnerable population due to limited verbal skills and a variable, often non-specific clinical presentation; all of which pose a significant diagnostic challenge. Moreover, treatment of these small children can be complicated due to limited access to appropriate weight-based epinephrine autoinjectors.^{3, 11}

Previous studies investigating trends in anaphylaxis hospitalization (including FIA) among children have reported conflicting results, and data with a specific focus on infants and toddlers are sparse. Several studies find similar trends of stable or declining anaphylaxis hospitalizations, with most studies focusing specifically on FIA, as this is the most common trigger of anaphylaxis among children.^{3, 12, 13} Our group previously reported a stable hospitalization rate among the youngest children (age <2 years) for FIA using the nationally-representative HCUP Kids database from 2000-2009, despite a rising rate of hospitalization for FIA among older children.¹⁴ Similarly, using data from NIS, one study reported a stable rate of anaphylaxis

hospitalizations among children and adults from 2001-2014 with a rise seen only in children with food-related reactions aged 5-14 years.¹⁵ Using a large administrative database of privately insured children from 2005-2014, there was a significant decline in hospitalization for children presenting with FIA despite a rise in emergency department (ED) visits.¹⁶ However, there was no specific analysis of younger children, infants or toddlers. In contrast, one study reported rising rates of FIA hospitalizations and ED visits among all children using a database of hospitals in Illinois from 2008 to 2012.¹⁷ The highest rates occurred in children aged 0-4 years.

While the underlying reasons for the stable trends in anaphylaxis hospitalizations among infants and toddlers are not known, we propose a few possible explanations. We do not believe our findings are due to a decline in overall prevalence of anaphylaxis or overall AAR. While studies focusing specifically on infants and toddlers are limited, recent studies on the trends in prevalence of anaphylaxis and food allergy support a rising prevalence.^{5, 16-19} A stable trend in hospitalization among only infants and toddlers, in the setting of rising hospitalizations among older children, is likely to be the result of factors unique to infants and toddlers including changes in disease recognition, severity, management and healthcare utilization.

This diagnostic challenge of anaphylaxis may lead to under-diagnosis of anaphylaxis among infants and toddlers and thus, could potentially result in a falsely low report of hospitalizations.³ Anaphylaxis, even among older children, is often missed.⁴ The common symptomology of infant and toddler anaphylaxis, though not well defined, often includes non-specific symptoms.³ Many of the more severe features of anaphylaxis (e.g. cardiovascular collapse) appear to be rare, while

more mild cutaneous and gastrointestinal symptoms appear to be common.¹¹ This may suggest that the presentation of anaphylaxis among infants and toddlers is less severe and potentially even more susceptible to under-diagnosis. Our findings of few procedures and a low rate of mechanical ventilation during hospitalization generally support a mild severity of anaphylaxis among infants and toddlers. Thus, it is plausible that among infants and toddlers with anaphylaxis, the mild severity of reactions may make hospitalization unnecessary in many cases. These issues merit further investigation.

While there are currently no specific guidelines on infant anaphylaxis, intramuscular epinephrine is widely accepted as first-line treatment.^{1, 3} Delay in administration of epinephrine is associated with poor outcomes.^{20, 21} In fact, early and appropriate treatment with epinephrine has been shown to decrease risk of hospitalization.²² Over time, rates of epinephrine administration for anaphylaxis in general are increasing.^{23, 24} Little is known about the trends epinephrine administration among infants and toddlers. It is possible that due to a less severe presentation of anaphylaxis, improved rates of epinephrine treatment among infants and toddlers would have a greater impact. Other changes in patterns of healthcare utilization including use of ED observation units and urgent care centers may have evolved during the study period, but we are unable to fully assess these trends in the current study.

Importantly, our study was conducted prior to the publication and dissemination of both the paradigm shifting Learning Early About Peanut (LEAP) study (2015)²⁵ and the addendum NIH Food Allergy Guidelines (2017)²⁶ for primary prevention of peanut allergy through early

introduction of peanut. During our study period, many high-risk children probably were not exposed to allergenic foods as infants and toddlers, which could lead to fewer high-risk children having severe reactions at young ages. To more fully understand recent trends of anaphylaxis among infants and toddlers, it is imperative that we continue to study the trends in anaphylaxis in the era of early allergen introduction. This will be complicated by the ICD-10-CM transition in late 2015 but, with additional years of data, it may be possible to ascertain temporal changes despite this methodological challenge.

Patterns of patient and hospital characteristics

During the study period, the proportion of infants and toddlers hospitalized for anaphylaxis were rising among NHB, Hispanics, publicly insured and from the lowest income quartile. Despite these trends, white males with private insurance from the highest income quartile were the more likely have an anaphylaxis hospitalization. This observed shift may represent a change in demographics of food allergy or differences in access to care.²⁷ Racial/ethnic disparities have been associated with poor outcomes in anaphylaxis and differences in health care utilization in food allergy.^{28, 29}

Chronic pulmonary disease, which includes childhood asthma, was increasingly more common among infants and toddlers during the study period with anaphylaxis hospitalizations. This is consistent with prior studies that have shown asthma is associated with severe anaphylaxis.^{20, 30} Consistent with prior studies, we found the highest number of anaphylaxis hospitalizations in the Northeast.^{14, 31} However, hospitalizations were rising significantly over time in the South.

Mechanical Ventilation, Length of Stay, Procedures and Mortality

In the current study, the use of mechanical ventilation or endotracheal intubation was rare and stable over time among infants and toddlers. The median number of procedures throughout the study period was 0 ($P_{\text{trend}}=0.44$). This is consistent with a prior study which found children hospitalized with FAAR received few interventions during hospitalization.³² Despite a rising trend in length of stay (days), the median length of stay remained less than one day throughout the study period ($P<0.001$). This is consistent with prior studies showing a short length of stay for children admitted with AAR or FIA.^{14, 32, 33} These findings support a low severity of anaphylaxis among hospitalized infants and toddlers – or possibly a quick recovery. Cohort studies are needed to explore this important issue.

Potential Limitations

This study has several potential limitations. First, due to the use of administrative data, coding errors resulting diagnostic misclassification is possible. Based on prior studies, anaphylaxis is often under-diagnosed by ICD-9-CM codes and thus we expect that we may be reporting an underestimate of the trend in hospitalization for anaphylaxis.⁴ As previously discussed, the diagnostic challenges of infants and toddlers may compound this under-diagnosis. However, we found similar results using ICD-9-CM codes for less severe allergic reactions including overall AAR and overall FAAR. Due to the transition from ICD-9-CM and ICD-10-CM in late 2015, we have data only from the first 3 quarters of 2015; however, the overall trends in hospitalization among infants and toddlers are present prior to 2015 and weighted estimates were used.

Importantly, based on the nature of data in our study (hospitalization), we are unable to determine if the observed trends are due to change in prevalence or severity of anaphylaxis or changes in health care utilization. Due to limitations of the database, we are unable to accurately account for ICU admission as a marker of severity. In the future, use of other data sets (e.g. State Inpatient Database) and cohort studies will allow for more detailed study of these important topics.

Conclusion

Using nationally representative data, we found that anaphylaxis hospitalizations among infants and toddlers were stable from 2006-2015, in contrast to rising trends in older children. Anaphylaxis hospitalization among infants and toddlers, as compared to other causes of hospitalization, was more likely in males, with private insurance, in the highest income quartile, with chronic pulmonary disease, admitted on a weekend day, to an urban teaching hospital, and located in the Northeast. Future research should focus on underlying trends in prevalence, severity, and healthcare utilization patterns of infants and toddlers with anaphylaxis. As additional years of data become available, we encourage future research on the trends in anaphylaxis among infants and toddlers in the era of early allergen introduction (i.e., after landmark publications during 2015-2017).^{25,26} We anticipate sufficient data through 2019 will be available in late 2021. Our current study will be the benchmark by which we are able to compare future trends in the era of early allergen introduction.

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TABLES

Table 1. Hospitalizations for allergic reactions among infants and toddlers (age <3 years) in the US, 2006-2015

Diagnosis Group*	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Absolute change	P _{trend}
	Weighted admissions (95% CI) per 100,000 Visits											
Anaphylaxis	10 (6, 13)	10 (7, 12)	9 (6, 12)	10 (7, 13)	13 (8, 18)	8 (6, 10)	11 (8, 14)	12 (9, 15)	12 (9, 14)	12 (8, 15)	2	0.14
Overall AAR	21 (16,26)	20 (16,24)	20 (16,25)	20 (15,24)	25 (18,32)	19 (15,22)	21 (17,25)	21 (17,25)	21 (17,25)	20 (15,24)	-1	0.89
FIA	7 (4, 11)	7 (5, 9)	6 (4, 9)	7 (5, 10)	9 (5, 14)	6 (4, 7)	8 (6, 10)	9 (7, 11)	7 (5, 9)	7 (5, 9)	0	0.70
Overall FAAR	13 (9, 17)	13 (10,16)	12 (8, 15)	12 (9, 15)	14 (9, 20)	11 (8, 13)	13 (10,16)	13 (10,16)	12 (9, 14)	11 (8, 14)	-2	0.49

Abbreviations: ARR, acute allergic reaction; FIA, food-induced anaphylaxis; FAAR, food-induced acute allergic reaction

*Overall AAR includes codes for anaphylaxis, FIA and FAAR. Anaphylaxis include FIA and non-food related anaphylaxis. Overall FAAR includes FIA and other food-related codes.

Table 2. Patient and hospital characteristics of infants and toddlers (age <3 years) hospitalized for anaphylaxis in the US, 2006-2015

Characteristics	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Absolute change	P _{trend}
Weighted admissions per 100,000 population												
Age (< 3)	10	9	9	9	13	8	11	12	11	11	1	0.12
Sex												
Male	11	12	11	11	14	10	14	14	15	16	5	0.06
Female	8	6	7	7	12	5	8	10	8	6	-2	0.72
Race/Ethnicity												
Non-Hispanic White	12	11	10	8	13	7	10	10	10	8	-4	0.33
Non-Hispanic Black	8	8	11	12	5	6	14	17	19	18	10	0.002
Hispanic	3	4	7	10	16	7	8	10	11	15	12	<0.001
Other	11	9	8	10	15	11	16	14	10	9	-2	0.33
Primary Health Insurance												
Public	6	7	7	7	11	6	12	10	13	9	3	0.003
Private	14	10	12	11	16	11	12	15	11	15	1	0.72
Self-pay	4	6	2	15	10	3	3	6	5	4	0	0.82
Other	3	8	16	4	14	3	0	15	4	5	2	0.68
Median Household Income Quartile*												
1 (Lowest)	6	6	8	8	9	6	9	12	12	8	2	0.01
2	9	9	7	6	9	7	7	10	11	11	2	0.40
3	9	8	9	11	16	9	11	9	10	10	1	0.76
4 (Highest)	17	12	14	12	20	10	19	18	14	17	0	0.53
Discharge Quarter												
First quarter (Jan - Mar)	9	7	5	6	13	6	12	9	11	12	3	0.10
Second quarter (Apr - Jun)	15	12	11	11	12	8	10	13	14	14	-1	0.78

Third quarter (Jul - Sep)	7	8	10	10	14	8	12	12	11	8	1	0.24
Fourth quarter (Oct - Dec)	8	9	11	9	14	9	11	14	10	-	-	-
Admission on weekend												
No	9	8	8	8	12	6	9	10	10	10	1	0.42
Yes	14	11	13	15	18	15	21	20	18	16	2	0.03
Hospital Region												
Northeast	29	10	25	18	19	16	21	24	16	25	-4	0.96
Midwest	7	11	4	5	5	7	9	14	9	4	-3	0.70
South	6	9	4	7	9	7	8	8	13	10	4	0.02
West	5	5	10	11	22	4	12	9	9	11	6	0.25
Hospital Size†												
Small	14	14	7	7	27	4	14	9	9	12	-2	0.57
Medium	11	8	10	11	11	7	10	12	7	11	0	0.97
Large	8	8	9	9	12	9	11	13	15	11	3	0.01
Hospital Status												
Rural	6	4	4	3	6	3	2	2	5	3	-3	0.42
Urban non-teaching	4	5	5	6	5	5	5	4	2	3	-1	0.16
Urban teaching	15	13	13	13	21	11	17	19	15	15	0	0.35
Endotracheal Intubation or Mechanical Ventilation												
No	10	9	9	9	13	8	11	11	11	11	1	0.18
Yes	11	14	4	7	24	12	20	28	12	21	10	0.09
Chronic Pulmonary Disease												
No	9	8	8	8	11	7	10	10	11	10	1	0.16
Yes	78	123	166	138	210	68	191	244	160	239	161	0.02
Hospitalization Disposition												
Home	10	9	9	10	14	8	11	12	12	11	1	0.10

Other medical facility	4	4	9	0	4	0	6	0	6	8	4	NC
Deceased	25	0	0	0	0	0	0	0	0	0	0	NC
Other	13	16	10	3	0	0	17	9	15	0	0	NC
Number of Procedures on Discharge, median (IQR)	0	0	0	0	0	0	0	0	0	0	0	0.44
Hospitalization Length of Stay (days), median (IQR)	0.6 (0.2, 0.9)	0.7 (0.3, 1.4)	0.6 (0.3, 0.9)	0.7 (0.3, 1.3)	0.7 (0.3, 1.3)	0.7 (0.3, 1.5)	0.6 (0.1, 1.0)	0.7 (0.3, 1.2)	0.7 (0.3, 1.6)	0.7 (0.2, 1.3)	0.08	<0.001

Abbreviations: NC, non-calculable

*Median Household Income Quartile 1) 0-25th percentile, 2) 26th -50th percentile 3) 51st – 75th percentile 4) 76th – 100th percentile

†Hospital size is determined by bedsize and classified by hospital region and teaching status.

For 95% confidence intervals please see **eTable 2**.

Table 3. Anaphylaxis hospitalization among infants and toddlers (age <3 years) in the US, 2006-2015

Variable	aOR	95% Confidence Interval	P
Year	1.04	(1.01, 1.07)	0.02
Age	5.64	(5.18, 6.14)	< 0.001
Sex			
Male	1.00	(Reference)	
Female	0.61	(0.53, 0.71)	< 0.001
Race/Ethnicity			
Non-Hispanic White	1.00	(Reference)	
Non-Hispanic Black	1.12	(0.90, 1.39)	0.29
Hispanic	0.83	(0.67, 1.03)	0.09
Other	1.22	(1.02, 1.46)	0.03
Primary Payer			
Public	1.00	(Reference)	
Private	1.48	(1.27, 1.73)	< 0.001
Self-pay	0.86	(0.55, 1.34)	0.50
Other	0.80	(0.50, 1.28)	0.35
Median household income quartile*			
1 (lowest)	1.00	(Reference)	
2	1.12	(0.91, 1.38)	0.28
3	1.23	(1.00, 1.51)	0.05
4 (highest)	1.64	(1.33, 2.01)	< 0.001
Discharge Quarter			
First quarter (Jan - Mar)	1.00	(Reference)	
Second quarter (Apr - Jun)	1.56	(1.33, 1.85)	< 0.001
Third quarter (Jul - Sep)	1.48	(1.24, 1.77)	< 0.001
Fourth quarter (Oct - Dec)	1.33	(1.11, 1.60)	0.002
Admission on weekend			
No	1.00	(Reference)	
Yes	1.57	(1.37, 1.81)	< 0.001
Hospital Region			
Northeast	1.00	(Reference)	
Midwest	0.41	(0.31, 0.55)	< 0.001
South	0.40	(0.32, 0.50)	< 0.001
West	0.62	(0.46, 0.84)	0.002
Hospital Size†			
Small	1.00	(Reference)	
Medium	0.94	(0.64, 1.38)	0.75
Large	1.03	(0.72, 1.47)	0.88
Hospital Status			
Rural	1.00	(Reference)	
Urban non-teaching	1.13	(0.76, 1.67)	0.54
Urban teaching	2.58	(1.80, 3.69)	< 0.001
Endotracheal intubation or			

mechanical ventilation			
No	1.00	(Reference)	
Yes	4.49	(2.85, 7.05)	< 0.001
Chronic Pulmonary disease			
No	1.00	(Reference)	
Yes	2.21	(1.78, 2.73)	< 0.001
Number of procedures on discharge	0.63	(0.54, 0.75)	< 0.001
Hospitalization length of stay (days)	1.00	(0.96, 1.04)	0.93

Abbreviations: aOR, adjusted odds ratio

*Median Household Income Quartile 1) 0-25th percentile, 2) 26th -50th percentile 3) 51st – 75th percentile 4) 76th – 100th percentile

†Hospital size is determined by bedsize and classified by hospital region and teaching status.

FIGURE LEGENDS

Figure 1. Hospitalizations among infants and toddlers (age <3 years) by type of allergic reaction in the US, 2006-2015.

Abbreviations: AAR, acute allergic reaction; FAAR, food-induced acute allergic reaction; FIA, food-induced anaphylaxis

Overall AAR includes codes for anaphylaxis, FIA and FAAR. Anaphylaxis include FIA and non-food related anaphylaxis. Overall FAAR includes FIA and other food-related codes.

Figure 2. Anaphylaxis hospitalizations by age group among children (age <18 years) in the US, 2006-2015.

FIGURES

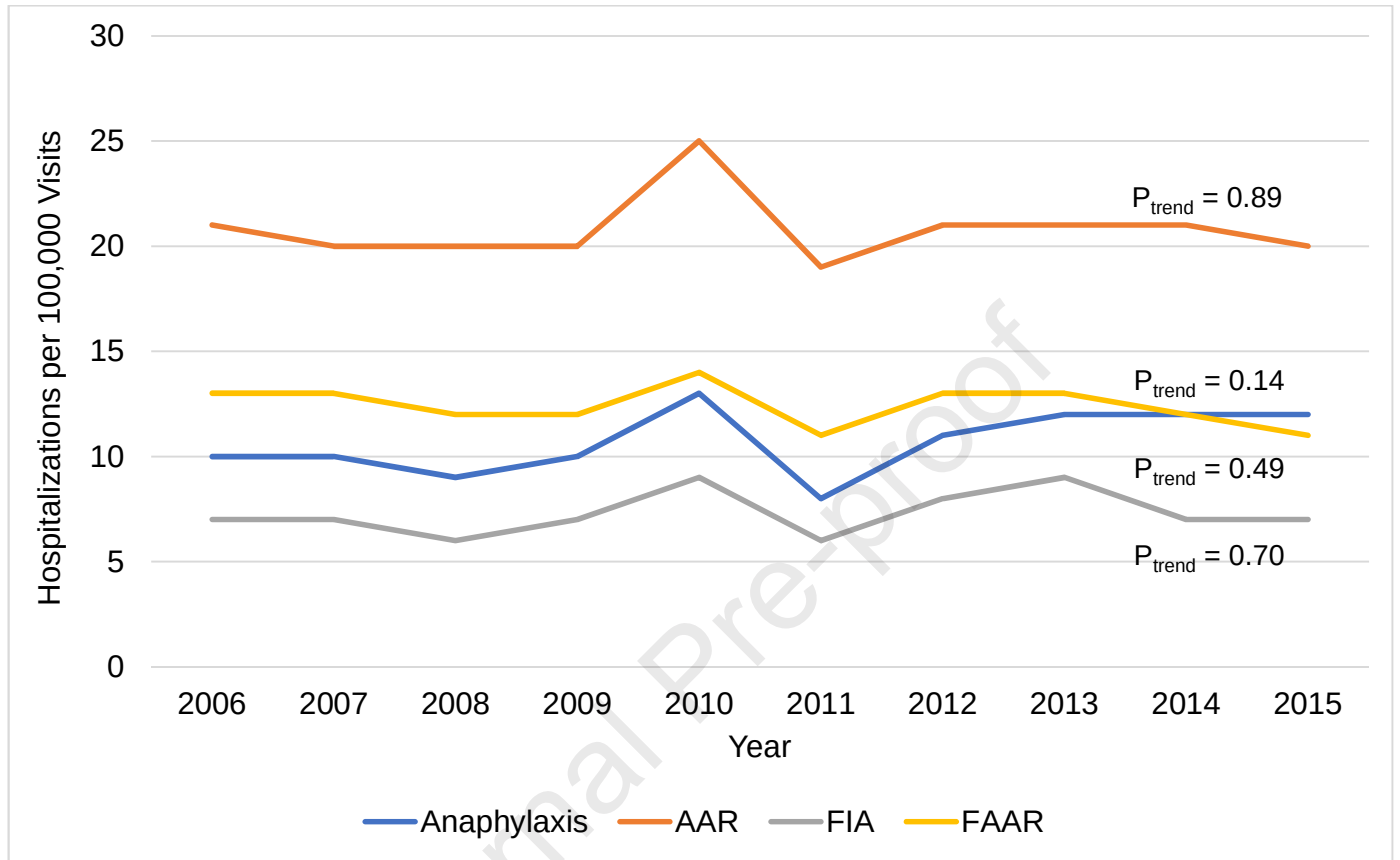
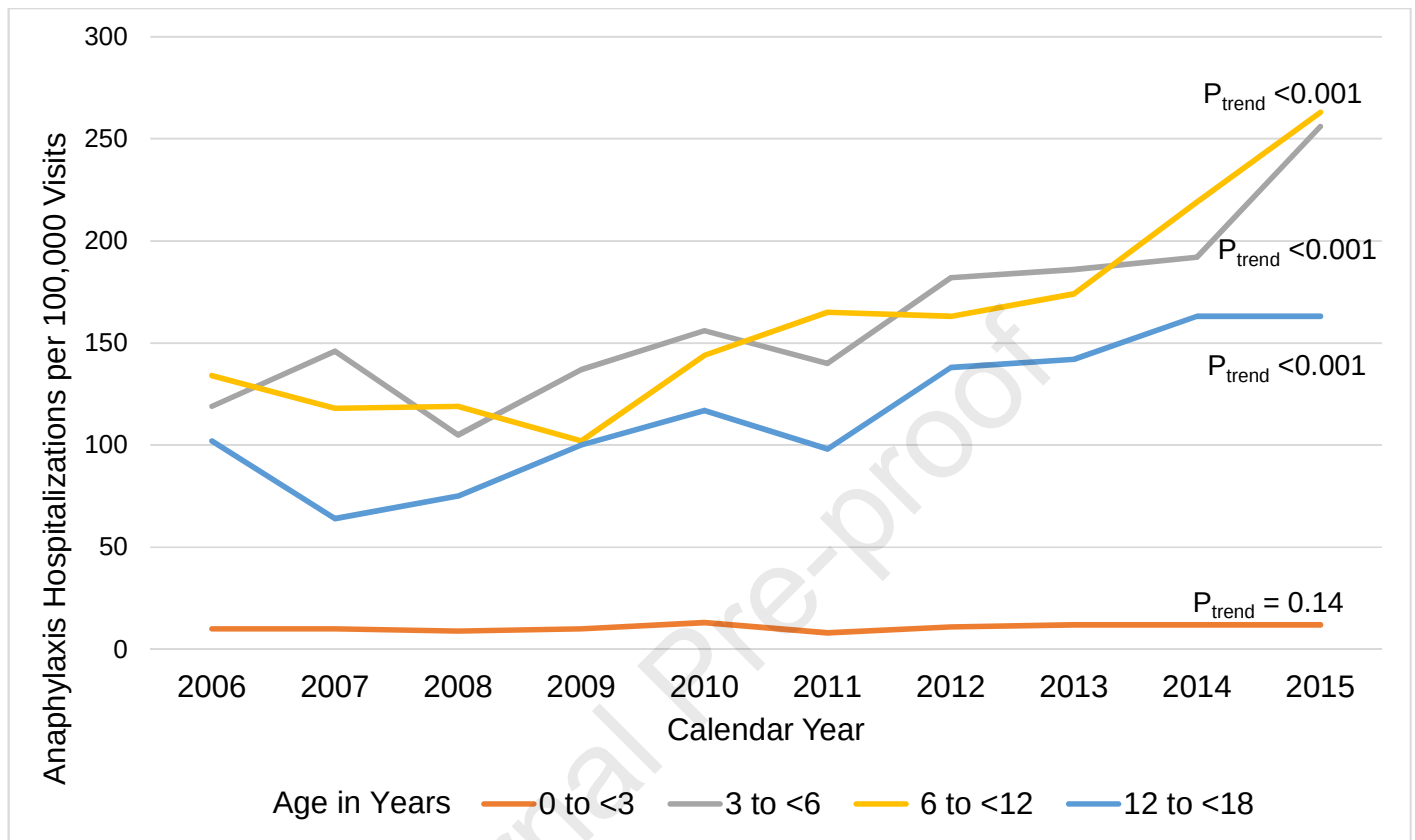
Figure 1.

Figure 2.

eTable 1. Hospitalizations for allergic reactions among children (age <18 years) in the US, 2006-2015

Age Group	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	P _{trend}
Weighted admissions (95% CI) per 100,000 visits											
Anaphylaxis											
0 to < 3	10 (6, 13)	10 (7, 12)	9 (6, 12)	10 (7, 13)	13 (8, 18)	8 (6, 10)	11 (8, 14)	12 (9, 15)	12 (9, 14)	12 (8, 15)	0.14
3 to < 6	119 (71,167)	146 (104,187)	105 (72,139)	137 (96,177)	156 (103,209)	140 (103,176)	182 (136,228)	186 (133,238)	192 (150,234)	256 (194,319)	< 0.001
6 to < 12	134 (83,185)	118 (80, 157)	119 (80,157)	102 (68,136)	144 (112,175)	165 (127,203)	163 (132,195)	174 (139,209)	219 (177,260)	263 (202,325)	< 0.001
12 to < 18	102 (69,135)	64 (44, 83)	75 (56, 94)	100 (73,127)	117 (88, 147)	98 (77, 118)	138 (114,162)	142 (117,166)	163 (137,189)	163 (135, 91)	< 0.001
Overall AAR											
0 to < 3	21 (16, 26)	20 (16, 24)	20 (16, 25)	20 (15, 24)	25 (18, 32)	19 (15, 22)	21 (17, 25)	21 (17, 25)	21 (17, 25)	20 (15, 24)	0.89
3 to < 6	231 (171, 290)	260 (201, 318)	204 (154, 254)	247 (186, 309)	261 (194, 327)	287 (231, 343)	339 (272, 405)	347 (265, 429)	329 (273, 385)	390 (311, 469)	< 0.001
6 to < 12	272 (210, 335)	222 (173, 271)	227 (173, 280)	237 (183, 290)	279 (212, 347)	320 (258, 382)	349 (276, 422)	311 (256, 365)	361 (308, 414)	404 (331, 476)	< 0.001
12 to < 18	188 (140, 235)	129 (104, 154)	130 (107, 153)	180 (147, 213)	232 (158, 305)	231 (162, 299)	260 (213, 307)	245 (210, 280)	241 (209, 274)	236 (203, 269)	< 0.001
FIA											
0 to < 3	7 (4, 11)	7 (5, 9)	6 (4, 9)	7 (5, 10)	9 (5, 14)	6 (4, 7)	8 (6, 10)	9 (7, 11)	7 (5, 9)	7 (5, 9)	0.70
3 to < 6	74 (25, 122)	79 (48, 110)	66 (36, 97)	90 (58, 121)	100 (65, 135)	88 (56, 119)	128 (91, 166)	102 (65, 138)	100 (68, 133)	104 (65, 143)	0.06
6 to < 12	74 (33, 114)	53 (32, 74)	56 (31, 80)	51 (30, 71)	55 (35, 74)	82 (54, 110)	87 (65, 109)	79 (56, 102)	108 (77, 139)	134 (95, 173)	0.001
12 to < 18	46 (31, 62)	24 (14, 34)	37 (26, 49)	44 (25, 62)	50 (33, 66)	35 (23, 47)	52 (39, 66)	47 (34, 61)	73 (55, 90)	60 (43, 77)	< 0.001
Overall FAAR											
0 to < 3	13 (9, 17)	13 (10, 16)	12 (8, 15)	12 (9, 15)	14 (9, 20)	11 (8, 13)	13 (10, 16)	13 (10, 16)	12 (9, 14)	11 (8, 14)	0.49
3 to < 6	111 (57, 166)	100 (65, 135)	108 (68, 148)	121 (82, 159)	124 (87, 161)	128 (89, 168)	161 (121,201)	134 (91, 176)	119 (82, 155)	152 (105,200)	0.09
6 to <12	104 (59, 149)	76 (50, 102)	81 (50, 112)	75 (49, 101)	65 (44, 87)	111 (77, 144)	109 (83, 134)	106 (78, 133)	136 (101,171)	158 (116,199)	0.005
12 to <18	60 (43, 78)	34 (22, 47)	45 (32, 58)	53 (35, 72)	59 (40, 77)	42 (29, 55)	61 (46, 76)	56 (41, 70)	80 (62, 99)	69 (51, 87)	0.01

Abbreviations: Overall ARR, acute allergic reaction; FIA, food-induced anaphylaxis; Overall FAAR, food-induced acute allergic reaction

Overall AAR includes codes for anaphylaxis, FIA and FAAR. Anaphylaxis include FIA and non-food related anaphylaxis. Overall FAAR includes FIA and other food-related codes.

Small	14 (2, 27)	14 (5, 22)	7 (1, 13)	7 (0, 15)	27 (0, 74)	4 (0, 8)	14 (6, 23)	9 (3, 14)	9 (3, 14)	12 (2, 23)	0.57
Medium	11 (0, 21)	8 (4, 12)	10 (5, 15)	11 (4, 18)	11 (3, 19)	7 (3, 11)	10 (4, 17)	12 (7, 16)	7 (4, 10)	11 (6, 16)	0.97
Large	8 (5, 12)	8 (5, 11)	9 (5, 14)	9 (6, 12)	12 (8, 16)	9 (6, 12)	11 (8, 14)	13 (9, 17)	15 (11,19)	11 (7, 14)	0.01
Hospital Status											
Rural	6 (1, 10)	4 (1, 8)	4 (1, 8)	3 (0, 6)	6 (0, 11)	3 (0, 7)	2 (0, 5)	2 (0, 5)	5 (0, 10)	3 (0, 8)	0.42
Urban non-teaching	4 (2, 7)	5 (3, 8)	5 (3, 8)	6 (3, 9)	5 (2, 8)	5 (2, 7)	5 (2, 7)	4 (2, 6)	2 (0, 5)	3 (0, 6)	0.16
Urban teaching	15 (8, 22)	13 (9, 17)	13 (7, 19)	13 (8, 19)	21 (11,31)	11 (8, 15)	17 (12,22)	19 (14,24)	15 (12,19)	15 (11,19)	0.35
Endotracheal Intubation or Mechanical Ventilation											
No	10 (6, 14)	9 (6, 11)	9 (6, 12)	9 (6, 12)	13 (7, 18)	8 (6, 10)	11 (8, 14)	11 (9, 14)	11 (9, 14)	11 (8, 14)	0.18
Yes	11 (0, 22)	14 (1, 26)	4 (0, 11)	7 (0, 18)	24 (7, 42)	12 (0, 25)	20 (3, 37)	28 (8, 48)	12 (0, 25)	21 (1, 42)	0.09
Chronic Pulmonary Disease											
No	9 (5, 13)	8 (6, 10)	8 (5, 10)	8 (5, 11)	11 (7, 16)	7 (5, 10)	10 (7, 12)	10 (8, 13)	11 (8, 13)	10 (7, 13)	0.16
Yes	78 (27,130)	123 (43,203)	166 (66,266)	138 (61,214)	210 (96,324)	68 (1,135)	191 (75,306)	244 (116, 372)	160 (57, 262)	239 (92, 386)	0.02
Hospitalization Disposition											
Home	10 (6, 14)	9 (6, 11)	9 (6, 12)	10 (7, 13)	14 (8, 19)	8 (6, 11)	11 (8, 14)	12 (9, 15)	12 (9, 14)	11 (8, 15)	0.10
Other medical facility	4 (0, 12)	4 (0, 12)	9 (0, 23)	0	4 (0, 13)	0	6 (0, 17)	0	6 (0, 17)	8 (0, 23)	NC
Deceased	25 (0, 74)	0	0	0	0	0	0	0	0	0	NC
Other	13 (1, 24)	16 (2, 31)	10 (0, 21)	3 (0, 8)	0	0	17 (0, 33)	9 (0, 22)	15 (0, 31)	0	NC
Number of Procedures on Discharge, median (IQR)	0	0	0	0	0	0	0	0	0 (0, 0.32)	0 (0, 0.31)	0.44
Hospitalization Length of Stay (days), median (IQR)	0.6 (0.2, 0.9)	0.7 (0.3, 1.4)	0.6 (0.3, 0.9)	0.7 (0.3, 1.3)	0.7 (0.3, 1.3)	0.7 (0.3, 1.5)	0.6 (0.1, 1.0)	0.7 (0.3, 1.2)	0.7 (0.3, 1.6)	0.7 (0.2, 1.3)	0.08

Abbreviations: NC, non-calculable

*Median Household Income Quartile 1) 0-25th percentile, 2) 26th -50th percentile 3) 51st – 75th percentile 4) 76th – 100th percentile

†Hospital size is determined by bedsize and classified by hospital region and teaching status.