ORIGINAL REPORT

Estimating pediatric inpatient medication use in the United States

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ABSTRACT

Purpose We demonstrated the feasibility of developing national estimates of pediatric inpatient medication use by analyzing data from a large administrative database.

Methods Pediatric inpatient data were extracted from Premier Perspective® database to calculate the prevalence of use of specific medications among hospitalized children in 2008. The database was validated by comparing characteristics to the HCUP KID sample of pediatric hospitalizations for 2006. Prevalence was calculated by categorizing patients as ever or never having received a specific drug.

Results The 10 drugs administered in the most pediatric hospitalizations were acetaminophen, lidocaine, ampicillin, gentamicin, fentanyl, ibuprofen, morphine, ondansetron, ceftriaxone, and albuterol.

Conclusions Although the database is not a probability-based sample, it bears sufficient similarity to a probability-based sample of pediatric hospitalizations (HCUP KID) to serve as a starting point in developing national estimates of inpatient pediatric medication use. Over 500 drug entities were administered to hospitalized children, but most are used by small percentages of hospitalized patients. The small numbers of children using any one drug has implications for efforts to study efficacy and safety, describe off-label use, monitor adverse events, describe practice, and conduct comparative effectiveness research. Copyright © 2010 John Wiley & Sons, Ltd.

KEY WORDS — children; pediatric; medication; prescription drug; utilization; hospital; inpatient

BACKGROUND

Concern about medication use in children has led to a range of policy efforts addressing the need for improved pediatric drug labeling, inclusion of children in drug trials, and the special metabolic and dosage issues pertaining to pediatric pharmacology.[1–8] In order to accomplish this agenda, it is desirable to obtain national estimates of pediatric medication use, and description of variables affecting use of medications in children. Such descriptive data may be more critical in children than in adults, because of the high level of off-label prescribing (a corollary to inadequate labeling), and the lack of clinical studies to inform guidelines and labeling. Further, the smaller numbers of children using medications compared to adults necessitates the identification of pediatric patients from multiple hospitals and the ability to generalize beyond individual hospitals. In this study, we demonstrate the feasibility of developing national estimates of pediatric inpatient medication use by analyzing data from a large administrative database. The analysis presented in this paper is an expansion of an earlier analysis using a single hospital system, Alfred I. DuPont Hospital for Children Nemours clinics.[9] The earlier analysis relied on data from 2000 to 2003 to prepare estimates of inpatient medication use, and was used to inform implementation of the Best Pharmaceuticals for Children Act.[10]

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METHODS

We used pediatric inpatient data extracted from Premier Perspective® database to calculate the prevalence of use of specific medications among hospitalized children in 2008. The database is the largest clinical and operational comparative data warehouse in the nation and comprises one-sixth of all hospital discharges in the nation. We validated the Premier Perspective® sample of hospitalizations by comparing characteristics of the sample to the HCUP KID sample of pediatric hospitalizations for 2006. The Kids' Inpatient Database (KID) is one of a family of databases and software tools developed as part of the *Healthcare Cost and Utilization Project* (HCUP), and is a national, probability-based sample, with an un-weighted total of 3 131 324 pediatric discharges. We compared the Premier Perspective® sample to the HCUP KID sample on the following patient characteristics: gender, major diagnostic category, admission source, and admission type, length of stay, disposition, APR-DRG disease severity score, and APR-DRG mortality risk score and on the following hospital characteristics: teaching versus non-teaching, urban versus rural, bed size region of the country. The HCUP data on race/ethnicity have large blocks of missing data for different states, and we did not compare the distribution of racial/ethnic groups in the HCUP sample to the Premier Perspective® sample.[11] Patients were categorized as ever or never having received a specific drug and prevalence (percentage) was calculated as the number of patients receiving a drug per 100 patients. Dose and number of doses were not considered in these analyses. Stratified prevalence estimates of medication use were calculated within gender, race/ethnic group, and age categories. The study proposal received exempt review by the University of Rhode Island Institutional Review Board. Statistical analysis was carried out using SAS 9.2 (Cary, North Carolina).

RESULTS

The dataset contained records for 877 201 hospitalizations of children under 18 at the time of admission with 50 879 (5.8%) being repeat admissions. A total of 12 040 196 medication charges for these stays were identified. After calculating an overall prevalence for each entity, we removed entities with less than 0.01% prevalence of use, leaving a list of 568 unique drugs or drug combinations. The study population was 50.9% male and 49.1% female, 48.5% white, 16.1% African-American, 12.2% Hispanic, 3.6% Asian/Pacific

Table 1. Characteristics of pediatric hospitalizations in the Premier Perspective® 2008 sample and the HCUP KID 2006 sample[*]

	Premier Perspective® 2008	HCUP KID 2006
Sex		
Male	50.9%	51.1%
Source of admission		
Routine including births and other sources	72.0%	78.3%
Other hospital or healthcare facility	13.7%	3.6%
Emergency department	14.8%	18.2%
Type of admission		
Emergency, urgent, trauma, other	23.7%	29.8%
Elective	8.3%	8.7%
Newborn	67.5%	61.5%
Discharge status		
Routine	94.0%	93.9%
Died	0.4%	0.4%
Other	5.6%	5.7%
APR DRG severity		
Minor	70.0%	69.4%
Moderate	22.1%	22.2%
Major	6.3%	6.7%
Extreme	1.4%	1.7%
APR DRG risk of mortality		
Minor	94.6%	93.7%
Moderate	3.4%	4.3%
Major	1.2%	1.3%
Extreme	0.5%	0.6%
Payer		
Medicare/medicaid/other government payer	45.9%	44.3%
Private insurance	46.2%	47.5%
Other	7.9%	8.0%
Mean length of stay		
Days	3.7	3.7
Region		
Midwest	18.7%	21.7%
Northeast	14.3%	17.0%
South	48.7%	38.0%
West	18.3%	23.3%
Teaching status		
Teaching hospital	41.5%	53.3%
Urban vs. rural		
Urban	89.2%	87.5%
Bed size		
Small	10.3%	12.3%
Medium	17.9%	26.7%
Large	71.8%	59.5%

[*]95% Confidence intervals are not displayed because they were extremely narrow around all estimates. For example, the estimate of the percentage of hospitalizations at teaching hospitals in the Premier Perspective® was 41.46 and the 95% confidence limits of the estimate were 41.37 to 41.57. In the HCUP sample the estimate for percentage of hospitalizations at teaching hospitals was 53.33% and the 95% confidence limits of the estimate were 51.80–54.86.

Islander, 18.7% other, and less than 1% American Indian. The average length of stay was 3.7 days. Private insurance paid for 46.2% of the hospital stays, government paid for 45.9% and self-pay, no charge, or other sources accounted for 7.9% of the hospital stays. Most of the hospitalizations took place in urban areas (89.2%) compared to rural areas (10.8%).

Both the Premier Perspective® sample in 2008 and the HCUP KID 2006 are large samples with extremely narrow confidence intervals around estimates of proportions when the sample is unstratified. For example, the estimate of the percentage of hospitalizations at teaching hospitals in the Premier Perspective® was 58.53 and the 95% confidence limits of the estimate were 58.42–58.63. In the HCUP sample, the estimate for percentage of hospitalizations at teaching hospitals was 53.33% and the 95% confidence limits of the estimate were 51.80–54.86. Thus, small as well as large differences in characteristics between the two datasets were statistically significant (Table 1). The largest absolute differences between the Premier Perspective® sample in 2008 and the KID national probability sample were in the source of admission, region of the country, teaching status of hospital, and bed size. The Premier Perspective® sample included a greater proportion of infants born in the hospital, from Southern hospitals, from non-teaching hospitals, and from large size hospitals compared to the HCUP KID sample. The two samples were similar with regard to proportions of male, routine discharge status, APR-DRGs severity, and proportions of urban. Age distributions were similar in both samples (Figure 1).

The 10 drugs administered in the most pediatric hospitalizations were acetaminophen, lidocaine, ampicillin, gentamicin, fentanyl, ibuprofen, morphine, ondansetron, ceftriaxone, and albuterol (Table 2). Acetaminophen was administered in 14.7% (95%CI 13.9–15.6) of hospitalizations in the Premier Perspective® database, and albuterol was administered in 5.1% (95% CI 5.0–5.2) of pediatric hospitalizations. Only two

drugs were used in more than 10% of all the hospitalizations in the database; acetaminophen was used in 14.7% of pediatric hospitalizations, and lidocaine was used in 11.0% of pediatric hospitalizations. Another 51 drugs were used in 1% or more and less than 10% of pediatric hospitalizations (Table 3), and 240 drugs were used in 0.1% or more and less than 1% of pediatric hospitalizations. All other drug entities were used in fewer than 0.1% of pediatric hospitalizations.

The 10 drugs administered in the most hospitalizations varied by pediatric sub-age group (Table 4). In children under 2, the 10 most frequently received medications were acetaminophen, lidocaine, ampicillin, gentamicin, ceftriaxone, albuterol, cefotaxime, fentanyl, lidocaine/prilocaine, and ibuprofen. In children 12–17 years of age, the 10 most frequently received drugs were ondansetron, fentanyl, acetamiophen, morphine, ibuprofen, oxytocin, lidocaine, midazolam, propofol, and ketorolac. Ranking and prevalence of use of specific medications changed over age sub-groups (Figure 2). For example, while acetaminophen ranked first in age groups under 2, 2–4, and 5–11, the percentages of hospitalizations with use of acetaminophen was 10.3, 39.7, and 34.9 in these age sub-groups, respectively. In the age group 12–17, acetaminophen ranked third, administered in 28.7 of hospitalizations in this age group.

DISCUSSION

We explored the Premier Perspective® dataset potential as a resource for developing national estimates of inpatient pediatric medication use. Although the database is not a probability-based sample, we compared the sample characteristics to a probability-based sample of pediatric hospitalizations (HCUP KID) to identify similarities and differences to the United States pediatric population. Because of the

Table 2. Top 10 drugs in national sample compared to single hospital system

Nemours system 2000–2003	Per 100	Premier, Inc. 2008	Per 100	95% CI of prevalence estimate
Acetaminophen	40.5	Acetaminophen	14.7	13.9–15.6
Midazolam	26.0	Lidocaine	11	10.6–11.5
Morphine	24.4	Ampicillin	8	7.8–8.3
Albuterol	22.4	Gentamicin	6.6	6.5–6.8
Acetaminophen-Codeine	22.4	Fentanyl	6.6	6.4–6.7
Cefazolin	16.7	Ibuprofen	6.3	6.2–6.5
Ondansetron	15.7	Morphine	6.2	6.1–6.4
Ranitidine	15.1	Ondansetron	6.2	6.0–6.3
Ibuprofen	10.1	Ceftriaxone	5.6	5.5–5.7
Amoxicillin	9.2	Albuterol	5.1	5.0–5.2

Table 3. Drug entities used in at least 1% of all pediatric hospitalizations

Drug name	Prevalence per 100	95%CI	
Acetaminophen	14.735	13.888	15.582
Lidocaine	11.013	10.551	11.475
Ampicillin	8.015	7.780	8.250
Gentamicin	6.649	6.491	6.806
Fentanyl	6.559	6.406	6.712
Ibuprofen	6.319	6.178	6.460
Morphine	6.226	6.090	6.362
Ondansetron	6.157	6.024	6.290
Ceftriaxone	5.638	5.528	5.747
Albuterol	5.075	4.989	5.162
Midazolam	4.536	4.469	4.604
Propofol	4.123	4.069	4.176
Cefazolin	2.881	2.859	2.904
Ranitidine	2.877	2.854	2.899
Diphenhydramine	2.859	2.836	2.881
Dexamethasone	2.546	2.529	2.562
Lidocaine/prilocaine	2.526	2.510	2.542
Cefotaxime	2.435	2.421	2.450
Ketorolac	2.361	2.347	2.374
Methylprednisolone sodium	2.317	2.304	2.330
Vancomycin	2.254	2.242	2.266
Oxytocin	2.174	2.163	2.184
Rocuronium	2.136	2.125	2.146
Clindamycin	2.123	2.113	2.133
Heparin	2.112	2.102	2.121
Hydrocodone/acetaminophen	2.068	2.059	2.078
Bacitracin	2.035	2.026	2.044
Glycopyrrolate	2.023	2.015	2.032
Acetaminophen/codeine	2.006	1.997	2.014
Prednisol	1.970	1.962	1.978
Metoclopramide	1.956	1.948	1.964
Ipratropium	1.918	1.911	1.926
Bupivacaine	1.868	1.861	1.875
Levalbuterol	1.846	1.839	1.852
Azithromycin	1.816	1.810	1.822
Furosemide	1.715	1.710	1.720
Lorazepam	1.664	1.659	1.669
Promethazine	1.640	1.636	1.645
Budesonide	1.600	1.596	1.604
Nystatin	1.568	1.564	1.572
Neostigmine	1.560	1.557	1.564
Oxycodone/aspirin	1.468	1.465	1.471
Famotidine	1.455	1.452	1.458
Desitin	1.446	1.444	1.449
Epinephrine	1.396	1.394	1.398
Succinyl choline	1.171	1.170	1.172
Hydromorphone	1.134	1.134	1.135
Lidocaine cardiac	1.083	1.082	1.083
Lansoprazole	1.043	1.043	1.043
Montelukast	1.020	1.020	1.020
Palivizumab	1.014	1.014	1.014

large size of both databases, differences of a few percentage points are statistically significant, but it is not clear if such differences require adjustment when estimating medication use. We noted differences between Premier Perspective® and the KID in hospital size, teaching status, regionality, and admission source but do not yet know if these variables are associated with probability of receiving a specific drug. For this

Table 4. Top 10 most frequently used drugs by age group

| Under 2		2–4 years		5–11 years		12–17 years	
Acetaminophen	10.30 (9.85–10.75)	Acetaminophen	39.70 (6.73–72.67)	Acetaminophen	34.95 (13.65–56.24)	Ondansetron	30.12 (18.91–41.33)
Lidocaine	9.81 (9.41–10.22)	Ceftriaxone	29.44 (11.47–47.40)	Ondansetron	30.17 (14.37–45.96)	Fentanyl	29.56 (18.77–40.35)
Ampicillin	9.09 (8.74–9.43)	Albuterol	25.55 (12.09–39.01)	Morpine	25.47 (14.28–36.66)	Acetaminophen	28.70 (18.54–38.86)
Gentamicin	7.46 (7.24–7.69)	Ibuprofen	23.19 (12.15–34.24)	Fentanyl	21.28 (13.53–29.02)	Morphine	27.64 (18.23–37.05)
Ceftriaxone	3.41 (3.37–3.45)	Ondansetron	19.37 (11.73–27.01)	Ceftriaxone	19.06 (12.88–25.24)	Ibuprofen	26.26 (17.79–34.74)
Albuterol	3.08 (3.05–3.11)	Morphine	15.16 (10.55–19.77)	Propofol	18.89 (12.83–24.96)	Oxytocin	19.33 (14.80–23.86)
Cefotaxime	2.48 (2.47–2.50)	Prednisol	14.66 (10.36–18.95)	Ibuprofen	18.44 (12.67–24.21)	Lidocaine	18.85 (14.55–23.15)
Fentanyl	2.13 (2.12–2.14)	Fentanyl	13.84 (10.03–17.65)	Midazolam	17.44 (12.29–22.58)	Midazolam	18.23 (14.22–22.24)
Lidocaine/prilocaine	2.10 (2.09–2.11)	Methylprednisolone sodium	13.28 (9.78–16.78)	Albuterol	17.29 (12.23–22.34)	Propofol	17.00 (13.52–20.47)
Ibuprofen	2.02 (2.01–2.03)	Midazolam	13.02 (9.66–16.37)	Lidocaine	13.85 (10.65–17.04)	Ketorolac	14.66 (12.10–17.23)
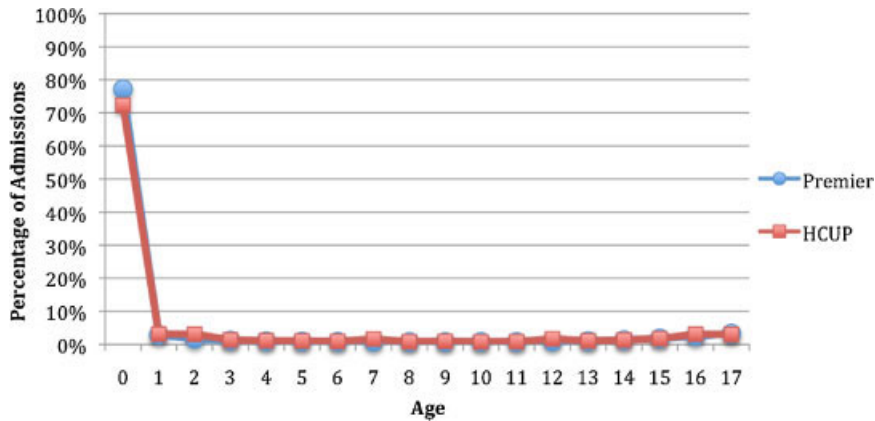
Figure 1. Age distribution in Premier Perspective® 2008 database and in HCUP KID 2006 sample

analysis, we did not adjust medication estimates with respect to variables differing between the two databases, but these variables may be of importance in future analyses. We did not compare the proportions of different racial and ethnic groups in Premier Perspective® to the KID because of well-documented limitations in racial and ethnic data within the KID, high rates of missing data resulting from state differences in collection and reporting of race and ethnicity.[11] It should also be noted, that the KID refers to hospitalizations in 2006, and we used Premier Perspective® data from 2008; KID data are released every 3 years, and KID data for 2009 have not yet been released.

The work presented here is a continuation of work begun in an earlier study of the Nemours system medication data for 2000–2003.[9] As with the earlier

analysis, we found a large number of drug entities administered to hospitalized children (well over 700 in both analyses). Although many different drugs are used, most are used by small percentages of the hospitalized patients. In terms of estimating exposure, or potential patients for a clinical trial, we can say that if a drug is not listed in Table 3, it was used in fewer than 1% of all pediatric hospitalizations, or fewer than 65 000 pediatric hospitalizations in a single year throughout the United States. For drugs used in fewer than 0.1% of all pediatric hospitalizations, fewer than 6500 children might be available for clinical or observational studies. As with the earlier analysis, patterns of medication use change greatly with age groups, and the direction of change (increases and decreases) and the type of change (linear, U-shaped, or other) appear to be specific to each drug. For example,
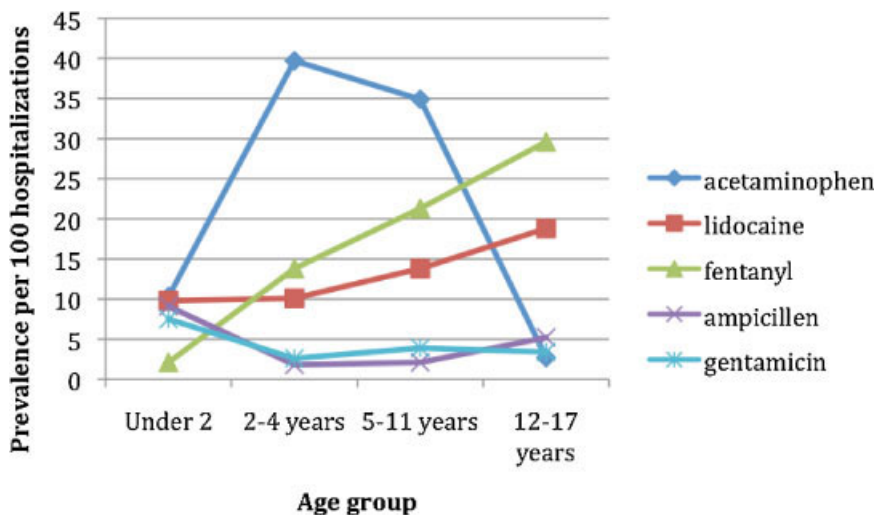

Figure 2. Five medications used in the most pediatric hospitalizations in 2008, prevalence by age group

use of fentanyl appears to increase linearly with age group, while acetaminophen increases and then decreases sharply. This suggests the importance of studying variation and determinants within age sub-groups, placing further constraints on sample size availabilities.

Several drugs were found in common in the top 10 drugs in the Nemours system and in the Premier Perspective® database: acetaminophen, morphine, albuterol, ondansetron, and ibuprofen, but usage of each drug was higher in the Nemours system than in the Premier Perspective® database. A recent study at a single hospital in Wisconsin reported the five medications with highest exposure rates to be acetaminophen, ranitidine, morphine, fentanyl, and propofol, but their study was restricted to patients admitted to the pediatric intensive care unit.[12] It was not the purpose of this study to explain differences between the large sample and any particular single hospital system, but these observations may indicate the extent to which patient characteristics, disease prevalence, and practice may vary across hospitals. It also indicates the limitations of using individual hospital systems, or individual units as sources of usage estimates for much larger populations such as the United States.

By definition, the analyses presented in this paper were limited to medication used in the inpatient setting. Other sources are necessary to describe outpatient use and to characterize the range of behaviors from physician prescribing, purchases of medications, and patient recall regarding medications used. Studies of outpatient use range from surveys through random-digit dialing to analyses of pharmacy claims databases.[13–15] We also did not attempt to quantify medication dose and number of administrations, but categorized patients as having ever received the medication during the hospital stay. Others have explored various measures of use ranging from defined daily doses, prescribed daily doses, days of drug use per 100 patient days, and number of doses administered/1000 patient days.[16,17] Further studies are also needed to describe the amount of off-label drug use in the pediatric inpatient setting.[18]

Accurate estimates of children exposed to specific drugs may be required for a variety of research and policy needs, including planning clinical trials, calculations of denominators for observational studies of efficacy and safety, descriptions of practice variation, efforts to curb anti-biotic use, and numerous other situations. Attainment of accurate estimates pose several challenges, including the smaller number of children in the population compared to adults, and the

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KEY POINTS

- Newly emergent databases permit calculation of national estimates of pediatric inpatient medication use.
- The 10 medications received by the most hospitalized children in 2008 were acetaminophen, lidocaine, ampicillin, gentamicin, fentanyl, ibuprofen, morphine, ondansetron, ceftriaxone, and albuterol.

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smaller number of children receiving medications compared to adults. The advent of large multi-system databases provides an unexplored opportunity to describe pediatric medication use on a scale not done previously.

CONFLICT OF INTEREST

The authors report no conflict of interest.

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