UNIVERSITÀ DEGLI STUDI DI TORINO

Adverse events in hospitalized pediatric patients: a systematic review and a meta-regression analysis

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ABSTRACT

Objectives. To gain insight into the incidence of pediatric adverse events (AEs); to assess if there are significant differences among study results and to what extent methodological issues can explain them.

Methods. From November 2012 to January 2013, systematic literature searches were conducted on PubMed, Scopus and the Cochrane Library. We selected studies from 1970 onwards that evaluated the incidence of AEs in hospitalized pediatric patients and included a minimum of 1000 patient records with the same definition of AE. Studies that reported only specific AEs or only a specific ward were not considered. Data were extracted on the method of data collection, study design, type of hospital, and the timing of the AE in relation to its discovery and the index admission (time frame). AE incidence and preventability were considered.

Results. The pooled incidence of AEs was 2.0% (95%CI: 1.3%-3.0%). Five methodological differences among studies were taken into account. Only the time frame of detected events had a statistically significant effect on the incidence of AEs ($p<0.0001$). The pooled incidence of preventable AEs was 46.2% (95% CI: 35.3%-57.5%) with a high variability among studies.

Conclusions. Our meta-analysis confirms that AEs are a major public health issue. Although studies use the same definition of adverse event, the reported incidence of AEs and preventable AEs varied considerably. To direct prevention efforts properly, studies methodologically more homogeneous and more detailed about the standard of health care provided and the health system organization, are needed.

INTRODUCTION

In literature, an adverse event (AE) is usually defined as an unintended injury or complication resulting in a prolonged hospital stay, disability at the time of discharge, or death caused by healthcare management rather than the patient's underlying disease process (1, 2).

Adverse events are widely agreed to be a serious problem with severe consequences on the patient safety (3) and they pose an economic burden on healthcare system as well, since high rates of AEs are associated with the increase in health care costs for patient management, mainly due to prolonged hospital stay and the use of additional treatments (4, 5).

A review performed by de Vries (6) reported a 9.2% median rate of in-hospital AEs with a large variability (interquartile range from 4.6% to 12.4%) and a median percentage of preventable AEs of 43.5% (interquartile range from 39.4 to 49.6%). This wide incidence variability might be due to a number of factors. Thomas (7) and Runciman (8) suggested it might arise from methodological differences between the studies, including the study design, the methods of documentation, the timing of the AEs in relation to their discovery and the index admission, as well as the types of events considered (many studies report only specific AEs, such as drug-related AEs, or AEs in a specific ward only, e.g., intensive care or surgery units (9-11)), the casemix, the patient and the hospital characteristics.

Approximately from 50 to 60% of the AEs are judged to be preventable (12). Recently a study estimated 210,000 to 400,000 deaths per year in the US due to preventable adverse events (13), more than twice the most quoted figure of 98,000 lethal preventable AEs from the IOM (14).

Having valid and reliable way to compare AEs from different sources is paramount for devising practical preventive strategies (15). Although the literature on this topic offers a significant improvement in the understanding of patient safety problems, by identifying and measuring patients safety concerns in hospitals (12, 16) few studies have specifically focused on adverse and preventable adverse events in hospital-based pediatric medical care (17, 18).

In this paper, we conducted a systematic review and a meta-analysis in order to: (i) examine the incidence of in-hospital AEs in pediatric patients and the preventability; (ii) assess if there are significant differences among study results and to what extent methodological issues can explain them.

METHODS

Data Collection

Two researchers independently performed systematic searches of medical literature to identify publications from PubMed, Scopus and the Cochrane Library using the following keywords: “adverse events”, “child”, “pediatrics”, “infant”, “newborn”, “adolescent”, “hospital”, “incidence”, “data interpretation”, “statistics and numerical data” in multiple combinations from November 2012 to January 2013. Additional studies were identified from the bibliography of each selected article. All papers written in English, French and Italian were considered for our study from 1970 onwards. Details of the search procedures are available from the authors.

Study selection

In the first stage the researchers analyzed the search results individually to find potentially eligible publications. The publications were sorted by title and abstract. A selection based on the following exclusion criteria was made: (i) studies not having precise or logical relevance to the matter at hand, such as communication about AE or training courses, which did not report incidences; (ii) identical articles found on more than one database; (iii) studies that reported only specific AEs, such as drug-related AEs; (iv) publications focused only on a specific ward, such as an intensive care unit; (v) studies that reported AEs in children with specific disease, such as cardiac disease AEs.

In the second phase, only studies that met the following inclusion criteria were selected: (i) definition of AE as an injury or complication that is caused by medical management, rather than by the disease process, and leads to a prolonged hospital stay or disability or death at discharge; (ii) evaluation of

the incidence of AE in hospitalized pediatric patients; (iii) inclusion at least 1000 patient records; (iv) the hospitalized pediatric population included people ≤20 years of age. This limit is because of the age limit usually ranges from birth up to 18 in Europe (19) and until age 21 in the United States (20).

Finally after full text review, articles that referred to a subset of the same series of data and that were not published independently were excluded.

Two independent reviewers performed the whole process; discrepancies were resolved by the intervention of a third reviewer.

Data Extraction and Study Assessment

The researchers independently reviewed each article for eligibility and extracted the required data. For each study, information regarding the method of data collection and study design (retrospective or prospective) and the time frame of the adverse events included were extracted. The time frame is the timing of the AE in relation to its discovery and the index admission (time frame), i.e. if the AE occurred before and/or during and/or after the index hospitalization and if it was detected during and/or after. The index admission is the admission sampled.

Data on type of hospital, AE incidence and preventability were also assessed.

Two independent reviewers worked separately and any discrepancies were resolved by the intervention of a third reviewer.

Statistical Analysis

We estimated the pooled incidence rate using a random effect model (21).

Meta-regression models were used to explore the extent to which the study-level variables explain differences between the study results (heterogeneity). Study-level variables include the study design, the number of reviewers, the type of hospital and the time frame. Heterogeneity was estimated using the maximum likelihood estimator. Finally, the proportion of heterogeneity explained by study level

variables was reported. It was computed as the ratio of the between-study variance estimated by the meta-regression model that included the study-level variable and the between-study variance when the study-level variable was omitted. All statistical analyses were carried out with R, version 2.15 (22).

RESULTS

A total of 239 articles were found. After reading titles and abstracts, 215 papers were excluded based on the exclusion criteria. After reading the remaining 24 articles, 15 were excluded because they did not met inclusion criteria. Nine studies were included in this review (see Figure 1).

Studies characteristics

The characteristics of the studies included in this meta-analysis are reported in table 1 and table 2. The studies were retrospective and admission years ranged from 1984 to 2009. They were from the United States, Canada and New Zealand; none of them was from Europe.

Three out of nine studies were based on computerized administrative data whereas in the remaining six studies the study sample was based on randomly selected hospital admissions.

Among the studies based on administrative data, Mark (23) used the ICD - 9 (International Classification of Diseases) criteria to identify potential AEs, while Miller 2003(24) and Miller 2004 (25) used the Patient Safety Indicators (26). In the other studies, two or three stage record review technique was adopted to determine whether an AE had occurred.

Initially (first stage) the records were screened by trained nurses; than if a record was screened as positive (second stage), one or two medical physicians independently reviewed it. The physicians, almost all of whom were internists or surgeons, were trained to assess the medical records for evidence of adverse events and negligence and to grade their confidence that an adverse event had occurred on a scale of 0 to 6.

Three studies used a six-point scale, on the basis of which a score ≥ 4 (27, 28) or ≥ 2 (29) was considered positive AE occurrence. Davis 2002 (30) and Davis 2003 (31) used the same scale without reporting the cutoff value. Finally, in Matlow (32), AE identification was based on the physician reviewer's judgment of whether the probability that the event had been caused by health care management was greater than 50% (Table 2). In Woods (28), where a three stage review process was adopted, after the first two stages, two further study investigators assessed the preventability of the AE.

In the six studies based on the random sample of hospitalizations, 29,227 patient records were analyzed; whereas the two studies conducted by mining administrative data considered 13,150,000 patients.

The number of hospitals per study ranged from 13 to 286; three studies (24, 25, 32) did not report the number of examined hospitals (Table 1).

The differences among studies in terms of the time frame of the included events (i.e. if the AEs occurred during the index hospitalization or were caused by medical management before the index hospitalization and detected only during or during/after it) are also included in Table 2.

Incidence and preventability

The data on hospital admissions, incidence and preventability reported by the studies are shown in Table 3.

Considering all the studies, the pooled incidence of AEs was 2.0% with a 95% confidence interval (95%CI) from 1.3% to 3.0% (top, Figure 2) and the pooled incidence of preventable AEs was 46.2%, with a 95%CI from 35.3% to 57.5% (bottom, Figure 2).

As shown in Figure 2, there was a high variability in the AE incidence among the studies. To assess this variability, univariate and multivariate meta-regressions were carried out. Table 4 reports the effect of (i) the study design (reviewing medical records vs mining administrative data), (ii) the number of reviewers, (iii) the type of hospital (general hospital or children's hospital), (iv) the time

frame of occurred events (before-during vs during index hospitalization), and (v) the time frame of detected events (after-during vs during index hospitalization) on the incidence of AEs.

With respect to the study design, review of medical records reported an incidence of AEs, which was about 4.6 percentage points higher than that reported mining administrative data ($p=0.031$); general hospitals boosted incidence of AEs of about 5.4 percentage points with respect to children's hospitals ($p=0.002$); wider time frame in observing detected events increased incidence of about 7.6% ($p<0.0001$). No statistically significant differences were due the number of reviewers and time frame of occurred events. The time frame effect of detected events explained 93% of the variability observed among the studies. When considering a multivariate model, the time frame of detected events is the only study-level variable statistically significant ($p<0.0001$).

The data on preventability were reported in very few studies. Since the high variability observed (Figure 2) across them is mainly due to the different definition of preventability that was used, no further analysis was carried on.

DISCUSSION

We have conducted a systematic review and random effect meta-regression on the incidence of in-hospital pediatric AEs. In this review, 9 studies from the United States, Canada, Australia and New Zealand were included. Although the studies used the same definition of AE, the reported incidence varied considerably. Previous studies have noted similar differences and suggested that the disparity might have been due to methodological differences (6-8).

In our study, at a univariate level of analysis, the study design (medical records), the time frame of detected events (before-during) and the hospital type (general hospital) were significantly associated with an increase in the reported incidence.

With regard to the study design, a first source of variability can arise from the different procedures for detecting AEs. For example, computerized mining administrative methods used classification of

disease codes (ICD9-CM) and algorithms for identifying both patients risk groups and electronic records containing AEs, whereas medical record reviews listed a number of screening criteria selected as potentially indicative of an adverse event.

Variability among medical record reviews can be explained by different numbers of inclusion criteria and the varying quality of the documentation (33). Whereas, the codes (ICD9-CM), the algorithms used for identifying patient risk groups and the administrative data containing AEs can explain the variability of estimates between studies carried out mining administrative data.

With regard to hospital type, while general hospitals are also equipped to care for pediatric patients, children hospitals typically recognize the difference between treating a child versus treating an adult and they are, therefore, designed and staffed accordingly. Studies have found that children often require a different style of care and treatment than an adult. Children hospitals are constructed and staffed with this in mind.

When considering the between-study variance (Table 4), it is apparent that there can be a synergic effect among the statistically significant variables, in fact, at a multivariate level of analysis, the only statistically significant variable, which impacts the incidence of AEs, was the time frame of detected events.

Regarding preventability, preventable events are not reported in the studies that used administrative data. Furthermore, only four studies reported how preventability was assessed: in two of them (28, 29), a 6-point scale (positive if ≥4) was used; in Matlow (32), an AE was considered preventable if "judged to have been more than 50% preventable"; in Davis 2003 (31) preventability was defined as "an evidence of an error in health – care management due to failure to follow accepted practice at an individual or system level". Because of such different definitions, preventability was analyzed at a descriptive level only.

The generalization of our results could be affected by the limits of the included studies. The major limitation is the retrospective nature of the studies, which are more subject to systematic errors, since

they depend on previously collected data in ways perhaps unreliable and these errors can be found in most studies relying on data mining.

The small number of studies encountered in literature, the limited number of countries, which are not representative of all health care systems, the lack of details about the quality of care delivered, which can also affect the incidence of AEs, are the other limitations.

In conclusion, our meta-analysis confirms that AEs are a major public health issue, occurring in 2.0% (1.3%-3.0%) of all admitted pediatric patients and shows that the different results from the studies presented in the literature are affected by the time frame of detected events.

Then, in order to have a deeper knowledge of the topic, of the variability in the AEs incidence and to direct prevention efforts properly, to carry out studies methodologically more homogeneous or multicentre and prospective instead of retrospective studies would be needed to collect more reliable and robust data; more details about the standard of health care provided and the health system organization would be needed.

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Figure legends

Figure 1. Study Flow Diagram – steps of selection of studies for inclusion in review.

Figure 2. Meta-analysis on incidence of AEs (top figure) and meta-analysis on incidence of preventable AEs (bottom figure).

Table 1. Included studies.

Reference	Publication year/Admission year	Country	No. of Hospitals	Population from	Population Age
Brennan [17]	1991/1984	USA	51	General hospitals † (no psychiatric patients)	0-15
Wilson [18]	1995/1992	Australia	28	General hospitals † (no psychiatric or day care patients)	0-14
Davis [19]	2002/1998	New Zealand	13	General hospitals † (no psychiatric, day-care or rehabilitation patients)	0-14
Davis [20]	2003/1998	New Zealand	13	General hospitals † (no psychiatric, day-care or rehabilitation patients)	0-14
Miller [13]	2003/1997	USA	NA	General hospitals † and children's hospitals*	0-18
Miller [23]	2004/2000	USA	NA	General hospitals † and children's hospitals*	0-18
Woods [12]	2005/1992	USA	27	General hospitals † and children's hospitals* (no psychiatric,	0-20

				rehabilitation or drug/alcohol patients)	
Mark [22]	2007/1996-2001	USA	286	General hospitals † and children's hospitals*	0-14
Matlow [21]	2012/2008-2009	Canada	NA	General hospitals † (no obstetric or psychiatric patients or transferred from or to other hospital)	0-18

† Hospitals with various wards including at least one pediatric ward

*Hospitals with only pediatric wards

Table 2 Studies design characteristics.

Reference	Study design	Method of data collection	Stages of record review			Time frame of included events*	
			Stage 1	Stage 2	Stage 3	Occurred	Detected
Brennan	Retrospective medical record review	Random sample of hospitalizations from 51 hospitals in New York	One nurse †	Two medical officers independently		Before-During	During
Wilson	Retrospective medical record review	Random sample of admissions from 28 hospitals in 2 states: New South Wales, South Australia	One nurse †	Two medical officers independently		Before-During	During-After
Davis	Retrospective medical record review	Random sample of admissions from 13 hospitals	One nurse †	One specially trained medical officer		Before-During	During-After
Davis	Retrospective medical record review	Random sample of admissions from 13 hospitals	One nurse †	One specially trained medical officer		During	During
Miller**	Retrospective review by mining administrative data	All hospitalizations from 22 states				During	During
Miller**	Retrospective review by mining administrative data	All hospitalizations from 27 states				During	During
Woods	Retrospective record discharge review	Random sample of hospitalizations from 27 hospitals	One nurse	One physician	Two investigators	Before-During	During
Mark**	Retrospective review by mining administrative data	All hospitalizations from 286 hospitals in California				During	During

Matlow	Retrospective record review	Random sample of hospitalizations from 4 predetermined age groups	One nurse or medical records technician ±	One physician	During-After	During-After

*AEs were recorded if they occurred before and/or during and/or after index hospitalization and if they were detected during and/or after

† First screening for one of 18 criteria

** Retrospective review by mining administrative data did not undergo a record review process

± First screening for one of 35 triggers

Table 3. Admissions, Incidence, and Preventability of adverse events

Reference	**Matlow**	**Woods**	**Wilson**	**Brennan**	**Mark**	**Miller 2003**	**Miller 2004**	**Davis 2002**	**Davis 2003**
No. of pediatric records	3669	3719	2020	6661	3.65 M.	3.8 M.	5.7 M.	1349	1333
Adverse events N (%)	279 (7.6)	39 (1.0)	218 (10.8)	86 (1.3)	5130 (0.14)	44023 (1.1)	51615 (0.9)	102 (7.6)	44 (3.3)
Preventable adverse events N(%)	125 (44.8)	22 (56.4)	105 (48.1)	19 (21.6)	NA	NA	NA		29* (28.4)

* Preventable adverse events occurred before and during index hospitalization and were detected during and after (two years) index hospitalization (n. 102).

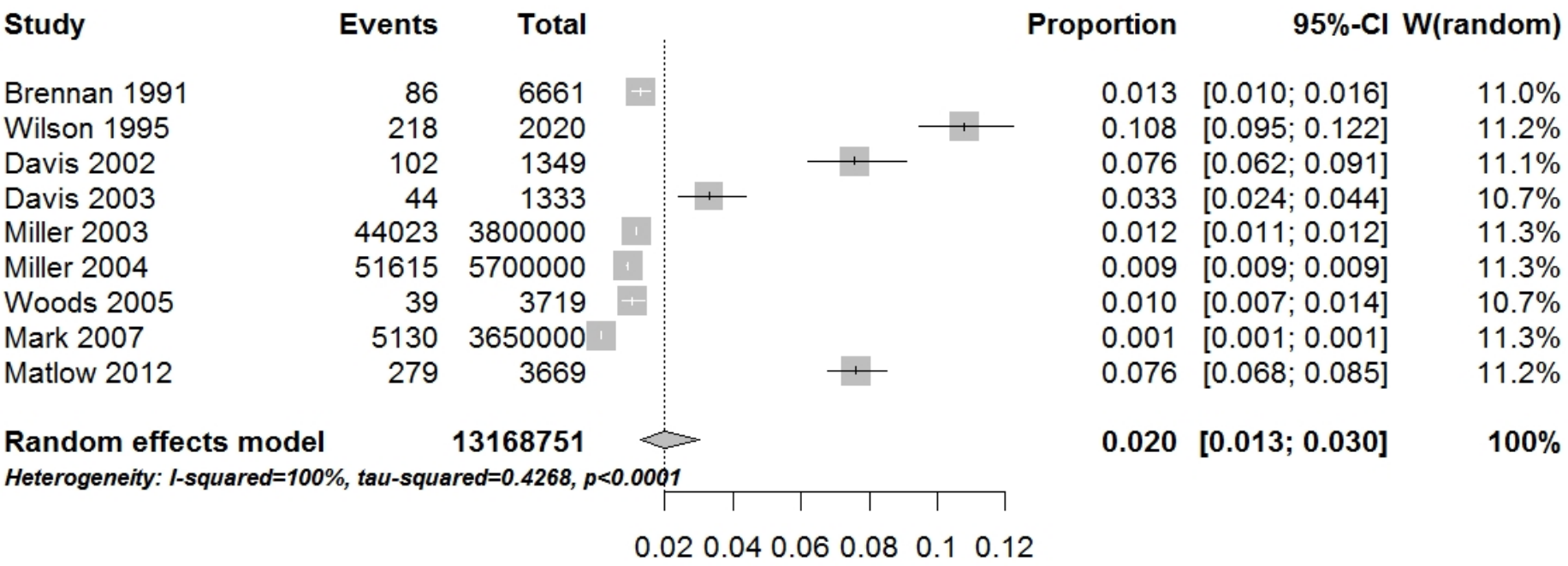
Table 4. Univariate and multivariate meta-regression analysis results of the incidence of adverse events. Estimates are reported on the relative risk scale.

	Univariate					Multivariate			
	Estimate	p-value	95%CI		Explained heterogeneity*	Estimate	p-value	95%CI	
Incidence of AEs									
Study design effect									
Medical records vs mining administrative data	1.0456	0.031	1.0041	1.0889	35%	1.0031	0.7238	0.9858	1.0207
*Reviewer effect***									
Two reviewers vs one reviewer	1.0112	0.72	0.9514	1.0745	2%	-	-	-	-
Hospital effect									
General hospital vs Children's hospital	1.0536	0.0019	1.0195	1.0888	53%	0.9892	0.2612	0.9795	1.0081
Time frame effect of occurred events									
Before-During vs During	1.0252	0.277	0.9801	1.0723	11%	-	-	-	-
Time frame effect of detected events									
During-After vs During	1.0762	<.0001	1.0599	1.0928	93%	1.0662	<.0001	1.0494	1.0833

***** Due to collinearity among study-level variables, the explained variability proportion does not sum up to 100%.

****** Because studies based on mining administrative data had no reviewers, the reviewer effect was estimated using studies based on medical records

Incidence of Adverse Events



Preventability of Adverse Events