INCREASING THE DETECTION OF ADVERSE DRUG EVENTS IN PEDIATRIC PATIENTS

by

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A thesis submitted to the faculty of
The University of Utah
in partial fulfillment of the requirements for the degree of

Master of Science

Department of Biomedical Informatics

The University of Utah

May 2010

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ABSTRACT

Patient safety has received unprecedented attention over the past decade. Some of that attention has been focused on the occurrence and prevention of harm from Adverse Drug Events (ADEs). Between 19 and 61 percent of ADEs are preventable. In order to prevent ADEs, they must first be detected. Several methods have been used to detect ADEs, including voluntary reporting, intensified surveillance, and computerized monitoring. Computerized monitoring has been shown to be complimentary to other methods in detecting ADEs. However, very little research has been completed on this method in pediatrics.

Pediatric patients pose unique challenges and risks because of physiological immaturity, lack of testing and information on medications, availability of appropriate medication formulations and strengths, and incomplete cognitive and communication development.

This study examined the modification and implementation of an adult computerized ADE monitoring tool at one pediatric medical center. It was implemented into the daily practice of pharmacy operations without increasing the pharmacy resources. Pharmacists printed daily reports containing alerts of possible ADEs. They investigated each of the alerts and noted whether an ADE occurred and how much time was needed to investigate. The main objective of this study was to increase the detection of ADEs in the pediatric population.

Over the 12-week study, 181 ADEs were identified via the computerized monitoring tool. An additional 88 ADEs were voluntarily reported. Overall, this represented a rate of 6.6 ADEs per 100 admissions and 14.8 ADEs per 1,000 patient days. This result represented a significant increase in the detection of ADEs ($p<0.0001$) as compared to the same timeframe from the previous year. The computerized monitoring tool had a positive predictive value (PPV) of 4.8 percent. It took an average of 6.1 minutes to investigate alerts associated with an ADE, which was significantly higher than the time it took to investigate alerts not associated with an ADE ($p<0.0001$). Of the ADEs found with this tool, 10.5 percent were considered preventable.

The use of a modified computerized ADE monitoring tool in the pediatric environment increased the overall detection of ADEs and warrants continued research.

This work is dedicated to my wife and children who have encouraged and supported me throughout my studies and journey into the field of biomedical informatics.

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ACKNOWLEDGEMENTS

I would like to express my appreciation to my committee chair, R. Scott Evans, for his patience and willingness to mentor me throughout this project. It was only with his guidance that I was able to understand the necessary components of computerized ADE monitoring. In addition, I would like to thank Joe Hales who has patiently given me encouragement and advice, which has greatly helped me to remain focused on completing this work. I also want to thank Jared Cash who has guided me through the inner workings of pharmacy process and pointed me in the right direction for obtaining needed knowledge.

I would also like to thank Intermountain Healthcare and Primary Children's Medical Center for allowing me to conduct this study and the Department of Biomedical Informatics for giving me the opportunity to continue my education.

I would like to lastly thank my family for their constant support and encouragement throughout this journey.

BACKGROUND

Introduction

Patients expect to receive care from highly trained and proficient medical professionals who will use the best practices known to modern medicine for their treatment. In most cases these expectations are met. However, even at the best of times, well laid plans do not always go as expected and mistakes are made. When this occurs and an injury to the patient can result, it is said to be an adverse event. At times there is nothing anyone could have done to predict or prevent an adverse event from occurring. For the remaining times, the adverse event is considered to be the result of medical error.

The topic of patient safety picked up momentum in 1991 with the publication of the results of the Harvard Medical Practice Study. That study reported that 3.7 percent of all hospitalized patients experienced an adverse event.[1,2] While patient safety has always been considered critical, it received an unprecedented amount of attention when, in 1999, the Institute of Medicine (IOM) published its report "To Err is Human".[3] That report, based on two previous studies,[1,4] estimated that between 44,000 and 98,000 people die each year in the United States from adverse events that are the result of medical error. There has been some debate whether these numbers are an accurate reflection of the true problem.[5-7] Whether the actual number is higher or lower than reported is not necessarily important. The important point is that adverse events occur far too often and many are preventable.

The Harvard Medical Practice study further reported that complications related to medications were the most common type of adverse event and represented 19.4 percent of all adverse events in their study.[2] This particular type of event has come to be known as an adverse drug event (ADE). The definition from the Institute of Medicine, recommended by Nebeker et al.,[8] and used in this study is "an injury resulting from medical intervention related to a drug."[3]

Pediatric patients are a particularly vulnerable population and have a greater potential to experience an ADE. There is evidence that the occurrence of errors that could have potentially been an ADE occur at a rate three times higher in pediatric patients,[9] even though incident rates have been shown to be approximately the same in pediatrics and adults.[10]

Differences in Pediatrics

Pediatric patients are a unique population with a distinct set of challenges unmatched by the adult population.

Off-Label Medication Use

The majority of medications that are used in pediatrics are used in a manner that is referred to as "off-label."[11-13] This means that the medication has been approved by the US Food and Drug Administration (FDA) for use in adults, but has not been adequately tested or labeled for treating children. There are three main reasons behind this lack of testing in children.[14-18] The first is that the medication market is smaller in children. A smaller market means that the monetary benefit a pharmaceutical company may see from a particular drug does not compensate for the cost to develop the medication and have it

approved for children. Therefore, their priority for pursing FDA approval for these medications would be greatly reduced. The second reason is the technical difficulties in carrying out pediatric studies for FDA approval. It is often difficult to enroll adequate numbers of children into a drug study because of the relatively small number of children are affected by many pediatric diseases. This lack of patients may require a study to have multiple study sites in order to enroll a sufficient number of subjects, again increasing the cost of testing. The inherent differences among age groups may also require a separate randomized control study for different age groups, such as infants, children, and adolescents. There are also issues surrounding the possible need for multiple formulations of the medication, performing testing on smaller volume blood samples, along with providing appropriate pediatric environments, techniques, and equipment. These technical issues lead to a higher cost of testing. The third reason for lack of testing in children is the complexity of ethical issues. Children are unable to give "consent" because of their inability to fully understand the risks. Therefore, a child's parents take on this role of giving consent and enrolling them into a study. However, even if a child's parents enroll them, children age seven or older have the right to assent or dissent to being involved. For example, a child may be enrolled in a study by their parents, but the child will dissent because one of the requirements is to obtain a blood sample and the child does not want to have a venipuncture to obtain the sample. In addition, medical ethics committees are hesitant to allow drug trials in children, generally viewing them as a vulnerable population needing additional protections.

Physicians can still prescribe these medications for pediatric patients, but without proper testing and labeling of medications for pediatric use, licensed independent

providers (LIP) which include physicians, nurse practitioners, and physician assistants, have inadequate information to make informed decisions about the benefits and risks of prescribing medications that may be advantageous in treating a child suffering from a particular disease or illness.

Even though the majority of medications are used in an "off label" manner, improvement is being seen in the number of medications that are being tested and labeled for pediatric use. This improvement is the result of the Best Pharmaceuticals for Children Act of 2002 (BPCA) and the Pediatric Research Equity Act of 2003 (PREA).[19,20] Both of these acts were reauthorized under the Food and Drug Administration Amendments Act of 2007 (FDAAA).[21] These two pieces of legislation provide incentives and requirements for drug companies in regards to testing medications for use in pediatric patients.

Physiological Differences

Medications cannot just be reduced in dosage based on the patient's size in relation to an adult. There is a great deal of difference among pediatric patients in the maturation of their physiological systems (especially hepatic and renal). These differences affect the pharmacokinetics of medications, that is how medications are absorbed, distributed, metabolized, and then excreted from the body. These differences are most significant in neonates and young infants during their first year of life.[11,13,18,22,23] Good examples of the differences in dosing among different pediatric populations as a result of differing physiologic maturation are seen in the medications Phenytoin, used to control seizures, and the antibiotic Gentamicin (see Table 1).

Table 1
Phenytoin and Gentamicin dosing recommendations

Drug – Intraveneous	Neonates	Infants and Children	Adults
Phenytoin	Loading Dose: 15-20 mg/kg in a single or divided dose Maintenance dose: Initial: 5 mg/kg/day in 2 divided doses; Usual: 5-8 mg/kg/day in 2 divided doses; some patients may require dosing every 8 hours	Loading Dose: 15-18 mg/kg in a single or divided dose Maintenance dose: Initial: 5 mg/kg/day in 2-3 divided doses; Usual doses: 0.5-3 years: 8-10 mg/kg/day 4-6 years: 7.5-9 mg/kg/day 7-9 years: 7-8 mg/kg/day 10-16 years: 6-7 mg/kg/day Some patients require every 8 hours dosing due to fast apparent half-life	Loading Dose: 15-18 mg/kg in a single or divided dose Maintenance dose: Usual: 300 mg/day or 4-6 mg/kg/day in 2-3 divided doses
Gentamicin	Premature neonate, <1000 g: 3.5 mg/kg/dose every 24 hours 0-4 weeks, <1200 g: 2.5 mg/kg/dose every 18-24 hours Postnatal age ≤7 days: 2.5 mg/kg/dose every 12 hours Postnatal age >7 days: 1200-2000 g: 2.5 mg/kg/dose every 8-12 hours >2000 g: 2.5 mg/kg/dose every 8 hours Once daily dosing: Premature neonates with normal renal function: 3.5-4 mg/kg/dose every 24 hours Term neonates with normal renal function: 3.5-5 mg/kg/dose every 24 hours	<5 years: I.M., I.V.: 2.5 mg/kg/dose every 8 hours* Once daily dosing in patients with normal renal function: 5-7.5 mg/kg/dose every 24 hours Children ≥5 years: I.M., I.V.: 2-2.5 mg/kg/dose every 8 hours* Once daily dosing in children with normal renal function: 5-7.5 mg/kg/dose every 24 hours	3-6 mg/kg/day in divided doses every 8 hours; studies of once daily dosing have used I.V. doses of 4-6.6 mg/kg once daily

*Information obtained from Pediatric Dosage Handbook by Lexicomp [24]

At times the lack of pediatric medication information combined with physiological differences has had serious and tragic results. One of the most tragic was the death of several newborns in the 1960s from the antibiotic chloramphenicol because their immature livers of the newborns were unable to break down and then excrete the medication.[12,16] As a result of similar potential dangers, LIP's may be hesitant to prescribe a medication out of fear of causing more harm than good.

In addition, infants and children, especially critically ill children, are at greater risk to suffer increased harm from an ADE that is the result of an overdose. This is because they have limited physiologic reserves with which to buffer the effects of this type of error.[25-27]

Pediatric Formulation and Dosage Availability

Since there are so few medications labeled for pediatric use, most medications are only available in adult dosages and formulations. As a result, potential for error is introduced as available forms of the medications must be split into smaller doses, extemporaneously compounded into an appropriate liquid formulation, or otherwise mixed or diluted at the time of use.[9,11,25-28] In some cases, the best option is to give injectable formulations orally.[11]

Medication formulations based on adult needs are difficult if not impossible to measure for neonatal patients. Even a small measuring error can result in a significant change to the prescribed dose of medication.[11]

Weight Based Dosing

Almost all medications used in pediatrics are dosed according to the patient's weight. Once an LIP has the recommended dosing regimen, they still have to calculate the correct dose using a formula like mg/kg/dose up to an amount that in most cases is not to exceed the normal or maximum adult dosage. Complicating the matter further, a child's weight, especially neonates and infants, changes rapidly and may require recalculation of the proper dose for adequate therapeutic dosing during an inpatient stay.[25] Calculating and/or recalculating dosage adds complexity to medication orders and introduces opportunity for errors resulting in therapeutic under or over dosing of the medication. These errors can include misplacement of decimals, resulting in 10- or even 100-fold overdoses or under-doses.[11,25,26,28]

Cognitive and Communication Development

Depending on a child's level of cognitive development compared to an adult's, they may be unable to recognize and then communicate that they are being given the wrong dose or the wrong medication. In addition, depending on their communication development, they may be unable to communicate when they are experiencing the symptoms or effects of an ADE.[9,26-28]

Methods of ADE Detection

There are three common methods that have been employed to detect and monitor the occurrence of an ADE. They include voluntary or spontaneous reporting, intensified surveillance (including manual chart review), and computerized monitoring.

Voluntary Reporting

Voluntary or spontaneous reporting is a method of reporting an ADE that has already been detected. When an ADE is detected by a clinician, that clinician using this method would generally report it to the hospital by filling out a paper form or possibly an electronic form and submit it to the designated hospital department that then investigates the ADE further. This type of reporting method is inexpensive and easy to implement as compared to the other methods that will be discussed later. As a result, it has been the most common method used to monitor for the incidence of ADEs. This method, though beneficial, has been known to underreport ADEs.[29-33] Its effectiveness has even been described as "dismal at best."[34] A survey of physicians and nurses conducted by Taylor et al. in 2004 gave several reasons why underreporting of medication errors and events occur using this method. The top four reasons were: one, the reporting individual being unsure about what is considered a medical error, two, the reporting individual being concerned about implicating others, three, the reporting individual being unsure about whose responsibility it is to report errors, and four, the idea that it is not important to report errors that did not reach the patient.[32] The rate of detection in adults using voluntary reporting was reported by Jha et al. to be just 0.7 ADEs per 1,000 patient days.[35] Another study completed in the pediatric population reported an incident rate of 1.9 ADEs per 100 admissions and 1.8 ADEs per 1,000 patient days.[36]

Intensified Surveillance

Intensified surveillance including manual chart review has been shown to be effective at detecting ADEs and has been considered the gold standard for measuring the incidence of ADEs. However, this method is resource intensive and comes at high

cost.[34,35,37,38] There is also some evidence that it does not capture the entire range of ADEs.[35] The detection rate of ADEs using this method among adult patients has been reported as 6.5 (adjusted) per 100 patient admissions[37] and between 11.5 and 13.3 ADEs (adjusted) per 1,000 patient days.[35,37] Among pediatric patients, intensified surveillance has reported ADE detection rates between 2.3 and 11.1 per 100 patient admissions and between 6.6 and 15.7 per 1,000 patient days.[9,10,39] The Harvard Medical Practice Study reported Drug-related Adverse Events for patients less than 15 years old at a rate of 2.36 per 1,000 discharges.[2]

Computerized Surveillance

Computerized surveillance has been reported to be, not only complementary to the previously mentioned methods, but also less expensive than intensified surveillance.[34,35] While there are many examples of computerized monitoring being used to detect ADEs in the adult population,[34,35,38] it is only now beginning to be explored and implemented in the pediatric population.[36,40] Studies using computerized surveillance in adults have shown ADE rates between two and 6.2 ADEs per 100 patient admissions,[34,35,41-43] with only the study from Jha et al. reporting 9.6 ADEs per 1,000 patient days.[35] Pediatric studies have shown ADE rates to be between 1.8 and 2.3 ADEs per 100 admissions and between 1.6 and 6.6 ADEs per 1,000 patient days.[36,40]

Complementary Methods

Surprisingly, when the ADEs detected using voluntary reporting and intensified surveillance are compared to those found using computerized ADE monitoring, there is very little overlap of the ADEs detected by both methods. The study by Jha et al. among

adults reviewed all three methods together and found an adjusted ADE rate of 21 per 1,000 inpatient days with only 12 percent or 76 of 617 ADEs being detected by both computerized and intensified surveillance. In addition, there was only 0.5 percent or three of 617 ADEs that were found to be overlapping when comparing voluntary reporting and computerized surveillance.[35] However, a study by Kilbridge et al.[43] did identify that 59 percent or 42 of the 71 voluntarily reported ADEs were also detected by their computerized surveillance system. They suspect that many of these were the result of pharmacists learning of ADEs from triggers and reporting them separately through the voluntary system. In pediatric patients, Ferranti et al. found that only 4.3 percent or four of 78 ADEs overlapped between their computerized detection system and their voluntary reporting system.[36] Kilbridge et al. found only three of the 160 ADEs, which represents 1.9 percent of ADEs, were reported by both voluntary and computerized surveillance.[40] In addition, one study by Takata et al.[39] used a manual trigger tool via chart review. These manual triggers were a set of 15 criteria that the person doing the chart review chart review looked for. If they found an item in the chart that met the criteria this triggered or prompted them to review the chart in more depth for an associated ADE. They only had four ADEs reported via voluntary reporting during their study period. All four of those ADEs were also detected by their manual trigger tool and represented 3.7 percent of their 89 ADEs found via their tool.

Preventability of ADEs

From the reviewed studies if an ADE was determined to be preventable, it indicated that there was some error of either omission or commission that occurred which

could have prevented the ADE from occurring. The percentage of ADEs that have been found to be preventable in the adult population ranged from 20 to 50 percent.[35,37,41,44,45]

The Adverse Drug Event Prevention Study Group, a consortium of individual researchers mostly from three instituations: the Brigham and Women's Hospital, Harvard University, and the Massachusetts General Hospital found that 28 percent of ADEs in their study were preventable. They also identified in two different articles[37,45] the stage where the error occurred in the process known as the drug ordering and delivery process (Table 2). This process describes the discrete steps used to get the medication to the patient after it has been prescribed. It has several stages: prescribing, order processing, order review, dispensing, administration, and monitoring. The Adverse Drug Event Prevention Study Group reported that errors occurred most often in physician ordering, followed by nurse administration, pharmacy dispensing, and then transcription and verification.[37,45]

In pediatrics, the preventable ADEs ranged from 19 percent to 61 percent.[9,10,39]

Table 2
Drug ordering and delivery process

Stage	Description
Prescribing	In this stage the provider determines a need for a medication and then prescribes the medication for the patient.
Order Processing	Generally done by the unit clerk who "takes off" the order and sends it to pharmacy. At Primary Children's this is completed by faxing the order into the POMS system previously described.
Order Review	An RN reviews the order medication orders for inclusion of proper components, proper dosage, any allergies to the medication, etc and then notes that review on the order. The nurse then transcribes the order to a medication administration record if still using a paper form to document medication administration; if they are documenting using the HELP system they would verify the order prior to administration. Also during the order review step a pharmacist separately reviews the incoming order for inclusion of proper components, proper dosage, allergies, etc.
Dispensing	Once satisfied with the order the pharmacist then dispenses the medication.
Administration	The nurse administers the medication as per the written order.
Monitoring	Depending on the medication given the nurse monitors the patient as needed.

The pediatric study by Takata et al. described that the most common error occurred in the monitoring stage followed by prescribing and dispensing. It is interesting to note that neither of the previous pediatric studies evaluating computerized surveillance determined the number of preventable ADEs found via computerized monitoring.

Impact of ADE

Two adult population studies looked at the impact that an ADE had on the length of stay (LOS) and on the cost of hospitalization for patients. The first study by Classen et al. was conducted at Intermountain's LDS Hospital on data from January 1, 1990 to December 31, 1993. It found that ADEs had an attributable increase in patient LOS of 1.74 days at a cost of $2,013 per admission.[41] The second study by Bates et al. was conducted at the Brigham and Women's and Massachusetts General Hospitals on data from February 1993 to July 1993. That study found an increased LOS of 2.2 days with an increased cost of $2,595. This same study also found that if the ADE was preventable the cost increased to $4,685.[46]

Hypothesis and Objectives

The hypothesis for the study reported here is that a modified adult computerized ADE trigger tool will increase the detection of ADEs in a Pediatric population when compared to the current voluntary reporting method. To accept or reject this hypothesis we conducted a study of the implementation of a modified adult tool in the pediatric environment using a Prospective Cohort study design.

The objectives of this study were as follows:

1. Modify existing triggers where necessary to better represent the differences in pediatric patients.
2. Add new triggers that have a potential to increase the detection of additional ADEs in the pediatric setting.
3. Implement the updated ADE alerting tool in a pediatric population.
4. Compare the detection rate of the computerized ADE tool at Primary Children's Medical Center to the current method of voluntary reporting.
5. Evaluate the effectiveness of the computerized surveillance ADE triggers in a pediatric setting.
6. Evaluate preventable ADEs found via the computerized ADE detection tool and compare them against the preventable ADEs found via voluntary reporting.
7. Evaluate the amount of time it takes to investigate non-ADE alerts versus alerts where an ADE was confirmed.

METHODS

Study Location

At the time of this study Primary Children's Medical Center, located in Salt Lake City, Utah, was a 252-bed, tertiary care pediatric medical center providing care for five states in the Intermountain West (Utah, Idaho, Montana, Nevada, and Wyoming) and primary pediatric care in Utah. It is owned and operated by Intermountain Healthcare, a nonprofit community owned system of hospitals, surgery centers, doctors, clinics, homecare, and hospice providers. Primary Children's Medical Center is also affiliated with the University of Utah School of Medicine and is its primary pediatric training site. This study was approved by the Institutional Review Boards (IRB) of the University of Utah and Intermountain Healthcare.

Patient Population

Study patients included all patients admitted to an inpatient bed in one of eight inpatient units during a 12-week period of time (84 days) from February 2, 2009 through April 26, 2009. The inpatient units included the Children's Medical Unit (CMU), Children's Surgical Unit (CSU), Immunocompromised Unit (ICS), Infant Medical Surgical Unit (IMSU), Newborn Intensive Care Unit (NICU), Neuroscience Trauma Unit (NTU), Pediatric Intensive Care Unit (PICU), and inpatients admitted to the Rapid Treatment Unit (RTU). The only inpatient unit not included was the Psychiatric Unit. It was excluded from this study because it is located in an off-site building away from the

primary campus and the processes necessary to include them in the study were considered impractical.

ADE Prevention Methods Already in Place

Licensed Independent Practitioner (LIP) orders were handwritten on order sheets with a few exceptions where a paper ordering template was used. Although orders were still handwritten, the facility had several methods for preventing ADEs already in place. The prevention methods included, but were not limited to, the Pharmacy Order Management System (POMS). Handwritten orders were scanned into POMS by the unit clerk on each unit. Once an order was scanned, it was transmitted to Pharmacy staff. The pharmacy staff was then able to review and track each incoming order. They were also able to tag individual orders that required follow-up with the ordering LIP. Once all tagged issues were resolved, the Pharmacy staff then hand entered each medication related order into the Pharmacy subsystem of the hospital's electronic medical record (EMR). The EMR in place at the facility was the Health Evaluation through Logical Processing (HELP) system.[47] This system was first developed under the direction of Homer R. Warner and has been in use for more than 35 years at Intermountain's LDS Hospital and for more than 15 years at Primary Children's Medical Center.[48] When orders were entered into the Pharmacy subsystem, the system checked them for allergies, high and low dose parameters, and drug-drug interactions. If an allergy, out of range order, or drug-drug interaction was found, an on-screen alert was generated.

Barcode Medication Administration (BCMA) was in place on five of the eight inpatient units included in the study. The three units not using BCMA, instead, used a pre-printed Medication Administration Record (MAR), which was generated from the

HELP Pharmacy subsystem. A McKesson medication dispensing robot was used to dispense standardized doses of medications and was responsible for dispensing approximately 40 percent of all medications to patients. Acudose dispensing cabinets were available on each of the inpatient units. A separate total parenteral nutrition (TPN) compounder, also in the pharmacy, was responsible for preparing and dispensing all of the TPN solutions used in the hospital. In addition to the above, pharmacists actively participated in multidisciplinary rounds.

Intervention

The computerized ADE monitoring tool that was the basis for this study was first developed at Intermountain's LDS Hospital and information regarding its effectiveness has been previously published.[34,49,50] Since first being described and implemented, the monitoring tool has had periodic modifications and enhancements and has subsequently been implemented extensively throughout Intermountain Healthcare hospitals.

Computerized ADE Monitoring Tool Basics

The monitoring tool was programmed with rules that contained specific criteria. When the criteria were met, the tool generated a notification that was included in a paper report. The term "trigger" was used to describe the rules of the tool, and the term "alert" was used to denote the notifications of possible ADEs generated by the rule or trigger that needed to be investigated and confirmed or ruled out as an actual ADE. A designated pharmacist received notification of the alerts by printing the Possible Adverse Drug Event Report. The pharmacist would then investigate the alert to determine if an ADE had occurred.

ADE Triggers

Prior to the beginning of this study, the ADE monitoring tool used in adults had 87 active triggers. Two of the trigger categories (Pharmacist and Nursing) were part of an enhanced voluntary reporting tool where suspected ADEs could be reported via this tool by pharmacy and nursing personnel for further investigation. Other categories of triggers included medication orders, laboratory results, including serum drug levels, and physiologic monitoring triggers.

Before being placed into service each trigger was reviewed by a team of pediatric pharmacists for relevance to the study location and population. Based on the review and recommendation of the pharmacist team, 14 triggers were modified, 11 new triggers were added, and 16 triggers were not implemented (Table 3). Of those triggers not implemented, 15 were part of the enhanced voluntary reporting tool and were not consistent with the processes already in place at the facility for nursing and pharmacy reporting of potential ADEs. For the 58 triggers that were implemented unchanged, some of those triggers were determined to be appropriate as written (for example potassium level, carbamazepine level and digoxin level), while other triggers were determined to be of little or no benefit to pediatrics and yet would be harmless if implemented without any changes (for example, opium and paregoric).

Some of the original triggers had rules to exclude patients with certain preliminary coded admission diagnoses. These coded diagnoses were entered into the adult patient's record shortly after the patient's admission. At Primary Children's, the diagnostic codes are not entered until after the patient has been discharged. Therefore, admission diagnoses were only entered as free-text. As a result, it was expected that the

Table 3
Triggers added, modified, or removed from monitoring tool

Action	Trigger	Detail
Modified	Heart rate less than 45	Included age specific values
	Respiratory rate less than 8	Included age specific values
	Prednisone dose greater than or equal to 50 mg	Excluded certain free text diagnoses related to asthma, bronchiolitis, and other respiratory diagnoses.
	Phenytoin ordered	Included administration of Fosphenytoin.
	Phenobarbital ordered	Excluded certain free text diagnoses related to seizure diagnosis and brain injuries.
	Vitamin K ordered and age greater than or equal to 1years old	Age changed to be greater than 30 days.
	Platelets less than or equal to 50	Turned off for ICS unit due to expected high false negative values
	WBC less than or equal to 2.5	Turned off for ICS unit due to expected high false negative values
	Valproic acid greater than 100	Changed to greater than 125
	Cyclosporin greater than100	Changed to greater than 500
	Vanco P greater than 40	Changed to greater than 50
	Gent P greater than 10	Changed to greater than 12
	Tobra P greater than 10	Excluded free-text diagnoses related to Cystic Fibrosis
	Tobra T greater than 2	Excluded free-text diagnoses related to Cystic Fibrosis
Added	Phentolamine	Phentolamine ordered
	Hydrochloric acid	Hydrocholoric acid ordered
	Racemic Epinephrine ordered	Racemic Epinephrine ordered
	Viokase 8 and Sodium Bicarbonate tablet	Viokase 8 and Sodium Bicarbonate tablet ordered
	Wydase	Wydase ordered
	Nubain	Nubain ordered <= 0.03 mg/kg/dose
	Acetylcysteine	Acetlycysteine ordered
	Tacrolimus level	Tacrolimus, greater than15
	Caffeine level	Any Caffeine level
	Anti-factor Xa	Anti-factor Xa greater than1
	EOS	EOS greater than or equal to 7
Removed	Abrupt stop order	
	Abrupt reduction of drug	
	Anaphylaxis	
	Mental change	
	Diarrhea	
	Fever	
	Respiratory change	
	Rash/hives/itching	
	Seizure	
	Hearing change	
	Heart Rate Change	
	Other	
	Hypertension	
	Hypotension	
	Incident report	
	Chlorphen ordered	

false positive rate would be higher and the Positive Predictive Value (PPV) would be lower for those triggers that relied on excluding certain diagnostic codes than in the adult facilities. In cases where the false positive rate was anticipated to be especially high, the free-text diagnoses that most closely matched the coded diagnoses were excluded from the trigger. Those triggers that were affected by not having coded diagnoses or where free text diagnosis exclusion was included were considered to not be modified.

After the modifications were completed there were 83 active triggers that were implemented (see Table 4).

Alert Generation

The information used to determine if trigger criteria were met and an alert should be generated came from different sources. Laboratory information was stored in HELP but originally received via an HL7 interface from the Sunquest laboratory information system. Physiological data was also stored in HELP and received via a direct RS237 connection from the Phillip's monitors. The rest of the information was generated inside of the HELP system via the pharmacy and nursing subsystems. When information that was used as a trigger was saved in the HELP system, it was exposed to the rules engine, which reviewed the data for the specified criteria in the triggers. If the criteria were met an alert was generated.

When the pharmacist logged into the computerized ADE Monitor on HELP, a menu was presented that had options to print the Possible Adverse Drug Event (Figure 1). Each menu option was specific to a particular pharmacy team and printed only the information pertinent to the units and beds that particular pharmacy team covered. Once

Table 4
Triggers implemented at PCMC

Type of Trigger	Trigger	Trigger Rule Detail
Lab Alerts & drug levels	SGOT	SGOT >= 150
	SGPT	SGPT >= 150
	Billirubin	Billirubin >= 10
	EOS	EOS >= 7
	Platelet count	Platelet Count <= 50 - Turned off on ICS due to anticipated high false positive rate
	WBC	WBC <= 2.5 - Turned off on ICS due to anticipated high false positive rate
	Carbamazepime	carbamazepine > 10
	Digitoxin	digitoxin > 30
	Digoxin	digoxin > 2
	Disopypamide	disopypamide > 5
	Ethosuximide	ethosuximide > 100
	Lidocaine	lidocaine > 5
	NAPA	NAPA > 20
	Procainamide	Procainamide > 10
	Phenobarbital	Phenobarbital > 45
	Phenytoin	Phenytoin > 20
	Quinidine	Quinidine > 5
	Theophylline	Theophylline > 20
	Valporic Acid	Valproic Acid > 125
	Cyclosporin	Cyclosporin > 500
	Vanco peak	Vancomycin Peak > 50
	Vanco trough	Vanco Trough > 20
	Gent peak	Gentamycin Peak > 12
	Gent trough	Gentamycin Trough > 2
	Tobra peak	Tobramycin Peak > 10 excluded are free-text diagnosis related to Cystic Fibrosis
	Tobra trough	Tobramycin Trough > 2
	Amikacin peak	Amikacin Peak > 30
	Amikacin trough	Amikacin Trough > 10
	C. difficile	C. difficile
	Doubling of Cr	Doubling of Creatinine
	Glucose	Glucose < 50
	Glucose	Glucose > 350
	Potassium	Potassium < 3.0 and decrease of .8 or < 2.6 and decrease of .5 within 72hrs and on K altering drug
	INR	INR > 3.0 (INR increase by 0.3 w/l 24hr or increase by 0.5 w/l 48hr and active warfarin order
	PTT	PTT > 100 (2 or more PTTs > 100 within 36hrs)
	Tacrolimus	Tacrolimus > 15
	Caffeine level	Caffeine level ordered
	Anti-factor Xa	Anti-factor Xa > 1
Pharmacy Orders	Diphenhydramine	Benadryl ordered but not ALG, OKT3, ampho, Cancer drug, cardiac drug within 3 hrs, Reopro, or HGB drop >= 3
	Steroid cream	Steroids ordered except (azmacort, nasalide, aerobid) and not QHS
	Epinephrine	Epinephrine ordered
	Naloxone	Naloxone ordered and previous narcotics

Table 4 (Continued)

Type of Trigger	Trigger	Trigger Rule Detail
	Phenytoin	Phenytoin ordered, exclude free-text diagnosis related to seizure disorder, brain tumor, stroke, or traumatic brain injury.
	Phenobarbital	Phenobarbital ordered, exclude free-text diagnosis related to seizure disorder, brain tumor, stroke, or traumatic brain injury.
	Prednisone	Prednisone ordered >=50 mg, exclude free-text diagnosis related to asthma, reactive airway disease (RAD), RSV, bronchiolitis, or croup
	Caladryl	Caladryl ordered
	Calamine	Calamine ordered
	Kayexalate	Kayexalate ordered
	Vitamin K	Vitamin K ordered but age >= 30 days and not on TPN
	Digibind	Digibind ordered
	Activated charcoal	Activated charcoal ordered
	Donnagel	Donnagel ordered
	Kaopectate	Kaopectate ordered
	Lomotil	Lomotil ordered
	Opium	Opium ordered
	Paregoric	Paregoric ordered
	Loperamide	Loperaminde ordered
	Atropine	Atropine ordered
	Benztropine	Benztropine ordered
	Inapsine	Inapsine ordered
	Protamine	Protamine ordered
	Flumazenil	Flumazenil ordered
	Haloperidol	Haloperidol ordered
	Solumedrol	Solumedrol ordered
	Alteplase	Altiplace ordered
	Argatroban	Agratroban ordered
	Lepirudin	Lepirudin ordered
	Phentolamine	Phentolamine ordered
	Hydrochloric acid	Hydrochloric acid ordered
	Racemic epinephrine	Racemic epinephrine ordered
	Viokase and Sodium Bicarbonate tablet	Viokase and Sodium Bicarbonate tablet ordered
	Wydase	Wydase ordered
	Nubain	Nubain ordered <= 0.03 mg/kg/dose
	Acetylcysteine	Acetylcysteine ordered
	Neostigmine	Neostigmine ordered
	Hydrocortisone IV	Hydrocortisone IV ordered
Physiology	Heart rate	Age > 10y: HR < 45 or > 120 Age > 5y and $\leq$ 10y: HR < 50 or > 160 Age > 3y and $\leq$ 5y: HR < 50 or > 160 Age > 12m and $\leq$ 3y: HR < 50 or > 160 Age > 1m and $\leq$ 12m: HR < 60 or > 205 Age $\leq$ 1m: HR < 60 or > 220
	Respiratory rate	Age > 10y: HR < 8 or > 25 Age > 5y and $\leq$ 10y: HR < 12 or > 30 Age > 3y and $\leq$ 5y: HR < 15 or > 50 Age > 12m and $\leq$ 3y: HR < 15 or > 55 Age > 1m and $\leq$ 12m: HR < 20 or > 80 Age $\leq$ 1m: HR < 20 or > 80

Table 4 (Continued)

Type of Trigger	Trigger	Trigger Rule Detail
	SPO2	SPO2 < 80 %
	blood pressure deviation	50% blood pressure deviation from baseline X 3
	SBP < 100	SBP < 100 (decrease by 20 w/l 48hrs and on hypotensive drug)
	SBP < 80	SBP < 80 (decrease by 20 w/l 48hrs and on hypotensive drug)

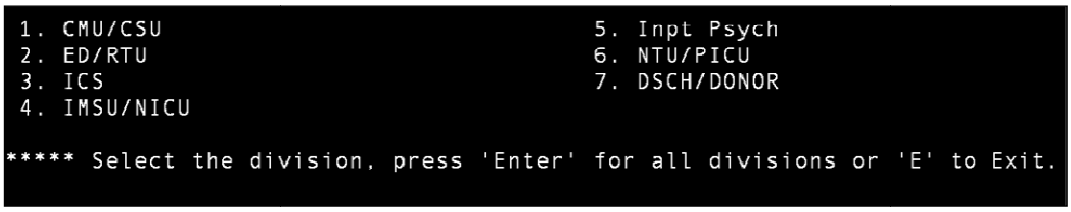

Figure 1. Menu options available to pharmacists in the computerized ADE monitor tool

an option was selected the pharmacist was given the opportunity to enter how many days in the past they wanted to retrieve alerts.

The ADE Monitor looked for any alerts that had been generated on the specified unit and within the specified time range. It then took the first alert that it found for the specific patient and organized the alert information (date and time of the alert along with the trigger name and its criteria), patient demographic data (encounter number, patient name, age, sex, room, medical record number, attending physician, admission date, and the free-text reason for admission), and current and discontinued medication information into one organized alert. The alert was then included in the printed Possible Adverse Drug Event report. The printed report only contained one alert per patient per day, even if multiple alerts were generated (see Figure 2). The original reasoning behind this was that only one alert was necessary because the pharmacist would then review the patient as a whole looking for any ADE that might have occurred.

Pharmacy Review of Alerts

The computerized monitoring tool was implemented directly into the pharmacist's normal daily workflow without increasing pharmacy staffing or other resources to investigate the alerts.

```
***** 03/29/09.09:40   @POTASSIUM < 3.0 & ON POTASSIUM ALTERING DRUG
@PAT: 057129140 XTRAIN, DEZRA                    6M  F   231X    MR#: 473796
 DOC: X7129 XTRAIN, CHARLIE
 ADMITTED: 03/13/09.06:49   ADMIT DIAG: STENT MALFUNCTION
 CURRENT DRUGS
  03/28/09.18:43 MILRINONE PD 0.2MG/ML, $DRIP 30.              Q 29 HRS
  03/29/09.01:49 *IV* CefUROXime (ZINACEF), PREDIL SYR 350.    Q  8 HRS
  03/29/09.01:49 ACETAMINOPHEN(TYLENOL), DROPS 105.            Q  6 HRS
  03/29/09.01:49 ACETAMINOPHEN(TYLENOL), SUPPOS. 105.          Q  6 HRS
  03/29/09.01:50 ACETAMINOPHEN(TYLENOL), DROPS 105.     PRN    Q  6 HRS
  03/29/09.01:50 ACETAMINOPHEN(TYLENOL), SUPPOS. 105.   PRN    Q  6 HRS
  03/29/09.01:50 MorphIne TUBEX / VIALS, FLOORSTOCK 0.7 PRN    Q  2 HRS
  03/29/09.01:51 MAGNESIUM SULFATE 8%, IV BOLUS 175.    PRN
  03/29/09.01:52 ASPIRIN, SUPPOS. 20.                          Q 24 HRS
  03/29/09.02:37 HEPARIN, VIAL 50.                             Q 50 HRS
  03/29/09.09:40 ***IV***FUROSEMIDE(LaSIX), VIAL 7.            Q  8 HRS
  03/29/09.09:41 RaNItidine (ZANtac), IVPB 7.                  Q  8 HRS
  03/29/09.11:51 ALBUTEROL (VENTOLIN HFA), HFA AER AD 4.PRN    Q  2 HRS
  03/29/09.11:51 LANOLIN/MIN OIL/PETROLAT WHT(LACRILUBE), OINT.(GM) 1.
  03/30/09.02:07 HEPARIN PD 100 UNIT/ML, $DRIP 30.             Q 43 HRS
  03/30/09.09:36 DOPamine PD 3.2MG/ML, $DRIP 30.               Q 77 HRS
  03/30/09.09:39 DEXMEDETOMIDINE HCL {ML} MCG/KG/HR, $DRIP 1.2Q 29 HRS
  03/30/09.09:39 FENTanyl MCG/KG/HR {1ML}, DRIP 10.            Q 36 HRS
  03/30/09.11:11 FENTanyl (SUBLIMAZE), VIAL 13.8        PRN    Q  1 HRS
  03/30/09.13:22 FENTanyl (SUBLIMAZE), VIAL 500.
  03/30/09.13:22 MIDAZOLAM (VERSED), VIAL 2.
  03/30/09.13:23 PROPOFOL(DIPRIVAN), VIAL 50.
 DISCONTINUED DRUGS
  03/30/09.09:08 MANNITOL 25%, VIAL 3500.
  03/30/09.09:08 THROMBIN TOPICAL, VIAL 1.
  03/30/09.09:08 GELATIN SPONGE ABSORBABLE 100CM(GELFOAM COMPRESSED), SPONGE 1.
 ADE? YES NO;    ENTERED INTO WEB EVENT? YES NO;    TIME REQUIRED?_____minutes;
```

Figure 2. Example of printed alert from the potential adverse drug event report

Pharmacists were trained on how and when to run the report from the computerized ADE monitoring tool, as well as what content would be available in the report. They were instructed to print the Possible Adverse Drug Event Report every morning Tuesday through Friday for the previous day. Due to decreased staffing in Pharmacy on Saturday and Sunday, the report was not printed on those two days. Instead it was printed on Monday for the previous three days, with the exception of President's day (Monday February 16, 2009) when the report was printed on Tuesday for the previous four days. The ICS unit Pharmacy staff, whose staffing patterns were different than the rest of the hospital chose to run the report every day for the previous day. Once the report was printed, the unit pharmacists were had been instructed to investigate each of the alerts for the occurrence of an ADE as they would normally investigate a voluntary

report from nursing staff or other clinicians. The pharmacy staff was instructed to the IOM definition of an ADE, what constituted an ADE, and were to note on the report whether an alert was associated with an ADE or not. If the alert was associated with an ADE, they were asked to report it to the hospital in the same manner that they would normally report an ADE that was discovered via another method. The normal method of reporting an ADE involved entering the details of the ADE into the voluntary, web-based reporting tool called Web Event. In addition to reporting ADEs, the pharmacist was also asked to note on the paper report the amount of time it took to investigate each alert. The minimum time for investigating an alert was set at one minute.

Once the ADE was entered into the Web Event system it was further reviewed by either a Risk Management staff member or by the Pharmacy Clinical Specialist and entered into another tool call Medication Event Verification (MEV) were it was assigned a severity of harm category. Each ADE discovered using the computerized monitoring tool was reviewed again by the Pharmacy Clinical Specialist to confirm that an ADE did occur. The Pharmacy Clinical Specialist also assigned the severity of harm category or confirmed the category that had been assigned by Risk Management. ADEs that occurred prior to admission or that were the result of an intentional overdose on the part of the patient were not included in the study.

The severity of harm incurred as a result of the ADE was determined using the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Index for Categorizing Medication Errors (Table 5).[51] Only categories "E" through "I" met the IOM definition of an ADE. Category "E" was defined as temporary

Table 5
Index for categorizing medication errors

Category	Description
A	Circumstances or event that have the capacity to cause adverse event
B	An event occurred but did not reach the patient
C	An event occurred that reached the patient but did not cause harm
D	An event occurred that resulted in the need for increased patient monitoring but no patient harm
E	An event occurred that may have contributed to or resulted in temporary harm to the patient and required intervention
F	An event occurred that required treatment and a higher level of care such as initial or prolonged hospitalization and caused temporary or reversible effects to the patient.
G	An event occurred that resulted in permanent patient harm
H	An event occurred that resulted in near-death requiring intervention necessary to sustain life from which the patient recovered
I	An event occurred that resulted in patient death

*Based on the NCC MERP Index for Categorizing Medication Errors 2001©

severity until category "I". Category I was defined as death of the patient due in part or entirely to the ADE. Therefore, only those events within these categories were deemed ADEs.

If the ADE was determined to be preventable, the ADE or event was further categorized according to the stage in which the drug ordering and delivery process error occurred. An error can be introduced at any one of the stages and may be perpetuated through to each phase if not discovered. Therefore, errors or ADEs may have an error type that is counted in more than one stage of the process, so actual number of events will not necessarily match the number preventable ADEs.

Statistical Analysis

The statistical significance of the findings was measured using Chi-Square, Unpaired t-Test, and Fisher's Exact Test as appropriate. Calculations were performed using Graph Pad QuickCalc's software.[52]

RESULTS

Patient Demographics

During the 12 week study timeframe there were a total of 3,562 unique patients. Females represented 44.7 percent and males 55.3 percent. The gender disparity seen is consistent with other studies.[53-55] There were 4,104 encounters or admissions to an inpatient bed on one of the eight units previously described. Females accounted for 44.4 percent of admissions and males 55.6 percent (see Table 6). The number of admissions per patient ranged from between one and eight, with 89.5 percent of the patients having only one admission and 97.2 percent of the patients having one or two admissions. The admission rates for male and female patients were compared against data from 2008 and 2007 and were found not to be statistically significant ($p = 0.8$).

Patient age was defined as age upon admission to the hospital. The average age of all admissions was 5.3 years, with a standard deviation of 5.9 years and a range of less than one day to 36.9 years (see Table 7). The age of male admissions were compared against the female admissions and were not found to be statistically significant ($p = 0.1$).

The number of patients greater than or equal to 18 years was 74 or 2.1 percent of

Table 6
Patients and admissions for study time frame and the previous two years

Gender	Study Patients (%)	Study Admissions (%)	Patients 2008 (%)	Patients 2007 (%)
Female	1,592 (44.7)	1,822 (44.4)	4,863 (45.3)	4,552 (45)
Male	1,970 (55.3)	2282 (55.6)	5,870 (54.7)	5,565 (55)
Total	3,562	4,104	10,733	10,117

Table 7
Patient age data upon admission

Gender	Study Patient Age (Std. Dev.)	Age Range Study Patients	2008 Patient Age Same Study Time frame (Std. Dev.)	Age Range 2008 Patients
Female	5.5 (6.1)	< 1 day to 36.9 years	5.4 (6.1)	< 1 day to 43.6 years
Male	5.2 (5.8)	< 1 day to 27.7 years	5.2 (6)	< 1 day to 56.7 years
All Patients	5.3 (5.9)	< 1 day to 36.9 years	5.3 (6.03)	< 1 day to 56.7 years

all patients and accounted for 122 encounters or three percent of all admissions and is similar to the study by Kaushal, et al.[9] It is noteworthy to mention that one patient with multiple admissions turned 18 during the study time frame between admissions to the hospital and was thus counted in both categories.

During the study timeframe, there were a total of 18,204 patient days (44 percent female, 56 percent male) with an average number of 5.1 study days per patient, a standard deviation of 8.5 days, and a range of 0.01 study days to 84 study days per patient (see Table 8). The average number of study days for females was compared against that for males and was not found to be statistically significant ($p = 0.12$). The low study day of 0.01 was the result of the patient being admitted 15 minutes prior to the end of the study.

ADEs

Overall, during the study period there were a total of 269 confirmed ADEs from the computerized monitoring tool and voluntary reporting. This total represented 6.6

Table 8
Description of patient study days

	Patient Days (%)	Avg Study Days	Std. Dev.	Range
Female	7,958 (44)	5	8.2	0.01 to 84
Male	10,240 (56)	5.2	8.8	0.01 to 84
Total	18,204	5.1	8.5	0.01 to 84

ADEs per 100 admissions and 14.8 ADEs per 1,000 patient days. Of the total ADEs, 181 were associated with the computerized monitoring tool and the other 88 were voluntarily reported. Of the 269 ADEs 83, or 31 percent were considered to be preventable. Nineteen of these were identified using the computerized ADE monitoring tool and 64 were from voluntary reporting.

ADEs by Nursing Unit

The ADEs were further parsed by unit and are represented in Table 9. The units with the highest number of ADEs per 100 admissions were the PICU, ICS, and NICU. These three units admit the highest acuity patients in the hospital and subsequently those patients receive the largest number of medications. They are also the three units where BCMA was not used during this study.

ADEs via Computerized Monitoring

The 181 ADEs associated with the computerized monitoring tool occurred in 136 unique patients over 140 admissions. Each patient had between one and five ADEs with

Table 9
ADEs by nursing unit

Unit	Patients	Patient Study Days	Total ADEs	Voluntarily Reported ADEs	Total ADEs	ADEs per 100 admissions	ADEs per 1000 pt. days
CMU	782	2441	16	14	30	3.8	12.3
CSU	781	2577	19	11	30	3.8	11.6
ICS	161	1753	18	4	22	13.7	12.5
IMSU	1059	3654	4	9	13	1.2	3.6
NICU	190	3200	10	14	24	12.6	7.5
NTU	591	1852	16	16	32	5.4	17.3
PICU	586	2404	98	20	118	20.1	49.1
RTU	261	325	0	0	0	0.0	0.0

79.4 percent of patients having only one ADE and 85.3 percent of patients having one or two ADEs. When normalized, these ADEs represented 4.4 ADEs per 100 admissions and 9.9 ADEs per 1,000 patient days. There were 179 ADEs categorized with the severity of "E" and two were categorized as "F" on the NCC MERP severity scale.

Nineteen or 10.5 percent of the ADEs were determined to be preventable. Of the preventable ADEs, 15 had available information regarding where the error occurred in the medication ordering and delivery process. The most common stage identified was administration, followed by prescribing, then dispensing and order review. The most common error type was IV infiltration, followed by overdose, and under dose (see Table 10).

There were 56 different drugs in 19 therapeutic drug categories that were listed as being responsible for at least one ADE with the most common drug categories being diuretics, antibiotics, narcotic analgesics, intravenous nutritional therapy, and antineoplastic agents. The most common drugs associated with ADEs were furosemide, vancomycin, bumetanide, morphine, and TPN (see Table 11).

Table 10
Description of preventable ADEs discovered via computerized monitoring

	Prescribing	Order Processing	Order Review	Dispensing	Administration	Monitoring	Totals
Overdose	4	0	2	2	4	0	12
Underdose	0	0	0	0	1	0	1
IV Infiltration	0	0	0	0	10	0	10
Totals	4	0	2	2	14	0	22

Table 11
Drug category and drugs involved in ADEs

Drug Category	Drug Name	# of ADEs
Diuretics	Furosemide	52
	Bumetanide	15
	Chlorothiazide	1
Antibiotics	Vancomycin	17
	Piperacillin-Tazobactam	5
	Ceftriaxone	4
	Gentamicin	4
	Cefazolin	2
	Ampicillin	2
	Ceftazidime	1
	Ciprofloxacin	1
	Amoxicillin-Pot Clavulanate	1
	Clindamycin HCl	1
	Nafcillin	1
	Metronidazole	1
	Linezolid	1
	Sulfamethoxazole	1
	Meropenem	1
Narcotic Analgesic	Morphine	9
	Fentanyl	5
	Hydrocodone-Acetaminophen	3
	Fentanyl-Bupivacaine in NS(PF)	2
	Hydromorphone	2
	Hydromorphone-Bupiv in NS (PF)	1
	Oxycodone	1
Intravenous Nutritional Therapy	Amino Acids 4.25%-Lytes-Ca-D10	6
	Amino Acids 4.25%-Lytes-Ca-D20	1
	Amino Acids 4.5 %-Lytes-Ca-D25	1
	Fat Emulsion	1
Antineoplastic Agent	Methotrexate	3
	Cytarabine	2
	Daunorubicin	1
	Cisplatin	1
	Pegaspargase	1
Bronchodilator	Albuterol	3
	Albuterol Sulfate	1
	Terbutaline	1
Anticoagulant	Enoxaparin	2
	Heparin (Porcine)	1
	Heparin (Porcine) in D5W	1
Immunosuppressant	Tacrolimus	3
	Cyclosporine	1
Corticosteroid	Methylprednisolone	1
	Prednisolone	1
	Dexamethasone	1
	Hydrocortisone	1
Benzodiazepine	Midazolam	1
	Lorazepam	1
Insulin, Rapid-Acting	Insulin Aspart	2

Table 11 (Continued)

Drug Category	Drug Name	# of ADEs
Antiviral	Valganciclovir	1
ACE Inhibitor	Enalapril Maleate	1
Immune Globulin	Lymphocyte,Anti-Thymo Imm Glob	1
Antifungal	Voriconazole	1
Anticonvulsant	Fosphenytoin	1
Mineral	Ferrous Sulfate	1
Antiemetic	Promethazine	1
NSAID	Ibuprofen	1
Intravenous Fluid	D10-1/2NS & Potassium Chloride	1

Voluntarily Reported ADEs during Study

In addition to the 181 ADEs that were identified with the computerized ADE monitoring tool, there were an additional 88 ADEs that were voluntarily reported via the hospital's Web-Event system during the study period.

Eighty seven of the voluntarily reported ADEs were categorized as "E" and one was categorized as "F" on the NCC MERP severity scale. These additional ADEs occurred in 78 different patients, over 79 admissions. These voluntarily reported ADEs represent 2.1 ADEs per 100 admissions and 4.8 ADEs per 1,000 patient days. In 71 of these ADEs the associated drug was listed. There were 39 different drugs involved in 18 therapeutic categories (see Table 12). The most common therapeutic categories were: antibiotics, intravenous fluid, intravenous nutritional therapy, narcotic analgesic, and anti-neoplastic.

Sixty-four of the 88 ADEs or 72.7 percent of the ADEs were determined to be preventable. Of the preventable ADEs, 62 had available information regarding where the error occurred in the medication management process. The most common stage identified was administration, followed by dispensing, prescribing, order review, and order processing. The most common error type was IV infiltration, followed by wrong drug, overdose, and drug not reordered (see Table 13).

Computerized Monitoring and Voluntary Reporting Overlap

We were not able to determine if there was any overlap between the ADEs identified by the Computerized Monitoring tool and those reported voluntarily because the computerized ADE monitoring tool was implemented to the same pharmacy staff that would have reported detected ADEs voluntarily without the tool. In order to detect any

Table12
Drug categories for voluntarily reported study ADEs

Drug Category	Drug Name	# of ADEs
Antibiotics	Vancomycin	10
	Ampicillin	2
	Cefotaxime	2
	Amoxicillin	1
	Amphotericin B	1
	Cefazolin	1
	Clindamycin HCl	1
	Meropenem	1
	Nafcillin	1
	Rifampin	1
Intravenous Fluid	D5-1/2 NS & Potassium Chloride	6
	D10-1/4NS & Potassium Chloride	2
	Dextrose 10%-1/2 Normal Saline	2
	Dextrose 5%-1/2 Normal Saline	1
	Dextrose 5% in Water (D5W)	1
	Dextrose 10% in Water (D10W)	1
	Lactated Ringers	1
Intravenous Nutritional Therapy	Fat Emulsion	5
	Amino Acids 4.25%-Lytes-Ca-D10	4
Narcotic Analgesic	Morphine	6
	Fentanyl-Bupivacaine in NS(PF)	1
	Hydrocodone-Acetaminophen	1
Antineoplastic Agent	Ifosfamide	3
	Methotrexate	2
Benzodiazepine	Diazepam	1
	Lorazepam	1
Anesthetic, General	Ketamine	1
Anticoagulant	Heparin (Porcine)	1
Antidote, Benzodiazepine	Flumazenil	1
Antifungal	Voriconazole	1
Antihypertensive	Nitroprusside	1
Beta Blocker	Esmolol	1
Hypoglycemic	Metformin	1
Immune Globulin	Immune Globulin (Human) (IGG)	1
Insulin, Long-Acting	Insulin Glargine	1
Insulin, Rapid-Acting	Insulin Aspart	1
Mineral	Calcium Gluconate	1
Phosphodiesterase Enzyme Inhibitor	Milrinone	1

Table 13
Preventable ADEs reported voluntarily during study time frame

	Prescribing	Order Processing	Order Review	Dispensing	Administration	Monitoring	Totals
Drug Not Reordered	0	0	0	0	1	0	1
Overdose	1	0	0	2	3	0	6
IV Infiltration	0	0	0	0	53	0	53
Wrong Drug	2	1	2	2	4	0	11
Totals	3	1	2	4	61	0	70

overlap, we would have had to create and then implement the monitoring tool within a separate more limited team of pharmacy staff that investigated and tracked ADEs independently of the floor pharmacists. However, all ADEs reported during the study timeframe were reviewed and ADEs identified via the monitoring tool were separated from those not related to the monitoring tool. The 88 ADEs not associated with the computerized monitoring tool were the voluntarily reported ADEs which have been previously described.

Voluntarily Reported ADEs in 2008 during same time period

During the same time period in 2008, there were 96 ADEs reported in 87 patients over 87 admissions via the voluntary reporting system. Of those, 95 were categorized as "E" and one was categorized as "F" on the NCC MERP severity scale. Those ADEs represented 2.5 ADEs per 100 admissions and 5.3 ADEs per 1,000 patient days. There were 69 ADEs where the implicated drug was listed; comprising 33 different drugs from 16 therapeutic categories (see Table 14). The most common therapeutic categories were: antibiotics, intravenous fluid, intravenous nutrition therapy, narcotic analgesic, and antihistamine.

Table 14
2008 voluntarily reported ADEs by drug category

Drug Category	Drug Name	# of ADEs
Antibiotics	Vancomycin	9
	Ampicillin	4
	Cefotaxime	2
	Clindamycin HCl	2
	Cefazolin	1
	Ceftriaxone	1
	Cefuroxime Sodium	1
	Doxycycline	1
	Nafcillin	1
Intravenous Fluid	D5-1/2 NS & Potassium Chloride	6
	Dextrose 5%-1/2 Normal Saline	3
	Dextrose 10% in Water (D10W)	2
	Dextrose 10%-1/4 Normal Saline	1
	Dextrose 10%-Normal Saline	1
Intravenous Nutrition Therapy	Amino Acids 4.25%-Lytes-Ca-D10	11
	Amino Acid Infusion 4.25%-D10W	1
Narcotic Analgesic	Morphine	4
	Fentanyl	1
	Hydrocodone-Acetaminophen	1
Antihistamine	Diphenhydramine	2
	Cyproheptadine	1
Antiarrhythmic	Amiodarone	2
Electrolyte Supplement	Potassium Phosphate	1
	Sodium Chloride	1
Antineoplastic Agent	Ifosfamide	1
Adrenergic Agonist Agent	Norepinephrine Bitartrate	1
Anesthetic, General	Pentobarbital	1
Antiemetic	Promethazine	1
Antifungal	Fluconazole	1
Bronchodilator	Albuterol	1
Diuretic	Furosemide	1
Hyperglycemic	Dextrose	1
Non Narcotic Analgesic	Ketorolac	1

Eighty six or 89.6 percent of these 2008 ADEs were determined to be preventable. Of the preventable ADEs, all 86 had available information regarding where the error occurred in the drug ordering and delivery process. The most common stage identified was administration, followed by dispensing, then order review and prescribing. The most common error type was IV infiltration, followed by overdose, other, dose omission, underdose, and then wrong drug and wrong rate-too fast. (see Table15).

Comparison of Computerized Monitoring and Voluntary Reporting

When comparing the two periods of voluntary reporting, the top four drug categories; antibiotics, intravenous fluid, intravenous nutrition therapy, and narcotic analgesic were the same. There were a total of seven therapeutic categories that were the same between the two time periods. The other three categories being: antineoplastic, general anesthetic, and antifungal. When these common categories were compared with the computerized monitoring ADE categories, three of the top four categories were in

Table 15
Preventable ADEs reported voluntarily during 2008 study time frame

Type of Error	Prescribing	Order Processing	Order Review	Dispensing	Administration	Monitoring	Total
Dose Omission	0	0	0	0	1	0	1
Overdose	0	0	1	1	2	0	4
Underdose	0	0	0	0	1	0	1
IV Infiltration	0	0	0	0	78	0	78
Wrong Drug	1	0	0	0	0	0	1
Wrong Rate-Too fast	0	0	0	0	1	0	1
Other	0	0	0	0	2	0	2
Total	1	0	1	1	85	0	88

common. Those categories were: antibiotics, narcotic analgesic, and intravenous nutrition therapy.

The increase in the number of detected ADEs during the study time frame in 2009 (219 of 4,105 admissions) when compared with the same time frame in 2008 (87 of 3,830 admissions) was found to be statistically significant ($p < 0.0001$).

In looking at preventable ADEs, errors were most often associated with the administration stage of the medication ordering and delivery process in both the computerized monitoring tool and voluntary reporting. Prescribing was the second most often associated stage for computerized monitoring, whereas dispensing was identified as the second most often associated stage between voluntary reporting. The most often reported error type for computerized monitoring was overdose followed by infiltration, whereas voluntary reporting identified infiltration, then wrong drug and overdose as third.

Triggers and Alerts

Of the 83 triggers that were implemented at PCMC, there were 51 triggers that generated a total of 3,769 alerts in 1,424 patients over 1,590 admissions. There were 25 triggers that generated 233 alerts which pharmacy staff had marked as being associated with an ADE. Of these 233 alerts, 181 were determined to be ADEs, while another 41 were alerts that fired multiple times and were related to a previously identified ADE. For example, a patient with a high phenytoin level, that was identified as an ADE, had two other levels reported over the next 3 days that were high, thus two additional alerts were generated related to the same event. Of the remaining 11 alerts that were reported as having been related to an ADE, five were related to an ADE that occurred prior to

admission, five were determined not to be an ADE upon further review, and one was an intentional overdose, and did not meet the criteria for inclusion in the study. After removing these 41 alerts, was a total of 24 triggers that were associated in 181 ADEs (see Table 16)

The Positive Predictive Value (PPV) of all triggers was 4.8 percent. The PPV for triggers that identified at least one ADE ranged from 88.2 percent for the Wydase Trigger to 0.17 percent for the Respiratory trigger.

There was an average of 44.9 triggers per day with a standard deviation of 17.9 alerts per day. The minimum number of alerts per day was eight and the maximum was 78.

Of the 11 new triggers that were added, eight fired a total of 406 alerts. Table 17 provides a summary of the performance of these new triggers as compared with the modified and unmodified triggers. Five of these triggers were associated with a total of 26 ADEs. The PPV for the new triggers was 6.4 percent. The most effective new triggers in order were Wydase ordered, Antifactor Xa level, Viokase 8 and Sodium Bicarbonate ordered, Tacrolimus level, and EOS level. Those triggers which had alerts but no associated ADEs were Racemic Epinephrine ordered, Acetylcysteine ordered, and low dose Nubain ordered. Those new triggers that did not alert during the study included caffeine level, hydrochloric acid ordered, and Phentolamine ordered.

Of the 14 triggers that were modified, 12 generated a total of 1,873 alerts. Of those, three were associated with 11 ADEs. The PPV for the modified triggers was 0.6 percent. The WBC trigger was the most effective with a PPV of 8.7 percent, followed by heart rate with a PPV of 0.8 percent, and then respiratory rate with a PPV of 0.2 percent.

Table 16
Description of trigger results

Name of Trigger	Trigger Modifications	Alerts	ADEs	PPV
Wydase	New	17	15	88.2%
Potassium	Unchanged	141	65	46.1%
Anti-factor Xa	New	5	2	40%
Viokase 8 and Sodium Bicarbonate tablet	New	5	2	40%
Naloxone	Unchanged	11	3	27.3%
C. difficile	Unchanged	46	9	19.6%
Benadryl	Unchanged	263	36	13.7%
SBP < 80	Unchanged	15	2	13.3%
Doubling of Cr	Unchanged	54	6	11.1%
Phenytoin Lvl	Unchanged	11	1	9.1%
WBC	Modified	46	4	8.7%
Vanco trough	Unchanged	52	4	7.7%
SBP < 100	Unchanged	25	1	4%
Tacrolimus	New	27	2	7.4%
Gent trough	Unchanged	42	3	7.1%
SGPT	Unchanged	64	4	6.3%
PTT	Unchanged	34	2	5.9%
Glucose_50	Unchanged	68	3	4.4%
Glucose_350	Unchanged	150	3	2%
EOS	New	268	5	1.9%
Billirubin	Unchanged	61	1	1.6%
Hydrocortisone IV	Unchanged	123	1	0.8%
Heart rate	Modified	763	6	0.8%
Respiratory rate	Modified	589	1	0.2%
Acetylcysteine	New	21	0	0%
Activated charcoal	Unchanged	2	0	0%
ALK PHOS	Unchanged	30	0	0%
Alteplase	Unchanged	51	0	0%
Atropine	Unchanged	27	0	0%
Benztropine	Unchanged	1	0	0%
Cyclosporin	Modified	9	0	0%
Epinephrine	Unchanged	37	0	0%
Flumazenil	Unchanged	1	0	0%
Gent peak	Modified	7	0	0%
Haloperidol	Unchanged	2	0	0%
INR	Unchanged	1	0	0%
Loperamide	Unchanged	40	0	0%
Neostigmine	Unchanged	14	0	0%

Table 16 (Continued)

Name of Trigger		Alerts	ADEs	PPV
Nubain	New	7	0	0%
Phenobarbital	Modified	116	0	0%
Phenobarbital Lvl	Unchanged	5	0	0%
Phenytoin	Modified	32	0	0%
Platelet count	Modified	3	0	0%
Prednisone	Modified	280	0	0%
Protamine	Unchanged	11	0	0%
Racemic epinephrine	New	56	0	0%
SGOT	Unchanged	29	0	0%
SPO2	Unchanged	29	0	0%
Steroid cream	Unchanged	50	0	0%
Tobra peak	Modified	24	0	0%
Vanco peak	Modified	2	0	0%
Vitamin K	Modified	2	0	0%
Totals		3,769	181	4.8%

Table 17
Performance of new, modified, and unchanged triggers

Trigger Status	Triggers (%)	Alerts (%)	ADEs (%)	PPV
Unchanged	58 (69.9)	1,490 (39.5)	144 (79.6)	9.7%
New	11 (13.3)	406 (10.8)	26 (14.4)	6.4%
Modified	14 (16.9)	1,873 (49.7)	11 (6.1)	0.6%
Total	83	3,769	181	

The heart rate trigger generated 763 alerts and the respiratory rate trigger generated 589 alerts for a total of 1,352 alerts or 35.9 percent of all alerts.

Of the remaining 58 triggers that were unchanged, 32 generated a total of 1,490 alerts. Sixteen of the 32 triggers were associated with 144 ADEs. The PPV for this set of triggers was 9.7 percent. The most effective triggers were Potassium, Naloxone ordered, C. Difficile, Benadryl ordered, and SBP < 80. There were 26 triggers in this set that did not generate any alerts.

Time Analysis of Alert Investigation

Of the 181 ADEs found during the study timeframe using the computerized ADE monitor, 178 had a time recorded for how long it took to investigate the alert and then enter it into the Web Events system. The average time was 10.4 minutes with a standard deviation of 18.3 minutes and a range of 1 minute to 30 minutes with one outlier of 240 minutes. If the outlier is not included, the average time of investigation is 9.1 minutes, with a standard deviation of 6 minutes. The distribution of the amount of time it took to investigate alerts associated with an ADE can be seen in Figure 3.

There were 3,484 alerts that were marked as not being involved in an ADE. Of these, 3,445 had a time recorded for how long it took to investigate the alert. It took an

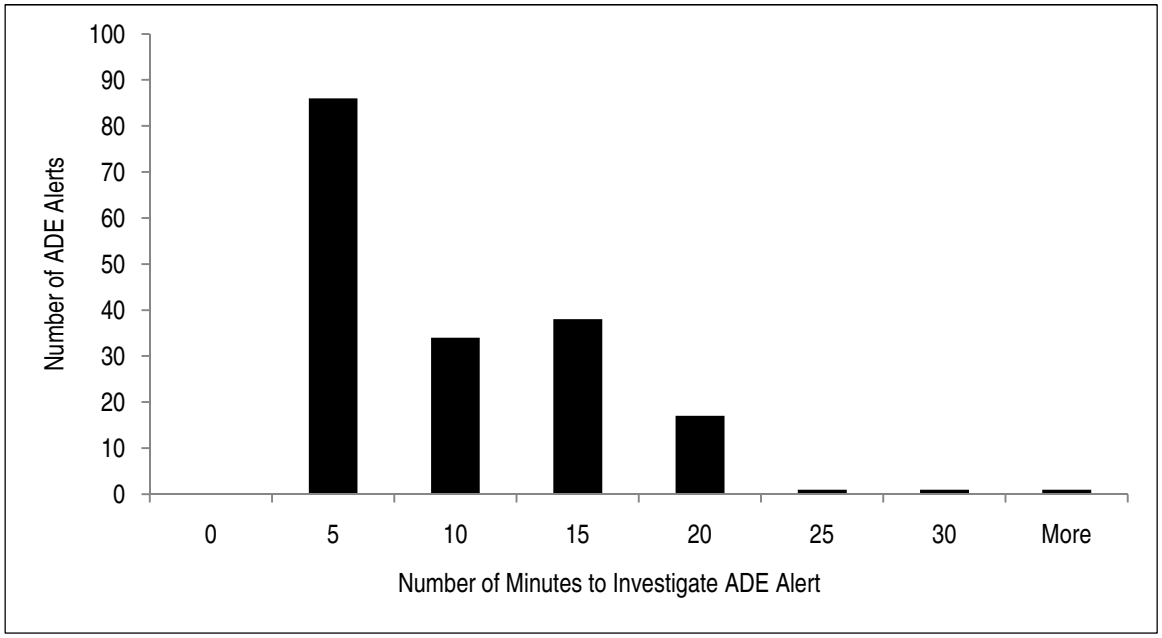

Figure 3. Distribution of time to investigate ADE associated alerts

average of 2.7 minutes with a Standard Deviation of 2.2 minutes to investigate each alert that was not associated with an ADE. The time range of investigation was from one minute to 20 minutes.

When both sets of alerts are combined, the average time to investigate an alert was 3.1 minutes with a standard deviation of 4.9 minutes.

The average amount of time it took to enter an ADE into the Web-Event system was estimated to be three minutes. The amount of time spent investigating alerts associated with an ADE minus the time it took to enter the ADE into the Web Event tool was compared to the 2.7 minutes spent investigating alerts not associated with an ADE. The comparison was completed on the results with the single outlier case of 240 minutes included. With the single outlier included the average time of investigation for alerts associated with an ADE was 7.4 minutes. The comparison was also made with the single outlier excluded. With the outlier excluded, the average time of investigation for alerts

associated with an ADE was 6.1 minutes per alert. In either comparison the amount of time to investigate a true ADE was significantly higher than the amount of time to investigate a non-ADE alert ($p < 0.0001$).

There were a total of 52 alerts or 1.4 percent of the alerts where insufficient or no information was entered by the pharmacists. This could have been the result of a busy work schedule and the pharmacist's inability to research all of the alerts, or it could have just been an oversight on the pharmacist's part, either investigating the alert and then not including the information or just accidentally bypassing the alert without reviewing it.

It is also important to note that on at least one unit, the pharmacists were confused about the minimum reporting time for alert investigation. This confusion was the result of at least one other active study within the pharmacy where input of time spent by the pharmacist involved was also required. The minimum time requirement for that study was 5 minutes. When discovered, the pharmacists were retrained to use 1 minute per alert for this study's minimum investigation time. As a result of the confusion, it was possible that the reported minimum time spent investigating alerts that were not involved in an ADE was artificially high.

DISCUSSION

This study had several objectives. One of the key objectives was to compare the detection rate of the computerized ADE tool at Primary Children's Medical Center to the current method of voluntary reporting. As would logically be expected with the introduction of a second detection method, the result was a significant increase in the detection of ADEs ($p < 0.0001$) when compared with the same time frame for the previous year. The reasoning for such a large increase in detection of ADEs is because the computerized ADE monitoring tool allowed every patient to be reviewed for the presence of known ADE indicators. It was able to do this using discrete data that is stored within the electronic medical record. This freed the pharmacy staff from having to complete manual chart review to find these indicators. It thus enabled them to focus on patients where the likelihood of an ADE was increased, instead of spending time manually reviewing the patient's record or having to wait for a clinician report of a possible ADE, as would have occurred with the voluntary reporting method. Another interesting point to note is that the increase may be due in part to the low percentage of ADE overlap that has been found among the methods of voluntary reporting and computerized monitoring in several previous studies. This overlap has previously been reported by most studies as being between 0.5 percent and 4.3 percent. Using the results of this study we were unable to definitively determine the amount of potential overlap that existed among the two methods because the tool was implemented directly into the

daily workflow of the pharmacists. In order to detect any overlap we would have had to implement the monitoring tool in a separate, more limited setting, with a team of pharmacy staff that investigated and tracked ADEs independent of the floor pharmacists.

Another key objective of this study was to implement the computerized ADE alerting tool into the daily workflow of the Pharmacy department without increasing the demand on pharmacy resources. Within this study we were successfully able to show that a computerized ADE monitoring tool can be implemented into daily workflow without increasing pharmacy staff. We were also able to show that it was sustainable over the course of the entire study. With so much concern about the rising cost of healthcare and the amount of uncertainty in the current healthcare environment, the ability of an institution to provide increased monitoring and improved quality of care with minimal budgetary impact is becoming an absolute necessity.

The ADE detection rate of 4.4 ADEs per 100 admissions or 9.9 ADEs per 1,000 patient days using computerized monitoring as reported in this study was higher than that reported in the two previous pediatric studies which also used computerized monitoring.[36,40] Those studies reported rates of 1.8 and 2.3 ADEs per 100 admissions and 1.6 and 6.6 ADEs per 1,000 patient days. However, the rate of ADE detection in this study did correspond to the rates of detection reported in adult studies that also used computerized monitoring. Those studies reported rates between two and 6.2 ADEs per 100 patient admissions[34,35,41-43] and 9.6 ADEs per 1,000 patient days.[35] The difference in the ADE detection rate of this study compared with the detection rates of the previous two pediatric studies may be the result of the number of triggers used by the computerized monitoring tool in this study. The computerized monitoring tool in this

study had a total of 83 triggers as compared with the other two pediatric studies which had 57 and 31 triggers each.[36,42] The difference in detection rates may have also been the result of differences in the triggers themselves. The triggers used in this study, with the exception of the newly added triggers, have been refined and modified ever since first being reported in 1991.[34] The difference in ADE detection rates were less likely to have been the result of different patient types treated, or patient acuity among the hospitals, since both of the other facilities were similar to PCMC in that they were tertiary care centers and had a wide variety of similar patient services available.[36,40,56-58]

The amount of time it took to investigate an alert associated with an ADE was 6.1 minutes. This was significantly higher than the 2.7 minutes that it took to investigate an alert that was not associated with an ADE ($p<0.0001$). This type of comparison has not previously been reported, and although the significant difference in investigation times may have just been assumed by many, it is still important to quantify just how much of a difference there is when investigating alerts that result in an ADE from alerts that do not.

The amount of time that pharmacists spent investigating alerts was compared to other computerized monitoring studies where the amount of time spent by pharmacy staff was reported.[35,36,40,43] Although, these studies did not specifically report the amount of time it takes to investigate an individual alert, there is enough information in the studies to extrapolate the data (Table 18). The average investigation time extrapolated from the reported data was found to be from 1.7 to 8.9 minutes per alert. From the results of this study we found that it took an overall average of 3.1 minutes to investigate an alert. This result falls within the range found in the data extrapolated from the other studies.

The ADE rates via voluntary reporting presented earlier in this study (2.1 per 100

Table 18
Comparison of alert investigation time with other studies

Study	Study Start	Study End	Length Days	Weekly Time Minutes	Total Alerts	Time per Alert Minutes
Current Study	2/2/2009	4/26/2009	84	946	3679	3.1
Kilbridge et al.[40]	2/1/2008	7/31/2008	182	420	1226	8.9
Kilbridge et al.[43]	3/1/2005	4/30/2005	61	900-1500	4604	1.7-2.8
Evans et al.[50]	5/1/1989	5/1/1990	365	600	4457	7.0
Jha et al.[35]	10/1/1994	5/31/1995	243	660	2620	8.7

admissions and 4.8 per 1,000 patient days during the study timeframe in 2009 and 2.5 per 100 admissions and 5.3 per 1,000 patient days for the same time period in 2008) were compared against the two other pediatric studies that investigated computerized surveillance in addition to voluntary reporting. The rates for Primary Children's were higher than the 1.9 ADEs per 100 admissions and 1.8 ADEs per 1,000 patient days found in the study by Ferranti et al.[36] This result could be the difference in definitions among the two studies. The study by Ferranti et al[36] used a seven point severity scoring system, where as we used the NCC MERP Index for Categorizing Medication Error in this study.[24] It could also be a difference in interpretation of the definition of an ADE or even differences in the evaluation techniques among those individuals reviewing the events.

The 11 new triggers added to the computerized ADE monitoring tool had an overall PPV of 6.4 percent. Five of those triggers detected a total of 26 ADEs or 14.4 percent of all ADEs detected via the computerized monitoring tool. Of those five, three triggers had a PPV at or above 40 percent. Refer to Table 17 for additional detail about the performance of new triggers and to Table 3 for a list of all 11 new triggers. Four of the triggers will need to be reviewed further for modification to improve the PPV or to remove them from the tool. It is clear that there was benefit in evaluating the existing

triggers and adding additional triggers that were determined to be beneficial to the pediatric population. Many of these triggers may also be beneficial in the adult population as well. The new triggers did not have as high a PPV as the 58 existing unmodified triggers, which had a PPV of 9.7 percent. The difference in the PPV may be the result of modifications previously made in the adult tool over time to maximize the PPV, while the new triggers will still need additional modifications and refinement to maximize their PPV result values.

Of the 14 triggers that were modified for pediatrics, only three were associated with a total of seven ADEs. The WBC trigger had the highest PPV of 8.7 percent while the heart rate respiratory rate triggers both had disappointing performances with PPVs less than 1 percent each.. The pharmacists reported that the heart rate and respiratory rate triggers were the two most cumbersome of all the triggers that generated alerts. This was because of the extremely high false positive rate of these two triggers. They generated 35.9 percent of the alerts but only accounted for 3.9 percent of the ADEs. The high false positive rate of these two triggers was the result of only limiting the trigger criteria to age specific values. It is clear that additional modifications will need to be made for these two triggers in order to increase the PPV. In addition, the pharmacists expressed that if these two triggers could be modified to filter out a large number of the false positives, the tool would be more acceptable. Modified triggers that need to be reviewed for further modification or removal include Heart Rate, Respiratory Rate, Prednisone, Phenytoin ordered, Phenobarbital ordered, WBC, and Tobra Peak.

A determination was made that depletion of electrolytes severe enough to cause overall body deficits as a result of potassium wasting medications qualified as temporary

harm to the patient and was therefore considered an ADE. The number of ADEs detected in our study with the low potassium trigger represented 35.9 percent of all ADEs found using computerized ADE monitoring. This definition and the subsequent results are similar to that of Kilbridge et al.[40] which found 66 ADEs of 223 alerts (PPV 30 percent) with their Hypokalemia trigger and represented 41 percent of the ADEs found during their study. These results may simply be the outcome of this definition being applied to represent an ADE in this study, where it has not been delineated as such in other studies. In order to determine if the results of this trigger represents a significant difference in ADE detection between pediatrics and adults, more investigation will need to be completed by applying the same definition to the adult population to determine how often the same situation occurs. Also, more investigation needs to be completed to determine how often this situation occurs when patients are receiving potassium wasting medications and if there is predictability to its occurrence. If this can be determined there is potential that it can be prevented from occurring.

Only two ADEs were categorized as an "F" on the NCC MERP scale out of 181 ADEs found using computerized monitoring. This is consistent with the number of ADEs categorized as "F" found via voluntary reports during the same time frame in 2009 (1 out of 88 ADEs) and during the same time period in 2008 (1 of 96 ADEs). That ratio is less than was found by Kilbridge et al.[42] in which 20 out of 160 ADEs detected were categorized as "F" with another five being categorized between "G" and "I." This finding may have been the result of preventative methods already in place at the study facility which have been previously described. It could have also been the result of

chance since the time frame of this study was only three months versus the six months for the study reported by Kilbridge et al.[40]

The overall percentage of preventable ADEs found during the study period via voluntary reporting and computerized monitoring was 31 percent. This finding is within the range of 19 and 61 percent found among previous pediatric studies.[9,10,39] The pediatric studies that reported rates of preventable ADEs used the method of intensified surveillance or a manual trigger tool conducted via manual chart review.

When we looked at the methods separately, it was clear that voluntary reports were more likely to capture preventable ADEs ($p<0.0001$) with 72.7 percent of voluntary reports from the study time frame and 89.6 percent of voluntary reports from the same time period in 2008 being identified as preventable. These rates were higher than what was found in the pediatric studies previously mentioned. This high rate is likely the result of IV infiltrations being considered a preventable ADE at the study facility.

Computerized surveillance captured more unpreventable ADEs with only 10.5 percent of the computerized surveillance ADEs being considered preventable. Ferranti et al. also reported that their voluntary reporting system was better at detecting system failures like drug omission, administration errors, and lapses in monitoring than computerized surveillance.[36] Neither of the pediatric studies that used computerized surveillance reported the rate of preventable ADEs found using that method. In adults, Jha et al. reported that 25.5 percent of ADEs found using computerized surveillance in their study were deemed to be preventable. However, they did not report any further detail regarding how these events occurred. Classen et al. reported that they felt almost 50 percent of the ADEs found in their study were preventable. They reported that 42

percent of all their ADE's were the result of excessive medication dosage for the patient's weight and calculated renal function and that these were felt to be preventable. They also reported that 4.6 percent of ADEs found in their study were the result of drug interactions and another 1.5 percent were the result of known drug allergies, both of which were felt to be preventable. During the current study's timeframe, the pharmacy system had many triggers that were specific to weight based dosing for pediatrics, drug interactions, and patient allergies. These triggers fired at the time the pharmacist entered the order into the system and are part of the preventative methods mentioned in the methods section. Thus, it is probable that most of the ADEs that were found to be preventable in the study by Classen et al. were prevented from occurring in this study. This reasoning would explain why ADEs found via computerized monitoring only had a preventable rate of 10.5 percent.

Of the preventable ADEs, the most common Drug Ordering and Delivery Process stage identified was administration, followed by prescribing, dispensing, order review, and order processing. This outcome was different than what was found in the Adverse Drug Event Prevention Study Group.[37,45] That group found that errors in their studies occurred most often in physician ordering, followed by nurse administration, pharmacy dispensing, and then transcription and verification. It is also different from what was found in the pediatric study by Takata et al.[39] which reported that the most common error occurred in the monitoring stage followed by prescribing and dispensing. Both the adult and pediatric studies[37,39,45] were conducted using the intensified surveillance method. However, the pediatric study[39] did include the use of a manual trigger tool. The difference in methods used to identify ADEs may explain the difference in findings of the

most common Drug Ordering and Delivery Process stages among the studies. It may also be the result of the type of ADEs that were included in this study as compared to the other studies mentioned.

There are several limitations to this study. We did not complete inter-rater reliability testing because this study was implemented into the daily workflow of the pharmacy department and the large number of different pharmacists who were reviewing alerts made it impractical. We did, however, have a second pharmacist review every positive ADE to validate the first pharmacist's findings. Due to cost and availability of resources, we did not conduct a concurrent chart review and therefore cannot compare the results of our study against the traditional gold standard. In addition, this study was conducted in one tertiary pediatric teaching medical center and may not be generalizable to other settings.

CONCLUSION

Prior to the initiation of this study there was little research that had been completed on ADEs in pediatrics, and no research on implementation of computerized surveillance to detect ADEs in pediatrics was discovered. Since the initiation of this study, two other studies have been published that report results on the implementation of computerized ADE surveillance tool in pediatrics. The results of this study reinforce those found in the other two studies and will continue to help lay the foundation for further study of the potential that computerized surveillance has for detecting ADEs in the pediatric population. By continuing to research ADEs in the pediatric population: triggers can be more thoroughly modified and defined to increase the PPV, additional detail can be discovered about the presence and relationship of pediatric ADEs resulting from potassium wasting medications, and more detail about the occurrence of this type of ADE in the adult population and the relationship to the pediatric population can be explored. The long term outcomes of continuing research ADEs in the pediatric population are that methods can be implemented that will help to reduce the amount of harm that pediatric patients undergo as a result of ADEs. In addition, it will also help to reduce the cost of healthcare in this population.

This study undertook the challenge of modifying an adult computerized ADE surveillance tool and then implementing that tool into the pediatric environment. The

modified tool significantly increased the detection of ADEs among the pediatric population when compared to voluntary reporting and reinforces previous reports that many ADEs go unreported and or unrecognized. The computerized surveillance of ADEs has previously been shown to be complementary to voluntary ADE reporting.

The results of this study describe in more detail than has previously been reported, the amount of time it takes to investigate alerts. The results also show that there was a significant difference if the alert identified an ADE. In addition, computerized surveillance detects fewer ADEs that are preventable or are the result of error.

The results of this study suggest that the types of ADEs that occur in children may be different than those that occur in adults. However further research is needed in order to make any conclusion on this point with confidence.

Work needs to continue on the modification of trigger rules to increase the PPV of each trigger in order to ensure that it is viewed as a beneficial tool in improving the healthcare that is provided to pediatric patients.

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