ADVERSE DRUG EVENTS AND MEDICATION ERRORS IN HOSPITALIZED CHILDREN AT JIMMA UNIVERSITY SPECIALIZED HOSPITAL, OROMIYA REGIONAL STATE, SOUTH WEST ETHIOPIA

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Adverse Drug Events and Medication Errors in Hospitalized Children at Jimma University Specialized Hospital, Oromiya Regional State, South West Ethiopia

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ABSTRACT

Background: The incidence and nature of adverse drug events (ADEs) and medication errors in hospitalized children have been well described in western countries unlike the case in developing countries though patient safety has become a serious global public health issue. Hence investigating adverse drug events and medication errors in our setting is essential from the local and global perspectives in medication safety and to improve the quality of health care.

Objective: To assess the magnitude and nature of adverse drug events, potential adverse drug events (PADEs) & medication errors (MEs) in hospitalized children at Jimma University specialized hospital

Methods and patients: we conducted a 3 month prospective observational study in the four medical units of the pediatric ward, Jimma University specialized hospital. The study populations were all admitted children with a length of hospital stay > 1 day over 12 week's period. Adverse drug events, potential adverse drug events and medication errors were main outcome measures and were identified using multifaceted approach involving daily chart review, interview of Parent/care giver(and or children themselves), Attendance at ward rounds and/or meetings , stimulated voluntary staff reports. We designed instruments for collection and evaluation of these medication related incidents/events. A review panel consisting of two senior pediatric residents evaluated the severity and preventability of adverse drug events using explicit criteria.

Results: A total of 634 admissions with 6182 patient-days of hospital stay were followed. There were 2072 medication orders written which account for 35,117 medication doses given. Fifty eight adverse drug events were identified with an incidence of 9.2 per 100 admissions, 1.7 per 1000 medication doses and 9.4 per 1000 patient days. The reviewers classified 67. 2% as non-preventable while 32.8% as Preventable ADEs. Regarding the severity of adverse drug events, 67% were category E while 7% were category G. The most common medication class associated with adverse drug events was anti-infectives. A total of 88 potential adverse drug events were identified with an incidence rate of 13.9 per 100 admissions, 2.5 per 1000 medication doses, 14.2 per 1000 patient-days. Of these, 81.8% were non-intercepted PADEs. Of 674 medication errors identified, 29.1% were improper dose followed by wrong administration technique (19.9%). The risk of adverse drug events increases with older age, longer length of hospital stay, and use of CNS, endocrine and antihistamine medicines.

Conclusion: Adverse drug events and medication errors are common in hospitalized children at study setting. The commonest type of medication error and stage of medication use system were improper dose and administration stage respectively.

Recommendations: The use of technology and non-technology based methods could reduce medication safety problems identified by this study.

Key words: adverse drug events, potential adverse drug events, medication errors, Hospitalized children

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LIST OF ACRONYMS AND ABBREVIATIONS

ADE	Adverse Drug Event
ADR	Adverse Drug Reaction
AE	Adverse Event
JUSH	Jimma University Specialized Hospital
LOS	Length of Stay
MAEs	Medication Administration Errors
MEs	Medication Errors
NCCMERP	National (USA) Coordinating Council for Medication error Reporting and Prevention
NICU	Neonatal Intensive Care Unit
NRU	Nutritional Rehabilitation unit
PADE	Potential Adverse Drug Event
PICU	Pediatric Intensive Care Unit
PRN	As needed
WHO-UMC	World health organization – Uppsala monitoring center

CHAPTER ONE
INTRODUCTION

1.1 Background information

Adverse events, defined as injuries caused by medical management, are one of the qualities of medical care indicators and these events are associated with cost imposition and occur frequently. Of the different forms of adverse events, nowadays adverse drug events (ADEs) and medication error has received extensive concern among the public and the medical community. The Harvard Medical Practice Study was one of the first investigations of adverse events[1, 2, 3].

The Institute of Medicine of USA in its report To Err Is Human [4] concluded that between 44 000 and 98 000 lives are lost per year in US hospitals as a result of medical error. This estimate was based on the lesson from the Harvard Medical Practice Study, which estimated that 3.7% of all hospitalized patients in a New York State cohort experienced an adverse event (AE) related to medical therapy. A further study from the Harvard group using more sophisticated detection methods revealed a 6.5% rate of adverse drug events (ADEs) alone in the adult inpatient setting, with 33% of these events described as preventable. Application of these methods to a pediatric population revealed a 2.3% ADE rate with 19% described as preventable [5].

The Harvard Medical Practice Study that out surfaces the incidence of ADEs and medication error served as an impetus for additional research regarding this issue.[6] Other studies most of which used the adverse drug reaction as the outcomes have also shown that injuries due to drugs are common in hospitalized patients, although the true incidence is controversial and varies widely (15% to 35%) depending on the rigor with which the event was sought [3].

Drugs represent a major cause of injury in hospitalized patients and were the single most frequent cause in the Harvard Medical Practice Study, accounting for 19.4% of injuries. In another study carried out at two large tertiary care hospitals, Brigham and Women's

Hospital and Massachusetts General Hospital, there were 6.5 adverse drug events (ADEs) per 100 admissions [3]. Of these ADEs, 28% were preventable, and 56% of these preventable ADEs occurred during prescribing. These reports underline the importance of developing strategies to prevent and ameliorate ADEs so as to improve the quality of patient care and to reduce health care costs [3].

Studies conducted in the pediatric inpatient setting are few, but those studies showed that ADEs and potential ADEs are found to occur frequently. Different studies that utilized ADR as an outcome report that the incidence of adverse drug reactions (ADRs) in pediatric inpatients varies from 5.6 to 16.8% based on the method of detection utilized[3,7,8].

Some published literatures showed that potential ADEs may be more common in pediatrics, suggesting that the epidemiologic characteristics of medication errors may be different between children and adults.[9] Furthermore, the incidence of these events is higher in an intensive care population than in a general pediatric population[10, 12].

In one meta analysis study conducted by P. Impicciatore et al (2001) which evaluated nine prospective studies that were performed in seven different countries, the reported ADR incidence in hospitalized children ranged from 4.37% to 16.78% among the studies, the overall incidence of ADRs (Meta-analytic weighted average) was 9.53%; severe reactions accounted for 12.29% of the total [11].

Long et al (2010) performed a retrospective, cross-sectional study at Duke University Health System, North Carolina, USA, a tertiary care teaching hospital by Review of historical ADE data and critical lab values found that 385 medication-related ADEs occurring in 353 pediatric patients. Replacement preparations and total parenteral nutrition comprised the majority (36.6%) of adverse drug events [13].

Of the little available studies about the frequency and nature of the adverse drug events in children, despite the extensive literature on ADEs in adult populations, one study based on concurrent order and chart review and error reporting by providers examined ADEs in

pediatric inpatients at two academic institutions in Boston city, USA and described an ADE rate of 2.3 per 100 admissions, or 6.6 per 1,000 patient-days [14].

A research done by Jeffrey Ferranti et al on Duke University Hospital pediatric inpatients, North Carolina, USA over a 1-year period found an adverse drug event rate of 1.8 events per 1000 pediatric patient-days based on medication-related reports entered in to the safety reporting system and an adverse drug event rate of 1.6 events per 1000 patient-days based up on computerized surveillance using triggers designed primarily for ADE detection in adults [15].

Medication use in pediatrics is complicated by a number of factors and hence particularly prone to error. Based on limited evidence from the US experience suggests that medication errors and corresponding harm could be higher in children than in adults. A number of reasons could support this report: most drug doses in pediatric medication are calculated individually, based on the patient's age, weight, body surface area and/or their clinical condition. Secondly, the majority of drugs used in children are unlicensed or off-label [16].

Numerous studies have described the incidence and types of adverse drug events (ADEs) as described above, but there is a discordant report regarding estimates of the incidence of ADEs that varies widely, depending upon definitions, measurement methodologies, and populations studied. Adverse drug events can be detected in a variety of ways, including voluntary reporting, prompted reporting, patient interviews, chart reviews and computerized monitoring using trigger systems. While chart review has traditionally been considered a gold standard, there is evidence that computerized surveillance detects many events that are not easily detected during chart review. It is generally agreed that voluntary reporting of ADEs is low yield and anecdotal in nature, and not valuable for ADE quantification [17, 18].

It is the light of the above, this study assessed the nature and frequency of ADEs, potential ADEs and medication errors in hospitalized children at the public referral specialized hospital in south west Ethiopia.

1.2 Statement of the problem

In this sub unit, studies that show the magnitude of problem due to ADEs and impact of ADEs, PADEs and medication errors on hospitalized children is presented.

Reducing, if possible eliminating of ADEs is a significant issue for pediatric health care providers as long as they are concerned about patient safety. There is often little pediatric-specific ADEs information on medications commonly used in children, because of limited number of pediatric clinical trials being conducted and the use of smaller sample sizes, which makes identifying rare events difficult prior to marketing of drugs for clinical use in children [19].

Available studies show that ADEs impose a larger impact on the overall health care cost. One study conducted in two large tertiary care hospitals in Boston, USA found that almost two percent of admissions experienced a preventable ADE, resulting in an estimate for post event costs of $4685 for a preventable ADE or about $2.8 million annually for a 700-bed teaching hospital. If these findings are generalizable, the increased hospital costs alone of preventable adverse drug events affecting inpatients are about $2 billion for the USA as a whole [4].

In their study at LDS Hospital, Salt lake city, USA; Evans et al (1993) found that patients with ADEs had an average cost of hospitalization of $10,584 compared to $5, 350 for those without and the attributable difference due to ADEs was $1,939, without including malpractice costs or the cost of injury to the patient. This indicates that the 569 ADEs at this hospital during 1992 resulted in an additional 1,104 extra patient days at a cost of $1, 103,291 [20].

According to Takata and colleagues (2008) review of 960 randomly selected charts from 12 children's hospitals across the United States, it was revealed that the mean ADEs rates were 11.1 per 100 patients, 15.7 per 1000 patient-days, and 1.23 per 1000 medication doses. This extrapolates to a mean of 174 preventable ADEs per children's hospital per year. Using an estimated cost of $4685 per preventable ADE, these preventable ADEs resulted in direct costs of $909 644 per children's hospital per year. This showed that

ADEs in pediatric inpatients are common, costly, & occasionally life-threatening or with fatal outcomes [5].

Some published reports showed that ADEs are common in most clinical settings including pediatric inpatients with a reported incidence of 2.3%.[14] Whereas adult inpatients with a reported incidence of 6.5% [3], adult outpatients with an incidence of 27.4% [9].

ADEs have substantial consequences including hospital admissions, prolonged hospital stay, additional resource utilization, and time away from work, as well as lower patient satisfaction [21].

A review article by Rosa Rodr´iguez-Monguio´ and colleagues(2003) considering ADR as an outcome showed that Patients who developed adverse effects due to drugs were hospitalized an average of 1.2 – 3.8 days longer than patients who did not, with additional hospital costs of $US2284–5640 per patient (2000 G.C values). The reviewer also described that the consequences after the occurrence of moderate or severe ADEs during hospitalization requires additional treatment and prolongs hospital length of stay (LOS), significantly increasing healthcare costs. Most studies carried out in hospitalized patients to assess costs associated with adverse drug effects have attempted to determine the excess stay and the cost caused by them, comparing length of stays and costs between patients who develop adverse effects (cases) and those who do not (controls) [29].

Regarding the economic impact of adverse effects due to drugs in acute care settings, most literatures are carried in USA, so the applicability of results to other countries is limited but it can give clues to the magnitude of the problem due to ADEs. According to Classen and colleagues study, it was found that ADEs complicated 2.43% of admissions. The average LOS for patients with ADEs was 7.69 days, compared with 4.46 days for matched patients. In addition, patients with ADEs had an average cost of hospitalization of $US10 010 compared with $US5355 for those without (1993 values). However, a linear regression analysis controlling all those matching variables revealed that, in fact, the occurrence of an ADE was associated with an increased LOS of only 1.91 days and

an increased cost of $US2262 (1993 values). When calculated, the excess hospital costs due to an ADE occurrence over a 4-year period is $US4 482 951 (1993 G.C values).When these figures are extrapolated to the US as a whole, the implication is that 770 000 hospital patients experience an ADE, and the direct hospital costs to treat these ADEs must be approximately $US1.56 billion annually (1993 values) [22].

Bates et al. studied a cohort of 4108 admissions to Brigham and Women's Hospital and Massachusetts General Hospital in Boston, MA, USA. They compared 190 patients who experienced an ADE with 190 controls who were patients in the same unit with similar pre-event LOS. The estimated post-event costs attributable to an ADE were $US2595 (1993 G.C.values) for all ADEs [23].

According to a study by Suh and colleagues that determined the economic impact of ADRs in hospitalization costs using data on ADRs from patients admitted to a hospital in New Jersey, The mean length of stay per patient differed significantly between the ADR case group and matched control group (10.6 vs. 6.8 d; $p = 0.003$), as did the total hospitalization cost ($22775 vs. $17292; $p = 0.025$). The adjusted LOS was increased by 3.8 days and hospital costs were increased by $US5456 (1999 G.C values) [24].

Senst and colleagues studied the frequency and cost of ADEs at a four hospital integrated health care network, the largest academic health network in Canada , The estimated ADE rate was 4.2 events per 100 admissions, 15% of which were judged to be preventable. The average post-event cost attributable to an ADE was $US2162 (1998 values), taking into account clinical variables. The projected annual cost to the projected annual cost to the organization was $US1.7 million, with a cost of preventable ADEs of $US260 000 (1998 G.C. values) [25].

A New Zealand study by Desiree´ L. Kunac, et al found that a preventable ADE was associated with an average marginal cost per day of $NZ900 of additional costs to the hospital. This estimate was based solely on the cost of hospital stay attributed to the event and did not include the costs of additional treatments or the costs of injuries to patients where the projected costs per annum to the pediatrics service were $NZ235 214

subdivided into $NZ148 287 for preventable ADEs and $NZ86 927 for non-preventable ADEs [7].

The consequences of ADEs range from relatively minor symptoms such as a rash to death, and ADEs also result in important consequences including hospital admission, prolonged hospital stay and additional resource utilization [22].

ADRs are a major burden on health care. It has been estimated that approximately 3–5% of all hospital admissions are related to ADRs Additionally, 5–8% of all hospitalized patients experience serious ADRs and 5–10% of in hospital costs are related to ADRs. [23]

Few of such kind are performed in developing countries, especially in Africa. One South African study in adults inpatients described that 6.3% of hospitalized patients developed at least one ADR with 46.2 % were deemed preventable [26].

There are no published data from Ethiopia regarding the subject in hospitalized children to ADEs. But one study about medication error done in JUSH pediatrics ward described that medication administration errors are very common. From 218 observations made, 89.9% of medication administrations were found to be accompanied by medication administration error (MAEs); majority of which occurred with intravenous (IV) bolus medications. The most frequent of the MAEs observed was wrong time error followed by dose errors and due to drugs omitted during drug administration. Furthermore, wrong administration technique errors and unauthorized drug errors were 41 (20.9 %) and 6 (3.1 %), respectively. The drug mostly associated with error was gentamicin with 29 errors (31.2 %). This study did not address the outcome of such error [32].

The costs in lives and money, due to medication safety problems (adverse drug events) as a result of poor product quality, adverse drug reactions (ADRs), and medication errors, is great in high-income countries, but the situation in low- and middle-income countries is likely to be much worse because of the poorer state of health system infrastructure, unreliable supply and quality of medicines, and lack of adequately trained health care staff. Many developing countries are now recognizing the need to set up systems to

monitor the safety of newly introduced medicines, such as Artemisinin based combination therapies (ACT) and antiretroviral therapies (ART), but they often lack the resources, including in-country expertise, to design and build a pharmacovigilance system from the ground up [27].

Considering the above facts, this prospective observational study described the profile of ADEs, Potential ADEs and medication errors occurring in the four medical units of the main pediatric ward of JUSH, Southwest Ethiopia.

CHAPTER TWO
LITERATURE REVIEW

2.1 Literature review of ADEs, Potential ADEs and Medication errors in Hospitalized pediatrics

A literature search was conducted to know previously reported incidence, severity and preventability of ADEs; the incidence and profile of PADEs and the types of medication errors with the stages at which those medication errors has occurred in pediatrics.

Adverse Drug Event Surveillance to the Pediatric Inpatient

A number of published articles described that ADEs, stated as medication related harm, were one of the most frequent causes of harm due to medical management in hospitals in developed countries [1, 4, 5, 13, 14,15,30,33, 34].

1. **Incidence of Adverse Drug Events**

Research studies about the frequency and nature of ADEs in children are less abundant than those studies in adult population, but there is an assumption that, due to various factors, ADEs and potential ADEs are more considered to occur more likely in children than adults. In those few published studies conducted in the inpatient setting, ADEs and potential ADEs are found to occur frequently. The reported range for ADEs rates for pediatric in patients extends from 6.6 to 15.7 events per 1000 patient days [13].

A study using computer ADE surveillance method based on triggers designed mainly for adults has examined ADEs on the pediatric inpatient service of a general hospital found an ADE rate of 1.6 per 1,000 patient-days [15].

Two pediatric studies using a combination of "voluntary and verbally solicited reports from house officers, nurses and pharmacists; and by medication order sheet, medication administration records and chart review of all hospitalized patients" measured ADE rates. In one of the study, Kaushal et al reported ADE rates in children on the inpatient wards at two urban teaching hospitals, in Boston city, USA to be 2.3 per 100 admissions (26

events), with an additional potential ADE rate of 10 per 100 admissions (115 events). Of the 26 true ADEs, 5 (19%) were determined to be preventable.[14] In the second study, Holds worth et al reported an ADE rate in pediatric inpatients in New York, USA (pediatric intensive care unit and general care unit) of 6 per 100 admissions (76 events), with 61% judged as preventable, and a potential ADE rate of 8.0 per 100 patient days (94 events) [33].

Takata and colleagues (2008), as part of a 12-site children's hospital study across the United States, utilizing trigger methodology to identify pediatric ADEs rates was undertaken. In this study, 960 inpatient pediatric admissions were reviewed for ADEs, revealing an ADE rate of 11.1 ADEs per 100 admissions. Twenty-two percent of these adverse events were deemed to be preventable, and the ratio of ADEs detected by the trigger tool compared to ADEs detected by occurrence reports, the second methodology in the study, was 22 to 1. Assuming that all ADEs identified in each of the above studies by Kaushal et al & Holds worth et al(2003) [14, 33] were accurately identified, the pediatric ADE trigger tool developed by Takata et al identified between 1.8 and 4.8-fold more ADEs than the methods using unfocused chart review and reports described above. The trigger tool used by Takata et al study was modified for pediatrics from the institute of health care improvement of USA general adult ADE trigger tool which identified an ADE rate in the adult population of 24 per 100 admissions [5].

Regarding the severity of the ADEs identified; in the study by Kaushal et al (2001), "the 26 ADEs identified were categorized as 66% "significant" 24% "serious" and 10% fatal/life threatening [14]. In the study by Holdsworth, et al, 76 ADEs were classified as 76% significant, 13% serious, and 11% life threatening. Severity in these 2 studies was defined on the basis of actual outcomes using a previously published scale [33]. But the severity scale in Takata's report showed that using the more detailed scale published by the National Coordinating Council for Medication Error Reduction and prevention, 97% were classified as "contributed to or resulted in temporary harm to the patient and required intervention" (severity level E), while only 3% were classified as "contributed to

or resulted in temporary harm to the patients and required initial or prolonged hospitalization" (severity level F). None was associated with permanent harm or death [5].

In a study of patients admitted to coronary intensive care, medical, surgical, and obstetric units in Brigham and Women's Hospital, Boston, USA over a 37-day period, the rate of drug-related incidents was 73 in 2,967 patient-days: 27 incidents were judged ADEs; 34 potential ADEs; and 12 problem orders. Of the 27 ADEs, five were life threatening, nine were serious, and 13 were significant. Of the 27 ADEs, 15(56 percent) were judged definitely or probably preventable [75].

2. Findings that used ADR as an outcome measure in children

Published reports describe that ADRs can lead to significant morbidity and mortality among children. [11, 34-42, 51, 80] ADRs can be considered not only as a reason for hospital admission or prolonged hospitalization but also may lead to permanent disability or even death. Notably, in a meta-analysis of 39 prospective studies in USA by Lazarou et al (1998), fatal ADRs among both adults and children ranked as the fourth to sixth leading cause of death in the United States. This analysis also found that the overall incidence of serious ADRs and of fatal ADRs was 6.7% and 0.32% respectively in hospitalized patients [36].

Another study demonstrated that ADRs were associated with an average of 243 reported deaths among young children, from new born to 2 years of age, each year. Although it has not yet been studied among children, the annual direct cost to manage ADRs among hospitalized adults was estimated at $1.6 to 4.2 billion [70].

On the basis of a meta-analysis of 17 prospective studies conducted in the United States and Europe, the incidence of ADRs among hospitalized children was 9.5%, with severe reactions accounting for 12% of the total, and in pediatric outpatients 1.46% (0.7–3.3) [11].

According to Jennifer Le et al(2006) report based on a study at Miller Children's Hospital, California, the overall incidence of ADRs per hospital admission during the 10-year study period was 1.6%. The annual incidence of ADRs ranged from 0.4% to 2.3%.

A significant increase in the reporting of ADRs was observed between 1998 and 1999 (0.9% vs. 2.0%).[34] On the basis of the number of medication orders, this Study also shows that the annual rate of ADRs was 1.2 to 1.8 ADRs per 1000 medication orders for years 2001 to 2004 [34].

A systematic review by Molokhia and colleagues (2009) indicated that ADR reporting can be improved by using computerized monitoring systems (CMS) to generate signals associated with changes in laboratory results with other methods. In line with this, educational interventions combined with reminders and/or prescription card reports can improve hospital based ADR reporting, and showed short to medium term improvement. This systematic review also described that ADRs have a major impact on public health, reducing patients' quality of life and increasing mortality and morbidity, whilst at the same time imposing a considerable financial burden on health care systems [35].

A review of eight prospective study of ADR in childhood, six of which were concerned about the ADR incidence in hospitalized children, by Bonati showed that the overall incidence of ADRs was 10.9% (95% CI 4.8 to 17.0) in hospitalized children and 1.0% in outpatient children. The rate of hospital admission due to ADRs was 1.8% (95% CI 0.4 to 3.2). The skin and gastrointestinal system were the organs most commonly affected and antibiotics were the drugs most commonly associated with ADRs. Safety alerts in the pediatric population were retrieved for 28 drugs, five of which were for psychotropic drugs and most of which were issued by the Food and Drug Administration (20 drugs). For 12 drugs, warnings were published in the 2006–2007 period. Antidepressants were the only drugs for which alerts were issued by all the drug regulatory agencies [36].

Different studies documented that ADRs are responsible for hospital admissions. In one of the study by Fattahi et al, the prevalence of ADRs at admission was 2.2% (9 admissions of 404 admissions); the prevalence during hospitalization was 9.9% (40 cases of 404 patients). [29] In another study by Annie Pierre Jonville-Bera et al that 1.53% of children were admitted to the regional children's hospital for ADRs in a 1 week prospective study in France and 2.64% developed ADRs during hospitalization [38].

A Brazilian study showed that "the cumulative incidence of ADRs was 12.5% (33/265); incidence density was 8 events per 1000 patient days (33/4042 patient-days). The skin was the most affected organ (49%); the drugs more implicated were systemic antibiotic (53.2%). The ADRs were mild or moderate in 97.9% of cases; causality was probable in 57.5% and the majority of events were independent of the dose given (55.3%). In multivariate analysis, the risk of ADR increased with the number of drugs, male gender, and ≥3 previous hospitalization courses [39].

According to S. Turner and his colleagues study at Alder Hey Children's Hospital, UK, ADRs are a significant problem following unlicensed or off-label drug prescriptions. ADRs occurred in 116 (11%) of the 1046 patient admissions. ADRs were associated with 112 (3.9%) of the 2881 licensed drug prescriptions and 95 (6%) of the 1574 unlicensed or off- label drug prescriptions [40].

A prospective study of ADRs in hospitalized children at a university hospital in Spain by I. Martinez-Mir et al documented that the cumulative incidence of ADRs was 16.6%, with no differences being observed between the two different periods of summer and winter time studies. Although there were no differences between patients under and over 12 months of age, risk was found to be significantly higher among girls compared with boys (RR=1.66, 95% CI 1.03–2.52) [41].

In Jutta Weiss et al study, a total of 68 ADRs were detected in 46 of 214 admitted patients studied by the pharmacoepidemiological team. Thirty four ADRs (50%) were detected by the staff physician, and 27 (40%) were detected primarily by analyzing laboratory parameters. Antibiotics-associated ADRs (50%) predominated, followed by glucocorticoids (16%), tuberculostatic (4%), and immunosuppressive agents (4%). In 5 cases, an ADR was responsible for the prolongation of hospital stay, and in 4 children, the ADR was responsible for hospitalization [42].

Based on a lesson from a medication safety program launched in a community hospital in Missouri Baptist Medical Center, USA ; indicated that the detection rate of ADRs would almost be doubled by a computerized monitoring system analyzing laboratory data than

voluntary reporting. Hence Implementation of a computer monitor system that automatically generates laboratory signals may help to identify more ADRs in children, and to reduce morbidity and hospital stay, as well as costs [43].

3. Methods used for detecting ADEs and PADEs

Methods used for ADE detection have included implicit and explicit chart review, voluntary and spontaneous staff reports and computerized signal detection using trigger tools with manual validation of alerts. [12, 17, 36 -39] While chart review has traditionally been considered a gold standard, there is evidence that computerized surveillance detects many events that are not easily detected during chart review. It is generally agreed that voluntary reporting of ADEs is low yield and anecdotal in nature, and not valuable for ADE quantification [17].

In one study, both systematic and voluntary reporting method in PICU was used to determine the incidence of adverse events; the number and severity of adverse events reported by two methods using Voluntary & systematic reporting were significantly different. Voluntary reporting did not capture major, severe catastrophic events related to medical/surgical diagnosis or management while systematic reporting captures serious events [12].

More sophisticated and substantially more expensive solutions to the problem of medication errors—such as computer assisted management, computer based alerts, computerized physician order entry, advanced monitoring, bar coding and robotics — have been proposed to reduce medication related misadventures , but their impact on the incidence of adverse drug events has not been consistently and reliably documented [43].

Terry S. Field et al studied the various strategies for the identification of ADEs and found that computer generated signals were the source of for 31% of the ADEs and 37% of the preventable ADEs [44].

Field et al. conducted a study, on a large population of Medicare enrollees receiving medical care in the ambulatory setting at New England– based health maintenance

organization in Massachusetts, to evaluate strategies to better detect ADEs among older people. They used multiple signals to detect ADEs, including computer-generated signals. They found that computer-generated signals were the source of 31% of the ADEs detected and also were the source of 37% of the preventable ADEs detected. Electronic notes were the source for 39% of the ADEs and 29% of the preventable ADEs detected. While provider reports captured only 11% of the ADEs and only 6% of the preventable ADEs identified during the study. They also found that voluntary reporting of ADEs by health care providers was inadequate and that multiple strategies for detection and prevention of ADEs are needed [44].

Reliance on spontaneous reporting has been found to systematically underestimate the rate of ADEs. While the traditionally acclaimed gold standard - manual chart review is highly labor intensive and costly to be employed for routine use of ADE surveillance [45].

A number of articles have described the importance of active surveillance using electronic triggers to detect adverse drug events in hospitalized patients for those who use electronic patient data base [46, 63, 65, 68, 69, 75, 77, 79, 81, 82].

Medication error and adverse drug events in children

As the case with other adverse events related injury due to medical management, ADEs can be associated with errors and are termed preventable. They can occur at any stage in the medication use process, including ordering, transcribing, dispensing, administering and monitoring.

Medication errors are any error in the medication use process; they are much more common than ADEs with one study finding them in 5.3% of medication orders, although they often do not result in harm [30].

Several studies suggest that about one third of ADEs are associated with medication error and are thus preventable [14].

Bates et al found that medication errors were common, occurring at a rate of 5 per 100 medication orders. However, only 7 in 100 medication errors had significant potential for harm, and 1 in 100 actually resulted in injury [3, 48].

ADEs and medication errors are frequent in many clinical settings and can occur at any point in the medication use process. Medication errors are much more common than ADEs. Depending on the setting, about a third to half of ADEs is typically associated with medication errors [21].

An Australian study based on systematic literature reviews and reports from data collections of the Australian Bureau of Statistics, Institute of Health and Welfare, Council for Health Care Standards and Patient Safety foundation found that ADEs are common in the Australian health system. Anticoagulant, anti-inflammatory, and cardiovascular drugs feature prominently as preventable, high impact problems, and collectively make up over one-half of all ADEs. In the study, 2–4% of all hospital admissions, and up to 30% for patients >75 years of age, are medication-related; up to three-quarters are potentially preventable based on medical record reviews while Of coded adverse events that contributed to death, 27% involved an ADE, as did 20% of adverse events identified at discharge and 43% at general practice encounters which shows that there is a strong correlation between increases in medication use and rates of adverse drug reactions (ADRs) associated with hospitalization based on Routine death certificate and hospital discharge data. Based on Australian Incident Monitoring System, the study shows that twenty-six per cent of 27,000 hospital-related incidents were medication related, as were 36% of 2000 anesthesia-related incidents, and 50% of 2,500 general practice incidents.

Error estimates in the study showed that errors occur in 15–20% of drug administrations when ward stock systems are used and 5–8% when individual patient systems are used. Previous allergic reactions to drugs may not be recorded more than 75% of the time [49].

In T. Morimoto et al study, they reviewed the incidence of ADEs, potential ADEs, and medication errors in a variety of clinical settings. The incidence of ADEs was 6.5 per 100 adult admissions and 2.3 per 100 pediatric admissions. In nursing homes ADEs were

found at a rate of 1.89 per 100 resident months, while the incidence of ADEs among outpatients was 27.4 per 100 adult patients. The incidence of potential ADEs was also reported to be 5.5 per 100 adult admissions, 10 per 100 pediatric admissions, and 0.65 per 100 nursing home resident-months. ADEs and potential ADEs are common in any setting but vary substantially in incidence, and the causes of errors and ADEs vary greatly by setting [21].

R. Kaushal et al (2001) reviewed 10778 medication orders and found 616 medication errors (5.7%), 115 potential ADEs (1.1%), and 26 ADEs (0.24%). Of the 26 ADEs, 5 (19%) were preventable. They described that the preventable ADE rate identified in the study was similar to that of a previous study but the potential ADE rate was 3 times higher. The rate of potential ADEs was significantly higher in neonates in the neonatal intensive care unit. Most potential ADEs occurred at the stage of drug ordering (79%) and involved incorrect dosing (34%), anti-infective drugs (28%), and intravenous medications (54%). Physician reviewers judged that computerized physician order entry could potentially have prevented 93% and ward-based clinical pharmacists 94% of potential ADEs. They conclude that medication errors are common in pediatric inpatient settings, and further efforts are needed to reduce them[14].

For a variety of reasons, children are at particular risk of medication errors, and this is be attributable primarily to incorrect dosages [4].

From the above studies, it is clear that ADEs , Potential ADEs , and medication error are an important segment of patient safety in clinical settings where by a preventive strategy should come in to place to reduce patient harm , health care cost.

2.2. Conceptual framework

This conceptual framework with an elaborative schematic diagram depicts a set of related variables and outcomes in the study. It shows the key factors and assumed relationships and possible outcomes in the study.

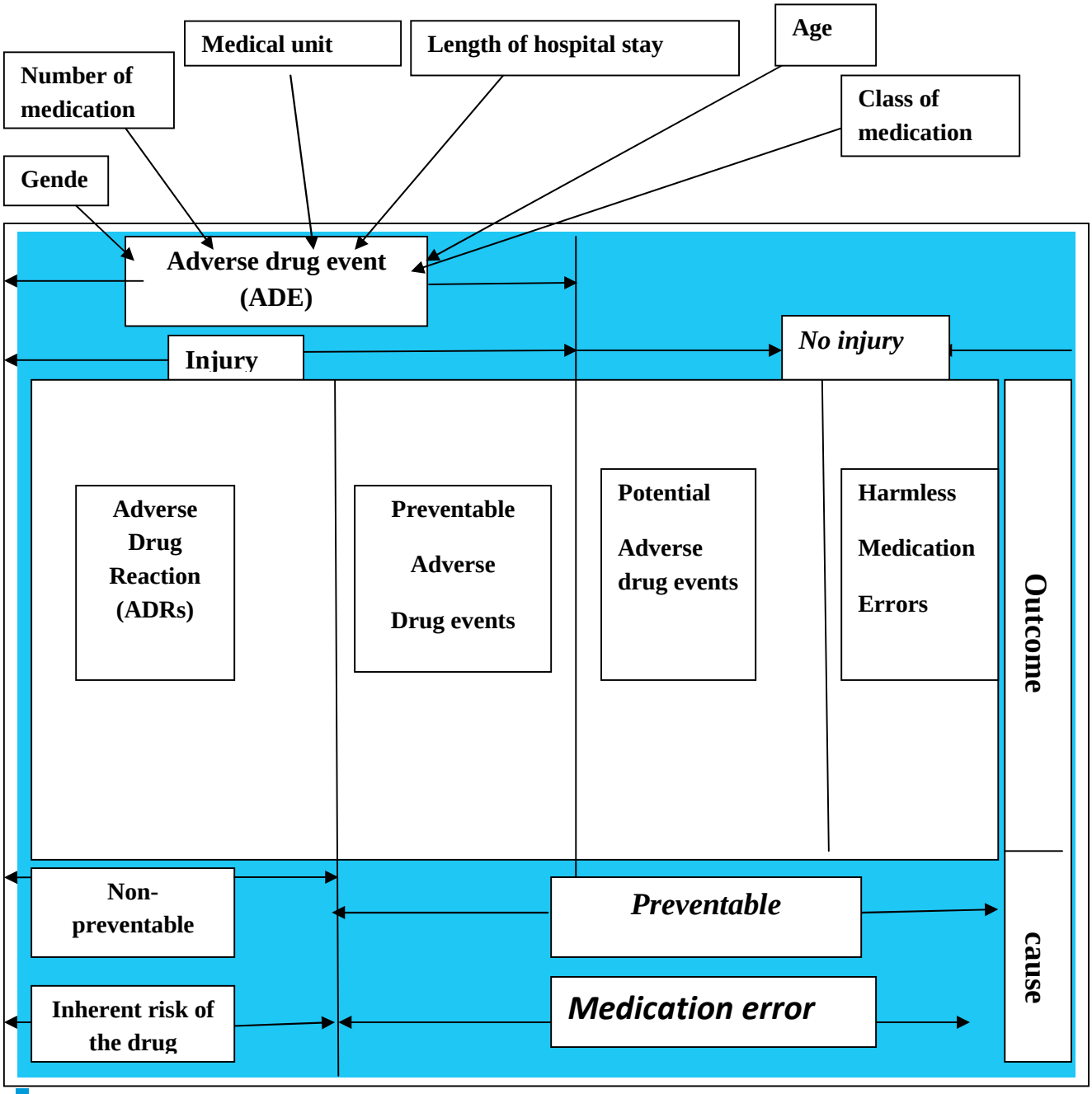


Figure 1: Conceptual framework showing the relationship between ADE, potential adverse drug events& medication error and key factors.

2.3. Significance of study

In USA, preventing medication related harm is considered as a national priority agenda, there are lots of reasons to believe that this problem will be appreciated by different nations as patient safety in recent decades is a serious global public health issue.

Nowadays, countries have increasingly recognized the importance of improving patient safety. To this effect, many initiatives have emerged to create systems and processes to prevent and reduce the adverse events in medications [83].

Based up on reports in the US & Europe, knowing the incidence, type, and preventability of ADEs and medication error helps to establish or strengthen science-based systems in the medication use process and patient safety which are crucial to improving quality of health care delivery and to reduce health care costs.

Hence this study will help to know the magnitude of the problem under study in resource poor setting and also it would help in devising preventive strategies and system development in the fight against medication related harm; the findings of this study will especially help in enhancing awareness among health professionals about medication related harm and medication error in JUSH.

This study can also serve as an additional impetus for further research regarding adverse drug events and medication error in different sector of the health care in the country for further understanding of the problem at national level.

CHAPTER THREE
OBJECTIVES

3.1. General objective

- To assess the magnitude and nature of adverse drug events, potential adverse drug events & medication errors in hospitalized children at Jimma University specialized hospital

3.2. Specific objectives

- To determine the incidence of adverse drug events
- To determine the incidence of potential adverse drug events
- To determine the incidence of medication errors
- To determine the types of medication errors
- To determine the severity of identified ADEs based on explicit criteria
- To determine the percentage of ADEs that is preventable, non-preventable
- To identify the stages in the medication use process at which medication errors has occurred
- To identify associated risk factors that predispose hospitalized children to develop ADEs, PADEs and medication errors

CHAPTER FOUR
METHODS AND PATIENTS

4.1 Study setting and period

This study was conducted over a 12-week period from 1 Feb - 1 May, 2011 in the pediatric ward of Jimma University Specialized Hospital (JUSH), a teaching hospital located in Jimma town, Oromia Region in southwestern Ethiopia, 335 km from the national capital, Addis Ababa. JUSH founded 70 years back by Italian invaders. Previously the hospital was a referral hospital run by Oromiya Regional State. The hospital had a total of 550 professional and supportive staff; Physician including specialists 65, Nurses 215, Pharmacy professionals 17, Laboratory professionals 20, Radiology 10, 26 health assistants, administrative staff more than 183. The hospital offers different specialized services by using 11 medical specialty and 3 other clinical departments that includes internal medicine, surgery, Pediatrics, Gynecology and obstetrics, ophthalmology, Psychiatry, Dermatology, dentistry, pathology, radiology, Anesthesiology, Nursing, pharmacy and medical laboratory.

The chief administrator of JUSH described that, based on an interview; on average the hospital provides health services for about 9000 inpatients and 80,000 out patients per year. It has 450 beds for inpatient services under 6 clinical departments.

JUSH serves as a teaching hospital for praticising health care professionals. The hospital serves as a teaching center for 65 postgraduate residents and more than 1000 undergraduate health students.

There were four medical units under the pediatric ward, i.e., General Pediatrics Ward A (admits non-emergency cases and those patients from critical unit to finish their medications), Critical, Neonatology that admits neonates with the age of the 1st 14 day for medical care and Nutritional Rehabilitation Unit (NRU). The pediatric ward of JUSH had 4 pediatricians, 5 senior residents, 12 junior residents and also 3 degree and 17 diploma holder nurses, respectively.

4.2 Study design

A prospective observational study was conducted over a 3 month period in JUSH pediatric ward.

4.3 Source and study population

4.3.1 Source population

All hospitalized pediatric patients at Jimma University specialized hospital pediatrics ward.

4.3.2 Study population

All hospitalized pediatric patients receiving medical care at pediatrics ward of Jimma University Specialized hospital during the data collection period.

4.3.2.1 Inclusion criteria

All admissions to the four medical units of the ward - General pediatrics Ward A, Critical Ward, Neonatology and NRU during the study period were eligible subjects for inclusion. All admitted pediatric patients were followed for the main outcome measure till either discharge, transfer to other ward out of pediatrics, death.

4.3.2.2. Exclusion criteria

Patients were excluded if the hospital admission was for < **24** hours, and / or if the admission was the result of an intentional (self-administered) overdose.

Up on admission; one nurse & two pharmacist data collectors recorded demographic and clinical information that includes admission diagnosis, medication history, history of allergy, medication dose, and frequency using the data collection tool.

Clinical data required when a medication related incident/event was identified include day of hospitalization, medical care given, patient age, number of drugs prescribed during the hospitalization including PRN medication, drug responsible for the incident and total number of medication dose the patient was receiving.

4.3 Sample size and sampling methods

In this study all pediatric patients admitted any time in between February 1 to May 1, 2011 were evaluated for the occurrence of ADEs, PADEs and medication errors. We followed all consequently admitted study patients, which happen to be available at the time of data collection, in the four medical units of pediatrics without any sampling for a period of 03 months.

4.4 Study variables

4.8.1 Independent variable: Age, diagnosis, number of medications, number of medication doses, length of hospital stay, medical unit under pediatric ward, gender, class of medication used, weight

4.8.2 Dependent variable: Adverse drug events, PADEs and Medication errors

4.5 Study definitions and main outcome measures

The study definitions used in this research project have been previously utilized in different similar researches conducted in different clinical settings [3, 5, 7- 9, 21, 33, 48, 50, 59 – 63].

An incident refers to any irregularity in the process of medication use. It might represent an ADE, potential ADE, medication error or none of these. An incident can occur at any stage of the medication use process (ordering, transcribing, dispensing, administrating and monitoring).

A medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient or consumer. Medication errors are errors in drug ordering, transcribing, dispensing, administering or monitoring.

Table: Types of medication errors: study definitions

Type of medication error	Definition
Dose omission	The failure to administer an ordered dose to a patient before the next scheduled dose. The failure to administer an ordered dose excludes patient's refusal and clinical decision or other valid reason not to administer.
Improper dose	**During ordering/prescribing**: an order for a medication dose that is either over or under dose for the children medical condition. **During dispensing or administration** : Dispensing or administration to the patient of a dose that is greater than or less than the amount ordered by the prescriber or administration of multiple doses to the patient i.e. one or more dosage units in addition to those that were ordered.
Wrong strength/concentration	**During Ordering:** an order for wrong concentration /strength of medication preparation **During dispensing/administration:** Dispensing or administering of a medication strength or concentration not as specified in the medication order to the patient.
Wrong drug	Dispensing or administration of medications to the patient that is not ordered. It includes look alike or sound alike medications
Wrong dosage form	Dispensing or administration to the patient of a drug product in a different dosage form than ordered by the prescriber
Wrong route of administration	Administering of a medication to the patient through a different route not specified in the order of the correct drug.
Wrong administration technique	Inappropriate procedure or improper technique in the administration of a drug other than wrong route ,including inappropriate crushing of tablet

Table 1: continued

Wrong frequency	Ordering or administering of a medication to the patient in a frequency that does not go in line with the pharmacokinetics and as specified in the guidelines though the mg/kg/day dose is within the recommended limit
Wrong duration	When a patient received an extended period of time while it should have been avoided based on current guidelines.
Wrong patient	When a patient received a medication that is not intended for him/herself though ordered for another patient due to failure to identify the identity of the patient
Monitoring error	includes when these conditions are faced : an order of Contraindicated Drugs(presence of Drug-Disease Interactions) , presence of Drug-Drug Interaction , Failure to use appropriate Clinical and or laboratory data for adequate assessment of patient response to prescribed therapy.
Deteriorated drug error	Dispensing or administration of a drug that has expired or for which the physical or chemical dosage-form integrity has been compromised.
Other medication* error	Any medication error that does not fall into one of the above predefined types

* = absence of route of administration, dosage form, strength & dose, and frequency of administration

An ADE is an injury due to a medication. ADEs may or may not result from medication errors. A preventable ADE is an injury that is the result of an error at any stage in the medication use—for example, a coma due to an overdose of a sedative.

A non-preventable ADE is an injury due to a medication where there is no error in the medication process—for example, an allergic reaction in a patient not previously known to be allergic to the medication. This type of ADE is also known as adverse drug reactions, or non preventable reactions.

Potential ADE/ PADE/ is an event that has a significant potential for injuring a patient but do not actually cause harm. This may be because the event is intercepted before

reaching the patient (intercepted PADE) or, due to particular circumstances or chance, the patient is able to tolerate the event (non-intercepted PADE), i.e. the error reached the patient without actually harming them.

Table 2: Adverse drug events and potential adverse drug events: study definition examples

Category	Case scenarios
Preventable ADEs	A child admitted with newly diagnosed type I DM without DKA developed moderate DKA while in the hospital due to omissions of insulin dose.
Non-Preventable ADEs	A child developed maculopapular rash with urticaria to cloxacillin without previous history of penicillin allergy.
Intercepted PADEs	1. On the revised order sheet, an order for **1gram** Dexamethasone, IV, QID was written, 1000 times the intended 1 mg dose, IV, QID for a child with pyogenic meningitis but the nurse intercepted and gave 1mg, IV, QID. 2. In the order sheet for a new born neonate , it calls for 1gm Vitamin K, IM, Stat but it was intercepted as 1mg, IM, stat 3. For a newborn, a nurse secured IV line on the artery and intercepted by medical intern before administration of Ampicillin and Gentamicin intra-arterial.

Table 2: continued

Non–Intercepted PADEs	1. An 8 year child with the diagnosis of CHF 2^0 to CRHD (MR+MS) + SAM she was receiving Lasix 10mg, P.O, BID + KCL 300mg/day + Digoxin 0.125mg per day + Spironolactone 7.5mg, P.O, BID 2. A nurse mixes Ampicillin , Gentamicin and Cloxacillin solution in a syringe for administration in to an IV line for a child with infective endocarditis 3. A child was found taking both Iron gluconate tablet 300mg, P.O,TID and Dried iron sulfate extract 200mg, P.O, TID in error (duplication therapy) 4. A child with Category I TB was ordered RHZE, 1/3 tab per day but she was dispensed RHZ tablet without Ethambutol from the TB clinic. 5. A 44 kg child was prescribed Iron sulfate 75mg,(1/4 of 300mg tablet) , P.O, TID for an intended 6mg/kg Elemental iron replacement(dose too low)

DKA= Diabetic Keto acidosis; DM =Diabetes Mellitus; IV = Intravenous; QID= every 6 hour; IM= Intramuscular; gm= gram; P.O. = per oral; TID =every 8 hourly; CHF=Congestive heart failure; CRHD= Chronic Rheumatic heart disease; SAM = severe acute malnutrition; MS= Mitral stenosis; MR= Mitral Regurgitation; KCL= potassium chloride; TB = tuberculosis; RHZE= Rifampicin /Isoniazid/Pyrizinamide/Ethambutol

The definition utilized for severity categories of ADEs was based on the NCCMERP [76] severity scale as described below

Table 3: Severity category for adverse drug events: study definitions

Category of Severity	Description
E	Temporary harm to the patient requiring intervention
F	Temporary harm to the patient requiring initial or prolonged hospitalization
G	Permanent harm to the patient
H	Intervention required to sustain life , e.g. Cardiovascular /Respiratory support required
I	Death of the patient

The primary target of most hospital medication risk management activities is preventable ADEs. These events harm patients, increase litigation potential and grab headlines.

The Food and Drug Administration (FDA), World Health Organization and International Committee on Harmonization define an adverse drug reaction as "a response to a drug which is noxious and unintended and occurs at doses used in man for prophylaxis, diagnosis, therapy or modification of physiologic functions. Therefore, an adverse drug reaction is an adverse event with a causal link to a drug. But ADEs included all traditional adverse drug reactions plus harm from overdoses, harm from inappropriate dose reductions or discontinuations and intolerable harm from dose titration.

The primary outcome measures in this study were an ADEs, Potential ADEs and medication errors. As a secondary outcome measurement; the Incidence, preventability,

and severity of adverse drug events were evaluated; the incidence and whether intercepted /non–intercepted type for potential ADEs. In the study, for preventable ADEs, potential ADEs and medication error, the type of error and the stage at which the error occurred were analyzed.

4.6 Inpatient medication use process in pediatrics ward

In the four medical units of pediatric ward, medication orders were handwritten that were prescribed mostly by physicians. Medication supply to the patient by nursing staff was largely from satellite pharmacy run by a pharmacist, a part of the central hospital pharmacy which stocks medicines required by the ward. The pharmacy also gave service for the nearby maternity ward. The satellite pharmacy collected medicines from the main store for a one week supply. The nurses were responsible for performing dose calculations during drug administration. They use unit dose dispensing in the ward collecting medications for 24 hr consumption only except in weekends based on the order written in the order sheet. The pharmacist working in the satellite pharmacy dispensed medications to the nurse by having separate written prescription with the patient medical record. In case a medication is not available, the patient care giver/ family purchased from nearby community drug retail out let.

4.7 Case detection methods and processes

A multifaceted approach was employed to identify medication related incidents/events in the ward to maximize data yield. As described elsewhere a broader system-focused approach to medication safety event detection that uses an array of event detection methods is recommended. In this study, multi-method event detection that includes non-voluntary to voluntary methods was used.

1. Daily chart review for all admissions in weekdays & once in a weekend until discharge/transfer/death : By visiting the ward the following documents were assessed for actual or potential ADEs , medication error including discharge summary, procedure notes, physician progress notes, pertinent laboratory reports, Physician orders, nursing / multi disciplinary progress notes and data about drug exposure [63].

During review of medical records, the investigators saw descriptions that may be due to ADE such as new symptoms or events that might represent an adverse drug event, changes in medication regimens (including acute discontinuations or initiations of medications that might be used to treat a drug-induced event), abnormal laboratory values etc [71].

Different studies have utilized pediatric trigger tools or 'clues', which are drugs or clues that have links to potential adverse drug events because either they are antidotes or given to reverse the action of a drug responsible for adverse drug event, for focused chart review process [45, 46, 63, 65, 66, 68, 75, 78 – 82]. During the chart review process in this study , a list of triggers, attached as annexe II, optimized from the above studies based on availability in the list of drugs in Ethiopia ,were utilized so as to have a watchful eye for detection of incidents and hence to increase data yield. The multidisciplinary health team was interviewed when questions arose during the medical record review for further elaboration of the case.

During chart review, when there was a dose change /either reduction or increment/, medication discontinuation or a hold order, new order, change in route of administration from previous order, the primary care provider was contacted for clarification why such changes are made and then decision was made whether the intervention was as a result of medication error, adverse drug event or potential adverse drug event or nothing. When an incident/event was identified, it was recorded on the ADE and medication error documentation format.

Daily visits to the ward by principal investigator and data collectors involved registering new patients and interviewing mother/patient attendants, reviewing medical records and attending clinical rounds (by principal investigator only).

All study patients were followed until discharge to ascertain the final diagnosis or until death or ward change.

2. Attendance at multidisciplinary ward rounds/ meetings: the principal investigator attended clinical rounds and/or meeting of the staff and solicited any alerts for PADEs ADE and medication error. The principal investigator also attended when available the department grand round, morning management sessions and so on.

3. Interview of parents/carer (and children) [39]: when further information or clarification of information is required. A questionnaire, available as annex, applied to the children's' mothers or relatives covering socio-demographic variables, personal and family medical history, information on previous drug use, and cause of admission. Interview of parent/children was used to solicit medication administration errors. Those who identify or become aware of any incidents was interviewed and stimulated to report to the data collectors or to the attending health professional.

4. Voluntary and verbally solicited and unsolicited reports from staff: all pediatric ward staff was informed about the study and invited to take part by submitting voluntary reports of any actual events or potentially unsafe medication systems that they noted during their daily activities. The staff that becomes aware of any ADE, potential ADE, or medication error was stimulated to report without any fear of litigation as there will not be reporter identification disclosure in data collection form.

Before initiating this study, the purpose and outcomes of the study was disclosed to all of the ward staff. Maximum support from the pediatric dept staff was sought. All health care professional in the ward and data collectors received formal orientations that emphasized how to use the event/incident documentation forms and how understanding the epidemiology, nature and causes of ADEs, PADEs and medication error will facilitate development of preventive strategies for safe guarding the children from adverse events. In the orientation the roles of complex systems and human factors in predisposing to medication error were reinforced, as opposed to individual blame.

4.8 Methods for classifying medication related incidents/events

Once suspected incidents/medication safety events were detected using above case detection methods; they were further evaluated and classified. They were classified

according to the following categories by the principal investigator: Whether an ADE, a potential ADE or medication error was present. If a medication error was found, then the type of error and stage in the process at which it occurred were also classified.

Adverse drug event case evaluation:

When suspected harm related to medication was identified based up on the above case detection methods. The principal investigator worked on the case and further evaluated its relationship with the medication mainly utilizing temporal relationship between the drug and the event; the biological plausibility, i.e. whether the event was a definitive pharmacological or phenomenological – an objective and specific medical disorder or a recognized pharmacological phenomenon as per WHO-UMC causality assessment criteria. The response to withdrawal plausibility pharmacological/phenomenological, if possible was also evaluated. Those in the category of possible, probable/ likely and certain were considered. We searched biomedical literatures to know the strength of published data, if any, on the relationship between the ADEs and the medication.

During this evaluation, the expertise of the pediatrics team was used when required for further work up especially on the exclusion of possible disease condition role in the adverse drug event. Since adverse drug events are actual patient harm, the pediatrics team intervene a specific medical care when applicable for preventing further damage or managing patient complaint. Those interventions in response to those adverse drug events were also recorded. We maximally utilized the expertise of the pediatric team and also we secured maximal support from the pediatrics ward staff and patient or their families.

In addition, actual occurrences of events for reliability that was originally reviewed by principal investigator, severities and preventability were evaluated by a panel of two senior pediatrics residents, who independently categorized the events using a prepared reviewer form. When disagreement affected classification of an event, the reviewers reached consensus through discussion. Inter-rater reliabilities were assessed using kappa statistics before they reach on consensus. This structured explicit review process has been used in prior studies of adverse drug events in various clinical settings.

Potential adverse drug event case evaluation

Potential adverse drug events were classified by principal investigator after reports from data collectors or himself the principal investigator on the following conditions that could have adverse consequences but did not happened ; medication dose orders that are too high or too low (whether intercepted or not) , wrong drug given in place of another, drug – drug interaction with major severity/good and above documentation as per micromedex[85] drug interaction classification scheme, when a contraindicated drug was given, Failure to discontinue or abrupt discontinuation of medications, for high risk medications an order without routes of administration. In collaboration with the pediatrics team, we followed patients who experienced the above medication misadventures which is not intercepted for possible harm to the patient but could not find any pertinent finding that tells harm (ADEs) has happened and hence classified as PADEs.

Medication errors case evaluation

An instrument was developed to identify and categorize medication error by using the above detection methods. All medications prescribed, dispensed and administered in the pediatrics ward were evaluated. The error types were categorized based up on NCCMERP (USA)[76] taxonomy of medication errors with slight modification that includes dose omission, improper dose (dose too high, too low and extra doses), wrong strength/concentration, wrong drug, wrong dosage form, wrong technique, wrong frequency, wrong routes of administration, wrong duration, wrong patient, monitoring error and others. An incident was classified as a medication error if the order, administration, dispensing and monitoring was not in accordance with standard, evidence based and up to date pediatric references that include pediatric dosing guidelines/drug monographs in MICROMEDEX© [85], Clinical pharmacology online[84], Lexi-comp pediatric online[86] /Lexi-Comp's Pediatric Dosage Handbook and WHO young infant dosing guideline (particularly for Cloxacillin) [87] and The Harriet Lane Book (18 edition) [89]. In categorizing medication dosing errors, these references were used for their recommended ranges in different age and or weight classification for each working

diagnosis. Some of these references have different dose range recommendations. For some medications, there is a wide range of acceptable doses - an appropriate dose using one recommendation may result in an overdose or under dose using the other recommendation. In case of such ties, to provide a conservative estimate of medication dosing error rates, we used from the above reference that provided the widest range in dosing. But we also included as a potential dosing error in cases where the calculated mg/kg doses falls within the range but it would be clinically unacceptable to order a medication dose near the upper limit while we could have started the lowest effective dose, if clinical condition allows. For instance in one child the dose of Aspirin ordered was 130 mg/kg/day but this dose is on the upper limit for aspirin for a child with Juvenile Rheumatoid arthritis while we could have started 90mg/kg/day and then titrating the dose based on clinical response. We categorized such medication dosing as errors since we believe that to miss recording of such as an error would bring a consequence latter allowing for missed opportunities for future prevention strategies.

All medication errors were stratified according to the stage in the medication use system at which the error occurred. We categorized the primary stages of medication use processes where they have occurred for each medication error type identified as prescribing, dispensing, administering, transcribing and monitoring considering the type of medication error as specified in the data collection instrument.

The detection and classification algorithm for this research project is depicted well in the figure 2 (optimized from reference 21 & 74).

4.9 Data processing and analysis

All data collected from multi detection methods was coded for further analysis. Qualitative variables were described as frequencies (percentages) and quantitative variables as mean ± standard deviation (SD) and categorical variables were described as numbers and percentages. SPSS 16 for windows version software was used for all statistical analysis. The independent covariates and their relationship with ADE, PADE and medication error occurrence were analyzed using univariate and multivariate logistic

regression analysis to predict the association between the dependent and covariates. We used kappa statistics for determining inter- rater reliabilities for the judgment of severity and preventability of ADE by the reviewers.

Analysis of outcomes included the following:

- ADEs and PADEs incidence per 100 admissions, per 1000 patient-days, per 1000 medication doses and per 100 medication order
- Severity of ADEs (defined as the highest level of harm applicable using the National (USA) Coordinating Council for Medication Error Reporting and Prevention severity scale[74].)
- Percentage of ADEs that is preventable, Non-preventable
- Stages (ordering/prescribing, transcribing, dispensing, administering, or monitoring) of the medication management process during which the medication error responsible for preventable ADE , PADEs and medication error
- Class of medications resulting in the ADE
- The medical unit in pediatrics where these incidents have occurred more

Formulas used for calculating incidence [78]:

1. ADEs/PADEs incidence per 100 admissions: (crude rate)
   $$total\ number\ of\ ADEs\ or\ PADEs \Big/ total\ number\ of\ admissions\ * 100$$
2. ADEs/PADEs incidence per 1000 patient-days:
   $$total\ number\ of\ ADEs\ or\ PADEs \Big/ total\ number\ of\ patient-days\ * 1000$$
3. ADEs/PADEs incidence per 1000 medication doses:
   $$total\ number\ of\ ADEs\ or\ PADEs \Big/ sum\ of\ medication\ dose\ given\ * 1000$$
4. ADEs/PADEs incidence per 100 medication orders:
   $$total\ number\ of\ ADEs\ or\ PADEs \Big/ sum\ of\ medications\ ordered\ * 100$$

5. Similar calculation was done for medication error incidence per 1000 medication doses , per 1000 patient- days and per 100 medication orders but for medication error per 100 admissions, it was calculated as : total number of patients with medication error / total number of admission * 100.

4.10 Quality assurance

The quality of the study was improved through training of data collectors (One degree holder nurse and two pharmacists) before starting the work on a simulated case and also further on time of data collection they were evaluated & supported when demand ensues especially on how and which data should be collected from the patient chart, supervision and daily check up of filled data collection forms were done, formal seminar was organized for the ward staff to make them understand the objective of the study and for facilitation of incident/event report habit; whenever problem exists regarding difficulty in reporting, inconsistency in data collection by data collectors, adequate measures were taken. In addition frequent consult of the pediatrics ward staff were done so as to stimulate for further medication safety event/incident report verbally or using designed reporting format to maximize data yield.

4.11 Ethical consideration

Ethical approval to conduct this study was obtained from Ethical review Board of Jimma University. The individual patient consent was asked verbally when information from patient/caregiver/ family member is required. The patient/caregiver/family members were informed that they have the right to refrain at any point of time during the interview process. During the data collection process; patient initials and ID were utilized for the patient privacy and appropriate intervention were recommended to the pediatrics team when serious medication error were identified.

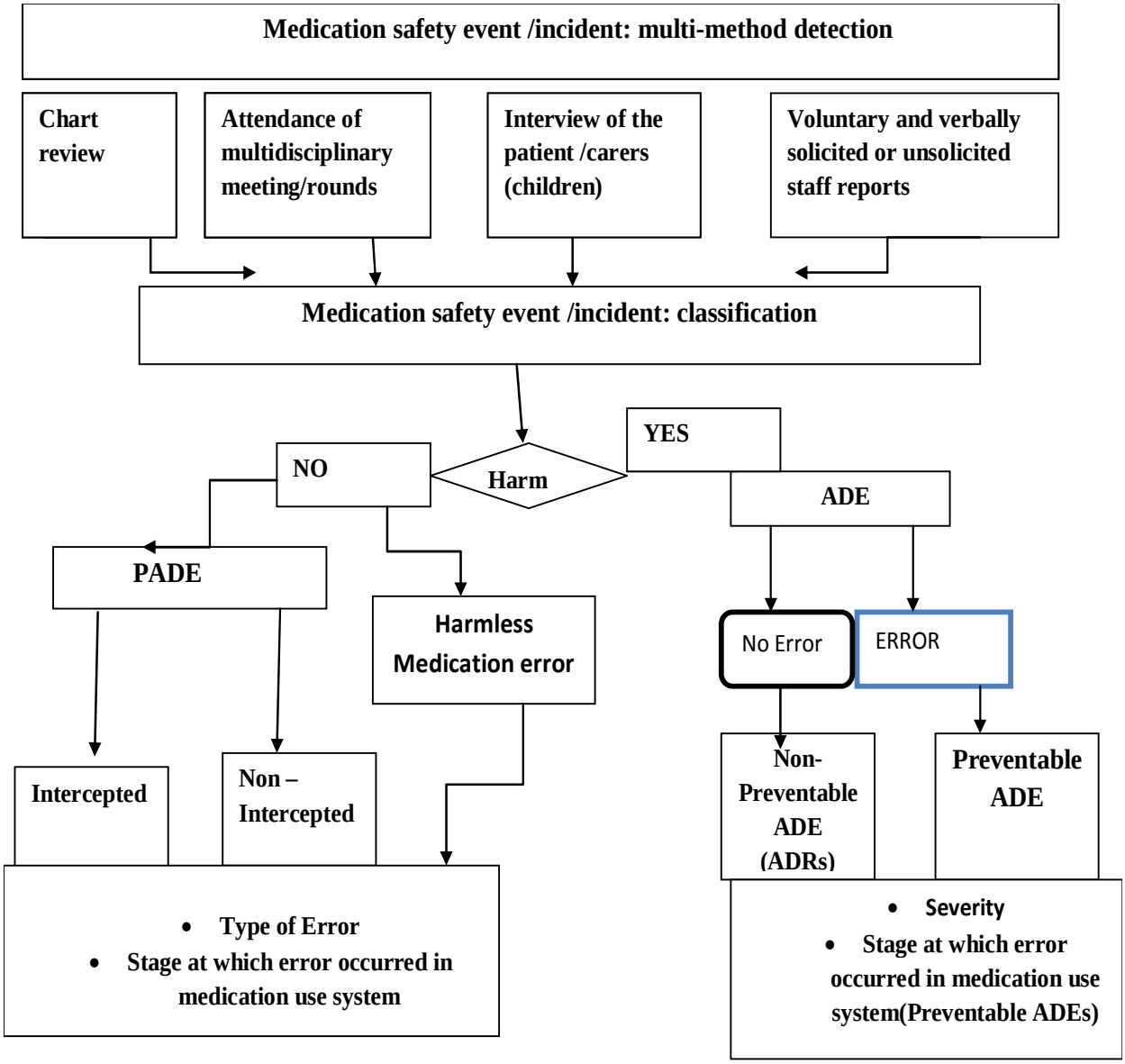


Figure 2: Medication safety event (ADEs, PADEs and Medication error) detection and classification

Confidentiality of information shared and anonymity by not revealing the identity of the pediatric staff who is involved in stimulated voluntary medication related incident/event report were maintained. This research study did not pose any risk or harm to the subjects under study.

4.12 Pre -test study

Before starting the actual study, the data collection tools and the whole method were pre tested on some patients' medical records using random sampling from source population to find out any errors, if there are any, on the method and to correct them before the actual study was done. Accordingly, data collection tools and methods were amended with slight modification on the content of data collections tools.

4.13. Limitation of the study

The lack of gold standard for ADE detection to compare our results and scarcity of literature in developing countries limited us to evaluate our study setting medication related harm and medication error in a similar country with low socioeconomic status. The long term effect of our study on the pediatric team might affect the study positively or negatively, especially it was our ethical principle to recommend to the team whenever serious medication error happened.

In some of the cases, especially for potential adverse drug events, there was deletion or removal of orders associated with medication error and replaced by corrected order sheet resulting missed opportunity to record as PADEs.

Any event that has occurred in patients less than 24 hours of hospital stay is not included but it is unlikely that we missed those events as such event most of the time require prolonged stay.

CHAPTER FIVE

RESULTS

Study population characteristics

During the 12 week study period, a total of 699 admitted patients to the pediatric ward of Jimma university specialized hospital were followed. Of these, 600 patients reflecting a total of 634 admissions were eligible subjects for analysis (figure 3). They represent a total of 6182 patient-days of length of hospital stay, during which 2072 medication orders were written. Of those included in the study, there were 15(2.4%) patients who did not receive any medication during their stay in the ward excluding IV fluids, parenteral/enteral nutrition's.

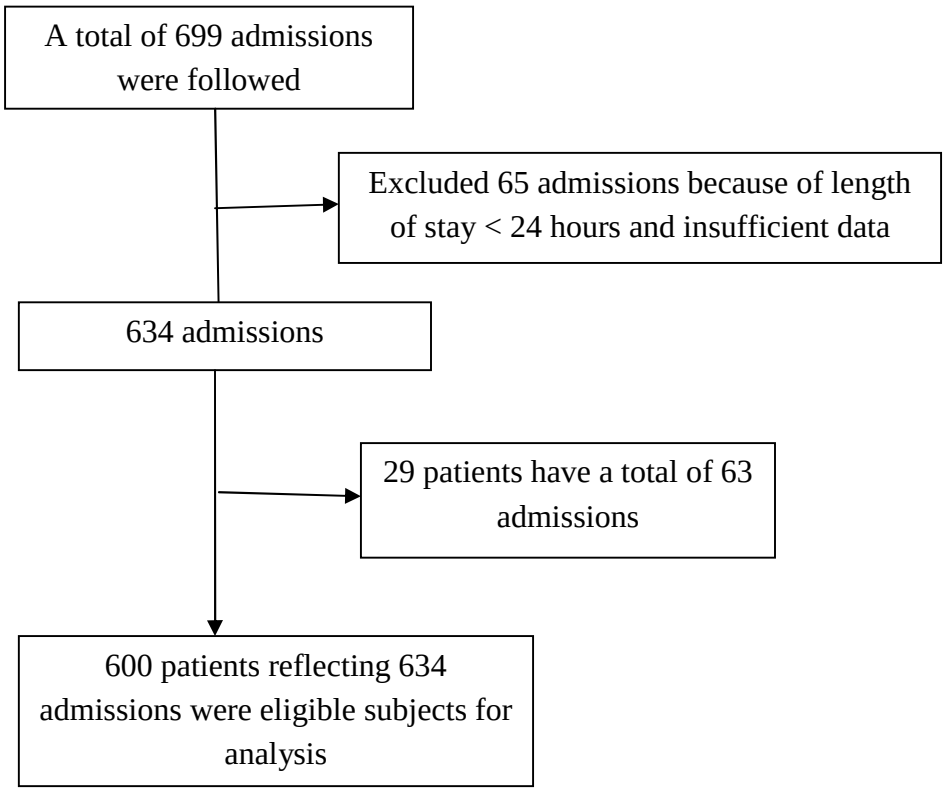


Figure 3: Summary of hospitalized children included in analysis at Jimma University specialized hospital, Feb-May, 2011.

Table 4: Characteristics of hospitalized children in Jimma University Specialized hospital, Feb - May, 2011

Category	Total	Mean	Standard Deviation
Age, years	n/a	2.9	3.7
Weight, kg	n/a	10.4	8.2
Length of hospital stay, days	6182	9.8	8.8
Number of medications ordered, Number	2072	3.3	1.9
Number of medication doses, Number	35117	55.4	64.6

n/a = not available

A total of 35,117 medication doses were given to the above patients which accounts for 55.4 medication doses per patient. The mean length of hospital stay and medications ordered was about 9.8 days (± 8.8 SD) and 3.3 medications (± 1.9 SD) respectively. The mean age of patients was 2.9 years (table 4). The age ranges for patients were from newborns to 14 years of age. Just around 215 (33.9%) of patients were infants and 126 (19.9%) were toddlers (Figure 4). Three hundred seventy one (58.5 %) of the patients studied were male in gender.

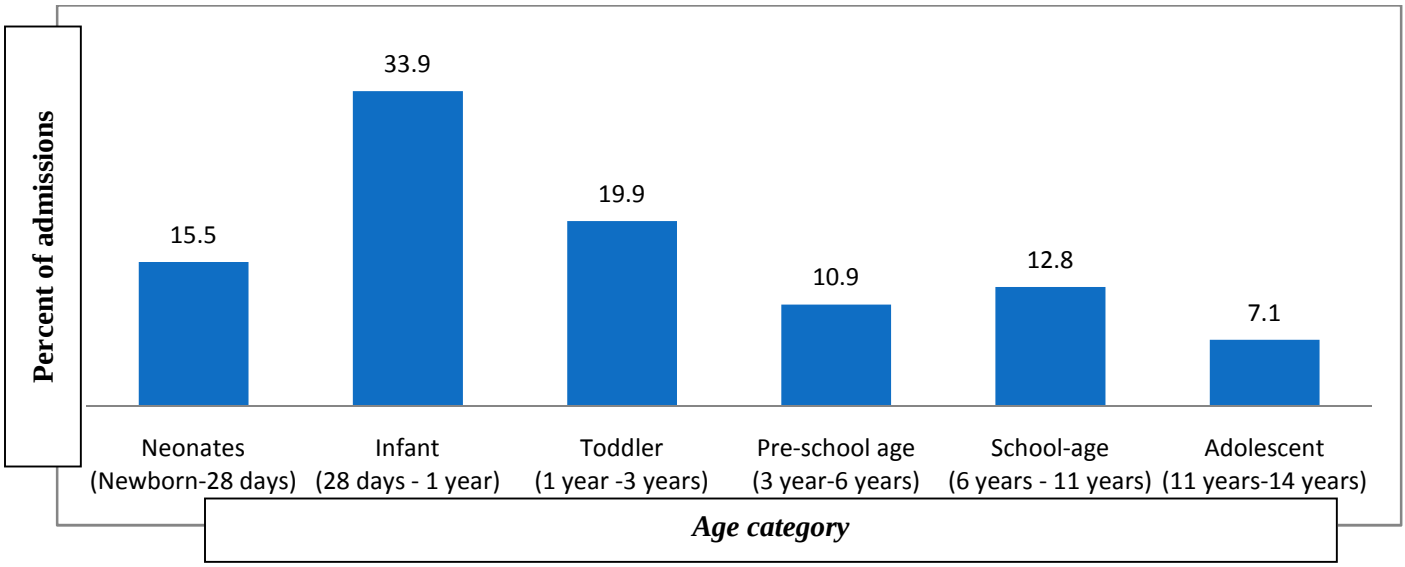


Figure 4: The age category of hospitalized children in Jimma University specialized hospital Feb-May, 2011.

The top 10 diagnosis made for hospitalized children were Severe Pneumonia in 173(27.3%) of admission, Severe acute malnutrition 120(18.9%), Early/Late onset Neonatal sepsis 108(17.0%), Meningitis 59(9.3%), acute gastroenteritis 46(7.3%), Malaria 39 (6.2%), Anemia's of different causes 43(6.8%), First episode of wheeze 32(5.1%), congestive heart failure 27(4.3%) and abscess 26(4.1%). Of 634 admissions, one hundred four (16.4%) and 75(11.8%) were found to be stunted and wasted with different degree of severity respectively (table 5).

Table 5: Final diagnosis made for hospitalized Children in Jimma University Specialized hospital, Feb - May, 2011

Diagnosis [#a]	***No. (%), n = 634***
Severe pneumonia	173(27.3)
Severe acute malnutrition	120(18.9)
Early/Late onset neonatal sepsis	108 (17.0)
Stunted	104(16.4)
Wasted	75 (11.8)
Meningitis	59 (9.3)
Acute gastroenteritis	46(7.3)
Anemia	43(6.8)
Malaria	39(6.2)
First episode of wheeze	32(5.1)
CHF(due to CRHD +VHD)	27(4.3)
Abscess	26(4.1)
Pneumonia	23(3.6)
Conjunctivitis	21(3.3)

Table 5: continued

Urinary tract infections	19(3.0)
Acute abdomen/Appendicitis, Bowel obstruction/	19(3.0)
Tuberculosis	16(2.5)
Cellulites	15(2.3)
Complicated Measles	14(2.2)
Oral Trush	13(2.1)
Congenital heart disease/Including VSD & PDA	10(1.6)
Hospital acquired infections	11(1.7)
Pulmonary Hypertension(PAH/PVH)	9 (1.4)
Recurrent wheeze	8 (1.3)
Bronchial asthma	7 (1.1)
Hypertension	**7** (1.1)
Hypovolumic shock	8 (1.3)
Nephrotic syndrome	8 (1.3)

One patient can have more than one diagnosis; **a** – represent common diagnosis seen. **CHF** = Congestive heart failure**, VSD** = Vascular septum defect**; PDA** = Patent Ductus Arteriosus**; CRHD/VHD** = Chronic Rheumatic heart disease/ Valvular Heart disease

Characteristics of Medication ordered during the study period

Six hundred nineteen (97.6 %) admissions out of 634 required medication orders for treating their medical condition. A total of 2072 medications have been ordered excluding medications ordered for patients excluded from the analysis. Anti-infective medications were the leading, 1330 (64.2%), class of medication frequently prescribed in the patients studied, followed by central nervous medicines 206(9.9%), (table 6).

Table 6: Frequency of medication classes prescribed for hospitalized children in Jimma University Specialized hospital, Feb – May, 2011

Code**	Medication Class	Frequency of prescription, N = 2072
AI.000	Anti-infective medicines	1330(64.2%)
NS.000	Central nervous system medicines	206(9.9%)
VT.000	Vitamins	158(7.6%)
CV.000	Cardiovascular medicines	103(5.0%)
RE.000	Respiratory medicines	66(3.3%)
ED.000	Medicines used in endocrine disorders	66(3.3%)
OP.000	Ophthalmic agents	30(1.5%)
BL.000	Blood products and medicines affecting the blood	28(1.4%)
DE.000	Dermatological agents	25(1.2%)
GI.000	Gastrointestinal medicines	20(1.0%)
AL.000	Antihistamines and anti-allergic medicines	10(0.5%)
MS.000	Medicines used in musculoskeletal and joint diseases	5(0.2%)
--------	Others	25 (1.2%)

Other includes calcium gluconate, calvitalis®, magnesium sulfate, etc. ** = Code given is based on Pharmacologic – Therapeutic classification scheme used in List of medicines in Ethiopia[91,] Sept 2010.

Incidence, preventability and severity of adverse drug events

A total of 58 ADEs were identified during the 12 week study period. In total, 46 patients accounted for these ADEs. The incidence of ADEs were found to be 9.2 per 100 admissions (crude rate), 1.7 per 1000 medication doses, 9.4 per 1000 patient days and 2.8 per 100 medication orders. Of those ADEs, 33(56.9%) occurred in ward A, 21(36.2%) occurred in the critical unit, the remaining one occurred in nutritional Rehabilitation Unit (3(5.2%)) and Neonatology unit (1ADE (1.72%)). Twelve patients were found to have more than 1 ADEs during hospitalization. A total of 4 of the 58 (6.9%) ADEs were the primary reason for initial hospitalization; one of these patients again developed another ADE while in hospital stay.

Of the 58 ADEs identified, the reviewers, that constituted two senior pediatric residents, classified 39 (67.2 %) of them as non- preventable ADEs while 19(32.8%) of them were preventable. Improper dose 8(42.1%) was the commonest type of medication error responsible for the preventable ADEs where 9(47.4%) of the errors occurred at the administration stage of medication use system (figure 5).

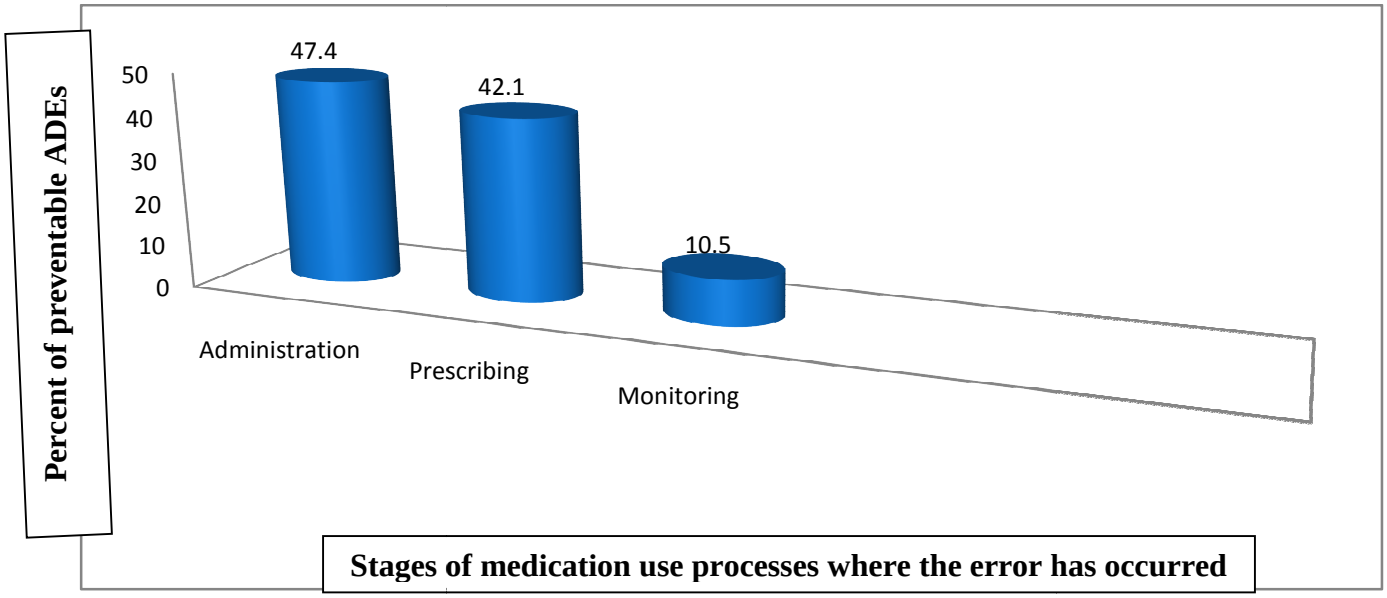
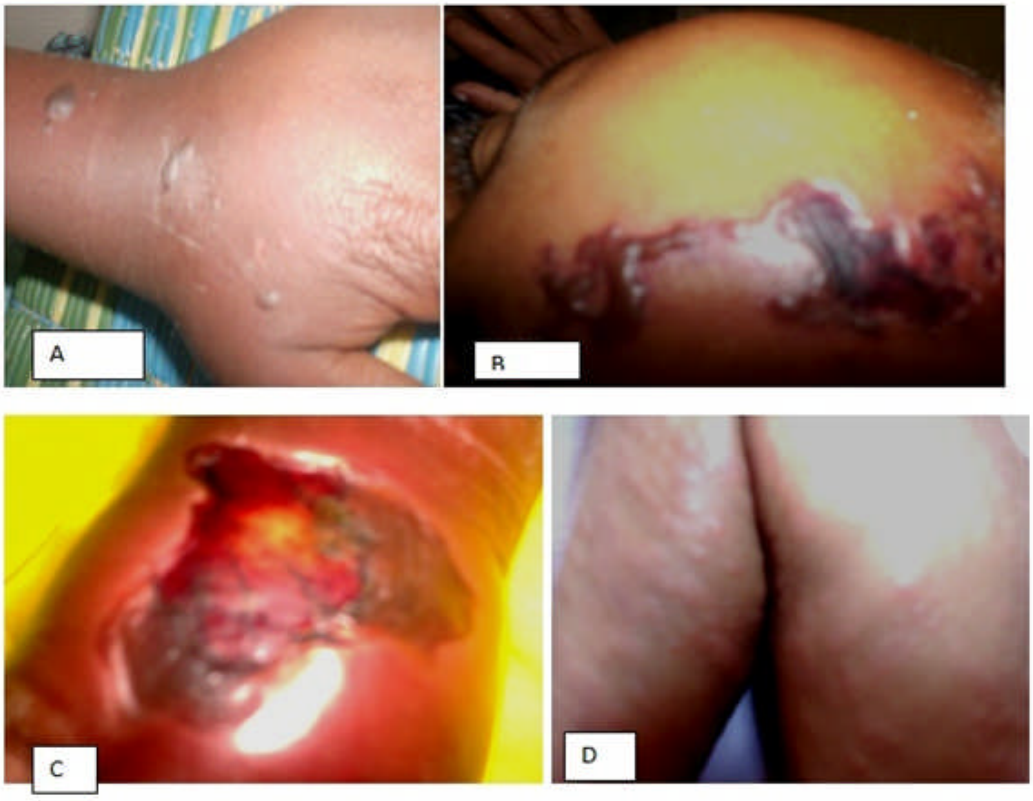


Figure 5: Stages of the medication use processes for medication error in preventable adverse drug events at Jimma University Specialized hospital, Feb - May, 2011

Of those ADEs, 13(22.4%) events were injection site Phlebitis that involved pain along the IV cannula, swelling and redness followed by maculopapular skin rash with or without urticaria 12(20.7%) events (figure 7).There was one fatality associated with monitoring error due to a failure to use appropriate clinical or laboratory data for adequate assessment of patient response to prescribed therapy(a failure to monitor response of the patient to crystalline penicillin prescribed for severe pneumonia). Some of the pictures of those ADEs are presented in figure 6 that involved extravasations induced necrosis, Cloxacillin induced Phlebitis and generalized skin rash after use of ketoconazole.



Key: A – Cloxacillin induced phlebitis; B & C – Extravasation induced necrosis on the scalp and dorsum of the foot; D – Ketoconazole induced skin rash

Figure 6: Diagrams of some of the identified adverse drug events in hospitalized children in Jimma University Specialized Hospital, Feb – May, 2011.

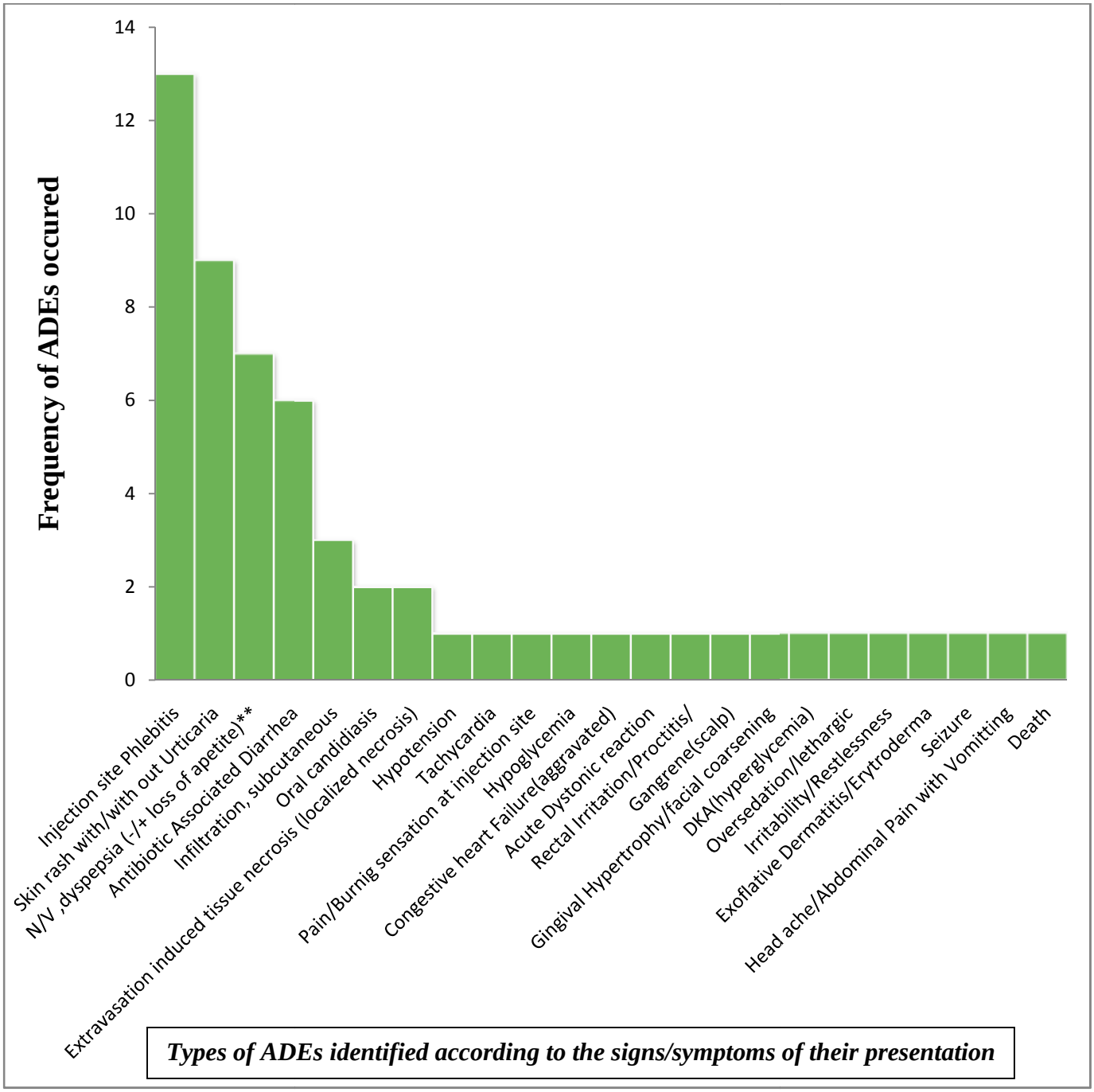
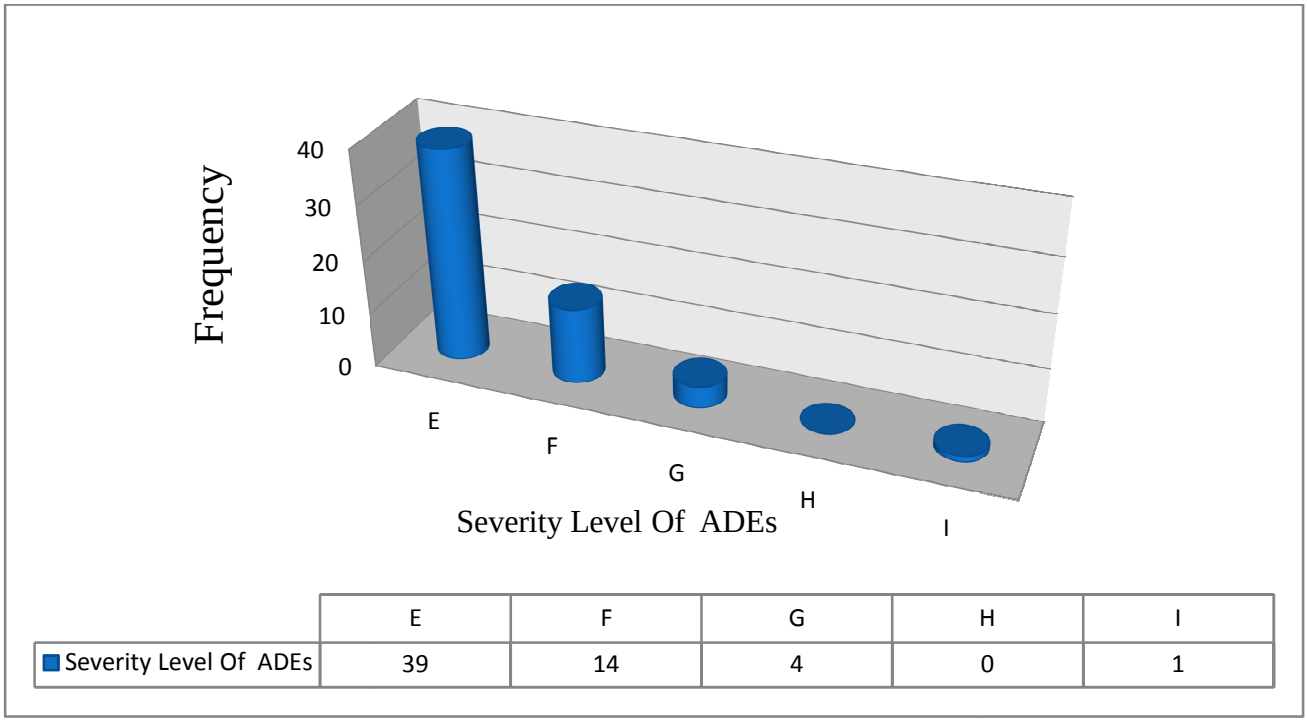


Figure 7: Types of adverse drug events identified in hospitalized children in Jimma University Specialized hospital, Feb -May, 2011

(** Nausea and vomiting, dyspepsia (epigastric discomfort) with/without loss of appetite



	E	F	G	H	I
Severity Level Of ADEs	39	14	4	0	1

Figure – 8: Reviewers severity scale rating of adverse drug events identified in pediatrics ward of Jimma University Specialized Hospital, Feb-May, 2011.

The reviewers have determined the severity of ADEs according to NCCMRP severity scale. Of 58 ADEs (Figure 8), 39(67.2%) were classified in to category E where as 4(6.9%) were classified as category G (Figure 8).

Inter- rater reliabilities for key judgments by the two senior pediatrics residents for the preventability, severity and presence of an adverse drug event were calculated using the kappa statistic (k) using SPSS for windows version 16.0. Inter rater agreement was determined on the basis of the ratings before a consensus was reached after discussion. Accordingly, the inter-rater agreement of these physicians on the preventability, severity of identified adverse drug events and the presence of adverse drug event or exclude using two way kappa analyses was presented below. The result shows that preventability versus Non-preventability agreement between the reviewers has a value of k = 0.46(95% CI 0.00-0.50) that is “moderate agreement’’ (table 7). The severity rating of ADEs, E versus

F or G between the reviewers was found to be k= 0.51 (95% CI 0.00-0.50), with a 'moderate' agreement (table 8). On the presence of adverse drug event, ADEs versus exclude the kappa statistic between the reviewers was found to be 0.65 (95% CI 0.00-0.51) with a 'good agreement'.

Table 7: Level of agreement between reviewers for Preventability of Adverse drug events in Jimma University Specialized hospital, Feb-May, 2011

		Preventability rating by reviewer 2		
		Non - Preventable	Preventable	Total
Preventability rating by Reviewer 1	Non-Preventable	12	15	27
	Preventable	0	31	31
Total		12	46	58
				Measure of Agreement (K) = 0.46

K= kappa statistics value , 0.4-0.6 = moderate agreement ; 0.6-0.8 = good agreement

Table 8: Level of agreement between reviewers for Severity of Adverse drug events identified in hospitalized children, Jimma University specialized hospital, Feb - May, 2011

		Severity rating by Reviewer 2		Total
		E	F or G	
Severity rating by Reviewer 1	E	36	0	36
	F or G	12	10	22
Total		48	10	58
		Measurement of agreement (K) = 0.51		

K= kappa statistics value, 0.4-0.6 = moderate agreement; 0.6 - 0.8 = good agreement

Table 9: Rates of Adverse Drug Events, Potential Adverse Drug Events and Medication Error in Hospitalized Children in Jimma University Specialized hospital, Feb-May 2011

Category	Total	Per 100 patient admissions	Per 1000 medication doses	Per 1000 patient-days	Per 100 medication orders
Medication orders	2072	326.8	59	335.2	n/a
Length of Hospital stay	6182	975	n/a	n/a	n/a
Medication doses	35117	5539	n/a	5680.5	1694.8
Adverse drug events	58	9.1(crude rate)	1.7	9.4	2.8
• **Preventable**	19	3.0	0.5	3.1	0.9
• **Non-preventable**	39	6.2	1.1	6.3	1.9
Potential Adverse drug events	88	13.9	2.5	14.2	4.3
• **Intercepted**	16	2.5	0.5	2.6	0.8
• **Non-Intercepted**	72	11.4	2.1	11.7	3.5
Medication Error	674	55.4	19.2	109	32.5

n/a: not available

The most common medication classes responsible for the development of adverse drug events were antiinfectives followed by cardiovascular drugs and central nervous system drugs (figure 9). Again anti-infectives were the primary class of medication that brought permanent damage to the patient as a result of inadvertent administration technique.

But for most of the preventable adverse drug events, Anti- infectives are not the leading causes of preventable adverse drug events rather cardiovascular, respiratory and endocrine medications were more responsible.

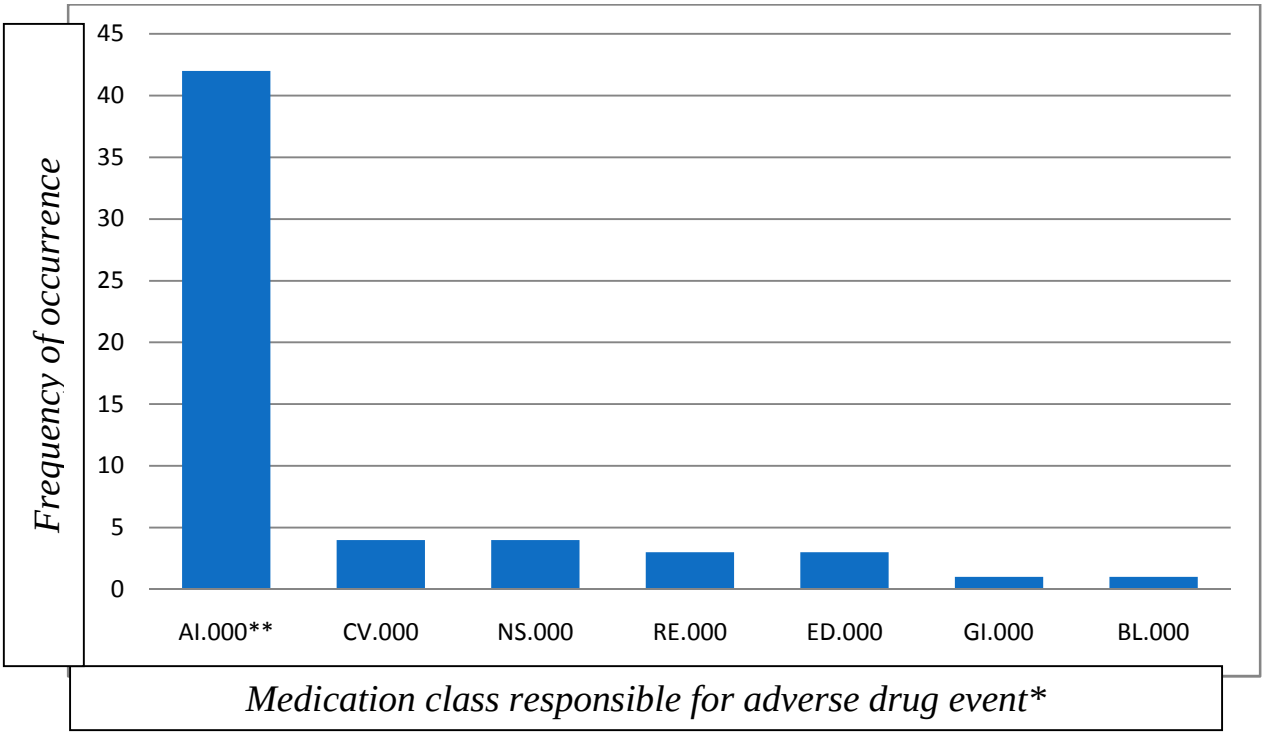


Figure 9: The class of medications responsible for adverse drug events in hospitalized children in Jimma University Specialized hospital, Feb - May, 2011

*Classification is based on Pharmacologic – Therapeutic classification scheme used in List of medicines in Ethiopia, Sept 2010.

** For one ADE, the maintenance fluid (Isotonic normal saline) also contributed for infiltration in additions to anti-infectives being used

Of 58 ADEs, 21(36.2%) of them occurred in infants and 14(24.14%) occurred in school – age children.

Thirty nine (67.24%) of the 58 ADEs occurred while the medications are being used by Intravenous route of administration followed by oral route of administration for sixteen (27.6%) adverse drug events.

Two ADES occurred while the medication responsible for is being given by subcutaneous route of administration and one event as a result of use of medication through rectal route of administration.

The most common interventions undertaken in response to adverse drug events in pediatrics ward were prescription of additional medications, a total of 30(51.7%) ADEs required prescription of another medication, followed by discontinuation of the offending agent in 16 (27.6) ADEs. Four (6.9%) ADEs required dose reduction. Fifteen (25.8%) ADEs required increased monitoring of Vital signs and or laboratory values (e.g. serial of random blood glucose level determinations). Other interventions include change of the IV access site for injection site phlebitis, an order to flush the IV line after administration, daily wound care and drainage.

Potential adverse drug event and medication error

A total of 88 medication errors from 674 identified were categorized as PADEs. Of these PADEs, 72(81.8%) were Non-intercepted PADEs while 16(18.2%) were intercepted PADEs (near misses). Based on a similar calculation for ADEs, the incidence of PADEs were found to be 13.9 per 100 admissions, 2.5 per 1000 medication doses, 14.2 per 1000 patient days, 4.3 per 100 medication orders. The incidences of intercepted and non intercepted PADEs were found to be 2.6 and 11.7 per 1000 patient-days. Eighteen patients had ≥ 2 Potential adverse drug events (table 10). Most frequent PADEs were found in infants, 22(25%) of PADEs while 18(20.5%) were found in toddlers (table 10).

Potential adverse drug events were frequently seen in Critical unit of pediatric ward, in 54.54 % of the total PADEs, while 25 %, 13.63% and 6.82% of PADEs were found in Ward A, Neonatology and Nutritional Rehabilitation Unit.

Most PADEs occurred at the prescribing/ordering stage of medication use processes (figure 10).

Table 10: The distribution of potential adverse drug events according to age category in Hospitalized children of Jimma University Specialized hospital, Feb-May, 2011

		Age of the patient in category						
		Neonate	***Infant***	***Toddler***	***Pre-school age***	***School-age***	***Adolescent***	*Total*
Number of PADEs	*0*	*88*	*196*	*112*	*62*	*70*	*38*	*566*
	1	*7*	*16*	*10*	*6*	*8*	*3*	*50*
	2	*2*	*3*	*4*	*1*	*2*	*4*	*16*
	3	*1*	*0*	*0*	*0*	*1*	*0*	*2*
Total		*98*	*215*	*126*	*69*	*81*	*45*	*634*

A total of 674 medication errors have been found in 351 patient admissions that represents an incidence of 19.2 per 1000 medication doses, 109 per 1000 patient-days, and 32.53 per 100 medication orders. Of 674 medication errors, 305(45.25%) of them have occurred in the critical units of pediatrics ward (figure 11).

The most common types of medication error detected in the ward were improper dose, 196(29.1%) followed by wrong administration technique, 134(19.9%). Of the improper doses, too high doses were the most common types of improper doses, followed by under doses (table 11). Infants were the most commonly exposed children for medication error (figure 12), 180(26.7%) followed by neonates, 131(19.4%).

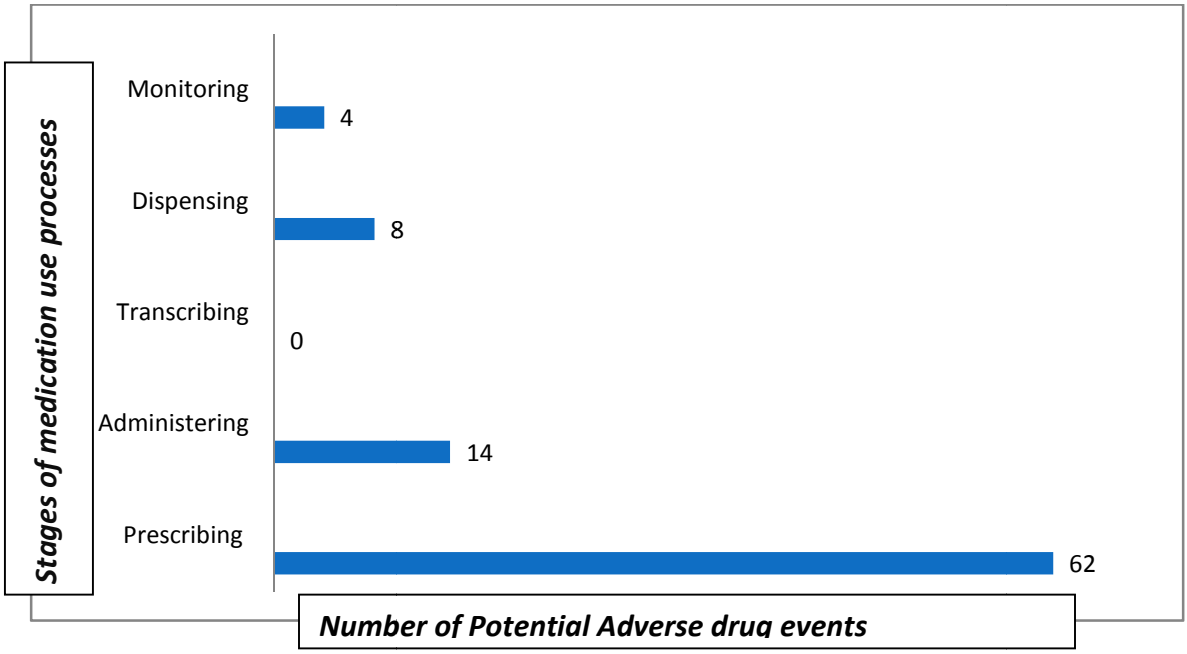


Figure 10: Stages of medication use processes for potential adverse drug events in Jimma University Specialized hospital, Feb – May, 2011

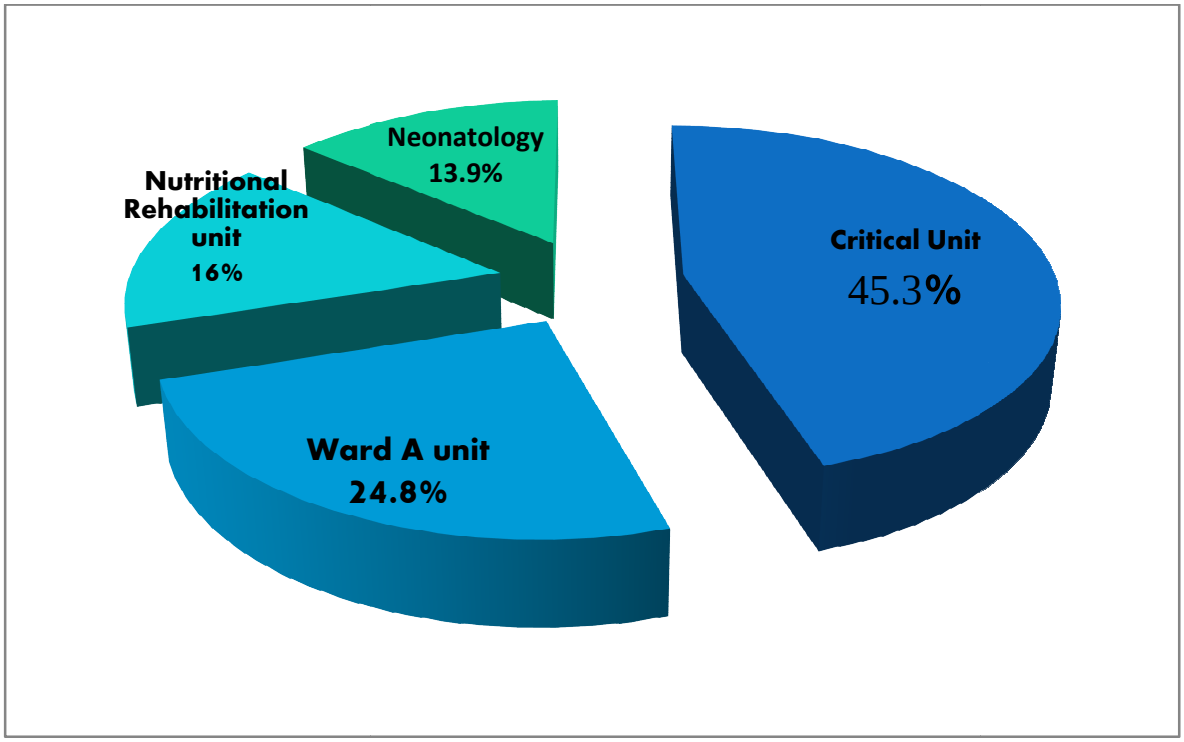


Figure 11: Percentage of medication errors that are identified in each unit of Jimma University Specialized hospital Pediatrics ward, Feb- May, 2011.

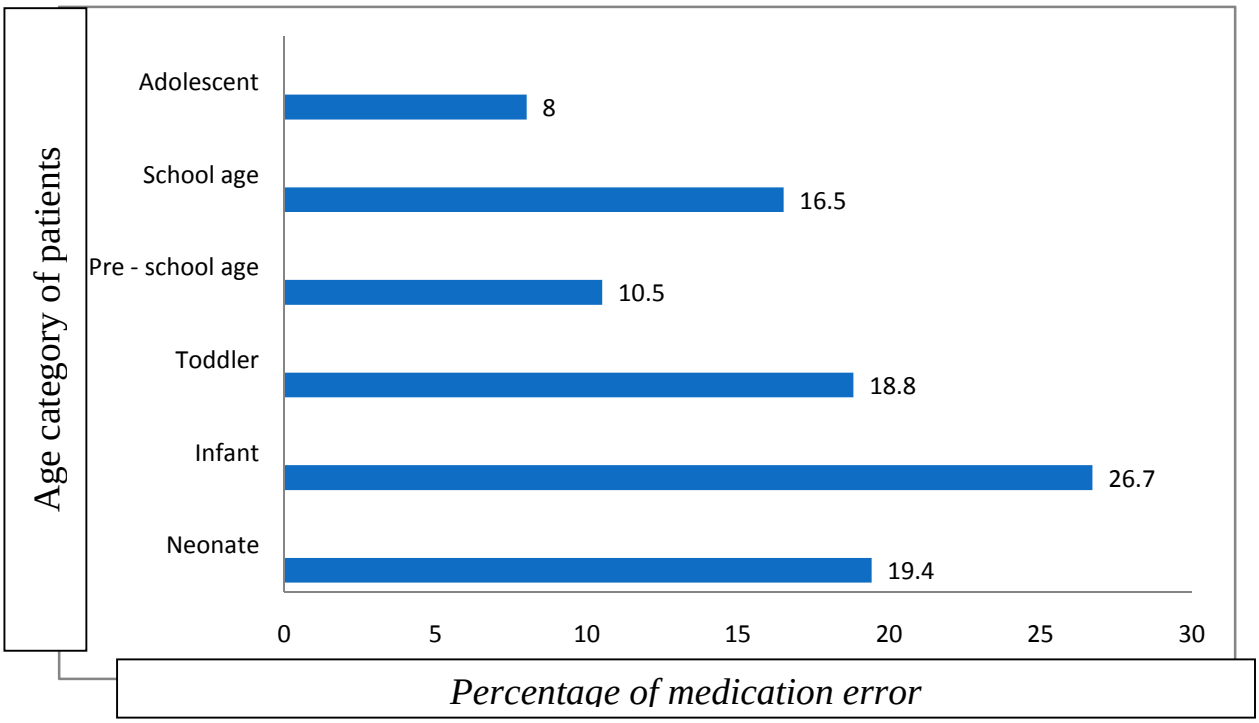
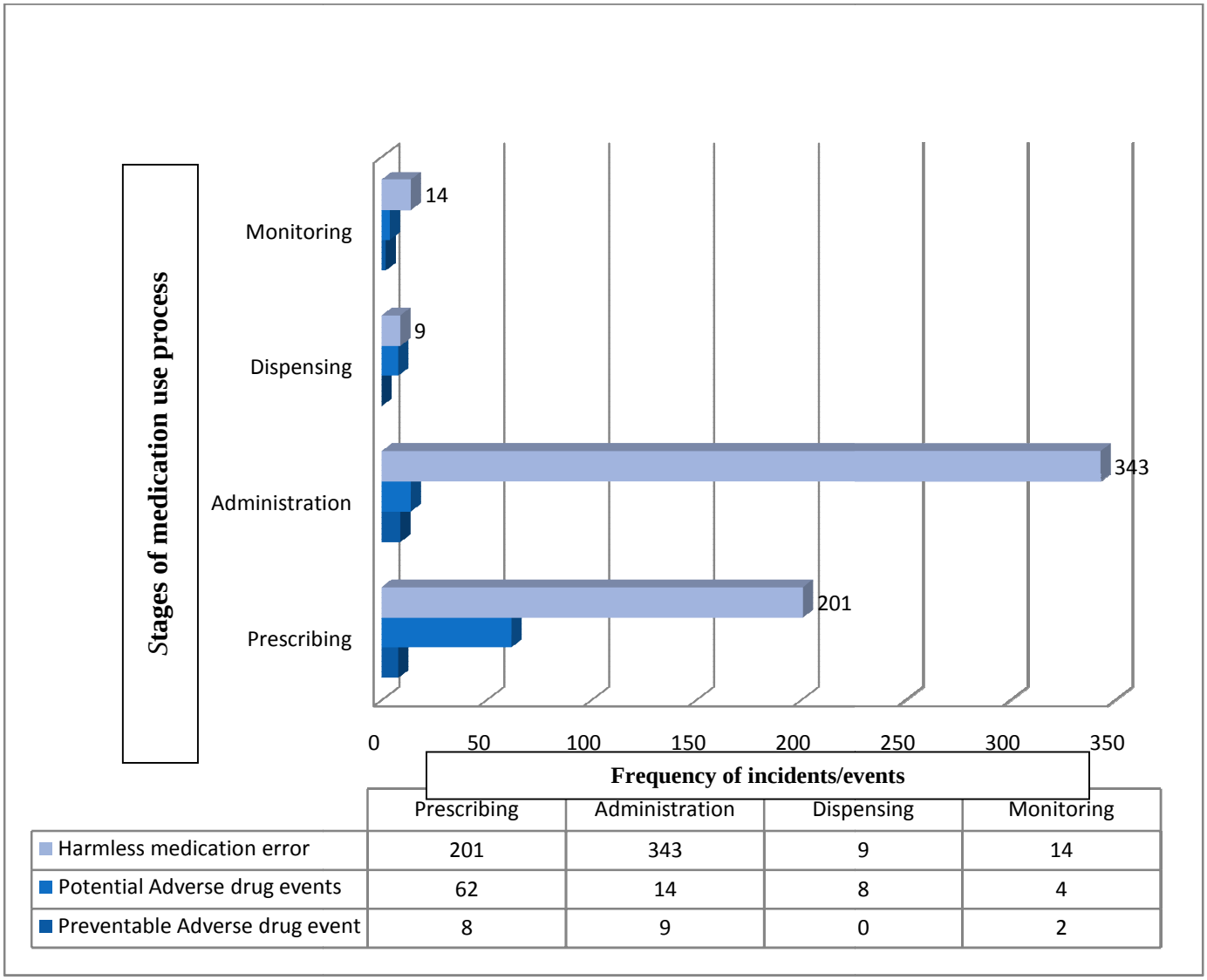


Figure 12: Distribution of Medication Errors according to age category of Hospitalized children in Jimma University specialized Hospital pediatrics ward, Feb – May, 2011

Three hundred sixty-six (54.3%) of the 674 medication errors identified occurred at the administration stage of medication use process followed by 271(40.2%) at prescribing /ordering (figure 13).

The relationship between ADEs, PADEs and medication errors is well depicted in figure 14.



	Prescribing	Administration	Dispensing	Monitoring
Harmless medication error	201	343	9	14
Potential Adverse drug events	62	14	8	4
Preventable Adverse drug event	8	9	0	2

Figure13: Frequency of medication errors at different stages of medication use processes in Jimma University Specialized hospital pediatrics ward, Feb – May, 2011

Table 11: Types of Medication errors identified in Jimma University Specialized Hospital pediatrics ward, Feb – May, 2011**

Types of medication error	Preventable ADEs	Intercepted PADEs	Non-intercepted PADEs	Harmless medication errors	Total	Rate per 1000 patient days	Rate per 100 medication orders
Dose omission	**2**	**0**	**3**	**127**	**132**	**21.4**	**3.8**
Improper dose	**8**	**13**	**44**	**131**	**196**	**31.7**	**5.6**
1. High dose	**8**	**12**	**27**	**69**	**116**	**18.8**	**3.3**
2. Under dose	**0**	**1**	**15**	**44**	**60**	**9.7**	**1.7**
3. Extra dose	**0**	**0**	**2**	**18**	**20**	**3.2**	**0.6**
Wrong strength/concentration	**0**	**0**	**0**	**11**	**11**	**1.8**	**0.3**
Wrong drug	**0**	**1**	**6**	**18**	**25**	**4.0**	**0.7**
Wrong dosage form	**0**	**0**	**0**	**11**	**11**	**1.8**	**0.3**
Wrong route of administration	**6**	**1**	**0**	**15**	**22**	**3.6**	**0.6**
Wrong technique of administration	**1**	**0**	**5**	**128**	**134**	**21.7**	**3.8**
Wrong frequency	**0**	**1**	**0**	**66**	**67**	**10.8**	**1.9**
Wrong duration	**0**	**0**	**2**	**6**	**8**	**1.3**	**0.2**
Wrong patient	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Monitoring error	**2**	**0**	**12**	**22**	**36**	**5.8**	**1.0**
Deteriorated error	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Others	**0**	**0**	**0**	**32**	**32**	**5.2**	**0.9**

** The classification is based on **NCCMERP Taxonomy of Medication Errors**[76]

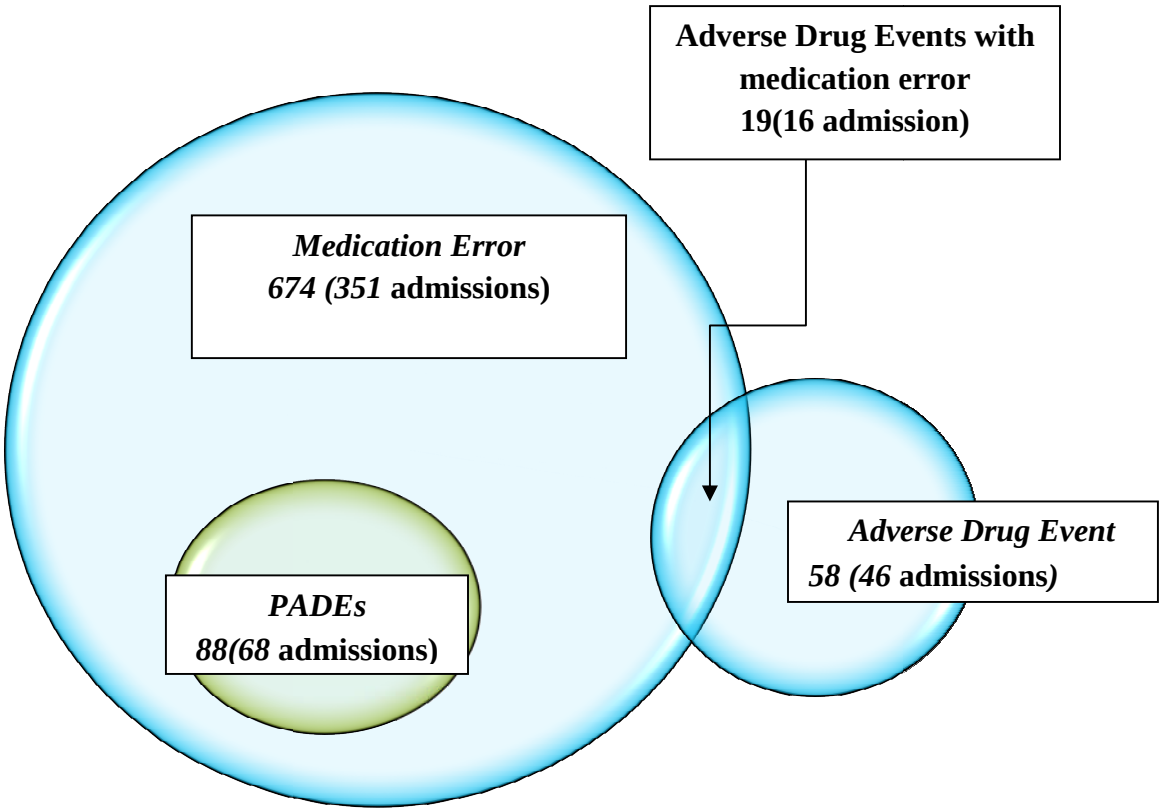


Figure 14: Relationship between adverse drug events, potential adverse drug events and medication error in Jimma University specialized hospital pediatrics ward, Feb – May, 2011

Factors associated with adverse drug events, potential adverse drug events and Medication Error

Factors associated with the risk of adverse drug events, potential adverse drug events and medication error are presented in table 12, 13 and 14 respectively.

In the univariate logistic regression analysis, the odds of ADEs increased with older age, longer length of hospital stay and use of CNS, endocrine and antihistamine medicine compared with those without these risk factors (table 12). In the results of the full multivariate model analysis, age was not associated with the risk of developing ADEs but presence of infectious disease, use of Antihistamines and anti allergic, CNS and Endocrine medicines were associated with risk of ADEs. The strongest association seen is the use of antihistamines and anti-allergic drug with the risk of developing ADEs (95%

CI 5.990-176.446); children are almost 32 times more likely to have adverse drug events than those without antihistamine order. In the full model analysis also, children with length of stay greater than 23 days were 8 fold times more likely to develop adverse drug events than children with less than 9 length of stay in the ward (95% CI 2.934 - 22.038).

For factors associated with the risk of potential adverse drug event(table 13), the odds increases as the number of medications prescribed increases, the length of hospital stay was prolonged, with the use of Cardiovascular, CNS, Gastrointestinal and Endocrine medicines, as well as the presence of CNS and cardiovascular disorders in the univariate logistic regression analysis but only the number of medications ordered, the order of GI medicines and presence of CNS disorder remained associated with the risk of developing potential adverse drug event. Children with more than 11 medication order (95% CI, 1.936-103.535) will have 14 fold odds of developing potential adverse drug event than children with number of medication order between 1 and 5. The odds for PADEs were about 11 fold higher in children with CNS disorders than children without this disorder (95% CI, 4.182-29.795).

Table 12: Odds Ratio for factors associated with adverse drug events in hospitalized children in Jimma University specialized hospital, Feb –May, 2011.

Characteristics	Crude OR (95%CI)	Adjusted OR (95%CI)
Weight	1.038(1.007 - 1.071)	0.997(.924- 1.075)
Number of medications ordered		
1- 5	1.0	1.0
6 - 10	2.856(1.373 -5.939) **	0.757(0.262-2.183)
≥ 11	5.020(0.509 - 49.550)	0.176 (0.003- 11.222)
Length of hospital stay		
1- 8	1.0	1.0
9 - 15	2.561(1.102 -5.950) **	2.474 (0.996- 6.144)
16 - 22	5.204(2.199- 12.317)*	5.056(1.975 -12.940) **
≥ 23	8.381(3.540- 19.840) *	8.041(2.934 -22.038) *

Table 12: continued

Age(Years)		
Neonate	1.0	1.0
Infant	1.889(0.615-5.807)	1.287(0.392-4.228)
Toddler	1.175(0.322-4.284)	0.394(0.089-1.740)
Pre-school age	0.346(0.038-3.161)	0.182(0.018-1.870)
School age	3.693(1.129-12.084) **	1.937(0.527-7.117)
Adolescent	5.081(1.443-17.896) **	2.690(0.674-10.744)
Use of CNS medicines		
NO	1.0	1.0
Yes	2.561(1.396-4.698) **	2.086(1.008- 4.318) **
Use of Endocrine medicines		
No	1.0	1.0
Yes	3.309(1.585-6.907) **	3.383(1.404- 8.152) **
Use of other medicines		
No	1.0	1.0
Yes	3.405(1.089-10.641) **	1.789 (0.370-8.648)
Use of Antihistamine and ant-allergic		
No	1.0	1.0
Yes	21.900(5.938-80.766)*	32.511(5.990-176.446)*
Presence of CNS disorders		
No	3.638(1.156 -11.450) **	2.568(0.644- 10.238)
Yes		
Presence of Endocrine Disorders	1.0	1.0
No	13.318(1.832 -96.824) **	3.215(0.228-45.327)
Yes		
Presence of Infectious disease		
No	1.0	1.0
Yes	3.764(1.464-9.681) **	3.430(1.187-9.911) **

* $p<0.001$, **$p<0.05$

Table 13: Odds Ratio for factors associated with potential adverse drug events in hospitalized children in Jimma University specialized hospital, Feb-May, 2011

Characteristics	Crude OR(95%CI)	Adjusted OR(95%CI)
Number of medications ordered		
1- 5	1.0	1.0
6 - 10	4.034(2.199-7.403) *	3.271(1.682-6.361) *
≥ 11	10.617(1.462-77.100) **	14.158(1.936-103.535) **
Length of hospital stay		
1- 8	1.0	1.0
9 - 15	1.719(0.892- 3.314)	1.440(0.716-2.897)
16- 22	2.817(1.371-5.788) **	1.670(0.715-3.899)
≥ 23	3.714(1.745-7.906) **	2.409(0.982-5.908)
Use of Cardiovascular medicines		
No	1.0	1.0
Yes	2.261(1.135-4.503)	0.586(0.192-1.787
Use of CNS medicines	1.0	1.0
No	2.410(1.443-4.026) **	0.586(0.192-1.787)
Yes		
Use of Gastrointestinal medicines		
No	1.0	1.0
Yes	5.298(2.010-13.960) **	3.844(1.284-11.509) **
Use of Endocrine medicines		
No	1.0	1.0
Yes	3.478(1.841-6.572) *	2.135(0.971-4.696)
Presence of Cardiovascular Disorders		
No	1.0	1.0
Yes	3.586(1.791-7.182) *	2.158(0.957-4.868)
Presence of CNS Disorders		
No	1.0	1.0
Yes	0.000,10.670(4.167-27.324)	11.162(4.182-29.795) *

CNS =Central nervous system medicines , * p<0.001, **p<0.05

Regarding factors associated with medication error (table 14), including that was responsible for preventable adverse drug event and potential adverse drug event, it was found that in univariate logistic regression analysis, the length of hospital stay, children with an order for CNS, anti-infective, GI, endocrine, Blood products and medicines affecting the Blood system, and vitamins have an increased odds for occurrence of medication error than children without these risk factors. In the multivariate full model analysis; use of vitamins, Blood products and medicines affecting the blood, presence of CNS and infectious disease were not associated with the risk for experiencing medication error, other variables remained associated with the risk for medication error. Children with length of stay in between 16 - 22 days have 6.2 fold times higher odds for experiencing medication error than in between 1 up to 9 days of length of hospital stay (95% CI, (3.087-12.525).

Table 14: Odds Ratio for factors associated with medication errors in hospitalized children in Jimma University Specialized hospital, Feb – May, 2011

Characteristics	Crude OR(95%CI)	Adjusted OR(95%CI)
Age(Years)		
Neonate	1.0	1.0
Infant	0.388(0.234-0.641) *	0.232(0.129-0.417) *
Toddler	0.0578(0.333-1.004) *	0.220(0.115-0.423) *
Pre-school age	0.601(0.318-1.139)	0.231(0.109-0.488) *
School age	0.640(0.346-1.181)	0.217(0.102-0.463) *
Adolescent	0.925(0.436-1.963)	0.397(0.161-0.978) *
Number of medications ordered		
1- 5	1.0	1.0
6 - 10	6.932(3.255-14.761) *	3.538(1.540-8.126)*
≥ 11	0.266(1.100	
Length of hospital stay		
1- 8	1.0	1.0
9 - 15	2.981(1.969-4.514)*	2.666(1.697-4.187)*
16- 22	7.171(3.732-13.778)*	6.218(3.087-12.525)*
≥ 23	6.207(3.028-12.720)*	5.657(2.531-12.643)*
Use of Anti-infective medicines		
No	1.0	1.0
Yes	2.359(1.294-4.299) **	2.617(1.064-6.435) **

Table 14: Continued

Use of CNS medicines		
No	1.0	1.0
Yes	1.680(1.174-2.403) **	1.607(1.043-2.475) **
Use of Gastrointestinal medicines		
No		
Yes	1.0	1.0
	15.243(2.022-114.898) **	25.495(2.687-241.896) **
Use of Endocrine medicines		
No	1.0	1.0
Yes	2.517(1.392-4.550) **	2.364(1.115-5.011) **
Use of Blood products and medicines affecting the Blood system		
No	1.0	1.0
Yes	4.891(1.671-14.312) *	2.456(0.755-7.982)
Use of Vitamins		
No	1.0	1.0
Yes	1.517(1.004-2.292)**	1.080(0.625-1.864)
Presence of Cardiovascular System Disorders		
No	1.0	1.0
Yes	2.581(1.316-5.060)**	2.474(1.115-5.489)**
Presence of CNS Disorders		
No	1.0	1.0
Yes	4.458(1.286-15.455)**	2.340(0.609-8.990)
Presence of Infectious Disorders		
No	1.0	1.0
Yes	1.736(1.233-2.446)**	1.375(0.870-2.173)

CNS =Central nervous system medicines
* p<0.001, **p<0.05

CHAPTER SIX
DISCUSSION

In this 12 week prospective study on admitted children in Jimma University specialized hospital, duration of hospitalization were longer than two similar studies [5, 7] but lower than one similar study [33] though the mean number of drugs ordered was low compared to above studies, 10 medications in[33] and 14.4 medications in[5]. Regarding the mean age of pediatrics studied, ours study was 2.9 years but in two of above, Takata[5] and Holdsworth [33]study in USA, was 5.9 years and 8.4 years respectively.

Estimation of the incidence of adverse drug events significantly depends on the trigger to which the event was searched, the methodology and definition used. Accordingly, multiple strategies were used to solicit all possible adverse drug events found in admitted children to maximize the yield of events. Still the absence of gold standard methodology to evaluate incidence of adverse drug events, comparison of our study with other findings will be restricted to those studies that used very similar methodology. As a result of these we are interested to compare our finding, mainly the incidence, with three papers, two of them done in the USA and 1 in New Zealand. As to our search, there is no any similar study done in African countries utilizing our methodology and definition of events. As described above, the incidence in our finding is consistent with these studies. In this study 33.9 % of subjects studied were infants that were comparable in Kaushal[14] studies in USA. Of the diagnosis made for studied children, 27.8% were children with severe pneumonia and almost 19% of children admitted in the study ward were with severe acute malnutrition. Regarding the medications characteristics ordered for admitted children, anti-infectives were prescribed most frequently; almost 64% of the prescriptions made were for anti-infectives followed by Central nervous system medication. Those medication characteristics might also affect the profile of adverse drug events to be expected.

Following an intensive follow up of admitted children in the study setting, we identified a total of 58 adverse drug events that corresponds to 9.2 per 100 admissions (crude rate),

1.7 per 1000 medication doses, 9.4 per 1000 patient days and 2.8 per 100 medication orders. This incidence when compared to other studies, done in different parts of the world with similar methodology, falls within the range (2.3 to 12.9 per 100 admissions) as described below. The incidence found in our study was higher when compared to 6 per 100 admissions and 7.5 per 1000 patient days in [33] and 2.3 per 100 admissions and 6.6 per 1000 patient days in[14] but ours finding was lower than in a New Zealand study [7], that was 12.9 per 100 admissions and 22.1 per 1000 patient days. One US study [5] conducted a retrospective focused chart review in 12 children hospitals using pediatric trigger tools and found out that the incidence of ADEs to be 11.1 per 100 admissions, 15.7 ADEs per 1000 patient days and 1.23 ADEs per 1000 medication doses. In comparison to our study, the ADEs detected is far higher. This should not be mistakenly noted that ours incidence is lower than that of the USA because of the methodology used to some extent is different (retrospective, focused chart review) though the definitions adopted are similar. But when we compare with Kaushal[14] and Holdsworth[33] studies that used similar methods, we found a higher rate of ADEs as described before. The difference might be attributed to methodology, the definition used, and prevalence of co morbid conditions, prolonged hospital stay and the use of high risk medications/class of medication; in general the quality of care between the study settings that is associated with the difference in the health care delivery system.

Though we said that it is difficult to compare the extent of ADEs occurrence in our setting with other study settings, but we can still appreciate that hospitalized children in our setting are facing a considerable amount of medications related harm.

Regarding the preventability of ADEs, the reviewer that included 2 senior pediatric residents rated that of 58 ADEs detected, 67.2 % of the events were non – preventable while 32.8% were deemed preventable. The preventability criteria used for rating of adverse drug events is based on the explicit criteria developed by Schmumock and Thornton[88]. Accordingly the primary medication error responsible for the preventable ADEs is improper dose while the most common medication use processes where those errors occurred were during administration stage. According to Takata[5] findings,

preventable adverse drug events occurred during monitoring stage, 62.5%; defined as failure to review a prescribed regimen for appropriateness and detection of problems or failure to use appropriate clinical or laboratory data for adequate assessment of patient response to prescribed therapy.

When we compare the preventability of ADEs of our findings with above similar findings, Holdsworth[33] was 61%, Kaushal[14] was 5 out of 26 events (19.2%), Kunnac[7] was 57%, 29% of 107 ADEs in Takata[5] were preventable events. Our study of preventability of ADEs is consistent with those studies indicating that almost 1/3 of the ADEs could be prevented if appropriate strategies has been in place. Of these preventable adverse drug events, 3 of the 4 events that were classified as resulted permanent harm were due to inadvertent route of administration of medication.

The severity rating for observed adverse drug events by two physician reviewers based on the explicit criteria of National Coordinating Council of Medication Error Reporting[76] of USA. Of 58 adverse drug events, 39(67%) were classified in to category E where as 4(7%) were classified as category G. When compared to other similar findings, Takata[5] study reported that 97.2 % of ADEs identified were classified as with severity category of E, while only 3 categorized as F. But in our findings, the severity of ADEs is much serious than those literature, here in the study 7% of ADEs resulted permanent harm to the children. So the impact of ADEs on children in our hospital would be significant than other similar studies. Though the incidence of ADEs in our study setting was comparable but the severity of the harm was with significant degree higher than previous reports.

The inter rater reliabilities between 2 senior residents for judgment of preventability and severity was found to be moderate agreement while presence of ADEs was found to be good agreement. When we compare these results with similar findings, Kunnac, Reith and kennedy study[90] found a similar result to our study, describing the reviewers inter rater rating were ‘‘substantial’’ agreement for the presence of an ADE (k = 0.73) while ‘‘moderate’’ agreement was found (k = 0.50) for seriousness versus non-serious though

our severity classification was as E versus F or G and in our study the reviewers were two physicians but in the above study there were three reviewers. According to the above study, for the preventability decision overall agreement was ‘‘fair’’ (k = 0.37), but in our study a moderate agreement (K= 0.461) was obtained. The difference might be due to the number of reviewers utilized. In Kaushal study[14], they described 87–100% agreement, k=0.65–1.0 but not clearly mentioned for which type of event classification. In our study, low level of agreement for preventability rating of adverse drug event indicates that reviewers were challenged by the complexity of judgment compared to the severity rating of ADEs.

The most commonly affected organ system with ADEs was Gastrointestinal, skin and followed by complications arising at the injection site. In kaushal[14], of the 21 non preventable ADEs, 14 were related to antibiotics use including *C.difficile* infections, rashes, allergic reactions, yeast infection etc. Again similar findings were seen in Takata study[5] where pruritis was the most common ADE. The most common medication classes responsible for the adverse drug events were antiinfectives followed by cardiovascular drugs and central nervous system medicines. During review of the literature, the most commonly mentioned medication classes associated with adverse drug event were analgesics/opioids followed by antibiotics[5, 33]. Narcotics were mentioned frequently as cause of ADEs in the literature and in the above literature that we described, but in our study setting narcotics are not available on the hospital formulary.

Regarding the additional interventions required as a result of the adverse drug events in hospitalized children were prescription of additional medications followed by discontinuation of the offending agent. Four adverse drug events required dose reduction. These additional interventions can predict the impact of adverse drug event on the hospital as well as to the patient. These interventions are associated with cost imposition to the system without including the cost of injury to the patient.

The incidence of PADEs was found to be to be 13.88 per 100 admissions, 2.51 per 1000 medication doses, 14.23 per 1000 patient days, 4.25 per 100 medication orders. Of the 88

PADEs, 81.82 % were non-intercepted PADEs that reached the patient. When we compare the incidence of PADEs with other similar studies, Holdsworth[88] found 8 per 100 admissions, 9.3 per 1000 patient days; ours was with a higher value but with that of Australian study[7] , they reported 14.6 per 100 admission and 25 per 1000 patient days , with similar findings in a US study[14] which identified 29 per 1000 patient days and 10 per 100 admissions - both are in the other end higher than our findings, when calculated per 1000 patient days , their value were two fold of our results but comparable when calculated with per 100 admissions. This reflects the difference of length of hospital stay and also possibly reflects the methodology where by investigators classified incidents as potential adverse drug events. Eighteen patients had ≥ 2 Potential adverse drug events. Most frequent PADEs were found in infants, 22(25%) of PADEs while 18(20.45%) were found in toddlers.

A total of 674 medication errors have been found in 351 patient admissions. The incidence of medication errors was found to be 19.2 per 1000 medication doses, 109 per 1000 patient-days, and 32.53 per 100 medication orders. Of 674 medication errors, 305(45.25%) of them have occurred in the critical units of pediatrics ward. When compared to other similar studies, Medication error rate in kaushal study[14] was 157 per 1000 patient days while 5.7 per 100 medication orders. A study in London area, UK[16] found that the prescribing error and administration error rate was 13.2% and 19.1% per 100 medication orders. The incidence of medication error per 100 medication order in our study is higher than in those studies, the reason could be the difference in the existing medication use system, the definition used for medication error types, the availability of medication safety programs both technology or non – technology methods might explain the difference.

The most common stage in the medication use system where medication error occurred is at the administering stage, i.e., 366 (54.3%). This goes in line with a New Zealand study[7], where they found that the most common stage was administering followed by prescribing stage. Among the types of errors, the most common error was an improper dose, 29% of all medication error followed by wrong administration technique and dose omission. Of

the dosing error, dose too high was the most common type followed by dose too low. The medication use process presents a unique challenge in pediatrics dosing error. Doses for children are most often calculated based on body weight, clinical condition, age, and sometimes in body surface area. Miscalculations particularly of the magnitude of 10 fold dosing error are common in pediatrics population. Ten fold dosing errors have been recently identified at a rate of 2 per 100 medication orders and contributed to a serious adverse drug event in Marcin study[92]. According to medication administration errors done by Girma and Feleke[32] in this ward, they found out that there is high frequency of administration error, 89.9% of direct observation was found to involve medication error

We conducted further analysis to find out the possible factors that would predict the occurrence of these medication related incidents/events in the study area. Factors associated with the risk of adverse drug events, potential adverse drug events and medication error were identified after running univariate and multivariate logistic regression analysis. On the full model for adverse drug events analysis, presence of infectious disease, use of Antihistamines and anti allergic, CNS and Endocrine medicines was associated with risk of ADEs. Of these factors associated, the indication that hospitalized children with a prescription for antihistamine and anti-allergic medication have a 32 fold times more likely to develop an ADEs. This well correlates to the notion that during monitoring for occurrence of adverse drug events, the use of antihistamines and anti-allergic medications a clue for further evaluation is very important. Again length of hospital stay is associated with ADEs. Children with length of stay greater than 23 days will develop adverse drug events 8 fold times than children with less than 9 days of length of stay in the ward. These factors were also found to predict the occurrence of adverse drug events as seen in Holdsworth study[33], Length of hospital stay and medication exposure were factors associated with occurrence of ADEs. After they adjusted for the duration of hospitalization, they found that the number of medications had a significant influence on the rates of adverse drug events and PADEs. In a study by Santos[39] using ADR as an outcome found that children with longer length of stay, greater

number of drugs administered experienced significantly higher ADR incidence compared to those without these characteristics.

In one study in adult hospitalized patients[93], they identified that exposure to psychoactive and cardiovascular drugs were independent correlates of preventable ADEs. Though this study shows the scenario in adults; our finding shows the association of use of CNS and endocrine medicines as well as presence of infectious disease as an independent correlate for ADE occurrence.

Regarding factors associated with PADEs and medication error: the number of medications ordered, the order of GI medicines and presence of CNS disorder are associated with the risk of developing potential adverse drug event. In addition, use of anti-infective, CNS and endocrine medicines were associated with occurrence of medication error. Regarding diagnosis, presence of cardiovascular disorder was associated with occurrence of medication error.

CHAPTER SEVEN
CONCLUSION

Adverse drug events are common in hospitalized children. This should alert the responsible individuals and organization to design systems so that they can reduce medication related harm.

ADEs were more likely to occur among children with longer length of hospital stay, presence of infectious disease, use of CNS, Endocrine and anti histamine medications. Anti-infectives were the most commonly implicated drugs for development of adverse drug events. Almost one third of ADEs were found to be preventable. Most of the ADEs found were temporary harm to the patient that required intervention but considerable number of hospitalized children also suffered medication related permanent harm. This calls for an alarming attention to the consequences of medication related harm to the pediatric patients. The most common organ system affected by ADEs was the gastrointestinal system.

Potential adverse drug events and medication errors are very common and nearly half of these errors have occurred at administration stage followed by prescribing stage. Majority of PADEs were non-intercepted. Of the types of medication error, improper dose was the most frequent followed by wrong administration technique.

Potential adverse drug events were likely to occur among children with multiple medications ordered, an order for GI medicines and presence of CNS disorders but the age; number of medications ordered; length of hospital stay; use of anti-infective, Central nervous system, Gastrointestinal and endocrine medicines; and presence of cardiovascular disorders were factors associated with the risk to experience medication error among hospitalized children.

CHAPTER EIGHT
RECOMMENDATIONS

Since most of the epidemiological characteristics of our study and those of similar studies done in developed countries share similar pattern, use of both technology and non-technology based methods tested in their study setting for preventing medication related harm and medication error to hospitalized children can be adopted to the study area.

We recommend the following points for preventing medication related harm including:

- Incorporation of ward based clinical pharmacists in to patient care teams
- The following interventions to support health care providers during ordering and administering of medications to patients may improve drug safety among hospitalized children as could reducing length of stay
    - Preparation of specialized protocols for high alert medications, especially we recommend developments of standardized dosing guidelines in neonates and infants, developing infusion therapy protocols, IV admixtures and compatibility, nurse double check protocols in administration of high risk medication
- The hospital pharmacy and drug therapeutics committee should work to make sure that essential pediatric formulation or child size medication are available and should work in collaboration with pediatrics ward for extemporaneous preparation of pediatrics formulation. They should take the lead to coordinate interventions to prevent medication related harm and encourage non-punitive blame free medication error reporting with the hospital
- Targeting high risk hospitalized children for adverse drug with extended length of hospital stay, receiving central nervous system and endocrine drugs for possible prevention of medication related harm
- Continuing education for nurses, pharmacists and physicians on the medication safety as well as patient safety concepts

- In the long run, Hospital administrators should think of implementation of information technology system including physician computer order entry
- We recommend undertaking of further similar studies in other parts of the country to know the burden of the problem and also to conduct root cause analysis for the medication errors identified.

CHAPTER NINE
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ANNEXES - I

DATA COLLECTION TOOLS

There are four data collection formats used in this research project

- Socio-demographic, diagnosis and medication therapy data abstraction form
- ADE data collection form
- Pediatric ADE patient record review sheet
- ADE monthly summary sheet
- Medication error reporting /data collection form
- Questionnaire used to solicit information from children /parent or relative

Socio-demographic, diagnosis and medication therapy data abstraction form

Unit: _____

Patient initials: _____Card. No.:_____ Bed No._____

Patient age: _____ Sex: M F ; Weight: _____ kg; Height: _____cm

Date of admission: _____

Current working Diagnosis:-

Medications ordered:-

Ser. No	**Drug name**	**Dose , Route, Frequency ,duration**	**Date started**	**Date stopped**	**Remarks**

N.B. For PRN medication, please include the dose, time and date given …….

Date of discharge: _____

Final Diagnosis (Discharge summary):

For this patient, fill the following up on discharge:

1. Total number of medications the patient took**:-**
2. Total number of medication doses s/he took during stay**:-**
3. If there is any adverse drug event/incident identified at any time in this patient, please use the adverse drug event and /or medication error collection form.

ADVERSE DRUG EVENT DATA COLLECTION FORM

Complete one for each patient

Patient identification number :
Admission date(dd/mm/yy):
Discharge date (dd/mm/yy):
Age : Weight : Kg Height : cm
Admission Diagnosis :
Unit : ____NRU _____ward A _____ Neonatology _____ Critical Ward
ADE found: Yes_____ NO_____
Describe the adverse drug event :
Date the event started : Date the event stopped:
Any relevant history, Allergies, Previous exposure, Baseline test results/lab data, hepatic/ renal dysfunction, etc.
Medication involved or suspected to involve ADE :(Name , dose , route , frequency, indication, date started)
Total medications the patient is receiving : **Total number _____ (Include Name of other drugs taken , Dose & Route, Frequency , Indication- reason for use**)

ADE outcome : Outcomes attributed to use of drug (check all that apply):

____ Intervention required to prevent permanent impairment or damage

_____Allergy

_____ Disability _____ Life threatening

_____ Hospitalization (prolonged) _____ Death : (mm/dd/yyyy)

Other outcome (describe)_____

Treatment of ADE : YES_____ NO_____

If yes , Please describe :

Interventions: Please tick in the space for action taken in response to ADE

- Administration of antidote/reversal agent _____
- Medication dose changed _____
- Medication D/C _____
- Required increased monitoring (Lab / or V/S)_____
- Transfer for higher level care_____
- Other intervention _____
  _____

Event Leading to ADE to occur in this patient:

If a medication error occurred , please use the medication error recording format

Pediatric ADE Patient Record Review Sheet

Patient Identification Number _____

Admission Date _____ Patient's Age _____

Discharge Date _____ Date _____

Ser. No.	ADE Found	Harm Category*	Description of ADE
Total ADEs for this patient:			
Total number of doses of medications for this patient			

***Harm Category (adapted from NCC MERP obtained from reference 68)**

Category E: Temporary harm to the patient and required intervention

Category F: Temporary harm to the patient and required initial or prolonged Hospitalization

Category G: Permanent patient harm

Category H: Intervention required sustaining life

Category I: Patient death

ADE Monthly Summary Sheet

Date _____

Unit _____

Patient identification No.	**Total # of ADEs for this patient**	**Total # of medication for this patient**	**Total number of medication doses for this patient**	**Length of stay (LOS) for this patient**
Pt #				
Pt #				
Pt #				
Pt #				
Pt #				
Pt #				
Pt #				
Pt #				
Pt #				
Pt #				
Pt #				
Pt #				
Pt #				
Pt #				
Pt #				
Pt #				
Pt #				
Pt #				
Pt #				
Pt #				
Pt #				
	Total:	Total:	Total:	Total:

MEDICATION ERROR REPORT/ COLLECTION FORM

General information: Patient information: Age: _____ Sex: ____M_____F

Weight: _____ kg Height: _____ (if possible)

Diagnosis: _____

1. Date of the event: _____(dd/mm/yr)
   Time of the event: _____ (hh/mm 24 hr)
   Type of Unit ME occurred:
   a. ward A._____ b. NRU_____ c. Critical ward _____d. Neonatology____

2. Please describe the error, include description / sequence of events.

3. In which process did the error occurred:

   _____ Prescribing _____ Dispensing (Including Filling) _____ Administration

   _____ Monitoring _____ Transcribing

PRESCRIBING ERROR

___Patient is allergic to medication prescribed

____Incorrect drug selection

____Incorrect drug dosage selection

____Incorrect drug form selection

____Incorrect drug quantity selection

____Incorrect drug route selection

____Incorrect drug concentration /strength selection

____Incorrect rate of administration selection

____Incorrect instructions for use of drug

DISPENSING ERROR

ed

_____ Wrong medication dispensed

_____Wrong dose/concentration dispensed

_____Expired drug dispensed

_____Wrong drug form dispensed

MEDICATION ADMINISTRATION ERROR

__ Medication omitted

___ Medication administered at wrong time

___Wrong patient received medication

___Wrong medication administered

___Wrong dose administered

___IV Flow/concentration incorrect

C**ontinued)**

(from Administration Error)

___Wrong route of administration

____Wrong form of administration

____Medication given without physician order

____Medication given after physician order discontinued

____ patients is allergic to medication administered

Monitoring error

_____Failure to review a prescribed regimen for appropriateness and detection of problems,

_____Failure to use appropriate clinical or laboratory data for adequate assessment of patient response to prescribed therapy

4. A). Did the error reach the patient: Yes_____ No_____?

B). Describe the direct result on the patient (type of harm, additional patient monitoring required, etc) if reaches the patient

C).Please Tick the appropriate error outcome category (select one)

No Error: ___ A. Potential error, circumstance / events have the potential to cause incident

Error, No harm: _____ B. Actual Error, did not reach the patient

_____ C. Actual Error, reached the patient but cause no harm

_____ D. additional monitoring required, cause no harm

Error, Harm: _____ E. Treatment / intervention required - caused temporary harm

_____ F. Initial /prolonged hospitalization – caused temporary harm

_____ G. Caused permanent harm

_____H. near death event

Error, Death: _____ I. Death

5. Indicate the possible Error causes(s) and contributing factor(s)

_____Unavailable pt information prior to dispensing or administering drug (lab values, allergies, etc)

_____ Unavailable drug information (written resources)

_____ Miscommunication of drug orders (similar names, inappropriate abbreviations, illegible handwriting, etc)

_____Problems with labeling, packaging

_____ Drug standardization, storage (look-alike containers, etc)

_____ Drug device use and monitoring (equipment malfunction, etc)

_____ Environmental stress (distractions, noise during transcription or dispensing, extended shifts, etc)

_____ Staff knowledge regarding medication

_____ Other: _____

8. Please complete the following for the medication involved. If you need more space you can add paper

Medication description	Medication
	Intended Error

1. Brand name:_____
2. Generic name (active ingredient):_____
3. Dose , Frequency , Duration , route:_____
4. Dosage form :_____
5. Strength/Concentration :_____

Questionnaire used to solicit information from the children's mothers or relatives (Amharic and Oromifa version are also attached)

1. Could you please tell us from where do your child come from and his /her age? _____
2. Is there any medical problem in the past in your child or family present that you seek for treatment in the hospital/health center?
   If yes, would you please share me the list:

   _____

   _____

   _____

   _____
3. A. Did your child has taken any medications before he/she came to this hospital? If so, what are those drugs?

   _____

   _____

   B. While your child was taking medications in the past, did he/she have any previous drug reactions/any allergic history to medications or food that you noted or you have been told by health professionals previously?

   _____

   _____

   _____
4. While you are attending your child here ;
   A. Is there any new problem seen in your child after he/she started to take his/her medications prescribed for his/her illness in the hospital after admission?

   _____

   _____

   _____

   _____

B. Is there any error that you noted in regards to your child medications he/she is currently taking that reached your child or intercepted before reaching your child? If so , could you explain to me

_____

_____

_____

_____

ANNEX - II

Trigger tools or clues for a focused chart review

A. Triggers medications

Trigger drugs are drugs that are links to a possible adverse drug events because either they are antidotes or are given to revere the action of a drug.

1. Atropine - bradycardia
2. Benzatropine/Trihexyphenidyl - extra pyramidal reactions
3. Blood transfusions - NSAID or drug induced gastric bleeds
4. Calcium chloride - Calcium channel blocker overdose
5. Dantrolene - hyperthermia, neuroleptic malignant syndrome
6. Dextrose 50% in water - hypoglycemia
7. Diazepam - drug induced seizures
8. Digoxin immune fab (Digibind) - digoxin overdose
9. Diphenhydramine - hypersensitivity reactions, drug rashes, extra pyramidal reactions
10. Epinephrine - hypersensitivity reactions
11. Flumazenil - benzodiazepine overdose
12. Fosphenytoin/Phenytoin - seizures, arrhythmias
13. Glucagon - hypoglycemia, beta blocker overdose
14. Naloxone - narcotic overdose
15. Phentolamine - dopamine extravasation
16. Vitamin K (Phytonadione) - Warfarin toxicity or hypoprothrombinemia
17. Physostigmine - anticholineric overdose, belladonna alkaloids overdose
18. Protamine - heparin overdose
19. Sodium polystyrene sulfonate (Kayexelate) - hyperkalemia
20. Steroids (inject able) - hypersensitivity reactions
22. Steroids (topical) - hypersensitivity reactions, drug rashes
22. Anti emetics: Nausea and vomiting can be the result of drug toxicity or Overdose, particularly in patients with impaired renal function.
23. Laxative or stool softeners**:** Look for evidence referring to the use of stool Softener or Laxatives

A. <u>New symptoms or events as triggers that may show a possible adverse drug events</u>

1. **PTT > 100 seconds:** This is not an infrequent occurrence when patients are on heparin. As With Vitamin K, look for evidence of bleeding to determine if an ADE has occurred.
2. **Rising serum creatinine:** A rising serum creatinine is defined as a serum creatinine which Becomes elevated relative to age-specific normal values or as an increase in serum Creatinine of >=0.4mg/dl.
3. **Over sedation, lethargy, falls, hypotension**: If found, look for a relationship between the event and administration of a sedative, analgesic, or muscle relaxant.
4. **Rash:** There are many causes for a rash. Look for evidence that the rash is related to drug administration, including overuse of antibiotics resulting in yeast infections.
5. **Abrupt medication stop:** In the order sets, whenever "hold" or "stop" medication orders Appear, look for the reason this was done. Frequently it indicates an event of some kind.
6. **Serum glucose >150 mg/dl:** Look for serum glucose values exceeding this level
7. **Hyperkalemia (High serum potassium):** Look for lab values outside of these ranges.The following are the normal ranges for patients based on age: 0 – 3 months = 3.7 – 5.9 mEq/L : 3 months – 1 year = 4.1 – 5.3 mEq/L: 1 year – adult = 3.6 – 5.0 mEq/L
8. Look in the progress notes for documentation; includes cardiac arrest, respiratory arrest, and respiratory distress; patients in ICU requiring emergency intubation. This may be associated with adverse drug event.

Informed Consent

Jimma University

College of public health and medical sciences

Clinical Pharmacy Postgraduate program

Department of pharmacy

ADVERSE DRUG EVENTS AND MEDICATION ERRORS IN HOSPITALIZED CHILDREN AT JIMMA UNIVERSITY SPECIALIZED HOSPITAL PEDIATRICS WARD.

Dear research participants,

I am Tesfahun Chanie from department of pharmacy and Masters Student in clinical pharmacy. I am conducting a research in pediatrics medication safety problems. The purpose of the study is to understand how much patients are exposed to injury as a result of adverse drug reactions and medication error. This study also characterizes the potential adverse drug events due to medication error.

The results obtained from this study are useful in order to develop better preventive strategies in the future and may also have the potential of being extrapolated to other hospitals.

Your participation in the study is voluntary and that you can chose not to be included in the study or withdraw at any time. Your refusal not to participate will in no way affect your service at the hospital. All personal identifiers will be removed and also no personal information will be forwarded to others.

You may not personally derive any benefits directly from participating in the study and also there is no any risk or harm that this research will bring to you.

Your personal information will be maintained through use of unique codes and of course restricting access to the data set to the principal investigator and those working with him.

I am very much grateful for your keen interest and honesty in sharing information. Whenever you have any questions or comments please call Tesfahun Chanie at 0912042050.

With regards!

በጂማ ዩኒቨርስቲ

የህብረተስብ ጤና ና ህክምና ሳይንሶች ኮሌጅ

የክሊኒካል ፋርማሲ ድህረ ምረቃ ትምህርት ክፍል

መድሃኒቶች በጅማ ዩኒቨርስቲ ስፔሻላይዝድ ሆስፒqል ተኝተው በሚqከሙ ህጻናት ላይ ስለሚያደርሱት ጉዳት

አቶ ተስፋሁን ጫኔ በፋርማሲ ት/ት ክፍል የማስተርስ ድግሪ የመመረቂያ ምርምሩን በዚህ ሆስፒqል ለህክምና በተኙ ህጻናት ላይ መድሃኒቶች በሚያደርሱት ጉዳት ላይ ሲሆን የጥናቱ ዋና አላማ በተለያዩ ምክንያቶች መድሃኒቶች የሚያደርሱትን ጉዳት መጠንና አይነት ማጥናት ነው፡፡ በተጨማሪም በመድሃኒቶች አጠቃቀም ሂደት ላይ በሚከስቱ ስህተቶች ተኝተው የሚታከሙ ህጻናትን ለአዳጋ ሊያጋልጡ የሚያስችሉ ሁነቶችን ያጠናል፡፡ይህ ጥናት አስፈላጊነቱ በዋናነት እንደዚህ አይነት ችግሮች ወደ ፊት ለመከላከል የሚያስችል ስልት ለመቀየስ የሚጠቅም ሲሆን በተጨማሪም በሀገሪቱ ባሉ ጤና ተቋማት ያለውን ሁኔታ ለማጥናት እንደ መነሻ ሁኖ ሊያገለግል ይችላል፡፡

የእናንተ ተሳትፎ በዚህ ምርምር ላይ በፍፁም በፍቃደኝነት የተመሰረተ ሲሆን በማንኛ ውም ሰዓት በምትፈልጉበት ግዜ ከምርምሩ ራሳችሁን ማግለል ተችላላችሁ፡፡ ይህም ከሆስፒታሉ የምታገኙትን አገልግሎት አያደናፍቅም፡፡ ሰለ እናንተ ማንነት የሚገልጹ መረጃ ች ጥናቱ በሚስጥር የሚይዝና በግልፀ በማይታይ ሚስጥራዊ ምህጻረ ቃል የሚጠቀም ሲሆን መረጃ ችንም ለሌላ ሦስተኛ ወገን በምንም አይነት መንገድ አሳልፎ አይሰጥም፡፡

በዚህ ምርምር ላይ በመሳተፍ በቀጥታ የሚያሰገኝል ት ጥቅም ባይኖርም ምርምሩ በርስ ላይ ምንም አይነት ጉዳት ሊያደርስ ና ሊያጋልጥ የሚያስችል ሁኔታ አይኖርም፡፡ የርስ ግለሰባዊ መረጃ በከፍተኛ ሚስጥር የሚያዝ ሲሆን በጥናቱ ውስጥ ያለ ትን ጥያቄ ወይም አስተያየት ለአቶ ተስፋሁን ጫኔ በስልክ ቁጥር 0912042050 ደውለው ማስተላለፍ እንደሚችሉ እየገለፅሁ ሰለተደርገልን ትብብር እናመሰግናልን፡፡

<u>መድሃኒቶች በጅማ ዩኒቨርስቲ ስፔሻላይዝድ ሆስፒq ል ተኝተው በሚq ከሙ ህጻናት ላይ ስለሚያደርሱት ጉዳት ለማወቅ ለልጁ ወይንም ለልጁ ተንከባካቢ ቤተሰብ የሚቀርብ ቃለ መጠይቅ</u>

1. **የልጅ ን እድሜ ና ከየት እንደመጣ ሊነግሩን ይችላሉ?**

2. **ከልጅ ወይንም ከቤተሰቡ ውስጥ ከዚህ በፊት ወደ ሆስፒታል ሂዶ መq ከም ያስፈለጋቸው የጤና ችግር ካለ ቢያብራሩልኝ?**

3. **ስለ ልጁ ከዚህ በፊት ስለ ወሰዳቸው መድሃኒቶች፤**

ሀ) ልጅ ወደዚህ ሆስፒታል ከመምጣቱ በፊት እየወሰደው የነበረው መድሃኒት ካለ ቢገልጹልኝ?

ለ).ከዚህ በፊት ልጅ መድሃኒት የወሰደ በነበረበት ግዜ መድሃኒቱ ያመጣው ጉዳት (የጎንዮሽ ጉዳት ወይንም ሌላ) ከነበረ ቢገልጹልኝ?

ሐ) በተጨማሪም ለመድሃኒት አለርጅ ካለው ለየትኛው መድሃኒት አንደሆነ ሊገልጹልኝ ይችላሉ?

መ) ልጅ የምግብ አለርጅ ካለውም አንዲሁ ለምን አይነት ምግብ እንደሆነ ቢያብራሩልኝ?

4. አሁን ከዚህ ሆስፒታል ልጅ ለህክምና ከመጣ ጀምሮ፤

ሀ) ልጅ መድሃኒት መውሰድ ከጀመረ ጀምሮ በልጅ ላይ የተመለከቱት አዲስ የጤና መታወክ ምልክት ካለ ቢገልጹልኝ?

ለ) በመድሃኒት አጠቃቀም ዙሪያ ልጅ ከሚወስዳቸው መድሃኒቶች ጋር በተያያዘ ስህተት ተሰርቶ የተገኘበት ካለ ቢያብራሩልኝ?

Yuunivarsitii Jimmaa

koolleejii fayyaa ummataa fi saayinsoota meedikaalaa

Sagantaa digirii lammafaa kiliinikal faarmaasii

Muummee faarmaasii

Dhibee qorichootaa, daa'iman hospitaala ispeeshaalayzdi yuunivarsitii Jimma ciisanii yaalamanu irran ga'an

Ani barataa digrii lammafaa kiliinikal Faarmaasi kanin ta'e Tasfaahun chaannee, qorannoo eebbaa koo daa'imman hospitaala kana ciisanii yaalaman irratti, dhibee qorichi irraan ga'u kan ilaalatu dha. Kaayyoo gooroon qorannoo kanas hammaa fi gosa dhibee qoricha fidee qorachuu dha. Itti dabalataanis, adeemsa fayyadamina qorichaa keessatti, dogogorri uumamanu daa'imman ciisanii yaalaman irratti haalawwan balaaf saaxilan ni qo'ata. Barbaachisummaan qorannoo kanaa inni hangafitni rakkoowwan akkanaa fuulduratti haala itti ittisuun danda'amu mala dha'uu yoo ta'u kana malees, dhaabilee fayyaa biyyattii (itophiyaa) kana keessa jiranuffi, haala jiru qorachuuf bu'uura ta'ee ni tajaajila .

Qoranno kana keessatti hirmaannan keessan fedhii irratti kan hundaa'ee ta'e, yeroo barbaddan adeemsa qorannoo keessaa of fo'u ni dandeessu. Kunis tajaajila isin hospitaala irraa argattan hingufachiisu ragooleen waa'ee keessan ibsan hundi icitiin kan qabamanii fi qaama hinkennamne dha.

Qorannoo kana irratti hirmaachuu keessaniif kallattiin fhayidaa isini argatani yoo hinjiranne illee, qoramichi dhibee akkamii iyyu kan isin irran hingenyeeffihin saxille dha. Ragaan dhuunfaa keessanii icitiin kan qabamu yoo ta'u gaafii yookiin ilaalacha of abdan obbo Tasfaahun caanneef lakkoofsa bilbilaa 0912042050 irratti bilbiluun kennun akka dandeessan ibsaa atooma naa godhameef nan galatomfadha.

Gaafii fi deebii daa’imaaf yookiin maatii daa’imaaf yookiin guddiftuu daa’imaaf dhi’ate.

1. umurii daa’imaa fi bakka inni dhufe natti himu dandessuu laata?

2. kanaan dura daa’imaan yookiin maatii keessan keessaa gara hospitaalaa dhaquun dhibeen fayyaa yaa’aman yoo jirate utuu ibsitanii

3. Naa’ee qorchoota daa’imni kanaan dura fudhate:
   A. daa’imni keessan hospitaalaa kana usoo hin dhufni dura qoricha yoo fudahta ture utuu na ibsitanii.

   B. Daa’imni keessan kanaan dura qoricha oggaa fudhatu, dhibee qorichichi irraan ga’e yoo jirate utuu na ibistanii

C. daad’imm keessan qorichaf yoo alerjikii ta’e, qoricha kamiif fakka ta’e natti himuu ni dnadeessu?

D. Da’imni keessan alerjikii nyataa yoo qabate nyaata kamiif akka ta’e utuu na ibsitanii

4. Daa’imini keessan yaalamuuf hospitaalaa kana erga dhufe asi:

A. daa’imni keessan erga qoricha fudhachuu jalabe mallatto dhibee fayyaa irratt argame yoo jirate utuu na ibsitanii

B, faayyadamna qorichaa ilaalchisee, qoricha daa’imni keessan fudhatuun walqabatee dogongorri uumame, kan hubattani yoo jirate utuu na ibsitani: