SERIOUS ADVERSE DRUG EVENTS IN PATIENTS PRESENTING TO EMERGENCY DEPARTMENTS AND ADMITTED TO HOSPITALS IN NEWFOUNDLAND AND LABRADOR

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SERIOUS ADVERSE DRUG EVENTS IN PATIENTS PRESENTING TO EMERGENCY DEPARTMENTS AND ADMITTED TO HOSPITALS IN NEWFOUNDLAND AND LABRADOR

by

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Abstract

The primary objective of this research was to examine the extent of adverse drug events (ADEs) in three age-related subgroups of patients (children aged ≤17 years, adults aged ≥18 years and elderly aged ≥65 years) either presenting to emergency departments (EDs) or admitted to hospitals in the Canadian province of Newfoundland and Labrador (NL). As secondary objectives, this research classified ADEs according to severity and preventability (wherever possible) and identified patients' demographic and clinical characteristics that can predict occurrence of ADEs.

This dissertation research was comprised of three empirical studies, each of which led to a manuscript for publication. The ***first*** and ***second*** studies used retrospective reviews of patients' ED charts to determine prevalence, severity, and preventability of ADEs among children and adults presenting to EDs. The ***third*** study used a population-based retrospective cohort design over a 12-year period to detect adverse drug reactions (ADRs) using diagnosis codes in the hospital discharge abstract. The aim of this study was to determine the incidence of ADRs among elderly hospitalized patients and to assess patient-related risk of ADRs.

We found that 2.1% (95% CI: 1.6–2.6) of pediatric ED visits and 2.4% (95% CI: 1.8–3.0) of adult ED visits were due to serious ADEs, of which 20% and 29%, respectively, were considered preventable. In the cohort of elderly hospitalized patients,

the incidence of ADRs was 15.2 per 1,000 person-years (95% CI: 14.8–15.7). Children with and without ADE-related ED visits were similar with respect to mean age and mean number of medications, whereas adults with ADE-related ED visits were older, prescribed more medications and had a higher number of comorbidities compared to their non-ADE counterparts. In elderly hospitalized patients, comorbidity from chronic diseases and the severity of patient's underlying illness, rather than advancing age and sex, increased the likelihood of recurrent events. The drug classes associated with or implicated to ADEs were dissimilar among the three age-related subgroups of patients.

By comprising the findings of the three studies together, we concluded that an ADE prevention strategy should be targeted at patient-specific physiologic and functional characteristics, and high-risk medications, as opposed to focusing individual's chronological age.

Dedication

To my parents Gaur Hari and Pushpa Rani Sikdar;

Your son finally finished school

Acknowledgement

I am eternally grateful for the loving support and enduring patience from my wife– Madhabi and our son– Dipto. Madhabi has not only been a tireless supporter of my academic pursuits, but also she shares the joy of parenting our son Dipto, who came along the midst of my doctoral journey.

I would like to express my whole hearted gratitude to Dr. Veeresh Gadag, supervisor of my dissertation, for his advice and wisdom given with positive synergy and attitude. He made every effort to make my work significant and worthwhile. I would like to thank members of my supervisory committee, Drs. Brendan Barrett and Peter Wang, whose feedback with respect to the technical and editorial aspects grounded my thesis in reality. I also wish to thank Dr. Michael Murray, the former Associate Dean of the Division of Community Health, who originally suggested me to go on for a doctoral program.

I must acknowledge the support of the Newfoundland and Labrador Centre for Health Information (NLCHI), without which my access to the data used for this dissertation would not be possible. A special thank you to my colleagues and friends in the Research and Evaluation Department at NLCHI for their assistance and

encouragement along the way. I am specifically indebted to Reza Alaghehbandan, Kayla Collins and Don MacDonald, who have been trusted mentors and friends with due encouragement during my doctoral study; Jeff Dowden and Nicole Edwards, who helped me through editing the first and fifth chapters of my thesis; and Jennifer Donnan, Julianne Melendy, and Lillian Wilson, who provided their cordial assistance in drug categorizations as well as identification of appropriate diagnosis codes for adverse drug reactions and comorbidities.

Thanks also extended to the Canada Health Infoway and Health Canada, for assisting with the funding support for the first two of the three studies comprising this dissertation.

Finally, a special thank you to the co-authors on the two papers published in the journals of Pharmacoepidemiology and Drug Safety and Annals of Pharmacotherapy, and those on the third paper submitted for publication in a peer-reviewed journal.

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List of Abbreviations

ADE	Adverse Drug Event
ADR	Adverse Drug Reaction
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
BDBC	Benefit Driven Business Case
CCI	Charlson Comorbidity Index
CI	Confidence Interval
CIHI	Canadian Institute for Health Information
CPSI	Canadian Patient Safety Institute
DAD	Discharge Abstract Database
DRP	Drug-related Problem
ED	Emergency Department
EHR	Electronic Health Record
ENT	Ear, Nose, Throat
HSC	Health Science Centre
ICD	International Classification of Diseases
ICD-10	International Classification of Diseases 10th Revision
ICD-10-CA	International Classification of Diseases 10th Revision – Canadian Enhancement
ICD-9	International Classification of Diseases 9th Revision

ICD-9-CM	International Classification of Diseases 9th Revision Clinical Modification
IOM	Institute of Medicine
LRT	Likelihood Ratio Test
ME	Medication Error
NB	Negative Binomial
NL	Newfoundland and Labrador
NLCHI	Newfoundland and Labrador Centre for Health Information
NSAID	Non-steroidal anti-inflammatory drug
OR	Odds Ratio
PADE	Possible Adverse Drug Event
P-Y	Person-Year
RFT	Request for Proposal
RR	Rate Ratio
SAS	Statistical Analysis Software
SCMH	St. Clare's Mercy Hospital
SD	Standard Deviation
SES	Socioeconomic Status
SPSS	Statistical Package for the Social Sciences
US	United States
USA	United States of America
ZINB	Zero-Inflated Negative Binomial

ZIP	Zero-inflated Poisson

List of Appendices

List of Publications

The following publications have been derived from the work of this dissertation.

Papers

Sikdar KC, Alaghehbandan R, MacDonald D, Barrett B, Collins KD, Gadag V. Adverse drug events among children presenting to a hospital emergency department in Newfoundland and Labrador, Canada. *Pharmacoepidemiol and drug saf* 19:132-140, 2010.

Sikdar KC, Alaghehbandan R, MacDonald D, Barrett B, Collins KD, Donnan J, Gadag V. Adverse drug events in adult patients leading to emergency department visits in Newfoundland and Labrador, Canada. *Ann Pharmacother* 2010; 44:641-9.

Sikdar KC, Dowden J, Alaghehbandan R, MacDonald D, Wang PP, Gadag V. Adverse drug reactions in elderly hospitalized patients: a population-based retrospective cohort study, NL, Canada. *(Submitted for publication in the Journal of Clinical Epidemiology).*

Abstract presented and published

Sikdar KC, Dowden J, Alaghehbandan R, MacDonald D, Gadag V. Modeling count data with an application to adverse drug reaction in hospitalized patients. In: Proceedings of the 2009 Annual Meeting of Statistical Society of Canada; May 31 – Jun 3, 2009; Vancouver, BC, Canada.

Sikdar KC, Alaghehbandan R, Donnan J, MacDonald D, Gadag V, Barrett B. Emergency Department visits in adult patients caused by Adverse Drug Events, Newfoundland and Labrador. In: Proceedings of the 2008 Data Users Conference-Linking the Health Information Chain; Sep 21-23, 2008; Ottawa, ON, Canada.

Donnan J, **Sikdar KC**, Alaghehbandan R, MacDonald D, Gadag V, Barrett B. Validation of an Adverse Drug Event Trigger Assessment Tool. In: Proceedings of the 2008 Annual General Meeting of the Canadian Society of Hospital Pharmacists - Ride the Tide; Aug 9-12, 2008; Saint John, NB, Canada.

Sikdar KC, MacDonald D, Alaghehbandan R, Barrett B, Collins KD. Adverse drug events among adults in emergency departments, Newfoundland and Labrador, Canada: a preliminary analysis. In: Proceedings of the 23rd International Conference on Pharmacoepidemiology and Therapeutic Risk Management; Aug 19-22, 2007; Quebec City, QC, Canada; *Pharmacoepidemiology and Drug Safety 2007; 16 (Suppl 2):S188.*

Sikdar KC, MacDonald D, Alaghehbandan R, Barrett B, Gadag V. Emergency department visits caused by adverse drug events, Newfoundland and Labrador, Canada. Presentation to the Community Health Seminar Series; Nov 21, 2008; Faculty of Medicine, Memorial University of Newfoundland, St. John's, NL, Canada.

Sikdar KC, MacDonald D, Alaghehbandan R, Barrett B, Gadag V. Adverse drug events in children and adults leading to emergency department visits in Newfoundland and Labrador. Presentation to the Patient Safety Research Affinity Group Meeting; Sep 16, 2009; Newfoundland and Labrador Centre for Applied Health Research, St. John's, NL, Canada.

The following abstract has been submitted for presentation.

Sikdar KC, Donnan J, MacDonald D. ADE Monitoring in Newfoundland and Labrador: Opportunities for Provincial Drug Information Systems. Submitted for oral presentation to the e-Health 2011 conference; May 29 – Jun 1, 2011; Toronto, ON, Canada.

Research Reports

Newfoundland and Labrador Centre for Health Information. Serious adverse drug events in adult patients leading to emergency department visits: a baseline study to investigate benefits of a provincial pharmacy network. Pre-pharmacy report 1 of 4. Report submitted to Health Canada and Canada Health Infoway, Government of Canada; 2009.

Newfoundland and Labrador Centre for Health Information. Serious adverse drug events in pediatric patients leading to emergency department visits: a baseline study to investigate benefits of a provincial pharmacy network. Pre-pharmacy report 2 of 4. Report submitted to Canada Health Infoway, Government of Canada; 2009.

Additional publications in peer-reviewed journals and presentation to national and international conferences during my doctoral studies are given in my curriculum vitae in Appendix G. Given that they were originated either from my work related to one of the doctoral courses or other collaborations, but not from the thesis, they have not been included in the thesis.

Personal Contribution to the Program of Research

This dissertation includes five chapters in total, with chapter 1 for a general introduction and overview, then chapter 2, 3 and 4 for reporting three empirical studies (each of which led to a manuscript for publication) and the final chapter for linking all three studies thematically together with providing implications and recommendations from the dissertation.

During my doctoral studies, I worked in the Research and Evaluation Department of Newfoundland and Labrador Centre for Health Information (NLCHI) as a statistical consultant until April 2007, and since then have been working as a senior biostatistician in addition to my role as a co-applicant on the investigation team for the first two studies. The work in chapter 2 and 3 is based on my work as a co-investigator on the larger benefit evaluation of the provincial drug information system (also refers to as the Newfoundland and Labrador Pharmacy Network). The two studies leading to these two chapters were made possible through funding by Canada Health Infoway and Health Canada, as well as through in-kind contributions by NLCHI.

My motivation for conducting this doctoral research was based on my experience on reviewing the literature to identify reliable and valid instruments measuring serious

adverse drug events among the people living in the community setting and subsequently presented to emergency departments. In both studies I was responsible for study conception, design and data management. In the design stage, I was the lead for preparing the trigger assessment tools and data collection tools used for collection of study data through patients' chart review, selecting study sample, and communicating to the research team with issues arising from data collection process. Following data entry performed by NLCHI employees, I performed data processing, including collation of data from multiple data entry points into one file, establishing measures for data validation checks, flagging records with inconsistent entries, and taking appropriate measures to mitigate issues.

Unlike the first two studies, the third study leading to chapter 4 was not part of benefit evaluation of the provincial drug information system. The study was added into the dissertation by enabling the use of administrative health data to capture and document a wide range of serious adverse drug reactions in hospitalized patients. I designed this study and wrote the SAS programs for data extraction and derivation of necessary variables for the study. The study data were derived through a data linkage system that linked five administrative health databases: 1) discharge abstract database, 2) health insurance registry database, 3) mortality system, 4) neighborhood socioeconomic status database, and 5) postal code conversion database.

In each of the three studies, I conducted all the analysis, except some assistance requiring clinical knowledge (e.g., categorizing patients' health conditions and drug utilizations) obtained from medical research and pharmacy research specialists. I performed interpretation of data, and drafted manuscripts for publication. I have presented the results in several international and national conferences. I took part in a series of presentations to academia, and provincial special interest groups, resulting in a widespread and ongoing dissemination of findings throughout the course of this doctoral research. I co-authored a final report for each of the first two studies that were submitted to Canada Health Infoway and Health Canada. The two manuscripts that were written based on the findings of the first two studies have been published in the February 2010 issue of the Journal of *Pharmacoepidemilogy and Drug Safety* and the April 2010 issue of *The Annals of Pharmacotherapy*. The other manuscript based on the findings of the third study has been submitted for publication in the *Journal of Clinical Epidemiology*. A list of publications and abstract presentations from my doctoral research is given at page xviii- xxi).

For all work reported in my dissertation, I made major intellectual and practical contribution in each of the general research stages specified in the guidelines for thesis and reports by the Memorial University's School of Graduate Studies: i) design and identification of the research proposal, ii) practical aspects of the research, iii) data analysis, and iv) manuscript preparation. This enabled me to be the principal author in all the three manuscripts and in most of the conference and meeting presentations. The

research team members who substantially contributed to meet the criteria for authorship stated in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals have been listed as co-authors.

Collectively, the three studies and three papers constitute a thesis that forms the basis for an ongoing and future program of research in the area of adverse drug events (ADEs), and our findings add to the existing literature by focusing on serious ADEs leading to health service utilization and draw attention to the need for prevention efforts that target patient in Canada at high risk for ADEs, and ultimately add to the discourse to improve patient safety.

CHAPTER 1

Introduction and Overview

1.1 The context of Patient Safety: Driving Forces and Policy Implementation

Patient safety is a major issue for everyone– healthcare professionals, providers and patients. The potential for medical care to cause harm has long been recognized throughout the history of medicine. However, the awareness of the problem of patient safety was stimulated following the rising rate of litigation in the 1970s and 1980s, which led to the development of risk-management programs in the United States, and later elsewhere [1]. Starting from almost exclusively a legal and financial focus to protect institutional concerns, the error prevention movement has accelerated through addressing clinical issues and acting as a gateway to the underlying problem of patient safety.

The topic of patient safety has become a focus of clinical care and research in recent years. Several studies have revealed the scale of harm to patients from healthcare management rather than disease. In the United States, the Harvard Medical Practice Study [2] reported that patients were unintentionally harmed by treatment in almost 4% of admissions in New York State. The resulting disability was slight or temporary for 70% of these patients, but in 7% it was permanent and 14% of these patients died, partly as a result of their treatment. In the United Kingdom, a review of patient records indicated a 10.8% adverse event rate, of which about half were judged to be preventable [3]. The Bristol inquiry was one of the few high-profile cases in Britain that painted a picture of a flawed system of care with poor teamwork between professionals by providing inadequacies at every point, from referral to diagnosis, surgery, and intensive care. The inquiry has continued to focus professional and public attention on patient safety in a manner unprecedented in both its depth and for the extent of professional involvement [4, 5].

Patient safety practices include scientific knowledge that continually informs improvement of efforts and reduces risk of adverse events related to exposure to medical care [6]. The increasing incidence of adverse events in health care has led to a growing concern in a number of countries about patient safety, and thus this issue remains a fundamental principle of patient care and a critical component of quality management [1]. Among the recent works on patient safety, the Institute of Medicine's (IOM) landmark report "*To err is human: building a safer health system*", a publication based-on a systematic review of patient safety-related medical literature, has aroused an enormous response [7]. Having focused on the potential for harm in modern medicine, the IOM report investigated preventable adverse drug events, the role of systems failures in the aetiology of medical errors, and the effects of the healthcare workforce on safety [2, 8, 9]. The report estimated that 44,000 to 98,000 patients die every year because of medical error in the United States alone. Medical errors included all problems that commonly occur during the course of providing health care such as adverse drug events and improper transfusions, surgical injuries and wrong–site surgery, suicides, and mistaken patient identities. Because reducing medical errors can save human lives and health care costs, the IOM report called for a broad national effort to include establishment of a Centre for Patient Safety, expanded reporting of adverse events, development of safety programs in health care organizations, and attention by regulators, health care purchasers, and professional societies [7]. A number of legislative and regulatory initiatives to document medical errors and to search for solutions have been started based on the strong

recommendation of the report to set a goal of reducing error related mortality in the United States by 50% over a 5-year period [6].

Several important new initiatives in the last few decades have been undertaken, especially by developed nations to build and advance safer health care systems for their populations. These initiatives underline the increasing attention paid to patient safety. The U.S. government established the National Patient Safety Foundation aimed at making health care safer for patients through an unprecedented partnership of health care practitioners, institutional providers, health product providers, health product manufacturers, researchers, legal advisors, patient/consumer advocates, regulators, and policy makers [10]. The Australian Patient Safety Foundation pioneered a sophisticated approach to patient safety by providing leadership in the reduction of harm to patients in all healthcare environments since 1988 [11, 12]. The National Patient Safety Agency in England contributes to improving the safety of patient care by informing, supporting and influencing organizations and people working in the health sector [10]. Following numerous legal cases and media stories that highlighted the consequence of unintentional adverse events, patient safety is receiving growing attention in Canada as well [14]. The Winnipeg inquiry in Canada was a notably high-profile case that played a part in raising public awareness and driving policy changes [11]. In 2002, the Canadian government budgeted $50 million over 5 years for the creation of the Canadian Patient Safety Institute (CPSI) that operated collaboratively with many health care organizations and regulatory bodies

to improve patient safety [14]. The mandate of the CPSI is to provide a leadership role with respect to patient safety issues in the context of improving health care quality. CPSI facilitates collaboration between governments and stakeholders to enhance patient safety initiatives to share best practices, and recognize the role of research, knowledge transfer and evaluation to ensure patient safety [15].

1.2 Overview of Drug-related Problems

Drug-related problems (DRPs) are a critical component of patient safety since these are the events or circumstances involving drug therapy that actually or potentially interferes with desired health outcomes. Drugs are prescribed for patients to achieve an optimal therapeutic outcome in treating various medical conditions. Despite the fact that the therapeutic benefits of medications have resulted in hundreds of millions of people living healthier and longer lives everyday, medications are not risk-free. As the number and strength of available drugs increase over time, prescription and utilization of drugs become more complex, leading to a variety of DRPs [16]. A DRP occurs when a patient experiences, or is likely to experience, either a disease or symptom having an actual or suspected relationship with drug therapy– meaning that an optimal therapeutic outcome could not be achieved [17]. In the existing literature [17, 18], eight different categories of DRPs have been described: untreated indication, improper drug selection, subtherapeutic dosage, failure to receive drugs (includes patient noncompliance), overdosage, adverse drug reaction, drug interaction, and drug used without an indication. Although many DRPs can be resolved without a major impact on patient health, some of these are a significant cause of hospitalization, emergency department visits and subsequent resource utilization. A US study reported that morbidity and mortality associated with drug-related problems accounted for $76.6 billion in health care costs, 17 million emergency department visits, and 8.7 million hospital admissions every year [19]. Bates and colleagues

reported that 76,000 deaths were due to adverse drug reactions annually in the United States [20]. Using the 1:10 ratio of the population of Canada to that of the US, it has been reported that adverse drug reaction fatalities would be ranked as the 7th leading cause of death in Canada, after cancer, heart disease, stroke, pulmonary disease and accidents [21].

An adverse event (AE) is an injury resulting from medical management rather than the underlying disease [22]. A great deal of research has been carried out in an attempt to identify rates of serious AEs in USA and Australia [20, 23-26]. However, much less information is available about these events in the Canadian population. This has been acknowledged in the National Steering Committee on Patient Safety report, "*Building a Safer Health System– A National Integrated Strategy for Improving Patient Safety in Canadian Health Care*" [27]. This report highlighted that Canada is significantly behind the United States, the United Kingdom and Australia in accepting that patients are at significant risk, in wanting to learn about the relevant issue of patient safety, and in investing in the creation of a culture of safety. One of a series of recommendations provided by the Steering Committee was to improve measurement and evaluation processes and adopt designated areas of research. A study by Baker et al. [14] provided the first national estimate of the incidence of adverse events among Canadian adult patients. The estimated rate of adverse events was found to be 7.5 per 100 hospital admissions and, after extrapolation, the number of hospital admissions attributed to adverse events was estimated between 141,250 and 232,250. As noted by the authors, the study provided

a starting point for understanding the incidence of adverse events and the burden of injury resulting from adverse events in Canadian acute care hospitals. Referring to the lack of Canadian data on adverse events, the study strongly recommended further research to explore the types of these events and their contributing factors. Medications are the most frequent cause of adverse events, and such injuries are referred as adverse drug events (ADEs) [2, 28-30]. Given that there has been a significant investment in the creation of a culture of patient safety in the Canadian Health System following the recommendation of the National Steering Committee on Patient Safety, it is important to carry out further research to quantify the magnitude of ADEs in the Canadian context, and examine whether there is any association between ADEs and patient-related factors. Identification of drug-related problems, in particular, those causing harm to patients (e.g., adverse drug events) and associated risk factors would allow providers to identify early symptoms of ADEs, and to respond to the patients quickly [31].

1.3 Adverse Drug Events

1.3.1 Adverse Drug Event Terminology

An adverse event is defined as "any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment" [32]. In other words, an AE may cause harm

in a patient administered a drug but the event may not necessarily be caused by the drug. When an adverse event refers to "circumstances that involve a patient's drug treatment that actually, or potentially, interfere with the achievement of an optimal outcome", this problem is termed as a drug-related problem [19, 33]. Drug-related problems include all issues that can potentially affect the success of pharmacotherapy in a given patient. These issues are described by several commonly used terms to denote a non-beneficial effect from a drug: adverse drug events, adverse drug reactions, medication errors, drug toxicities and side effects, etc.

The term "adverse drug event" (ADE) is defined as any undesirable effect caused by the interaction of a drug (prescription or nonprescription) with a patient [28]. Events may be the result of normal or inappropriate use of a medication, and could range from minor reactions such as a skin rash to serious and life-threatening events, and even death. ADEs can arise from inappropriate prescribing of a medication (e.g., misdiagnosis, inappropriate medication, inappropriate dose, inappropriate regimen, etc.), medication errors, self-medication, side effects, allergies, genetic predispositions, drug-drug interaction, drug-disease interaction, or patient non-compliance (taking more or less of a drug than the prescribed amount).

Adverse drug reaction (ADR) is a term used to describe the undesirable effects of medications. According to the World Health Organization, an ADR is "Any response to

a drug which is noxious and unintended, and which occurs at doses normally used in humans for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function" [34]. Clearly, this definition of ADR requires a judgment as to noxiousness of the response as well as to the intention of an unspecified party. Kramer (1981) [35] argued that whether an event is adverse or noxious depends on the clinical setting and the intentions of the treating physician, and that his or her judgment should be made separately for each case.

The term "Medication errors" (ME) include mishaps that occur during prescribing, transcribing, dispensing, administering, adherence, or monitoring a drug. Examples of medication errors include misreading or miswriting a prescription. Medication errors that are stopped before harm can occur are sometimes called "near misses", "close calls" or more formally, a *potential adverse drug event* (Figure 1.1). Not all prescribing errors lead to adverse outcomes. Medication errors are more common than adverse drug events, but result in harmful events less than 1% of the time; about 25% of adverse drug events are due to medication errors [32]. Figure 1.1 adapted with permission (Appendix B.3) from Morimoto et. al. [28] and Nebeker et al. [32] demonstrates the relationship among medication errors, ADRs, ADEs and potential ADEs.

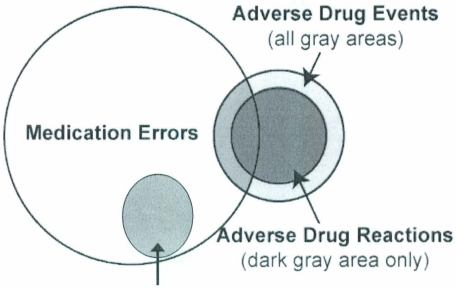

Figure 1.1: Relationship between ADEs, ADRs, Potential Adverse Drug Events, and MEs

Although ADEs and ADRs are sometimes used interchangeably, they do not have the same meaning. An ADR refers to adverse effects of medications when they are used appropriately at normal doses, either for prophylaxis, diagnosis or treatment [36]. The term ADE includes ADRs in which no error occurred and/or complications that result from medication errors. The term ADR implies that drugs are properly prescribed and administered, and thus the reactions are difficult to prevent, their reduction mostly depends on development of new and safer agents. However, ADEs due to medication errors are preventable and developing strategies to prevent these reactions are relatively easy [37]. The term ADE has been broadened by Nebeker et al. [32] in which it refers to as "any undesirable effect related to the use or misuse of a drug (prescription or

nonprescription)", and is considered to be a relatively better definition given that it includes errors of omission. An error of omission involving the failure to provide an effective treatment in the setting of a severe disease poses very substantial risks for patient safety and outcome.

A "possible adverse drug event" (PADE) is defined as an event that may have been related to a current medication; however, it may also have been due to another cause (e.g., viral infection), and therefore, confirmation of ADE is not possible. When ADE studies were carried out based on retrospective study design, in particular reviewing patients' medical charts, the term of possible ADE was found favorable over potential ADE due to the fact that necessary information may not have been available in patient charts to identify a confirmed reason leading to adverse event.

Dutchman Meyler was the first who provided a systematic overview of 'side effect of drugs, in 1951 [38, 39]. The term "side effect" does not imply that the response is adverse. A side effect usually includes any response other than the main therapeutic effect of the drug and may be desirable, undesirable, or inconsequential [33]. An event of side effect might also imply that the effect can be beneficial. These events can range from harmless epiphenomena to innocuous nuisances to harmful and possibly irreversible injuries to death. Both terms "side effect" and "ADR" imply that the observed effect is caused by a particular drug. Because ADRs are often erroneously classified as "side

effects", it has been recommended the term "side effects" no longer be used as this tends to minimize the injury from drugs [33, 40].

1.3.2 Severity and Preventability of Adverse Drug Events

The severity of ADEs is usually determined when detection of ADEs involve prospective follow-up of study patients or manual review of medical charts. Previous studies [20, 41-43] have classified ADEs into four categories: 1) fatal, 2) life threatening, 3) serious and 4) significant. An ADE was considered to be significant if the event caused symptoms that while harmful to the patient pose little or no threat to the patient's life function. An event is referred as a serious ADE if it caused symptoms associated with a serious level of risk while it was not high enough to be life threatening. An ADE is also serious if it caused persistent alteration of life function. An ADE is considered to be life threatening when an event caused symptoms that if not treated, would put the patient at risk of death. An ADE is fatal when the event results in death of a patient [43].

Classification of the severity of ADEs usually takes into consideration several pieces of information such as the impairment of the patient's quality of life; hospitalization or prolonged hospital stay; temporary or permanent malfunction of an organ system; temporary or permanent inability to work; elevated or depressed lab values resulting in medical interventions; life threatening; and discontinuation or substitution of the drug [44].

Gurwitz et al. [42] noted examples in clarifying severity of ADEs. A nonurticarial skin rash, a fall without associated fracture, hemorrhage not requiring transfusion or hospitalization, and oversedation were examples of significant ADEs. Serious ADEs included urticaria, a fall with an associated fracture, hemorrhage requiring transfusion or hospitalization but without hypotension, and delirium. Any harm such as hemorrhage with associated hypotension, hypoglycemic encephalopathy, profound hyponatremia, and acute renal failure requiring hospitalization were given as examples of life-threatening ADEs.

Preventable ADEs were those due to error that could have been prevented by any means available [40]. Preventability was categorized as definitely preventable, probably preventable, probably not preventable, or definitely not preventable. When the data collection involves a physician and/or pharmacist reviewer, the determination of preventability is usually based on the reviewer's presumed knowledge at the time the drug was prescribed. This information was used in conducting subjective assessment of categorization following consensus between reviewers [41]. Although the data collection and recording in this thesis follows these categories, results were often collapsed into preventable and non-preventable categories to reduce sampling error associated with small number of events [42]. A preventable ADE is an adverse event attributable to a medication error, whereas an event causing injury, with no error involved, is known as a non-preventable ADE. An example of a preventable ADE includes allergic reaction in a patient known to be an allergic to a particular drug. On the contrary, allergic reaction in a patient not known to have drug allergy is an example of a non-preventable ADE [45].

1.3.3 Detection of Adverse Drug Event

Multiple epidemiological methods exist for the detection of adverse drug events. Different methods of ADE identification include voluntary reporting, chart review, direct observation, patient interview and electronic surveillance. The methodology used depends on the research questions, study design and scope of the study based on available resources.

In voluntary reporting, healthcare professionals, drug manufacturers and drug consumers are provided a pre-designed form by which they can report any suspected drug-related incidents. In the context of ADE reporting, the term 'voluntary' reporting is also referred to as 'spontaneous' or 'incident' reporting, which means reporting is not compulsory [38]. Voluntary reporting depends on the ability of health professionals to recognize errors and their willingness to disclose them in error reports [46]. Although this method remains an attractive source of information for researchers, because the information is generally readily available, the problem of under reporting greatly limits its utility for patient safety research. Studies have shown that voluntary reports identify only 5% of ADEs [47-49]. Daily chart review and solicited reporting have detected five times as many ADEs as voluntary coding in hospital separation or mortality records [20, 21]. Interruption in workflow, perception that completing a form does not result in any improvement, lack of knowledge that an ADE has occurred, and fear of exposing oneself

to litigation have been identified as possible reasons why incident reports are underutilized [50].

Medical chart reviews have been employed in retrospective cohort studies and case-control studies to detect ADEs. Murff et al [50] summarized chart review studies citing several high quality studies, including the California Medical Insurance Feasibility Study [51], the Harvard Medical Practice Study [52], and the Colorado-Utah Study [53]. In this method of ADE detection, patient charts usually undergo a two-phase screening process. Initially a trained reviewer, usually a research nurse at the first phase, examines charts using a set of pre-defined screening criteria. Charts identified with at least one of the screening criteria then undergo physician review in the next phase to judge whether physician reviewers believe an adverse event had occurred based on the information in the chart. Usually two physicians independently review each chart flagged at the first phase, and if the physician reviewers disagree on whether an adverse event occurred, the physicians come to a consensus or involve a third party to resolve the disagreement [50].

There are several limitations with the use of patient chart review to identify ADEs. First, identifying and classifying ADEs through chart review requires implicit judgment by the researchers; this process may introduce bias [54]. Second, this method for ADE identification has been predominantly used in retrospective studies, where

supplemental information cannot be obtained and this may cause underestimation of ADEs [54, 55]. Third, there is a tendency of the nurse reviewer at the first phase to flag a large number of charts as a probable ADE even if there may be very little documentation of having an ADE. A study focusing on reliability and validity of judgment concerning adverse events reported that the positive predictive value of the initial screening process was as low as 21%, and as a result physicians reviewed a high number of false positive charts [56]. A final, but possibly the greatest limitation to this methodology, is the overall resources required, which can be significant when compared to other screening modalities [50]. Since chart reviews are very costly and time consuming, some investigators have used fewer screening criteria to help reduce the overall resource burden [57]. Therefore, medical chart review, in general, remains an impractical means for routine adverse event detection.

Patient interview is another method of ADE detection. A study by Forster et al. [22] utilized patient interviews as well as information from sign-out notes, discharge summaries, and laboratory results to prepare case summaries for physician reviewers. ADEs were determined based on review of these case summaries. The study reported that nearly one in five patients experienced an ADE during the transition from the hospital to home. A review paper [50] citing studies that used patient interview data reported that 20% to 42% of patients experienced and were aware of an error occurring with their medical

care. The major limitation of patient interview is that it requires a substantial resource commitment.

Computer-based approaches (i.e., computer-based monitoring programs) have recently been incorporated in research to identify ADEs. This program identifies 'alerts', which are situations suggesting that an ADE might be present. Following these alerts, a trained reviewer examines patients' hospital records to determine whether an ADE had occurred [58]. This approach has an advantage over chart review in that it is a more cost-effective method [54]. Computer-based programs have been shown to identify more events than spontaneous reporting [58]. However, there is limited use of this method to identify ADEs because of the huge cost for institutions to develop this system and the uncertainty regarding its effectiveness. Previous studies have used medical chart review and compared the results to computer based programs and other methods to identify ADEs [58-59]. A study by Jha et al [58] reported that more events were identified through chart review compared to the computer-based monitoring strategy and voluntary reporting (13.3 vs. 9.6 vs 0.7 ADEs per 1,000 patient-days, respectively). In a study with nursing home residents, Gurwitz et al [59] ascertained ADEs by utilizing both chart review and incident reporting by health care providers. It was reported that the method of chart review identified many more ADEs than using health care provider reporting (83% vs. 17%, respectively).

While each method illustrated above has its own strengths and limitations, the scope of available resources often dictates which methodology is used for detecting ADEs. In Newfoundland and Labrador (NL), having a sample frame through an electronically available Emergency Department (ED) triage database allowed for selection of a representative sample to carry out two of the studies (described in the next sections) included in this dissertation. The step-wise chart review method that used a trigger assessment tool and subsequently a data collection tool, illustrated in chapters 2 and 3, greatly simplified the chart review process by allowing relatively rapid and systematic examination of charts to extract relevant data for the detection of ADEs. Additionally, in NL, there is a unique opportunity to study a large, geographically isolated population using pre-existing data sources. Utilization of the hospital discharge abstract database for assessing ADRs and its linkability with other administrative data was found to be a cost effective method that offered a potential to capture a large population of patients. This method was also employed in detecting ADRs used for this dissertation. A brief description is provided in the next sections of this chapter, along with further detail in chapter 4.

1.3.4 Measurement of Adverse Drug Event Occurrences

A central task in adverse drug event epidemiology is to quantify the occurrence of ADEs in study populations. In order to express the extent of the problem resulting from

ADE occurrence, we need to be able to measure the frequency of ADE occurrences. Incidence rate, cumulative incidence and prevalence are the three basic measures of "disease" or "incident" occurrence. Although ADEs are termed as an incident rather than a disease, definitions of terminologies to measure the frequencies discussed in this section mostly with reference to a disease. This is just to be consistent with the epidemiology and public health literature in defining and illustrating terminologies. However, a concluding paragraph was given with respect to ADE occurrence to clarify the fact that these terms can be used to express the extent of an incident as well.

The *incidence rate* is the number of new cases of disease of interest that occur during a specified period of time in a population at risk for developing the disease. In estimating incidence rate, the number of new cases of disease is divided by the sum of the time periods of observations for all individuals in the population. Because the denominator of the incidence rate is the sum of the person-time of the at risk population, it is also known as the *incidence density rate* or *person-time incidence rate* [60, 61]. The *cumulative incidence* refers to the proportion of people who convert, during a specified period of time, from non-disease to disease. If risk is defined as the probability of an individual developing a disease in a specified time interval, then cumulative incidence is a measure of average risk. Cumulative incidence is calculated as the number of new disease cases divided by the number of persons at risk of developing the disease during that period of time. The critical element in the definition of incidence density or cumulative incidence is *new* cases of disease. These two terms are a measure of events for which the disease is identified in a person who develops the disease and did not have the disease previously.

Prevalence measures the proportion of a population that is affected by disease or incident at a specified time. Prevalence is calculated as the number of disease cases

present in the population at a specified time divided by the number of persons in the population at that specific time. As a measure of disease occurrence, prevalence can be viewed as a slice through the population at a point in time at which it is determined who has the disease and who does not [62]. Prevalence can be used in two ways – point prevalence and period prevalence. The term *point prevalence* refers to prevalence of the disease measured at a point in time. The other term *period prevalence* measures prevalence of the disease at any time during a certain period, such as during a single calendar year. When we think of a survey as the source of obtaining data, it is virtually impossible to survey an entire city on a single day. Therefore, prevalence measured from survey data often conceptually think of in terms of single point in time, but in reality, the survey would take much longer. This is why, in some situations researchers are to choose prevalence that measures how many people have had the disease at any time during a given period. In estimating period prevalence, it is considered that some people may have developed the disease during that period, and others may have had the disease before and died or been cured during that period.

The numerator of prevalence includes a mix of people with different durations of disease or incident, and the denominator includes the number of population at that specified time as opposed to population at risk. Thus, prevalence is not a measure or risk. If the aim is to measure risk, the term *incidence* must be used, because in contrast to prevalence, it includes only new cases and a specific time period during which these events occurred [61, 62].

Similar to any disease occurrence, the frequency of ADEs can be measured using rates or proportions. Incidence density or cumulative incidence can be treated as *rates* and are used to comprehend how fast the ADE is occurring in a population, whereas

prevalence is a proportion which is used to tell us what fraction of the population is affected [62]. When an ADE is an outcome of interest, these events are not inevitable or may not occur during the period of observation. In this situation, prevalence is considered as the measure of ADE frequency. However, in an attempt to measure the frequency of ADE occurrence in a population, it is insufficient merely to record the number of ADEs occurred in that population. It is also necessary to take into account the length of time contributed by all persons during the period they were in the population [61], which justifies the importance of incidence. Although the terminologies discussed in this section have importance to express the magnitude of a disease or incident of interest, which measures to be used to express the frequency of an event depends on the study design that permits identification of the event through clearly defining when the event occurred. The sources of data from which cases are identified influence how we use measures of occurrence to express the extent of disease or incident.

1.4 Research Engagement

Over the last decade, the province of Newfoundland and Labrador has undertaken an initiative to develop a province-wide Electronic Health Record (EHR). The EHR will allow data linkage of major clinical and administrative information systems together to allow authorized health care providers secure access to a patient's key health history and care within the heath system. One of the systems under the arms of EHR is the Newfoundland and Labrador Pharmacy Network. This system is undergoing a benefit evaluation using pre and post comparative study designs. The pre-implementation evaluation of the Pharmacy Network included several studies aimed at gathering baseline data on drug related problems, including the occurrence of serious ADEs, which has formed the basis of this dissertation research. This involved two separate studies that used retrospective review of patient ED charts to determine prevalence, severity and preventability of ADEs occurring in children and adults in the community setting and resulting in ED visits. In addition to these studies, a third study, which is not part of the benefit evaluation of Pharmacy Network, involved the detection and analysis of ADEs among elderly hospitalized patients using a population-based retrospective cohort study. This dissertation research was comprised of these three studies.

The EHR initiatives in Newfoundland and Labrador included several information systems. While other information systems (e.g., Telehealth, Laboratory, Picture Archiving and Communication Systems) considered part of the EHR are out of scope for this dissertation, the project ideas illustrating how the Pharmacy Network fits in with the overall EHR implementation plan deserve elaboration.

1.4.1 Electronic Health Record Initiatives in Newfoundland and Labrador

An electronic health record provides health care professionals with online real-time access to their patient's complete medical profile. It holds key health information about every person in the province through building a secure and private lifetime record of a person's health and healthcare history. It shares selected aspects of patients' health information, from medications or x-rays to blood tests or vaccines, with all authorized health care professionals [63]. Recognizing the importance of the EHR in improving the quality and efficiency of health care, the federal government of Canada established Canada Health Infoway (*Infoway*) in 2001 to accelerate the development and adoption of Electronic Health Records across the country. *Infoway* was provided with $1.2 billion in funding and a 7-year mandate to work with all jurisdictions in Canada in both planning and implementing their EHR initiatives. With an aim to have 50% of Canadians

connected to an EHR by the end of 2010, *Infoway* identified core components of an EHR in their 2003/04 Business Plan [64-65].

The Newfoundland and Labrador Centre for Health Information (NLCHI) has received funding from *Infoway* to implement six key building blocks of the EHR: (1) a unique personal identifier/client registry, (2) a pharmacy network, (3) a laboratory network, (4) telehealth, (5) a provider registry and (6) a diagnostic imaging network [65-66]. To determine the benefits of the EHR, a number of research initiatives have been undertaken to establish baseline data on the delivery of various aspects of health care in Newfoundland and Labrador. Once the EHR is in full operation, these studies will be repeated as a means to assess benefits to health care delivery using a pre/post-comparative design.

1.4.2 The Newfoundland and Labrador Pharmacy Network

The Newfoundland and Labrador Pharmacy Network is a provincial drug information system that will offer province wide online, real-time medication profiles, as well as comprehensive drug information. A personal medication dispensing history built up within the Pharmacy Network involves linking community and hospital pharmacies

and physician offices, so that a patient's historical and current medication profile is available to health professionals at the point of care. Once all pharmacies in the province are connected to the Pharmacy Network, medication information of a patient will be stored in one record – the patient's profile. It is expected that giving health professionals access to that record will provide many benefits to the patient, as well as the patient's health care providers [63]. Health professionals' access to information about the medications a patient takes is expected to improve the quality of the patient's healthcare. The information will support better decision making about medications, diagnosis and treatments, and therefore it will be easier and quicker for health professionals to decide whether a patient's new medication will react with others the patient is taking. One of the many expected benefits of the Pharmacy Network in Newfoundland and Labrador is the reduction of serious adverse drug events occurring in the community. With a drug information system and an interactive database offering accurate real-time prescription profiles, health professionals would be able to intervene before and after an adverse event occurs. This system can help avoid harmful drug interactions and lead to a decrease in the cost of doctor visits, emergency department visits, and hospitalizations [63, 65]. The personal medication dispensing history would also result in more appropriate prescribing and dispensing, recognition of contraindication, improved counseling, improved compliance monitoring and reduced abuse of prescription drugs. A Benefit Driven Business Case (BDBC) submitted by the NLCHI to the Government of NL in 1998 suggested the Personal Medication Dispensing History would deliver savings to the health system by reducing ADEs, both in the community and the hospital settings [64]. The BDBC predicted

approximately $4.1 million in annual savings to the health system following the implementation of the provincial Pharmacy Network.

The provincial EHR, including the Pharmacy Network, is a collaborative initiative between the Newfoundland and Labrador Centre for Health Information, the Government of Newfoundland and Labrador, Canada Health Infoway, and the Regional Health Authorities, along with many supporting stakeholders. The Provincial Government and *Infoway* have committed $8.6 million and $17.9 million, respectively in its development and implementation. The provincial government has committed necessary funding for the ongoing operation of the Pharmacy Network. In May 2002, NLCHI received approval from the provincial government to carry out a Pharmacy Network project scoping involving a high level analysis to determine the required functionality of the system, and the resources needed for its implementation. Following the completion of the project scoping and subsequent dialogue and clarification, the government granted approval for NLCHI to move forward with issuing a Request for Proposals (RFP) for the implementation of the Pharmacy Network in October 2004. In June 2006, the provincial government and *Infoway* signed an agreement to partner on the implementation of the Pharmacy Network. Newfoundland and Labrador began connecting community pharmacies to the provincial Pharmacy Network in May 2010. Implementation in more than 190 community pharmacies province wide will continue in a phased-in approach

throughout 2010 and 2011. After community pharmacies, the next step is connecting health care facilities in the four regional health authorities to the Pharmacy Network [67].

As previously stated, the Newfoundland and Labrador Pharmacy Network is undergoing a benefit evaluation using a pre- and post-comparative study design. The pre-implementation evaluation of the Pharmacy Network encompasses several studies to gather baseline data on drug-related problems. Two of the studies were carried out to gather information on serious ADEs occurring in the community setting and resulting in Emergency Department visits. Given that children and adults have very different drug utilization and in many other ways with regard to medical care, two separate studies were carried out – one in children and the other in the adult population. The overall objectives of these two studies were:

1) To estimate the prevalence of ADEs separately in children and adults presenting at Emergency Departments in St. John's over a one year period, and to classify these ADEs with respect to severity and preventability.

2) To use the results of these studies as a baseline; which then will be compared to the results of the repetition of the same studies to be carried out post-Pharmacy Network implementation. Comparisons of pre-post Pharmacy Network will be

made on the overall prevalence of ADEs presenting at EDs, as well as the severity and preventability of the ADEs.

3) To build research capacity in the province of Newfoundland and Labrador in the area of optimal drug utilization through enhanced information systems.

1.5 Program of Research for Dissertation

The objectives of the two pre-Pharmacy Network studies noted above provided the basis for this doctoral dissertation. While the second and third objectives are more in line with the larger program of benefit evaluation and achievable following the post-implementation of Pharmacy Network studies, attainment of the first objective was possible based solely on existing data of the two pre-Pharmacy Network studies. Although, the focus of the benefit evaluation initiatives through these two studies was to determine the frequency of ADEs and their distribution with respect to severity and preventability, investigating how these ADEs differ by patients' demographic and clinical characteristics was one of the primary focuses of this dissertation research. Serious ADEs also have great impact on inpatient admission and length of stay, which is especially more common in elderly patients who usually take multiple drugs to control multiple comorbidities. Hence, considering this high risk group as another subpopulation, ADEs

have been identified using diagnosis codes in the hospital discharge abstracts and included as a third study in this dissertation.

A majority of patients with mild or non-serious ADEs typically seek care from primary health care providers (e.g., pharmacists, family physicians, etc.) rather than present to EDs or be admitted to hospitals [68]. Therefore, this research examines serious ADEs only requiring utilization of health care resources such as ED visits, hospital admission or prolonged hospital stay for an existing patient. Although studying ADEs in hospitalized patients was not part of the benefit evaluation, this has been included for the following two reasons:

1) Serious ADEs are clinically significant drug-related problems that result in increased health care resource utilization and may either lead to ED visits or hospital admissions. A more thorough study including ADEs in the hospital setting was chosen to make this doctoral research more comprehensive concerning serious ADEs in NL, which could lead to more rational interventions to improve quality and safety.

2) Since the small number of events in the two pre-Pharmacy Network studies would potentially introduce high sampling error, a more robust study, investigating ADEs in elderly hospitalized patients, with a strong retrospective cohort design that made us of fairly recent statistical advances, allowed for the identification of patient-related factors that can predict rare events such as serious ADEs.

This dissertation was comprised of these three studies, each of which was carried out as a distinct study and led to a "stand-alone" chapter (Chapters 2, 3 and 4). However, the three studies complement each other by focusing attention on serious ADEs which represent important aspects of quality of care, and drawing attention to the need for increased efforts to improve patient safety. Of the three studies, the two pre-Pharmacy Network studies were carried out for the first time in NL. The third study is considered one of the most comprehensive studies on recurrent event of serious ADRs undertaken to date.

1.6 Research Questions

The key research questions for this dissertation are given below:

1) What is the prevalence of ADEs in (a) children aged less than 18 years, (b) adults aged 18 years and older presenting to EDs over a one year period?

2) What was the proportion of ADEs in these two groups of population (children and adults presenting to EDs) severe and preventable?

3) How does the occurrence of ADEs in these two groups of population (children and adults presenting to EDs) relate to the patients' demographic and clinical characteristics?

4) What is the incidence of ADR occurrences in the elderly population aged 65 years and older admitted to hospitals?

5) What does the impact, if any, age, comorbidity and other covariates have on the number of ADRs in elderly hospitalized patients?

The events identified from the first two studies were termed as 'adverse drug events', which was the focus of the research question 1, 2 and 3 as the primary outcome variable. The event that was detected from the third study was referred to as 'adverse drug reactions'. This ADR was used as a primary outcome variable to answer research questions 4 and 5. As evident in the research questions above, this dissertation focused on the unified goal of detecting and characterizing serious ADEs requiring utilization of health care resources. However, due to the differences in study design and data sources among the three studies, there is a subtle difference in the primary outcome variables (ADE vs. ADR) and measures of occurrences considered (prevalence vs. incidence). These differences have been reflected in the research questions given above. To answer question 1, a measure of period prevalence was considered that indicated how many people of the specified age groups had ADEs leading to an ED visit during the one-year period. However, for research question 4, a measure of incidence was computed which referred to the incidence rate (or, incidence density) at which the number of new events occurred in the population at risk during a specified time period (e.g., annually). Consideration of estimating period prevalence for the first two studies and incidence rate for the third study to measure the extent ADE occurrence is just a reflection of recognizing the study designs and sources of data from which ADE were identified.

The incidence of ADEs in the elderly hospitalized patients referrers to the incidence of ADRs, which is a conservative estimate of ADEs as defined in section 1.3.1. Research questions 1, 2 and 4 generated knowledgeable data about the magnitude of the problem of ADE occurrence in EDs and in high risk hospitalized patients. This information is necessary prior to the investment of resources to find ways to reduce preventable discomfort, disability, and death directly attributable to adverse outcomes associated with drugs. Although knowledge of the proportion of ADEs in elderly hospitalized patients that could have been prevented and their level of severity is an important concern, this was not included as part of the research questions since the administrative database used to answer these questions could not classify ADEs with respect to severity and preventability. Given that EDs and in-hospital are two different settings with distinct level of care, these are separated into two distinct studies and thus research questions are separated by study setting. It has been illustrated that the epidemiology of adverse events and preventable adverse events in children is different than in adults since children differ from adults in many ways with regard to medical care [69]. Therefore, prevalence of ADEs was measured separately in children and adults. Research questions 3 and 5 are important to direct how patient safety initiatives should be focused in different parts of the population. Patient-related factors associated with serious ADEs need to be better understood in order to implement interventions that can reduce the incidence and burden of drug-related problems in the population.

1.7 Ethics Approval and Copyright Permissions

Ethics approval for this doctoral dissertation was obtained from the Human Investigation Committee of Memorial University of Newfoundland (Appendix A). The two papers were written based on the findings of the first two studies and subsequently published in the Journal of *Pharmacoepidemiology and Drug Safety* and *the Annals of Pharmacotherapy.* The both journals granted written permission to include the papers in my doctoral thesis (Appendices B.1 and B.2). As noted earlier, the written permissions were also obtained from the original authors regarding the adoption of Figure 1.1 in the thesis (Appendix B.3).

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CHAPTER 2

Adverse drug events among children presenting to a hospital emergency department in Newfoundland and Labrador, Canada

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Abstract

Objectives: The aim of this study was to examine epidemiologic characteristics of Adverse Drug Events (ADEs) among children and adolescents presenting to an Emergency Department (ED) in Newfoundland and Labrador (NL), Canada.

Materials and Methods: This study was conducted in three phases and included an ED chart review of visits to the Janeway Hospital in St. John's, NL, between April 27th, 2006 and April 26th, 2007. The first phase narrowed the sampling frame by excluding visits highly unlikely to be drug-related. In the second phase, a random sample of ED charts was selected for review by two research nurses using a Trigger Assessment Tool that classified ED visits according to their likelihood of being drug related ("high", "moderate", "low", "very low" or "no" probability). The third phase included a full chart review of all "high", "moderate", "low", and "very low" probability ADE charts, carried out independently by two ED pediatricians and two clinical pharmacists. Each ADE was also scored for severity and preventability, and consensus was reached among all four reviewers during meetings held at the end of this phase.

Results: In this study, 69 patients presented to the ED either due to an ADE or a possible ADE (PADE). After a sample-weight adjustment, the prevalence of ADEs/PADEs was found to be 2.1%. The number of comorbidities was inversely associated with medication-related visits. There was no significant difference found between patients with and without medication related visits with respect to mean age of the patient and the mean number of current medications being taken. Of the 69 confirmed ADE/PADEs,

none were fatal, six (8.7%) were serious/life-threatening, and 63 (91.3%) were considered significant. Antimicrobial agents (45.0%) were the most common drug classes associated with ADEs/PADEs. Approximately 20% of the 69 ADEs/PADEs identified were considered preventable.

Conclusions: In St. John's NL, emergency department visits as a result of ADEs are common among the pediatric population and in many cases preventable. Age and number of current medications do not appear to be associated with ED visits related with ADE. Antimicrobial agents were found to be to the cause of most ADEs/PADEs.

Keywords: Adverse Drug Event (ADE), Pediatrics, Emergency Department, Newfoundland, Canada

Introduction

An Adverse Drug Event (ADE) is defined as any undesirable effect related to the use or misuse of a drug (prescription or nonprescription) [1]. It has been estimated that such events account for 17 million emergency department (ED) visits and 8.7 million hospital admissions annually in the United States [2, 3]. Studies of ADEs among children and adolescents is not well understood, mainly because research regarding drug usage in pediatric populations is generally lacking. [4]. To date, pediatric ADEs have been evaluated mostly in hospital settings [5-10]. It has been estimated that 70,000 children hospitalized in the United States experience an ADE each year, and that 60% of these events are preventable [5]. Considering the limited research on ADEs among pediatric ambulatory care visits and particularly ED visits, this study was conducted to examine the epidemiologic characteristics of ADEs presenting to a pediatric ED in the city of St. John's, the capital of Newfoundland and Labrador (NL), Canada.

Methods

This study was conducted at the Janeway Children's Health Care Centre (the Janeway) in St. John's, NL, Canada (the only tertiary care centre for children in the

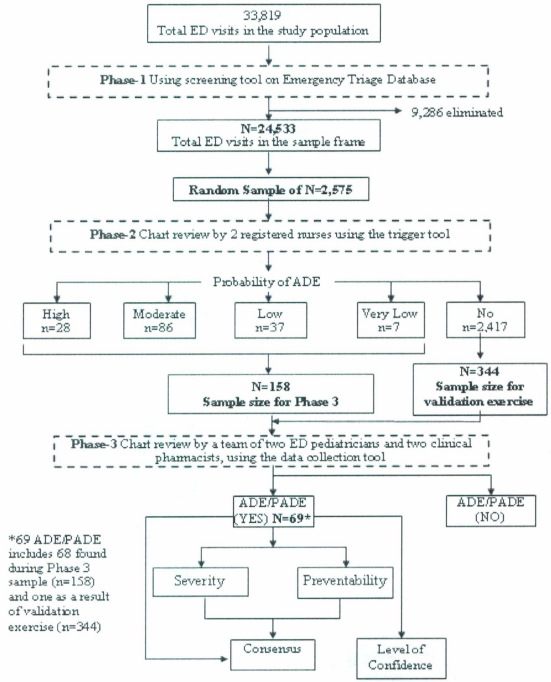

Figure 2.1: Illustrative flow-chart for identification of pediatric patients with ADEs

province) in three phases from April 27th, 2006 to April 26th, 2007 (Figure 2.1).

The inclusion criteria were: 1) patients aged ≤ 17 years, and 2) resident of NL. Exclusion criteria included: 1) patients whose reason for the ED visit was unlikely to be the result of an ADE (e.g., alcohol-related, cut-related injuries, burn, wound dressing, drug abuse, attempted suicide, etc.), and 2) visits where the ED charts were found to lack documentation or had missing information. The main reasons we excluded visits due to drug abuse or intentional overdose was to avoid overestimating the true frequency of ADE-related visits to the EDs, given such events would not constitute a drug-related problem (DRP) according to widely accepted criteria of DRPs. These criteria can be broken out into 8 categories: 1) untreated indication, 2) improper drug selection, 3) sub-therapeutic dosage, 4) failure to receive drugs (includes patient non-compliance), 5) overdosage, 6) adverse drug reaction, 7) drug interaction, and 8) drugs used without an indication [11].

In the first phase, the Janeway ED triage data file containing all ED visits during the study period was examined based on the inclusion/exclusion criteria. This data file included patient demographic information, hospital chart number, date and time of the ED visit, and self-assessed reason for the visit. In order to obtain the sampling frame, a screening tool was developed to exclude those ED visits having a high probability of not being attributed to ADEs (e.g., alcohol-related, cut, burn, wound dressing, etc.).

Recognizing that conditions such as attempted suicide and drug abuse would not likely be the complaint of the presenting patient (i.e., adolescents), these ED visits may not have been excluded at this phase of the study; rather, they were excluded case by case at a later phase when the actual chart reviews were conducted.

To permit identification of an estimated prevalence of 1.7% for ADEs with a 95% confidence interval half width of 0.5%, a sample size of 2,575 (including a 10% over sample) were selected from the sample frame for initial review. The estimate of 1.7% was the average ADE prevalence reported in the published literature for pediatric settings [12-14]. The initial review was carried out by two research nurses, who classified the visits according to their likelihood of being ADE-related ("high", "moderate", "low", "very low" and "no" probability). In this phase, a Trigger Assessment Tool (Appendix C.1) was used, which listed 38 screening criteria (triggers) known to be sensitive to the occurrence of ADEs among the pediatric population. Charts were selected from the sampling frame using a simple random sampling design. Recognizing that a patient may have had more than one ED visit during the study period, only one visit per patient was randomly selected during the sampling process.

Following the screening of visits for their likelihood of being ADE-related, a full review of ED charts was carried out by two ED pediatricians and two clinical pharmacists on all those identified as having "high", "moderate", "low", and "very low" probability of

being ADEs. A validation exercise was considered to assess how good the trigger assessment tool was in separating the sampled visits with respect to probable ADE classes. As part of the validation exercise of the Trigger Assessment Tool, a full review was also carried out on a sample of charts for visits classified as having "no" probability of being due to an ADE. A random sample of 344 patients from the "no" probability group was selected by assuming that, at most, 1.5% of the visits in the "no" probability ADE category were actually the result of an ADE, and by using a 95% confidence level with a one-sided error of 1.0%.

A data collection tool developed by the research team was used by the review team to collect relevant information and assess whether the ED visit was due to an ADE (Appendix C.2). The data collection tool was developed based on the tool used by Gandhi et al. [15], was piloted and minor revisions were made prior to the chart review. Using the data collection tool, the reviewers recorded demographic and clinical information including presenting complaint, past medical history, drug history, history of allergy, medication dose, frequency, and reaction to the event, as well as the patient's most recent laboratory results. This information was used to assess whether the ED visit was the result of an ADE, a possible ADE (PADE), or a medication error (ME). In this study, an ADE was defined as any undesirable effect caused by the interaction of a drug with a patient. The term 'possible adverse drug event' (PADE), was defined as an event that may have been related to a current medication, however it may also have been due to

another cause (e.g. viral infection), and therefore confirmation of the ADE was not possible. A medication error was defined as a mishap that occurred during prescribing, transcribing, dispensing, administering, adherence, or monitoring a drug. Only a small proportion of medication errors lead to adverse outcome [1, 16]. A medication error that did not cause harm or was stopped before harm occur (i.e., near misses or close calls) was included as a potential outcome in the data collection sheet; however because of the retrospective nature of our study, and the limited documented clinical information in the patient charts, we did not expect, nor did we find any medication errors that could be considered "near misses" or "close calls".

Each reviewer classified the events (i.e. ADE or a PADE) according to their severity and preventability. Severity was classified as "fatal" (resulted in death), "life threatening" (the event caused symptoms that, if not treated, would have put the patient at risk of death), "serious" (the event caused symptoms that were associated with a serious level of risk, but was not high enough to be life threatening), or "significant" (the event caused symptoms that, while harmful to the patient, posed little or no threat to the patient's life). Preventability was classified as "error intercepted", "definitely preventable", "probably preventable", "probably not preventable", or "definitely not preventable" [15]. Each member of the review team reviewed each chart independently and consensus was reached among all four reviewers during meetings held at the end of this phase. Because disagreement about classification of ADEs, and their severity and

preventability were resolved during consensus meetings, measuring inter-rater reliability was beyond the scope of the study.

Due to small counts the primary outcome variables (i.e., ADE and PADE) were combined into a single variable (ADE/PADE), as we assumed that the causes of possible ADEs were quite similar to that of confirmed ADEs [17]. The methodological benefit of pooling these two categories of events was to reduce the random error associated with small number of events. The estimation of prevalence of ADEs/PADEs was based on the sample reviewed in Phase 2 (reported as per 100 ED visits). To adjust for the sampling fraction in the study design, sampling weights were used to estimate the overall prevalence of ADEs/PADEs. The calculation of the sample weights were based on the inverse of the sampling fraction for Phase 2 and Phase 3, which resulted in an adjusted number of total visits to be studied (i.e., the denominator), as well as an adjusted number of ADEs/PADEs identified (i.e., the numerator). The rate of severity and preventability of ADEs/PADEs was derived by dividing the number of events in the respective categories by the total number of ADEs/PADEs confirmed by the reviewers. Comparison of mean age, mean number of co-existing health conditions and current medications were performed between ADE and non-ADE related visits using Student's t-test. A similar analysis was carried out to compare percentage of female between these two groups using Binomial proportion test. The number of ADEs and PADEs was extrapolated to the study population by multiplying the weighted estimate of prevalence by the number of ED

visits in the study population. Events that were assessed as "definitely" or "probably" preventable were merged into "preventable", and those assessed to be definitely or probably not preventable were merged into "not preventable". Fisher's exact tests were used to determine whether there was any association between severity and preventability of ADEs/PADEs. All data were entered and stored electronically using Microsoft Access and were analyzed using the SPSS 15.0 software package (Statistical Package for Social Sciences, Chicago, IL).

This study was approved by the Human Investigation Committee of Memorial University of Newfoundland.

Results

During the study period, 33,819 ED visits to the Janeway were identified. Of these, 9,286 did not meet the inclusion criteria for continued review, resulting in 24,533 ED visits (14,347 unique patients) eligible for the second phase of the study. The mean age (±SD) of this cohort was 6.8 (±5.3) years, with 51.2% of all visits being attributed to males. Of the 2,575 patients that were sampled in the second phase, 158 (6.1%) were identified by the research nurses as having a "high" (n=28), "moderate" (n=86), "low" (n=37), or "very low" (n=7) probability of an ADE. Skin rashes and gastrointestinal symptoms (e.g., nausea, vomiting, and abdominal pain) were found to be the most

common manifestations of patients identified as having "high" or "moderate" probability of ADE. Table 2.1 presents the demographic and clinical characteristics of these 158 patients identified for full chart review. Of the 158 patients identified for full chart review, 68 were confirmed by the review team to either have had an ADE (n=15) or a PADE (n=53). As part of the validation process, a sample of 344 charts from 2,417 ED visits classified as "no" probability for ADE in phase 2 of the study was reviewed in the third phase. As a result of this review, one of the 344 (0.3%) visits was found to be the result of a PADE, making the total number of ADEs/PADEs identified in this study 69. This one event was weighted to the inverse of the sampling fraction (i.e., 1 x 1/(344/2,417)=1 x 1/0.142=7.03, or rounding, 7), yielding an estimated count among the random sample of 2575 charts to 68+7=75 ADEs/PADEs (numerator). The denominator of the prevalence of ADE/PADE was set to 3,550 (i.e., 2575 * 1/(24533/33819)=3550) to account for the excluded ED visits at Phase 1, with the assumption that none of the visits were attributed to an ADE/PADE. After accounting for the sample weight given above, the overall prevalence of ADEs/PADEs was found to be 2.1% (95% CI: 1.6-2.6).

Note that we only used this adjusted ADE number of 75 to calculate prevalence and for extrapolation. Information related to those 69 ADEs/PADEs actually identified were used for further analysis given severity, preventability and drug related information was not available for these estimated 6 ADEs (75-69=6).

Table 2.1: Demographic and clinical characteristics of patients selected for chart review (n = 158)

Characteristics	No. of patients	(%)
Age, mean (±SD)	6.5 (±5.6)	-
Age group, years		
<1	32	20.3
1-4	37	23.4
5-12	55	34.8
13-17	34	21.5
Sex		
Female	90	57.0
Male	68	43.0
Mean (±SD) of comorbidities	1.0 (± 1.1)	-
Distribution of comorbidities		
0	71	44.9
1	45	28.5
2	24	15.2
3	13	8.2
≥4	5	3.1
Mean (±SD) number of current medications	1.5 (± 0.9)	-
Distribution of number of current medications		
0*	10	6.3
1	79	51.3
2	52	32.9
3	9	5.7
≥4	6	3.8

* Nurse reviewers did not note that the patient had not taken drugs.

Of the 69 ADE/PADE cases, four were hospitalized. None of the 69 confirmed ADE/PADE patients died, while six of the events (8.7%) were serious/life-threatening, and 63 (91.3%) were significant. Approximately 20% of the 69 ADEs/PADEs identified were considered preventable (Table 2.2). Extrapolating from our prevalence of 2.1%, it was estimated that during the year under study, approximately 710 patients (95% CI: 554-875) were treated for ADEs/PADEs at the Janeway ED, of which approximately 145 visits were considered to be preventable. Further, we estimated that 41 of these 710 patients were hospitalized because of an ADE.

Table 2.2: Distribution of ADEs/PADEs by severity and preventability categories

	Category of preventability		**Total**	**P-value**
Category of Severity	*Preventable* *No. (%)*	*Not Preventable* *No. (%)*		
Significant	13 (20.6)	50 (79.4)	63	0.65 [a]
Serious or life threatening	1 (16.7)	5 (83.3)	6	
Total	14 (20.3)	55 (79.7)	69	

[a] Fisher's exact test was used for comparing two independent binomial proportions.

Table 2.3 presents factors associated with the ADE/PADE visits. Following the full review of the 158 patient charts, 90 were found to have no evidence of an ADE or PADE; these 90 visits were then considered the control group for the purpose of comparison to the 69 patients considered to have presented with an ADE/PADE. There was no statistically significant difference found between the mean age, percentage of females/males, or the number of current medications, for patients with and without ADE-related visits. The number of comorbidities was inversely associated with ADE related visits ($P < 0.01$).

Table 2.3: Comparison of factors associated with drug-related and not drug-related visits to ED

	Type of visit; no., (%) of visits		**P-value**
	Drug-related *n = 69* [a]	Not drug-related *n = 90*	
Age, mean (±SD)	6.2 (±5.2)	6.7 (±6.0)	0.57 [b]
Female sex (%)	56.5	57.8	0.87 [c]
No. of comorbidities, mean (±SD)	0.7 (±0.9)	1.2 (±1.2)	< 0.01 [b]
No. of current medications, mean (±SD)	1.6(±0.8)	1.4 (±1.0)	0.16 [b]

[a] 69 ADE/PADE includes 68 found during Phase 3 and one as a result of validation exercise; [b] Student's t-test was used for comparing two means; [c] Binomial proportion test was used for comparing two independent proportions/percentages;

Table 2.4 presents the distribution of medication classes associated with the 69 ADE-related visits and the 90 non-ADE related visits. The percentage of antimicrobial medication was significantly higher among patients with ADEs compared to those without ADEs (45.1% vs 23.4%, $p<0.01$). The medications most frequently associated with ADEs/PADEs, either on their own or in combination with other agents, were macrolide antibiotics (e.g., azithromycin, clarithromycin) (26.1%, 18/69) and amoxicillin (23.2%, 16/69).

Table 2. 4: Medication class associated with drug-related and not drug-related visits to ED

Medication class	**Drug-related** *n (%)*	**Not drug-related** *n (%)*	**P-value** [a]
Antimicrobial agents	51 (45.1)	30 (23.4)	<0.01
Musculoskeletal agents	13 (11.5)	21 (16.4)	0.28
Central nervous system agents	4 (3.5)	7 (5.5)	0.47
Hormone-modifying agents	3 (2.7)	4 (3.1)	0.83
Cardiovascular agents	1 (0.9)	2 (1.6)	0.64
Other	41 (36.3)	64 (50.0)	<0.05

[a] Binomial proportion test was used for comparing two independent binomial proportions

Discussion

The extent of ADEs presenting to EDs among the pediatric population has not been previously studied in NL. This study found that drug-related events accounted for 2.1% of child and adolescents ED visits at the Janeway (the only tertiary pediatric care centre in NL), of which 20% were considered preventable. Comparisons with other studies, particularly in Canada, are challenging since there are limited Canadian studies that have investigated pediatric ADEs presenting to EDs. A Canadian study by Kozer et al. [18] at the Hospital for Sick Children in Toronto reported prescribing errors in 10.1% and drug administration errors in 3.9% of all ED pediatric charts reviewed. The most common types of prescribing errors were dosing errors, followed by drugs given with incorrect frequency. An Australian multicentre study [19] showed 3.3% (95% CI: 2.9–3.7%) of pediatric ED visits were due to drug-related problems over an 18 week-period, of which 51.3% were judged to be preventable. A prospective Italian study estimated the rate of ADEs to be 6.2% (95% CI: 4.3–8.1%) among patients aged 0-19 years visiting EDs. The prevalence of ADEs/PADEs determined in our study may not be comparable with that of other studies because of differences in definitions (e.g. ADE, PADE, ME, etc), and variations in methodological designs. It is worth noting that not only is there limited research conducted on pediatric visits to EDs due to ADEs, but most literature on ED visits focuses on MEs, drug-related problems and adverse drug reactions, rather than

studying ADEs that encompass both ADRs in which no error occurred and complications that result from MEs [20].

In a national surveillance study of ED visits for ADEs among children and adolescents in the USA, most children experiencing an ADE (88.7%) were treated and released; 5.1% were admitted to the hospital, and 2.9% were held for extended observation in the ED [21]. Cohen et al. also reported that children aged 1-4 years had a rate of hospitalization for ADEs that was almost 10 times higher than other pediatric age groups. Selbst et al. [22] reported that of 33 children visiting the ED at the Children's Hospital of Philadelphia, only one required admission to the hospital as a direct result of the medication error. The Easton-Carter study [19] from Australia found that of the 280 pediatric ADE patients, 62 (22%) were admitted to hospital, including three to the intensive care unit. Based on the findings of our study, we estimate that approximately 710 children were treated for drug-related events at the Janeway ED over the 12-month study period, with 41 (5.8%) requiring hospitalization. We extrapolated the prevalence of ADEs/PADEs found in this study to the study population by multiplying 2.1% by 33,819 (total ED visits in the study population).

In this study no significant difference was found between the mean age and number of current medications for patients with and without ADE-related visits, while the number of comorbidities was found to be inversely associated with ADE-related

visits. This may be due to the fact that children with higher numbers of comorbidities are prescribed multiple medications, and as such, receive a closer monitoring in the community. Moreover, drug exposure has been shown to be a predictor of ADEs in the inpatient pediatric settings, where patients are normally much sicker than those presenting to outpatient or ED settings [23]. Overall, our study sample was found to have low drug exposure which explains why we observed no association between number of drugs and ADE-related ED visits. Nonetheless, further investigation is needed to explore this finding.

In this study, antimicrobial agents were found to be the most commonly prescribed drugs and were most frequently associated with ADEs/PADEs, which is consistent with the findings of other studies [13, 14, 19, 21, 24]. Because antimicrobial drugs are prescribed frequently in children, and a number of children have allergies to some commonly used antimicrobial drugs, the Canadian Pediatric Society recommends that antimicrobial therapy should be limited to those situations in which there is a clear indication, and should only be administered for the shortest effective duration [24, 25]. Cohen et al. [21] reported antimicrobial agents, analgesic medications, and respiratory medications accounted for almost half of all ADEs (25.2%, 13.7%, and 10.6%, respectively) in a national surveillance study of ED visits among children in the USA. They also found that almost half of the antimicrobial agent ADEs (47%) were caused by amoxicillin, whereas more than half of the ADEs from analgesic medications (62.8%)

were caused by acetaminophen and nonsteroidal anti-inflammatory medications [21]. Similarly, in the Easton-Carter study [19], the most frequently occurring drugs were antimicrobial agents and analgesic medications such as amoxicillin, paracetamol (acetaminophen), cefaclor, amoxicillin and clavulanic acid, erythromycin, and penicillin V. Since antibiotics seem to be the most common medications causing ADEs among children, educational interventions need to focus on both the optimal approach to diagnosis and management of infection, and the negative consequences of unnecessary antibiotic use.

This study faced several limitations. First, there is a lack of a "gold standard" approach for accurately determining the prevalence of ADEs in the community setting, perhaps due to the cost involved and time needed to carry out such a study. For this reason, researchers have used both prospective and retrospective methods, as well as different data sources such as administrative systems and medical charts, to study the magnitude of ADE prevalence among the pediatric population. Secondly, using a retrospective chart review design limited the accuracy with which we could determine an ED visit as being caused by an ADE. Ideally, a prospective design with a large sample including patient/physician interviews and obtaining key information could have increased the accuracy of estimates of ADE-related visits and their preventability. Thirdly, this study attempted to identify ADEs treated in EDs, and did not consider ADEs treated in outpatient clinics, physician offices, or those patients who did not seek medical

care. However, the ED is likely the most appropriate setting to capture severe, acute outpatient ADEs.

Fourthly, in our analysis ADEs and PADEs were combined into a single variable (ADE/PADE), which may result in an overestimate of the true prevalence of ADE, although we assumed that the causes of possible ADEs were similar to that of confirmed ADEs. Fifthly, during Phase 2 of the study we used a Trigger Assessment Tool that was developed for the study to identify ED visits based on their likelihood of being an ADE. Upon validation of the Trigger Assessment Tool we found that there was one visit (chart) identified initially as "no" probability of being an ADE that was in fact a PADE. This suggests that the Trigger Assessment Tool may not have been as sensitive as we had hoped, and as such, we may be underestimating the true prevalence of ADEs in the community, although it is recognized this would be by a very small margin. The Janeway Hospital is a referral centre and is located in St. John's, the capital of Newfoundland and Labrador. Thus, findings from our study cannot be considered representative of EDs treating children elsewhere in the province. Another limitation of this study may have been reviewer bias. A professional's ability to detect an ADE from reviewing a medical chart is based on his/her clinical experience and knowledge. Though this bias was minimized by having four reviewers independently review the charts and then reaching consensus, we were still limited to certain areas of clinical expertise with each of the reviewers.

Conclusion

Emergency Department visits as a result of ADEs are not uncommon among the pediatric population in St. John's, Newfoundland, and in many cases may be preventable. Age and number of current medications do not appear to be associated with pediatric ADE, although it is recognized that our study sample was not taking many different drugs. Antimicrobial agents were found to be most frequently associated with ADEs/PADEs. Further education along with tools to make health care professionals more aware of potential ADEs and their implications is needed. The optimal strategy may involve interventions outside the hospital to improve prescribing practices and monitoring, particularly among high-risk patients or patients taking high-risk medications.

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CHAPTER 3

Adverse Drug Events in Adult Patients Leading to Emergency Department Visits in Newfoundland and Labrador, Canada

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Abstract

Background: Adverse drug events (ADEs) occurring in the community and treated in Emergency Departments (EDs) have not been well studied.

Objective: To determine the prevalence, severity and preventability of ADEs presenting at EDs in two university-affiliated tertiary care hospitals in the Canadian province of Newfoundland and Labrador (NL).

Methods: A retrospective chart review was conducted on a stratified random sample (n = 1,458) of adult patients (≥ 18 years) that presented to EDs from January 1 to December 31, 2005. Prior to the chart review, the sample frame was developed by first eliminating visits that were clearly not the result of an ADE. The ED summary of each patient was initially reviewed by two trained reviewers in order to identify probable ADEs. All eligible charts were subsequently reviewed by a clinical team, consisting of two pharmacists and two ED physicians, to identify ADEs and determine their severity and preventability.

Results: Of the 1,458 patients presenting to the two EDs, 55 were determined to be the result of an ADE, or a possible adverse drug event (PADE). After a sample-weight adjustment, the prevalence of ADE/PADE was found to be 2.4%. Prevalence increased with age (0.7%, 18-44 years; 1.9%, 45-64 years; 7.8%, ≥65 years) and the mean age for patients with ADEs was higher than those with no ADEs (69.9 vs. 63.8 years, $P < 0.01$). A higher number of comorbidities and medications were associated with drug-related

visits. Approximately 29% of the ADEs/PADEs identified were considered to be preventable, with 42% requiring hospitalization. Cardiovascular agents (37.4%) were the most common medication class attributed with ADEs/PADEs.

Conclusions: Adult ADE-related ED visits are frequent in NL, and in many cases preventable. Further efforts are needed to reduce the occurrence of preventable ADEs leading to ED visits.

Keywords: Adverse Drug Event (ADE), Prevalence, Severity, Preventability, Emergency Departments.

Introduction

Prior research indicates that adverse drug events (ADEs) are a concern in both inpatient and outpatient settings [1-5]. These unfavorable occurrences are a significant cause of morbidity and mortality [6, 7], and result in significant resource utilization, including increased emergency department (ED) and physician visits, diagnostic tests, medication use and hospital admissions [8]. Such events account for 17 million ED visits and 8.7 million hospital admissions in the United States each year [9, 10]. Between 1995 and 2000, costs associated with ADEs in the United States rose from US$76.6 billion to over US$177.4 billion [10, 11].

An ADE is any injury resulting from medical interventions related to a drug whose outcome is unexpected and unacceptable to the patient and health care provider [12, 13]. ADEs have been studied mostly among hospital patients, and it has been estimated that 5%–25% of hospital admissions are drug-related [14, 15]. However, ADEs occurring in outpatient settings and treated in EDs receive less attention, even though more than 80% of community-dwelling adults use medications on a weekly basis, and approximately threefold more patients are treated in EDs for ADEs compared to those admitted to hospital [4, 16].

The Institute of Medicine report *To Err Is Human: Building a Safer Health System* concluded that the solution to preventing medical errors is "building a safer health system" that identifies patient safety as a pre-requisite to high quality care [17]. Despite widespread recognition of the need for a safer health system, ADEs occurring in community settings remain a substantial cause of ED visits. The aims of this study were: (1) to determine the prevalence of ADEs presenting at adult EDs in Newfoundland and Labrador (NL), Canada, and to classify them according to severity and preventability; and (2) to describe demographic and clinical factors associated with ADEs.

Methods

Setting and study population

The study setting was two adult acute care hospitals, the Health Science Center (HSC) and St. Clare's Mercy Hospital (SCMH), both of which deliver tertiary care in St. John's, NL, Canada. These two hospitals serve a catchment area of approximately 280,000 residents, and together have an average of 28,000 admissions and 80,000 emergency room visits per year.

Eligible subjects included all patients aged ≥18 years who were residents of NL and presented to one of the two EDs between January 1st and December 31st, 2005. ED visits with a high probability of not being due to an ADE (e.g., motor-vehicle accident, substance abuse, drug abuse, attempted suicide, cut- or burn-related injuries, etc.) were excluded to narrow the sampling frame. The main reasons we excluded visits due to drug abuse or intentional overdose was to avoid overestimating the true frequency of ADE-related visits to the EDs, given such events would not constitute a drug-related problem (DRP) according to widely accepted criteria of DRPs [18]. Patients who presented to EDs through a referral process, and subsequently identified as a valid ED visit were included in this study. Ethics approval was obtained from the Human Investigation Committee of Memorial University of Newfoundland.

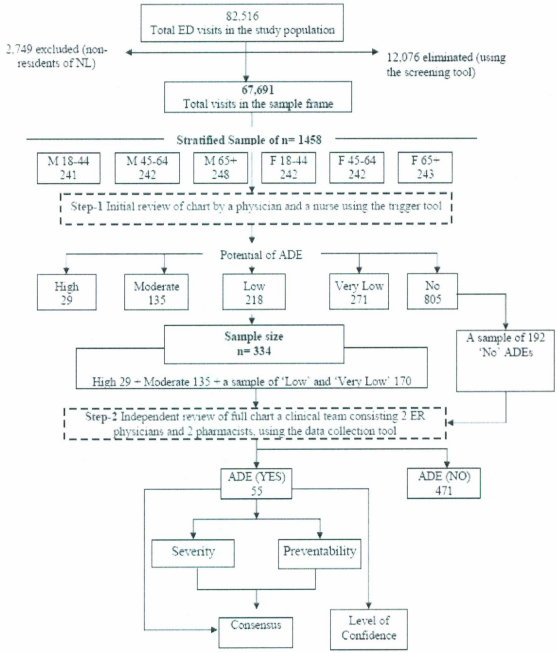

Figure 3.1: Illustrative flow-chart for identification of ADEs in adult patients presenting to EDs

Study sample

Charts were selected using a stratified random sampling design (Figure 3.1). There were six strata (Male 18-44 years, Male 45-64 years, Male ≥65 years, Female 18-44 years, Female 45-64 years, and Female ≥65 years) based on patients sex and age at ED visit. Evidence in the literature regarding the prevalence of ADEs was found to be inconsistent, ranging from 2.5% to 35%, which can be mostly attributed to differences in study designs and patient demographics [19-22]. To determine our study sample we estimated an average of 10% of ED visits would be attributed to ADEs in patients aged ≥18 years. To achieve a 95% confidence interval (±4%), we initially calculated a sample size of 217 ED visits for each stratum, resulting in a total of 1,302 ED visits. To reduce the sampling error, and to compensate for the exclusion of ED visits attributed to suicide attempts and drug abuse, we added a 10% over-sample. After the chart review was completed, the final sample size for the study was 1,458; resulting in a 12% over-sample. This difference of 2% was attributed to inclusion of ED visits through referrals as previously described. For patients with multiple ED visits during the study period, only one visit was selected at random for review.

Outcomes and definitions

An ADE is defined as any undesirable effect caused by the use or misuse of a drug (prescription or nonprescription) with a patient [13, 23]. Events may be the result of normal or inappropriate use of a medication, and range from minor reactions such as a skin rash to serious and life-threatening events, even death. In this study, we used another term "possible adverse drug event" (PADE) was defined as an event that may have been related to a current medication, but could not be confirmed using the patient chart. Medication errors are mishaps that occur during prescribing, transcribing, dispensing, administering, compliance, or monitoring of a drug. Example of medication errors includes misreading or miswriting a prescription. Medication errors are more common than ADEs, but result in harm less than 1% of the time [13]. We studied ADEs/PADEs involving either prescription or over-the-counter drugs encompassing all traditional adverse effects. We also included those medication errors that caused harm.

Data Collection

Data collection involved a 2-step review of ED charts using the Meditech system, a hospital information system whereby all electronic patient information, including ED summaries, is scanned and uploaded to the patient's profile (Figure 3.1). In the first step,

the ED summaries of each chart were reviewed by a team consisting of a physician and a registered nurse using a manually enabled Trigger Assessment Tool developed by the research team (Appendix D.1). This tool listed 39 screening criteria (triggers) known to be sensitive to the occurrence of ADEs among adults. The reviewers combined these triggers with the patient's history of medication use, as well as a subjective assessment, to determine whether an ADE was the reason for the ED visit. If it was classified as being a probable ADE, the reviewers through a consensus process coded the reason for the visit as having either a high, moderate, low, or very low probability of being an ADE.

The second step included a full review of all ED charts identified as having "high" and "moderate" probability ADEs, and a random sample of "low/very low " probability ADEs. As part of the validation process, a full review was also carried out on a sample of those ED visits classified as having "no" probability of being an ADE. Two ED physicians and two clinical pharmacists independently reviewed each of the charts using a data collection tool that was a modified version of the tool developed by Gandhi et al [24] (Appendix D.2). The reviewers were blinded to the first step review that identified probable ADEs. The reviewers first obtained demographic and clinical information, including presenting complaints, past medical history, drug history, history of allergy, medication dose, frequency, and reaction for the event, as well as the patient's most recent laboratory records. The reviewers used this information to assess whether the ED visit was a result of an ADE, PADE or medication error. Each reviewer also classified the

event according to its severity and preventability. Using an adapted version of previously published criteria, severity was classified as being "fatal", "life threatening", "serious" or "significant"; and preventability was classified as "definitely preventable", "probably preventable", "probably not preventable", or "definitely not preventable"[2, 24-25]. Disagreement about classification of ADEs, and their severity and preventability were resolved during consensus meetings. The principal investigator of the study (Dr. Don MacDonald) was present during all consensus meetings to ensure healthy discussion among all reviewers and to mitigate potential influences of any dominant personalities. As a result, consensus by all 4 reviewers was always reached.

In this analysis we used 2 data sets: (1) summary data on all patients from the first review, and (2) detailed information on the sub-sample of patients collected through the chart review.

Statistical Analysis

We generated descriptive statistics including means, standard deviations and ranges. The primary outcome variables ADE and PADE were combined into a single variable ADE/PADE, as we assumed that the causes of possible ADEs were similar to confirmed ADEs.[2] The methodological benefit of pooling these two categories was to

reduce the random error associated with small number of events. The unit of analysis was the ED visit. Prevalence of ADEs/PADEs was calculated per 100 ED visits and presented with p-values using the binomial proportion test. We considered the inverse of the sampling fraction for step 1 and step 2 to obtain an adjusted number of total visits to be studied (i.e., the denominator), as well as an adjusted number of ADEs/PADEs identified (i.e., the numerator). Each study subject was assigned a weight to represent the number of ED visits in the study population by each sampled ED visit. The prevalence of ADE/PADE was estimated after sample weight adjustment to account for the sampling fraction and stratification in the sampling design (Appendix E). Events that were assessed as definitely or probably preventable were merged into "preventable", and those assessed as definitely or probably not preventable were merged into "not preventable". Rate of severity and preventability were derived by dividing the number of events in the respective categories by the total number of ADEs confirmed by the reviewers. Mantel-Haenszel chi-square analysis was performed to determine whether there was an association between severity and preventability of ADEs. Factors (i.e., age, sex, number of co-existing health conditions and current medications) associated with ADE/PADE-related visits were tested using Student's *t*-test for mean and Binomial proportion test for proportion. The number of ADEs was extrapolated to the study population by multiplying the weighted estimate of prevalence by the number of ED visits in the study sample. Number of preventable ADEs and hospitalization due to ADEs were extrapolated to the study population in a similar manner. Data analysis was carried out using SPSS for Windows version15.0 (SPSS Inc., Chicago, IL).

Results

During the study period, 82,516 adult ED visits were identified. Of these, 2,749 visits were excluded because they were by non-residents of NL, and 12,076 were excluded since they did not meet the inclusion criteria. A total of 67,691 ED visits (41,135 unique patients) were available for the sample frame. The mean age (±SD) of this cohort was 46.9 (±19.6) years with 54.4% (36,814/67,691) were female.

Of the 1,458 ED visits sampled from the 67,691 visits, 653 (44.8%) were identified as having a high (29), moderate (135), low (218), or very low (271) probability of being the result of an ADE. Gastrointestinal symptoms (e.g., nausea, vomiting, and diarrhea) and skin rashes were found to be the most common manifestations of patients identified as high or moderate probability of having an ADE.

Patients identified as having a "high" (n=29) or "moderate" (n=135) probability of having ADEs, along with a random sample of 170 ED visits out of 489 classified as having a "low" or "very low" probability of having ADEs, were independently reviewed by two ED physicians and two clinical pharmacists. Table 3.1 presents demographic and clinical characteristics of the 334 (29 + 135 +170) patients selected for chart review. The

mean (±SD) number of comorbidities and current medications for this group were 3.5 (± 1.9) and 5.6 (± 3.6), respectively.

Fifty-five of the 334 patients were identified by the team as having an ADE (n=29) or a PADE (n=26). Of the 55 ADEs/PADEs, 52 (31.7%) were identified from the 164 ED visits classified as "high/moderate" probability for ADE visits and the remaining 3 (1.8%) were from the sample of 170 ED visits classified as "low/very low" probability. As part of the validation process, a sample of 192 charts from 805 ED visits classified as "no" probability for ADE visits were reviewed for validation of the trigger tool exercise. None of these 192 visits was found to be ADE-related.

Table 3.1: Demographic and clinical characteristics of 334 patients selected for chart review

Characteristics	No. of patients	(%)
Age, mean (±SD)	64.8 (±16.6)	-
Age group, years		
18-44	38	11.4
45-64	105	31.4
65+	191	57.2
Sex		
Female	199	59.6
Male	135	40.4
Total no. of comorbidities, mean (±SD)	3.5 (± 1.9)	-
No. of comorbidities		
0	9	2.7
1	41	12.3
2	58	17.4
3	74	22.2
4	68	20.4
5	33	9.9

>5	51	15.3
Total no. of medications, mean (±SD)	5.6 (± 3.6)	-
No. of medications [a]		
Not available	2	0.6
1	21	6.3
2	35	10.5
3	55	16.5
4	51	15.3
5	34	10.2
>5	136	40.7
Previous history of allergy	101	30.2

[a] "current medication" means medication or medications (prescription or non-prescription) that the patient had been taking prior to presenting to EDs, not those that may have been given after arriving at EDs.

We have weighted to the inverse probability of the sampling fraction ((i.e., 3 x 1/(170/489)=8.6, rounding to 9), yielding an estimated count among the random sample of 1,458 charts to 52+9=61 ADEs/PADEs (numerator). The denominator of the prevalence of ADEs/PADEs was set to 1,777 (i.e., 1458 × 1/(67691/82516)=1,777) to account for the excluded ED visits prior to the chart review, with the assumption that none of the visits was attributed to an ADE/PADE. The age group and sex of the 6 additional patients with an ADE/PADE in the numerator (61-55=6) were assigned in

proportion to the actual number of ADE/PADE (55) and those for 319 (1777-1458=319) patients in the denominator were in proportion to the study sample (1,458), with rounding to the nearest whole number. After a sample weight adjustment to account for the sampling fraction given above and stratification in our study, the overall prevalence of ADEs/PADEs was 2.4% (95% CI: 1.8-3.0). Note that we only used this adjusted ADE number of 61 to calculate prevalence and for extrapolation. Information related to the 55 ADEs/PADEs actually identified was used for further analysis, given that severity, preventability, and drug related information was not available for the 6 estimated ADEs. We estimated the results of our validation exercise that the rates of ADEs/PADEs among high, moderate and low probability groups were 72.4% (21/29), 22.2% (30/135) and 3.7% (3/82). None of those reviewed from the very low probability (88) and no probability (192) groups were found to be ADE-related. This suggests that the Trigger Assessment Tool was sensitive to trigger the true ADEs/PADEs in the ED charts.

The mean (±SD) age for patients with an ADE/PADE was 69.9 (±14.2) years; 71.6±9.9 years for males vs. 68.7±16.5 years for females. The distribution of ADEs/PADEs by age and sex is presented in Table 3.2. The prevalence of ADEs/PADEs among males (1.6%, 95% CI 1.0-2.2) and females (3.1%, 95% CI 2.1-4.2) was similar, and increased with age, peaking at 7.8% for patients aged ≥65 years. Twenty-three (41.8%) of the 55 patients with ADEs/PADEs required hospitalization.

Table 3.2: Prevalence of ADEs/PADEs by age and gender

	No of patients with ADE/PADE	Weighted prevalence of ADE/PADE, % (95% CI) [a]
All	55	2.4 (1.8, 3.0)
Sex		
Male	22	1.6 (1.0, 2.2)
Female	33	3.1 (2.1, 4.2)
Age (years)		
18 – 44	4	0.7 (0.0, 1.4)
45 – 64	10	1.9 (0.8, 2.9)
65+	41	7.8 (5.6, 9.9)

[a] Point estimates and CIs were weighted to account for stratification in the sampling design and sampling fraction associated with the selection of number of charts for review.

Table 3.3 presents the analysis of factors associated with ADE/PADE visits (i.e., number of comorbidities present and number of medication used). The mean age for patients with ADEs/PADEs was higher than for those having no drug-related visits (69.9 vs. 63.8 years, $P< 0.01$). A higher number of comorbidities and medications was associated with drug-related visits ($p < 0.05$ and $p<0.01$, respectively). Of the 55 confirmed ADE/PADE patients, one (1.8%) case was fatal, 2 (3.6%) were life-threatening, 25 (45.5%) serious, and 27 (49.1%) significant. Approximately 29% (95%

CI: 17.1 - 41.1) of the 55 ADEs/PADEs identified were considered to be preventable. Of the serious, life-threatening, and fatal events, 35.7% were identified as potentially preventable, compared with 22.2% of the significant events; however, the difference was not statistically significant (Table 3.4). Of the 23 hospitalizations due to ADE/PADEs, 8 (34.8%) were considered preventable.

Based on the 55 ADE/PADE patients, we estimate that approximately 2,000 adult patients (95% CI: 1,458-2,495) were treated in the St. John's region for ADEs/PADEs in the two EDs during the one-year study period; of these, an estimated 570 ADEs/PADEs would have been preventable. Further, it is estimated that 826 of the 2,000 would have been hospitalized. This estimate is based on the total ED visits in the study population (n=82,516).

Table 3.3: Factors associated with drug-related visits (ADEs/PADEs) to EDs

	Type of visit; no., (%) of visits		
	Drug-related	Not drug-related	**P-value**
	n = 55	n = 279	
Age, mean (±SD)	69.9 (±14.2)	63.8 (±16.9)	< 0.01 [a]
Female sex (%)	60.0	59.5	0.94 [b]
No. of comorbidities, mean (±SD)	4.0 (±1.9)	3.4 (±1.8)	< 0.05 [a]
Total no. of medications [c], mean (±SD)	7.4(±3.9)	5.2 (±3.5)	< 0.01 [a]

[a] Student's t-test was used for comparing two means; [b] Binomial proportion test was used for comparing two independent binomial proportions; [c] "current medication" means medication or medications (prescription or non-prescription) that the patient had been taking prior to presenting to EDs, not those that were taking at the time of ED visits.

Table 3.4: Number and rates of preventability of adverse drug events by severity

Category of Severity	Category of preventability		Total	P-value
	Preventable	Not Preventable		
	No. (%)	No. (%)		
Significant	6 (22.2)	21 (77.8)	27	
Serious, life threatening or fatal	10 (35.7)	18 (64.3)	28	0.43 [a]
Total	16 (29.1)	39 (70.9)	55	

[a] Mantel-Haenszel chi-square test was used for comparing two independent binomial proportions.

The distribution of clinical complications associated with ADEs/PADEs is presented in Table 3.5. Hematologic complications (43.6%) were the most common complications associated with ADEs/PADEs, followed by gastrointestinal (32.7%), neurological (14.5%), skin (12.7%), cardiovascular (12.7%), metabolic (9.1%), respiratory (7.3%) and renal (5.5%) complications.

Table 3.5: Number and rates of clinical complications associated with ADEs/PADEs

Clinical complications	No. of patients	(%)[a]
Hematological (including bleeding)	24	43.6
Gastrointestinal	18	32.7
Neurological	8	14.5
Skin	7	12.7
Cardiovascular	7	12.7
Metabolic	5	9.1
Respiratory	4	7.3
Renal	3	5.5
Other	6	10.9

[a] A patient may have had more than one complication as a result of ADEs/PADEs. The total number of patients with ADEs/PADEs is used as denominator.

Table 3.6 presents the distribution of drug classes implicated in the 55 ADE/PADE related visits, with cardiovascular (37.4%), hormonal (11.2%), and hematologic (9.8%) being the most common agents. Medications most frequently associated with ADEs/PADEs, either on their own or in combination with other agents,

were antiplatelets agents (24%), warfarin (18%), antibiotics (15%), antihypertensive agents (13%), and chemotherapy agents (11%). Warfarin, divalproex, and chemotherapy agents, drugs with a narrow therapeutic index and high risk for toxicity, were found to be the cause of nearly one-third (31.7%) of ED-treated ADEs/PADEs in patients aged ≥65 years.

Table 3.6: Distribution of medication class implicated in the 55 ADEs/PADEs patients

Medication class	No.	%
Cardiovascular agents	153	37.4
Diuretics	30	7.3
Angiotensin-converting-enzyme inhibitors	30	7.3
Cholesterol Agents	28	6.8
b-Blockers	27	6.6
Calcium Channel Blockers	16	3.9
Other cardiovascular agents	9	2.2
Nitrates	6	1.5
Angiotensin II receptor blockers	4	1.0
Combination blood pressure medications	3	0.7
Hormone agents	46	11.2
Oral hypoglycemics	22	5.4
Corticosteroids	11	2.7
Thyroid Agent	6	1.5
Insulin	3	0.7
Other hormone-modifying agents	3	0.7

Estrogen	1	0.2
Hematologic agents	40	9.8
Platelet inhibitors	25	6.1
Oral anticoagulants	13	3.2
Other Hematological Agents	2	0.5
Gastrointestinal drugs	39	9.5
Central nervous system agents	31	7.6
Benzodiazepines	14	3.4
Antidepressants	8	2.0
Narcotics	6	1.5
Antipsychotics	1	0.2
Anticonvulsants	1	0.2
Other central nervous system agents	1	0.2
Vitamins and Minerals	19	4.6
Musculoskeletal agents	16	3.9
Nonsteroidal anti-inflammatory drugs	7	1.7
Acetaminophen	5	1.2
Cyclo-oxygenase-2 inhibitors	2	0.5
Other Musculoskeletal Agents	2	0.5

Medication class	No.	%
Respiratory tract agents	16	3.9
Antimicrobial agents	15	3.7
Beta-Lactam agents	4	1.0
Fluoroquinolones	3	0.7
Macrolides	2	0.5
Antifungals	2	0.5
Other antimicrobial agents	4	1.0
Chemotherapy	11	2.7
Herbal Agents	5	1.2
Others	18	4.4
Total	409	100.0

Discussion

This study is the first of its kind in NL, and one of the few studies in Canada to investigate ADEs among the adult patients presenting to EDs. Our study found that ADEs accounted for 2.4% of ED visits, of which 29% were considered preventable. Based on the findings of this study, we estimate that approximately 2,000 patients were treated for drug-related events in EDs in the two St. John's hospitals in 2005, with more than 800 of the visits resulting in hospitalization. Few of the ADEs were fatal or life threatening, with most considered either serious or significant. Compared with those having no ADEs, patients with ADEs/PADEs were older, were prescribed more medications, and had a higher number of comorbidities.

Comparisons with other studies are challenging since the prevalence of ADE-related ED visits varied from 2.5% to 35.0% [19-22]. This variability may be attributed to differences in study populations (e.g., ≥18 years vs. ≥65 years), methodology (e.g, retrospective vs. prospective), and inclusion/exclusion criteria. A recent Canadian study by Zed et al. [5] reported that 12.0% of ED visits at Vancouver General Hospital over a 12 week-period period were due to ADEs, of which 68.0% were preventable. A systematic review of retrospective and prospective trials found 28% of ED visits were drug-related, of which 70% were preventable [18]. A US study using the National Electronic Injury

Surveillance System estimated the rate of ADEs to be 2.4 per 1,000 population treated in EDs, with the elderly having a higher rate of ADEs (4.9 per 1,000 population) [22]. Similar studies on ADEs in non-ED settings, such as hospital and ambulatory care, reported variable ADE rates with the elderly being at greater risk of ADEs [3, 19, 24, 26-28]. The prevalence of ADEs/PADEs found in our study is at the lower end of previously reported ranges. These differences can be explained in part by variations in case definitions (e.g. ADE, PADE, medication error, etc.), study designs, patient population, medical practices and health systems [5, 29, 30].

Hohl et al. investigated the frequency of ADEs among patients aged ≥65 years presenting to the ED in Montreal, Quebec and found 10.6% of ED visits to be the result of an ADE [31]. This is comparable to the prevalence of ADE (7.8%) among the elderly in our study. Although there is debate in the literature as to whether age itself is a risk factor for an ADE-related visit or hospitalization [32], the mechanism relating age to risk for ADEs may include administration of multiple drugs in treating multiple comorbidities which is more common among the elderly [7]. While an aging population tends to take a higher average number of medications, the people are more likely to be unsure of proper administration of drugs and also less likely to tolerate certain medications for various reasons, as outlined in the Beers Criteria [33, 34].

We found that medications such as warfarin, divalproex, and chemotherapy agents with narrow therapeutic index and high risk for toxicity caused about one-third (31.7%, 13/41) of ED-treated ADEs in patients aged ≥65 years. This finding supports findings in a US study that found medications with narrow therapeutic index and high risk of overdose or toxicity (warfarin, insulin, and digoxin) caused nearly one third of the ED-treated ADEs in patients aged ≥65 years [22]. A similar study based in an ED setting in Spain reported that the preventability of ADEs was related to drugs with narrow therapeutic index (OR: 9.83, 95% CI: 5.26-18.40). However, in our study this association could not be established due to the small number of narrow therapeutic index-related preventable ADEs [35].

An interesting finding of this study was that more serious ADEs/PADEs were deemed to be preventable, although the difference was not statistically significant. A US study confined to older outpatients found a similar association between severity and preventability of ADEs [25]. Consistent with both the hospital and nursing home settings, more serious ADEs were more likely to be identified as preventable.

Information on ADE epidemiology comes mostly from studies carried out in the United States. Our study is one of the few carried out within the Canadian context, a country that unlike the USA, has a nationwide universal health care system. A recent review comparing health outcomes between Canada and the US reported that, in general,

health outcomes may be superior in patients cared for in Canada versus those in the United States [36]. Although the two countries have looked to each other for ways to improve their respective health care systems, differences still exist. For example, the US health care system is highly privatized and has higher per capita spending compared to Canada [37, 38]. The US is the only wealthy industrialized country in the world that lacks some form of universal health care, and thus the relative merits of health care outcomes may differ between the two systems [39]. Therefore, our findings add to the existing literature by focusing on a population with universally funded health care and draw attention to the need for prevention efforts that target patients in Canada at high risk for ADEs, and ultimately add to the discourse to improve patient safety.

Limitations

This study had several limitations. Firstly, using a retrospective chart review may underestimate the true frequency of ED visits as being caused by an ADE. Ideally, a prospective design with a large sample would have increased the accuracy of estimates of drug-related visits and their preventability. Secondly, compared to patients aged ≥65 years we found fewer ADEs in younger age groups which makes our estimates of ADE prevalence more prone to sampling error in these age groups. Nevertheless, the prevalence of ADE among elderly patients was 7.8% which is relatively close to our pre-study assumption of 10% considered in the study design. Thirdly, we may have missed

certain ADEs such as drug induced traffic accidents and suicidality. Inclusion of such events, which would be very rare, might have increased the prevalence of ADE obtained in our study. Fourthly, we could not extrapolate our data to the entire province, since the Health Science Centre and St. Clare's Mercy Hospital are located in St. John's, the capital of the province, and cannot be considered representative of all hospitals in the province.

Conclusions

Emergency Department visits as a result of ADEs are not uncommon. A focus on further education along with appropriate tools need to be in place so that physicians and pharmacists can collaborate more closely to improve prescribing practices and monitoring, particularly among high-risk patients, and thereby contribute to the reduction of that subset of ADEs considered preventable.

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CHAPTER 4

Adverse drug reactions in elderly hospitalized patients: a population–based retrospective cohort study over a 12-year period

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Abstract

Objective: To determine the incidence of adverse drug reactions (ADRs) among elderly hospitalized patients; to describe observed ADRs with respect to responsible drug classes; and to examine whether comorbid conditions, patient's age and other socio-demographic factors are associated with recurrent events of ADRs.

Design: Population-based retrospective cohort study using administrative and patient hospital discharge records.

Setting: All acute care hospitals in the Canadian province of Newfoundland and Labrador.

Participants: 64,446 patients aged ≥65 years who had at least one hospital admission over a period of 12 years (April 1, 1995 to March 31, 2007).

Main outcome: Number and incidence density of ADRs.

Results: 4,056 (6.3%) patients had a total of 4,858 ADRs ranging from 1 to 8 per patient. The incidence of ADRs was 15.2 per 1,000 person-years (95% confidence interval 14.8 to 15.7). The most common drug categories implicated in ADRs were cardiovascular agents (17.7%), followed by analgesics/antipyretics/anti-inflammatory drugs (16.1%), systemic agents (11.8%) and agents affecting blood constituents (9.7%). A strong dose-response relationship was found between Charlson comorbidity index

(CCI) and recurrent events of ADR (Rate ratio 1.67, 95% confidence interval 1.41 to 1.98 for CCI 2–3; 2.38, 1.98 to 2.87 for 4–5; 3.83, 3.21 to 4.57 for ≥6). Comorbid congestive heart failure (1.58, 1.33 to 1.89), connective tissue disorder (1.57, 1.07 to 2.29), dementia (3.91, 2.48 to 6.17), diabetes (with complications) (2.42, 1.64 to 3.56), cancer (3.12, 2.58 to 3.76), metastatic cancer (1.49, 1.05 to 2.11), peptic ulcer diseases (1.82, 1.34 to 2.49) and renal diseases (2.17, 1.55 to 3.04) were strong predictors. Rural areas (1.22, 1.01 to 1.46) were associated with increased risk for experiencing recurrent ADRs, whereas advancing age and sex had no effect on recurrent ADRs.

Conclusions: Comorbidity from chronic diseases and the severity of patient's underlying illness, rather than individual characteristics (advancing age and sex), increased the likelihood of recurrent events of ADR in elderly hospitalized patients. Substantial changes in the organization and delivery of health care that focus on the monitoring of prescribed drugs in elderly patients with comorbidities could mitigate the recurrence of ADRs.

Introduction

Adverse drug reactions (ADRs) are a major public health problem given such events are the most common type of injuries experienced by hospitalized patients [1]. ADRs may lead to hospitalization, or occur during hospitalization and contribute to an increased length of stay. The recent focus on patient safety and the concern about the number of negative outcomes resulting from drug use, rather than the underlying diseases, has prompted health care professionals to take a critical look at these drug responses. A series of studies examined ADRs among hospitalized patients in USA and Australia [2-6], however, much less information is available about these events in hospitalized patients in Canada. A meta-analysis by Lazarou et al. revealed the incidence of serious ADRs in patients during hospitalization and those admitted to hospital in the United States as 2.1% and 4.7%, respectively [6]. The study reported ADRs as being the fourth and sixth leading cause of death. Other studies indicated ADRs occurred in 2-20% of hospitalized patients [4, 5]. Recently, Baker et al. [7] provided the first national estimate of the incidence of adverse events among adult patients in Canada (7.5 per 100 hospital admissions). After extrapolation, the number of hospital admissions attributed to adverse events was estimated between 141,250 and 232,250 in 2000. Furthermore, Canadian incident reporting data indicated a 35% increase of adverse reactions from 2008 to 2009 [8].

Adverse drug reactions are common and can have serious consequences in an older population. According to a recent census report, the Canadian population is aging rapidly. The growth rate in Canadians over the age of 65 years was more than double (12%) the rate of overall population increase (5%) in the 5-year period from 2001 to 2006, and, at present, the Canadian senior population represents about 14% of the total population, up from about 10% in 1981 [9, 10]. Elderly individuals are vulnerable to ADRs because of the multiple drugs they take to manage multiple comorbid conditions and because of pharmacokinetics and pharmacodynamics changes [6, 11]. Furthermore, ADRs can be recurrent events, in that an individual may experience one or more such events over a period of time. It is important to identify the magnitude of ADRs in this high risk group to aid physicians in their decisions about prescribing, delivering and monitoring of drug therapy. If predictive factors can be identified, this would allow providers to identify early symptoms of ADRs, and to respond to them quickly [12].

Although prior research has identified several risk factors for the occurrence of ADRs among older adults (e.g., age, female sex, drug regimen, type of drugs, and comorbidities) [6, 12-16], little is known about the risk factors associated with recurrent events of ADR. For public-health planning and the evaluation of quality management programs, it is important to study recurrent ADRs, rather than only the first event [17]. Because the risk of both health service utilization and the burden of illness increase with each subsequent ADR, the number of ADRs is a more robust indicator of risk than a

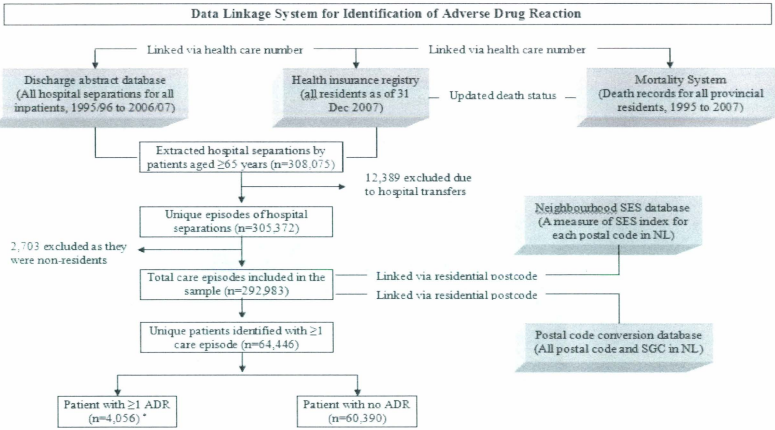
single event[18]. The objectives of this paper are to: (1) estimate the incidence of ADR among elderly hospitalized patients, (2) characterize observed ADRs with respect to responsible drug classes, and (3) examine whether comorbid conditions, patient's age, or other socio-demographic factors are associated with recurrent ADRs in elderly hospitalized patients.

Methods

Study design and data sources

We conducted a population-based retrospective cohort study using province-wide administrative data on hospital separations from all community- and teaching-based acute care hospitals in Newfoundland and Labrador (NL): a province with 506,000 population (2007). The study population consisted of all residents aged ≥65 years (at first hospital separation) with at least one hospital admission during the study period from April 1, 1995 to March 31, 2007. The study data were derived through a data linkage system that linked five administrative health databases: 1) discharge abstract database (DAD), 2) health insurance registry database, 3) mortality system, 4) neighborhood socioeconomic status (SES) database, and 5) postal code conversion database (Figure 4.1).

The DAD is the hospital separation database containing the patient health care number, care episode number, date of admission, date of separation (i.e., transfer, discharge, or in patient death); nomenclature from the international classification of diseases (ICD) codes for main diagnosis and up to 24 additional diagnoses and up to 10 medical procedures. Patient's hospital records were coded in the DAD using ICD-9 from April 1, 1995 to March 31 2001 and ICD-10-CA from April 1, 2001 to March 31, 2007. The health insurance registry is a comprehensive plan of medical care insurance for the residents of NL. This database contains participants demographic information including, health care number, date of birth, sex, postal code of residence, insurance start and end date. The mortality system includes data compiled from provincial death notifications provided by the provincial Vital Statistics Division. The neighborhood SES database contains a measure of SES for each postal code within NL. This database contains participants demographic information including, health care number, date of birth, sex, postal code of residence, insurance start date and end date. The mortality system includes data compiled from provincial death notifications provided by provincial vital statistics division. The neighborhood SES database contains a measure of SES for each postal code within NL. The SES score, developed by Audas, Cirtwill, and O'Keefe (2007) [19], is a composite value based on a number of measures related to social and economic conditions, including employment, education, and income from the 2001 census. The overall SES scoring system provides a numerical scale ranging from -24.0 to +24.0, where -24.0 indicates "poorest" SES and +24.0 is "richest" SES.



ADR= Adverse drug reaction; SES=Socio-economic status; NL=Newfoundland and Labrador;
The shaded boxes indicate the database used for data linkage and boxes with solid border indicate the number of records extracted.
* Number of ADRs experienced by each patient ranged from 1 to 8, resulting a total of 4858 ADRs.

Figure 4.1. Illustrative flowchart for data linkage system to identify ADRs in the elderly hospitalized patients

Data linkage

Patient records across all databases, with exception of the neighborhood level SES database, were individually linked using patient's health care number as the unique identifier. A de-identified study ID was assigned to each patient and identifiable information was removed to protect patient privacy. A SES score was assigned to each study subject by linking their record to the neighbourhood SES database by residential postcode. Ethics approval was obtained from the Human Investigation Committee of Memorial University of Newfoundland.

Definition and identification of ADR

We studied ADRs that either caused a hospital admission or extended an existing patient's hospital stay. We adopted the definition of ADR from Edwards and Aronson [20]: "An appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen or withdrawal of the product". We have chosen to use the term 'adverse drug reaction' rather than adverse drug event (ADE) given that according to the definition of these terms

[3, 20], we believe that ADR is the most appropriate term for our data as it does not include medication errors.

External causes of injury associated with the use of a drug were recorded in the DAD using either E-code (E930 - E949) for ICD-9 or Y-code (Y40-Y59) for ICD-10-CA. These codes include any adverse effects caused by correct drugs use, medicines or biological substances properly administered in therapeutic or prophylactic doses, but exclude accidental overdoses of a drug, wrong drug given or taken in error, accident in technique of administration of drug, and abuse of a drug. Because a patient might have been transferred from one hospital to another before discharge, we checked all records for transfer between hospitals and, if admissions were as a result of transfer, we combined them into a single episode for analysis to avoid a possible double counting of an ADR. We excluded records of hospital separations related to non-residents of NL (0.9%) since, unlike residents of NL, they did not have a health care number or any other unique identifier to carry out linkage between data sets.

Primary outcome measure

Our primary outcome measure was the number of ADRs occurring during the study period for existing hospital patients or those that resulted in hospital admission. We

included patients meeting all inclusion criteria as a cohort and followed them up from the first hospital separation (since April 1, 1995) until the insurance end date due to death, termination of insurance coverage for another reason (e.g., moving out of province), or end of study (March 31 2007). Drugs responsible for ADRs were obtained from the E- or Y-codes on the hospital separation data.

Other variables

Patient related factors considered for analysis included baseline age, individual comorbidity, severity of illness as measured by Charlson comorbidity index (CCI), sex, SES and residential locality (urban/rural). Comorbidity at baseline was estimated using the CCI which is a weighted score of 17 comorbidities that was initially used to predict in-hospital and 1-year mortality [21], and subsequently adapted for use with administrative data with the ICD-9 and ICD-10-CA [22-23]. We calculated CCI scores by adding scores assigned to each specific diagnosis (Table 4.1). To account for patients that did not have an illness within the 17 predefined conditions, a relative weight was given to address the issue of missing CCI scores when a patient appeared to have an illness equally severe but not related to one of those 17 comorbidities. The relative weight assigned was based on the subjective assessment by a physician and a registered nurse, who reviewed the complete list of patients' health conditions. Since the study population consisted of only elderly patients who were likely to have many comorbid conditions, assigning such

relative weights judged to be more appropriate than modifications of Charlson index previously highlighted [24]. Given that we were interested in non-ADR comorbidity, ADR was not included in assigning such weights. Note that comorbidity in this article means co-existing health conditions since we considered primary diagnosis and other diagnosis for health conditions contributing patients to be hospitalized. A higher score on the Charlson index indicated a greater burden of comorbid disease. Subjects were grouped into four CCI categories: 0–1 (least severe), 2–3, 4–5 and ≥6 (most severe). About 0.39% of study subjects had missing SES and therefore values were imputed using median value imputation method [25]. Because SES indicators were not available for individuals, a measure of neighborhood level SES score, including continuous values of the indexes, was grouped into quintiles.

Table 4.1: Charlson comorbidity conditions (with weights) present at baseline in hospitalized patients aged 65 years and older, Newfoundland and Labrador, 1995/96 -2006/07

Charlson's comorbid conditions [†]	Weight
Acute myocardial infarction	1
Congestive heart failure	1
Peripheral vascular disease	1
Cerebrovascular disease	1
Dementia	1
Chronic pulmonary disease	1
Connective tissue disorder	1
Peptic ulcer disease	1
Mild liver disease	1
Diabetes (mild to moderate)	1
Diabetes with complication	2
Paraplegia	2
Renal disease	2
Cancer [‡]	2
Metastatic cancer	6
Severe liver disease	3

[†] although AIDS was one of the comorbid conditions in the Charlson index, no patients were found with a diagnosis of AIDS in our study sample.
[‡] includes any malignancy such as lymphoma, leukemia.

Statistical Analysis

Descriptive statistics on ADR incidence were calculated by patients' baseline characteristics with the drugs responsible for the ADRs described in percentages. We calculated incidence density of ADRs per 1,000 person-years for age groups, sex, CCI severity scores, residential locality (urban/rural) and SES. Distribution of the drug categories (at the three-digit E-code and two-digit Y-code level) implicated in the ADR-related hospitalizations and further detail on the drug groups (at the four-digit E-code and three-digit Y-code level) most commonly responsible for ADRs were calculated based on the total number of ADRs following a classification system that was a modified version of the classification developed by Zhang et al.[6].

We tested the overdispersion by using the goodness-of-fit statistical test proposed by Bohning [26]. To account for the complexity in data characterized by excess zeros and overdispersion, we considered several modeling strategies in an effort to find the most appropriate model for this analysis. We fitted Poisson, negative binomial (NB), zero-inflated Poisson, (ZIP) and zero-inflated negative binomial (ZINB) regressions models (see Appendix F for details about these models) using the number of ADRs experienced by a patient as the dependent variable. Age (as a continuous variable), sex, CCI severity category, SES and residential locality were included in the models to adjust for differences in case mix of patients. To account for potential biases due to differences in

the observation periods we computed the logarithm of follow-up time (measured in months) as an offset variable [27]. The likelihood ratio test (LRT) was used to test if over-dispersion was present in the data while the Vuong test was used to assess if zero-inflation was present [28]. In the final analysis the model that proved to be the most appropriate was the ZINB model.

A separate regression analysis was repeated after replacing the CCI severity category by a set of comorbid condition indicator variables: acute myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disorder, peptic ulcer disease, mild liver disease, diabetes (mild to moderate), diabetes with complication, paraplegia, renal disease, cancer, metastatic cancer and severe liver disease. Referring it to as a rate ratio (RR), the effect of predictor was described using the incidence rate ratio to report an incidence of ADR increase using a relative rate. The Wald test [29] was used to assess whether the model coefficients were significantly different from zero (α=0.05). We used SAS 9.2 and R 2.8.1 for our analysis. For regression models, we used PROC COUNTREG in SAS 9.2

Results

There were a total of 308,075 hospital separations, of which 12,389 were excluded due to hospital transfers and 2,703 were identified with non-resident patients. The final number of separations included in the study was 292,983.

For the study sample of 64,446 patients (male 47.9%; female 52.1%), the total person-years of follow-up was 319,207. For the full 12-year study period, 4,056 (6.3%) patients were identified having experienced a total of 4,858 ADRs with the number of ADRs experienced by each of 4,056 patients ranging from 1 to 8. Table 4.2 presents the distribution of the 20 broad categories of drugs implicated in ADR-related hospitalizations. The most common drug categories implicated in ADRs were cardiovascular agents (17.7%), followed by analgesics/antipyretics/anti-inflammatory (16.1%), systemic (11.8%) and blood constituents (9.7%).

Table 4.2: Drug categories [*] responsible for adverse drug reactions (ADRs) in hospitalized patients aged 65 years and older, Newfoundland and Labrador, 1995/96 -2006/07

Drug category [‡]	ICD-9	ICD-10-CA	No. (%) [†] of ADR
Systemic antibiotics [§]	E930	Y40	310 (6.4)
Other systemic anti-infectives/ antiparasitics	E931	Y41	89 (1.8)
Hormones (including synthetics and antagonists)	E932	Y42	368 (7.6)
Primarily systemic agents	E933	Y43	574 (11.8)
Agents primarily affecting blood constituents	E934	Y44	473 (9.7)
Analgesics/antipyretics/anti-inflammatory drugs	E935	Y45	780 (16.1)
Antiepileptics/antiparkinsonian drugs	E936	Y46	151 (3.1)
Sedatives, hypnotics, antianxiety drugs	E937	Y47	75 (1.5)
Anaesthetics and therapeutic gases	E938	Y48	47 (1.0)
Psychotropic drugs [‖]	E939	Y49	242 (5.0)

Drug category ‡	ICD-9	ICD-10-CA	No. (%) † of ADR
Drugs primarily affecting autonomic nervous system ¶	E941	Y51	153 (3.2)
Agents primarily affecting cardiovascular system	E942	Y52	858 (17.7)
Agents primarily affecting gastrointestinal system	E943	Y53	34 (0.7)
Agents affecting water balance/minerals/uric acid **	E944	Y54	233 (4.8)
Agents affecting muscles/respiratory system	E945	Y55	63 (1.3)
Topical agents affecting skin, eyes, ENT, dental	E946	Y56	104 (2.1)
Other and unspecified drugs and medicines	E947	Y57	296 (6.1)
Bacterial vaccines	E948	Y58	4 (0.1)
Other and unspecified vaccines/biologicals	E949	Y59	4 (0.1)
Total			**4858 (100.0)**

ADR= Adverse drug reaction; ICD= International classification of diseases; ENT=ear, nose, throat.

* Drugs responsible for ADRs obtained from the E-codes (ICD-9) or Y-codes (ICD-10-CA) of the diagnosis variable in the hospital separation data;

† Percent were calculated with respect to 4,858 ADRs.

‡ The name of drug category was chosen according to the definition of the corresponding Y-codes in the ICD-10-CA.

[§] Excludes antineoplastic antibiotics (E930.7) from ICD-9 (were added to primarily systemic agents, which include antineoplastics).
[‖] Excludes benzodiazepines (E939.4) from ICD-9/ICD-9-CM (were added to group sedatives, hypnotics, antianxiety drugs, which includes benzodiazepines in ICD-10).
[¶] Excludes sympatholytics (E941.3) from ICD-9/ICD-9-CM (were added to agents primarily affecting cardiovascular system, which include these in ICD-10).
[**] Excludes theophylline (E944.1) from ICD-9/ICD-9-CM (was added to agents affecting muscles/respiratory system, which includes antiasthmatics).

Specific details on the top 30 drug groups most often implicated with ADRs are presented in Table 4.3. The drugs most frequently associated with ADRs were antineoplastics or immunosuppressive drugs, coronary vasodilators/cardiac rhythm regulators and other antihypertensive drugs, cardiac stimulant glycosides or similar drugs, anticoagulants and NSAIDs/antirheumatics agents.

The overall incidence of ADRs was 15.2 per 1,000 person-years (95% CI, 14.8 to 15.7). Based on this univariate analysis, the incidence of ADR appeared to be greater among those who were older, female, having higher severity of illness, higher level of SES (4th and 5th quintile) and living in urban areas (Table 4.4). These variables were then included as potential predictors of the number of ADRs.

Table 4.3: Top 30 drug groups* most commonly implicated in adverse drug reactions (ADRs) in hospitalized patients aged 65 years and older, Newfoundland and Labrador, 1995/96 -2006/07

Drug groups ‡	ICD-9	ICD-10-CA	No. (%)† of ADR
Systematic Antibiotics			
Other systematic antibiotics	E9308	Y408	89 (1.8)
Unspecified systematic antibiotics	E9309	Y409	86 (1.8)
Penicillins	E9300	Y400	44 (0.9)
Cephalosporin	E9305	Y401	43 (0.9)
Sulfonamides	E9310	Y410	38 (0.8)
Hormones (including synthetics and antagonists)			
Glucocorticoids and synthetics	E9320	Y420	197 (4.1)
Insulins and oral antidiabetic drugs	E9323	Y423	125 (2.6)
Primarily systematic agent			

Drug groups [‡]	ICD-9	ICD-10-CA	No. (%)[†] of ADR
Antineoplastic/immunosuppressive drugs	E9331/E9307	Y431-4	537 (11.1)
Agents primarily affecting blood constituents			
Anticoagulants	E9342	Y442	377 (7.8)
Thrombolytic drugs	E9344	Y445	24 (0.5)
Analgesics/antipyretics/anti-inflammatory drugs			
NSAIDs and antirheumatics	E9354	Y452-4	367 (7.6)
Opioids and related analgesics	E9350	Y450	159 (3.3)
Salicylates adverse effect Rx use	E9351	Y451	147 (3.0)
Other analgesics/antipyretics /antirheumatoid agents	E9358-9	Y458-9	66 (1.4)
4-Aminophenol derivatives (e.g., acetaminophen)	E9352	Y455	41 (0.8)
Antiepileptics and antiparkinsonian drugs			

Drug groups [‡]	ICD-9	ICD-10-CA	No. (%)[†] of ADR
Hydantoin derivatives	E9361	Y462	62 (1.3)
Other and unspecified antiepileptics	E9363	Y466	49 (1.0)
Antiparkinsonism drugs	E9364	Y467	22 (0.5)
Psychotropic drugs			
Antipsychotics/ neuroleptics	E9391-3	Y493-5	112 (2.3)
Antidepressants	E9390	Y490-2	72 (1.5)
Benzodiazepines	E9394	Y471	72 (1.5)
Agents primarily affecting cardiovascular system			
Coronary vasodilators/cardiac rhythm regulators and other antihypertensive	E9420 /E9424-6	Y517 /Y521-525	504 (10.4)
Cardiac stimulant glycosides/similar drugs	E9421	Y520	415 (8.5)
Agents affecting water balance, mineral/uric acid metabolism			

Drug groups [‡]	ICD-9	ICD-10-CA	No. (%)[†] of ADR
Loop and other diuretics	E9444	Y544-5	118 (2.4)
Uric acid metabolism drugs (such as colchicine)	E9447	Y548	47 (1.0)
Benzothiadiazine derivatives	E9443	Y543	41 (0.8)
Agents affecting muscles/respiratory systems			
Antiasthmatics (including theophylline)	E9441/E9457	Y556/Y515	46 (0.9)
Topical agents affecting skin, eyes, ENT, dental			
Local anti-infectives/ anti-inflammatory drugs	E9460	Y560	93 (1.9)
Other and unspecified drugs and medication			
Other drugs or medicines	E9478	Y578	136 (2.8)
Unspecified drugs or medicines	E9479	Y579	130 (2.7)

ADR= Adverse drug reaction; ICD= International classification of diseases; NSAIDs= Non-steroidal anti-inflammatory drugs; ENT=ear, nose, throat.
[‡] Drugs responsible for ADRs obtained from the E-codes (ICD-9) or Y-codes (ICD-10-CA) of the diagnosis variable in the hospital separation data;
[†] Percent were calculated with respect to 4,858 ADRs.

‡ The name of drug category was chosen according to the definition of the corresponding Y-codes in the ICD-10-CA.

Table 4.4: Descriptive data on ADR incidence by age, sex, comorbidity and severity of illness

	n	P-Y follow-up	No. of ADR	Incidence/ 1,000 P-Y (95% CI)
All individuals	64,446	319,207	4,858	15.2 (14.8, 15.7)
Age at baseline (years)				
65-74	33,487	190,976	2,696	14.1 (13.6, 14.7)
75-84	23,552	106,519	1,752	16.4 (15.7, 17.2)
≥85	7,407	21,712	410	18.9 (17.1, 20.7)
Sex				
Male	30,867	14,6084	2,166	14.8 (14.2, 15.5)
Female	33,579	17,3123	2,692	15.5 (15.0, 16.1)

	n	P-Y follow-up	No. of ADR	Incidence/ 1,000 P-Y (95% CI)
CCI severity				
0-1 (least severe)	26,570	146,108	1,329	9.1 (86.1, 95.9)
2–3	21,307	106,238	1,523	14.3 (13.6, 15.1)
4–5	8,132	37,882	872	23.0 (21.5, 24.6)
>=6 (most severe)	8,437	28,979	1,134	39.1 (36.9, 41.4)
Socioeconomic status				
1st Quintile (poorest)	12,836	62,490	859	13.8 (12.8, 14.7)
2nd Quintile	12,714	64,058	857	13.4 (12.5, 14.3)
3rd Quintile	12,363	61,733	810	13.1 (12.2, 14.0)
4th Quintile	13,289	66,429	1,283	19.3 (18.3, 20.4)
5th Quintile (richest)	13,244	64,496	1,049	16.3 (15.3, 17.3)

	n	P-Y follow-up	No. of ADR	Incidence/ 1,000 P-Y (95% CI)
Residential locality				
Urban	25,280	125,277	2,193	17.5 (16.8, 18.2)
Rural	39,166	193,930	2,665	13.7 (13.2, 14.3)

P-Y= Person-year; ADR=adverse drug reaction; CI=Confidence interval; CCI=Charlson comorbidity index

Model results and comparison

Out of 64,446 patients, 60,390 (93.7%) were found with zero value of ADR count, with the sample variance ($s^2 = 0.10$) exceeding the sample mean ($\bar{x} = 0.08$). According to the goodness-of-fit testing, the overdispersion test was statistically significant (O=64.14, $p<0.001$). This indicated that the Poisson model was not appropriate for describing the ADR count data. Predicted probabilities of 'null' models were compared with the observed probability of the ADR counts (Figure 4.2a-b). Due to the large proportions of zeroes which tends to flatten the distribution for ADR count ≥ 1 in Figure 4.2a, the same probabilities excluding those for ADR count=0 were plotted in Figure 4.2b. Clearly, the Poisson and ZIP models were a poor fit. Both underestimated the probability at ADR count=0 and overestimated at ADR count =1. There was somewhat under-prediction by the Poisson model and over-prediction by the ZIP model for ADR count ≥ 2. The NB and ZINB models made better predictions for the entire range of ADR count values. This important fact suggested exclusion of the Poisson and ZIP models due to poor fit, and to do the model comparison between the NB and ZINB regressions.

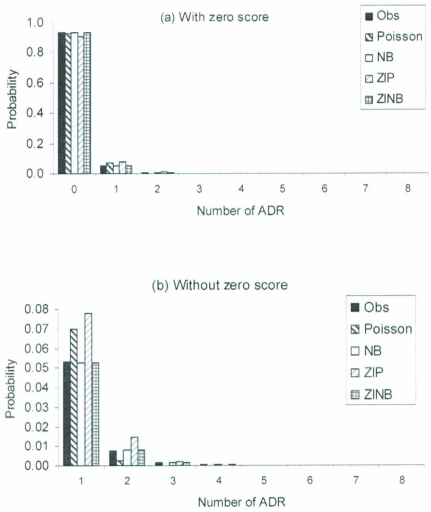


Figure 4.2. Predicted probabilities of intercept-only Poisson, NB, ZIP and ZINB models compared with the observed probabilities of ADR counts. (a) with zero score, (b) without zero score.

In the regression analysis of NB model, the test of dispersion parameter, alpha, indicated significant over-dispersion (t =21.36, p<0.001). When comparing the NB to Poisson, the likelihood ratio test gave a highly significant chi-square value (χ^2=1548.0, p<0.001). These results were consistent with the results of Bohning's over-dispersion test which was statistically significant, and indicated that NB model is preferred over Poisson model. In comparing ZIP and ZINB models, we found that the ZINB model was more favorable than the ZIP model, given that the LR test statistic was significant (χ^2=42.0, p<0.01). The Vuong test statistics of V= -12.9 (p<0.001) indicated that ZIP model fitted better than Poisson model, and ZINB model fitted better than NB model (V=-3.06, p<0.001). Additionally, based on the AIC values for the regression models (Poisson=36,576; NB=35,025; ZIP=34,296; and ZINB=34,256), the ZINB model appears to be fitted slightly better compared to the other models.

As demonstrated above, our analysis indicated that the ZINB model most accurately reflected the data; which means over-dispersion was as a result of unobserved heterogeneity, temporal dependency, as well as excess zeroes. Therefore, we considered results only from the ZINB regression model when interpreting predictors of ADRs.

Identifying and interpreting significant predictors

The results of the ZINB regression analysis to the ADR counts with the predictor variables are presented in Table 4.5. This model produced two sets of parameter estimates. First, a logistic procedure yielded the odds ratios (ORs), given in the right half of the table, predicting the odds of "zero" ADRs. The left side of the table contains the rate ratios (RRs) for the NB component of ZINB analysis. With a focus on predictors of recurrent event of ADR, only RRs have been considered for interpreting significant predictors to indicate the relative change in the number of ADRs according to the change in the level of a specific predictor variable. Patients with CCI score of 2-3 had a 67% increase in the number of ADR compared to patients having a CCI score 0-1 (RR=1.67, 95% confidence interval 1.41 to 1.98). Compared to patients with CCI score 0–1, patients with a CCI score 4–5 were more than twice as likely to experience an ADR (2.38, 1.98 to 2.87), whereas those with a CCI score ≥6 were at 4 times the risk (RR=3.83, 3.21 to 4.57). Similarly, a patient classified in the 4th quintile of the neighbourhood SES class had a 50% increase in the number of ADRs compared to a patient classified in the 3rd SES quintile (1.50, 1.21 to 1.86). No other SES categories were significant. There was a 22% percent increase in the number of ADRs for rural patients compared to their urban counterparts (1.22, 1.01 to 1.46). Age and sex were not significant predictors of the number of ADRs.

Table 4.5: Zero-inflated negative binomial regression predicting the occurrence and number of ADRs according to the selected patient-related factors (n=64,446)

	Negative binomial component		Logistic component	
Variable	**RR**	**95% CI**	**OR**	**95% CI**
Age (years)	1.00	0.99 to 1.01	1.01	0.99 to 1.02
Sex				
Male	Reference		Reference	
Female	0.95	0.85 to 1.07	0.83	0.71 to 0.98
CCI Severity				
0–1 (least severe)	Reference		Reference	
2–3	1.67	1.41 to 1.98	1.09	0.86 to 1.39
4–5	2.38	1.98 to 2.87	0.90	0.69 to 1.17
≥6 (most severe)	3.83	3.21 to 4.57	0.88	0.68 to 1.12
Socioeconomic status				

	Negative binomial component		Logistic component	
Variable	**RR**	**95% CI**	**OR**	**95% CI**
1st Quintile	0.97	0.79 to 1.19	0.91	0.69 to 1.20
2nd Quintile	0.97	0.79 to 1.18	0.89	0.67 to 1.19
3rd Quintile	Reference		Reference	
4th Quintile	1.50	1.21 to 1.86	1.17	0.85 to 1.60
5th Quintile	1.17	0.96 to 1.42	1.02	0.77 to 1.35
Residential locality				
Urban	Reference		Reference	
Rural	1.22	1.01 to 1.46	1.39	1.06 to 1.81

ADR=adverse drug reaction; CCI=Charlson comorbidity index; RR= Rate ratio (indicating relative change in number of ADRs); OR=Odds ratio (indicating odds of zero ADR); CI=Confidence Interval

Table 4.6 presents the ZINB analysis for individual comorbid conditions. RRs for the NB component indicated that patients with congestive heart failure (1.58, 1.33 to 1.89), connective tissue disorders (1.57, 1.07 to 2.29), peptic ulcer diseases (1.82, 1.34 to 2.49) and metastatic cancer (1.49, 1.05 to 2.11) experienced a significant increase in the number of ADRs compared to those patients without these comorbidities. Patients having diabetes with complications (2.42, 1.64 to 3.56) or renal diseases (2.17, 1.55 to 3.04) were more than twice as likely to experience ADRs, while those having dementia (3.91, 2.48 to 6.17) or cancer (3.12, 2.58 to 3.76) were more than three times at risk compared to patients without these conditions.

Table 4.6: Zero-inflated negative binomial regression predicting the occurrence and number of ADRs according to the Charlson comorbidities [*], (n=64,446)

Charlson's comorbid conditions [†]	No. (%) of patients	No. (%) of patients with ADR	Negative binomial component		Logistic component	
			RR	95% CI	OR	95% CI
Acute myocardial infarction	4120 (6.4)	318 (7.8)	1.08	0.88 to 1.32	0.76	0.55 to 1.05
Congestive heart failure	4269 (6.6)	413 (10.2)	1.58	1.33 to 1.89	0.74	0.55 to 0.99
Peripheral vascular disease	1581 (2.5)	107 (2.6)	0.91	0.64 to 1.29	0.77	0.44 to 1.37
Cerebrovascular disease	3514 (5.5)	240 (5.9)	1.07	0.83 to 1.38	0.70	0.46 to 1.06
Dementia	1057 (1.6)	55 (1.4)	3.91	2.48 to 6.17	6.21	3.59 to 10.74
Chronic pulmonary disease	4452 (6.9)	394 (9.7)	1.10	0.91 to 1.32	0.61	0.44 to 0.83

Charlson's comorbid conditions †	No. (%) of patients	No. (%) of patients with ADR	Negative binomial component		Logistic component	
			RR	95% CI	OR	95% CI
Connective tissue disorder	485 (0.8)	72 (1.8)	1.57	1.07 to 2.29	0.55	0.29 to 1.04
Peptic ulcer disease	926 (1.4)	116 (2.9)	1.82	1.34 to 2.49	0.82	0.52 to 1.30
Mild liver disease	146 (0.2)	9 (0.2)	0.91	0.33 to 2.51	0.58	0.09 to 3.90
Diabetes (mild to moderate)	5746 (8.9)	522 (12.9)	1.17	0.99 to 1.37	0.68	0.52 to 0.88
Diabetes with complication	706 (1.1)	66 (1.6)	2.42	1.64 to 3.56	1.28	0.72 to 2.30
Paraplegia	293 (0.5)	26 (0.6)	1.49	0.77 to 2.86	1.06	0.34 to 3.29
Renal disease	940 (1.5)	92 (2.3)	2.17	1.55 to 3.04	0.99	0.55 to 1.78
Cancer ‡	6882 (10.7)	448 (11.0)	3.12	2.58 to 3.76	2.47	1.95 to 3.13

Charlson's comorbid conditions †	No. (%) of patients	No. (%) of patients with ADR	Negative binomial component		Logistic component	
			RR	95% CI	OR	95% CI
Metastatic cancer	1782 (2.8)	96 (2.4)	1.49	1.05 to 2.11	1.30	0.79 to 2.14
Severe liver disease	101 (0.2)	6 (0.1)	1.42	0.38 to 5.26	0.94	0.12 to 7.37

ADR=adverse drug reaction; SES=Socioeconomic status; RR= Rate ratio (indicating relative change in number of ADRs); OR=Odds ratio (indicating odds of zero ADR); CI=Confidence Interval

* Model includes age, sex, SES and residential locality

† although AIDS was one of the comorbid conditions in the Charlson index, no patients were found with a diagnosis of AIDS in our study sample.

‡ includes any malignancy such as lymphoma, leukemia.

Discussion

In this population-based cohort of 64,446 elderly hospitalized patients, the incidence of ADRs was found to be 15.2 per 1,000 person-years over a 12-year period. The most common drug category implicated in the ADRs was cardiovascular agents, while antineoplastics or immunosuppressive, anticoagulants and NSAIDs/antirheumatics were the specific drug groups most often contributing. Comorbidities from chronic diseases, rather than advancing age, were the single-most important factor associated with ADR-related hospitalizations. Specifically, congestive heart failure, dementia, chronic pulmonary disease, connective tissue disorder, peptic ulcer disease, diabetes with complications, renal disease, cancer and metastatic cancer were all strong predictors of the number of ADRs experienced. Patients living in rural areas were also associated with increased risk for ADRs.

The contribution of ADRs to hospital admissions or prolonging hospital stays has been investigated in several studies [3-4, 30-33]. The proportion of ADR-related hospitalizations varied from 1% to 35% in patients of all ages [30], and from 3% to 24% in an older population [3, 30, 32-33]. Studies based on meta-analyses estimated the range of ADR incidence in Australia from 2.4% to 3.6% [4] and in North America from 3.1% to 6.2% [3]. As highlighted by Alexopoulou et al. [31], ADR-related hospital admissions in European

studies varied from a minimum of 1.8% in the Netherlands to a maximum of 9.2% in the UK. Clearly, the incidence of ADR-related hospitalization in the elderly population that we observed (1.52 per 100 person-years) is at the lower end of previously reported research. The low incidence in our study may be explained by two factors. First, because our study subjects had different durations of follow-up, we calculated incidence rate by dividing the number of ADRs by the length of follow-up. Although this is the most meaningful denominator for quantifying risk [18], most previous research did not consider person-time at risk when estimating incidence rate, which may have contributed to a higher-incidence than that of our study. A second factor is that the incidence of drug-related hospitalizations and ED visits appears to be lower in Canadian population compared to other nations [7, 34], although further work is needed to confirm these findings.

A major risk factor for recurrent events of ADR identified in our study was the burden of illness. Since there is a lack of longitudinal data examining predicting factors associated with the frequency of ADRs, comparison with other studies is challenging. A recent Australian study by Zhang et al. [6] reported that comorbidities, rather than age, increased the rate of repeat ADRs among hospitalized patients aged ≥60 years; most of the Charlson comorbidity conditions were found as predictive factors for ADRs. Although the primary outcome variable of Zhang's study (i.e., occurrence of a repeat admission for an ADR) was slightly different from that of our study (i.e., count of frequent occurrences of ADR), our results were consistent with factors that predicted

repeat admissions for ADRs in the Australian population. A US study among nursing home residents also found that both the number of medical problems and the burden of illness (as measured by CCI) were associated with ADEs (which includes ADRs) [12].

Elderly patients are at greater risk of serious injury from adverse events than younger patients [2, 35-36]. However, in our analysis of hospitalized patients aged 65 years and older, age was not independently predictive of the number of ADRs, rather we found a strong dose-response relationship between severity of illness and the recurrence of ADRs. This suggests that within a restricted elderly age range in which multiple comorbidities can be expected, age *itself* may not increase the likelihood of an ADR. This finding is consistent with other studies confined to older age groups [6, 37-38]. A positive relationship between age and drug related health problems have been found in studies using all ages [37]. Reasons for an increased risk for rural patients and patients living in middle-high class neighborhood (4th quintile of SES) are not clear. To our knowledge, the same risk factors for recurrent events of ADRs or first-time ADR have not been previously investigated.

Strengths and limitations

An important limitation of our study is the absence of drug data in the DAD. It is worthwhile to note that our analyses of the relationship between patient-related factors and ADRs did not focus on identifying specific drugs or drug groups that contributed to ADRs. Rather, we presented descriptive data on drug categories found to be primarily responsible for ADRs. Being unable to include the number of drugs in the list of independent variables should not have a significant impact on the observed relationship between ADRs and other factors in our study, given that counts of medical conditions and number of drugs taken are likely to be correlated, and thus not generally used simultaneously in multiple regression modeling [12]. The findings of a disproportionately high contribution of cardiovascular and systematic agents including antineoplastic or immunosuppressive drugs, NSAIDs, and anticoagulants to ADRs are similar to those from earlier studies of persons aged ≥65 years in hospital setting [37, 39-40]. A likely explanation for this finding is that these were the most common medication groups taken by the elderly population [37], and would be the most frequently implicated drugs for ADRs [37, 40-41].

In studies that use administrative data, variations in clinical coding may influence outcomes. While the accuracy of diagnosis is important, we could not perform a sensitivity analysis. A validation study reviewing the coding practices in Canada found a

relatively high sensitivity of 82% considering the top 50 most responsible diagnosis [42]. However, another study which validated the coding practices for drug-related events, which is similar to the one used in the present study, found that the ADR identifying algorithm had a relatively low sensitivity (56%) and high specificity (100%) [43]. The low sensitivity indicates that the clinical coding of drug relative events is less accurate in the DAD compared to disease coding, which may have led us to under-estimate the true burden of ADRs in this population.

Finally, our outcome of interest was the number of ADRs that either caused hospital admission or extended an existing patient's length of stay, whereas most ADRs (~90%) are fairly minor [41] and occur in the community without admission to hospital. Therefore, our findings of ADR incidence rate should be interpreted just as 'the tip of the iceberg', given we only considered hospital admission, which represent only the most severe adverse reactions to medication.

The strength of our study includes the cohort design with population-based longitudinal administrative data. This design allowed us to identify recurrent events of ADRs experienced by patients, regardless of changes in the treating hospitals. Having a unique health care number is an advantage of the universal health care system in Canada that allowed us to link all relevant administrative data. In fact, 99% of hospital records

were successfully linked to the other health care data, thus allowing us to overcome issues related to selection and recall bias.

Previous studies experienced an issue of under-ascertainment of Charlson comorbidity index score because a patient may have an illness beyond the 17 illness used for CCI score [6, 44]. We have overcome this limitation by assigning a relative score for the illness that is equivalently severe to 1 of 17 listed comorbidities.

Our study demonstrated the usefulness of fairly recent statistical advances that allowed us to overcome unique problems associated with the prediction of rare events such as ADRs. We felt it important to address complexity in our data (e.g., over-dispersion and excess zeroes), by comparing several modeling strategies and considered the process as a means to choose the "most appropriate" model to examine factors predictive of ADRs. We believe that the process of choosing statistical approaches to data analysis is dependent not only on the research question, but also on the characteristics of observed data. To our knowledge, this is the first study of its kind in Canada, and one of a few studies worldwide, investigating predictors of recurrent events of ADR among the high risk elderly patients admitted to hospital while illustrating the importance of carefully considering appropriate models that best represent the observed data.

Our study provides a starting point for understanding the recurrent events of ADRs and the risk factors associated with these events in the elderly hospitalized patients. Future research should examine this association beyond the acute care setting and include drug doses and multiple drug regimens. Identification of risk factors for ADR counts in varying study settings is likely to play an important role in providing efforts to improve medication safety. Given that the greatest gains in improving patient safety are believed to come from modifying the work environment of health professionals [7], interventional studies focusing on organization change and delivery of care are the next step towards prevention.

Conclusions

This study used a population-based cohort design to determine the incidence of ADRs in the elderly hospitalized patients considering all events, rather than restricting analyses to only first events of ADR, and identify predictors on recurrent events of ADR considering the appropriateness of statistical models. Comorbidity from chronic diseases and the severity of the patient's underlying illness, rather than the characteristic of individual patients (advancing age, sex), increased the likelihood of recurrent events of ADRs in elderly hospitalized patients. The majority of Charlson comorbidities were associated with increased number of ADRs experienced by the elderly. Substantial

changes in the organization and delivery of health care focusing on careful and frequent monitoring of prescribed drugs in elderly patients would mitigate the recurrence of ADR. Interventional studies are recommended to ascertain whether recurrent events of ADR in this most vulnerable group of patients can be prevented.

Acknowledgements

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CHAPTER 5

General Discussion and Summary

5.1 General Discussion

An important focus of the work for this doctoral dissertation was to investigate the extent of serious adverse drug events (ADEs) in children and adults presenting to Emergency Departments (EDs), and elderly individuals admitted to hospitals in Newfoundland and Labrador. This research provided a unique opportunity to utilize three datasets: two collected through a retrospective review of ED charts allowing characterization of ADEs by patients' demographic and clinical factors; and a third obtained from linked administrative data enabling the use of multiple regression modeling techniques to identify patient-related factors that can predict recurrent events of ADR.

This is the most extensive and comprehensive research program of its kind ever conducted in Newfoundland and Labrador (NL) to document the serious ADEs. The three studies under the program were designed to capture and document a wide range of serious ADEs. The studies originated from the idea of gathering baseline information prior to implementing a province-wide Pharmacy Network, and later expanded to build up benchmark information for risk factors associated with recurrent events of ADRs in the high risk group of elderly hospitalized patients. The ultimate intent is to inform and provide a better understanding of this negative outcome resulting from drug use, rather

than the underlying diseases, that led to an increased burden of illness to the individual patient and increased burden of health care resources to the health system.

This final chapter contains a summary discussion of each study, together with implication of findings and future directions. The summary discussion of the three studies focuses on the similarity and dissimilarity in methods and measures among the studies. The implication of findings focuses on what the provincial Pharmacy Network can do and what could be expected from health care professionals to ensure quality of care given the findings of the studies included in this research. Future directions include recommendations for an ongoing analysis of ADE data in other clinical settings and vulnerable subgroups of populations to gain a better understating of the patterns of ADEs, and their preventability, and suggestions for improvement of system factors, education and indications for further studies.

5.2 Summary Discussion of the Three Studies

The magnitude of drug-related adverse incidents and their patient-related factors that can predict these incidents were studied in three age groups (children and youth aged 17 years and younger; adults aged 18 years and older; and elderly aged 65 years and older) in NL. Drug-related adverse incidents in the elderly were studied in a hospital

setting, and the events in the other two subsets were studied in ED setting. The three studies differed in their definitions of adverse incidents, outcomes measures, and in their study design, including the methods of data collection employed. An introduction to how drug-related adverse events occur, the different terminologies used, and how the data are typically collected in observational studies was provided in Chapter 1. Although providing illustrations of statistical theories used in the analysis of ADE data was not a focus of this research, multiple regression modeling for analysis of count data (which is rarely used for ADE studies) were briefly discussed in Chapter 4, with further details in Appendix F.

5.2.1 Summary of Methodological Perspectives of the Three Studies

The ***first*** and ***second*** studies (Chapters 2 and 3, respectively) examined the extent to which ADEs among pediatric and adult patients resulted in ED visits, how these events differed by patients' demographic and clinical characteristics, and what proportion of them were classified into severity (significant, serious, life threatening, fatal) and preventability (preventable and not preventable) classes. For the first study, the sample was selected using a simple random sampling technique, restricting one visit per patient, from a sampling frame which included a previous one-year ED visit by children aged ≤17 years meeting inclusion criteria. The study sample for the second study was selected with the same restriction of one visit per patient, but it used a stratified random sampling

technique given that a secondary objective of this study was to determine age-sex specific prevalence of ADEs. In both studies, a two-step review of patients' ED charts was employed in collecting baseline information prior to implementing the Pharmacy Network. Following a retrospective review of ED charts, the reviewers determined whether an ADE was deemed to be a reason for an ED visit. If it was, the reviewer also classified the event with respect to severity and preventability.

The focus of the ***third*** study (Chapter 4) was to examine the incidence of ADRs, a conservative estimate of ADEs, occurring among elderly hospitalized patients and whether patients-related factors such as age, sex, chronic diseases, socioeconomic status and residential locality can predict recurrent events of ADRs in this population. This was a population-based study in which the dataset was developed through a linkage of five administrative health databases and ADRs were identified through the external causes of injury codes associated with the use of a drug that were recorded in the Discharge Abstract Database (DAD).

Given that a representative sample of one-year ED visits were reviewed retrospectively for each of the first two studies, it was not possible to determine the onset of the event. Some people may have developed ADEs during the one-year study period, and others may have had the events prior to the study period but presented to EDs, were cured or died during the study period. Therefore, the extent of the event was estimated as

prevalence of ADEs, as it was deemed to be the most appropriate measure. When the word 'prevalence' was used in presenting results of the first two studies it was meant to be a period prevalence, which revealed how many people had an ADE at any time during the one-year period. The third study included records of all hospitalizations of patients aged 65 years and older over a period of 12 years and considered all events, rather than the first event only, to determine ADR counts. Using the duration of follow-up for each study subject, the incidence density was estimated to measure the occurrence of these events. Incidence density was reported in terms of the frequency (density) of ADR per 1,000 person-years. Because of its use of person-time observed as a denominator, the incidence density is a composite measure of the number of individuals observed and the period of observation contributed by each individual [1].

The first two studies which identified and characterized ADEs in an ED setting were limited in sample size and number of ADEs. In order to maintain predictive power associated with small samples, only bivariate analysis was considered to determine the association between prevalence of ADEs and a patient-related factor. This means that the observed effect of a factor (e.g., age) on ADEs may not be the true effect due to the inability to adjust for confounding. The third study was population-based and therefore overcame the issue of small sample. The study allowed for the use of multiple regression analysis that accounted for confounding factors and determined independent predictors for ADR counts.

5.2.2 Summary of Key Findings from the Three Studies

In an effort to examine the size and nature of the problem of serious ADEs, and therefore, create a basis for targeting preventive strategies to mitigate these unwanted events, this research revealed several important findings: (1) 2.1% of pediatric ED visits and 2.4% of adult ED visits were due to ADEs, of which 20% and 29%, respectively, were considered preventable; (2) children with and without ADE-related ED visits were similar with respect to mean age and mean number of medications, whereas adults with ADE-related ED visits were older and were prescribed more medications compared to their non-ADE counterparts; (3) the adults with ADE-related ED visits had a higher number of comorbidities compared to adults without ADEs; (4) the varying distribution of ADEs were observed in relation to the types of drugs involved between study populations; (5) in a cohort of elderly hospitalized patients, the incidence of ADR was 15.2 per 1,000 person-years; (6) comorbidity from chronic diseases and the severity of a patient's underlying illness, rather than the characteristic of individual patients (e.g. advancing age, sex), increased the likelihood of recurrent events of ADR in elderly hospitalized patients.

The occurrence (or number) of ADEs/ADRs that either caused ED visits, hospital admissions or extended hospital stay was our outcome of interest, whereas most drug-related adverse events are fairly minor and occur in the community without ED visits or

admission to hospital [2]. Therefore, our findings on magnitude of ADEs should be interpreted with caution, since we only considered ADEs resulting in ED visits or hospitalizations that may represent the most severe adverse events of medication use and lead to considerable morbidity and financial burden. Furthermore, the three studies included in this dissertation were designed to describe drug-related events separately in each subset of the population. Because of this design, coupled with the variable mechanism for detection and measures of occurrences, no attempts have been taken to compare results among the three studies. However, these findings are informative in that they quantified the number of ADEs and characterized them according to the patient-related factors including health conditions (all three studies) and medications (the first and second studies).

In identifying drug-related adverse incidents in all three studies, we have taken a conservative approach that keeps the ADE estimates low by applying very specific exclusion criteria. The study sample for the two studies in ED setting excluded any visits related to drug-induced traffic accidents, drug abuse and attempted suicide. Similarly, the study of elderly hospitalized patients excluded adverse effects caused by accidental overdoses of a drug, wrong drug given or taken in error, accident in technique of administration of drug, and abuse of a drug. Hence, we are probably not over-estimating the ADE/ADR estimates despite the fact that the events may include suspected ADE or ADR given that (1) the possible ADEs were combined with the confirmed ADEs in

estimating prevalence of ADE in the first two studies, and (2) confirmation of each individual event of ADRs detected retrospectively using ICD codes in the third study may not be realistic [3-5].

The first two studies focused on ADEs, which included errors in administration. The findings of these studies are useful to alert health professionals and policy makers about the preventability of many ADEs. In contrast, the third study on ADRs, which excluded medication errors, had a different objective: to demonstrate that there are a large number of ADRs even when drugs are properly prescribed and administered. Because serious ADRs can be a great burden of harm to a population that is measured in lost lives, reduced functionality, and wasted resources, the magnitude of these events is an important clinical issue [6-8]. As illustrated in section 1.3, ADRs are more difficult to prevent than ADEs. However, it is possible to mitigate many ADRs depending on what type of events they are. Adverse drug reactions can be classified into two types: Type A (dose-dependent and predictable) and Type B (idiosyncratic or bizarre effects that are dose-independent and unpredictable) [6, 9]. Although our research did not attempt to determine the type of ADRs, a meta-analysis [6] of prospective studies demonstrated that the majority of ADRs (over three-fourths of the total events) in a hospital setting were attributed to dose dependent causes (i.e., Type A events). Therefore, we are in agreement with the authors' explanation in that health care focusing on careful and frequent

monitoring of drugs may lead to a reduction of many of these events, as their occurrences are likely due to the use of drugs with unavoidably high toxicity.

This thesis showed the distribution of ADEs varied in relation to the types of drugs involved between study populations. For example, antimicrobial agents (45.0%) were the most common drug classes associated with ADEs in children, whereas in adult patients cardiovascular agents (37.4%) were the drug class most often associated with ADEs. In the elderly hospitalized patients, the most common drug categories implicated in ADRs was cardiovascular agents (17.7%), %), followed by analgesics/antipyretics/ anti-inflammatory (16.1%), systemic (11.8%) and blood constituents (9.7%. These results indicate that much of the variation in the occurrence of ADEs and their association with patient characteristics and drug types are due to heterogeneity in the populations examined in the three different studies. Unlike the first two studies that collected information on drug utilization of each study patient prior to the ED visit, the third study used the hospital discharge abstract database as the source of patient clinical information on which information on drug utilization before or during hospitalization was not available. Only drugs that lead to an ADR were identified using diagnosis codes. Although the drugs most frequently associated with ADEs in children and adults were identified in the first two studies, only descriptive data on the distribution of ADR-related drug classes among elderly hospitalized patients was available in the third study. This means that the study of elderly hospitalized patients was not able to conclude whether the

top drugs were more likely to cause ADRs due to the lack of data on the quantity and overall types of drugs consumed. The top drugs could just be more commonly prescribed drugs among the elderly patients [10]. However, from a policy perspective focusing efforts on the drug classes with the greater number of ADRs may have the biggest impact on reducing the burden of ADRs in the population.

The three studies included in this dissertation were limited as noted above by retrospective data extraction either through chart review or by using diagnosis fields with ICD coding criteria. It is worthwhile to acknowledge a few additional limitations. First, the small sample sizes for the first two studies restricted the analysis to bivariate techniques, thus limiting conclusions one can draw from these results. The analysis identified factors with a statistically significant association with ADE-related ED visits, but whether these associations would be independent after considering confounding variables is unclear. A multiple regression approach which would have supported the investigation of predictors of observed ADEs but that requires a large sample or population-based study as was carried out for the study of elderly hospitalized patients (Chapter 4). Second, sensitivity and specificity are two well-recognized measures of validity of a new test or tool. However, in order to estimate sensitivity and specificity of the trigger assessment tools used in the first two studies, it would require to carry out the full review of all sampled ED charts in the both studies. Because of limited resources available for the studies, a full review was carried out on a sample of charts for visits

classified as having "no" probability of being due to an ADE, and therefore a different form of validity assessment has been performed (Chapters 2 and 3). Third, when it was influenced by a context of a situation, the three studies has been referred to with reference to the three age-related subgroups, although there was a little overlap in the study subjects between 2nd and 3rd studies. Following an investigation we found that, of all elderly patients in the 3rd study admitted via EDs, there were 108 patients included in the 2nd study. Because this overlapping component is very small (~7.4% of 2nd study subjects and ~0.2% of the 3rd study subjects), we believe that the impact of this overlap on study findings or answering the research questions would be negligible. Fourth, at the design stage of the first two studies, the intent was to gather other types of events such as potential ADEs and medication errors (see section 1.3.1 for definitions), which are not only a major part of drug-related events, but also the extent of such events would likely be mitigated by a new intervention such as a Pharmacy Network. However, necessary information was not available in patients' ED charts. Moreover, the data collection plan included gathering information on many other variables such as cause of adverse events, who was primarily responsible for the event, and what were the consequences to the patient. However, these data were not collected comprehensively for each event due to the unavailability of the information in the patients' ED charts. Thus these factors were not considered for analysis as to do so would introduce high sampling error associated with the small number of events and potential bias due to selective recording of the data in the records. These limitations demonstrate the necessity to conduct a well-designed prospective cohort study that would be in a better position to investigate the extent of the

events beyond what we studied together with the characteristics illustrating their causes and consequences for the patients and the health system. A last limitation worthy of note was that preventability was assessed using a 4-point Likert scale, but was subsequent collapsed into two categories ("preventable" and "not preventable") resulted in a loss of more detailed information. A larger sample size would have facilitated analysis at the 4-point scale level.

While the findings of this research must be viewed with some circumspection, as noted above, several factors lend strength to this work, especially the identification of high risk patients requiring close monitoring of their drug consumptions. Apart from those that have been described separately for each study in the previous chapters, this research brings additional strengths to the understanding of the problem of drug safety and contributes to the development of the necessary solutions. Given that this research is the first in this province to capture comprehensive information on serious ADEs, the findings can be used as a source of learning and as a basis for preventive action in the future. If an investigation of an event is not conducted locally where it occurred, then the lessons cannot be learned more widely; the opportunity to generalize the problem is lost and the capability to produce powerful and more widely applicable solutions will not be realized [11]. The three studies encompassing this dissertation revealed an unrecognized burden of serious ADEs in this province, requiring attention to the quality improvement of the health system. The three manuscripts and several presentations to international and

national conferences, academia and provincial special interest groups (e.g. Patient Safety Research Affinity Group), resulting from this work lead to a widespread and ongoing dissemination of findings throughout the course of this doctoral research in order to promote the sharing of important methodological aspects and research findings among the research community and other key stakeholders.

The observation of the positive correlation between prevalence of ADE and age (Chapter 3), coupled with an increased risk of ADR associated with certain comorbidities and severity of comorbid illness, rather than advancing age (Chapter 4), not only supports the fact that older patients experience more ADEs than younger patients, but the higher number of ADEs in an older population may be attributed in part to the fact that older patients consume more medications and are likely to have more comorbid illness than younger patients. These findings, in conjunction with the dissimilar drug classes associated with (or implicated in) ADEs in the three subgroups, suggests that a prevention strategy should be targeted at patient-specific physiologic and functional characteristics, and the high-risk medications to treat coexisting health conditions, as opposed to being focused on an individual's true chronological age, as noted previously in the literature [2, 3, 12].

There have been few ADE studies in the Canadian population [13-15], and they focused either on all events including drug and non-drug related adverse outcomes or

were conducted in a single setting. This dissertation research differs from those reports in many respects: (1) we examined the frequency of a wide range of serious ADEs experienced by patients in the community setting and resulting in either ED visits, hospital admissions, or prolonged hospital stay for an existing patient, (2) we separately studied the events in three age groups to take into consideration the heterogeneity among these groups, and did not attempt to combine them, (3) we studied prevalence of ADEs and incidence of ADRs to maintain the appropriateness of study designs, (4) we detected and analyzed ADEs and their severity and preventability followed by a bivariate analysis for the association of these events with patient-related factors given the small number of events and the possibility of sampling error (Chapters 2 and 3), (5) we estimated all ADR-events in elderly hospitalized patients across the province over a 12-year period, and gave special emphasis to choosing an appropriate regression model approach to determine predictors of recurrent ADR events (Chapter 4). The serious ADE events that were captured using different detection methods in the hospital and ED settings, in conjunction with the separate analysis for each subset of patients, provides guidance in tailoring the list of high-risk medications based on age, comorbidities, and setting in order to optimize ADE prevention. By presenting findings of the three studies together, this dissertation research provides good information to advance the planning and management of health care improvement so that the impact of a new system such as a Pharmacy Network can be measured. Subsequent research may lead to understanding of the causative reasons for certain medications being more frequently associated with

ADEs and new ways of caring for patients can be designed and implemented to reduce these events.

5.3 Implications of Findings

5.3.1 Prioritizing Medication Safety Research and Intervention

This research adds to the growing body of literature suggesting which medications should be considered as high-alert or high-risk medications for children and adults. While identification of such high-risk medications for ADRs in the elderly hospitalized patients was beyond the scope of this research due to the limitations of the administrative data, varying distributions of ADRs in relation to different type of drugs consumed by them have been provided. This stratified information would likely be useful for characterizing a group of high-alert patients who have specific clinical attributes that present with specific medical problems and place them in a particular risk group for developing ADEs/ADRs [3]. Identification of high-risk patients, high-risk drugs, and top drugs (or drug classes) responsible for ADEs would help in selecting target groups for preventive strategies. As suggested by Budnitz et al. [16], because a few drugs that typically require periodic monitoring accounted for most ADEs, investing resources focusing on ADEs associated with these drugs may be one way to prioritize further medication safety research and intervention.

5.3.2 Development of Active Medication Monitoring and ADE Surveillance System

Identification of the importance of high-risk chronic diseases and severity of illness was an important step in determining the factors that render patients at greater risk for ADRs. This research provides valuable baseline information for designing or evaluating interventions for improving drug safety. Having a complete list of high-risk medications along with high-risk illness in a specific subgroup can help to develop active medication monitoring systems [3]. Considering the planned infrastructure of the provincial Pharmacy Network, embedded with a computerized decision support system, an active medication monitoring system would be desirable to improve medication safety. Another implication of these findings of this research that warrants attention is the need for an active ADE surveillance system to identify and help prioritize medication safety issues in inpatient and outpatient settings through a timely, and jurisdictionally representative surveillance system for adverse drug events [16]. It is expected that the process and methodology followed for these studies, the lessons learned, and the findings presented will contribute to future research and drug-related policy initiatives. This work along with the establishment of a Pharmacy Network will enhance development of an active ADE surveillance in the health system which will ultimately provide timely post-marketing safety information on specific drugs and thus contribute to improved patient outcomes.

5.3.3 Building Research Capacity in Newfoundland and Labrador

This research was the first assessment of ADEs treated in EDs and in the inpatient settings in Newfoundland and Labrador. Our estimates of the occurrences of ADEs will help in evaluating the effectiveness of any future intervention. We found that 20% of serious ADEs in pediatric patients and 29% of those in the adults should be preventable. Given that one of the expectations of the Newfoundland and Labrador Pharmacy Network is improving prescribing and making progress in drug safety, these findings offer a measurable goal for the post-Pharmacy Network studies aimed at reducing ADEs leading to ED visits of 20% and 29%, respectively. Without this research, the health system of NL would not have any data on the burden of ADEs, and thus would have no way of measuring the impact of the provincial Pharmacy Network in reducing adverse drug-related events.

Furthermore, there has been a few ADE research carried out in Canada. Our analysis provides a basis for identifying issues associated with drug-related serious adverse events, including their measurement and assessment, requiring action for therapeutic improvement by health care professionals and leaders of the health system. While no further studies were conducted previously in the province, this research has successfully built benchmark information on serious ADEs requiring utilization of health

care resources. It is expected that our research, along with the availability of data from the provincial Pharmacy Network, will significantly contribute to building research capacity in the province of Newfoundland and Labrador in the area of optimal drug utilization through enhanced information systems. The findings in this doctoral dissertation may trigger an in-depth investigation to identify underlying systems failures and lead to efforts to redesign the systems to prevent recurrence. Further ADE studies with more well-established ADE identification systems may help us to better understand the etiology of adverse drug events through answering questions relating to ADEs and identifying patients for further studies (e.g., pharmacogenetic studies) and ultimately lead to the adoption of a well-developed patient safety culture.

5.3.4 Providing Alert to Health Care Professionals

The drug classes associated with or implicated in ADEs were dissimilar among the three age groups. The drugs that were found to be associated with greater risk for ADEs, along with patients' underlying health conditions are informative for designing and implementing interventions for ADE prevention. Given that the majority of ADEs are predictable, and therefore potentially avoidable, a new system allowing physicians to check medication lists with high-risk patients more carefully (even obsessively) may help avoid ADEs and other drug-related adverse incidents. Previous work suggested that good communication is pivotal in developing an effective therapeutic partnership with the patient and fellow health professionals [17]. An intervention program such as a Pharmacy Network, consisting of a well-designed information technology infrastructure and offering computerized prescribing and monitoring system, can help establish a better communication for rationalizing drug therapy while alerting pharmacists and physicians to potentially harmful drug-related problems.

5.3.5 Choosing Medications with Highest Therapeutic Index

Medications with a narrow therapeutic index (e.g., warfarin, divalproex and chemotherapy) were found to cause the majority of ED-treated ADEs in patients aged 65 years and older. This finding was supported by earlier studies [18-19]. Provided efficacy is

comparable, health care professionals may consider prescribing medications with the highest therapeutic ratio, fewest number of possible drugs and keeping the dosing regimen as simple as possible [17, 20]. Close monitoring of these drugs has also been advocated as a way of avoiding or mitigating harm from these drugs. As demonstrated by Coleman et al. [21], if a drug has a narrow therapeutic range, monitoring drug concentrations or effects may allow the dose to be adjusted so that the optimal balance of efficacy and safety is achieved.

5.3.6 Addressing Issues Associated with Seamless Care

Many health professionals, in particular physicians and pharmacists, are not familiar with other areas of practice and not aware of the consequences of the gap between areas of care. Seamless care is the desirable continuity of care delivered to a patient in the health care system across the spectrum of caregivers and their environments [22]. It has been recommended to encourage patients towards seamless care by using only one primary care physician and one community pharmacy, if possible, and discussing any medical products to limit potential interactions leading to adverse events. However, providing seamless care is a very challenging task in a population that is large and geographically wide spread such as in Canada. As has been initiated from this research, frequent studies may help in establishing a comprehensive list of high-risk drugs causing adverse events. Once this information is built into the provincial Pharmacy Network, all

pharmacies in the province are connected to that network, and health professionals have access to their patient's dispensing history, it is expected that health professionals would be able to intervene before and after an adverse event occurs. One benefit might be by avoiding harmful drug interactions leading to a decrease in the cost associated with doctor visits, emergency department visits and hospitalizations through using the patient-specific drug information system and an interactive database offering accurate real-time prescription profiles within the Pharmacy Network [23].

5.4 Future Directions

Adverse drug events are an important cause of emergency department visits and hospital admissions, resulting in significant economic burden to the health care system and threatening the safety of drug therapy. This dissertation research provides baseline information with a broad understanding of drug safety and quality of care in a hospital and ED setting in Newfoundland and Labrador. Further work is required to help identify the burden, severity and preventability of ADEs and medications responsible for them in long term care, home care and non-hospital settings. In addition to age-related subgroup analyses that were performed in this dissertation, future analyses should also focus on other vulnerable groups such as the poor and Aboriginal populations. This should give more insight into the patterns of ADEs, and their preventability, and thereby lead to suggestions for improvement of system factors and education for further studies.

Another area which deserves further attention is the method of gathering additional information and analysis. Researchers should include more targeted studies so that study reviewers can detect ADEs and identify the patient factors, drug factors and system factors responsible for each event. Understanding the causative reasons for certain drugs being more frequently associated with ADEs will be useful in identifying potential areas for improvement in the community setting and gaining insights into areas of intervention. It is important to consider a problem solving approach that explores what could be done differently, and what changes can be made at the individual and institutional level to prevent the recurrence of the incidents.

Other topics not addressed in this dissertation include the consideration of benefit-harm ratio and genetic factors. The findings and the subsequent discussion of this dissertation was related to harm only. Without consideration of the benefit-harm ratio, it is difficult to provide conclusive evidence whether the harm of a drug outweighs the benefit [10]. The susceptibility to serious ADEs may also be linked to genetic factors and the identification of predisposing genotypes may improve patient management through the prospective selection of appropriate candidates for given drugs. Future large-scale prospective studies are needed to identify genetic risk factors for serious ADEs , particularly Type B reactions (illustrated in section 5.2.2), that could significantly decrease healthcare costs and improve the process of drug development [24].

There are many measurement issues associated with estimating the magnitude of adverse drug events in a manner that permits comparison between populations from different nationalities while identifying population-level factors associated with their occurrence. As illustrated in the earlier chapters, the rate of drug-related hospitalizations or ED visits seems to be lower in the Canadian population compared to other nations, but further research with robust study designs aiming to compare Canada with other countries is needed to confirm these findings.

In conclusion, these findings suggest that the magnitude of serious adverse drug events in Canada, while perhaps lower than some other nations, is substantial. This analysis was able to discern how predictors of ADEs shifted from demographic factors to patient-specific physiologic conditions. To better serve the needs of patients and to reduce the pressure on health care resources, a prevention strategy should be targeted at patient-specific physiologic and functional characteristics, and at high-risk medications, as opposed to focusing on individuals' chronological ages.

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APPENDIX A

Ethics approval from the Human Investigation Committee of Memorial University of Newfoundland

MEMORIAL

Faculty of Medicine

Human Investigation Committee
Suite 200, Seamount Place
95 Bonaventure Avenue
St. John's, NL Canada A1B 2X5
Tel: 709 777 6974 Fax: 709 777 8776
hic@mun.ca www.med.mun.ca/hic

September 21, 2009

Reference #09.176

Dr. Khokan Sikdar
Community Health
Memorial University

Dear Dr. Sikdar:

RE: "Adverse drug events in hospitalized patients and patients presenting to emergency departments in Newfoundland and Labrador"

Your application received an expedited review by a Sub-Committee of the Human Investigation Committee and **full approval** was granted effective September 17, 2009.

This approval will lapse on **September 17, 2010**. It is your responsibility to ensure that the Ethics Renewal form is forwarded to the HIC office prior to the renewal date. *The information provided in this form must be **current to the time of submission** and submitted to the HIC **not less than 30 nor more than 45 days** of the anniversary of your approval date.* The Ethics Renewal form can be downloaded from the HIC website http://www.med.mun.ca/hic/downloads/Annual%20Update%20Form.doc

The Human Investigation Committee advises THAT IF YOU DO NOT return the completed Ethics Renewal form prior to date of renewal:

- *Your ethics approval will lapse*
- *You will be required to stop research activity immediately*
- *You may not be permitted to restart the study until you reapply for and receive approval to undertake the study again*

Lapse in ethics approval may result in interruption or termination of funding

For a hospital-based study, it is **your responsibility to seek the necessary approval from Eastern Health and/or other hospital boards as appropriate.**

Modifications of the protocol/consent are not permitted without prior approval from the Human Investigation Committee. Implementing changes in the protocol/consent without HIC approval may result in the approval of your research study being revoked, necessitating cessation of all related research activity. Request for modification to the protocol/consent must be outlined on an amendment form (available on the HIC website) and submitted to the HIC for review.

This research ethics board (the HIC) has reviewed and approved the research protocol and documentation as noted above for the study which is to be conducted by you as the qualified investigator named above at the specified site. This approval and the views of this Research Ethics Board have been documented in writing. In addition, please be advised that the Human Investigation Committee currently operates according to *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* and applicable laws and regulations. The membership of this research ethics board is constituted in compliance with the membership requirements for research ethics boards as per these guidelines.

Notwithstanding the approval of the HIC, the primary responsibility for the ethical conduct of the investigation remains with you.

We wish you every success with your study.

Sincerely,

Fern Brunger, PhD
John D. Harnett, MD, FRCPC
Co-Chairs
Human Investigation Committee

C Dr. R. Gosine c/o Office of Research, MUN
Mr. W. Miller c/o Patient Research Centre, Eastern Health
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On Dec 8, 2010, at 10:19 AM, Khokan Sikdar wrote:

Dear Dr. Nebeker,

My Name is Khokan Sikdar. I am a Ph.D. candidate in the Faculty of Medicine at Memorial University of Newfoundland, St. John's, NL, Canada. I am presently writing my doctoral thesis titled, "Serious Adverse Drug Events in Patients Presenting to Emergency Departments and Admitted to Hospitals in Newfoundland and Labrador". While writing definitions of adverse drug events and related terminologies in the introduction chapter of my thesis, I found your article on "Clarifying adverse drug events: a clinician's guide to terminology, documentation, and reporting" published in Ann Intern Med 2004; 140:795-801 is very interesting. I have cited your article in my doctoral thesis. I also felt that it would be worthy to provide a figure similar to the figure titled "Relationships of key terms" in your article, but it requires your permission.

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Memorial University of Newfoundland
and
Senior Biostatistician
Research and Evaluation Department
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Email: khokan.sikdar@nlchi.nl.ca, Web:www.nlchi.nl.ca

APPENDIX C

Trigger Assessment Tool and Data Collection Tool Used to Review of ED Charts for Detecting ADEs in Pediatric Patients

Appendix C.1. Pediatric ADE Trigger Assessment Tool

Study of Adverse Drug Events in Children Presenting to the Janeway Emergency Department

Study Code ☐ Date of Birth (dd/mm/yyyy) / /

Gender ☐ Male ☐ Female Date of ER visit (dd/mm/yyyy) / /

☐ 1. Joint swelling

☐ 2. Stridor

☐ 3. Jaundice

☐ 4. Urticaria or Eczema

☐ 5. Skin rash/ purpura

☐ 6. Wheeze

☐ 7. Chest pain or Palpitation

☐ 8. Arrhythmias

☐ 9. Pruritus

☐ 10. Respiratory Depression

☐ 11. Difficulty breathing

☐ 12. Nausea or vomiting

☐ 13. Headache

☐ 14. Abdominal pain

☐ 15. Nose bleeds

☐ 16. Seizure

☐ 17. Diarrhea

☐ 18. Altered level of consciousness

☐ 19. Constipation

☐ 20. Angioedema

☐ 21. Difficulty in sleeping

☐ 22. Recent Extrapyramidal effects, Dystonia/ tremors (not diagnosed due to any disease)

☐ 23. Lethargy/Somnolence

☐ 24. Hypertension

☐ 25. Hypotension

☐ 26. Increased serum creatinine/BUN Levels

☐ 27. Coagulation Abnormalities

☐ 28. Hypoglycemia/Hyperglycemia

☐ 29. Hyperkalemia/Hypokalemia

☐ 30. Leukopenia

☐ 31. Increased liver function test results

☐ 32. Hypernatremia/ Hyponatremia

☐ 33. *Clostridium difficile* positive stool

☐ 34. Neutropenia or thrombocytopenia

☐ 35. Anemia

☐ 36. Tinnitus

☐ 37. Mucous membrane changes

☐ 38. Other (please specify)

_____

39 (a) Did this event happen intentionally? ☐ ***Yes*** ☐ ***No***

39 (b) Is there a history of medication use within past two weeks? ☐ ***Yes*** ☐ ***No***

39 (c) Is it classified as a potential ADE? ☐ *Yes* ☐ *No*

39(d) If YES, what would be the probability of being an ADE?

☐ *Very low* ☐ *Low* ☐ *Moderate* ☐ *High*

Appendix C.2. Pediatric ADE Data Collection Form

Study of Adverse Drug Events in Children Presenting to the Janeway Emergency Department

(Pediatric ED Chart Review)

1. Reviewer ID (Choose only one to identify yourself)

Team 1: B. Porter B. Brennan

Team 2: S. Noseworthy E. Tucker

2. Study Code: ____

3.1 Patient's Age: ____ years ____ months (if <2 years) ____ days (if <1 month)

3.2 Height: ____ cm or ____ feet ____ inch

3.3 Weight: ____ lb or ____ kg

4. Has the patient been admitted to the hospital? ____ (1=Yes, 2= No)

4.1 If YES, has the patient been admitted to the Critical Care Unit? ____ (1=Yes, 2= No)

5. What is the chief complaint of the patient? _____

6. Patient's other presenting complaints

1 _____
2 _____
3 _____
4 _____
5 _____

7. Is there evidence in chart of any of the following health conditions? *Check all that apply.*

___1 Asthma

___2 Reactive Airways Disease

___3 Cerebral Palsy

___4 Spina Bifida

___5 Down Syndrome

___6 Other Genetic Syndrome

___7 Leukemia or other cancer

___8 Congenital Heart Disease

___9 Acquired Heart Disease

___10 Cardiac Arrythmia

___11 Neuromuscular Disease

___12 Inflammatory Bowel Disease

___13 Diabetes

___14 Kidney Disease

___15 Arthritis

___16 Seizure Disorder

___17 Substance Abuse

___18 Hypertension

___19 Migraine Headache

___20 Psychiatric Disorder

___21 Pulmonary Disease

___22 Hypercholesterolemia

___23 GI Disturbance

___24 Prolonged QT syndrome

___25 Other _____

___26 None

8. Current medication list :

1 _____
2 _____
3 _____
4 _____
5 _____
6 _____
7 _____
8 _____
9 _____
10 _____

9. Is there a history of new medication use within past two weeks? ☐ (1=Yes, 2= No, 3=Unknown)

	Name of drug	Duration of use (days)	Dosage
9.1 If YES, Please record	_____	_____	_____
	_____	_____	_____

10. History of allergies / reactions? Medication ☐ (1=Yes, 2= No, 3= Unknown) Environmental ☐ (1=Yes, 2= No, 3= Unknown)

10.1 If YES, give details of the allergy /reaction and list suspected substances

_____

_____

_____

11. Adverse Drug Event? ____ 1 ADE

(choose only one) 2 Potential ADE (PADE)

3 Medication Error (ME)

4 Exclude

12. comments

****CONTINUE only if ADE, PADE or ME judged as present, otherwise STOP here*****

13. Confidence regarding above judgment ____ 1 Little or no evidence

2 Slight to modest evidence

3 Less than 50-50 but close call

4 More than 50-50 but close call

5 Strong evidence

6 Virtually certain evidence

14. Information on medication, dose, frequency and reaction for each event (i.e., for ADE, PADE or ME)

14.1 Name of the drug that results with the event	_____

14.2 Categories of complications of the event. *Check all that apply*	____ 1 Bleeding ____ 2 CNS ____ 3 Allergic ____ 4 Anaphylaxis ____ 5 Cutaneous ____ 6 Metabolic	____ 7 Cardiovascular ____ 8 GI ____ 9 Renal ____ 10 Respiratory ____ 11 Marrow Depression ____ 12 Other_____
14.3 Was the event caused by any of the listed errors? *Check all that apply*	____ 1 Overdose ____ 2 Missing dose ____ 3 Underdose ____ 4 Wrong dose form ordered ____ 5 Dose omitted from order ____ 6 No dose units ____ 7 Incorrect frequency ____ 8 Frequency omitted ____ 9 Drug-drug interaction	____ 10 Inappropriate drug (includes duplicate) ____ 11 Allergy to ordered drug ____ 12 Wrong drug ordered ____ 13 Wrong patient ____ 14 Illegible order ____ 15 Preparation error ____ 16 Other _____
14.4 Did the patient have a documented previous allergy or reaction to the drug that caused the event?	____ 1 No 2 Intolerance (e.g. nausea, headache) 3 Allergy (reaction not documented) 4 Allergy, not anaphylaxis (e.g. rash)	

	5 Anaphylaxis 6 Other_____
14.5 What was the result of the event?	____ 1 No signs or symptoms 2 Laboratory abnormality only requiring change therapy 3 Up to one day of symptoms 4 1-7 days of symptoms 5 7 days-1 month of symptoms 6 >1 month of symptoms 7 Other_____
14.6 Who is the person primarily responsible? (*if multiple, choose the service you feel was the most responsible*)	____ 1 Physician 5 Other_____ 2 Pharmacy 6 None 3 Patient 7 Unknown 4 Parents
14.7 Did this event result in an additional visit?	____ 1 Yes 2 No (*skip to question# 14.9)*
14.8 If yes, what type of visit? (*check all that apply*)	____ 1 Required clinic visit only ____ 2 Required emergency room visit ____ 3 Required admission to hospital ____ 4 Required admission to long-term facility ____ 5 Other_____
14.9 Was the event caused by a medication that required outpatient	____ 1 Yes 2 No (*skip to question# 15)*

Blood monitoring?	
14.10 If yes, was there an elevated/ abnormal level with the event?	____ 1 Yes (*explain*) _____ 2 No _____
14.11 Was there regular monitoring of the blood level prior to the event?	____ 1 Yes 2 No

15. Record any relevant lab data

_____
_____
_____
_____

****For ADE & PADEs (only)*****

16. Severity of ADE (*choose only one*) ____ 1 Fatal ADE
2 Life-threatening ADE
3 Serious
4 Significant ADE

17. Disability/Injury associated with ADE (*choose only one*) ____ 1 Up to 1 day of symptoms
2 Laboratory abnormality only requiring change in therapy
3 More days of symptoms or

prolongation of hospitalization

4 Non-permanent disability at discharge

5 Permanent disability

6 Death

*****For ADEs, PADEs & MEDICATION ERRORS*****

18. Preventability—Implicit (*choose only one*) ____

1 Error intercepted

2 Definitely preventable

3 Probably preventable

4 Probably not preventable

5 Definitely not preventable

19. Could the event have been prevented by any of the following checks? *Check all that apply*

__1 Drug-drug check

__2 Drug-pt. characteristics test

__3 Drug-dose check

__4 Drug-allergies test

__5 Guided dose algorithm

__6 Other_____

20. Describe what failures occurred, and how they occurred.

21. Any other comments:

ADE SEVERITY CLASSIFICATION

ADE is defined as an injury due to a drug. Severity of ADE is classified into four categories; 1= Fatal ADE, 2= Life-threatening ADE, 3= Serious and 4= Significant ADE. Definitions/ characteristics of them are given below.

II. LIFE THREATENING	III. SERIOUS	IV. SIGNIFICANT
Definition *An ADE is considered life threatening if the event causes symptoms that if not treated, would put the patient at risk of death.* Life threatening ADEs also include laboratory values that are either elevated or depressed to the point that a critical physiologic function is at risk of failure.	Definition An ADE is considered to be serious if the event causes symptoms that are associated with a serious level of risk that is not high enough to be life threatening. In addition, an ADE is also serious if it causes persistent alteration of life function. Serious ADEs can also include elevated or depressed lab values that require medical intervention, especially if they suggest organ system dysfunction.	*Definition* An ADE is considered to be significant if the event causes symptoms that while harmful to the patient pose little or no threat to the patient's life function. Significant ADEs can include elevated or depressed laboratory test levels.

Symptoms/Lab information:*	*Symptoms/Lab information*:*	*Symptoms/Lab information*:*

POTENTIAL ADE SEVERITY CLASSIFICATION

A potential ADE (PADE) is a medication error that has the potential to harm the patient, but did not do so because it was intercepted or because the patient was lucky. Severity of PADE is classified into four categories; 1= Fatal ADE, 2= Life-threatening ADE, 3= Serious and 4= Significant PADE. Definitions/ characteristics of them are given below.

II. LIFE THREATENING	III. SERIOUS	IV. SIGNIFICANT
Definition *A potential ADE is considered life threatening if the event has the potential to cause symptoms that if not treated, would put the patient at risk of death.*	Definition A potential ADE is considered to be serious if the event has the potential to cause symptoms that are associated with a serious level of harm that is not high enough to be life threatening. In addition, a potential ADE is serious if it has the potential to cause persistent alteration of life function.	*Definition* A potential ADE is considered to be significant if the event has the potential to cause symptoms that while harmful to the patient pose little or no threat to the patient's life function.
Symptoms/Lab information:*	*Symptoms/Lab information*:*	*Symptoms/Lab information*:*

**Please indicate symptoms/lab information that you considered to classify the event to a severity category.*

APPENDIX D

Trigger Assessment Tool and Data Collection Tool Used to Review of ED Charts for Detecting ADEs in Adult Patients

Appendix D.1. Adult ADE Trigger Assessment Tool

Study of Adverse Drug Events in Adult Patients Presenting to the Emergency Departments of

Health Science Center and St. Clare's Mercy Hospital

Study code ☐ Date of Birth (dd/mm/yyyy) / /

Gender ☐ Male ☐ Female Date of ER visit (dd/mm/yyyy) / /

Triggers:

☐ 1. Fever ☐ 2. Anaphylaxis

☐ 3. Icter ☐ 4. Urticaria or Eczema

☐ 5. Skin rash/ purpura/ lesion ☐ 6. Flushing

☐ 7. Bradycardia or Tachycardia ☐ 8. Acute chest pain or Palpitation

☐ 9. Cough ☐ 10. Dyspnea

☐ 11. Respiratory depression ☐ 12. Nausea or vomiting

☐ 13. Headache ☐ 14. Abdominal pain

☐ 15. Diarrhea or Constipation ☐ 16. Altered level of consciousness

☐ 17. Hallucination/Delusion ☐ 18. Angioedema

☐ 19. Acute non-traumatic eye problem (not due to DM)

☐ 20. Seizure

☐ 21. Edema associated with introduction a new drug

☐ 22. Recent tremor (not diagnosed due to any disease)

☐ 23. Falls

☐ 24. SBP < 90 or > 180 mmHg

☐ 25. Hypoglycemia/Hyperglycemia (>20 or <2.8 mol/L)

☐ 26. Hypernatremia/ Hyponatremia (>150 or <130 mmol/L)

☐ 27. Hyperkalemia/Hypokalemia (>5.5 or <3.5 mmol/L)

☐ 28. Leukocytosis/leukopenia (>30000 or <4000/mm^3)

☐ 29. Coagulation Abnormalities (PTT> 90 sec or INR> 5 or Platelet < 150,000)

☐ 30. Renal Fuction (Cr> 133 µmol/L)

☐ 31. LFT (AST/ ALT/bilirubin 3 × ULN)

☐ 32. Digoxin serum level >2.5 nmol/L

☐ 33. Theophylline serum level > 110 µmol/L

☐ 34. Phenytoin serum level> 80 µmol/L

☐ 35. Clostridium difficile positive stool

☐ 36. Lithium serum level > 1.5 mmol/L

☐ 37. Creatine Kinase (3 × ULN)

☐ 38. Anemia (Hb < 100 g/L)

39 (a) Is there a history of medication use prior to ER visit? ☐ ***Yes*** ☐ ***No***

39 (b) Is it classified as a potential ADE? ☐ ***Yes*** ☐ ***No***

39(c) If YES, what would be the probability of being an ADE?

☐ ***Very low*** ☐ ***Low*** ☐ ***Moderate*** ☐ ***High***

Comments:

Appendix D.2. Adult ADE Data Collection Form

Study of Adverse Drug Events in Adult Patients Presenting to the Emergency Departments of

Health Science Center and St. Clare's Mercy Hospital

(Adult ED Chart Review)

1. Reviewer ID Team 1: Team 2:

(Choose only one to identify yourself) C. Seviour J. Hawboldt C. Pollock S. Young

2. Study Code ____

3. Patient's marital status ____

1 Single
2 Married
3 Separated
4 Divorced
5 Widowed
6 Unknown

4. Has the patient been admitted to the hospital? ____ (1=Yes, 2= No)

4.1 If YES, has the patient been admitted to the Critical Care Unit? ____ (1=Yes, 2= No)

5. What are the complaints of the patient?

1 _____ 5 _____

2 _____ 6 _____

3 _____ 7 _____

4 _____ 8 _____

_____ _____

6. Is there evidence in chart of any of the following health conditions? *Check all that apply.*

___1 Diabetes ___5 Seizure Disorder ___9 Migraine Headache ___13 GI Disturbance

___2 Kidney Disease ___6 Substance Abuse ___10 Psychiatric Disorder ___14 Other _____

___3 Arthritis ___7 Hypertension ___11 Pulmonary Disease

___4 Cardiovascular Disease ___8 CVA ___12 Cholesterol ___15 None

7. Current medication list :

1 _____ 6 _____

2 _____ 7 _____

3 _____ 8 _____

4 _____ 9 _____

5 _____ 10 _____

8. Is there a history of allergies? ☐ (1=Yes, 2= No, 3= Unknown)

8.1 If YES, what are the drugs that results an allergy/ reaction?

_____

_____

9. Adverse Drug Event? (choose only one)	____ 1 ADE 2 Potential ADE (PADE) 3 Medication Error (ME) 4 Exclude	9.1 The category of event after consensus WITHIN Team (if applicable)

10. Any comment at this point?

****CONTINUE only if ADE, PADE or ME judged as present, otherwise STOP here*****

11. Confidence regarding above judgment ____ 1 Little or no evidence
2 Slight to modest evidence
3 Less than 50-50 but close call
4 More than 50-50 but close call
5 Strong evidence
6 Virtually certain evidence

12. Information on medication, dose, frequency and reaction for each event (i.e., for ADE, PADE or ME)

12.1 Name of the drug that results with the event	_____	
12.2 Categories of complications of the event. *Check all that apply*	____ 1 Bleeding ____ 2 CNS ____ 3 Allergic/ cutaneous ____ 4 Metabolic ____ 5 Cardiovascular	____ 6 GI ____ 7 Renal ____ 8 Respiratory ____ 9 Marrow Depression ____ 10

		Other_____
12.3 Was the event caused by any of the listed errors? *Check all that apply*	____ 1 Overdose ____ 2 Missing dose ____ 3 Underdose ____ 4 Wrong dose form ordered ____ 5 Dose omitted from order ____ 6 No dose units ____ 7 Incorrect frequency ____ 8 Frequency omitted ____ 9 Drug-drug interaction	____ 10 Inappropriate drug (includes duplicate) ____ 11 Allergy to ordered drug ____ 12 Wrong drug ordered ____ 13 Wrong patient ____ 14 Illegible order ____ 15 Preparation error ____ 16 Other _____
12.4 Did the patient have a documented previous allergy or reaction to the drug that caused the event?	____ 1 No 2 Intolerance (e.g. nausea, headache) 3 Allergy (reaction not documented) 4 Allergy, not anaphylaxis (e.g. rash) 5 Anaphylaxis 6 Other_____	
12.5 What was the result of the event?	____ 1 No signs or symptoms 2 Laboratory abnormality only requiring change therapy 3 Up to one day of symptoms 4 1-7 days of symptoms	

	5 7 days-1 month of symptoms 6 >1 month of symptoms 7 Other_____
12.6 Who is the person primarily responsible? (*if multiple, choose the service you feel was the most responsible*)	____ 1 Physician 4 Other_____ 2 Pharmacy 5 None 3 Patient 6 Unknown
12.7 Did this event result in an additional visit?	____ 1 Yes 2 No (*skip to question# 12.9)*
12.8 If yes, what type of visit? (*check all that apply*)	____ 1 Required clinic visit only ____ 2 Required emergency room visit ____ 3 Required admission to hospital ____ 4 Required admission to long-term facility ____ 5 Other_____
12.9 Was the event caused by a medication that required outpatient Blood monitoring?	____ 1 Yes 2 No (*skip to question# 13)*
12.10 If yes, was there an elevated/ abnormal level with the event?	____ 1 Yes (*explain*) _____ 2 No _____
12.11 Was there regular monitoring of the blood level prior to the event?	____ 1 Yes 2 No

13. Patients most recent labs prior to visit

13.1 Creatinine (Cr) _____ date ___/___/___

dd/mm/yyyy

13.2 Bilirubin (BILT) _____ date ___/___/___

dd/mm/yyyy

13.3 Albumin (ALB) _____ date ___/___/___

dd/mm/yyyy

****For ADE & PADEs (only)*****

14. Severity of ADE ____ (*choose only one*) ADE

1 Fatal ADE

2 Life-threatening

3 Serious

4 Significant ADE

14.1 The category of severity after consensus WITHIN Team (if applicable)

15. Disability/Injury associated with ADE ____ (*choose only one*)

1 Up to 1 day of symptoms

2 Laboratory abnormality only requiring change in therapy

3 More days of symptoms or prolongation of hospitalization

4 Non-permanent disability at discharge

5 Permanent disability

6 Death

*****For ADEs, PADEs & MEDICATION ERRORS*****

16. Preventability—Implicit ____ 1 Error intercepted

(*choose only one*) 2 Definitely preventable

3 Probably preventable

4 Probably not preventable

5 Definitely not preventable

16.1 The category of preventability after consensus WITHIN Team (if applicable)

17. Could the event have been prevented by any of the following checks? *Check all that apply*

__1 Drug-drug check

__2 Drug-pt. characteristics test

__3 Drug-dose check

__4 Drug-allergies test

__5 Guided dose algorithm

__6 Other_____

18. Do you feel the Pharmacy Network would have avoided this event? ☐ (1=Yes, 2= No, 3=May be, 4=Unknown)

19. Describe the system stage at which the failures identified above occurred, and the way in which they occurred:

_____

_____

_____

_____

20. Any other comments?

ADE SEVERITY CLASSIFICATION

ADE is defined as an injury due to a drug. Severity of ADE is classified into four categories; 1= Fatal ADE, 2= Life-threatening ADE, 3= Serious and 4= Significant ADE. Definitions/ characteristics of them are given below.

II. LIFE THREATENING	III. SERIOUS	IV. SIGNIFICANT
Definition *An ADE is considered life threatening if the event causes symptoms that if not treated, would put the patient at risk of death.* Life threatening ADEs also include laboratory values that are either elevated or depressed to the point that a critical physiologic function is at risk of failure.	Definition An ADE is considered to be serious if the event causes symptoms that are associated with a serious level of risk that is not high enough to be life threatening. In addition, an ADE is also serious if it causes persistent alteration of life function. Serious ADEs can also include elevated or depressed lab values that require medical intervention, especially if they suggest organ system dysfunction.	*Definition* An ADE is considered to be significant if the event causes symptoms that while harmful to the patient pose little or no threat to the patient's life function. Significant ADEs can include elevated or depressed laboratory test levels.

Symptoms	*Symptoms*	*Symptom*
• Patient transferred to ICU • Cardiac arrest • Respiratory failure requiring intubation • Mental status change- pt falls and gets intracranial hemorrhage • Anaphylaxis • Any use of fresh frozen plasma AND Vitamin K to reverse anticoagulation • 7-unit gastrointestinal bleed	• A two-unit gastrointestinal bleed • Symptom requiring hospitalization • Altered mental status/ excessive sedation • Allergic reaction- shaking chills/ fever • Angioedema, lip swelling • Symptomatic hypoglycemia • Bradycardia/dizziness/syncope • Jaundice • Orthostatic hypotension • Urinary incontinence • Persistent sexual dysfunction • Confusion • Tardive dyskinesia • Clostridium Difficile colitis	• Rash • Diarrhea • Nausea and vomiting • Muscle weakness • Oral thrush • Dyspepsia • Cough • Dizziness • Fatigue • Constipation • Muscle cramps • Insomnia • Headaches • Pedal edema

Lab Abnormality	*Lab Abnormality*	*Lab Abnormality*
• Any potassium ≤ 2.5 mEq/L or ≥ 7.0 mEq/L • Any phenytoin ≥ 139 µmol/L • Any theophylline ≥ 167 µmol/L • Any glucose < 1.67 µmol/L • Any INR ≥ 10 • Any digoxin level > 3.0 ng/ml • Lithium >4.0 mmol/L	• Any potassium: 2.6≥ & <2.7 mEq/L or 6.5 ≥ & < 7.0 mEq/L • Any phenytoin: 119 ≥ & < 139 µmol/L • Any theophylline: 139 ≥ & < 167 • µmol/L • Any glucose: 1.67 ≥ or < 1.94 µmol/L • Any INR: 8 ≥ or < 10 • Any digoxin: 2.5 ≥ & < 3.0 ng/ml • Elevated QTc > 500 millisec • Decreased platelet count to < 20,000	• Any potassium: 2.8≥ & 2.9 mEq/L • or 6.0 ≥ & < 6.5 mEq/L • Any phenytoin: 99≥ & <119 µmol/L • Any theophylline: 111 ≥ & < 139 µmol/L • Any glucose: 1.94≥ & <2.22 µmol/L • Any INR: 6 ≥ INR < 8 • Elevation in SGPT > 150 U/L (ALT)

POTENTIAL ADE SEVERITY CLASSIFICATION

A potential ADE (PADE) is a medication error that has the potential to harm the patient, but did not do so because it was intercepted or because the patient was lucky. Severity of PADE is classified into four categories; 1= Fatal ADE, 2= Life-threatening ADE, 3= Serious and 4= Significant PADE. Definitions/ characteristics of them are given below.

II. LIFE THREATENING	III. SERIOUS	IV. SIGNIFICANT
Definition *A potential ADE is considered life threatening if the event has the potential to cause symptoms that if not treated, would put the patient at risk of death.*	Definition A potential ADE is considered to be serious if the event has the potential to cause symptoms that are associated with a serious level of harm that is not high enough to be life threatening. In addition, a potential ADE is serious if it has the potential to cause persistent alteration of life function.	*Definition* A potential ADE is considered to be significant if the event has the potential to cause symptoms that while harmful to the patient pose little or no threat to the patient's life function.
• Symptoms/ Lab Abnormality •	• Symptoms/ Lab Abnormality •	• Symptoms/ Lab Abnormality •

II. LIFE THREATENING	III. SERIOUS	IV. SIGNIFICANT
• Digoxin level greater than 2.5 ng/mL AND Potassium level greater than 5.0 mEq/L • Patient with a prior penicillin→ anaphylaxis reaction and receiving a penicillin and no reaction • 2 concurrent tylenol prescriptions with a total daily dose > 15 grams	• Chronic Indomethacin use for an older adult • Concurrent non-aspirin NSAIDs prescribed to an older adult • Rofecoxib and Naproxen prescribed together • 2 concurrent tylenol prescriptions with a total daily dose of > 10 grams but ≤ 15 grams	• Inappropriate medication for elderly • Phenobarbital not monitored >1 year • Clozapine prescribed and WBC not monitored >1 month • Digoxin prescribed and Digoxin level not monitored >1year • Woman taking finasteride • 2 concurrent tylenol prescriptions with a total daily dose > 4 grams but ≤ 10 grams • Cyclosporine levels not monitored >1year • Ketorolac prescribed for 7 days • Divalproex levels not monitored >1year • Elevated Lithium level due to drug-drug interaction between Lithium and Indomethacin

APPENDIX E

Estimation of ADE/PADE Prevalence in Adults Presenting to EDs: Sample Weight Adjustment to Account for the Sampling Fraction and Stratification in the Sampling Design

General description on sampling design has been given in chapter 3 for steps to prepare a sample frame followed by a two-step chart review to determine adverse drug events (ADEs) in adults presenting to Emergency Departments (EDs). Given that the study employed a stratified random sampling design along with a multistep review of ED charts, estimation of ADE prevalence was performed using a sample weight to account for the sampling fraction and stratification in the sampling design. This appendix provides a brief description on the sampling scheme related to the sample weight selection, and then a detail about the process of selecting sample weight leading to calculation of ADE/PADE prevalence.

Sampling scheme and data collection

The study population included a total of 82,516 ED visits by patients aged 18 years and older in the calendar year 2005. After excluding ED visits that were by non-residents or associated with high probability of not being due to an ADE (e.g., motor-vehicle-accident, substance abuse, drug abuse, attempted suicide, cut-or-burn injuries, etc.), there were 67,691 ED visits available for the sample frame. A stratified random sample of 1,458 ED charts were selected from this sample frame and reviewed for this study. Although the plan was to review an equal number of ED visits from each of the six strata, the number of ED visits actually reviewed differs slightly (Table E.1).

Table E.1. Sampling scheme for the first step chart review: Stratum-specific number of ED charts in the study sample

Strata	Sample Size (Number of ED charts)
Stratum 1: Male aged 18 – 44 years	241
Stratum 2: Male aged 45 – 64 years	242
Stratum 3: Male aged 65+ years	248
Stratum 4: Female aged 18 – 44 years	242
Stratum 5: Female aged 45 – 64 years	242
Stratum 6: Female aged 65+ years	243
Total	**1,458**

ED =Emergency Department

In the first step, the ED summaries of each of the 1,458 charts were reviewed by a team consisting of a physician and a registered nurse using a manually enabled Trigger Assessment Tool. Following this review of the 1,458 ED visits, 653 were identified as having a high (29), moderate (135), low (218), or very low (271) probability of being the result of an ADE. Because of limited resources available for the study we were not able

to carry out the second step review for all of these 653 charts. Therefore, the review by the team, consisting two physicians and two pharmacists, at the step-2 was carried out on all charts that were classified having a "high" (n=29) or "moderate" (n=135) probability of having ADEs, and only a sample of 170 ED visits classified as having a "low" or "very low" probability of having ADEs. Of the 526 ED charts reviewed in step 2, 334 (29 + 135 +170) was considered as the main sample and the remaining 192 was reviewed to validate the Trigger Assessment Tool. There were 55 (52+3=55) charts determined to have an adverse drug event or a possible adverse drug event (ADE/PADE) (Table E.2).

Table E.2. Results of the first step chart review followed by the sampling scheme for and results of the second step chart review

Results of step 1 review by a physician & a nurse		Step 2 review by 2 ED physicians & 2 clinical pharmacists	
Probability of ADE	**# of ED charts**	**Sample size** [*]	**# of ED charts with an ADE/PADE**
High	29	29	52
Moderate	135	135	
Low	218	170 [‡]	
Very Low	271		
None	805	192	3
Total	**1,458**	**526**	55

[*] The main sample for the second step review included 334 (i.e., 29+135+170=334) ED charts and the remaining 192 charts (a sample from the no probability of ADE group) were reviewed as part of the validation exercise.

[‡] included a random sample of 170 ED charts selected from the pool of low and very low probability classes consisting 489 charts (i.e., 218+271=489).

Sample weight adjustment and calculation of ADE/PADE prevalence

Given the complexity in sampling design employed in this study, the analysis was carried out to calculated the prevalence of ADE/PADE by using: (1) adjusted numerator and denominator to account for sampling fraction associated with exclusion of ED visits in two-step review, and (2) the sample weight variable to account for stratification in the sampling design so that the sample estimate of prevalence of ADE/PADE is closer to the true prevalence in the study population.

Numerator and denominator of prevalence of ADE/PADE to account for sampling fraction

The 2-step review of the sampled ED charts identified 55 ADEs/PADEs. If the sample of 1,458 ED charts were selected from the entire population, and each of these charts was reviewed in both steps, the prevalence of ADE/PADE would have been calculated by dividing 55 (numerator) by 1,458 (denominator). However, in recognizing the need to adjust for the excluded ED visits prior to selecting the study sample and for

not reviewing all eligible charts at step 2, the numerator and denominator counts were adjusted to account for sampling fraction.

Given that 3 of the 55 ADEs/PADEs were identified after reviewing 170 of 489 ED charts classified as "low/very low" probability for ADE, we have taken inverse probability of the sampling fraction and estimated that there would be 9 events ((i.e., 3 x 1/(170/489)=8.6) if all 489 charts were reviewed, yielding an estimated count among the random sample of 1,458 charts to 52+9=61 ADEs/PADEs (numerator). The denominator of the prevalence of ADE/PADE was set to 1,777 (i.e., 1458 * 1/(67691/82516)=1777) to account for the excluded ED visits prior to the chart review, working with the assumption that none of the excluded visits were attributed to an ADE/PADE.

In order to include the 6 additional numerator counts (61-55=6) and the 319 denominator counts (1,777-1,458=319) in calculating the prevalence of ADE/PADE, we estimated the age group and sex for these additional patients. The age group and sex for the 6 patients with ADE/PADE were assigned in proportion to the actual number of ADE/PADE (55) while the 319 were assigned in proportion to the study sample (1,458), with rounding to the nearest whole number (Table E.3).

Table E.3. Distribution of 6 numerator and 319 denominator counts into six strata with reference to actual ADE/PADE counts (55) and study sample (1,458)

Strata	x_{1h}	$x_{2h} = x_{1h} * 6/55$	$x_{3i} = x_{1i} + x_{2i}$	n_{1h}	$n_{2h} = n_{1h} * 319/1{,}458$	$n_{3h} = n_{1h} + n_{2h}$
Male aged 18 – 44 years	0	0	0	241	53	294
Male aged 45 – 64 years	3	0	3	242	53	295
Male aged 65+ years	19	2	21	248	53	301
Female aged 18 – 44 years	4	0	4	242	53	295
Female aged 45 – 64 years	7	1	8	242	53	295
Female aged 65+ years	22	3	25	243	54	297

Total	**55**	**6**	**61**	**1458**	**319**	**1777**

x_1 = Number of ADE/PADE determined through chart review, x_2 =additional counts to the numerator following the adjustment for the sampling fraction, x_3 =Adjusted numerator counts, n_1 = Size of the study sample, n_2 = additional counts to the denominator following the adjustment for the sampling fraction, and $n3$ =Adjusted denominator counts. The subscript h indicates h^{th} stratum, where $h = 1,2,.....,\ 6$.

Sample weight variable to account for stratification in sampling design

The sample weight variable was derived to adjust for stratification in the sampling design so that each ED visit in the study sample represents the stratum-specific number of visits in the study population (Table E.4).

Table E.4. Derivation of sample weight to account for stratification in sampling design

Strata	Adjusted denominator	Population Size	Sample weight
Male aged 18 – 44 years	294	20,113	1/(294/20,113)=68.41
Male aged 45 – 64 years	295	11,827	1/(295/11,827)=40.09
Male aged 65+ years	301	7,035	1/(301/7,035)=23.37
Female aged 18 – 44 years	295	23,027	1/(295/23,027)=78.06
Female aged 45 – 64 years	295	11,813	1/(295/11,813)=40.05
Female aged 65+ years	297	8,701	1/(297/8,701)=29.29
Total	**1,777**	**82,516**	

Calculation of prevalence of ADE/PADE and its 95% confidence interval

In calculating prevalence of ADEs/PADEs, we used (1) adjusted numerator (61 ADEs/PADEs) and denominator (n=1,777) to account for sampling fraction, and (2) the sample weight variable to account for stratification in the sampling design.

The prevalence of ADE/PADE was calculated as

$$\hat{P}_{str} = \Sigma(N_h/N)*\hat{P}_h$$

where h indicates strata, h=1, 2, 3, 4, 5, 6.

N_h is the number of ED visits in the h^{th} stratum of the study population,

$N= \Sigma N_h$ is the total number of ED visits in the study population

$\hat{P}_h = x_h/n_h$ is the estimated proportion of ADE/PADE in stratum h

x_h is the adjusted number of ADE/PADE in stratum h

n_h is the number of ED visit in denominator (adjusted sample size) stratum h

To determine the confidence interval for a prevalence or proportion estimated from stratified random sampling, the standard error (SE) of the proportion was derived using the following equation:

$$SE(p_{\hat{}str}) = \Sigma(1-n_h/N_h)*(N_h/N)\hat{}2*P\hat{}_h(1-P\hat{}_h)/(n_h-1)$$

The 95% confidence interval for prevalence of ADE/PADE was calculated as

$$95\%\ CI = P\hat{}_{str} \pm 1.96*SE(P\hat{}_{str})$$

The formulae with the notations given above have been taken from Lohr, SL (1999) [1].

Table E.5 presents a worksheet used to calculate the overall prevalence of ADE/PADE. After a sample weight adjustment to account for the sampling fraction and stratification in this study, the overall prevalence of ADEs/PADEs was determined to be 2.4%, the standard error of the prevalence estimate was 0.003206042, and the 95% CI was 1.8 - 3.0. The prevalence of ADEs/PADEs and its 95% CIs for males, females, and for three age groups were calculated using a similar approach.

Note that we only used the adjusted ADE number of 61 to calculate prevalence and for extrapolation. Information related to those 55 ADEs/PADEs identified through the chart review were used for additional analysis given severity, preventability and drug related information was not available for these estimated 6 ADEs (61-55=6).

Table E.5. Worksheet to calculate the weighted prevalence of ADE/PADE is given below.

Strata (h)	Strata Name	N_h	n_h	x_h	$\hat{P}_h$	$(1-n_h/N_h)*(N_h/N)^2$ $*\hat{P}_h(1-\hat{P}_h)/(n_h-1)$	(N_h/N) $*\hat{P}_h$	$\hat{P}_{str}-1.96$ $*SE(\hat{P}_{str})$	$\hat{P}_{str}-1.96$ $*SE(\hat{P}_{str})$
1	M 18-44	20,113	294	0	0.0000	0	0.000		
2	M 45-64	11,827	295	3	0.0102	6.85829E-07	0.001		
3	M 65+	7,035	301	21	0.0698	1.50516E-06	0.006		
4	F 18-44	23,027	295	4	0.0136	3.49752E-06	0.004		
5	F 45-64	11,813	295	8	0.0271	1.79325E-06	0.004		
6	F 65+	8,701	297	25	0.0842	2.79694E-06	0.009		
Total		**82,516**	**1,777**	**61**		**0.003206042**	**0.024**	**0.018**	**0.030**

	SE(p^str)= Σ(1-	P^str=Σ(Nh/N)	95% Confidence
	nh/Nh)*	*P^h =**2.4%**	interval = **(1.8, 3.0)**
	(Nh/N)^2*P^h (1-		
	P^h) /(nh-1)		
	=**0.003206042**		

N_h is the number of ED visits in the h^{th} stratum of the study population; $N = \Sigma N_h$ is the total number of ED visits in the study population; $P_h = x_h/n_h$ is the estimated proportion of ADE/PADE in stratum h; x_h is the adjusted number of ADE/PADE in stratum h; n_h is the number of ED visit in denominator (adjusted sample size) stratum h; P^str = prevalence of ADE/PADE after accounting or sampling fraction and stratification; SE(P^str)= Standard error of prevalence estimate

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APPENDIX F

Multiple Regression Models for Analysis of ADR Count Data

The background information and theoretical aspects concerning the four models (Poisson, negative binomial, zero-inflated Poisson, and zero-inflated negative binomial) used in the analysis of the recurrent events of adverse drug reaction (ADR) in Chapter 4 are briefly described below.

Background

The data analyzed in Chapter 4 were from a population-based, retrospective, cohort study using administrative and patient hospital discharge records over a period of 12 years. The study identified recurrent events of adverse drug reactions (ADRs), rather than only the first event. Frequencies of ADRs experienced by a patient in a given interval of time can be referred to as "count data". These count data consist of only non-negative integers, and its typical distribution is highly positively skewed, consisting of a high proportion of zero scores; this is because ADR incidents are relatively rare, and most will not sustain a serious ADR if they do experience minor reactions of medication use [1]. This type of data can be modeled by a number of different probability distributions, depending on how the variance compares to the mean and whether there are a disproportionate number of zero counts. It is important to explicitly account for zeroes in analysis given that, similar to positive counts, they are outcome values. Proper statistical modeling is needed to generate accurate and reliable estimates in predicting number of ADRs, taking into account the large proportion of zero counts and the possibility of recurrent ADRs. As highlighted by Robertson et al. [2] and Ullah et al. [3], several studies

have incorrectly assumed that count data followed a normal distribution and subsequently used inappropriate statistical models. Other studies used a transformation to induce normality [4], although this can be problematic given that transformations often do not yield normally distributed data and can make the interpretation of regression coefficients cumbersome as they are not estimated on the original scale.

A potential solution to the aforementioned problem is to use Poisson regression. Poisson regression is a commonly used statistical technique to model count data [5]. For such counts, the Poisson regression model is better suited to explain the relationship between the outcome variable and a set of explanatory variables. However, count data often exhibit greater variability than allowed by the Poisson model– a condition called over-dispersion. If unaccounted, over-dispersion may have undue consequences such as biasing estimates. A common statistical method used to account for over-dispersion is negative binomial (NB) regression. In modeling the NB regression, the variance and mean are not assumed to be equal and the assumption of independence of observations is lifted [6]. The NB model can also be appropriate when count data are recurrent [3, 7].

Rose and Martin [8] have demonstrated three potential reasons for over-dispersion: unobserved heterogeneity, temporal dependency and/or excess zeroes in the data. Unobserved heterogeneity may be an issue when a population consists of several sub-populations resulting from the fact that the participants enrolled in the study sample are distinct with respect to their socio-demographic or health-related factors, but the sub-

population membership has not been observed in the data. Temporal dependency associated with multiple comorbidities diagnosed over time for each participant may be an issue resulting in over-dispersion. Although NB regression is able to model the data with over-dispersion, it is possible that this modeling approach still could fail to fit a set of data with many zero counts because of zero-inflation, over-dispersion, or both [9]. For this type of data, more zeroes are observed than would be predicted by a standard Poisson or NB models. As an alternative means, zero-inflated regression models such as zero-inflated Poisson (ZIP) and zero-inflated negative binomial (ZINB) address the issue of excess zeroes in their own rights of handling count data [10].

In the analysis of zero-inflated models, it is assumed that there are two latent or unobserved groups that could contribute to the excess zeroes. These two categories of excess zeroes are also referred to as structural or sampling zeroes [8]. For example, a subpopulation of patients may be from the zero state as they are not at risk of experiencing an ADR requiring hospitalization due to their personal characteristics (structural zeroes) and another subpopulation of patients may be susceptible to serious ADR requiring hospitalization in which occurrence of zero would be due to chance (sampling zeroes). ZIP and ZINB are the two models that recognize the existence of these two groups, and also allow for covariate adjustments in each group [11]. For patient safety studies, the zero-inflated portion can be thought of as the odds of moving from the non-

risk to the at-risk group. Once in the at-risk group we can determine the expected number of events or the risk of an event for one group versus another group [8].

The modeling considerations raised above have significant implications for the description of ADR data. When determining predicting factors of a rare event outcome such as ADR, and their directionality and magnitude of association, correctly specifying the statistical models is of the utmost importance in getting proper inferences. Count data with an excess of zero counts have been analyzed in several areas of research including manufacturing defects [10], road safety [12], agriculture and horticulture [13], species abundance [14], medical consultation [15], sexual behavior [16] and injury [17]. However, to our knowledge, there have been no studies to date that focused on risk factors associated with recurrent events of ADR taking into consideration the complexity in data characterized by excess zero and over-dispersion. An appropriate statistical model may allow for a better understanding of the relationship between patient-related factors and recurrent ADRs, and help identify potential risk factors that provide accurate and reliable information to guide policy decisions in relation of priority setting and intervention investments to tackle these unwanted events.

The counts of ADRs in elderly hospitalized patients were modeled using the Poisson, NB, ZIP and ZINB. The basic regression equations directing how ADR counts

were modeled using the four target regression models deserve methodological elaboration given in the following section.

Theoretical Concepts of the Four Regression Models

The Poisson regression model is the most basic model that explicitly takes into account the non-negative integer-valued aspect of the dependent count variable. Because the Poisson distribution is usually appropriate to model the number of events, this regression model can be used in the prediction of likelihood or frequency of ADRs. In a study of ADRs, let Y_i be the random variable that represents the number of ADRs experienced by the patient i over the study period, and y_i is a value of Y_i. The mean of Y_i is μ_i, which is also a random variable with values μ_i. In this situation, the Poisson probability distribution of an ADR count Y_i is

$$P(Y_i = y_i; \mu_i) = \frac{e^{-\mu_i} \mu_i^{y_i}}{y_i!} \qquad (1)$$

where y_i is a non-negative integer, that is, y_i=0, 1, 2, 3, … … …;

i indicates the number of cases or study patients with the data,

that is, i = 1, 2, 3, … … …, n;

It is usually assumed that the number of events Y_i follows a Poisson distribution with a conditional mean (μ_i) depending upon a set of regressors $(x_{i0}, x_{i1}, x_{i2}, ..., x_{ik}, where \quad x_{io} = 1)$ and corresponding parameters $(\beta_0, \beta_1, \beta_2, ..., \beta_k)$ for participants' linear predictor. Using a log link, the expected number of events for participant i can be written as

$$\mu_i = E(y_i \mid x_i) = e^{\sum_j \beta_j x_{ij}}$$

Where x_{ij} is the ij^{th} element of the regressor x_j, where i = 1, 2, 3, … … …, n, and j = 0, 1, 2, 3, … … …, k;

β_0 is the intercept term: and

$\beta_1, \beta_2, ..., \beta_k$ are the coefficients for k covariates/predictors.

Because of the property of the Poisson distribution having equal mean and variance, the variance of Y_i is

$$V(y_i \mid x_i) = \mu_i$$

The mean μ_i is always a positive value given that it represents the average number of ADRs of a specific patient i in the study. Taking the exponential of $\Sigma_j \beta_j x_{ij}$ ensure that the mean parameter μ_i is non-negative.

The Poisson regression model is also referred to as the log-linear model since the logarithm of the conditional mean is linear in the parameters:

$$\ln[\ \mu_i\ ] = \ln[\ E(y_i \mid x_i)] = \Sigma_j \beta_j x_{ij}$$

As noted earlier, the Poisson regression has been criticized due to its restrictive property that the conditional variance equals the conditional mean. Real-life data are often characterized by over-dispersion— that is, the variance exceeds the mean. If over-dispersion is an issue, the estimated parameter based on Poisson regression will be inefficient [5].

The equality of variance assumption of Poisson can be relaxed by using the negative binomial model. The NB regression model is a generalization of the Poisson regression model that allows for over-dispersion by introducing an unobserved heterogeneity term for study participants. In NB model, study subjects are assumed to

differ randomly in a manner that is not fully accounted for by the observed covariates. The probability distribution of an ADR count Y_i is given by

$$P(Y_i = y_i) = \frac{\Gamma(y_i + 1/\theta)}{\Gamma(y_i + 1)\Gamma(1/\theta)} \frac{(\theta\mu_i)^{y_i}}{(1+\theta\mu_i)^{y_i+1/\theta}} \qquad (2)$$

where μ_i, θ and $\Gamma(\bullet)$ are the expected number of events, the NB dispersion parameter, and the gamma function, respectively. The conditional mean parameter μ_i can be expressed as $\mu_i = E(y_i \mid x_i) = e^{\Sigma_j \beta_j x_{ij}}$ and the conditional variance of y_i is $V(y_i \mid x_i) = \mu_i(1+\theta\mu_i)$. Here, θ is a dispersion in the NB model that represents over-dispersion resulting from unobserved heterogeneity and/or temporal dependency. As θ approaches zero, y becomes a Poisson distribution, and as θ becomes larger, the distribution of y becomes more dispersed.

Zero-inflated Poisson and zero-inflated negative binomial models can be used to fit a set of data with many zero counts because of zero-inflation, over-dispersion or both [9, 18-19]. The ZIP model for an ADR count Y_i can be defined as a mixture of two distributions incorporating extra zeroes:

$$P(Y_i = y_i) = \begin{cases} \pi_i + (1-\pi_i)e^{\mu_i} & y_i = 0 \\ (1-\pi_i)\dfrac{e^{\mu_i}\mu_i^{y_i}}{y_i!} & y_i > 0 \end{cases} \quad (3)$$

where π_i is the probability of being an extra zero that is often modeled by using logistic regression. Here for zero inflated portion of ZIP and ZINB regressions, we used the logistic model to estimate π_i, and hence the π_i is estimated by using

$$\pi_i = \frac{1}{1+e^{-\eta_{ij}}}$$

where, $\eta_{ij} = \Sigma_j \beta_j x_{ij}$ is a linear predictor of explanatory variables (x). Zero- inflated models put more weight on the probability of observing a zero by using a mixing distribution. Hence, for ZIP model (3) the probability of observing a zero is given by the sum of observing an excess zero plus the probability of observing a zero in the Poisson model. Clearly, the ZIP models allows for two separate processes. As a first step, it models the structural zeroes (e.g., logistic regression) and the second step models the Poisson distribution conditional on the excess zeroes, i.e., the Poisson regression models the sampling zeroes and counts[8]. The mean and variance of the ZIP model are given by

$$E(y_i \mid x_i) = (1-\pi_i)\mu_i$$

$$V(y_i \mid x_i) = \mu_i(1-\pi_i)(1+\mu_i\pi_i)$$

It can be seen here that when π_i equals zero the ZIP model reduces to the standard Poisson model, but when π_i approaches one the variance increases and the data exhibit greater overdispersion. The over-dispersion accounted for in the ZIP model is conceptually a result of the structural zeroes. Interpretation of the ZIP model depends upon what is being modeled. For patient safety studies, the zero-inflated portion can be thought of as the odds of moving from the non-risk to the at-risk group. Once in the at-risk group we can determine the expected number of events or the risk of an event for one group versus another group.

Zero-inflated negative binomial models are sometimes preferred because they allow for more flexibility in the variance. The ZINB takes care of both over-dispersion and zero-inflated issues. The zero part performs analysis of dichotomous outcome and takes care of the zero-inflation (e.g., no ADR vs. ADR), and the negative binomial part carry out analysis of continuous outcome (e.g., number of ADRs). The ZINB is formulated as equation (3), replacing the Poisson distribution $\frac{e^{\mu_i}\mu_i^{y_i}}{y_i!}$ with the negative binomial distribution in equation (2). Therefore, the ZINB model for Y_i can be written as follow.

$$P(Y_i = y_i) = \begin{cases} \pi_i + (1-\pi_i)\dfrac{1}{(1+\theta\mu_i)^{1/\theta}} & y_i = 0 \\ (1-\pi_i)\dfrac{\Gamma(y_i+1/\theta)}{\Gamma(y_i+1)\Gamma(1/\theta)}\dfrac{(\theta\mu_i)^{y_i}}{(1+\theta\mu_i)^{y_i+1/\theta}} & y_i > 0 \end{cases} \quad (4)$$

The mean of ZINB model is same as the mean for ZIP model but the variance is given by $V(y_i \mid x_i) = \mu_i(1-\pi_i)[1+\mu_i(\pi_i+\theta_i)]$. It should be noted that the variance depends on π_i and the dispersion parameter θ_i. The ZINB model takes into account that the non-zero counts might be correlated [5]. The added flexibility of ZINB model is that it allows for over-dispersion arising from excess zeroes and heterogeneity, whereas the ZIP model only accommodates over-dispersion from excess zeroes.

Model selection is one of the fundamental tasks of scientific inquiry that choose the best model from a set of potential models. While several criteria can be used to compare and contrast the models given above, nested models can be tested using a likelihood ratio test (LRT). Since the Poisson model is nested within the NB model, and accordingly the ZIP model is nested with the ZINB model, a LRT can be used for this comparison. A maximum likelihood ratio [20] ρ^2 is given by

$$\rho^2 = 1 - \frac{L(\beta)}{L(0)} \qquad (0 \le \rho^2 \le 1) \quad (5)$$

where $L(\beta)$ is the log likelihood function

and $L(0)$ is restricted log likelihood.

Of the four models, the Poisson model is not nested within the ZIP, and the NB model is not nested within the ZINB model. Therefore, for the purpose of the comparison between non-nested models, the test proposed by Vuong (1989) can be used. If $\hat{P}_1(y_i \mid x_i)$ and $\hat{P}_2(y_i \mid x_i)$ are opposing predicted probability distributions, the Vuong statistic is computed as follows [8, 20]

$$m_i = \ln[\frac{\hat{P}_1(y_i \mid x_i)}{\hat{P}_2(y_i \mid x_i)}] \tag{6}$$

$$V = \frac{\overline{m}\sqrt{n}}{S_m} = \frac{\sqrt{n\left[\frac{1}{n}\sum_{i=1}^{n} m_i\right]}}{\sqrt{\frac{1}{n}\sum_{i=1}^{n}(m_i - \overline{m})^2}} \tag{7}$$

In comparing the non-nested models given above, $P_1(y_i \mid x_i)$ represents ZIP (or, ZINB) model and $P_2(y_i \mid x_i)$ represents the standard Poisson (or, NB) model. For a sample of size n, the statistic m has a mean $\overline{m}$ and standard deviation S_m. The Vuong statistic V asymptotically follows standard normal distribution. If V>1.96 then it favors the zero inflated model and V<-1.96 favors the standard Poisson or NB model.

In addition to above two tests, the multiple regression models for the ADR study data leading to chapter 4 were compared by using the Bohning's [21] goodness-of-fit statistical test, the Wald test [22], and the Pearson's chi-square test. A graphical presentation of predicted probabilities and Aaike information criteria (AIC) were also used to compare models.

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APPENDIX G

Curriculum Vitae

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- Dissertation: "Serious Adverse Drug Events in Patients Presenting to Emergency Departments and Admitted to Hospitals in Newfoundland and Labrador"

M.A.S. (Applied Statistics) — Oct 2003
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- Dissertation: "Application of Geographically Weighted Regression for Assessing Spatial Non-stationarity"

M.Sc. (Statistics) — Oct 1997
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AWARDS AND FELLOWSHIPS

Front and Centre Award — Nov 2010
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Fellow of the School of Graduate Studies Award, Distinction in Community Health — May 2010
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Graduate Fellowship in Medicine (Community Health) — May 2004 –Aug 2008
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Graduate Fellowship in Applied Statistics — Sep 2001-Aug 2003
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IFNA Travel Award for Interface Symposium — Apr 2002
Interface Foundation of North America (IFNA), Montreal, QC

Distinction in M.Sc. (Statistics) - First Class First — Oct 1997
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Undergraduate Scholarship in Statistics — Jan 1993 – Dec 1995
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PROFESSIONAL EXPERIENCE

Current Position

Senior Biostatistician — Apr 2007 - Present
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Statistical Consultant — Feb 2004 – Apr 2007
Research and Evaluation Department, NL Centre for Health Information, St. John's, NL

Sessional Faculty/ Per-course Lecturer — Sep 2008 – Dec 2008, Jan 2002– Apr 2002
Department of Mathematics and Statistics, Memorial University of Newfoundland, St. John's, NL

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Project Development Officer (Monitoring and Evaluation) — Dec 2000 – Aug 2001
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Technical Officer (Monitoring and Evaluation) — Jun 2000 – Dec 2000
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Statistician — Jun 1998 – Jun 2000
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- Monte Carlo methods for estimation and optimization — May 2009
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- Holistic Approach of Household Livelihood Security — Jan 2001

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- SPPS Information Session for Data Analysis, Nov 2009
  NL Centre for Health Information, NL

- Wealth Ranking Exercise. Nov 2000
  CARE International, Dhaka, Bangladesh

- Household Livelihood Security Mar 2001
  CARE *International, Cox's Bazar, Bangladesh*

- Participatory Monitoring & Evaluation, and Process & Outcome Evaluation Jul 2000
  CARE International, Dhaka, Bangladesh

- Beneficiary Selection through Baseline Survey Jul 1999
  PROSHIKA, Dhaka, Bangladesh

- Impact Assessment Study of Microcredit Intervention Jan 1999
  PROSHIKA, Dhaka, Bangladesh

JOURNAL PUBLICATIONS

- **Sikdar, K.C.**, Alaghehbandan, R., MacDonald, D., Barrett, B., Collins, K.D., Donnan, J. Gadag, V. Adverse drug events in adult patients leading to emergency department visits. *Ann Pharmacother*.2010; 44:641-9.

- **Sikdar, K.C.**, Wang, P.P., MacDonald, D., Gadag, V. Diabetes and Its Impact on Health-related Quality of Life: A Life Table Analysis. *Qual Life Res* 2010; 19: 781-87.

- **Sikdar, K.C.**, Alaghehbandan, R., MacDonald D., et al. Adverse drug events among children presenting to a hospital emergency department in Newfoundland and Labrador, Canada. *Pharmacoepidemiol and drug saf* 19(2):132-140, 2010.

- Alaghehbandan, R., **Sikdar, K.C.**, MacDonald, D., Collins, K.D., Rossignol, A.M. Unintentional injuries among children and adolescents in aboriginal and non-aboriginal communities, Newfoundland and Labrador, Canada. *Int J Circumpol Heal*. 69(1):61-71, 2010.

- Edwards, N., Alaghehbandan, R., MacDonald, D., **Sikdar, K.C.**, Collins, K.D., Avis, S. Suicide in Newfoundland and Labrador: a linkage study using Medical Examiner and Vital Statistics data. *Can J Psychiatry* 53(4):252-59, 2008.

PAPERS SUBMITTED FOR PUBLICATION

- Dowden, J.J., **Sikdar, K.C.**, Wang, P. Association between self-perceived occupational stress and binge drinking: an examination of income differences in a representative sample of working Canadian. *Int J Occup Env Heal* (Submitted November 2009).

- De Silva,T.S., MacDonald, D., Paterson, G., **Sikdar, K.C.**, Cochrane, B. Systematized nomenclature of medicine clinical terms (SNOMED CT) to represent computed tomography procedures. Computer Methods and Programs in Biomedicine. *Int J Occup Env Heal* (Submitted November 2009). *Comput Methods Programs Biomed* (Submitted October 2010).

PAPERS IN PREPARATION

- **Sikdar, K.C.**, Dowden, J., Gadag, V., Alaghehbandan, R., MacDonald, D.. Adverse drug reactions in elderly hospitalized patients: a population-based retrospective cohort study over a 12-year period

- **Sikdar, K.C.**, Roy, M., Dowden, J., Wang, P. Association between diabetes and the incidence of hospital admission in Canadian adults

- Walsh, S.J., **Sikdar, K.C.**, Gladney, N., Murphy, M., Mao, Y., Collins, K.D. Diabetes and the risk of cancer: a population-based retrospective cohort study over a 11.5-year period".

REVIEWER

- Journal of Canadian Medical Association Oct 2007

CONFERENCE PAPERS (REFERRED, PUBLISHED)

- **Sikdar, K.C.**, Dowden, J., Alaghehbandan, R., MacDonald, D., Gadag, V. Modeling count data with an application to adverse drug reaction in hospitalized patients. *2009 Annual Meeting of Statistical Society of Canada, Vancouver, BC*, May 31 – June 3, 2009.

- Dowden, J., **Sikdar, K.C.**, Alaghehbandan, R., MacDonald, D., Statistical Inferences of Childhood Injury Data using Mixed-Effects Zero-Inflated Poisson Models. *2009 Annual Meeting of Statistical Society of Canada, Vancouver, BC*, May 31 – June 3, 2009.

- Alaghehbandan, R., **Sikdar, K.C.**, MacDonald, D., Collins, K.D., Rossignol, A.M. Childhood unintentional injuries in urban and rural communities in Newfoundland and Labrador. *7th International Conference on Urban Health, Vancouver, BC*, October 29-31, 2008.

- Alaghehbandan, R., **Sikdar, K.C.**, MacDonald, D., Collins, K.D., Rossignol, A.M. Epidemiology of traffic injuries among children and adolescents in urban areas, Newfoundland and Labrador. *7th International Conference on Urban Health, Vancouver, BC*, October 29-31, 2008.

- Murphy, D., MacDonald, D., Collins, K.D., Alaghehbandan, R., Colbourne, A., Dowden, J., **Sikdar, K.C.** Determinants of early vs. late diagnosis of diabetes in Newfoundland and Labrador, Canada. *136th Annual Meeting American Public Health Association, San Diego, CA, USA*, October 25-29, 2008.

- **Sikdar, K.C.**, Alaghehbandan, R., Donnan, J., MacDonald, D., Gadag, V., Barrett, B. Emergency Department visits in adult patients caused by Adverse Drug Events, Newfoundland and Labrador. *Data Users Conference 2008: Linking the Health Information Chain, Ottawa, ON*, September 21-23, 2008.

- Donnan, J., **Sikdar, K.C.**, Alaghehbandan, R., MacDonald, D., Gadag, V., Barrett, B. Validation of an Adverse Drug Event Trigger Assessment Tool. *Canadian Society of Hospital Pharmacists: Annual General Meeting 2008 - Ride the Tide, Saint John, NB*, August 9-12, 2008.

- Chislett, T., Alaghehbandan, R., **Sikdar, K.C.**, MacDonald, D., Collins, K.D., Rossignol, A.M. Childhood unintentional injuries among Aboriginal and non-Aboriginal communities in Newfoundland and Labrador. *First Nations and Inuit Health Branch's Inaugural First Nations, Inuit and Métis Research Meeting, Montreal, QC*, April 16-18, 2008, Conference Proceedings.

- Alaghehbandan, R., Edwards, N., MacDonald, D., **Sikdar, K.C.**, Collins, K.D., Avis, S. Epidemiology and precipitating factors of suicide in Newfoundland and Labrador, Canada. *Twenty Fourth Biennial Congress of the International Association for Suicide Prevention, Killarney, Ireland*, August 28 - September 1, 2007, Conference Proceedings, P 113-114.

- **Sikdar, K.C.**, MacDonald, D., Alaghehbandan, R., Barrett, B., Collins, K.D. Adverse drug events among adults in emergency departments, Newfoundland and Labrador, Canada: a preliminary analysis. *23rd International Conference on Pharmacoepidemiology and Therapeutic Risk Management, Quebec City, QC*, August 19-22, 2007. *Pharmacoepidemiology and Drug Safety 2007; 16 (Suppl 2):S188.*

- Alaghehbandan, R., Edwards, N., **Sikdar, K.C.**, MacDonald, D., Avis, S. Suicide mortality in Newfoundland and Labrador, Canada, 1997-2001. *134th Annual Meeting American Public Health Association, Boston, MA, USA*, November 4-8, 2006.

- **Sikdar, K.C.**, Alaghehbandan, R., MacDonald, D., Collins, K.D., Rossignol, A.M. Comparing epidemiology of suicide attempts in rural and urban communities, Newfoundland and Labrador: a population-based approach. *2006 Canadian Association for Suicide Prevention (CASP) Annual Conference - Complexity of Suicide: Prevention, Intervention and Aftermath, Toronto, ON*, October 25-27, 2006.

- MacDonald, D., Alaghehbandan, R., **Sikdar, K.C.**, Collins, K.D., Rossignol, A.M. Epidemiology of childhood injury in Newfoundland and Labrador. *Global Health Educational Conference 2006, Canadian Institute of Public Health Inspectors Educational Conference, St. John's, NL*, October 23-24, 2006.

- MacDonald, D., **Sikdar K.C.**, Collins, K.D., Alaghehbandan, R. Epidemiology of childhood burn injuries in Newfoundland and Labrador, Canada. *American Journal of Epidemiology 2006; 163 (Suppl):S11.*

- MacDonald, D., Alaghehbandan, R., **Sikdar, K.C.**, Collins, K.D., Rossignol, A.M. Epidemiology of childhood injury in Newfoundland and Labrador: a population-based study. Canadian Pediatrics Society: Annual Meeting 2006, St. John's, NL, June 13-17, 2006, *Paediatrics & Child Health 2006; 11 (Suppl B): 51B.*

- Alaghehbandan, R., **Sikdar, K.C.**, Collins, K.D., Rossignol, A.M., MacDonald, D. Epidemiology of occupational injury in Newfoundland and Labrador: a population-based approach. Research on Workplace Health and Safety: *From the Core to the Margins, a joint international conference by SafetyNet and the Canadian Association for Research on Work and Health (CARWH), St. John's, NL*, June 7-10, 2006, Conference Proceedings, P 66.

- Alaghehbandan, R., **Sikdar, K.C.**, MacDonald, D., Collins, K.D., Rossignol, A.M. Childhood unintentional injuries among Aboriginal and non-Aboriginal communities in Newfoundland and Labrador. *Canadian Public Health Association 97th Annual Conference, Vancouver, BC*, May 28-31, 2006.

- Alaghehbandan, R., **Sikdar, K.C.**, MacDonald, D., Collins, K., Rossignol, A.M. Childhood unintentional injuries among Innu, Inuit, Métis and non-Aboriginal communities, Newfoundland and Labrador. *Community Health Research in Labrador: Listening, Learning, and Working Together, Goose-Bay, NL*, May 16-18, 2006, Conference Proceedings, P 9.

- **Sikdar, K.C.,** Alaghehbandan, R., MacDonald, D., Gates, K.D., Rossignol, A.M. Children and adolescents injury morbidity in Newfoundland and Labrador. 2005 *Canadian Injury Prevention and Safety Promotion Conference, Halifax, NS,* November 6-8, 2005, Abstract Book, #19.

- Alaghehbandan, R., **Sikdar, K.C.**, MacDonald, D., Gates, K.D., Rossignol, A.M. Epidemiology of traffic injury among children and adolescents in Newfoundland and Labrador. *Atlantic Networks for Prevention Research Forum 2005, White Point, NS,* October 25-26, 2005, Final Program, P 47-8.

- MacDonald, D., Gates, K.D., **Sikdar K.C.**, Alaghehbandan, R. Epidemiology of childhood burn injuries in Newfoundland and Labrador, Canada. *Annals of Epidemiology* 2005; 15(8):657-8.

- Alaghehbandan, R., MacDonald, D., Gates, K.D., Edwards, N., **Sikdar K.C.** Hospitalization for pneumonia among Aboriginal compared to non-Aboriginal people, Newfoundland and Labrador. *Epidemiology Without Borders – a joint meeting of the Society for Epidemiologic Research (SER) and the Canadian Society for Epidemiology and Biostatistics (CSEB), Toronto, ON,* June 27-30, 2005, American Journal of Epidemiology 2005;161(Suppl):S37.

- Alaghehbandan, R., Edwards, N., MacDonald, D., **Sikdar, K.C.**, Collins, K.D., Avis, S. Epidemiology and precipitating factors of suicide in Newfoundland and Labrador, Canada. *Twenty Fourth Biennial Congress of the International Association for Suicide Prevention, Killarney,* Ireland, Aug 28-Sep 1, 2007.

- Collins, K.D., Roberts, A., MacDonald, D., O'Keefe, T., **Sikdar, K.**C., Murphy, M., Organ, M., Alaghehbandan, R. Diabetes, associated comorbidities and health service utilization among the Miawpukek First Nation, Newfoundland and Labrador. *The 7th International Conference on Diabetes and Indigenous Peoples, Ottawa, ON,* August 29 – September 1, 2007.

ACADEMIC/ PROFESSIONAL RESEARCH REPORTS

- West, R., MacDonald, D., Street, C., **Sikdar, K.C.,** Rahman, P. Keeping an Eye on Prescription Drugs: Keeping Canadians Safe Dr. Proton Rahman responds: Guest blog contributor to a Health Council Canada's Commissioned paper. Canada Values Health Dialogue on Health Care, Nov 17, 2010.

- Squires, J, **Sikdar, K.C.**, Stares, J, Collins, K. Enhancing chronic disease surveillance in Newfoundland and Labrador: adjustment of rates of diabetes based on physician payment method. *A report submitted to the Public Health Agency of Canada, Government of Canada. (June, 2010).*

- Walsh, S, **Sikdar, K.C.**, Gladney, N, Murphy, M, Collins, K. Assessing the association between diabetes and cancer in Newfoundland and Labrador. *A report submitted to Public Health Agency of Canada, Government of Canada. (March, 2010).*

- MacDonald, D., Barrett, B., **Sikdar, K.C.**, Collins, K., Donnan, J., Alaghehbandan, R. Serious adverse drug events in adult patients leading to emergency department visits: a baseline study in the community benefits of a pharmacy network. *A report submitted to Health Canada, Government of Canada. (2009)*

- **Sikdar, K.C.** Dowden, J., Gladney, N. SPSS information session manual. A user's guide for new researchers in Research and Evaluation Department, *NL Centre for Health Information (2009).*

- MacDonald, D., Barrett, B., **Sikdar, K.C.**, Collins, K., Donnan, J., Snow, A., Alaghehbandan, R. Serious adverse drug events in paediatric patients leading to emergency department visits: a baseline study in the community benefits of a pharmacy network. *A report submitted to Canada Health Infoway, Government of Canada. (2009).*

- Collins, K.D., **Sikdar, K**.C., Murphy, M.,. Diabetes, associated comorbidities and health service utilization among the Miawpukek First Nation, Newfoundland and Labrador. *A report submitted to the Public Health Agency of Canada, Government of Canada. (2008).*

- Alaghehbandan, R., **Sikdar, K.C.**, MacDonald, D., Gates, K.D. Rossignol, A.M. Epidemiology of children and adolescent injuries in Newfoundland Labrador: a population-based study. *A report to the Department of Health and Community Services, Government of Newfoundland and Labrador. NL. (2007).*

- Edwards, N., Alaghehbandan, R., MacDonald, D., Collins, K.D., **Sikdar, K.C.**, Avis, S. Epidemiology of suicide in Newfoundland and Labrador. *A report to the Department of Health and Community Services, Government of Newfoundland and Labrador, NL. (2007).*

- **Sikdar, K.C.** Application of geographically weighted regression for assessing spatial non-stationarity. *A thesis for Masters of Applied Statistics program to the School of Graduate Studies, Memorial University of Newfoundland, NL.* (2003).

- **Sikdar, K.C** & Smith, H. Perspective of international students: A survey report on Memorial University's international students. *A report to the Graduate Student Union, Memorial University of Newfoundland, NL.* (2002).

- **Sikdar, K.C.** A guideline on design, monitoring and evaluation (DM&E). *An user's guide to the Locally Intensified Farming Enterprise and New Options for Pest Management Phase II project, CARE International, Dhaka, Bangladesh.* (2001).

- Hasan, M. & **Sikdar, K.C.** Annual monitoring report on intervention delivery to project participants. *A report to the Strengthening Household Access to Bari Gardening Project, funded by the Department for International Development (SHABGE-DFID), CARE International, Dhaka, Bangladesh.* (2001).

- Rahman, R., Chakrabarty, S.K., Khan, S.I. & **Sikdar, K.C.** Monitoring and evaluation guideline for partner non-government organization's (NGO) intervention programs. *An user's guide to the SHABGE-DFID project, CARE International, Dhaka, Bangladesh.* (2001).

- **Sikdar, K.C.,** Rahman, M. & Khan, S.I. SHABGE-DFID Project Implementation Report. *A report to the SHABGE-DFID project, CARE International, Dhaka, Bangladesh.* (2001).

- **Sikdar, K.C.**, Chowhan, G., Khan, M.A., & Hasan, R. Impact of the Locally Intensified Farming Enterprise (LIFE) project. *A report to the LIFE project, CARE International, Dhaka, Bangladesh.* (2000).

- **Sikdar, K.C**. Periodic measures of interventions to the LIFE'S participants. *A monitoring report to the LIFE project, CARE International, Dhaka, Bangladesh.* (2000).

- **Sikdar, K.C**. Monitoring and Evaluation Workshop Report. *A report to the LIFE project, CARE International, Dhaka, Bangladesh.* (2000).

- Naser, A., Biswas, G.S., & **Sikdar K.C.** Internal Periodic Monitoring Survey. *A report to PRHOSHIKA- A Center for Human Development, Dhaka, Bangladesh..* (2000).

- Naser A., & **Sikdar, K.C.** Group development stage quality control study. *A report to PRHOSHIKA- A Center for Human Development, Dhaka, Bangladesh..* (2000).

- Shahabuddin, M., Naser, A., Rahman, R.A., Beck, T., Ali, M.A., Mondal, S.H., **Sikdar, K.C.**, Hossain, M.S., Rahman, M.M., Biswas, G.S., Seema, F.J., Islam, M.A., Khan, Z.A., Salim, M., Rashim, M., Rahman, M., Koli, N.B., Mustary, S. Impact assessment study of PROSHIKA's program. *An evaluation report to PRHOSHIKA- A Center for Human Development, Dhaka, Bangladesh.* (1999).

- Naser A., Biswas, G.S., & **Sikdar, K.C.** Group development stage quality control study. *A report to PRHOSHIKA- A Center for Human Development, Dhaka, Bangladesh..* (1998).

COMPUTER SKILLS

- Statistical Software: SAS, SPSS, SPLUS and R
- Spreadsheet database: Microsoft Access and Excel

PROFESSIONAL AFFILIATIONS/ COMMITTEE MEMBERSHIP

Science Committee, Canadian Chronic Disease Surveillance System Public Health Agency of Canada, Ottawa, ON	2010 - Present
Statistical Society of Canada, Ottawa, ON	2009 - Present
Patient Safety Research Affinity Group, St. John's, NL	2009 - Present
Quantitative Research Affinity Group, St. John's, NL	2006 - Present
Stroke Surveillance System Working Group	2009 - Present

Public Health Agency of Canada, Ottawa, ON

Technical Support Working Group, Canadian Chronic Disease Surveillance System, Public Health Agency of Canada, Ottawa, ON — 2004 - Present

Institute of Mathematical Statistics, MD, USA — 2002 - Present

Bangladesh Statistical Association, Dhaka, Bangladesh — 2001 - Present

Live Birth and Death Registration committee
NL Centre for Health Information, St. John's, NL — Jan 2005 – Dec 2008

Pre-diabetes Case Ascertainment Technical Working Group
Public Health Agency of Canada, Ottawa, ON — Jan 2007 – Dec 2007

Facilities Management Board of Graduate Students' Union
Memorial University of Newfoundland, St. John's, NL — May 2001 – Aug 2003

Cultural Program Committee at Department of Statistics
Shahjalal University of Science and Technology, Sylhet, Bangladesh — Jan 1996 – Oct 1997

World University Service of Bangladesh
Shahjalal University of Science and Technology, Sylhet, Bangladesh — Jan 1993 – Dec 1995
