A RECORD LINKAGE STUDY WHICH EXAMINES THE IMMUNIZATION AND HOSPITALIZATION EXPERIENCES OF A BIRTH COHORT OF MANITOBA CHILDREN IN THE FIRST YEAR OF LIFE

BY

JANICE D. ROBERTS

A Thesis
Submitted to the Faculty of Graduate Studies
in Partial Fulfillment of the Requirements
for the Degree of

MASTER OF SCIENCE

Department of Community Health Sciences
University of Manitoba
Winnipeg, Manitoba

ISBN 0-315-77858-X

A RECORD LINKAGE STUDY WHICH EXAMINES THE IMMUNIZATION AND HOSPITALIZATION EXPERIENCES OF A BIRTH COHORT OF MANITOBA CHILDREN IN THE FIRST YEAR OF LIFE

BY

JANICE D. ROBERTS

A practicum submitted to the Faculty of Graduate Studies of the University of Manitoba in partial fulfillment of the requirements of the degree of

MASTER OF SCIENCE

ABSTRACT

Review of the current literature indicates that a number of serious adverse clinical events have been uncommonly or rarely associated in time with routine childhood immunization using diphtheria-tetanus-pertussis and polio vaccines. However, the exact nature of these temporal associations is not understood, and population rates of incidence for the events of interest have not been established. A population-based active surveillance system is required to provide accurate and complete data concerning these serious events and their relationship to immunization.

The universal health insurance plan of the province of Manitoba maintains a computerized population registry, on which hospitalization and immunization files have been constructed. The study used this database to investigate the feasibility of implementing such a surveillance system in the province.

Separate examination of the files enabled description of both the immunization status and hospitalization status of the 1988 birth cohort of Manitoba children in the first year of life. Immunization and hospitalization rates were calculated for the cohort, as were rates of incidence for hospitalization with the adverse events of interest. Record linkage by unique identifier permitted the

immunization and hospitalization experiences of the cohort in the first year of life to be related and examined together. Examination of overall hospitalization in relationship to routine immunization with DTP/DT and polio vaccines found no temporal association to exist between the two in the first year of life. Using diagnostic discharge codes to identify hospitalizations with the adverse events of interest, the study concluded that a true temporal association in the first year of life between DTP/DT immunization and hospitalization with convulsions does exist. The study was also able to describe the immunization and/or hospitalization experiences of special groups of children. It was concluded that the implementation of an active surveillance system using this technique is entirely feasible. Annual repetition of the analysis, with data accumulation, will permit further investigation into the nature of the temporal relationships between immunization and adverse events, the calculation of incidence rates, and the analysis of the findings concerning of special groups.

ACKNOWLEDGEMENTS

For the successful completion of this project, I am indebted to the following people: Dr. Leslie L. Roos, Dr. Thomas H. Hassard, Dr. Barbara Law, and Dr. Linda Poffenroth. Their assistance, sustained interest, and encouragement are greatly appreciated. My thanks go also to Ms. Judith Bebchuk, who contributed her technical ability and patience to the study.

TABLE OF CONTENTS

	Page
ABSTRACT	iv
ACKNOWLEDGEMENTS	vi
LIST OF FIGURES	xii
LIST OF TABLES	xiii
1. GENERAL INTRODUCTION	1
1.0 Introduction	1
1.1 The Objectives of the Thesis	5
2. IMMUNIZATION AND AGENTS USED IN THE FIRST YEAR OF LIFE - MANITOBA	8
3. REVIEW OF THE LITERATURE	9
3.0 Introduction	9
3.1 The Current State of Knowledge Concerning Adverse Events Following the Administration of Immunizing Agents Routinely Used in the First Year of Life	9
3.1.0 Immunization	9
3.1.1 Approaches to Active Immunization	12
3.1.2 History of the Development of Immunizing Agents	14
3.1.3 Agents Currently Routinely Used In Active Immunization in the First Year of Life	19
3.1.4 Vaccine Recommendations	20
3.1.5 Adverse Events - Background	22
3.1.6 Classification of Adverse Events	26
3.1.6.0 Introduction	26

3.1.6.1 Transient Local and Systemic Reactions 26

3.1.6.1.0 Introduction 26

3.1.6.1.1 Pertussis Vaccine and Combinations 27

3.1.6.1.2 Poliomyelitis Vaccines 28

3.1.6.2 Major Reactions and Temporally Associated Events 28

3.1.7 Major Reactions and Adverse Events Temporally Associated with Specific Vaccines 30

3.1.7.0 DTP and DT Vaccines 30

3.1.7.0.0 Introduction 30

3.1.7.0.1 Neurologic Illness and Death 31

3.1.7.0.1.0 Encephalopathy, Encephalitis 31

3.1.7.0.1.1 Infantile spasms 34

3.1.7.0.1.2 Death 36

3.1.7.0.1.2.0 Sudden Infant Death Syndrome (SIDS) 36

3.1.7.0.1.1.0 Non-SIDS deaths 38

3.1.7.0.1.3 Neuropathy 38

3.1.7.0.2 Other Major Adverse Events 40

3.1.7.0.2.0 Introduction 40

3.1.7.0.2.1 Anaphylaxis 40

3.1.7.0.1.2 Very High fever 41

3.1.7.0.1.3 Persistent crying and unusual high pitched crying/screaming 43

3.1.7.0.1.4 Excessive somnolence 44

3.1.7.0.1.5 Seizures 44

3.1.7.0.1.6 Hypotonic-hyporesponsive state 54

3.1.7.0.1.7 Other Major Events Reported 55

3.1.7.1 Poliomyelitis vaccine 55

3.1.7.1.0 Introduction 55

3.1.7.1.1 Inactivated Poliomyelitis Vaccine (IPV) 57

3.1.7.1.2 Live Attenuated Poliovirus Vaccine (OPV) 58

3.2 An Overview of Medical Record Linkage 61

3.2.0 Introduction 61

3.2.1 History 61

3.2.2 Concepts 66

3.2.3 Record Linkage in Manitoba 69

3.3 Summary of the Literature Reviews 72

4. STUDY METHOD 75

4.0 Introduction 75

4.1 Sources of Data 75

4.2 Structure and Maintenance of the Manitoba Immunization Monitoring System 77

4.3 Immunization Rates - Manitoba 80

4.4 Data Organization and Software 82

4.5 Sample 84

4.6 Definition of Variables Used in the Examination of the Temporal Association Between Immunization in the First Year of Life and Adverse Clinical Events 85

4.7 Data Quality 87

5. STATISTICAL METHOD AND THE SCOPE OF THE THESIS 92

5.0 Adverse Events of Interest and Expected Incidence Rates 92

5.1 Methods of Achieving the Specific Objectives of the Thesis 95

5.2 Considering Selection 100

5.2.0 Children Receiving Only Two Doses or Only One Dose 100

5.2.1 Children Immunized in Hospital 100

5.2.2 Children Receiving No Immunizations 101

5.3 Testing the Reality of the Temporal Associations 101

6. RESULTS 106

6.0 The Study Cohorts 106

6.1 Descriptive Findings 110

6.1.0 Immunization Status 110

6.1.1 Hospitalization Status 116

6.2 Rates of Incidence, for the Main Cohort, of Those Uncommon or Rare, Serious Adverse Events Which Have Been Temporally Related to Immunization 121

6.3 The Temporal Relationship Between Hospitalization and Immunization 123

6.3.0 Hospitalization for Any Reason - The Main Cohort 123

6.3.1 Hospitalization with Designated Diagnoses - The Main Cohort 127

6.3.2 The Effect of Service Date Errors 132

6.4 Children Who Received Only Two Doses or Only One Dose 133

6.5 Children Immunized in Hospital 134

6.6 Children Receiving No Immunizations 135

6.7 Immunized Children Who Died in the First Year of Life 147

6.8 Data Quality - The Provider Code 149

7. DISCUSSION 151

8. CONFIDENTIALITY 159

9. FUTURE RESEARCH 160

10. REFERENCES 162

APPENDICES

Appendix 1: Manitoba Provincial Immunization Schedule

Appendix 2: Essential Elements of MIMS

Appendix 3: MIMS Tariff Codes and Immunization Alternatives

Appendix 4: MIMS Monitoring Activities

Appendix 5: MIMS Follow-up Record

Appendix 6: List of ICD-9-CM Diagnostic Codes Signifying Adverse Events Related to DTP/DT/Polio Vaccine Administration

Appendix 7: Flow Diagram, Selection of Main Study Cohort

Appendix 8: Flow Diagram, Selection of Unimmunized Study Cohort

LIST OF FIGURES

		page
1.	Immunization status, main cohort	110
2.	Simultaneous immunization	111
3.	Immunization status, combined cohorts	113
4.	Age at DTP immunization	114
5.	Hospitalization by age, main cohort	117
6.	Length of hospital stay over 7 days, immunized cohort	118
7.	Hospitalization by age, unimmunized cohort	138
8.	Length of hospital stay over 7 days, unimmunized cohort	140

LIST OF TABLES

		page
1.	Expected incidence rates of adverse events	94
2.	Immunization rates, combined cohorts	113
3.	Age at immunization, in months	115
4.	Distribution of primary discharge diagnoses, main cohort	120
5.	Designated diagnostic codes, admissions over 30 days of age	122
6.	DTP immunization, hospitalization for any reason	123
7.	OPV immunization, hospitalization for any reason	124
8.	Number of hospitalizations with designated diagnostic discharge codes before and after OPV immunization, by dose	128
9.	Number of hospitalizations with designated diagnostic discharge codes before and after DTP immunization, by dose	128
10.	Children receiving only one or two vaccine doses	133
11.	Distribution of primary discharge diagnoses, unimmunized cohort	142
12.	Designated diagnostic codes, admissions over 30 days of age, unimmunized cohort	143

1. GENERAL INTRODUCTION

1.0 Introduction

Immunization programs target whole populations and aim to protect all individuals in the population from vaccine-preventable diseases.[1] They are among the most successful prevention programs in public health.[2] It is generally accepted of immunization that no modality, with the exception of safe water, has had a greater impact on the health of the global population.[3] Active immunization programs have resulted in the global eradication of smallpox, and the near elimination of poliomyelitis, rubella, measles, diphtheria and tetanus from Canada[4] and the United States.[1] This remarkable success is the result of the appropriate use of safe and effective vaccines.[2]

This appropriate use of vaccines requires ongoing assessment, particularly as new vaccines are developed and licensed. Orenstein and Bernier[2] describe the importance of maintaining a vaccine information system which permits measurement of health impact, definition of target populations for immunization, evaluation of the impact of the immunization program, and detection of problems requiring alterations in immunization strategies. The two principal components of such an

information system are surveillance and special studies or investigations.

Public health surveillance has been defined as "...the ongoing systematic collection, analysis, and interpretation of health data essential to the planning, implementation, and evaluation of public health practice, closely integrated with the timely dissemination of these data to those who need to know..." (Centers for Disease Control, Atlanta[5]) As noted by Thacker and Berkelman in their comprehensive review,[6] surveillance systems are usually designed to monitor trends, to detect and describe problems, and to establish hypotheses to be tested in more refined research designs. Surveillance systems are ongoing, and collect limited data on each case, and data analysis is traditionally straightforward. They differ from special studies, which are usually designed to test specific hypotheses, are time-limited, and involve more complex data collection and more sophisticated analyses.

With regard to immunization programs, surveillance systems not only monitor trends in the reporting of communicable diseases, but monitor vaccine coverage and the adverse events associated with immunization.[7,8] This paper deals with the critical role of surveillance in monitoring immunization-associated adverse events.

Paradoxically, control of many infectious diseases through the use of vaccines has led to increasing awareness of vaccine-related problems. In the virtual absence of these diseases, it has been recognized that severe but infrequent (1 per 100,000 to 1 per several million immunizations) adverse events may occur in association with vaccines. Such infrequent events are usually called adverse events temporally related to immunization rather than adverse reactions, since the word reaction incorrectly implies a known causal relationship with vaccine. Often these events are not clinically distinguishable from events that occur in the absence of receipt of vaccine. Such adverse events must be considered when the risks and benefits of routine immunization programs in populations from which the diseases in question have been almost or entirely eliminated are weighed.[9]

Common adverse reactions caused by vaccine can usually be detected in prelicensure randomized, double-blind, placebo-controlled clinical trials. However, the relationship of an uncommon or rare event to the receipt of vaccine usually needs to be evaluated through postlicensure surveillance.[2] The general objectives of the postmarketing surveillance of adverse events temporally related to immunization have been described:[2,10]

(a) To identify adverse events of infrequent occurrence that may be caused by immunizing agents.

(b) To monitor for unusually high rates of previously-described adverse events.

(c) To monitor for the occurrence of unusual and unexpected adverse events.

(d) To develop accurate estimates of rates of occurrence of serious adverse events temporally related to immunization, by type of vaccine.

(e) To identify hypotheses which require more detailed epidemiological investigation and special study.

Canada and the United States both rely primarily on passive surveillance systems for the detection of uncommon or rare adverse events temporally related to the administration of immunizing agents.[2,10] Passive reporting systems rely upon unsolicited reports from health care providers to public health authorities concerning events considered by those providers to be due to the administration of immunizing agents.[10] The limitations of passive reporting systems have been described in detail,[11] and include temporal reporting bias, underreporting, and the lack of baseline rates and accurate denominator data. More importantly, passive reporting systems cannot measure the true incidence of adverse events nor can they provide evidence of a causal association between the temporally related event and

immunization. Even if reporting were complete and a denominator provided, passive systems do not allow measurement of the incidence of the event in the absence of immunization. True determination of causation usually requires special studies. Active surveillance systems have to date involved the periodic solicitation of case reports by public health authorities from reporting sources such as physicians. Such active systems, though likely to produce more reports per patient seen than passive systems, are more expensive. In addition, they cover smaller populations, since limited numbers of physicians participate, and are less likely to detect relatively rare clinical events.[2] Passive reporting systems have therefore remained the only practical means of identifying uncommon or rare adverse events temporally related to immunization, since they involve surveillance of large populations.

This study intends to investigate the feasibility of implementing, in the province of Manitoba, a population-based active surveillance system for adverse events temporally related to routine childhood immunization.

1.1 The Objectives of the Thesis

The general objective of the thesis is to investigate the feasibility of using data from the

provincial health insurance plan and the provincial immunization monitoring system of the province of Manitoba to implement a provincial population-based active surveillance system. This system would continuously monitor the entire infant population to provide timely, complete and accurate data concerning the occurrence of serious adverse events temporally related to immunization with vaccines routinely used in the first year of life.

The specific objective of the thesis is to demonstrate that the population-based, computerized hospitalization and immunization records of the 1988 birth cohort of Manitoba children can be linked, so that the immunization and hospitalization experiences of the cohort in the first year of life, remote from one another in time and place, can be related in order to:

1.1.0 Describe the immunization and hospitalization experiences of the cohort.

1.1.1 Determine true population-based rates of incidence for the cohort of these uncommon or rare, serious events.

1.1.2 Assess the nature of the temporal association between immunization in the first year of life and these events.

1.1.3 Determine population-based rates of incidence for the cohort of those adverse events for which the

study produces evidence of a true temporal association with immunization in the first year of life.

2. IMMUNIZATION AND AGENTS USED IN THE FIRST YEAR OF LIFE - MANITOBA

The Manitoba provincial immunization schedule (Appendix 1) calls for all children in the first year of life to receive routine immunization with preparations containing the following agents: diphtheria toxoid, tetanus toxoid, pertussis vaccine and poliomyelitis vaccine. The diphtheria and tetanus toxoids are administered in a combined preparation (DT vaccine) and most children receive these toxoids in a preparation which also contains pertussis vaccine (DTP vaccine). The schedule calls for DTP/DT vaccine administration at each of two, four and six months of age. Poliomyelitis vaccine is administered separately, almost always as the live vaccine (oral poliomyelitis vaccine or OPV) and uncommonly as the killed vaccine (inactivated poliomyelitis vaccine or IPV). The schedule calls for poliomyelitis vaccine administration at each of two and four months of age.

3. REVIEW OF THE LITERATURE

3.0 Introduction

Reviews of the literature concerning both adverse events which have been reported in temporal association with immunization using those agents routinely used in Manitoba in the first year of life and medical record linkage have been conducted. The current state of medical knowledge of the adverse events and their associations with immunization is summarized. An overview of medical record linkage demonstrates the development and current status of knowledge in this field.

3.1 The Current State of Knowledge Concerning Adverse Events Following the Administration of Immunizing Agents Routinely Used in the First Year of Life

3.1.0 Immunization

Immunization is the act of artificially inducing immunity from disease.[1] Protection from infectious diseases through immunization may be actively or passively conferred.

In active immunization, "an attempt is made to replace the natural primary contact with a hostile organism by a safer artificial contact so that any subsequent natural contact takes place in a state of heightened immunity".[12] The body is stimulated to

develop an active immunologic defense (antibodies) in preparation for meeting the challenge of future natural exposure. This is done through the administration of a vaccine or toxoid prior to natural contact with a hostile organism.[1,13] The introduction and widespread use of active immunization has resulted in the global eradication of smallpox, the near elimination of poliomyelitis, rubella, measles, diphtheria and tetanus from Canada[4] and the United States,[1] and dramatic reductions in the incidence rates of other communicable diseases.[1,4]

Passive immunization is the provision of temporary immunity through the administration of preformed human or animal antibodies to individuals already exposed, or about to be exposed, to certain infectious agents.[1,12] Passive immunization is indicated only in the following circumstances:[12]

(a) In individuals deficient in synthesis of antibody as a result of congenital or acquired B-lymphocyte cell defects.

(b) When no vaccine for a given disease is available and prevention or modification is possible by antibody.

(c) When time does not permit adequate protection by active immunization alone.

(d) When a specific toxic effect of venom is best managed by antibody administration.

(e) Therapeutically, when a disease already is present and antibody may ameliorate or aid in suppressing the effects of a toxin.

Edward Jenner demonstrated in 1796 that inoculation of an uninfected human with pustular material from a human lesion caused by cowpox produced a similar infection, and that the inoculated individual was protected from inoculation with smallpox after recovery.[14] Jenner termed this process vaccination, and this term has been used since that time to describe the process of inoculating humans against smallpox with strains of vaccinia virus. In modern medical literature, the terms immunization and vaccination are used interchangeably to describe all active immunization processes.

The best means of reducing the occurrence of vaccine-preventable communicable diseases is the establishment of a highly immune population, resulting in the interruption of person to person spread of disease in the community and the provision of protection to those who are not themselves immunized. This indirect protection is often called herd immunity.[15] Tetanus is the one vaccine-preventable disease which is not communicable but acquired through environmental exposure.[16]

3.1.1 Approaches to Active Immunization

Two major approaches to active immunization have been used and two major types of vaccines are in current use: live and killed.[1,14] The pathogenicity of the intact organism must be reduced by either creating an attenuated (meaning weakened and less likely to cause clinical illness than the natural disease-causing agent[17]) living organism, or by killing the agent.

Live vaccines contain a small dose of infectious agents - generally attenuated. Attenuation has been successful for immunization against poliomyelitis, measles, mumps, rubella, smallpox, tuberculosis and typhoid fever.[14] The organisms multiply in the recipient, and antigen production generally increases until it is checked by the onset of the immune response that it is intended to produce. Following this, the immune system can be exposed to a large dose of antigen without the host becoming ill.[1]

Killed or inactivated vaccines are of two types:[14] killed whole organisms, as in whole cell pertussis and inactivated poliomyelitis vaccines, or purified components of the whole organism containing protective antigens, as in tetanus and diphtheria toxoids and polysaccharide vaccines (such as *Haemophilus influenzae* type b vaccine).

For many diseases (including poliomyelitis and measles), both approaches have been used. Live, attenuated vaccines are believed to induce an immunologic response more closely resembling that resulting from natural infection than do killed vaccines.[1]

The immune response to some vaccines or toxoids can be potentiated by the addition of adjuvants, such as aluminum salts.[1] They are particularly useful with inactivated products such as the combined diphtheria-pertussis-tetanus (DPT) vaccine.

The specific nature and content of immunobiological agents may differ because of the inclusion by various manufacturers of differing active and inert ingredients, including suspending fluids, preservatives, culture proteins, stabilizers, antibiotics, and adjuvants.[1] Measles and mumps vaccines are prepared in chicken embryo tissue culture,[18,19] the antibiotic neomycin is used in the production of both these vaccines,[18,19] and inactivated poliomyelitis vaccine contains trace amounts of streptomycin and neomycin.[20]

The factors which influence recommendations concerning the age at which vaccines are administered include the age-specific risks of disease, age-specific risks of complications of disease, the ability of individuals to respond to the vaccine(s), and the potential interference with the immune response by

passively transferred maternal antibody.[1] In general, the approach is to administer vaccine at the earliest possible age at which the vaccine is reliably effective.[15]

Some active immunizing products, such as those used against diphtheria, tetanus, pertussis and poliomyelitis, require more than one dose for full protection.[1] In addition, it is necessary to administer periodic reinforcement (booster) doses of some preparations to maintain protection. The recommendations for the ages and/or intervals for multiple doses take into account current risks from disease and the objective of inducing satisfactory protection.[1]

3.1.2 History of the Development of Immunizing Agents

The history of smallpox vaccination dates at least from the time of Edward Jenner's demonstrations with cowpox virus in 1796, and in 1885 the first human rabies vaccine was used successfully by the Pasteur group in Paris.[3] Passive immunization for tetanus treatment and for prevention following wounds became common practice in World War I, using antitoxin prepared in large animals.[16]

These early agents were known to cause neurological complications and anaphylactic reactions. The reactions associated with these active and passive immunizing

techniques were generally inflammatory in nature and associated with demyelination.[21]

(a) Smallpox vaccines

The differing incidence across the world of encephalopathy and encephalitis following smallpox vaccination (in those without known contraindications to vaccination) appears to have been related to the pathogenicity of the many differing strains used in vaccination.[14] The world was declared free of smallpox in 1980, ending the need for routine vaccination.[15]

(b) Rabies vaccines

The solution to the problem of the safety of rabies vaccine lay in the development, in the early 1960s, of vaccines prepared from rabies virus grown in tissue culture free of brain tissue. During the seventy years for which only rabies vaccines containing nervous tissue were used, not only did neurological reactions attributed to that tissue occur, but cases of paralysis after vaccination were caused by imperfectly inactivated vaccine virus.[22]

(c) Tetanus Vaccines

Tetanus Immune Globulin (human) became available early in the 1960s to replace equine antitoxin and permit passive immunization without the frequent allergic and serum sickness reactions which were

experienced with the former agent, and with greater clinical efficacy. Tetanus toxoid became commercially available in 1938, but was not widely administered until the military services began routine prewound prophylactic inoculation in 1941.[16]

Immunizing agents currently used with the goal of providing complete community protection from vaccine-preventable diseases and administered in the first year of life have been developed and refined throughout the twentieth century.

(a) Pertussis Vaccine

The first era of production of pertussis vaccine began prior to World War II, when killed whole cell vaccines, which were "produced by rather hit-or-miss methods",23 were clinically tested. After World War II, a reproducible laboratory test was devised to measure the potency and protective efficacy of whole cell pertussis vaccines, and permit their standardization. The current era of pertussis vaccine development, toward less reactogenic vaccines, has seen the separation of the antigens responsible for clinical immunity from other components of the organism in purified, 'acellular' pertussis vaccines.[21,24,25]

The pertussis immunization regimens and the vaccines used in the early days of pertussis immunization

were different from those in use today. For example, some children received repeated doses of vaccine with undoubtedly high concentrations of endotoxin through a short period of time.[21] Some of these children may have experienced subsequent illness secondary to iatrogenically prolonged endotoxemia.

(b) Diphtheria Toxoid

Diphtheria toxin was discovered and its antitoxin developed in the last part of the 19th century.[26] It was subsequently discovered that balanced mixtures of toxin and antitoxin successfully immunized humans. The current immunizing preparation, diphtheria toxoid, came into being in the early 1920s, when Ramon showed that diphtheria toxin, when treated with heat and formalin, lost its toxic properties but retained its ability to produce serologic protection against the disease diphtheria. Toxoid gradually replaced the toxin-antitoxin preparation for primary immunization in the United States and Canada over the next fifteen years. In 1926, Glenny found that alum-precipitated toxoid was more immunogenic.[26]

(c) Tetanus Toxoid

The purification of tetanus toxoid and its successful chemical inactivation without loss of

immunogenicity led to the commercial availability of tetanus toxoid in 1938.[16] It was not widely administered until the military services began routine prewound prophylactic inoculation in 1941.[16] Because of the success of active immunization, the universal risk and high death-to-case ratio of disease, and frequent reactions and incomplete efficacy of equine antitoxin, routine tetanus toxoid inoculation in childhood was recommended in 1944 by the American Academy of Pediatrics.[16]

(d) Combined Diphtheria, Tetanus and Pertussis Vaccines

In the mid 1940s, diphtheria toxoid, tetanus toxoid and pertussis vaccine were combined (as DTP), which permitted administration of all three antigens in a single injection.[16] Adsorption of all three onto an aluminum salt followed shortly thereafter. In 1951, the American Academy of Pediatrics recommended routine use of DTP in infancy,[16] and its universal use in infancy and childhood is currently recommended unless contraindications exist.[4,13] The current preparation, combined diphtheria and tetanus toxoids and pertussis vaccine, adsorbed (DTP), became available in the 1970s and has been used routinely in Canada since 1981.[27]

(e) Poliomyelitis Vaccines

The inactivated poliovirus vaccine (IPV) was first licensed in the United States and Canada in 1955,[20,28] and licensing and routine use of live attenuated poliovirus vaccine (OPV) began in many countries in 1960. In Canada, OPV was licensed in 1962, while DPT-Polio, DT-Polio and the tetanus-inactive poliovirus combination vaccine T-Polio had been licensed in 1959.[28]

3.1.3 Agents Currently Routinely Used in Active Immunization in the First Year of Life

Diphtheria and tetanus toxoids and pertussis vaccine adsorbed (DTP vaccine) and diphtheria and tetanus toxoids adsorbed for pediatric use (DT vaccine) are combinations of antigens used for the immunization of infants and children under seven years of age. Tetanus and diphtheria toxoids adsorbed for adult use (Td) is for administration in those seven years of age and older because it contains less diphtheria toxoid.[16]

Immunization against poliomyelitis may be achieved using live attenuated poliomyelitis vaccine, given orally (oral poliomyelitis vaccine, or OPV - also known as Sabin vaccine), or, less commonly, inactivated poliomyelitis vaccine (IPV - also known as killed or Salk vaccine) constituted singly or in combination with diphtheria,

tetanus and pertussis vaccines (as DPT-Polio or DT-Polio).[28]

As stated in Section 2, it is currently recommended in Manitoba that all children receive DTP and OPV vaccines in the first year of life, unless contraindications exist.[4] It is recommended that primary series be complete by eighteen months of age. The primary series of DTP consists of four doses; the primary series of OPV consists of three doses. A fifth dose of DTP is recommended at four to six years of age, with tetanus and diphtheria toxoids adsorbed for adult use (Td) boosters administered every ten years thereafter. A fourth dose of OPV is also recommended at four to six years of age. The current Manitoba provincial immunization schedule is reproduced in Appendix I.

3.1.4 Vaccine Recommendations

Recommendations for use of a vaccine depend on the balance of benefits of immunization, risks of disease, and risks of immunization. This balance must be assessed continually.

Hinman[15] describes the process by which vaccine schedules and recommendations are developed and publicized in the United States. Recommendations concerning civilian groups who should receive a vaccine

and the schedule of vaccination have been developed in that country by two advisory bodies: the Immunization Practices Advisory Committee (ACIP) of the Public Health Service, whose recommendations have been directed primarily toward public sector immunization, and the Committee on Infectious Diseases of the American Academy of Pediatrics, with recommendations primarily directed towards private sector immunization. Recommendations of the ACIP are published as issued in *Morbidity and Mortality Weekly Report*, while those of the American Academy of Pediatrics are published in the *Report of the Committee on Infectious Diseases* (the Red Book), which is regularly revised. New or revised recommendations of the American Academy of Pediatrics developed between editions of the Red Book are published as issued in *Pediatrics*.

In Canada, national immunization recommendations are developed by the fully representative National Advisory Committee on Immunization, and are published in the *Canadian Immunization Guide*, which is regularly revised. New statements or revisions of existing recommendations are published in the *Canada Diseases Weekly Report* and in the *Canadian Medical Association Journal*.

3.1.5 Adverse Events - Background

Given the uncertain nature of early immunizing agents, it is not surprising that temporal associations between vaccines and adverse events have been considered and documented, and that causal associations between immunization and adverse outcomes sought and even assumed. Cherry, writing about pertussis vaccine, says that "the major problem has been the failure of observers to separate sequences from consequences. The two are not synonymous".[29]

An adverse event or experience associated with a drug or biological agent has been defined as one "...associated with the use of a drug, whether or not it is considered drug-related, and any side effect, injury or toxicity, or sensitivity reaction or significant failure of pharmacological action" (United States Code of Federal Regulations 21:310.310.b).[30]

Adverse events may be specifically caused by the immunizing agent, and the medical literature generally terms these 'reactions'. The mechanism of the reactions may vary with the type of vaccine administered, the quantity and quality of vaccine components, the route of administration, and the host sensitivity. Bart[1] describes the ways in which these may occur.

(a) Adverse reactions caused by inactivated vaccines

These include immediate and delayed type hypersensitivity and Arthrus reactions.

Potential predisposing conditions may be injection of vaccines, such as DTP, into the subcutaneous rather than muscular tissue (this is believed to predispose to local inflammation, and abscess and granuloma formation), or hyperimmunization with toxoids such as tetanus (this is believed to lead to severe local reactions).

Reactions may occur in response to the large antigenic mass present in most inactivated vaccines - these reactions are likely to occur within the first few days to one week after immunization.

In addition, inactivated vaccines contain preservatives and adjuvants which may cause adverse reactions.

(b) Adverse reactions caused by live vaccines

Live vaccines contain small quantities of organisms which must replicate to induce the immune response, and reactions to these vaccines may represent the clinical effects of organism replication. Vaccine-associated poliomyelitis, for example, is caused by vaccine virus invading and destroying anterior horn cells. These reactions generally appear later than those caused by inactivated vaccines, such as the fever and rash associated with measles vaccine which

generally occur five to twelve days after immunization.

Live vaccines may contain impurities such as egg protein and other inert ingredients such as antibiotics (for example, neomycin in MMR vaccine). Reactions to these compounds may occur shortly after vaccination.

(c) Adverse events may also be caused by improper vaccine use or handling, and multidose vials may become contaminated with bacteria leading to infective complications subsequent to injection.

As Bart points out, many post-immunization adverse events are not specifically caused only by the agent, and the occurrence of an adverse event after immunization does not necessarily mean that the agent caused the event.

"To epidemiologically prove causation requires that the incidence of the event after vaccination is significantly greater than the incidence of the disease in the absence of vaccination".[13] Even then, finding a statistically significant association between two independent variables at the 5% level does not necessarily mean that one event caused the other. Additional evidence concerning the illnesses of interest which would support a causal association would be that they were:[31]

(a) Clinically distinctive.

(b) Restricted to immunized children.

(c) Closely related in time to immunization.

(d) Associated with a biologically plausible pathogenesis.

(e) Without alternative explanation.

Anecdotal case reports cannot prove a causal relationship. Epidemiological studies can provide strong suggestive evidence, and can be used to develop risk figures for adverse outcomes.

Adverse events which have been associated in time with immunization but whose etiology and causal relationship with immunization is uncertain are generally termed in the medical literature 'adverse events temporally associated with immunization'. This temporal association may occur for a number of reasons:[21]

(a) There may be a direct cause-and-effect relationship due to a property of the vaccine.

(b) There may be an indirect cause and effect relationship due to an idiosyncrasy of the host.

(c) There may be no causal relationship with the vaccine, but rather with a preexisting, unrelated host problem. In this case, the association with the immunization may:

(a) occur completely by chance,

or (b) the event may be moved forward in time by the immunization and would have occurred regardless of immunization.

3.1.6 Classification of Adverse Events

3.1.6.0 Introduction

Apparent reactions associated with the use of immunizing agents must be considered with respect both to their frequency and severity, and to the likelihood that they are due to the vaccine.

The classification of adverse events used here will therefore be that employed by the Task Force on Pertussis and Pertussis Immunization,[21] which divided all reported vaccine reactions into two categories: transient local and systemic reactions and major reactions and temporally associated events.

3.1.6.1 Transient Local and Systemic Reactions

3.1.6.1.0 Introduction

The nature and frequency of common (defined as occurring with a frequency of the order of 1 in 100 doses), mild, transient local and systemic reactions to DTP and inactivated and live poliomyelitis vaccines are well documented.

3.1.6.1.1 Pertussis Vaccine and Combinations

Despite the fact that reactions occurring in association with pertussis immunization have been noted for more than fifty years, there have been virtually no placebo-controlled studies from which quantitative data are available.[21] Early studies in the United States and Britain included control populations, but these studies were primarily concerned with vaccine efficacy, and quantitative and qualitative reaction data were not obtained.[23,32] DTP immunization has been a routine part of well baby care for some decades, precluding on ethical grounds the inclusion of a placebo group in a vaccine study to differentiate vaccine caused events from temporally associated events due to other causes. However, in the past fifteen years relatively large controlled prospective studies have been carried out in the United States which give quantitative and qualitative data concerning the occurrence of common reactions to DTP.[33-38] In addition, similar data have been gathered in the past ten years from studies comparing reaction rates in recipients of DTP vaccines containing whole cell and acellular pertussis components.[39-41]

3.1.6.1.2 Poliomyelitis Vaccines

A very large controlled trial of inactivated poliomyelitis vaccine was conducted in 1954,[20,42] and large scale field trials of live attenuated poliomyelitis vaccine were conducted in many countries, under a variety of conditions, between 1955 and 1959.[43,44] Mild transient local and systemic reactions have been reported in these and subsequent studies.[45]

3.1.6.2 Major Reactions and Temporally Associated Events

Less is known about the etiology of uncommon (defined as occurring with a frequency of the order of 1 in 1000 doses) or rare adverse events which have been temporally associated with immunization. Of particular importance are those which are serious or have permanent sequelae, such as neurological events.

The study of the causal nature of the temporal association between the diagnosed onset of serious illness and immunization is compounded by the following difficulties:

(a) The infrequency of these events. The background rates of these illnesses are not insignificant, and studies with the power to detect statistically significant differences between the frequencies of illnesses occurring before and after immunization

require very large study populations followed over long periods of time.

(b) The need to include a control group in the study population. Prospective, randomized and controlled trials are not possible, on ethical grounds, following the licensure of vaccines.

(c) The clinical nonspecifity of the illnesses of interest. Neurological events, such as seizures, occurring in young children are associated with many different etiologic possibilities.[21,46]

'Encephalopathy' and 'encephalitis' encompass a broad group of etiologies. The term encephalopathy, meaning in its broadest sense 'illness of the brain', is generally used when an illness clinically resembles an encephalitis but no inflammatory response within the brain (or within the meninges - meningoencephalitis) is evident.[21]

In addition, the developing nervous system displays a limited range of responses to insults of various kinds. Impairment most commonly involves the motor system, special senses (vision and hearing), language, higher cognitive function, or any combination of these problems. Not only is the assessment of the integrity of the infant nervous system a difficult task, but an abnormality or pattern of abnormalities can rarely be used to implicate a specific cause.[21]

Damage to the brain may first manifest in early infancy as nonspecific abnormalities in feeding, responsiveness, sleep patterns, or interpersonal contact.[21] In many instances there is a latent interval, during which the infant appears to be progressing well, before the processes of maturation call for the functional use of damaged areas and clinical abnormalities become apparent.

Other complicating issues include the frequency of these uncommon or rare events, greatest during the period of life at which children normally receive immunizations, and the demonstration that deficits of motor function found during the first year of life may disappear, leaving a child who is unimpaired.[47]

3.1.7 Major Reactions and Adverse Events Temporally Associated with Specific Vaccines

3.1.7.0 DTP and DT Vaccines

3.1.7.0.0 Introduction

Attempts to establish a causal association between the administration of pertussis vaccine and serious acute sequelae date back to 1933 with the report by Madsen[48] of two infant deaths following the administration of the vaccine. Golden[49] notes that, since the collation by

Berg[50] in 1958 of 107 reports citing neurological complications temporally associated with the administration of pertussis vaccine, "there has been prolonged and often acrimonious debate concerning the existence of a causal relationship between pertussis immunization and neurologic disease".

3.1.7.0.1 Neurologic Illness and Death

The epidemiological study of the temporal association between the administration of pertussis vaccine and its combinations and serious neurological events began in the late 1970s in Britain. Encephalitis, encephalopathy (including the onset of epilepsy with retardation, infantile spasms, Reye syndrome, Guillain-Barré syndrome, transverse myelitis, and cerebellar ataxia) and death have all been noted in temporal relationship with DTP immunization.[21]

3.1.7.0.1.0 Encephalopathy, Encephalitis

Pertussis vaccine has long been implicated in the etiology of severe neurological illness and brain damage. Epidemiological studies using several designs have failed to document a causal relationship between pertussis immunization, DTP immunization or DT immunization and brain damage.[49]

The most widely quoted epidemiological study on the possible adverse effects of pertussis vaccine is the National Childhood Encephalopathy Study (NCES).[51] This was a case control study of all severe, acute neurological illnesses leading to hospital admissions in children aged from 2 to 36 months in England, Scotland and Wales during a three year period between 1976 and 1979. The initial results[31] of this study suggested a risk of permanent brain damage from pertussis immunization of 1 per 330,000 vaccine doses and a risk of encephalopathy of 1 per 140,000 vaccinations. No causal association was found between pertussis immunization and infantile spasms. Recent analyses of the NCES data indicate that both of these rate estimates are incorrect.[29]

Golden[49] describes the intensive reanalysis of the NCES study in the form of a legal trial. The case of Loveday v Renton and the Wellcome Foundation was heard in the High Court of Justice in London in 1987 and 1988. The review of the primary data led to the exclusion of many of the subjects included by the authors in the original analysis. The critical findings were reviewed by Griffith.[52] No patient had encephalopathy with characteristics similar to those in anecdotal case reports. No child who was previously normal sustained permanent brain damage. All children who had prolonged

febrile convulsions were found to be normal on follow-up examination. MacRae[53] found that the increased relative risk that was observed within seven days of immunization was offset by a decreased relative risk over the subsequent three week period. This indicates, therefore, not a cause and effect relationship, but perhaps a redistribution of events over time similar to that observed with the occurrence of infantile spasms.[29] In an analysis of the cases that led to the calculated rate of 1 per 140,000 for all encephalopathy, Stephenson[54] has shown that this is an artefact caused by the inclusion of nine children with febrile convulsions. The final verdict was that the probability that pertussis vaccine could cause permanent brain damage could not be supported.[55]

Pollock and Morris[56] found 12 instances of neurologic disorders following DTP and two following DT immunization. In six of the twelve neurological disorders that followed DTP immunization, the interval between the immunization and the onset of the disorder was eight days or longer (eight weeks in one case). Of the six cases following DTP immunization, one child had infantile spasms, four had evidence of viral infection at the time of illness, and one had petit mal seizures. In the Hospital Activity Analysis, no neurological disorders other than convulsions were noted. The authors concluded

that no convincing evidence indicated a causal relationship between DTP and DT immunization and neurological damage. They also noted that, despite the administration of over 400,000 doses of DTP vaccine, no cases of the syndrome associated with "pertussis encephalopathy" were seen.

Walker[57] and Griffin[58] detected no cases of unexplained encephalopathy within 29 and 14 days respectively of DTP immunization.

3.1.7.0.1.1 Infantile spasms

Infantile spasms represent a seizure disorder in which almost all cases have an onset in the first year of life, and 77% have their onset in the six months from two to seven months of age.[59,60] Most cases of infantile spasms therefore have their onset at the age when primary DTP immunization is given, and by chance alone about 12% of all cases of infantile spasms that occur between two and seven months of age will have their onset within seven days of DTP immunization, and 5% will have their onset within 72 hours of DTP immunization.[21]

A link between pertussis immunization and infantile spasms was proposed 25 years ago.[61]

Fukuyama[62] studied 110 cases of infantile spasms: a total of five cases met the authors' criteria for

possible vaccine association, but they stated that this number could be explained on the basis of chance association.

Melchior[60] studied the occurrence of infantile spasms in Denmark in the period 1970 to 1975, during which pertussis immunization was given at ages 5 weeks, 9 weeks, and 10 months. Results were compared with the occurrence of infantile spasms noted in a previous study, when pertussis vaccine was administered at 5, 6, 7 and 15 months of age. No significant difference in the time of onset of infantile spasms in the two series was demonstrated. In each series, 42% of the cases had their onset before the age of 5 months.

The Danish data of Shields[63] showed no association between the onset of infantile spasms and the time of pertussis immunization.

The data from the NCES were used to examine the relationship between infantile spasms and DTP vaccine.[51] Case control analysis showed no relationship within the 28 days after immunization. There did appear to be a clustering of new cases in the seven days after immunization, but this was balanced by a deficit of new cases during the following 21 days.

3.1.7.0.1.2 Death

3.1.7.0.1.2.0 Sudden Infant Death Syndrome (SIDS)

There have been suggestions in the medical literature and the lay media that DTP vaccine may cause some cases of SIDS. These suggestions arise from small, uncontrolled clinical experiences.[64,65]

Several major controlled studies using different investigative methods have indicated no association of DTP immunization and SIDS.

The Cooperative Epidemiological Study of Sudden Infant Death Syndrome Risk Factors (National Institute of Child Health and Human Development) is a multi-centre, population-based case control study.[66] A total of 757 case infants who, after pathologic examination, were classified as definitely or probably having died of SIDS, were matched with 1515 control infants. There were two living control subjects for each research subject. Analysis indicated that the infants with SIDS were less likely to have received any DTP vaccine than the control infants.

An eight year study including 222 cases of SIDS was conducted in Norway.[67] There were 53 SIDS cases which occurred within one month of DTP immunization. The observed dates of occurrence were compared with the expected frequency distribution, and there was no

evidence that DTP immunization was an etiological factor in SIDS.

Griffin[68] studied a cohort of 129,834 Medicaid children from a defined geographic area of Tennessee to examine the relationship between DTP immunization and SIDS. Each child had received at least one dose of DTP vaccine from a public health clinic or Medicaid provider. Immunization records were linked with death records, and 109 cases of SIDS were found. The relative risk of SIDS was determined by comparing the first 30 days after immunization with the period beginning 31 days after immunization. The relative risk in the first three days after immunization was 0.18. Subsequent periods gave a relative risk at 4 to 7 days of 0.17; 8 to 14 days of 0.75; 15 to 30 days of 1.0. A multivariate analysis of several important demographic factors also failed to support a relationship between immunization and SIDS.

Walker conducted a case control study in which the relationship of DTP immunization and 29 SIDS cases was investigated for a twelve year period in a health maintenance organization in Washington.[69] In this study, the relative risk for the occurrence of SIDS within three days of immunization in the first year of life was 7.3 (95% confidence limits 1.7 to 31), suggesting a causal association. Two points concerning this study should be noted: the small sample size (and there were only four

cases of SIDS within three days of immunization); in addition, nonimmunized SIDS cases and their controls were eliminated from the analysis because of the authors' belief that delayed immunization represents a known risk factor for SIDS. In this study, the mortality rate from SIDS in nonimmunized infants was 6.5 times that of immunized infants of the same age (95% confidence limits 2.2 to 19).

3.1.7.0.1.2.0 Non-SIDS deaths

Madsen[48] first noted the occurrence of death in temporal association with pertussis immunization when he reported the deaths of two babies in 1933. Since that time, there have been scattered reports of deaths associated with pertussis vaccine and its combinations. These reports have been reviewed,[21,70,71] and it is clear that many of the non-SIDS deaths occurring soon after DTP immunization are due to other causes. There is little evidence to support an association between DTP immunization and non-SIDS temporally related deaths.[21]

3.1.7.0.1.3 Neuropathy

There have been a number of case reports of polyneuropathy occurring hours to weeks following tetanus

toxoid administration. These reports and laboratory findings have been reviewed by Rutledge,[72] who summarized reports of 19 published cases. These cases had an age range of 9 to 54 years, and 85% had received more than one injection.[73] In the majority of cases, the onset of polyneuropathy occurred within 14 days of the last injection,[72] and ranged in severity from a single nerve palsy,[74] profound sensorimotor neuropathy,[72] to extensive involvement of the central nervous system including cord and cortex.[75,76] Recovery was usually complete, although the degree of recovery correlated with the interval between the administration and the onset of symptoms. One patient had relapsing signs and symptoms after repeated doses of toxoid.[77] The estimated incidence of these reactions is 0.4 per million doses of vaccine.

These case reports are anecdotal, and do not demonstrate proof of a cause and effect relationship between tetanus toxoid and polyneuropathy, mononeuropathy, myelopathy, or encephalopathy.[72] The reports are, however, consistent with neuropathy as a manifestation of immune complex disease, similar to that following administration of equine tetanus antitoxin.[16]

Other neurological events, including seizures, have been reported following tetanus toxoid administration.[76,78]

3.1.7.0.2 Other Major Adverse Events

3.1.7.0.2.0 Introduction

Other major adverse events which have been noted in temporal relationship with DTP immunization are anaphylaxis, very high fever, persistent crying and unusual high-pitched screaming, excessive somnolence, convulsions and hypotonic-hyporesponsive state (collapse, shock).[21]

3.1.7.0.2.1 Anaphylaxis

There have been case reports suggesting anaphylactic reactions to DTP vaccine[79] and to tetanus toxoid[80-82] and although these reactions appear to be rare, there are few data available.[83]

During the Monitoring System for Adverse Events Following Immunization surveillance period from 1979 to 1982,[83] the rate of allergic reactions attributed to DTP vaccine was five per million doses of administered vaccine.[21] Eight instances of anaphylaxis associated with DTP were noted.

In the North West Thames region study of Pollock and Morris,[56] anaphylaxis/collapse was noted eight times in association with DTP immunization (one per 50,000 doses), and twice in association with DT immunization (one per 200,000 doses).

3.1.7.0.1.2 Very High fever

Temperature elevation following DTP immunization is common and occurs significantly more frequently after DTP immunization than after DT immunization.

As described in the Report of the Task Force on Pertussis and Pertussis Immunization,[21] the UCLA study, prospectively evaluated 16,536 immunizations. A total of 15,752 DTP and 784 DT immunizations were given to children, zero to six years of age and routinely scheduled for immunization, who were then evaluated for reactions that occurred within 48 hours of vaccine administration. During the study, a substudy, which was a double-blind comparison of DTP vs DT in 305 children, was carried out to assess the reliability of the results of the total study. As the rates of common reactions in the double-blind portion of the study were similar to the rates in the overall study, it was thought by the investigators that parent or study worker bias had little effect on the overall findings.

The degree of temperature elevation was evaluated in the UCLA study.[21,33] Temperature was elevated following 7,753 DTP and 292 DT immunizations. 6.1% of DTP recipients had a temperature of greater than or equal to 39°C, whereas only 0.7% of DT recipients had a similar temperature elevation. 1.5% and 0.3% of the DTP recipients had temperatures greater than or equal to 40°C

and 40.5°C respectively, while none of the DT recipients had temperatures of a similar magnitude.

Long and colleagues[84] conducted a longitudinal prospective study which evaluated immunogenicity and adverse reactions to DTP in 538 children given 1553 doses of DTP. Subjects were randomized to the standard four dose immunization schedule or to a three dose schedule (with a saline injection substituted for DTP at 6 months of age). Parents and study personnel were unaware of the assignment of injection at 6 months of age. High fever (temperature >39.4°C) occurred within 48 hours of immunization with 2.7% of doses overall, in significantly more DTP than placebo subjects at 6 months, and no temperature exceeded 40.5°C.

Two studies in Britain noted fever in only 3% to 8% of children immunized with DTP and in none of the children was the temperature elevation marked.[85,86] In one of these studies,[86] axillary rather than rectal or oral temperatures were taken and the temperature was determined only at 4 and 24 hours after immunization. In the other study,[85] fever was determined by the parents by palpation. It seems likely that the study techniques may explain some of the discrepancies in rates between the two British studies and the others.

3.1.7.0.1.3 Persistent crying and unusual high pitched crying or screaming

Persistent crying has been commonly noted after DTP immunization and would appear to be a reaction to immunization.[21] In the UCLA study, 3.1% of DTP immunizations resulted in persistent crying of greater than one hour duration occurring within 48 hours of immunization, whereas only 0.7% of DT recipients had similar crying.[21,33]

Unusual high-pitched crying has been characterized as screaming or "a cerebral cry",[21] usually described by the parents as a high-pitched scream, and distinguished by the parents as one they have never heard their child produce before.[33] In the UCLA study, the parents of 0.11% of DTP recipients reported such unusual crying occurring within 48 hours of immunization. Valid statistical comparison between DTP and DT recipients was not possible. In this study an attempt was made to record children with unusual screaming, but evaluators were unable to differentiate the cry on a representative tape of one screaming child from the cry of an unvaccinated child.[87]

In a British study,[86] neither persistent crying nor high pitched screaming were more common in DTP (adsorbed vaccine) than DT (adsorbed vaccine) recipients, with rates for both similar to those in the UCLA study. Long[84] also reported similar rates. However in the

British study, persistent crying and screaming attacks were both significantly more common in recipients of plain (unadsorbed) DTP vaccine.

No long term adverse effects have been observed in children who have had either persistent crying or unusual high pitched cry.[21]

3.1.7.0.1.4 Excessive somnolence

Drowsiness is a common response to DTP immunization. In the UCLA study, drowsiness within 48 hours of immunization was noted in 31.5% of DTP recipients but in only 14.9% of DT recipients.[21] Long reported drowsiness or sleepiness within 48 hours of immunization in 42.9% of DTP recipients.[84]

Excessive somnolence is difficult to quantitate and separate from the drowsiness which commonly occurs. In the UCLA study one of the immunizations was associated with excessive somnolence, defined as prolonged unnatural drowsiness.[33]

3.1.7.0.1.5 Seizures

In studies of the relationship between seizures and immunization adverse events, a clinical classification of seizures similar to that used by Hauser and Kurland[88] is

usually employed - Griffin and associates used the following clinical classification:[58]

(a) neonatal seizures - those occurring within the first 28 days of life.

(b) febrile seizures - defined below.

(c) afebrile seizures - those unaccompanied by fever or an acute neurological illness.

(d) symptomatic seizures - those associated with an acute neurological illness.

Febrile seizures are one of the most common neurological disorders in clinical pediatrics.[46] The Consensus Statement on Febrile Seizures defines a febrile seizure as "an event in infancy or childhood, usually occurring between 3 months and 5 years of age, associated with fever but without evidence of intracranial infection or defined cause".[89] Seizures in children who have suffered a previous nonfebrile seizure are excluded from the definition. "Complex" febrile seizures are defined as those with one or more of the following characteristics: more than 15 minutes duration, more than one seizure in 24 hours, or focal features.[90] "Simple" febrile seizures lack all of the preceding characteristics. Febrile seizures must be distinguished from epilepsy, which is characterized by recurrent nonfebrile seizures.[89] Reported prevalence rates of febrile seizures range from 0.1 to 15.1 per hundred, with

an average prevalence of 5.3 per hundred.[46] The wide variation is due to the use of different methods of case ascertainment and definitions of febrile seizures. Studies in which populations of children have been followed longitudinally and standard definitions used have yielded prevalence rates of between 2.4 and 4.2 per hundred.[46,90-92]

Prospective and retrospective studies indicate that convulsions after DTP immunization are relatively common. These seizures have the clinical characteristics, in most cases, of febrile seizures, and there is no evidence that they produce central nervous system injury, indicate the onset of epilepsy, or worsen preexisting neurological disease. Although there is an increased risk of postimmunization seizures in children with a personal or family history of convulsions, there is no evidence of an increased risk that other neurological problems will develop after immunization.

The National Collaborative Perinatal Project enrolled 52,360 pregnant women, and followed 91% of children born live to these women for one year and 75% for seven years. It was found that 616 of the children born to these women had a seizure that occurred between one month and one year of age.[93] Therefore it can be estimated that, by chance alone, seven infants per 10,000 will have a convulsion within one week of DTP

immunization, and two per 10,000 will have a convulsion within two days of DTP immunization.[21] In the study, eight children (1.5/10,000) were noted to have had a convulsion within two days of DTP immunization. Data analysis combined the data on all children, so the role of the different vaccines administered cannot easily be determined. As a group, however, the seizures almost always occurred in the presence of fever and were brief. More than half of the children had a personal or family history of convulsions. No child developed epilepsy, and the authors concluded that the immunization-related seizures closely resembled febrile seizures.

In the UCLA study,[33] there were nine instances overall of convulsions occurring within 48 hours of immunization (all occurred within 24 hours), giving a rate of one seizure per 1,750 immunizations (or 5.7 per 10,000). Seven of the nine children were febrile, a finding similar to that of Strom[94] and others,[56,95] and seven of the nine children had no previous history of convulsions or neurologic disorders, and two had prior febrile convulsions. Five were examined by a pediatric neurologist, and in all cases the examination was normal.

Pollock and Morris[56] conducted a seven year longitudinal, prospective cohort study of disorders attributable to immunization in the North West Thames region in Britain. During the study period, 134,000

children received three doses of DTP vaccine and 133,500 children completed courses of DT vaccine. A voluntary reporting system was established, and all children identified were examined within four weeks. A convulsion without evidence of neurological damage occurred within 48 hours of immunization in fifteen children in the DTP group (one per 26,800 immunizations) and in one child in the DT group (this event was associated with intercurrent infection). None of the children had a close personal or family history of convulsions. A hospital activity analysis was made on records for 1979 of children under two years of age admitted to hospital with relevant neurological diagnoses. The febrile convulsion rate for admissions in these children was found to be 6.6 per 1,000. The denominator for children receiving immunizations during this year was underestimated, but, of 64 children admitted to hospital within 28 days of immunization, 16 had received DTP (15 febrile convulsions) and 18 had received DT (all febrile convulsions).

Walker, in a study of neurological events following DTP immunization, used information from a large HMO database in Seattle, Washington, in which hospital discharge records were linked to medical, pharmacy and death records.[57] The records of 35,581 children over 30 days of age who had received DTP immunization over an 11

year period were examined. Children with uncomplicated first febrile seizures were not likely to have been hospitalized or treated with drugs, and the study objective was not to seek these events but to search for new, serious neurological events by identifying hospitalizations for neurological disease. The study found that the incidence of first seizures occurring at any time within 29 days following DTP immunization was no greater than that expected by chance alone. The incidence of six hospitalizations for first seizure in the 29 days following the approximately 106,000 immunizations included in this study was similar to the count of four cases following approximately 51,000 DTP immunizations and three cases following 54,000 DT immunizations reported by Pollock and Morris[56] in Britain. One child in the Seattle study had the onset of a seizure disorder three days after immunization, but this was to be expected on the basis of chance alone. The cumulative incidence of idiopathic postneonatal seizures in this population of healthy children was 3.1 per 1,000. The closest corresponding figure from the National Collaborative Perinatal Project[93] was 170 such seizures in approximately 40,000 children followed to age seven years (4.3 per 1,000). An analysis showed that the incidence of recorded febrile seizures in the immediate postimmunization period was 3.7 times (95% confidence

interval 1.4 to 10) that in the period 30 days or more after immunization, after adjustment for age.

Griffin[58] conducted a retrospective study in which hospital and medical files were linked with the immunization and pharmacy records of 38,171 Tennessee Medicaid (predominantly poor, nonwhite) children, who received 107,154 DTP immunizations in their first three years of life. ICD-8 codes, claims for an electroencephalogram, and prescriptions for anticonvulsant medication within seven days of a hospitalization were used to screen for neurological outcomes of interest. Of 1,187 children with such outcomes, records were available for review in 70%, and 358 children finally met the case definitions. The study found the risks of febrile seizures which generated hospital-based medical contact in the 0-7 day and 0-29 day intervals following DTP immunization to be 1.1 (95% confidence interval 0.6 to 2.2) and 1.0 (95% confidence interval 0.7 to 1.5) respectively times that of the period 30 or more days following DPT immunization. The corresponding risks for afebrile seizures which generated a medical contact were 1.8 (95% confidence interval 0.5 to 6.3) and 1.1 (95% confidence interval 0.4 to 2.6). This study probably underestimated the risk of seizures following DTP immunization in at least two important ways: it is possible that some of the highest-risk

children did not receive immunization or did not receive hospital-based care in the event of a seizure; and 359 children identified as possible cases did not have their records reviewed because non-hospital-based outpatient records were not sought.

Shields[63] conducted a retrospective study examining the relationship between the time of onset of neurological disorders with the time of pertussis immunization in two cohorts of Danish children aged one month to two years who received pertussis immunization at different ages because of a change in the immunization schedule. A significant statistical association between first febrile seizures and the scheduled age of administration of pertussis vaccine was found. The peak in first febrile seizures in Denmark changed from age 15 months to age 10 months corresponding to the change in age of scheduled pertussis immunization, while a similar shift in timing of these seizures was not observed with the simultaneous change in pertussis immunization from the age of 4-8 months to the age of 1-3 months. This finding is consistent with the observation that febrile seizures most often begin after three months of age.[46] No relationship was found between the age of onset of epilepsy and the vaccine administration schedule.

Hunt[96] examined the relationship between immunization (with DPT or DT vaccine), the onset of

seizures, and the severity of cognitive deficit in children with tuberous sclerosis. There was no evidence that the vaccine precipitated seizures. The profoundly affected children all had seizures before seven months of age, and more of these children had never been immunized, or had been immunized after the first seizure, than had received the vaccine before the first seizure occurred. There was also no evidence that the vaccine caused additional brain damage; children with severe convulsions were in the groups that had not been immunized or had received only DT vaccine.

Children with either febrile or nonfebrile convulsions are more likely to have a personal or family history of convulsions. 2,062 reports of adverse neurological events from the Monitoring System for Adverse Events Following Immunization (Centers for Disease Control) were reviewed.[97] In children with a neurological event after DTP immunization, the likelihood of a personal or family history of convulsions was 7.2 and 4.5 times higher respectively than in those with a non-neurological adverse event. In the great majority of cases the neurological event was a convulsion. Febrile seizures after immunization were more likely to occur in children with a family history of convulsions. Children with either febrile or nonfebrile convulsions were more likely to have a personal history of convulsions.

Baraff[37] found the rate of febrile seizures in siblings of children who experienced either convulsions or hypotonic-hyporesponsive episodes to be 16%. Hirtz[95] reported a prenatally ascertained family history of febrile or nonfebrile seizures in 23% of children with immunization-associated seizures, and in 14% of children with febrile seizures. Hauser[98] reported an 8% rate and van den Berg[99] an 11.5% rate of seizures among siblings of children with febrile seizures.

Baraff[100] carried out follow-up examinations of nine children who had convulsions and nine who had hyptonic-hyporesponsive episodes within 48 hours of DTP immunization. Sixteen children were available for follow-up six or seven years later, and in each case the parents considered the child normal. Neurologic and psychometric examinations were performed in 13 cases. Neurological findings were essentially normal, and psychometric testing revealed normal performance IQ scores but low verbal IQ scores (explained by the high proportion of bilingual children in the sample. There is agreement that simple convulsions following DTP immunization are not followed by neurological sequelae in the majority of cases.[70,101,102]

To date, only the study of Pollock and Morris[56] has had both DPT and DT recipients in numbers sufficient to permit a statistically valid comparison of the two

groups. This study was carried out in Britain between 1975 and 1981, during which time pertussis vaccine was the subject of much unfavourable discussion in the lay media. Consequently, the investigators believed the comparison to be biased by overreporting of reactions to DTP vaccine relative to DT vaccine.

3.1.7.0.1.6 Hypotonic-hyporesponsive state (collapse, shock)

This illness has its onset between one and twelve hours after immunization.[21] Most children are initially febrile and irritable, then become pale, limp and unresponsive. Respirations are shallow and cyanosis is frequently noted. The duration of illness may be minutes or a day or more. No adverse long-term effects have been reported.[21]

This illness was noted in six immunized children by Hopper[103] in 1961, and has been observed repeatedly since that time.[33,56,94]

In the UCLA study,[33] nine children were noted with this reaction (one per 1,750 immunizations). Because the control group (DT recipients) was small, the relationship between pertussis vaccine and this illness could not be examined. It has, however, been the belief of many experts that it is a specific pertussis vaccine reaction. The study by Pollock and Morris[56] suggests that a similar

illness may also occur following DT immunization. In this study, in which approximately equal numbers of children received DTP and DT vaccines, five DTP recipients and four DT recipients had episodes consistent with this diagnosis.

3.1.7.0.1.7 Other Major Events Reported

There have been rare case reports of hemolytic anemia, thrombocytopenic purpura and conditions affecting the skin and soft tissues occurring in association with DTP immunization.[21]

3.1.7.1 Poliomyelitis vaccine

3.1.7.1.0 Introduction

Polioviruses spread primarily by fecal-oral transmission, and consist of three types: 1, 2 and 3. IPV is a mixture of poliovirus types 1, 2 and 3 inactivated with formalin, while OPV contains a mixture of the three types of poliovirus that have been attenuated and produced in monkey kidney cell cultures.[13]

From the experience in many countries, it is evident that paralytic poliomyelitis due to wild poliovirus can be eliminated using either IPV or OPV.[104]

Varughese et al describe the eradication of indigenous poliomyelitis in Canada.[28] This country experienced two major epidemics of polio, one which peaked in 1953 (28.3 cases per 100, 000 population) and the other in 1959 (10.7 cases per 100, 000) population). The first epidemic began in 1951 and lasted four years, with a total of 9,568 cases reported. IPV was licensed in Canada in 1955, and, by June of 1957, nine million doses had been administered. The second epidemic began in 1958, and peaked in 1959 with a total of 1,887 cases, by which time 43% of Canadians under 40 years of age had received three doses of IPV, but only 45% of those under five years of age and 10% of those aged between 20 and 40 had received the required three doses. By 1960, 69% of the Canadian population under 40 years of age had received three or more doses of IPV.

OPV was licensed in Canada in March, 1962, and Manitoba commenced an immunization program using OPV in April of that year. In Manitoba, 85% of children under one year of age born in 1988 and registered with the Manitoba Immunization Monitoring System (MIMS) had received two doses of poliovaccine by their first birthday.[105] Of almost 70,000 doses of poliovirus vaccine administered in 1989 to the population of Manitoba children registered with MIMS and born on or after January 1, 1980, only 18 were doses of IPV.[106]

Canadian vaccine coverage is currently estimated to exceed 90% for school-aged children, and between 1965 and 1988 only 51 cases of paralytic poliomyelitis were reported.[28] The United States experienced a shift from the IPV to an OPV program in 1961,[107] and, by 1969, only about a dozen cases were reported in the entire country.[107] In 1990, the Pan American Health Organization reported a doubling in OPV coverage in the Region of the Americas (the U.S. and Latin America) for children one year of age, to 73% in 1989.[108] Reported cases of paralytic disease have fallen from an average of 16,000 cases per year, for the four years prior to the introduction of IPV in 1955, for the U.S. alone[109] to 130 confirmed cases in the Americas in 1989.[108]

3.1.7.1.1 Inactivated Poliomyelitis Vaccine (IPV)

No serious side effects of currently available IPV have been documented. Trivalent IPV caused some early problems.[110] Material from one manufacturer, in which formalin treatment had not inactivated the viruses, caused 192 cases of paralytic poliomyelitis.[111] With purification of the virus before formalin treatment, and improved testing, there have been no further cases of paralysis attributed to IPV, nor any other serious adverse reactions.[104]

Since IPV contains trace amounts of streptomycin and neomycin, a theoretical possibility of hypersensitivity reactions in individuals sensitive to these antibiotics exists.[20]

3.1.7.1.2 Live Attenuated Poliovirus Vaccine (OPV)

The occurrence of paralytic poliomyelitis in OPV recipients and contacts of recipients has been recognized in recent years in the light of the enormous decline in the incidence of the wild disease.[28]

From the beginning of experimental trials in humans, extensive excretion of virus, both pharyngeal and fecal, by vaccinees had been documented, as had spread of virus to close contacts.[112] Poliovirus vaccines must multiply in the alimentary tract in order to immunize, and all strains, regardless of how highly attenuated, retain the ability to multiply and exert neurotropic effects.[112] Laboratory techniques are such that different degrees of neurotropism, even among attenuated strains, can be readily detected, and licensed attenuated strains are those which exhibit, simultaneously, maximum immunogenic and minimum neurotropic effects.[112]

Nevertheless, as stated in report of the WHO Expert Committee on Poliomyelitis, "virus excreted in the stools can be more neurotropic than that which was fed".[113] The

general view is that OPV strains, mainly type 2 or type 3, do occasionally cause paralytic poliomyelitis.[110] Results of genetic manipulations of the OPV seed strains, especially type 3, promise that a more stable mutant may be developed, with preservation of immunogenicity but loss of the potential for reversion to neurovirulence.[107]

In order to establish the possible role of OPV in the development of paralytic poliomyelitis, a thorough assessment must be taken into account in each case, taking into consideration all clinical, laboratory, and epidemiological data.[28] Cases are epidemiologically classified into two groups: non vaccine-associated (caused by wild polioviruses, endemic or imported) and suspected as vaccine-associated.

In Canada, the classification criteria for each case are those recommended by the WHO Consultative Group.[114] These criteria define a "vaccine recipient" case as one in which the illness began within 7-30 days after the patient received vaccine. A "contact/possible contact" case is one in which the patient was known to have been in contact with a vaccine recipient, and became ill within 7-60 days after the vaccine recipient had taken the vaccine.[28] In recipients of OPV, poliovirus persists in the throat for one to two weeks, and is excreted in the feces for several weeks and, rarely, for more than two months.[13] Recipients are potentially contagious as

long as fecal excretion persists. A committee established in Canada in 1989 by the National Advisory Committee on Immunization to review the four poliovirus-associated cases identified in Canada in 1987-88 extended the upper limit of 60 days to 80 days for a case deemed a vaccine-associated contact/possible contact case.[115]

Of the 51 reported cases of paralytic poliomyelitis reported in Canada between 1965 and 1988, 16 were suspected to be vaccine-associated.[28] Four cases, ranging in age from 2 to 8 months, occurred in OPV recipients, and twelve cases occurred among contacts of OPV recipients (five of these were under age 5, and the remaining seven were between 19 and 40 years of age). The estimated number of trivalent OPV doses distributed in Canada between 1965 and 1988 was 38 million, leading to an estimated risk of vaccine-associated paralysis of one case per 9.5 million doses distributed for recipients, and one case per 3.2 million doses distributed for contacts. These figures are similar to those reported by the WHO Consultative Group from six countries in 1970-1979.[114]

In the United States, Nkowane et al[109] estimated the incidence of paralytic poliomyelitis following OPV at one case per 500,000 first doses given to infants, and one case per 12 million subsequent doses. The overall rates for recipient and contact cases were estimated to be one

recipient case to 7.8 million doses distributed, and one contact case to 5.5 million doses distributed, respectively.

A small proportion (under 10%) of vaccine-associated cases occur in individuals with severe immunodeficiency disorders.[107]

3.1 An Overview of Medical Record Linkage

3.1.0 Introduction

The idea of linking records is simply the bringing together of information from two independent source records that are believed to relate to the same individual or family.[116] Such records are said to be "linked" and may be treated as a single record for one individual or family. With successive linkings, the information may take on the characteristics of a collection of personal or family histories.

3.1.1 History

The term "medical record linkage" was first used in 1946 by H.L. Dunn, Chief of the United States National Bureau of Vital Statistics.[117] As Acheson describes in his classic text *Medical Record Linkage*,[116] Dunn introduced the new term to a group of Canadian vital

statisticians in this way: "Each person in the world creates a book of life. This book starts with birth and ends with death. Its pages are made up of the records of the principal events in life. Record linkage is the name given to the process of assembling the pages of this book into a volume."

This literature review is concerned with record linkage as it relates to the health care system's need for information about the whole population, but the same principles may be applied to any field in which it is necessary to bring together information recorded about persons in different places or at different times.[116] Acheson has outlined the historical development of medical record linkage.[116] Concern with the correlation of community information had risen during the eighteenth and nineteenth centuries, as populations became more mobile, and life and the fiscal requirements of the State became more complex. With twentieth century medicine came the view of the cumulative personal file of health data as a tool to advance knowledge of chronic disease and genetics. The trend toward illness documentation by all agencies delivering health care produced what Bothwell termed, in 1965, an "epidemic of medical records",[118] and the definition of a new type of medical problem: that "where the data to solve the problem exist in part or in full, but are inaccessible".[116] The lack

of continuity of health records maintained by physicians, hospitals, and local health and education authorities was emphasized in 1967 by Godber,[119] who said "we are stuck with a record in its most primitive manuscript form that is almost useless for later reference".

Dunn, in 1946, first envisaged the assembly of health records into personal files over a lifetime, with linkage implying that records are brought together by means of common identification data (for example names, date of birth) which ensure that the records are assigned to the correct file.[116] By 1957, Canadian geneticist H.B. Newcombe had recognized the full implications of extending the principle to the arrangement of personal files in family groups,[120] and the year 1959 saw the application in Britain of the computer to the problems of sorting and matching personal records with discrepant identification data.[116] Commenting on the first use of computerized medical records by a government medical officer in Britain, Godber noted:[119] "It is not coincidental that he is about the only Medical Officer of Health in the country...who manages to get about 90 per cent. of the children immunized".

The National Health Service in Britain, under which a single system provided virtually all health care, presented an ideal opportunity to British researchers to examine for the first time the practical application of

prospective record linkage for a whole population.[116] In 1962, a regional pilot study, the Oxford Record Linkage Study, was begun.[121] The early pilot study was later described by Godber[119] as "pioneer work" and "a pretty primitive example of record linkage", but in its fully developed form the Oxford Record Linkage Study was highly influential outside the region, and laid the foundation for the Office of Population Censuses and Surveys (OPCS) Longitudinal Study in England and Wales, and for the Scottish national system of medical record linkage.[121]

The definition of medical record linkage used by the Oxford Record Linkage Study remains appropriate: "A system of linked health records which brings together selected data of biological interest for a whole population commencing with conception and ending in death, in a series of personal cumulative files, the files being organized so that they can be assembled in family groups. The term record linkage may apply specifically to the techniques of assembling the files in spite of errors and omissions in the identifying particulars, or may be used in a more general sense to apply to the organization involved".[116]

Both the idea and technique of family record linkage were developed in Canada, by Newcombe.[116] This work began in 1957, and was possible because vital statistics identifying data collected in Canada surpassed that of

any other country, and because material was already collected in a form accessible to computers.[116] Early studies by Newcombe linked British Columbia health and vital records, and strongly supported the case that linkage and integration of various source records could be used in health care administration, demographic studies, the provision of health statistics, and for medical research.[122] Over more than 20 years, Newcombe and his colleagues carried computer techniques of linking records to a high level of sophistication,[116] and since that time Statistics Canada has contributed definitively to the mathematical theory of record linkage, and has developed an exceedingly flexible computer system for handling all aspects of a linkage operation.[123]

Record linkage systems are currently in operation in a number of centres throughout the world,[124,125] including Britain, Northern Ireland, Canada and the United States. In North America, record linkage and long-term follow-up have generally been carried out centrally at Statistics Canada for Canadian mortality data, and at the National Center for Health Statistics for American mortality data.[125] During the past decade, Statistics Canada has made available, to medical investigators, automated facilities for follow-up studies.[126] Two such centralized follow-up facilities, the Canadian Mortality Data Base and the National Cancer

Incidence Reporting System, have been used to monitor very large study populations for delayed effects on health, and consist of provincial records converted into a standardized format under the custody of Statistics Canada.[127] The U.S. National Center for Health Statistics reported 122 users of the National Death Index in the November 1981-December 1985 period, with studies involving exposure cohorts, disease cohorts, lifestyle and risk factors, clinical trials, and general population cohorts.[125]

Roos and Nicol[128] point out that, while Statistics Canada data have received considerable attention, an alternative non-centralized data processing approach has also been taken in Canada. Provincial databases, developed from data routinely collected as part of administering Canada's national health insurance within each province, have also been successfully used in a similar fashion in several provinces.[125,127]

3.1.2 Concepts

The task of keeping a population-wide file of general health histories up-to-date requires a computer-based information processing system.[124] When presented with a new health record, this system must be capable of determining to which individual in the master health

history file the record should be attributed, following which the process of incorporating the new health information into the master history by linkage is relatively simple.

There are two principal steps prior to any linking operation.[124,129-131] The first is the searching step, in which potentially linkable pairs of records are sought, narrowing interest to a small number of records in the main health file which seem to have special relevance to the new record. In this step, it is essential to reduce the number of failures to bring potentially linkable records together for comparison, and this must be done without resort to excessive amounts of additional searching. The second step is the matching step, in which pairs of records are compared to determine whether they should be linked. This entails detailed comparison of the new record with each of the existing records in the group or block. In the automated process, the machine must apply in numerical form the rules of judgment by which a human clerk would decide whether or not a pair of records relates to the same person when some of the identifying information agrees and some disagrees.[129] Linking is the process by which pairs of correctly matched records are brought together in such a way that they may be treated as a single record for one individual.[131]

Newcombe[129] describes the optimization of the searching step, in which errors in the form of failure to bring potentially linkable pairs of records together for comparison must be minimized. These errors could be reduced to zero by comparing each incoming record with all of the records already present in the master file, but, where the files are large, this procedure entails enormous numbers of wasted comparisons of pairs of records that are unlinkable. For this reason, the file is arranged in an orderly sequence, using identifying information that is common to both the incoming records and those already present in the master file. Detailed comparisons need then be carried out only within the small portions of the master file for which the sequencing information is the same as that on the incoming records. Any kind of identifying information available on all the records may be used for sequencing the files, and the identifier should subdivide the file with the greatest efficiency and an acceptably low level of wasted comparisons.

Gill and Baldwin describe the practical aspects of matching and linking.[131] The fundamental requirement for correct matching is that there should be a means of uniquely identifying the individual (or episode or family) on every document to be linked. Where records include unique identifiers, matching is a relatively

simple process, and is "all-or-none" matching since the pairs of records compared either do or do not match. Where no unique identifier is available, matching depends on achieving the closest equivalent to unique identification by using several matching variables, each of which is only a partial identifier, but which in combination provide a match which is sufficiently accurate for the intended uses of the linked data. The use of several identifiers to match records is called "probability matching" since the object is to estimate the probability that the records in each pair refer to the same individual. Based on the discriminating power and reliability of each identifier, numerical values can be calculated for the amount of agreement or disagreement and expressed as weights which indicating the likelihood that a pair of records belong to the same individual.

3.1.3 Record Linkage in Manitoba

Roos and colleagues[125,132] describe the health insurance database in the province of Manitoba. The Manitoba Health Services Commission (MHSC) computer registry or master enrolment file has been constructed from individual histories generated from the population registry and from health insurance claims filed routinely with MHSC. The MHSC data are population-based, and are

designed to cover all the individuals in the province. All hospital and medical care, with a few minor exceptions (such as private room, cosmetic surgery and some out-of-province care) is available to all provincial residents registered with MHSC. Non-participation in the Manitoba health plan is minimal, as residents are not required to pay any premiums to register for insured benefits, and no limitations are placed on provider or use. The health database contains information on all registrants, regardless of where care was received.

The MHSC enrolment file includes a unique individual patient identification number (the PHIN, personal health identification number), other individual identifiers, the date of enrolment with MHSC, and the date of enrolment termination (migration or death). The date of death is recorded regardless of whether death occurred inside or outside a hospital.

Following each hospital discharge in the province, a claim is filed by the hospital with MHSC. The MHSC hospital file therefore contains the information taken from this hospital discharge abstract, including personal identifiers, and accompanying diagnoses.

Wajda and Roos[125] report that record linkage has proven both possible and practical in Manitoba, and in several other Canadian provinces, particularly

Saskatchewan. In Manitoba, different health care files can currently be linked using the identification numbers and other variables to form individual-based data which permits statistics (such as those relating to hospital admissions) to be compiled according to the number of individuals involved rather than simply the number of events. These researchers, outlining the need for simpler and less expensive methods of carrying out record linkage, demonstrated the use of advanced software in the linkage of 1979-1984 information from the MHSC registry file with the Canadian Mortality Data Base. In Manitoba, retrospective cohort analyses of the outcomes of common surgical procedures have also been conducted,[133-135] and record linkage has also been successfully used to expand data collected for other purposes and with various combinations of data, such as survey, clinical, claims, and mortality data.[125]

The Manitoba Immunization Monitoring System (MIMS)[136] file is also built on the MHSC population registry. Children born on or after January 1, 1980 are automatically entered into MIMS at birth or after transfer into the province. Children who die or move out of the province are automatically removed from the monitoring system, but remain in the MIMS database until their file has been inactive for two years. The MIMS file contains the individual patient identifier (the

PHIN), the date of birth, the sex, date of termination (death or migration), and the attached immunization records (including immunization tariff code, service date, and restrictions).

The MHSC registry file, the MHSC hospital file and the MIMS file can therefore be readily linked using the unique identifier to obtain exact matches. A child's immunization history can be linked to his or her hospitalization history, while linkage to the registry file can be used to provide a check on mortality, migration out of province, and the quality of the PHIN identifier.

3.2 Summary of the Literature Reviews

From the literature review concerning adverse events following the administration of the immunizing agents routinely used in the first year of life it is concluded that, in the weighing of risks and benefits of routine childhood immunization with the vaccines routinely used in the first year of life, there remains considerable doubt and confusion in many minds regarding the risks of uncommon or rare serious sequelae to routine immunization with these vaccines. No evidence exists of a true temporal association between DTP/DT immunization and permanent neurological illness or death. For those

adverse events for which there is some evidence of a true temporal association with vaccine administration, no accurate quantification of risk by serious event and by immunizing agent is currently available. Our first need is for true population rates of incidence of these uncommon or rare, serious events. Next, we need to assess in a scientific manner the nature of temporal associations between the administration of routinely-used vaccines and clinical adverse events, and to determine rates of incidence for those adverse events which show a true temporal association. Finally, we need a surveillance system which continuously monitors the entire population to provide timely, complete and accurate data concerning the occurrence of serious adverse events related to all vaccines.

The extent of the ability of the thesis to address each of these issues is discussed in Section 5 (Statistical Method and the Scope of the Thesis).

The literature review concerning medical record linkage has demonstrated that record linkage studies are both possible and practical in Manitoba, using the universal provincial health insurance database (Manitoba Health Services Commission). Different health care files can currently be linked using the identification numbers and other variables to provide individual-based data which permit statistics (such as those related to

hospital admissions) to be compiled according to the number of individuals concerned, rather than according simply to the number of events. In Manitoba, the unique opportunity exists to study the immunization and hospitalization experiences of children, and the temporal association between childhood immunization and adverse health events. This can be accomplished by linking the immunization and hospital files of a birth cohort of children, and examining their hospitalization histories, and the relationship in time between their immunization and hospital experiences during the first year of life.

4. STUDY METHOD

4.0 Introduction

The universal health insurance system of the province of Manitoba provides a unique opportunity for the study of the hospitalization experiences of children, and of the temporal association between childhood immunization and adverse health events. This can be accomplished by linking the immunization and hospital files of a birth cohort of children, and examining their hospitalization histories, and the relationship in time between their immunization and hospital experiences during the first year of life.

4.1 Sources of Data

Roos and colleagues have described the health insurance database in the province of Manitoba.[125,132] The Manitoba Health Services Commission (MHSC) computer registry or master enrolment file has been constructed from individual histories generated from the population registry and from health insurance claims filed routinely with MHSC. The MHSC data are population-based, capturing virtually all hospital and medical care. Non-participation in the provincial plan is minimal, and the health database contains information on all registrants,

regardless of where care was received. The MHSC enrolment file includes a unique individual patient identification number (the PHIN, personal health identification number), other individual identifiers, the date of enrollment with MHSC, and the date of enrollment termination (migration or death). The date of death is recorded regardless of whether death occurred inside or outside a hospital.

Following each hospital discharge in the province, a claim is filed by the hospital with MHSC. The MHSC hospital file therefore contains the information taken from this hospital discharge abstract, including individual identifiers (the PHIN) and other personal identifiers, admission and discharge dates, accompanying diagnoses, and the occurrence of death during hospitalization.

The Manitoba Immunization Monitoring System (MIMS)[136] file is also built on the MHSC population registry. Children born on or after January 1, 1980 are automatically entered into MIMS at birth or after transfer into the province. The MIMS file contains the individual patient identifier (the PHIN), the date of birth, the sex, date of termination (death or migration), and the attached immunization records (including immunization tariff code, service date, and restrictions). The structure of the Manitoba

Immunization Monitoring System and the manner in which it is maintained are described in Section 4.2.

Changes in the MHSC registry file (including personal information and address changes) are automatically transferred to the MIMS file at two-weekly intervals, so that current registry information is contained in the MIMS file.

The MHSC hospital file and the MIMS file can therefore be readily linked using the unique identifier (PHIN) to obtain exact matches. This permits, for the population of Manitoba children born on or after January 1, 1980, the examination of their individual hospital experiences in temporal relationship to the administration of immunizing agents.

4.2 Structure and Maintenance of the Manitoba Immunization Monitoring System

The essential elements of MIMS are presented diagrammatically in Appendix 2, and described in the Manitoba Immunization Monitoring System User Manual.[136] MIMS is built on the MHSC population registry. Children born on or after January 1, 1980 are automatically entered into MIMS at birth or after transfer into the province. Children who die or move out of the province are automatically removed from the monitoring system, but remain in the MIMS database until their file has been

inactive for two years. Each person in the MHSC registry has a unique identifier which never changes and is used to link MIMS to the registry.

MIMS is a mainframe system, with terminals in key public health units throughout the province, including federal and municipal units. Information concerning immunizations given by public health nurses is entered directly at health units. Physician immunizations are captured directly and automatically from the immunization tariff codes on their billing cards. A copy of the tariff codes, for recommended vaccines and their acceptable alternatives, recognized by the MIMS system is given in Appendix 3. Address changes recorded in the MHSC registry are used to update the MIMS file automatically, so that each child is assigned to the correct regional health unit. This is done using the municipal code, or, in some cases, the postal code.

The records in MIMS are subject to monitoring activities, as shown in Appendix 4. The quality of the information in the database is improved by the monitoring system which, at specific ages, checks each child's record for completeness. Monitoring is conducted in the month of the child's first, second and sixth birthdays. During the monitoring process, MIMS looks for the tariff code specific to each dose of vaccine. Immunizations which are not documented or are incorrectly coded are

regarded by MIMS as missing. If the record indicates that the child is missing a scheduled immunization, a letter is produced and sent to the health care provider of last record requesting that the record be updated or corrected (MIMS follow-up record, Appendix 5).

For the cohort of children born on or after January 1, 1988, the immunization records of all children in the province immunized by physicians and provincial and municipal health units are essentially complete. Immunization services to status Indian children are however provided by federal public health units, and since MIMS was not fully operational in these units in 1988, the immunization records of status Indian children are incomplete for this cohort. MHSC data show that there were 1,854 status Indian children under one year of age registered as of June 1, 1988, and 1,925 as of June 1, 1989 (Manitoba Health Services Commission: personal communication).

The records of all children born in 1988 have been subjected to at least one round of monitoring, thus improving the quality of the immunization information. This does not apply however to the records of children served by federal Medical Services Branch. These records have not been monitored because immunization information is known to be incomplete.

4.3 Immunization Rates - Manitoba

Through MIMS, Manitoba has the unique ability to determine and monitor population-based immunization rates. The first complete review of the MIMS database, for children born in 1988, has shown the following:[106]

a) Age at immunization was almost always equal to or greater than the recommended age, and spans a 5 to 12 week period, depending on the dose. It will therefore be difficult to analyze adverse outcomes by age and dose.

b) Almost all children who received the two- and four-month doses of DTP/DT received poliomyelitis vaccine simultaneously, and a high proportion of children who received the six-month dose of DTP/DT also received poliomyelitis vaccine simultaneously, although the schedule no longer recommends the six-month dose. It will not therefore be possible to look at these immunizations separately. However, the serious event of interest temporally associated with poliomyelitis vaccine (paralytic poliomyelitis) is clinically quite distinct from those serious events which have been temporally associated with DTP/DT vaccine.

c) 87% of children had received first doses, and 85% of children had received second doses, of DT, pertussis and poliomyelitis vaccines by the time of their

first birthday. 80% of children had received third doses of DT by this time, while 79% had received a third dose of pertussis vaccine and 45% a third dose of polio vaccine.

In summary, the MIMS data indicated that only 77% of these infants met the recommended immunization schedule. This figure is likely to be low for the following reason. While all children born in 1988 were included in the analysis, the recording of immunizations given to children served by federal Medical Services Branch (approximately 10% of all children in MIMS) was incomplete.

MIMS records immunizations by tariff codes - four digit numbers which are specific to both vaccine and dose. Coding errors decrease the apparent immunization coverage. While the system will accept repeat immunization codes if they are recorded as having been administered on different dates, the monitoring process will assess the true tariff code as missing, and generate a follow-up letter for correction. For the first database review,[106] records were considered complete only if they contained the correct tariff codes for the three doses of diphtheria and tetanus toxoids, the three doses of pertussis vaccine, and the two doses of poliomyelitis vaccine recommended in the provincial schedule for first year of life. A second review of the database, for

children born in 1988, was conducted in 1991.[137] In this review, doses were sought by incidence (one, two, three and so on). This change in technique resulted in only minor changes to provincial immunization rates.

4.4 Data Organization and Software

Files containing the records of the cohort of Manitoba children born in 1988 were examined.

The linkage of three files was required:

a) The MIMS file. This file included all children born in 1988. Status Indian children were excluded. The file contained the scrambled individual patient identifier (PHIN), the date of birth, the sex, the date of termination, and the attached immunization records (with tariff code, service date and restrictions). The file was generated after all the children had passed their first birthday and had been monitored once. Current registry information is contained in the MIMS file, including date of death (regardless of whether that death occurred in or out of hospital) or termination.

b) The MHSC hospital file for the years 1988 through March 1990. This file included all

children born in 1988. Status Indian children were excluded. The file contained all hospitalizations, and the date of hospital admission, the occurrence of death during hospitalization, accompanying diagnoses (using codes from the *International Classification of Diseases, Ninth Revision, Clinical Modification* or ICD-9-CM[138]), and scrambled individual patient identifiers (PHIN) will be included. Linkages used the individual patient identifiers noted above as also on the MIMS file.

c) The MHSC registry file. This file provided a check on mortality, migration out of province, and the quality of the personal identifiers.

The MIMS file generated in June, 1990, and updated from the registry to that date, was selected for examination. This file was selected for two reasons. First, to maximize the quality of the immunization data, it was desirable to permit one round of MIMS monitoring to have taken place. At least three months must have elapsed since the first birthday of the youngest child in the birth cohort. Secondly, in an operational surveillance system, the MIMS file must allow for a three-month lag in the entry of physician billing data to the system.

The hospital file valid to March, 1990 was selected for examination since, in an operational surveillance system, the hospital file must be generated at a time which allows for a three-month lag in the entry of vital statistics and hospitalization data.

Record linkage and data analysis were performed using the SAS data analysis and programming software system. Record linkage by scrambled individual patient identifier (PHIN) was achieved through the SAS step MERGE, and the data then organized and analysed using the wide range of SAS procedures.

4.5 Sample

The final main file contained the immunization and hospital records of all non-status Indian children born in 1988 and registered with MHSC who had received at least one immunization in the first year of life. A separate file contained the hospital records of all non-status Indian children born in 1988 and registered with MHSC who had received no immunizations of any kind in the first year of life. The records of children who died or transferred out of the province were available.

4.6 Definition of Variables Used in the Examination of the Temporal Association Between Immunization in the First Year of Life and Adverse Clinical Events

Since serious adverse clinical events are expected to lead to hospital admission, admission to hospital was used as a proxy for the severity of the clinical event. The dependent variable, hospitalization, was represented categorically as hospitalized/not hospitalized. As in other studies,[51,57] children whose hospitalizations may be related to predisposing conditions or those specific to the neonatal period of life with no plausible causal association with immunization were excluded, and only hospitalizations occurring after 30 days of age were examined. Examination of the MIMS database[139] prior to study confirmed that a very small number of immunizations (36) were recorded as having been administered to all Manitoba children born in 1988 and aged 30 days of age or younger. Hospitalizations occurring in the first 56 weeks of life were examined in order to include those hospitalizations associated with immunizations administered 28 days or less before the first birthday.

Only immunizations given in the first year of life were counted. All immunization records for the cohort had therefore been subjected to one round of monitoring. Other investigators had used a period of four weeks post-immunization to define the time period during which adverse clinical events as a group may reasonably be

associated in time with immunization.[28,51,56,57] In this study, the explanatory variable representing the time periods around immunization administration was categorized, for the examination of hospitalization for any reason, as "before immunization" (admission date within 28 days pre-immunization, or on or between day -1 and day -28 from day 0, the date of immunization) or "after immunization" (admission date on the day of immunization, day 0, or on or between day 1 and day +28 post-immunization).

Age was both categorized into four-week age groups (4-8,...48-52,52-56), and also examined as a continuous variable, age in days (1...366).

Dose was represented categorically as first/second/third. As has been stated, most children receive DTP/DT and poliomyelitis vaccines concomitantly. The MIMS system records immunizations by the tariff codes specific to both vaccine and dose. To avoid problems caused by miscoding, the study did not look at dose by tariff code, but examined dose by chronological occurrence.

Hospital discharge diagnoses were represented by the ICD-9-CM code assigned to them in the MHSC hospital file. It is required that one major diagnosis (that "which describes the most significant condition for which the patient was hospitalized") and minor diagnoses (in order

of their importance in causing the hospitalization), up to a total of 16 diagnoses, be attributed to each hospital discharge.[140] In this study, all available diagnoses were used.

4.7 Data Quality

The reliability and validity of the Manitoba claims and registry data for research purposes have been investigated extensively over the past fifteen years.[141-143] Comparisons of diagnoses on hospital claim forms against hospital records have shown a high level of agreement.[143] Comparisons of diagnoses recorded in hospital medical records and hospital claims have shown that those made by different physicians for the same patient/same illness correspond reasonably closely, as do those made by the same physician on different occasions during the same illness.[141-143] The MHSC database has been used to study common surgical procedures,[135,144-146] screening and preventive services,[147] physician practice patterns[148,149] and disease prevalence.[150]

Misidentification of individuals in the hospital or the MIMS files can occur, for example with same-sex twins. This is possible because the physician claim for the immunization service is electronically processed as soon as the unique registration number assigned to each

registry family plus two of three individual identifiers (initial, sex, year of birth) correspond on both claim and record. This process differs from that used in record linkage, which matches a unique, enduring, identification number assigned to each individual in the registry. As immunization information is entered on the MIMS record at the time of claim processing, the immunization data for one same-sex twin might be entered on the record of a twin with the same first initial. It has been determined, however, that the overall probability of errors of identification are small.[142]

Checking the MIMS file against the registration and hospital files at study outset showed little disagreement on family registration number, sex and birth year. Twins were clearly identified as two individuals. When comparisons were made between the MIMS and registration files, the scrambled personal identifiers disagreed in 19 cases out of a total of over 15,000. Although the reasons for this are unclear, some of the disagreements may be due to typographical errors; others may result from incorrect reassignment of identification numbers to children returning after an absence from the province.

The internal consistency of the MIMS file was analyzed in several ways. Birth date (year-month-day) was complete in all cases but one. In 66 cases immunization date (service date) or death date preceded

birth date. As MHSC registry checks are conducted routinely and regularly, the error may be assumed to be in immunization date. Service date was coded zero intentionally by MHSC in 224 cases. Such coding indicates a deliberate restriction on use of the immunization data.

Unpublished studies conducted for Manitoba Health have examined the reliability and validity of the MIMS data, and indicate excellent agreement between the computerized MIMS data and physician-patient immunization records.

A previous study by the author (Roberts, 1990) compared physicians' client immunization records and the MIMS immunization records for first year of life immunizations of a birth cohort of 122 infant patients belonging to a large rural group practice. This study found that, of immunizations documented on the patient record, 6.6% were not billed to MHSC and produced no MIMS record. 5% of immunizations billed to MHSC and recorded on MIMS were not documented on the client record.

In rural areas of Manitoba, provision of immunization is divided, overall, almost equally between family physicians and public health nurses. The population is stable, and patient movement between medical practices is limited. Approximately half of the province's children live in the city of Winnipeg,

however, where a large number of family physicians and pediatricians provide about 97% of all immunizations[106] to a more mobile population.

Another study by the author (Roberts, 1991) obtained information concerning MIMS data from the city of Winnipeg in order to provide a more complete picture of provincial MIMS data quality. This study examined the first year of life immunization records of a birth cohort of 131 infant patients of a large Winnipeg pediatric group practice. As in the rural practice study, this study examined the extent of record agreement with respect to coding error, billing and documentation, and also looked at agreement with respect to the date of immunization. The miscoding rate was found to be equivalent to 5 errors per 1,000 pairs of DTP/OPV immunizations given, while the rate of failure to claim for immunization service was equivalent to 8 per 1,000 pairs of DTP/OPV immunizations given. When the physician record was used as the standard, service dates agreed 98% of the time. For 1% of immunization events, the MIMS-recorded date of immunization differed from the actual date by one day, and for another 1% the MIMS-recorded date of immunization differed by 2-6 days. The effect of these service date errors on the present study is discussed in Section 6.3.2.

To maximise MIMS data quality, the two groups of children known to have incomplete MIMS records were excluded from the present study: those of status Indian children and children whose enrolment with MHSC was interrupted during the first year of life.

5. STATISTICAL METHOD AND THE SCOPE OF THE THESIS

5.0 Adverse Events of Interest and Estimated Incidence Rates

The literature review concerning adverse events which have been temporally associated with immunization with agents routinely used in the first year of life (Section 3.1) revealed that many large, controlled prospective and retrospective studies conducted in different parts of the world over more than twenty five years have consistently failed to produce evidence of a true temporal association between DTP/DT immunization and permanent neurological illness or death. Nevertheless, past reports of associations and apparently conflicting evidence have led to the persistence of considerable public and professional uncertainty regarding the safety of these vaccines. For this reason, adverse events sought in this study included encephalitis, encephalopathy (epilepsy, infantile spasms, Reye syndrome, Guillain-Barré syndrome, transverse myelitis, and cerebellar ataxia) and death (both SIDS and non-SIDS).

Some evidence exists for a true association between DTP/DT immunization and other major adverse events: anaphylaxis, very high fever, unusual high-pitched crying, excessive somnolence, seizures (characteristically febrile) and hypotonic-hyporesponsive

state. The population incidences of these events in the general population of infants and in infants following immunization are not known, but have been estimated in a number of well-conducted studies. The occurrence of paralytic poliomyelitis in OPV recipients is accepted as a rare adverse sequel to this immunization; the incidence of this event has been estimated in Canada and the United States from numerator data concerning investigated reports of the disease and denominator data concerning the number of doses distributed. The ranges of the estimates of incidence of these adverse events following DTP/DT and OPV administration are summarized in Table 1 (page 94).

Table 1
Expected Incidence Rates of Adverse Events **

adverse event	incidence rates, previous studies	time period of interest following immunization
very high fever	15 per 1,000 doses fever >40 C; 3 per 1,000 doses fever >40.5 C (ref.21)	48 hours
unusual high pitched crying or screaming	11 per 1,000 doses following DTP (ref.21)	48 hours
excessive somnolence	no rate available	48 hours
seizure	7 per 10,000 doses (ref.93)	7 days
hypotonic/ hyporesponsive state	6 per 10,000 doses (ref.33)	24 hours
anaphylaxis	1 per 50,000 doses to 5 per 1 million doses (refs.21,56)	24 hours
vaccine-associated poliomyelitis	1 per 500,000 doses to 1 per 12 million doses (refs.28,109))	7-30 days

** Incidence rates, derived from previous studies, of uncommon or rare, serious adverse events temporally associated with immunization using DTP/DT or poliomyelitis vaccines

5.1 Methods of Achieving the Specific Objectives of the Thesis

The methods used to achieve the specific objectives of the thesis are described below.

Method 5.1.0

In order to describe the immunization and hospitalization experiences of the cohort, the files were examined in the following manner.

Method 5.1.0.0

To describe the immunization experiences of the immunized cohort, the MIMS file was examined. The immunization rates for these cohort members, by vaccine and by dose, and the distribution of age at immunization, both in days and in four-week age categories, was determined.

Method 5.1.0.1

To describe the hospitalization experiences of the cohort, the linked hospital and MIMS files examined the hospitalization records of each immunized child. In order to describe the most significant conditions occasioning hospital admissions in the first year of life, the most responsible discharge diagnostic codes associated with each hospital admission in the cohort were grouped into the 17 ICD-9-CM Classification of Diseases and Injuries categories.[138] The distribution of these

categories among first year of life admissions was determined.

The rate of hospitalization, for any reason, for the whole immunized cohort and for the immunized cohort by four-week age group was determined.

The distribution of length of hospital stay in days was determined both for children admitted on the first day of life and children admitted after the first day of life.

Method 5.1.1

To determine the true population-based rates of incidence for the immunized cohort of the uncommon or rare, serious events considered to be either major reactions to immunizing agents or major events having a temporal relationship with immunization, a list of the diagnostic codes (ICD-9-CM) which apply to these events was prepared. This list was generated from the review of the literature and consultation with other scientists studying this field, and is found in Appendix 6 (which also provides the time periods within which these events would reasonably be expected to occur following immunization). The clinical adverse events themselves, and the groups of codes which relate to them, are listed in Appendix II. The codes identifying the clinical adverse events are referred to in the study as

"designated", and all other diagnostic codes were referred to as "non-designated".

The linked hospital and MIMS files were examined to determine the rates of incidence of designated discharge diagnostic codes, among all primary and secondary diagnostic discharge codes, in hospitalizations of immunized children between 30 days and 56 weeks of age.

Method 5.1.2

To assess the nature of the temporal association between immunization in the first year of life and the uncommon or rare, serious adverse events, the linked hospital and MIMS files examined together the hospitalization and immunization records of each study child.

Method 5.1.2.0

The number of hospitalizations, for any reason (any discharge diagnostic code), in the 28 days before immunization, the day of immunization, and the 28 days after immunization during the first 56 weeks of life were determined, for each vaccine, both for all immunizations and for immunizations by dose category (first, second, third).

This was done in order to determine whether the hospitalization rates in the periods immediately following immunization were really higher than those in the period immediately preceding immunization.

To examine the association between time period around immunization and the occurrence of hospitalization, the presence or absence of hospitalization "before immunization" and "after immunization" were determined for each individual. The analysis of these paired qualitative results concentrated on the number of pairs with the outcomes "hospitalized, before immunization"/"not hospitalized, after immunization" and "not hospitalized, before immunization"/"hospitalized, after immunization" to examine potential differences between the two time periods (that before immunization and that after immunization) being compared. Potential differences in hospitalization rates between the time period prior to immunization and the corresponding time period following immunization hospitalization were then tested.

Method 5.1.2.1

To determine whether the rates of hospitalization associated with those discharge diagnoses signalling major clinical adverse events were really higher in the period immediately following immunization than rates in the period immediately preceding immunization (both for all immunizations and for immunizations by dose category), the data were used

to generate a list of the codes associated with hospital admissions in immunized children. This list of diagnostic codes was compared with the list of designated diagnostic codes (ICD-9-CM) described in Method 5.1.1.

The data was then analyzed to determine the rate, for the immunized cohort, of hospitalization associated with each of the designated diagnostic codes in the before and after immunization time periods appropriate to each code. Potential differences in hospitalization rates, with designated diagnostic codes, between the time period prior to immunization and the corresponding time period following immunization hospitalization were then tested.

Method 5.1.3

To determine population-based rates of incidence for the immunized cohort of those serious adverse events which show a true temporal association with immunization in the first year of life, the hospitalization rates for the immunized cohort related to the designated diagnostic code for which there was evidence of a true temporal association with immunization were calculated.

5.2 Considering Selection

5.2.0 Children Receiving Only Two Doses or One Dose

It is possible for further immunizations to be withheld from children who experience important illness at the time of scheduled immunization, in the four week period following immunization, or at any time thereafter. Therefore, the counts and procedures described in Method 5.1.2 were applied to children receiving only two doses or one dose of DTP (or alternative), or only one dose of OPV (or alternative), to see the extent to which selection was operating.

5.2.1 Children Immunized in Hospital

Since the experiences of children who were admitted at or after birth and remained in hospital through one or more immunization ages were not captured by searching the linked MIMS and hospital files for admissions in the four week periods around immunization, the records of children who received an immunization during a hospital stay (immunization service date occurred between admission date and discharge date) were examined individually. As it was still possible to miss children with very prolonged stays and no available discharge date, the distribution of length of hospital stay in days was separately determined for main cohort members admitted at

birth and for those admitted after birth. It was established that discharge dates were available for all hospitalized main cohort members.

5.2.2 Children Receiving No Immunizations

Examination of the MIMS database prior to study, in a review which included all Manitoba children born in 1988,[137] showed zero immunizations on record for 8.5% of children born in 1988. For members of the study cohort who received no immunizations of any kind and might represent a special group of infants, the hospitalization rate for any reason was determined, and the procedures of Method 5.1.0.1 applied, in order to describe this group.

5.3 Testing the Reality of the Temporal Associations

The study involved repeated measures (of hospitalization) on the same individual. The relationship between the categorical explanatory variable, representing the time periods around immunization administration, and the dependent variable, hospitalization, was therefore tested for statistical evidence of association using McNemar's paired Chi-squared test of association for paired qualitative results.[151] The review of the literature indicated that a hypothesis that the rate of hospitalization in the

cohort would decrease in the time period following immunization could be dismissed. Therefore, the specific alternative hypothesis, that the rate of hospitalization in the cohort would increase in the time period following immunization, was explored and a one-tailed test of statistical significance used. In the event that a significant association was shown to exist, the relationship would be appropriately described by the relative odds of being hospitalized in the time periods after/before immunization.

Since it was of prime importance in this study to detect real differences, if present, in hospitalization rates associated in time with immunization, it was essential that the risk of failing to pick up these differences (Type II error) be kept acceptably small. For this reason, the Type I error was maintained at the 0.05 level for each individual statistical test, despite the fact that multiple statistical testing was carried out on the data, so that the power of the study was maintained. The Type II error was maintained at 10%.

Since paired tests are more powerful than unpaired tests, the sample size required to detect real differences, if present, between the two effects with respect to hospitalization rates was smaller than necessary in an unpaired study.

Advance calculation of the sample size required to detect a statistically significant increase in the hospitalization rate following immunization, with a power of 90% while maintaining the level of Type I error at 5%, required knowledge of the following hospitalization rates for this age group: that in the time period before immunization, that in the time period following immunization, and the rate for infants who are hospitalized during both time periods, before and after immunization (carryover rate). Since these rates were unknown prior to study, rates for the cohort were calculated from the data.

The sample size for this study was fixed. The number of live births in Manitoba in 1988 was approximately 17,000.[152] Whether or not the study would have the power to detect true differences, if present, in hospitalization rates was uncertain prior to study, but could be estimated. If for example the rate of hospitalization, for any reason, in the cohort was 10 per 10,000 in the four weeks before immunization, that in the four weeks after immunization was 20 per 10,000 and the carryover rate was 5 per 10,000, the sample size needed to detect this doubling in the hospitalization rate for any reason following immunization, while controlling Type I error at 5% and Type II at 10%, would be 17,053. Since, from our prior knowledge of the immunization rates

in the cohort, a sample size approximating 40,000 immunizations was expected, the search for a rate increase for hospitalization for any reason, for all immunizations and immunizations by dose category, was quite reasonable.

From the data, the rates, as above, of hospitalizations bearing designated discharge diagnostic codes were determined. Putting these rates into the power calculations, as previously described, allowed us to determine for which designated diagnostic codes the study had the power to detect significant rate increases for the relevant time periods following immunization. The literature review provided estimates, prior to study, of the incidences of serious adverse clinical events in temporal association with immunization of the order of between 1 per 1,000 and 1 per 1,000,000 immunizations given. It was reasonable to expect the study to have the power to detect increases in hospitalization rates after immunization for temporally associated neurological events which are uncommon but not rare, such as febrile convulsions. Rates of febrile seizures from previous studies provide an example.[21,95] If a study rate of hospitalization associated with the ICD-9-CM discharge diagnostic code 780.3 relating to convulsions (unspecified, febrile, infantile) or convulsive disorder, seizure or fit (unspecified) in the 48 hour period

following DTP immunization of 6 per 10,000 immunizations represented a trebling of the study rate for the 48 hour period preceding DTP immunization, and the carryover rate was 0.1 per 10,000 immunizations, the sample size required would be 41,566 DTP immunizations. The search for a rate increase for this event was then quite reasonable. There was, however, no information available concerning the proportion of infants who receive hospital care for febrile seizures, and it was possible that the rates of hospitalization for this event would be too low to permit statistical comparison. It was also likely that analysis by dose category would not be possible.

The search for increases in the rates of rare conditions (occurring at a rate of 1 per million doses) was clearly quite unreasonable, and was not an objective of this study.

6. RESULTS

6.0 The Study Cohorts

The flow diagram describing the selection of the main study cohort is set out in Appendix 7. The MIMS file defined the cohort of non-status Indian infants born in 1988, enrolled with MHSC as of June, 1990, who received at least one immunization in the first year of life. This group numbered 15,281.

1,121 members of this birth cohort were excluded from the final main study cohort. 66 were excluded on the basis of incorrect death or service dates, when these were checked and found to precede birth dates. 1,055 members were excluded because they did not meet the criteria for duration of enrolment. For 143 of these, enrolment began after the first birthday. For 912 children, enrolment was not consistent from birth through the first year of life. The enrolment of 590 children began at a date later than birth but prior to the first birthday, and the enrolment of 322 children began at birth but terminated within 56 weeks of birth. 17 of the enrolment terminations within 56 weeks of birth in Manitoba represented deaths in the first year of life.

895 members of the original birth cohort therefore experienced interrupted enrolment in the first year of life, due not to death but to migration into and out of

Manitoba in the first year of life (derived from enrolment file separation codes). As there is no reason to suspect a relationship between migration and immunization, hospitalization or a combination of the two, and since immunizations administered out-of-province cannot be considered to have been reliably captured by MIMS, this group was excluded from study. As it was considered important to examine the immunization experiences of the children whose enrolment in the first year of life was interrupted by death, the linked immunization and hospitalization records of all children who died in the first year of life were examined individually.

The final main study cohort of non-status Indian infants born in 1988, enrolled with MHSC as of June 30, 1990, who received at least one immunization in the first year of life, and whose enrolment with MHSC endured to 56 weeks from birth numbered 14,160.

The flow diagram describing the selection, from the original birth cohort, of the separate study cohort whose members received no immunizations of any kind, is set out in Appendix 8. This selection was accomplished by merging the MIMS file containing the records of immunized children born in 1988 with the enrolment file containing records for all children born in 1988, and selecting all records for which there was no match. This file was

merged with the hospitalization file in order to examine the hospitalization experiences of the unimmunized cohort (Section 6.6). The group of unimmunized infants numbered 1,093.

764 members of this birth cohort who did not meet the criteria for duration of enrolment were excluded from the final unimmunized study cohort. The enrolment of 391 non-status Indian, unimmunized infants born in 1988 began at a date later than birth (after birth and before the first birthday for 217, after birth and after the first birthday for 174). For the other 373 children, enrolment began at birth but terminated within 56 weeks of birth. 85 of the enrolment terminations within 56 weeks of birth in Manitoba represented deaths in the first year of life. The hospitalization records of each of these 85 deceased children were examined individually.

679 unimmunized members of the original birth cohort therefore experienced interrupted enrolment in the first year of life, due not to death but to migration into and out of Manitoba in the first year of life (derived from enrolment file separation codes), and were excluded from study.

The final cohort of infants born in Manitoba in 1988, enrolled with MHSC as of June, 1990, who received no immunizations in the first year of life and whose

enrolment with MHSC endured to 56 weeks from birth numbered 329.

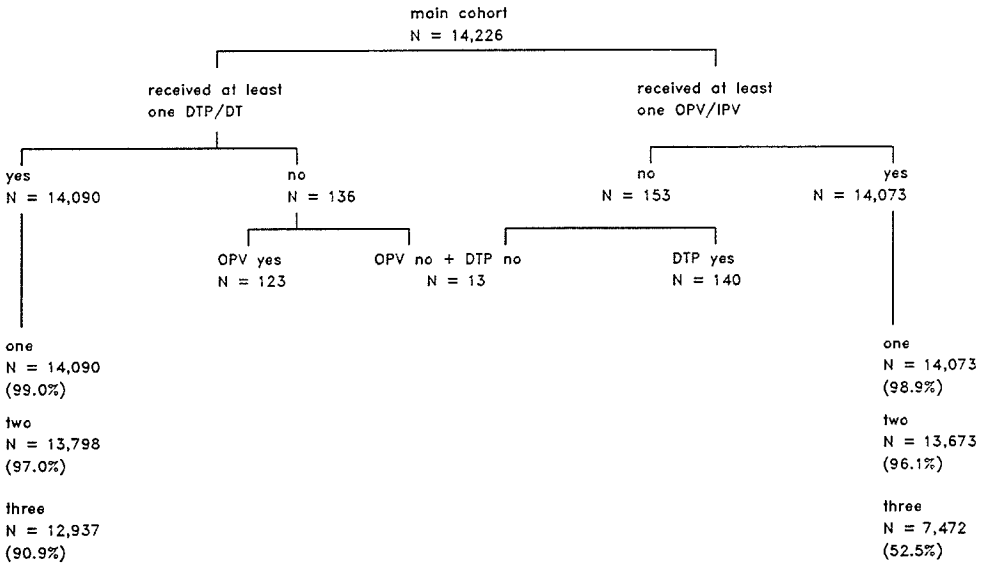
6.1 Descriptive Findings

6.1.0 Immunization Status

Each of the children in the main cohort had received at least one immunization, of any kind.

The immunization status of the main cohort is shown in Figure 1. 14,090 children (99.0% of the cohort) received at least one DTP (or alternative) by the first birthday. 14,073 children (98.9% of the cohort) received at least one OPV/IPV by the first birthday. 13 children received neither DTP nor OPV, but received at least one dose of another vaccine in the first year of life.

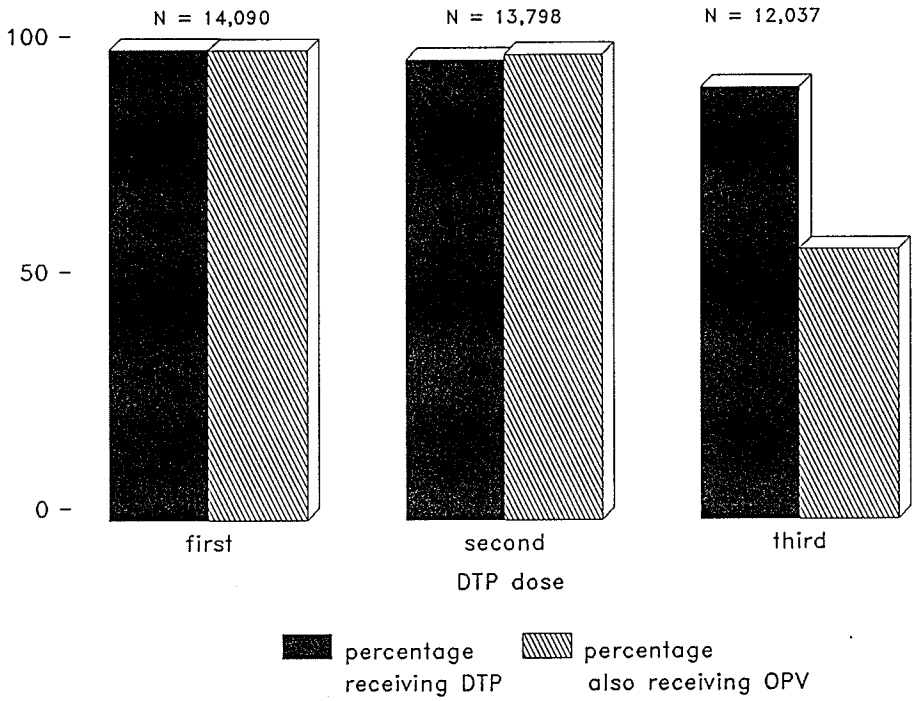
Figure 1
Immunization Status, Main Cohort



97.0% of the immunized cohort received two doses of DTP, and 90.9% three. 96.1% of the cohort received two doses of OPV, and 52.5% received three, even though the schedule no longer recommends the third dose.

The DTP and OPV (or alternatives) were almost always administered on the same day, as shown in Figure 2.

Figure 2
Simultaneous Immunization



90.7% of the main cohort was fully immunized, according to provincial recommendations, by the first birthday i.e. had received three doses of DTP and two doses of OPV.

Of children receiving up to three doses of DTP (or alternative), fewer than 1% received DTP alternatives for any dose. While 35,218 doses of poliovaccine were administered to children receiving at least one dose of OPV (or alternative), the IPV alternative was used in only 14 instances.

It is therefore reasonable to use the term DTP to describe DTP vaccine or its alternatives and the term OPV to describe either OPV or IPV in further discussion.

The immunization experiences of the total cohort of infants born in Manitoba in 1988, enrolled with MHSC as of June, 1990, whose enrolment with MHSC endured to 56 weeks from birth are described by the combined experiences of the main immunized cohort and the cohort receiving no immunizations of any kind. Figure 3 (page 113) describes the immunization status of these combined cohorts. Combination of the cohorts produced the rates shown in Table 2 (page 113). 89.0% of the total cohort was fully immunized, according to provincial recommendations, by the first birthday.

Figure 3
Immunization Status, Combined Cohorts

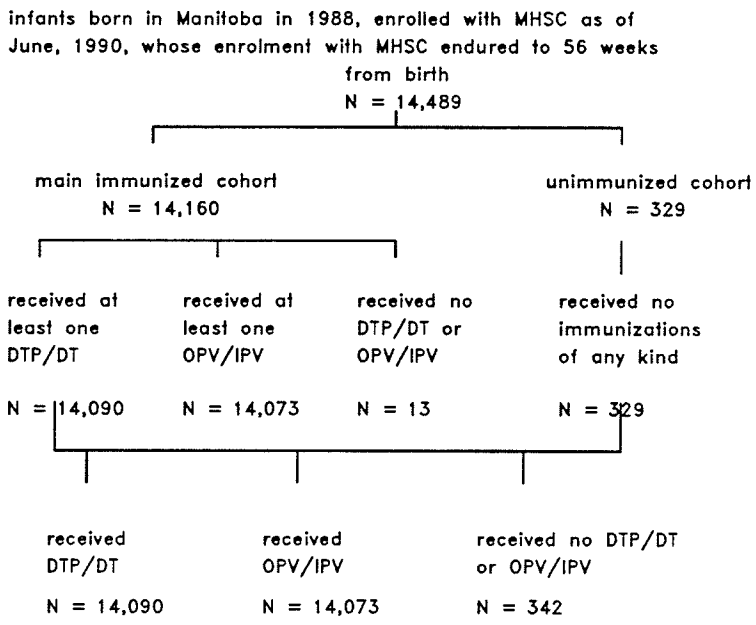


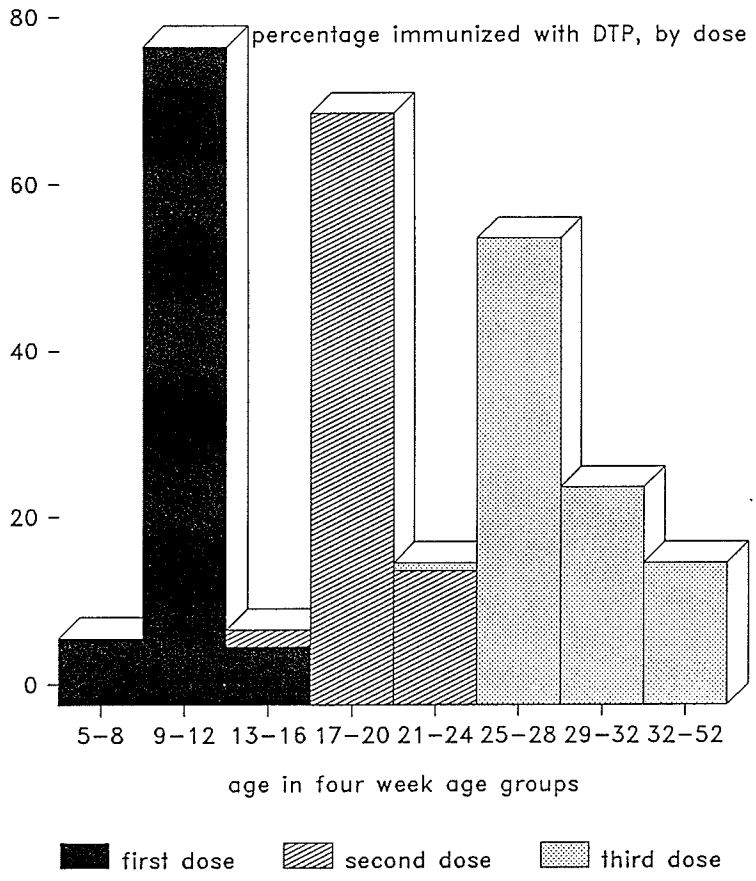
Table 2
Immunization Rates, Combined Cohorts*

immunization status	number	percentage of cohort
received at least one dose of DTP/DT by the first birthday	14,090	97.2
received two doses of DTP/DT by the first birthday	13,798	95.2
received three doses of DTP/DT by the first birthday	12,937	89.3
received at least one dose of OPV/IPV by the first birthday	14,073	97.1
received two doses of OPV/IPV by the first birthday	13,673	94.4
received three doses of DTP/DT and two doses of OPV/IPV by the first birthday	12,899	89.0

* Total cohort of children born in Manitoba in 1988, enrolled with MHSC as of June 30, 1990, whose enrolment with MHSC endured from birth to age 56 weeks
N = 14,489

Examination of the frequency of immunization by vaccine and dose by age at immunization in four week age groups is summarized in Figure 4, which gives results for DTP immunization. The majority of each of the doses of DTP and OPV were given in the four week time period immediately following the recommended immunization age, but age group at immunization exceeded the recommended age group more often with successive doses.

Figure 4
Age at DTP Immunization



The frequency of immunization by vaccine and dose by age at immunization in days was also examined. In Table 3 the findings have been expressed, for simplicity, in months, with one month representing 30 days of life.

Table 3
Age at Immunization, in Months

dose	age by which 90% of cohort immunized (months)	range (months) in which 80% of cohort immunized	average age at immunization (months)
first DTP/DT	2.9	1.9–2.9	2.1
first OPV/IPV	2.9	1.9–2.9	2.1
second DTP/DT	5.7	4.0–4.7	4.3
second OPV/IPV	5.7	4.0–4.7	4.3
third DTP/DT	8.1	6.0–8.1	6.5
third OPV/IPV	7.7	6.0–7.7	6.3

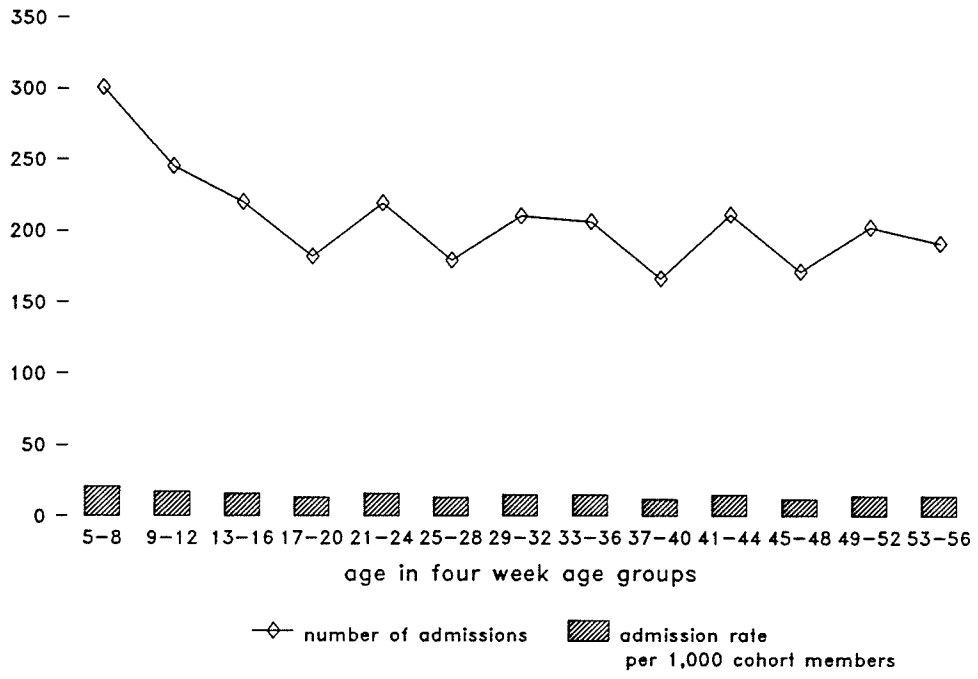
The tariff code appropriate to each individual immunization is assigned by the provider when a MIMS input document is created by a public health nurse or a billing claim is created by a physician. Correct tariff codes were assigned between 96-97% of the time, for each dose of both vaccines.

6.1.1 Hospitalization Status

17,557 hospitalizations occurred in members of the main cohort during the first 56 weeks of their lives. 14,854 of these hospitalizations occurred in the first four weeks of life. 14,138 of these admissions occurred at age day 0, and for 14,043 of these the discharge codes indicated a live birth admission. The remaining 95 day 0 represented inter-hospital transfers of newborns and admissions of children born outside Manitoba hospitals.

The rate of hospital admission was highest in the 0-4 week age category. Following exclusion of the 14,043 live birth admissions from this category, the rate was 57 per 1,000 cohort members, with 841 admissions in this period. The admission rate declined sharply to 21 per 1,000 for the 5-8 week category. Figure 5 (page 117) shows the numbers and rates of hospital admission by four-week age groups from 5 to 56 weeks. The admission rate fell to around 15 per 1,000 cohort members in the 9-12 week category and remained constant from 9 to 56 weeks. The overall rate of hospital admission for the main cohort in the first 56 weeks of life was 247.0 per 1,000 cohort members (live birth admissions excluded).

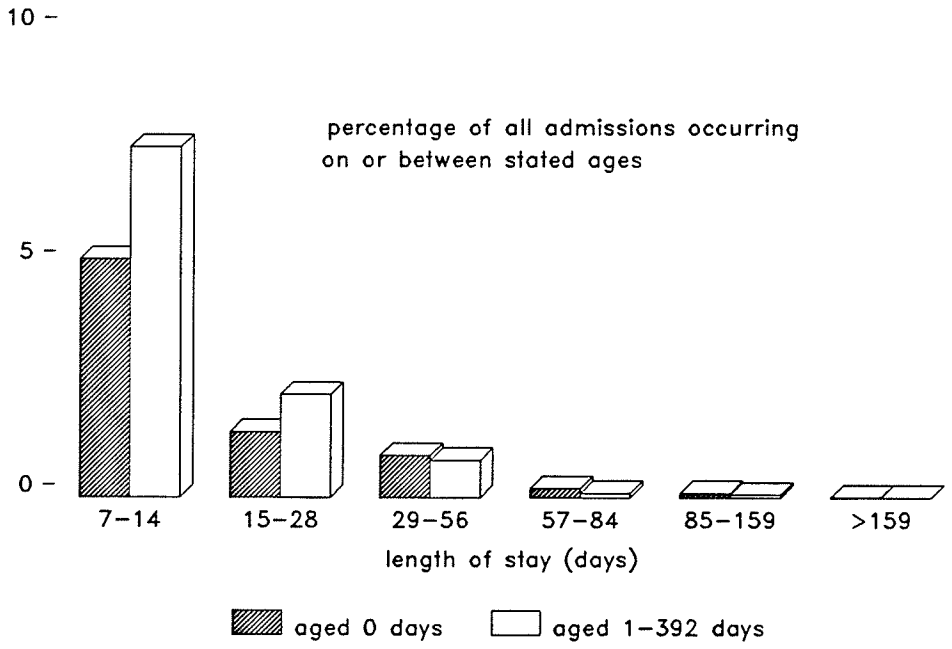
Figure 5
Hospitalization By Age
Main Cohort



The admission rate in the first four weeks of life underestimates the amount of illness in this age category, as exclusion of live birth admissions excluded infants whose birth stay was prolonged due to illness. Of 14,138 admissions occurring at age day 0, 13,052 (92.3%) lasted 6 days or less. When the frequency of length of stay in days of all admissions occurring on or

between age day 1-392 was examined, it was found that, of 3,419 such admissions, 2,930 (85.7%) of these lasted 6 days or less. Figure 6 contrasts lengths of stay greater than 7 days for all admissions occurring at age day 0 with those of all admissions occurring on or between age day 1-392. While a substantial proportion of day 0 admissions lasted 7 days or longer, a higher proportion of day 1-392 than day 0 admissions lasted 7-28 days.

Figure 6
Length of Hospital Stay Over 7 Days
Immunized Cohort



Of the 17 ICD-9-CM Classification of Diseases and Injuries categories, Category 8 (Diseases of the Respiratory System) was responsible for the highest proportion of hospital admissions in the first 56 weeks of life. This category encompassed the most responsible discharge diagnosis in almost 26% of all admissions in the first 56 weeks of life (Table 4, page 120). When the distribution of categories was examined by four-week age group, the category most frequently responsible for admission in the 0-4 week category was Category 15 (Certain Conditions Originating in the Perinatal Period) which encompassed the primary discharge diagnosis in almost 32% of admissions in the 0-4 week age group, and describes illnesses specific to the neonatal period of life. Respiratory diseases represented the most frequent cause of admission in all other four week categories, giving rise to over 32% of admissions between 5-56 weeks of age.

Table 4
Distribution of Primary Diagnoses, Main Cohort **

ICD-9-CM category of diseases	total no.	%age of all admissions	%age of 0-4 wk admissions	%age of 5-56 wk admissions
8.Respiratory	812	25.6	4.5	32.4
9.Digestive	423	12.0	3.3	14.6
15.Perinatal	307	8.7	31.6	1.5
16.Ill-Defined	287	8.1	3.8	9.4
6.Nervous	277	7.8	1.0	10.0
14.Congenital	261	7.4	7.7	7.3
1.Infectious	202	5.7	1.8	7.0
10.Genitourin.	142	4.0	1.7	4.7
17.Injury	86	2.4	0.5	3.0
12.Skin	51	1.4	0.6	1.7
2.Neoplasms	32	0.9	0.4	1.1
4.Blood	16	0.5	0	0.6
3.Endocrine etc	13	0.4	0.2	0.4
7.Circulatory	11	0.3	0.4	0.4
13.Musculoskeletal 6		0.2	0	0.2
Factors Not Causing Current Illness (V Codes)	513	14.5	42.7	5.9
TOTAL	3,538	100.0	100.0	100.0

** Distribution of primary discharge diagnoses, main cohort, over all admissions in the first 56 weeks of life (live birth admissions excluded), by ICD-9-CM Classification of Diseases and Injuries categories

6.2 Rates of Incidence, for the Main Cohort, of Those Uncommon or Rare, Serious Adverse Events Which Have Been Temporally Related to Immunization

All hospital admissions of main cohort members between the ages of 30 and 392 days (56 weeks) were examined. The occurrence of designated diagnostic discharge codes among the primary and secondary discharge diagnostic codes of these admissions was sought in order to determine the incidence of these codes in admissions occurring in this age group. A total of 4,884 primary and secondary discharge diagnostic codes relating to 2,674 hospital admissions of cohort members between the ages of 30-392 days were examined for the occurrence of the 56 designated codes. There were no occurrences of 40, and 210 occurrences of 16, of the 56 designated codes. Table 5 (page 122) shows the number of occurrences and the incidence of each code per 1,000 admissions occurring between 30-392 days of age.

Data was available concerning the occurrence of designated codes in the first 30 day period of life. It was of interest to compare the distribution of designated codes among admissions occurring between 30 and 392 days of age with that among admissions occurring on the first day of life (referred to as day 0) and between days 1 and 30 of life. This comparison showed that the designated code 781.4 (transient paralysis of limb) occurred only in day 0 admissions (two instances), codes 781.0 (abnormal

day 0 admissions (two instances), codes 781.0 (abnormal involuntary movements - two instances) and 785.5 (shock without mention of trauma - 1 instance) occurred only in admissions between days 0-30, and code 780.3 (convulsions) appeared only in admissions between 30-392 days of age (97 instances).

Table 5

Designated Diagnostic Codes Admissions Over 30 Days of Age**

ICD-9-CM Code	Definition	Number	Incidence per 1,000 admissions occurring between 30 and 392 days of age
682.6	cellulitis and abscess leg, except foot	5	1.87
780.0	coma and stupor	3	1.12
780.3	convulsions (excludes epileptic and in newborn)	97	36.28
780.6	pyrexia of unknown origin	87	32.54
781.3	lack of coordination	4	1.50
999.9	other and unspecified complications of medical care, not elsewhere classified	6	2.24
E948	external cause: bacterial vaccine	*	
048	other enterovirus diseases of central nervous system	*	
682.3	cellulitis and abscess upper arm and forearm	*	
780.2	syncope and collapse	*	
995.1	angioneurotic edema	*	
999.5	other serum reaction	*	
995.2	unspecified adverse effect of drug, medicinal and biological substance	*	
TOTAL DESIGNATED		210	78.53

** Designated diagnostic discharge codes among a total of 4,884 primary and secondary codes for 2,674 hospital admissions occurring between 30 and 392 days of age in 14,160 main cohort members in first 56 weeks of life

* numbered 2 or less

6.3 The Temporal Relationship Between Hospitalization and Immunization

6.3.0 Hospitalization For Any Reason - the Main Cohort

The total number of hospitalizations (any diagnostic codes) between the first four and 56 weeks of life of the cohort in each of the two time periods (the 28 days before the day of immunization, and the 29 days from day 0 to day 28 after immunization) are shown for DTP immunization in Table 6, and for OPV immunization in Table 7. These tables list these hospitalizations over all immunizations, and for immunizations by dose category ("first", "second", "third").

Table 6
DTP immunization: Hospitalization For Any Reason

dose	number of admissions in time category *		N
first DTP	before	196	14,090
	after	175	
second DTP	before	163	13,798
	after	140	
third DTP	before	111	12,937
	after	123	
TOTAL DTP	before	470	40,825
	after	438	

* before time category includes admissions occurring in the 28 day period before the day of immunization;
after time category includes admissions occurring on the day of immunization and in the 28 day period after the day of immunization

Table 7
OPV Immunization, Hospitalization For Any Reason

dose	number of admissions in time category *		N
first OPV	before	213	14,073
	after	192	
second OPV	before	174	13,673
	after	154	
third OPV	before	67	7,472
	after	54	
TOTAL OPV	before	454	35,218
	after	400	

** before time category includes admissions occurring in the 28 day period before the day of immunization; after time category includes admissions occurring on the day of immunization and in the 28 day period after the day of immunization

Since the analysis did not concern individuals who were hospitalized in both time periods, the number of such individuals was determined and the total number of hospitalizations in each of the two time periods reduced accordingly. The number of children hospitalized in both time periods included both children who experienced admissions during each time period (totals: DTP N = 38, OPV N = 32), and children admitted in the "before" time period who were immunized during a hospital stay which

was then prolonged into the "after" period (totals: DTP N = 16, OPV N = 16).

As Tables 6 and 7 show, over all three doses of each vaccine considered together the total number of hospitalizations which occurred in the 29 day time period following immunization was lower than that which occurred in the 28 day time period before immunization. Sample size calculations showed that the study had the ability to detect a true relative increase of 20%, if present, in hospitalizations over all three doses of each vaccine, with a power of 90% while controlling type I error at 5%.

Findings of lower numbers of hospitalizations in the time period after rather than before immunization were repeated for each dose of each vaccine considered separately, with the exception of the third dose of DTP, for which there was a slight rise in hospitalization after immunization. The association between immunization with the third dose of DTP and the increase in hospitalization in the time period following immunization was statistically insignificant (Chi-square 0.52 with 1 df, one-tailed test, N.S.). As the sample sizes for each dose of the vaccines were considerable smaller than that for all three doses combined, the study was less sensitive to real increases in hospitalization following each dose of the vaccines. The study was capable of detecting true relative increases, if present, in

hospitalizations occurring after immunization, of 30% for the first dose of DTP (N = 14,090) and OPV (N = 14,073) and the second dose of DTP (N = 13,798) and OPV (N = 13,673), and between 45-50% for the third dose of DTP (N = 12,937) and OPV (N = 7,472), with a power of 90% while maintaining type I error at 5%.

It is therefore concluded that, over all three doses in the first year of life, hospitalization after 30 days of age for any reason is no more likely to occur in the period from the day of the immunization with DTP/OPV to 28 days after the day of these immunizations than in the 28 days before immunization.

The sensitivity of the investigation into the nature of the association between hospitalization and immunization with each dose of vaccine would be directly increased by increasing the sample size. This could be accomplished by adding more years of data from an ongoing surveillance system.

6.3.1 Hospitalization With Designated Diagnoses - the Main Cohort

The appearance of each designated diagnostic code among the primary and secondary discharge diagnoses of hospitalizations occurring within the appropriate time spans before and after immunization (all three doses together and each of the three doses) was sought. The number of individuals hospitalized with designated diagnoses in both time periods was determined and the number of such hospitalizations in each of the two time periods reduced accordingly. On page 128, Table 8 describes the number of hospitalizations associated with designated diagnostic codes and the time periods of relevance around OPV immunization, and Table 9 repeats this description for DTP immunization.

Table 8

Number of Hospitalizations With Designated Diagnostic Discharge Codes Before and After OPV Immunization, By Dose

dose	time period	number of admissions	time period (days)	number of cases	ICD-9-CM code and description
first	before	*			
	day 0	*			
	after	*	7-28	*	781.3 lack of coordination
second	before	*			
	day 0	*			
	after	*			
third	before	*			
	day 0	*			
	after	*			

*numbered 2 or less

Table 9

Number of Hospitalizations With Designated Diagnostic Discharge Codes Before and After DTP Immunization, By Dose

dose	time period	number of admissions	time period (days)	number of cases	ICD-9-CM code and description
first	before	*	7-28	*	048 other CNS enterovirus dis.
	day 0	*			
	after	3	7-28	*	781.3 lack of coordination
			2-7	*	780.3 convulsions
			1	*	780.6 pyrexia of unknown origin
second	before	*			
	day 0	*	0	*	780.6 pyrexia of unknown origin 999.9 complications of medical care E948 bacterial vaccines
	after	5	2-7	*	999.5 vaccination
			1-7	3	780.3 convulsions
			1	*	780.3 convulsions
third	before	*	2-7	*	780.3 convulsions 780.6 pyrexia of of unknown origin
	day 0	*			
	after	3	2-7	*	780.3 convulsions
			1	*	780.6 pyrexia of unknown origin 780.3 convulsions 999.9 complications of medical care

*numbered 2 or less

Over all three doses of OPV considered together, one designated diagnostic code relevant to this vaccine appeared in the appropriate "after" time period. This code was 781.3 (lack of coordination), and it did not appear in the appropriate "before" time period. The association between immunization with OPV and the increase in hospitalization with this designated code in the appropriate time period following immunization was statistically insignificant (Chi-square 1.00 with 1 df, one-tailed test, N.S.).

Over all three doses of DTP considered together, four designated codes relevant to this vaccine appeared in the appropriate "after" time periods. These codes were: 780.3 (convulsions), 780.6 (pyrexia of unknown origin), 999.9 (other and unspecified complications of medical care, not elsewhere classified), and E948 (external cause bacterial vaccine). Codes 780.3 and 780.6 also appeared in the "before" time period, but their numbers in the "after" time period were increased (Table 9).

The realities of the associations between immunization with DTP and the increases in hospitalization with each designated code in the appropriate time periods following immunization were tested using McNemar's paired Chi-squared test as before. The test statistic for code 780.3 (convulsions) did reach

statistical significance (Chi-squared 4.50 with 1 df, $p<0.05$). The test statistic for the other three codes failed to reach statistical significance in each case. McNemar's Chi-squared values for codes 780.6 (pyrexia of unknown origin), 999.9 (other and unspecified complications of medical care, not elsewhere classified), and E948 (external cause bacterial vaccine) were 0.50, 1.00 and 1.00 respectively, with 1 df, N.S. Sample size calculations showed that the study did have the ability to detect true 10-12 fold increases, if present, in hospitalizations with codes 780.6, 999.9 and E948 over all three doses of DTP, with a power of 90% while maintaining type I error at 5%.

It is concluded that, over all three doses of DTP in the first year of life, hospitalization after 30 days of age with the diagnostic code 780.3 (convulsions) is more likely to occur in the 7 days following the day of DTP immunization than in the 7 days before the day of this immunization, and that a true temporal association between DTP immunization and hospital admission for convulsions exists in the first year of life.

For hospitalizations with ICD-9-CM code 780.3 convulsions, the incidence rate in the 7 days following the day of DTP immunization in the first year of life was 7 per 40,825 doses (1.72 per 10,000 doses).

The small sample size rendered the study insensitive to analysis of the association between hospitalization with designated codes and immunization by dose. Increasing the sample size would also directly increase the sensitivity of the investigation into the nature of the association between hospitalization with designated codes and immunization, both over all doses of vaccine and with each dose.

6.3.2 The Effect of Service Date Errors

Only one study has examined the quality of MIMS data with respect to service dates. This study was discussed in Section 4.7. It was conducted in a specialized situation and used a small sample size and the physician record as the standard. Service dates agreed 98% of the time, with the service dates of 1% of immunization events disagreeing by one day and the other 1% by 2-6 days with the actual date. Service date discrepancies are random errors occurring during physician documentation or during claim preparation or input. The larger the sample size, the smaller will be their effect, particularly on the search for the rare events anticipated to occur between days 7-28 following immunization. In addition, the present study did not depend on the reliability of physician documentation. Assuming the worst effect, that the occurrence of 1% of events anticipated to occur on or between days 0-7 following immunization may have been classified in the wrong time category, recalculation of study results has shown no difference in outcome.

6.4 Children Who Received Only Two Doses or Only One Dose

For children who received only one dose (N = 292) or two doses (N = 861) of DTP, or only one dose (N = 400) of OPV, the procedures applied in Section 6.3.0 were repeated. The results are shown in Table 10.

Although the same trend to no increase in hospitalization after immunization appears to be present, the very small sample size permits no conclusions to be drawn from these findings.

Table 10
Children Receiving Only One or Two Vaccine Doses

dose	time period (days) around immunization	number of admissions	time category*		
children receiving only two doses of DTP (N = 861)					
second DTP	28 before	14	before	14	
	day 0	0	after	14	**
	28 after	14			
children receiving only one dose of DTP (N = 292)					
first DTP	28 before	10	before	10	
	day 0	0	after	7	**
	28 after	7			
children receiving only one dose of OPV (N = 400)					
first OPV	28 before	13	before	13	
	day 0	0	after	6	**
	28 after	6			

* after category includes admissions on day 0 and in 28 days after time periods

6.5 Children Immunized in Hospital

A total of 45 immunizations were administered during hospital stays of 20 main cohort members, as follows: 19 first doses of DTP and OPV, two second doses of DTP and OPV, two third doses of DTP, and one third dose of OPV. One child received the first two doses of DTP and OPV in hospital, and one child received all recommended first year of life immunizations (three doses of DTP and two doses of OPV) in hospital. A discharge date was available for each hospitalized main cohort member, so that all recorded immunizations administered in hospital were captured. No designated codes were found amongst the primary or secondary discharge diagnostic codes of children whose immunization was administered during a hospital stay.

6.6 Children Receiving No Immunizations

The records of the 13 main cohort members who received neither DTP nor OPV nor alternatives, but received at least one dose of another vaccine in the first year of life were examined individually. One of these children had never been hospitalized, and for the other twelve the only hospital admission was the birth admission (average length of stay 3.25 days). For nine children, B.C.G. (Bacillus Calmette-Guérin vaccine for the prevention of tuberculosis) given at birth was the only recorded immunization. B.C.G. is no longer recommended for routine use in the general population but is still suggested by Medical Services Branch, Ottawa, for newborn Status Indian children.[153] The finding of nine children with records of B.C.G. immunization at birth and no other immunizations suggests that these were non-Status Indian babies considered to be at risk for tuberculosis. It is likely that these children received medical service after birth through federal Medical Services Branch, and that subsequent immunizations were not entered on MIMS. One child received a DTP immunization coded as the fourth dose (recommended at 18 months of age) and not included in the computer search for first year of life DTP immunizations.

Three children were recorded as receiving only measles or combined measles-mumps-rubella vaccine in the

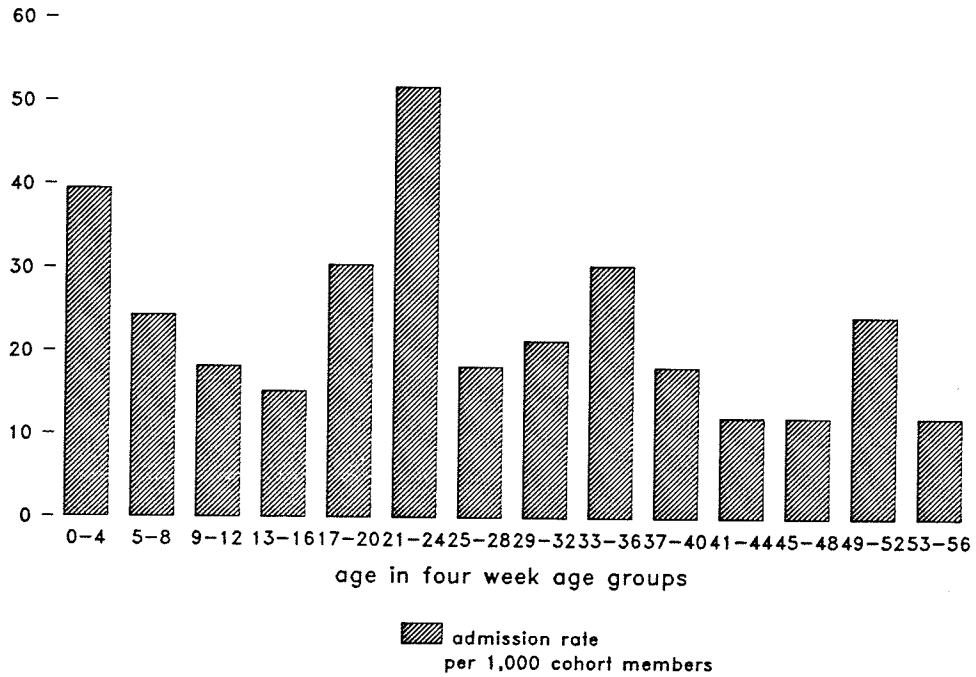
first year of life. For none of the 13 children did the MIMS record indicate medical inability to receive immunizations.

The hospitalization experiences of the cohort receiving no immunizations of any kind were examined separately. This cohort numbered 329. 335 hospitalizations occurred in members of the unimmunized cohort during the first 56 weeks of their lives. 240 of all hospitalizations occurred in the first four weeks of life. For 227 day 0 admissions the diagnostic discharge codes indicated live-born infant care and represented the hospitalization in which birth took place. For 95 children, no hospital admissions at all were recorded. This group included children born outside Manitoba hospitals. While no figures are kept on the numbers of out-of-province births to Manitoba residents, the College of Physicians and Surgeons of Manitoba records that 34 home births occurred in Manitoba in 1988 (College of Physicians and Surgeons of Manitoba: personal communication). The group of 95 also included children adopted in the first year of life whose birth admission was recorded under the MHSC registration number of the birth mother and lost when the child's registration by that number was erased, as required by provincial law, at the time of adoption. Subsequent records of health care contacts would be then listed under the MHSC registration

number of the adopting family, with MHSC coverage back-dated to birth. In 1988, the Manitoba Child and Family Services Agency completed 65 adoption placements of children under one year of age, and estimates that a similar number of Manitoba children were placed by private arrangement. While Agency placements occur at varying ages, private placements almost always occur at less than ten days of age. (Manitoba Child and Family Support: personal communication).

Figure 7 (page 138) shows the numbers and rates of hospital admissions by four week age categories in the first 0-56 weeks of life, following exclusion of the 227 live birth admissions from the 0-4 week category.

Figure 7
Hospitalization By Age
Unimmunized Cohort*



* Live birth admissions excluded

Comparison of Figure 7 with Figure 5 (page 117), showing numbers and rates in the same way for the immunized cohort from 5-56 weeks of life, demonstrates that, while absolute numbers of admissions are small for the unimmunized cohort, the falling trend among the immunized after 0-4 weeks of age is no longer present and admission rates among the unimmunized remain generally higher throughout the first 56 weeks of life. The overall rate of hospital admission for the unimmunized cohort in the first 56 weeks of life was 431.6 per 1,000 cohort members (live birth admissions excluded), far higher than that for the immunized cohort.

In order to examine severity of illness as measured by the length of hospital stay of unimmunized cohort members, the frequency of length of stay in days of all admissions occurring at age day 0 was determined. This showed that, of 227 such admissions, 200 (88.1%) lasted 6 days or less. When the frequency of length of stay in days of all admissions occurring on or between ages 1-392 days was examined, it was found that, off 108 such admissions, only 75 (69.4%) lasted 6 days or less. Figure 8 (page 140) contrasts lengths of stay greater than 7 days for these two admission types. As with the immunized cohort, a higher proportion of day 1-392 than day 0 admissions lasted 7-28 days. When compared with Figure 6 (page 118), it also demonstrates that a higher

proportion of admissions occurring between 1-392 days of life in the unimmunized cohort lasted 7-28 days.

Figure 8
Length of Hospital Stay Over 7 Days
Unimmunized Cohort

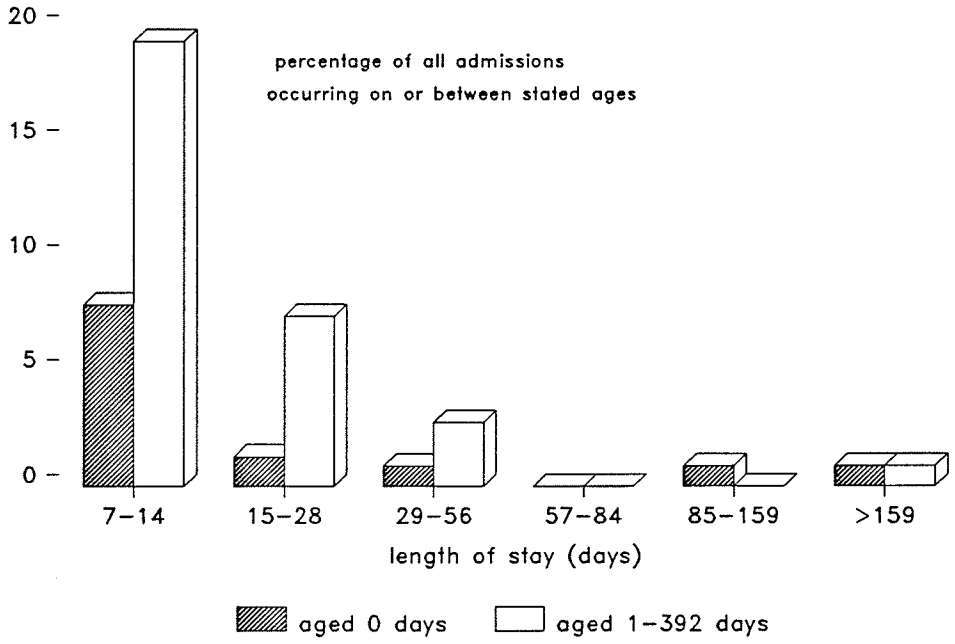


Table 11 (page 142) shows the results of determining the distribution of the 17 ICD-9-CM Classification of Diseases and Injuries categories, overall and by four-week age group, among primary diagnoses in unimmunized cohort hospital admissions occurring in the period 0-56 weeks of life. Comparison with Table 4 (page 120) shows that the same general categories of disease occasioned most of the admissions of both immunized and unimmunized children. That is, the category responsible for the highest proportion of hospital admissions overall and in 5-56 week admissions was Category 8 (Diseases of the Respiratory System), leading to 40.7% and 45.3% of admissions respectively. The category most often responsible for admission in the 0-4 week category was Category 15 (Certain Conditions Originating in the Perinatal Period), which encompassed the primary discharge diagnosis in 23.1% of 0-4 week admissions.

Table 11
Distribution of Primary Diagnoses
Unimmunized Cohort**

ICD-9-CM category of diseases admissions	total no.	%age of all admissions	%age of 0-4 wk admissions	%age of 5-56 wk admissions
8.Respiratory	44	40.7	0	46.3
9.Digestive	12	11.1	15.4	10.5
15.Perinatal	4	3.7	23.1	1.1
16.Ill-Defined	5	4.6	7.7	4.2
6.Nervous	10	9.3	7.7	10.5
14.Congenital	7	6.5	0	7.4
1.Infectious	9	8.3	0	9.5
10.Genitourin.	*	*	*	*
17.Injury	*	*	*	*
12.Skin	3	2.8	0	3.2
2.Neoplasms	*	*	*	*
4.Blood	*	*	*	*
3.Endocrine etc	3	2.8	0	3.2
7.Circulatory	*	*	*	*
13.Musculoskeletal *		*	*	*
Factors Not Causing Current Illness (V Codes)	6	5.6	46.2	0
TOTAL	108	100.0	100.0	100.0

** Distribution of primary discharge diagnoses, unimmunized cohort, over all admissions in the first 56 weeks of life (live birth admissions excluded), by ICD-9-CM Classification of Diseases and Injuries categories
*numbered 2 or less

The occurrence of designated diagnostic discharge codes among the primary and secondary discharge diagnostic codes of admissions of unimmunized cohort members was sought in order to determine the incidence of these codes in admissions occurring in this age group. A total of 233 primary and secondary discharge diagnostic codes relating to 95 hospital admissions of unimmunized cohort members between the ages of 30-392 days were examined for the occurrence of the 56 designated codes. There were no occurrences of 53, and 10 occurrences of 3, of the 56 designated codes.

Table 12

Designated Diagnostic Codes Admissions Over 30 Days of Age**
Unimmunized Cohort

ICD-9-CM Code	Definition	Number	Incidence per 1,000 admissions occurring between 30 and 392 days of age
780.3	convulsions (excludes epileptic and in newborn)	6	63.16
780.6	pyrexia of unknown origin	*	*
781.3	lack of coordination	*	*
TOTAL DESIGNATED		10	105.26

** Designated diagnostic discharge codes among a total of 233 primary and secondary codes for 95 hospital admissions occurring between 30 and 392 days of age in 329 unimmunized cohort members in first 56 weeks of life

*numbered 3 or less

Table 12 (page 143) shows the number of occurrences and the incidence of each code per 1,000 admissions occurring between 30-392 days of age. As with the immunized cohort (Table 5, page 122), codes 780.3 (convulsions) and 780.6 (pyrexia of unknown origin) were the most frequently detected designated codes. In order to generalize the rates or perform a statistical comparison with those in the immunized cohort, a large sample size would be required.

Examination of the deaths which terminated the enrolment of 85 unimmunized children in the first year of life showed that 36 such deaths occurred on day 0 of life, 66 occurred by day 22 of life, and 76 occurred prior to the recommended age (60 days) for the first immunization dose.

Individual examination of the hospitalization records of the 9 children who died after age 60 days showed that this group experienced 32 admissions, in addition to birth admissions, before death. 6 children died in hospital with diagnoses indicative of severe congenital or perinatal disease. In addition one unimmunized cohort member, hospitalized from birth with respiratory disease, died in the second year of life.

In summary, the size of the unimmunized cohort is very small. Some of its members may have been immunized, such as non Status Indian children served by federal

Medical Services Branch, who may have received immunizations which were not recorded on MIMS. Also, since the immunization record of an adopted child must be actively transferred to the new registration number, some children may have lost both their birth hospitalization records and their immunization records at the time of adoption. This explanation merits future investigation. At present it remains a theoretical possibility, and its possible impact can only be roughly estimated. The records of Manitoba Child and Family support show simply that, of the 66 placements of Manitoba children completed in 1988, 52 were under six months of age and 13 were aged from six months to one year. The number of children meeting the cohort criteria, and adopted at ages greater than the recommended ages for immunization, is unknown.

It should, however, be assumed that most members of the unimmunized cohort received no immunizations. While it is known that a small proportion of families make a conscious decision to reject immunization, an additional explanation is suggested by the study findings. There was evidence that the unimmunized children, as a group, experienced more severe and prolonged illness in the first year of life than their immunized counterparts. For a number of these children, medical contraindications to immunization may have existed and explain its absence. In this study, because of the manner in which the

unimmunized cohort was selected, the empty MIMS records of unimmunized children were not available for scrutiny. Therefore, even though MIMS provides a field in which a medical restriction on the use of immunization may be recorded, it is not possible to comment on the presence or absence of such restrictions for the unimmunized cohort.

6.7 Immunized Children Who Died in the First Year of Life

The enrolment of 17 children born in Manitoba in 1988 and immunized in the first year of life was terminated in the first year of life by death. The dataset contained the primary and secondary hospital discharge diagnoses for all children who experienced hospital admissions, but did not contain cause-of-death information (available only from the Manitoba Vital Statistics registry).

The combined immunization and hospitalization records of each of these children were examined individually. Age at death ranged evenly from 11-350 days, and for 16 children exceeded the minimum recommended age for commencement of immunization. For nine of the deceased children the birth admission was the only admission. Four of these nine children, dying at ages 72, 78, 127 and 135 days of age, were immunized with DTP and OPV simultaneously within 12 days of death (range 5-12 days).

The other eight children experienced a total of 23 admissions, in addition to their eight birth admissions, before death. Two of these children died within 30 days of simultaneous DTP/OPV immunization. Both were children with primary and secondary diagnoses indicative of severe health problems. The first child, hospitalized from birth, died 9 days following the administration of the

first dose. The second experienced seven hospitalizations after birth, dying 19 days following administration of the third dose. For none of the 17 children who died did the MIMS record indicate medical inability to receive immunizations.

No conclusions can be drawn from these findings. Their interpretation would be enhanced by the addition of vital statistics data and/or data taken from individual hospital chart reviews.

6.8 Data Quality - The Provider Code

The examination of the individual linked records of children whose immunizations were administered during a hospital stay provided the first opportunity to examine the quality of data derived from the MIMS field denoting the immunization provider. This field requires the entry of a single letter indicating the type of provider. The options are: Blank = immunization is restricted; U = unspecified; F = facility; P = physician; R = regional health unit. This field is supplemented by a five digit provider number field which identifies the facility, physician, or regional health unit, or enables an out-of-province code to be entered.

In this study, a total of 45 immunizations were administered during the hospital stays of 20 main cohort members. The providers of these 45 immunizations were recorded as follows: physician 22, regional health unit 2, facility 11, unknown 10. Only one immunization, with physician recorded as provider, had, amongst the primary and secondary discharge codes for the relevant admission, one of the specific ICD-9-CM codes intended to denote "need for prophylactic vaccination and inoculation..." against listed communicable diseases.

These findings indicate that data concerning immunizations associated with provider code F will

capture only a small proportion of immunizations administered in facilities.

7. DISCUSSION

The specific objectives of the thesis have been met. Data from the population-based, computerized hospitalization and immunization records of the 1988 birth cohort of Manitoba children whose enrolment with the provincial health insurance plan was continuous throughout the first 56 weeks of life were linked, and the immunization and hospitalization experiences of the cohort in the first year of life examined together.

The immunization status of the 1988 birth cohort with continuous enrolment has been described. DTP and OPV vaccine (or alternatives) were almost always administered simultaneously. Immunization rates were calculated for the entire birth cohort of children born in Manitoba in 1988, with the exception of status Indians, with continuous enrolment with MHSC from birth through 56 weeks of age. These rates were found to be high, at 96.6% for the first DTP dose, 93.7% for the second, and 88.7% for the third. Compliance with the recommended provincial immunization schedule was also high, with 88.4% of children completely immunized, according to the schedule, by the first birthday. The great majority of each of the doses of DTP and OPV were given in the four week time period immediately following

the recommended immunization age, but age at immunization tended to increase with successive doses.

The immunization status of all children born in Manitoba in 1988 has been described in the MIMS 1990 Annual Report,[106,139] and the differences in findings between the two studies are noteworthy. Low immunization rates described in the earlier report[106] caused concern - only 77% of infants met the recommended immunization schedule.[137] This report sought immunizations by tariff code, and it was considered that miscoding, together with inclusion of the incomplete records of status Indian children, had artificially lowered the rates. A later review of the data[137] revealed that immunization rates were altered very little when immunizations were sought by incidence. The present study also sought immunizations by incidence, the proportion of coding errors was found to be very low, with an error rate of only 3-4% for each dose of both vaccines. However, exclusion of status Indian children (N = approximately 1,900) and those whose enrolment with the provincial health insurance plan was interrupted in the first 56 weeks of life (N = 1,502) has demonstrated higher immunization rates. Of children whose enrolment with MHSC began after birth but before the first birthday, and whose out-of-province immunization records must be sought and back-entered on MIMS (N = 807), 36.8% were recorded

as completely immunized. Of children whose enrolment with MHSC began at birth but was terminated before the age of one year by migration or death (N = 695), 22.6% were recorded as completely immunized. It is reasonable to believe that the immunization rates in the present study were also artificially lowered, by the inclusion of the records of non-status Indian children living off-reserve but receiving immunization services through federal Medical Services Branch.

The findings suggest that the major contributions to the artificially low provincial immunization rates were made by the incomplete immunization records of several well-defined groups whose members may or may not be incompletely immunized. In order to monitor real trends in provincial vaccine coverage, it appears necessary to intensify efforts to obtain complete records for these groups and to monitor them separately over time.

The study provided other new information concerning MIMS data quality. Of immunizations provided by a medical facility, only 24% were recorded with the specific facility provider code. While the provider code data reliably distinguishes immunizations given by physicians from those given by public health nurses, it clearly cannot be relied upon to capture immunizations given in facilities.

The hospitalization status of the cohort has been described. This provides new information for Manitoba concerning this age group with respect to hospitalization rates, length of stay and hospitalization by diagnosis. It demonstrates the feasibility of using record linkage studies to examine pediatric hospital utilization and to monitor trends in utilization and illness rates.

Overall hospitalization rates do not appear to rise after immunization with DTP or OPV in the first year of life. A larger study of higher power would be preferred, and this could be accomplished by the accumulation of more years of data. However, the figures actually point to an overall decrease in hospitalization rates following immunization. One possible explanation of this finding is sought in the trend in hospitalization rates as the cohort ages through the first year of life. It was, however, demonstrated that the high hospitalization rate of the newborn period fell sharply after four weeks of age, and that the chance of being hospitalized at any time after 30 days of age during the first 56 weeks of life remained quite constant. Contact with the health care provider at the time of immunization may prevent some of the health crises which result in hospitalization.

The examination of the temporal association between immunization and hospitalization with specific adverse

events demonstrates the feasibility of using ICD-9-CM diagnostic codes to identify those known adverse events of sufficient severity to warrant hospitalization. Not only did the study produce evidence of a statistically significant increase in hospitalization with the code for convulsions in the 7 day period following DTP immunization overall, but this event was identified by a single code which was present only among hospital diagnoses in the age group of interest. Final acceptance of this finding will require validation of the code for convulsions by review of the hospital record of each child hospitalized with the code. The ability to determine true population rates of incidence of adverse events of interest and true population rates of incidence of adverse events which show a real association with immunization was also demonstrated. The study produced an overall population rate of incidence of admissions with non-epileptic convulsions in children between 5 and 56 weeks of age of 36.3 per 1,000 admissions, and a population rate of incidence of non-epileptic convulsions requiring hospitalization within 7 days of DTP immunization in children between 5 and 56 weeks of age of 1.72 per 10,000 doses. The latter rate is considerably lower than incidences for the same time period reported in previous studies. One explanation of this phenomenon is that only the most severe events, those leading to

hospitalization, were captured. To expand the investigation of the nature of the association between immunization and adverse events, similar investigative techniques may be used to determine physician visit rates and diagnoses following immunization. Another explanation may be that the small number of adverse events have artificially lowered the rate. Increasing the sample size through data accumulation will permit the calculation of a more accurate rate. It will also permit definition of the trend in hospitalization rates with non-epileptic convulsions as children age through the first year of life, presently unknown. An increasing tendency to hospitalization with this condition through the first year may help explain the increase in hospitalization with convulsions after DTP. It is unlikely that hospitalization or immunization data were missing to an extent which invalidated the findings. The data contained in the hospitalization file is reliable and accurate. The rate of loss of immunization data to MIMS through failure of physicians to claim and generate a record entry appears to vary among practice groups, but has not been found to exceed 7%. The very high immunization rates for the cohort suggest little immunization data loss. Considering the very low numbers of adverse events detected in temporal association with immunization, the impact of missing data on the findings

must be very small. Again, accumulating years of data would allow further conclusions to be drawn concerning the nature of the temporal relationships between routine immunization and admission with the adverse events of interest, and admission rates with these events to be calculated with increased accuracy.

These record linkage techniques can clearly be used to implement a provincial population-based active surveillance system, and the general objective of the thesis has been satisfied. Such a system would provide continuous monitoring of the entire infant population, and highly complete and accurate data concerning the occurrence of serious, known adverse events. The time delay in data generation would be 18 months to allow for MIMS monitoring, claims processing and the transfer of Vital Statistics update information to the enrolment file. This time delay is necessary to ensure good quality data but unacceptable for the detection and remediation of severe, unexpected adverse events following immunization. It would be necessary to conduct other forms of surveillance which provide timely information though no population denominator. The present passive reporting system would continue. In addition, a pilot study of hospital-based active surveillance for vaccine-associated adverse events (IMPACT) is currently being conducted in five Canadian

pediatric hospitals by the Canadian Pediatric Society.(Dr. Barbara Law: personal communication) This active system will enable the timely detection and diagnostic validation of adverse events leading to hospitalization. It would be possible to incorporate the detection of unexpected, serious adverse events into the active MIMS-based system by performing year-by-year comparisons of the distributions of all diagnostic codes associated with admissions in the age group concerned.

In addition to its monitoring function, the surveillance system and continuous data collection would permit a large study to provide further evidence concerning the true risks of routinely used vaccines and population incidence rates of risk. In addition, valid information could be obtained concerning special groups of children. These groups include status Indian children, who were excluded from this study only because their MIMS records are known to be incomplete, and groups which this study was able only to describe - the unimmunized, the partially immunized, children immunized in hospital, and children who die.

8. CONFIDENTIALITY

No information regarding names was used, nor was this type of information included in the data set. In addition, no patient contact was made as a part of this research project. This study had the approval of the Access and Confidentiality Committee, Manitoba Health Services Commission. The transfer of any data out of the province will proceed only after confidentiality review and with the permission of Manitoba Health Services Commission. Any papers or reports prepared for publication or distribution will be submitted to Manitoba Health Services Commission for confidentiality review to ensure that the anonymity of individuals is preserved.

9. FUTURE RESEARCH

Prior to the implementation of a surveillance system, the hospital discharge diagnostic codes signifying possible adverse events must be verified by review of the hospital records of each individual hospitalized with the code of interest. Following verification, a final decision can be made concerning the annual repetition of the analysis and the form of the surveillance system.

The 1989 Manitoba birth cohort is now available for similar study, since the MIMS records of its members have been completely monitored at the first birthday and claims data entered. In July of each coming year a further birth cohort will become available. The analysis of additional years of data concerning first year of life immunization and hospitalization experiences would expand our knowledge of these events. Rates of admissions with the adverse events of interest could be calculated with increased accuracy, and further conclusions drawn concerning the nature of the temporal relationships between routine immunization and admission with these events. The inclusion of status Indian children in the cohort would give complete population-based information for the province, and enable us to examine and describe the experiences of this special group of children.

Similar techniques may be used to study routine immunizations given later in childhood, such as those given in the second year of life (measles-mumps-rubella vaccine and the 18-month dose of DTP/DT/polio vaccine). The MIMS records of the members of the 1988 Manitoba birth cohort have now been completely monitored at the second birthday and claims data entered, so that the same methodology may be applied to the examination of the

cohort's second year of life immunization and hospitalization experiences. In July of each coming year a further birth cohort will become similarly available.

In addition, new vaccines, such as the proposed varicella vaccine, and those not routinely used, such as *Haemophilus influenzae* type b vaccine, may also be studied in the same way.

Since hospitalizations represent only the most severe proportion of illness, investigation of physician visit rates and diagnoses following immunization, using similar research methods, would provide a more complete picture of the nature of adverse events following immunization. This investigation would require a preliminary study concerning the reliability and validity of physician tariff codes representing the diagnoses of interest on physician claims.

10. REFERENCES

1. Bart KJ, Orenstein WA, Hinman AR. The current status of immunization principles: recommendations for use and adverse reactions. J Allergy Clin Immunol 1987;79:296-315.

2. Orenstein WA, Bernier RH. Surveillance: information for action. Ped Clin North Am 1990; 37:709-734.

3. Plotkin SL, Plotkin SA. A Short History of Vaccination. In: Plotkin SA, Mortimer EA, eds. Vaccines. Toronto: W.B. Saunders Company, 1988:1-7.

4. National Advisory Committee on Immunization. Canadian Immunization Guide. 3rd ed. Ottawa: Minister of Supply and Services Canada, 1989.

5. Centers for Disease Control: Comprehensive plan for epidemiologic surveillance. Atlanta: Centers for Disease Control, August, 1986:ii.

6. Thacker SB, Berkelman RL. Public health surveillance in the United States. Epidemiol Rev 1988; 10:164-190.

7. Eddins DL. Immunization status of the nation's 2-year-old children. In: Proceedings of the 21st Immunization Conference. Louisiana, June 8-11: New Orleans, 1987:63-66.

8. Stetler HC, Mullen JR, Brennon JP, et al. Monitoring system for adverse events following immunization. Vaccine 1987; 5:169-174.

9. Chin J. Communicable Disease Control. In: Last JM, ed. Maxcy-Rosenau Public Health and Preventive Medicine. 12th ed. Norwalk, Connecticut: Appleton-Century-Crofts, 1986:103-127.

10. Duclos P, McCarthy R, Koch J, Carter AO. Adverse events temporally associated with immunizing agents: 1988 report. Can Dis Wkly Rep 1990; 16:157-166.

11. Centers for Disease Control. Adverse events following immunization. Atlanta: Surveillance Report No.3, 1985-1986, 1989.

12. Zimmerman B, Gold B, Lavi S. Adverse effects of immunization. Is prevention possible? Postgrad Med 1987; 82:225-232.

13. Committee on Infectious Diseases AAP. Report of the Committee on Infectious Diseases. 21st ed. Illinois: American Academy of Pediatrics, 1988.

14. Henderson DA. Smallpox and Vaccinia. In: Plotkin SA, Mortimer EA, eds. Vaccines. Toronto: W.B. Saunders Company, 1988:8-30.

15. Hinman AR. Public Health Considerations. In: Plotkin SA, Mortimer EA, eds. Vaccines. Toronto: W.B. Saunders Company, 1988:587-611.

16. Wassilak SGF, Orenstein WA. Tetanus. In: Plotkin SA, Mortimer EA, eds. Vaccines. Toronto: W.B. Saunders Company, 1988:45-73.

17. Ellis RW. New Technologies for Making Vaccines. In: Plotkin SA, Mortimer EA, eds. Vaccines. Toronto: W.B. Saunders Company, 1988:568-575.

18. Preblud SR, Katz. Measles Vaccine. In: Plotkin SA, Mortimer EA, eds. Vaccines. Toronto: W.B. Saunders Company, 1988:182-222.

19. Weibel RE. Mumps Vaccine. In: Plotkin SA, Mortimer EA, eds. Vaccines. Toronto: W.B. Saunders Company, 1988:223-234.

20. Salk J, Drucker J. Noninfectious Poliovirus Vaccine. In: Plotkin SA, Mortimer EA, eds. Vaccines. Toronto: W.B. Saunders Company, 1988:158-181.

21. Cherry JD, Brunell PA, Golden GS, Karzon DT. Report of the task force on pertussis and pertussis immunization 1988. Pediatrics 1988; 81(Suppl):938-984.

22. Wiktor T, Plotkin SA, Koprowski H. Rabies Vaccine. In: Plotkin SA, Mortimer EA, eds. Vaccines. Toronto: W.B. Saunders Company, 1988:474-491.

23. Mortimer EA. Pertussis Vaccine. In: Plotkin SA, Mortimer EA, eds. Vaccines. Toronto: W.B. Saunders Company, 1988:74-97.

24. Edwards KM, Lawrence E, Wright PF. Diphtheria, tetanus and pertussis vaccine: A comparison of the

immune response and adverse reactions to conventional and acellular pertussis components. Am J Dis Child 1986; 140:867-871.

25. Hinman AR, Onorato IM. Acellular pertussis vaccines. Pediatr Infect Dis J 1987; 6:341-343.

26. Mortimer EA. Diphtheria Toxoid. In: Plotkin SA, Mortimer EA, eds. Vaccines. Toronto: W.B. Saunders Company, 1988:31-44.

27. Matthias RG. Reactogenicity of fluid compared with adsorbed diphtheria-pertussis-tetanus vaccine. Can Med Assoc J 1984; 130:1561-1565.

28. Varughese PV, Carter AO, Acres SE, Furesz J. Eradication of indigenous poliomyelitis in Canada: Impact of immunization strategies. Can J Public Health 1989; 80:363-368.

29. Cherry JD. 'Pertussis vaccine encephalopathy': It is time to recognize it as the myth that it is. J A M A 1990; 263:1679-1680.

30. Hopps HE, Meyer BC, Parkman PD. Regulation and Testing of Vaccines. In: Plotkin SA, Mortimer EA, eds. Vaccines. Toronto: W.B. Saunders Company, 1988:576-586.

31. Miller DL, Alderslade R, Bellman MH, Rawson NSB. Pertussis immunization and serious neurological illness in children. Br Med J 1981; 282:1595-1599.

32. Lapin JH. Whooping Cough. Springfield, Illinois: Charles C. Thomas, 1943.

33. Cody CL, Baraff LJ, Cherry JD. Nature and rates of adverse reactions associated with DTP and DT immunizations in infants and children. Pediatrics 1981; 68:650-660.

34. Barkin RM, Pichichero ME. Diphtheria-pertussis-tetanus vaccine: reactogenicity of commercial products. Pediatrics 1979; 63:256-260.

35. Baraff LJ, Cherry JD, Marcy SM. DTP reactions: relationship of manufacturer lot, potency and endotoxin to reaction rates, abstracted. Pediatr Res 1986; 20:877.

36. Baraff LJ, Cody CL, Cherry JD. DTP-associated reactions: an analysis by injection site,

manufacturer, prior reactions, and dose. Pediatrics 1984; 73:31-36.

37. Baraff LJ, Cherry JD, Cody CL, et al. DTP vaccine reactions: effect of prior reactions on rate of subsequent reactions. Dev Biol Stand 1985; 61:423-428.

38. Baraff LJ, Cherry JD, Cody CL. Pertussis vaccine project: rates, nature and etiology of adverse reactions associated with DTP vaccine, Bureau of Biologics, accession No. PB81-140-634. Springfield, VA: Department of Commerce, National Technical Information Service, 1980.

39. Lewis K, Cherry JD, Holroyd J, Baker LR, Dudenhoeffer FE, Robinson RG. A double-blind study comparing an acellular pertussis-component DTP vaccine with a whole-cell pertussis-component DTP vaccine in 18-month-old children. Am J Dis Child 1986; 140:872-876.

40. Morgan CA, Blumberg DA, Cherry JD. Comparison of acellular and whole-cell pertussis-component DTP vaccines. Am J Dis Child 1990; 144:41-45.

41. Pichichero ME, Badgett JT, Rodgers GC. Acellular pertussis vaccine: immunogenicity and safety of an acellular pertussis vs. a whole cell pertussis vaccine combined with diphtheria and tetanus toxoids as a booster in 18- to 24- month old children. Pediatr Infect Dis J 1987; 6:352-363.

42. Francis TM, Jr, Korns RF, Voight RB, et al. An evaluation of the 1954 poliomyelitis vaccine trials. (Summary Report). Am J Public Health 1955; 45(5.pt.2).

43. Pan American Sanitary Bureau: Live poliovirus vaccines. 44th ed. Special Publication of the Pan American Sanitary Bureau, 1959.

44. Pan American Health Organization: Live poliovirus vaccines. 50th ed. Special Publication of the Pan American Health Organization, 1960.

45. Ruuskanen O, Salmi TT, Stenvik M, Lapinleimu K. Inactivated poliovaccine: adverse reactions and antibody responses. Acta Paediatr Scand 1980; 69:397-401.

46. Holmes G. Febrile seizures. In: Diagnosis and Management of Seizures in Children. 30th ed. Toronto: W.B. Saunders Co., 1987:226-236.

47. Nelson KB, Ellenberg JH. Children who 'outgrew' cerebral palsy. Pediatrics 1982; 69:529-536.

48. Madsen T. Vaccination against whooping cough. J A M A 1933; 101:187-188.

49. Golden GS. Pertussis vaccine and injury to the brain. J Pediatr 1990; 116:854-861.

50. Berg JM. Neurological complications of pertussis immunization. Br Med J 1958; 2:24-27.

51. Alderslade R, Bellman MH, Rawson MSB, et al. The National Childhood Encephalopathy Study. In: Whooping Cough: Reports From the Committee on Safety of Medicines and the Joint Committee on Vaccination and Immunization. London: Department of Health and Social Security, 1981:79-154.

52. Griffith AH. Permanent brain damage and pertussis vaccination: is the end of the saga in sight? Vaccine 1989; 7:199-210.

53. MacRae KD. Epidemiology, encephalopathy, and pertussis vaccine. In: Proceedings of the Conference Organized by the Society of Microbiology and Epidemiology of the GDR. Berlin: FEMS-Symposium Pertussis, April 20-22, 1988.

54. Stephenson JBP. Pertussis vaccine on trial: science vs the law (High Court of London). In: Proceedings of the Conference Organized by the Society of Microbiology and Epidemiology of the GDR. Berlin: FEMS Symposium, April 20-22, 1988.

55. Scheifele DW. Pertussis vaccine and encephalopathy after the Loveday trial. Can Med Assoc J 1988; 139:1045-1046.

56. Pollock TM, Morris J. A 7-Year survey of disorders attributed to vaccination in North West Thames Region. Lancet 1983; April 2:753-757.

57. Walker AM, Jick H, Perera DR, et al. Neurological events following diphtheria-tetanus-pertussis immunization. Pediatrics 1988; 81:345-349.

58. Griffin MR, Ray WA, Mortimer EA, et al. Risk of seizures and encephalopathy after immunization with the diphtheria-tetanus-pertussis vaccine. J A M A 1990; 263:1641-1645.

59. Bellman MH, Ross EM, Miller DL. Infantile spasms and pertussis immunization. Lancet 1983; 1:1031-1033.

60. Melchior JC. Infantile spasms and early immunization against whooping cough: Danish survey from 1970 to 1975. Arch Dis Child 1977; 52:134-137.

61. Jeavons P, Bower B. Infantile spasms: a review of the literature and study of 112 cases. London: Heinemann Medical, 1964.

62. Fukuyama Y, Tomori N, Sugitake M. Critical evaluation of the role of immunization as an etiological factor of infantile spasms. Neuropediatrics 1977; 8:224-237.

63. Shields WD, Nielsen C, Buch D, et al. Relationship of pertussis immunization to the onset of neurological disorders: a retrospective epidemiologic study. J Pediatr 1988; 113:801-805.

64. Torch WC. Diphtheria-pertussis-tetanus (DPT) immunization: a potential cause of the sudden infant death syndrome (SIDS). Neurology 1982; 32:A169-A170.

65. Baraff LJ, Ablon WJ, Weiss RC. Possible temporal association between diphtheria-tetanus toxoid-pertussis vaccination and sudden infant death syndrome. Pediatr Infect Dis J 1983; 2:7-11.

66. Hoffman HJ, Hunter JC, Damus K, et al. Diphtheria-tetanus-pertussis immunization and sudden infant death: results of the National Institute of Child Health and Human Development epidemiological study of sudden infant death syndrome risk factors. Pediatrics 1987; 79:598-611.

67. Solberg LK. DPT immunization, visit to child health center and sudden infant death syndrome (SIDS). Oslo: Report to the Oslo Health Council, 1985:131.

68. Griffin MR, Ray WA, Livengood JR, Schaffner W. Risk of sudden infant death syndrome after immunization with diphtheria-tetanus-pertussis vaccine. N Engl J Med 1988; 319:618-623.

69. Walker AM, Jick H, Perera DR, et al. Diphtheria-tetanus-pertussis immunization and sudden infant death syndrome. Am J Public Health 1987; 77:945-951.

70. Griffith AH. Reactions after pertussis vaccine: a manufacturer's experiences and difficulties since 1964. Br Med J 1978; 1:809-815.

71. Centers for Disease Control. Diphtheria, tetanus and pertussis: guidelines for vaccine prophylaxis and other preventive measures. M M W R 1985; 34:405-426.

72. Rutledge SL, Snead OC. Neurologic complications of immunizations. J Pediatr 1986; 109:917-924.

73. Reinstein L, Pargamet JM. Peripheral neuropathy after multiple tetanus toxoid injections. Arch Phys Med Rehabil 1982; 63:332.

74. Blumstein GI, Kreithen H. Peripheral neuropathy following tetanus toxoid administration. J A M A 1966; 198:1030.

75. Holliday PL, Bauer RB. Polyradiculoneuritis secondary to immunization with tetanus and diphtheria toxoids. Arch Neurol 1983; 40:56.

76. Schlenska GK. Unusual neurologic complications following tetanus toxoid administration. J Neurol 1977; 215:299.

77. Pollard JD, Selby G. Relapsing neuropathy due to tetanus. J Neurol Sci 1987; 37:113.

78. Levine L, Edsall G. Tetanus toxoid: what determines reaction proneness? J Infect Dis 1981; 144:376.

79. Werne J, Garrow I. Fatal anaphylactic shock: occurrence in identical twins following second injection of diphtheria toxoid and pertussis antigen. J A M A 1946; 131:730-735.

80. Zalogna GP, Chernow B. Life-threatening anaphylactic reactions to tetanus toxoid. Ann Allergy 1982; 49:107-108.

81. Ratliff DA, Burns-Cox CJ. Anaphylaxis to tetanus toxoid (unreviewed reports). Br Med J 1983; 288:114.

82. Engler R, Zalogna G. Anaphylaxis to tetanus toxoid: IgE mediated disease. 41st annual meeting American Academy of Allergy and Immunology, March 16 to 20, 1985, New York. J Allergy Clin Immunol 1985; 75:abstract #422.

83. Anonymous. Adverse events following immunization: surveillance report No.1, 1979-1982, August. Atlanta: Centers for Disease Control, 1984.

84. Long SS, Deforest A, et al. Longitudinal study of adverse reactions following diphtheria-tetanus-pertussis vaccine in infancy. Pediatrics 1988; 85:294-302.

85. Pollock TM, Miller E, Mortimer JY, et al. Symptoms after primary immunization with DTP and with DT vaccine. Lancet 1984; 2:146-149.

86. Waight PA, Pollock TM, Miller E, et al. Pyrexia after diphtheria/tetanus/pertussis and diphtheria/tetanus vaccine. Arch Dis Child 1983; 58:921-933.

87. Katz S. Discussion. In: Manclark CR, Hill JC, eds. International symposium on pertussis. Government Printing Office: US Department of Health, Education and Welfare publication No. (NIH) 79-1830, 1979:304-315.

88. Hauser WA, Kurland LY. The epidemiology of epilepsy in Rochester, Minnesota, 1935 through 1967. Epilepsia 1975; 16:1-66.

89. Consensus Statement on Febrile Seizures. National Institutes of Health consensus development conference summary. In: Nelson KB, Ellenberg JH, eds. Febrile Seizures. New York: Raven Press, 1981:301-306.

90. Nelson KB, Ellenberg JH. Prognosis in children with febrile seizures. Pediatrics 1978; 61:720-727.

91. Verity CM, Butler NR, Golding J. Febrile convulsions in a national cohort followed up from birth. I-Prevalence and recurrence in the first five years of life. Br Med J 1985; 4 May:1307-1310.

92. Tsuboi T. Seizures of childhood. A population-based and clinic-based study. Acta Neurol Scand 1986; 74(Suppl.110):47-50.

93. Ellenburg JH, Hirtz DG, Nelson KB. Age at onset of seizures in young children. Ann Neurol 1984; 15:127-134.

94. Strom J. Further experience of reactions, especially of a cerebral nature, in conjunction with triple vaccination: a study based on vaccinations in Sweden 1959-65. Br Med J 1976; 4:320-323.

95. Hirtz DG, Nelson KB, Ellenburg JH. Seizures following childhood immunizations. J Pediatr 1983; 102:14-18.

96. Hunt A. Tuberous sclerosis: a survey of 97 cases. I.Seizures, pertussis immunization and handicap. Dev Med Child Neurol 1983; 25:346-349.

97. Stetler HC, Orenstein WA, Bart KJ. History of convulsions and use of pertussis vaccine. J Pediatr 1985; 107:175-179.

98. Hauser WA, Annegers JF, Anderson V, et al. The risk of seizure disorders among relatives of children with febrile convulsions. Neurology 1985; 35:1268-1273.

99. van den Berg BJ. Studies on convulsive disorders in young children: IV. Incidence of convulsions among siblings. Dev Med Child Neurol 1974; 16:457-464.

100. Baraff LJ, Shields WD, Beckwith L, et al. Infants and children with convulsions and hypotonic-hyporesponsive episodes following diphtheria-tetanus pertussis immunization. Pediatrics 1988; 81:789-794.

101. Whooping Cough Vaccination: Review of the evidence by the Joint Committee on Vaccination and Immunization. London: Her Majesty's Stationery Office, 1977.

102. Stephenson JBP. Pertussis immunization: convulsions are not evidence of encephalopathy. Lancet 1979; 2:416.

103. Hopper JMH. Illness after whooping cough vaccination. Med Officer 1961; 106:241-244.

104. Robbins FC. Polio - Historical. In: Plotkin SA, Mortimer EA, eds. Vaccines. Toronto: W.B. Saunders Company, 1988:98-114.

105. Manitoba Communicable Disease Control. MIMS Report. Epidemiologic Notes 1990; 147:1.

106. Manitoba Immunization Monitoring System. Report of immunizing agents by provider and type, March 22. Winnipeg: Manitoba Health Services Commission, 1990.

107. Katz SL. Poliovirus vaccine policy: another perspective. Am J Dis Child 1989; 143:1007-1009.

108. Update: progress toward eradicating poliomyelitis from the Americas. M M W R 1990;39:557-561.

109. Nkowane BM, Wassilak SG, Orenstein WA, et al. Vaccine-associated paralytic poliomyelitis: United States: 1973 through 1984. J A M A 1987; 257:1335-1340.

110. Beale AJ. Polio vaccines: time for a change in immunization policy? Lancet 1990; 335:839-842.

111. Nathanson N, Langmuir AD. The Cutter incident. Am J Hyg 1963; 78:16-28.

112. Melnick JL. Live attenuated poliovaccines. In: Plotkin SA, Mortimer EA, eds. Vaccines. Toronto: W.B. Saunders Company, 1988:115-157.

113. World Health Organization. Expert committee on poliomyelitis: second report. WHO Tech Rep Ser 1958; No.145:1-83.

114. WHO Consultative Group. The relation between acute persisting spinal paralysis and poliomyelitis vaccine - results of a ten-year enquiry. Bull World Health Organ 1982; 60:231-242.

115. Evaluation of Canadian poliovirus-related cases. Can Dis Wkly Rep 1989; 15:185-188.

116. Acheson ED. Medical Record Linkage. London: Oxford University Press, 1967.

117. Acheson ED. Preface. In: Acheson ED, ed. Record Linkage in Medicine. Proceedings of the International Symposium, Oxford, July 1967. Edinburgh: E. & S. Livingstone, 1968:v.

118. Bothwell PW. A New Look at Preventive Medicine. London: Pitman Medical Publishing, 1965.

119. Godber G. In: Acheson ED, ed. Record Linkage. Proceedings of the International Symposium, Oxford, July 1967. Edinburgh: E. & S. Livingstone, 1968:1-4.

120. Newcombe HB. Detection of Genetic Trends in Public Health. In: Effect of Radiation on Human Heredity. Geneva: WHO, 1957.

121. Acheson ED. Introduction. In: Baldwin JA, Acheson ED, Graham WJ, eds. Textbook of Medical Record Linkage. Toronto: Oxford Medical Publications, 1987:1-12.

122. Newcombe HB. Early Stages of Linked Records. In: Acheson ED, ed. Record Linkage in Medicine. Proceedings of the International Symposium, Oxford, July 1967. Edinburgh: E. & S. Livingstone, 1968:7-34.

123. Newcombe HB. Handbook of Record Linkage. Toronto: Oxford Medical Publications, 1988:v.

124. Hassard TH. Writing the Book of Life: medical record linkage. In: Brook RJ, et al, eds. The Fascination of Statistics. New York: Marcel Dekker, 1986:25-46.

125. Wajda A, Roos LL. Simplifying record linkage: software and strategy. Comput Biol Med 1987; 17:239-248.

126. Beebe GW. Record linkage systems - Canada vs the United States. Am J Public Health 1980; 70:1246-1248.

127. Smith ME, Newcombe HB. Automated follow-up facilities in Canada for monitoring delayed health effects. Am J Public Health 1980; 70:1261-1268.

128. Roos LL, Nicol JP. Building individual histories with registries. Med Care 1983; 21:955-969.

129. Newcombe HB. Record Linking: the design of efficient systems for linking records into individual and family histories. In: Baldwin JA, Acheson ED, Graham WJ, eds. Textbook of Medical

Record Linkage. Toronto: Oxford Medical Publications, 1987:15-38.

130. Newcombe HB. Handbook of Record Linkage. Toronto: Oxford Medical Publications, 1988:5-8.

131. Gill LE, Baldwin JA. Methods and Technology of Record Linkage: some practical considerations. In: Baldwin JA, Acheson ED, Graham WJ, eds. Textbook of Medical Record Linkage. Toronto: Oxford Medical Publications, 1987:39-54.

132. Roos LL, Fisher ES, Sharp SM, et al. Postsurgical mortality in Manitoba and New England. J A M A 1990; 263:2453-2458.

133. Roos LL, Wajda A, Nicol JP. The art and science of record linkage: methods that work with few identifiers. Comput Biol Med 1986; 16:45.

134. Wennberg JE, Roos NP, Sola L, Schori A, Jaffe R. Use of claims data systems to evaluate health care outcomes: mortality and reoperation following prostatectomy. J A M A 1987; 257:933-936.

135. Roos NP, Wennberg JE, Malenka DJ, Fisher ES, et al. Mortality and reoperation after open and transurethral resection of the prostate for benign prostatic hyperplasia. N Engl J Med 1989; 320:1120-1124.

136. Manitoba Immunization Monitoring System User Manual. Winnipeg: Manitoba Health, 1988.

137. Manitoba Health Services Commission. Manitoba Immunization Monitoring System. Report of immunizing agents by provider and type. Winnipeg: 1991.

138. U.S. Department of Health. *International Classification of Diseases*, 9th rev. (clinical modification). Ann Arbor, Michigan: 1986.

139. Manitoba Health Communicable Disease Control. MIMS update: vaccine coverage in Manitoba for children born in 1988. Epidemiologic Notes 1990; 147:1-3.

140. Roos NP, Freeman JL. Potential for inpatient-outpatient substitution with diagnosis-related groups. Health Care Fin Rev 1989;10:31-38.

141. Roos NP, Henteleff PD, Roos LLJ. A new audit procedure applied to an old question: is the frequency of T & A justified? Med Care 1977; 15:1-18.

142. Roos LLJ, Nicol JP, Johnson CF, Roos NP. Using administrative data banks for research and evaluation: a case study. Eval Q 1979; 3:236-255.

143. Roos LLJ, Roos NP, Cageorge SM, Nicol JP. How good are the data? Reliability of one health care data bank. Med Care 1982; 20:266-276.

144. Roos NP. Hysterectomy: variations in rates across small areas and across physicians' practices. Am J Public Health 1984; 74:327-335.

145. Roos LL, Cageorge SM, Roos NP, Danzinger R. Centralization, certification and monitoring: readmission and complications after surgery. Med Care 1986; 24:1044-1066.

146. Roos LL, Roos NP. Assessing existing technologies: the Manitoba study of common surgical procedures. Med Care 1983; 21:454-462.

147. Cohen MM, Hammerstrand KM. Papanicolaou test coverage without a cytology registry. Am J Epidemiol 1989; 129:388-394.

148. Roos NP. Predicting hospital utilization by the elderly: the importance of patient, physician, and hospital characteristics. Med Care 1989; 27:905-919.

149. Roos NP. Impact of the organization of practice on quality of care and physician productivity. Med Care 1980; 18:347-359.

150. Young TK, Roos NP, Hammerstrand KM. Estimated burden of diabetes mellitus in Manitoba according to health insurance claims: a pilot study. Can Med Assoc J 1991; 144:318-324.

151. Hassard TH. Understanding Biostatistics. St. Louis: Mosby-Year Book, Inc., 1991.

152. Maternal and Child Care. 1988 Manitoba Vital Statistics. 14th ed. 1990.

153. MacMorran J. Tuberculosis: A handbook for public health nurses and other interested health care

workers. Province of Manitoba: Department of Health, 1990.

APPENDIX 1

MANITOBA PROVINCIAL IMMUNIZATION SCHEDULE

RECOMMENDED IMMUNIZATION SCHEDULES

Table 1
Routine Immunization Schedule for Infants and Children

Age	Immunization Against			
2 months	Diphtheria	Pertussis	Tetanus	Poliomyelitis
4 months	Diphtheria	Pertussis	Tetanus	Poliomyelitis
6 months	Diphtheria	Pertussis	Tetanus	Poliomyelitis [1]
12 months	Measles	Mumps	Rubella [2]	
18 months	Diphtheria Haemophilus influenzae b [3]	Pertussis	Tetanus	Poliomyelitis
4-6 years	Diphtheria	Pertussis	Tetanus	Poliomyelitis
14-16 years	Diphtheria [4]		Tetanus [4]	Poliomyelitis [1]

Notes:

1. This dose should be omitted if live (oral) polio vaccine is being used exclusively.
2. Rubella vaccine is also indicated for all girls and women of childbearing age who lack proof of immunity. At medical visits, the opportunity should be taken to check whether girls and women need rubella vaccine.
3. A single dose of Haemophilus influenzae b (Hib) conjugate vaccine may be administered to children aged 18 to 24 months. Children aged 25 to 60 months may also be considered for vaccination, particularly those in day care centres or at increased risk of invasive Hib disease. Conjugate vaccine and diphtheria pertussis tetanus (DPT) vaccines may be given simultaneously at different sites.
4. Diphtheria and tetanus toxoid (Td), a combined adsorbed "adult type" preparation for use in persons 7 years of age or more, contains less diphtheria toxoid than preparations given to younger children and is less likely to cause reactions in older persons.

Manitoba
Health
Communicable
Disease
Control

APPENDIX 2

ESSENTIAL ELEMENTS OF MIMS

IMMUNIZATION ALTERNATIVES

A number of alternative immunizations may be accepted in place of those currently recommended due to changes in the recommended schedule, different immunization practices in other provinces, or adverse reactions or health problems.

RECOMMENDED		AGE	ACCEPTABLE ALTERNATIVE
8601	DPT	2 months	8641 DT or 8921 DPTP
8602	DPT	4 months	8642 DT or 8922 DPTP
8603	DPT	6 months	8643 DT or 8923 DPTP
8609	DPT	18 months	8649 DT or 8929 DPTP
8609	DPT	5 years	8649 DT or 8929 DPTP or 8659 TD
8659	Td	14 years	8609 DPT or 8649 DT or 8929 DPTP
8611	OPV	2 months	8921 DPTP or 8931 IPV
8612	OPV	4 months	8922 DPTP or 8932 IPV
*8613	OPV	6 months	8923 DPTP or 8933 IPV
8619	OPV	18 months	8619 OPV or 8929 DPTP or 8939 IPV
8619	OPV	5 years	8929 DPTP or 8939 IPV
8670	MMR	12 months	8621 MEASLES
8661	RUBELLA	12 years (females only)	8670 MMR if administered at or after one year of age.

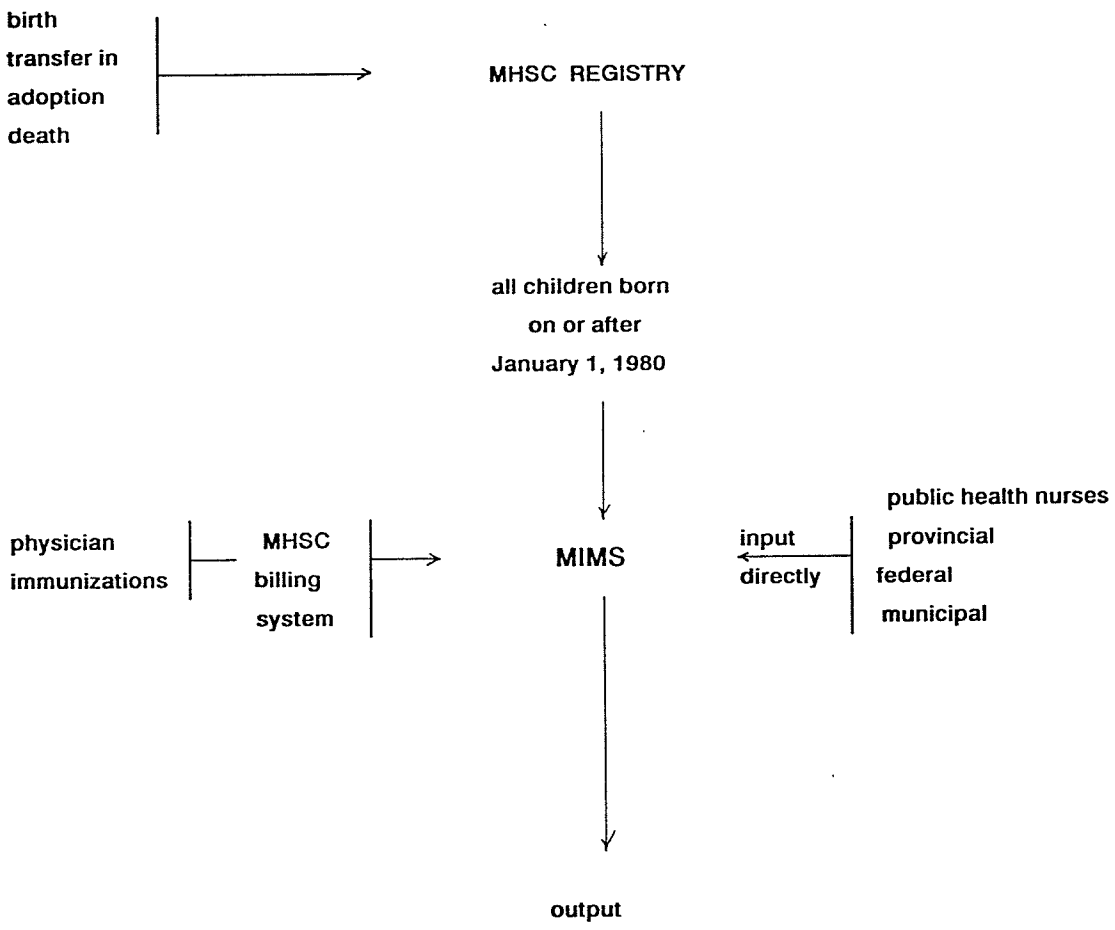
*An 8613 OPV booster is no longer recommended at six months, however, it or one of its acceptable alternatives may appear on the records for some children.

Source: Manitoba Immunization Monitoring System User Manual. Winnipeg: Manitoba Health, 1988.

APPENDIX 3

MIMS TARIFF CODES AND IMMUNIZATION ALTERNATIVES

THE ESSENTIAL ELEMENTS OF MIMS



online enquiry: individual immunization records
summaries (e.g. school lists)

monitoring: followup report
reminder letter

reports: clinic status listing
statistical reports
monthly list physician immunizations,
children born before January 1, 1980

APPENDIX 4

MIMS MONITORING ACTIVITIES

MIMS MONITORING PROCESS

		FOLLOW-UP REPORT	REMINDER LETTER	IMMUNIZATION CERTIFICATE	CONSENT LETTER	FOLLOW-UP LISTING	
PRESCHOOL	1 YEAR	SERVICE PROVIDER *MISSING IMMUNIZATIONS ONLY*					
	2 YEARS	SERVICE PROVIDER *MISSING IMMUNIZATIONS ONLY*					
	5 YEARS		PARENT *ALL CHILDREN IN THE MONTH THEY TURN 5*				
SCHOOL PROGRAM	6 YEARS	SERVICE PROVIDER *MISSING IMMUNIZATIONS ONLY*		PARENT *ALL CHILDREN IN THE MONTH THEY TURN 6*		HEALTH OFFICE *ALL CHILDREN FLAG THOSE N/D IMMUNIZATION*	*PRODUCED BY REGION/ DISTRICT/ SCHOOL ON REQUEST*
	12 YEARS				PARENT *ALL FEMALES REQUIRING RUBELLA*	HEALTH OFFICE *ALL FEMALES FLAG THOSE N/D RUBELLA*	
	14 YEARS				PARENT *ALL CHILDREN REQUIRING ADULT dT*	HEALTH OFFICE *ALL CHILDREN FLAG THOSE N/D ADULT dT*	
	15 YEARS		PARENT *ONLY CHILDREN REQUIRING IMMUNIZATION(S)*				
	17 YEARS			PARENT *ALL CHILDREN IN THE MONTH THEY TURN 17*			

Source: Manitoba Immunization Monitoring System User Manual. Winnipeg: Manitoba Health, 1988.

APPENDIX 5

MIMS FOLLOW-UP LETTER

DATE YY/MM/DD **MANITOBA IMMUNIZATION MONITORING SYSTEM**
A4MI490 **FOLLOW-UP RECORD**

MHSC NO.	CHILD SURNAME	GIVEN	SEX	BIRTHDATE
XXXXXX	XXXXXXXXXXXXXXXXXXX	XXXXXXXXXXXXXXX	X	XX/XX/XX

ALTERNATE SURNAME XXXXXXXXXXXXXXXXXXX YY MM DD

RES XXXXXXXXXXXXXXXXXXXXXXXX MAIL XXXXXXXXXXXXXXXXXXXXXXXXX
ADDR. XXXXXXXXXXXXXXXXXXX ADDR. XXXXXXXXXXXXXXXXXXX XXX XXX

PARENT/GUARDIAN: XXXXXXXX XXXXXXXXXXXXXXXXXXX HOME PHONE: XXX XXXX
WORK PHONE: XXX XXXX

SERVICE PROVIDER: XXXXX
XXXXXXXXXXXXXXXXXXXXXXXXXXXXX
XXXXXXXXXXXXXXXXXXX
XXXXXXXXXXXXXXXXXXX
XXXXXXXXXXXXXXXXXXX XXX XXX

HEALTH UNIT: XX XXX PH: XXX XXX
XXXXXXXXXXXXXXXXXXXXXXXXXXXXX
XXXXXXXXXXXXXXXXXXX
XXXXXXXXXXXXXXXXXXX
XXXXXXXXXXXXXXXXXXX XXX XXX

===

OUR RECORDS SHOW THAT THE ABOVE NAMED CHILD HAS NOT RECEIVED THE FOLLOWING IMMUNIZATIONS AS OF THE PROCESSING DATE. PLEASE CHECK YOUR RECORDS. IF YOU HAVE PROVIDED ANY OF THESE IMMUNIZATION(S), PLEASE COMPLETE THE SERVICE DATE, AND ENTER YOUR PROVIDER CODE. IF YOU PROVIDED ANOTHER IMMUNIZATION IN LIEU OF ANY OF THOSE SHOWN BELOW PLEASE ALSO CHANGE THE TARIFF CODE AND ABBREVIATION ACCORDINGLY. IF ANY OF THE IMMUNIZATIONS LISTED ARE NOT BEING GIVEN DUE TO HEALTH PROBLEMS OR REACTIONS, PLEASE COMMENT IN THE SPACE PROVIDED. PLEASE RETURN THIS DOCUMENT TO THE HEALTH UNIT SHOWN ABOVE.

IMMUNIZATIONS NOT ON OUR RECORD AS OF XXXXXXXX

RECOMMENDED AGE/MTHS	CODE	DESCRIPTION	SERVICE DATE YY/MM/DD	PROVIDER
XX XXXXX	XXXX	XXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX	__/__/__	_ ______
XX XXXXX	XXXX	XXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX	__/__/__	_ ______
XX XXXXX	XXXX	XXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX	__/__/__	_ ______
XX XXXXX	XXXX	XXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX	__/__/__	_ ______
XX XXXXX	XXXX	XXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX	__/__/__	_ ______
XX XXXXX	XXXX	XXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX	__/__/__	_ ______
XX XXXXX	XXXX	XXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX	__/__/__	_ ______
XX XXXXX	XXXX	XXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX	__/__/__	_ ______
XX XXXXX	XXXX	XXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX	__/__/__	_ ______
XX XXXXX	XXXX	XXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX	__/__/__	_ ______

COMMENTS:

Source: Manitoba Immunization Monitoring System User Manual. Winnipeg: Manitoba Health, 1988.

APPENDIX 6

LIST OF ICD-9-CM DIAGNOSTIC CODES SIGNIFYING ADVERSE EVENTS RELATED TO DTP/DT/POLIO VACCINE ADMINISTRATION

DIAGNOSTIC CODE (ICD-9-CM)	AND DISEASE DEFINITION	TIME PERIOD OF INTEREST FOLLOWING IMMUNIZATION (days)
045	acute poliomyelitis	0-28
047	meningitis due to enterovirus	0-28
048	other enterovirus diseases of central nervous system	0-28
049	other non-arthropod-borne viral diseases of central nervous system	0-28
320	bacterial meningitis	0-28
321	meningitis due to other organisms	0-28
322	meningitis of unspecified cause	0-28
323	encephalitis, myelitis, encephalomyelitis	0-28
330.9	unspecified cerebral degeneration in childhood	0-28
331.8	other cerebral degeneration: Reye's syndrome, other	0-28
331.9	cerebral degeneration, unspecified	0-28
336.8	other myelopathy, including drug-induced	0-28
336.9	unspecified myelopathy	0-28
341.9	demyelinating disease CNS, unspecified	0-28
342	hemiplegia	0-28
343	infantile cerebral palsy	0-28

344	other paralytic syndromes	0-28
345	epilepsy	0-28
348	other conditions of brain	0-28
349	other and unspecified disorders of nervous system	0-28
350	trigeminal nerve disorders	0-28
351	facial nerve disorders	0-28
352	disorders of other cranial nerves	0-28
353	nerve root and plexus disorders	0-28
354	mononeuritis of upper limb and mononeuritis multiplex	0-28
355	mononeuritis of lower limb	0-20
356.9	hereditary and idiopathic peripheral neuropathy, unspecified	0-28
357.0	acute infective polyneuritis - Guillain-Barré syndrome, postinfectious polyneuritis	0-28
357.6	polyneuropathy due to drugs	0-28
357.8	other inflammatory and toxic neuropathy	0-28
357.9	unspecified inflammatory and toxic neuropathy	0-28
680.3	carbuncle and furuncle upper arm and forearm	0-7
680.6	carbuncle and furuncle leg, except foot	0-7
682.3	other cellulitis and abscess upper arm and forearm	0-7
682.6	other cellulitis and abscess leg, except foot	0-7

682.9	other cellulitis and abscess unspecified site	0-7
780.0	coma and stupor (drowsiness, semicoma, somnolence, unconsciousness)	0-1
780.2	syncope and collapse	0-1
780.3	convulsions unspecified, febrile, infantile, generalized, epileptiform; convulsive disorder unspecified; convulsive seizure unspecified; fit unspecified	0-7
780.6	pyrexia of unknown origin	0-2
781.0	abnormal involuntary movements	0-28
781.2	abnormality of gait	0-28
781.3	lack of coordination	0-28
781.4	transient paralysis of limb	0-28
785.5	shock without mention of trauma	0-1
798.0	cot death, crib death, sudden death of nonspecific cause in infancy	0-7
799.9	other unknown and unspecified cause (undiagnosed disease, not specified as to site or system involved, unknown cause of morbidity or mortality)	0-1
995.0	anaphylactic shock	0-1
995.1	angioneurotic edema - giant urticaria	0-1
995.2	unspecified adverse effect of drug, medicinal and biological substance - adverse effect/allergic reaction/hypersensitivity/ idiosyncrasy due to correct	

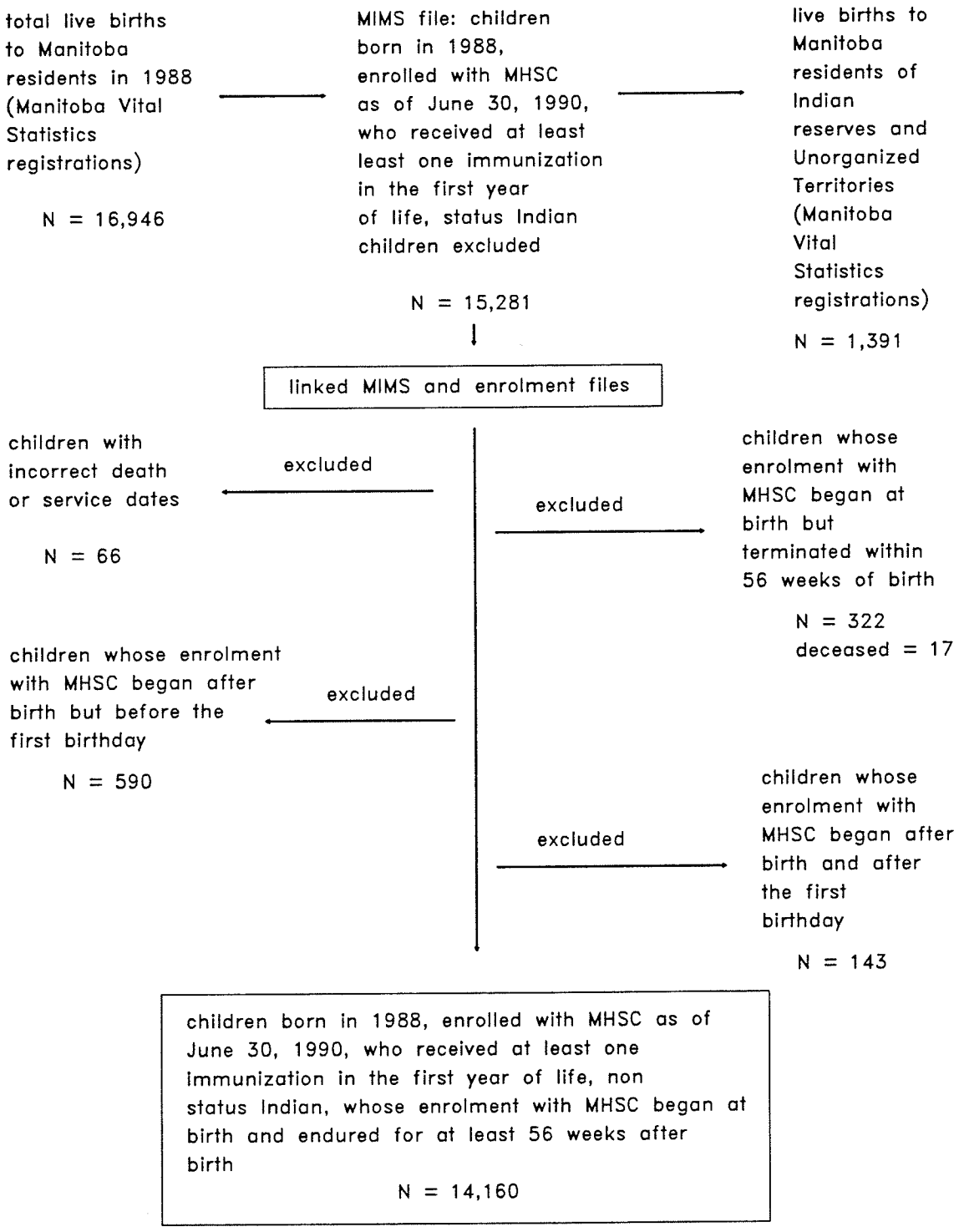
	medicinal substance properly administered or unspecified drug hypersensitivity or drug reaction	0-1, 0-2
995.3	allergy unspecified - allergic reaction, hypersensitivity or idiosyncrasy	0-1
999.3	other infection (infection, sepsis, septicemia) following infusion, transfusion or vaccination	0-1, 0-2
999.5	vaccination (intoxication by serum, protein sickness, serum sickness)	0-28
999.9	other and unspecified complications of medical care, not elsewhere classified	0-1, 0-2
E948	bacterial vaccines	
death	any code	

APPENDIX 7

FLOW DIAGRAM

SELECTION OF MAIN STUDY COHORT

Flow Diagram of Cohort Selection, Main Cohort

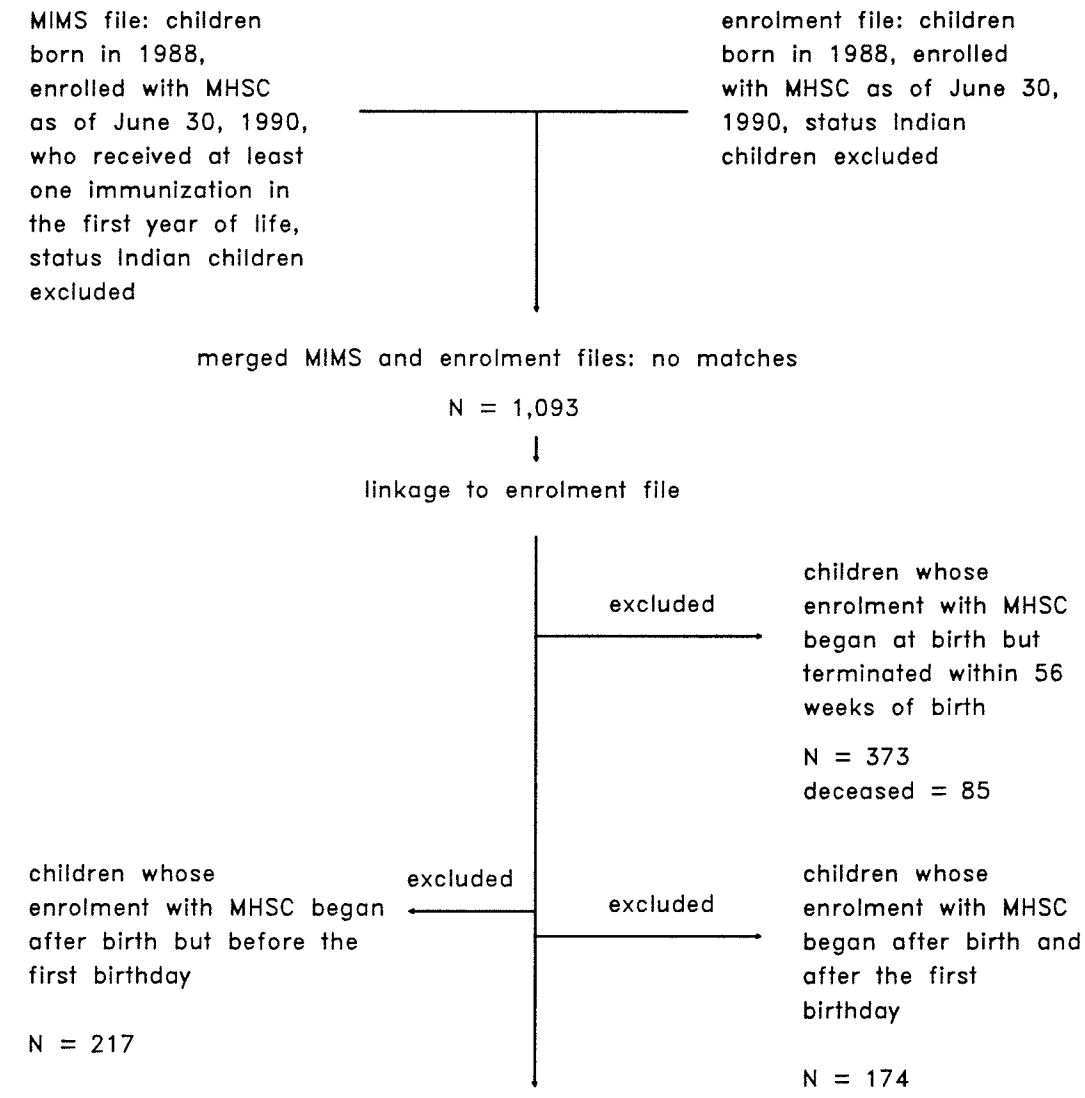


APPENDIX 8

FLOW DIAGRAM

SELECTION OF UNIMMUNIZED STUDY COHORT

Flow Diagram, Cohort Selection, Unimmunized Cohort



children born in 1988, enrolled with MHSC as of June 30, 1990, non Status Indian, whose enrolment with MHSC began at birth and endured for at least 56 weeks after birth, who received no immunizations in the first year of life

N = 329