AN EXAMINATION OF THE IMMUNIZATION AND HOSPITALIZATION EXPERIENCES IN THE FIRST YEAR OF LIFE OF THE 1987, 1988 AND 1989 MANITOBA BIRTH COHORTS

BY

JANICE DOROTHY ROBERTS

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LANGUAGE, LITERATURE AND LINGUISTICS
- Language
  - General 0679
  - Ancient 0289
  - Linguistics 0290
  - Modern 0291
- Literature
  - General 0401
  - Classical 0294
  - Comparative 0295
  - Medieval 0297
  - Modern 0298
  - African 0316
  - American 0591
  - Asian 0305
  - Canadian (English) 0352
  - Canadian (French) 0355
  - English 0593
  - Germanic 0311
  - Latin American 0312
  - Middle Eastern 0315
  - Romance 0313
  - Slavic and East European 0314

PHILOSOPHY, RELIGION AND THEOLOGY
- Philosophy 0422
- Religion
  - General 0318
  - Biblical Studies 0321
  - Clergy 0319
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  - Philosophy of 0322
- Theology 0469

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- American Studies 0323
- Anthropology
  - Archaeology 0324
  - Cultural 0326
  - Physical 0327
- Business Administration
  - General 0310
  - Accounting 0272
  - Banking 0770
  - Management 0454
  - Marketing 0338
- Canadian Studies 0385
- Economics
  - General 0501
  - Agricultural 0503
  - Commerce-Business 0505
  - Finance 0508
  - History 0509
  - Labor 0510
  - Theory 0511
- Folklore 0358
- Geography 0366
- Gerontology 0351
- History
  - General 0578
  - Ancient 0579
  - Medieval 0581
  - Modern 0582
  - Black 0328
  - African 0331
  - Asia, Australia and Oceania 0332
  - Canadian 0334
  - European 0335
  - Latin American 0336
  - Middle Eastern 0333
  - United States 0337
- History of Science 0585
- Law 0398
- Political Science
  - General 0615
  - International Law and Relations 0616
  - Public Administration 0617
- Recreation 0814
- Social Work 0452
- Sociology
  - General 0626
  - Criminology and Penology 0627
  - Demography 0938
  - Ethnic and Racial Studies 0631
  - Individual and Family Studies 0628
  - Industrial and Labor Relations 0629
  - Public and Social Welfare 0630
  - Social Structure and Development 0700
  - Theory and Methods 0344
- Transportation 0709
- Urban and Regional Planning 0999
- Women's Studies 0453

THE SCIENCES AND ENGINEERING

BIOLOGICAL SCIENCES
- Agriculture
  - General 0473
  - Agronomy 0285
  - Animal Culture and Nutrition 0475
  - Animal Pathology 0476
  - Food Science and Technology 0359
  - Forestry and Wildlife 0478
  - Plant Culture 0479
  - Plant Pathology 0480
  - Plant Physiology 0817
  - Range Management 0777
  - Wood Technology 0746
- Biology
  - General 0306
  - Anatomy 0287
  - Biostatistics 0308
  - Botany 0309
  - Cell 0379
  - Ecology 0329
  - Entomology 0353
  - Genetics 0369
  - Limnology 0793
  - Microbiology 0410
  - Molecular 0307
  - Neuroscience 0317
  - Oceanography 0416
  - Physiology 0433
  - Radiation 0821
  - Veterinary Science 0778
  - Zoology 0472
- Biophysics
  - General 0786
  - Medical 0760

EARTH SCIENCES
- Biogeochemistry 0425
- Geochemistry 0996
- Geodesy 0370
- Geology 0372
- Geophysics 0373
- Hydrology 0388
- Mineralogy 0411
- Paleobotany 0345
- Paleoecology 0426
- Paleontology 0418
- Paleozoology 0985
- Palynology 0427
- Physical Geography 0368
- Physical Oceanography 0415

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- Environmental Sciences 0768
- Health Sciences
  - General 0566
  - Audiology 0300
  - Chemotherapy 0992
  - Dentistry 0567
  - Education 0350
  - Hospital Management 0769
  - Human Development 0758
  - Immunology 0982
  - Medicine and Surgery 0564
  - Mental Health 0347
  - Nursing 0569
  - Nutrition 0570
  - Obstetrics and Gynecology 0380
  - Occupational Health and Therapy 0354
  - Ophthalmology 0381
  - Pathology 0571
  - Pharmacology 0419
  - Pharmacy 0572
  - Physical Therapy 0382
  - Public Health 0573
  - Radiology 0574
  - Recreation 0575
  - Speech Pathology 0460
  - Toxicology 0383
- Home Economics 0386

PHYSICAL SCIENCES

Pure Sciences
- Chemistry
  - General 0485
  - Agricultural 0749
  - Analytical 0486
  - Biochemistry 0487
  - Inorganic 0488
  - Nuclear 0738
  - Organic 0490
  - Pharmaceutical 0491
  - Physical 0494
  - Polymer 0495
  - Radiation 0754
- Mathematics 0405
- Physics
  - General 0605
  - Acoustics 0986
  - Astronomy and Astrophysics 0606
  - Atmospheric Science 0608
  - Atomic 0748
  - Electronics and Electricity 0607
  - Elementary Particles and High Energy 0798
  - Fluid and Plasma 0759
  - Molecular 0609
  - Nuclear 0610
  - Optics 0752
  - Radiation 0756
  - Solid State 0611
- Statistics 0463

Applied Sciences
- Applied Mechanics 0346
- Computer Science 0984
- Engineering
  - General 0537
  - Aerospace 0538
  - Agricultural 0539
  - Automotive 0540
  - Biomedical 0541
  - Chemical 0542
  - Civil 0543
  - Electronics and Electrical 0544
  - Heat and Thermodynamics 0348
  - Hydraulic 0545
  - Industrial 0546
  - Marine 0547
  - Materials Science 0794
  - Mechanical 0548
  - Metallurgy 0743
  - Mining 0551
  - Nuclear 0552
  - Packaging 0549
  - Petroleum 0765
  - Sanitary and Municipal 0554
  - System Science 0790
- Geotechnology 0428
- Operations Research 0796
- Plastics Technology 0795
- Textile Technology 0994

PSYCHOLOGY
- General 0621
- Behavioral 0384
- Clinical 0622
- Developmental 0620
- Experimental 0623
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Enseignement supérieur 0745
Évaluation 0288
Finances 0277
Formation des enseignants 0530
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Langues et littérature 0279
Lecture 0535
Mathématiques 0280
Musique 0522
Orientation et consultation 0519
Philosophie de l'éducation 0998
Physique 0523
Programmes d'études et enseignement 0727
Psychologie 0525
Sciences 0714
Sciences sociales 0534
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Langues
- Généralités 0679
- Anciennes 0289
- Linguistique 0290
- Modernes 0291

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- Généralités 0401
- Anciennes 0294
- Comparée 0295
- Médiévale 0297
- Moderne 0298
- Africaine 0316
- Américaine 0591
- Anglaise 0593
- Asiatique 0305
- Canadienne (Anglaise) 0352
- Canadienne (Française) 0355
- Germanique 0311
- Latino-américaine 0312
- Moyen-orientale 0315
- Romane 0313
- Slave et est-européenne 0314

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Philosophie 0422
Religion
- Généralités 0318
- Clergé 0319
- Études bibliques 0321
- Histoire des religions 0320
- Philosophie de la religion 0322

Théologie 0469

SCIENCES SOCIALES
Anthropologie
- Archéologie 0324
- Culturelle 0326
- Physique 0327

Droit 0398
Économie
- Généralités 0501
- Commerce-Affaires 0505
- Économie agricole 0503
- Économie du travail 0510
- Finances 0508
- Histoire 0509
- Théorie 0511

Études américaines 0323
Études canadiennes 0385
Études féministes 0453
Folklore 0358
Géographie 0366
Gérontologie 0351
Gestion des affaires
- Généralités 0310
- Administration 0454
- Banques 0770
- Comptabilité 0272
- Marketing 0338

Histoire
- Histoire générale 0578
- Ancienne 0579
- Médiévale 0581
- Moderne 0582
- Histoire des noirs 0328
- Africaine 0331
- Canadienne 0334
- États-Unis 0337
- Européenne 0335
- Moyen-orientale 0333
- Latino-américaine 0336
- Asie, Australie et Océanie 0332

Histoire des sciences 0585
Loisirs 0814
Planification urbaine et régionale 0999
Science politique
- Généralités 0615
- Administration publique 0617
- Droit et relations internationales 0616

Sociologie
- Généralités 0626
- Aide et bien-être social 0630
- Criminologie et établissements pénitentiaires 0627
- Démographie 0938
- Études de l' individu et de la famille 0628
- Études des relations interethniques et des relations raciales 0631
- Structure et développement social 0700
- Théorie et méthodes. 0344
- Travail et relations industrielles 0629

Transports 0709
Travail social 0452

SCIENCES ET INGÉNIERIE

SCIENCES BIOLOGIQUES
Agriculture
- Généralités 0473
- Agronomie. 0285
- Alimentation et technologie alimentaire 0359
- Culture 0479
- Élevage et alimentation 0475
- Exploitation des pâturages 0777
- Pathologie animale 0476
- Pathologie végétale 0480
- Physiologie végétale 0817
- Sylviculture et faune 0478
- Technologie du bois 0746

Biologie
- Généralités 0306
- Anatomie 0287
- Biologie (Statistiques) 0308
- Biologie moléculaire 0307
- Botanique 0309
- Cellule 0379
- Écologie 0329
- Entomologie 0353
- Génétique 0369
- Limnologie 0793
- Microbiologie 0410
- Neurologie 0317
- Océanographie 0416
- Physiologie 0433
- Radiation 0821
- Science vétérinaire 0778
- Zoologie 0472

Biophysique
- Généralités 0786
- Medicale 0760

SCIENCES DE LA TERRE
Biogéochimie 0425
Géochimie 0996
Géodésie 0370
Géographie physique 0368
Géologie 0372
Géophysique 0373
Hydrologie 0388
Minéralogie 0411
Océanographie physique 0415
Paléobotanique 0345
Paléoécologie 0426
Paléontologie 0418
Paléozoologie 0985
Palynologie 0427

SCIENCES DE LA SANTÉ ET DE L'ENVIRONNEMENT
Économie domestique 0386
Sciences de l'environnement 0768
Sciences de la santé
- Généralités 0566
- Administration des hôpitaux 0769
- Alimentation et nutrition 0570
- Audiologie 0300
- Chimiothérapie 0992
- Dentisterie 0567
- Développement humain 0758
- Enseignement 0350
- Immunologie 0982
- Loisirs 0575
- Médecine du travail et thérapie 0354
- Médecine et chirurgie 0564
- Obstétrique et gynécologie 0380
- Ophtalmologie 0381
- Orthophonie 0460
- Pathologie 0571
- Pharmacie 0572
- Pharmacologie 0419
- Physiothérapie 0382
- Radiologie 0574
- Santé mentale 0347
- Santé publique 0573
- Soins infirmiers 0569
- Toxicologie 0383

SCIENCES PHYSIQUES
Sciences Pures
Chimie
- Généralités 0485
- Biochimie 487
- Chimie agricole 0749
- Chimie analytique 0486
- Chimie minérale 0488
- Chimie nucléaire 0738
- Chimie organique 0490
- Chimie pharmaceutique 0491
- Physique 0494
- PolymÈres 0495
- Radiation 0754

Mathématiques 0405
Physique
- Généralités 0605
- Acoustique 0986
- Astronomie et astrophysique 0606
- Électronique et électricité 0607
- Fluides et plasma 0759
- Météorologie 0608
- Optique 0752
- Particules (Physique nucléaire) 0798
- Physique atomique 0748
- Physique de l'état solide 0611
- Physique moléculaire 0609
- Physique nucléaire 0610
- Radiation 0756

Statistiques 0463

Sciences Appliqués Et Technologie
Informatique 0984
Ingénierie
- Généralités 0537
- Agricole 0539
- Automobile 0540
- Biomédicale 0541
- Chaleur et thermodynamique 0348
- Conditionnement (Emballage) 0549
- Génie aérospatial 0538
- Génie chimique 0542
- Génie civil 0543
- Génie électronique et électrique 0544
- Génie industriel 0546
- Génie mécanique 0548
- Génie nucléaire 0552
- Ingénierie des systèmes 0790
- Mécanique navale 0547
- Métallurgie 0743
- Science des matériaux 0794
- Technique du pétrole 0765
- Technique minière 0551
- Techniques sanitaires et municipales 0554
- Technologie hydraulique 0545

Mécanique appliquée 0346
Géotechnologie 0428
Matières plastiques (Technologie) 0795
Recherche opérationnelle 0796
Textiles et tissus (Technologie) 0794

PSYCHOLOGIE
Généralités 0621
Personnalité 0625
Psychobiologie 0349
Psychologie clinique 0622
Psychologie du comportement 0384
Psychologie du développement 0620
Psychologie expérimentale 0623
Psychologie industrielle 0624
Psychologie physiologique 0989
Psychologie sociale 0451
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ABSTRACT

Problem

Although the routinely used vaccines have occasionally been linked in time with serious adverse health events, traditional methodologies have produced little evidence that the temporal relationships are real. "Baseline" incidences of the adverse events in the population are unknown. No accurate measurements of vaccine-related risk are available.

Methods

Linked data from the registry, immunization and hospitalization files of the Manitoba Health database were used to develop immunization and hospitalization profiles for the 1987, 1988 and 1989 birth cohorts in first year of life. Data were analyzed retrospectively to assess the nature of the associations between routine DTP/DT/poliomyelitis immunization and adverse events. ICD-9-CM diagnostic discharge codes identified hospitalizations with possible events; codes detected post-immunization were validated by hospital record review.

Results

There was no increase in overall hospitalization rates following immunization. Statistically significant

increases in hospitalizations were found with code 780.3 (*non-epileptic convulsions*) in the seven days following the second and third DTP/DT, and with code 345.6 (*infantile spasms*) in the 28 days following the second DTP/DT. Overall, DTP/DT immunization was associated with increased rates of hospitalization with codes 780.3 and 345.6, with code 999.5 (*complications of medical care, not elsewhere classified: other serum reaction*) in the 28 day post-immunization period, and with codes 780.6 (*pyrexia of unknown origin*) and 999.9 (*other and unspecified complications of medical care, not elsewhere classified*) in the two day post-immunization period.

Record review showed that codes 780.3, 345.6 and 780.6 accurately described the conditions present; codes 999.5 and 999.9 represented diagnoses of possible adverse events.

Conclusions

The study produced evidence of true temporal associations between the use of DTP/DT vaccine in the first year of life and hospitalization with fever, non-epileptic convulsions and infantile spasms within two, seven and 28 days respectively of immunization.

The techniques could be used to conduct population-based active surveillance for vaccine-related adverse events. Data accumulation would facilitate accurate

measurement of the baseline incidence rates of events, detailed assessment of the nature of their temporal relationships with vaccine use, and the quantification of vaccine-related risk.

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LIST OF FIGURES

LIST OF TABLES

TABLE OF CONTENTS

1. INTRODUCTION

The impact of immunization on global health cannot be overstated. No public health modality, with the exception of safe water, has had a greater effect on mortality reduction and population growth.[1]

Critical to the appropriate use of vaccines is an information system which allows ongoing assessment of the immunization program, particularly as new vaccines are developed and licensed. Its principal objectives are the definition of target populations for immunization, the evaluation of the impact of the immunization program, and the detection of problems requiring alterations in immunization strategies. The two components of such an information system are surveillance and special studies. Immunization surveillance includes the continuous monitoring of trends in the reporting of vaccine-preventable diseases, in vaccine coverage levels and in the occurrence of vaccine-related adverse events. Special studies, on the other hand, are one-time investigations designed to answer specific research questions.

Manitoba's immunization program is supported by a computerized information system, the Manitoba Immunization Monitoring System. This system, a component of the large Manitoba Health database, conducts surveillance of immunization coverage for the province's

entire population of children. Other capabilities include active surveillance for immunization-related adverse events and descriptive and longitudinal research. This population-based study used data routinely collected by the Manitoba Immunization Monitoring System and the Manitoba Health database to conduct a special investigation into the nature of adverse events temporally related to routine childhood immunization.

Although the routinely-used vaccines have proven extremely safe, their use has occasionally been linked with the occurrence of serious adverse health events which, although uncommon or rare, have been the subject of much concern and controversy. Their temporal associations with routine childhood immunization, particularly those related to diphtheria-tetanus-pertussis and polio vaccines, have been extensively reviewed.[2-9] Nevertheless, the exact nature of these associations, while of great consequence to providers and policy makers, remains poorly understood. The study addressed the following needs: for true population rates of incidence of these uncommon and serious events; for confirmatory scientific evidence relating to the risks of routinely-used vaccines; and for rates of incidence for those adverse events which show a true temporal association with immunization.

2. BACKGROUND

2.0 REVIEW OF THE LITERATURE: SURVEILLANCE IN THE CONTROL OF VACCINE-PREVENTABLE DISEASES

Childhood immunization programs target entire populations with the aim of protecting all individuals from vaccine-preventable diseases.[10] They are among the most successful and cost effective preventive programs in public health,[11,12] and have led to the global eradication of smallpox and the control of poliomyelitis, rubella, measles, diphtheria and tetanus in Canada[13] and in the United States.[10]

This remarkable success is the result of the appropriate use of safe and effective vaccines.[11] A critical feature of any immunization program is the information system which allows its ongoing assessment, particularly as new vaccines are developed and licensed.

The two components of such an information system are surveillance and special studies or investigations.[14] Whereas special studies (such as detailed herein) are one-time investigations designed to answer specific research questions, immunization surveillance includes the continuous monitoring of trends in the reporting of vaccine-preventable diseases, of vaccine coverage levels and of the occurrence of adverse events related to immunization.[15,16]

Disease surveillance is defined as "the ongoing, population-wide, systematic collection of disease data

together with data analysis, interpretation and dissemination".[17] Manitoba maintains a structured, centralized system of province-wide communicable disease surveillance based, as in other western jurisdictions,[18] on reports generated under local public health legislation and submitted by physicians, hospitals and laboratories.

However, whereas almost all other jurisdictions continue to rely on population surveys to estimate vaccine coverage,[14,19-21] Manitoba has adopted a policy of ongoing, complete population immunization surveillance. Implemented in 1988, the Manitoba Immunization Monitoring System or MIMS (Section 5.1) records and monitors all immunizations delivered to all children born on or since January 1, 1980. Immunization data enter a file constructed on the province's computerized population registry. The registry and its principal companion files (immunization, hospitalization and medical) make up the population-based Manitoba Health database, developed for the administration of the provincial health care plan (Section 5.0).

Most adverse events related to immunization are considered to be specifically caused by vaccines and are minor in nature, such as fever. They occur perhaps once in every ten to one hundred doses and are usually termed "reactions".[10] More worrisome are the severe events,

such as death and brain damage, which have been associated in time with the administration of vaccines but whose causal relationship with immunization is uncertain. These occur perhaps once in every one thousand to one million doses and are usually termed "immunization-related adverse events".[10]

Canada established a national reporting system for adverse events related to immunization in 1987.[22] It is, as in other countries, a passive system - that is, it receives and records unsolicited reports of events considered by immunization providers to be due to the administration of vaccine, and calculates rates of reported events. Passive reporting systems are population-based and report adverse events in a fairly timely fashion. They cannot, however, measure the true incidence of adverse events[23] since incomplete reporting under-estimates event numbers and the actual size of the population at risk for the events is unknown. Interpretation of the rates estimated by the reporting system is further complicated by our ignorance of the events' baseline rates in the general population. Most importantly, passive systems cannot provide evidence of a causal link between the event and immunization.[15]

In an attempt to overcome the problems of the passive system, the Canadian Pediatric Society launched in 1989 an active surveillance system for vaccine-related

adverse events, based in Canada's pediatric hospitals.[24] Active surveillance seeks out persons with the event of interest; no reliance is placed on health care providers to report. The hospital-based system captures the most serious events, is very timely, and ensures that the diagnoses of serious events are verified by specialist physicians. However, like the passive system, it cannot measure the frequency of event occurrence nor can it provide evidence of their causal association with immunization.

A feasibility study (Section 2.3) has demonstrated that the Manitoba Health database can be used to implement a population-based active surveillance system for serious immunization-related adverse events. This project builds on its methodology to expand our knowledge of such events and to examine the nature of their temporal associations with routinely-used vaccines.

The complete review of the medical literature concerning surveillance in the control of vaccine-preventable diseases appears in Appendix 1.

2.1 REVIEW OF THE LITERATURE: ADVERSE EVENTS RELATED TO THE ADMINISTRATION OF IMMUNIZING AGENTS ROUTINELY USED IN THE FIRST YEAR OF LIFE

While routine childhood immunization is of unquestionable benefit to society, its increasingly widespread use has called attention to vaccine-related problems.[25]

The routinely-used vaccines have been shown to be extremely safe,[26] but the medical literature records that a number of serious adverse health events have been associated in time (albeit infrequently) with their use.2-9 Despite over thirty years of vaccine experience, there remains considerable public and professional uncertainty regarding the safety of these products, particularly that of pertussis vaccine.[4,5] As the incidence of vaccine-preventable disease falls towards zero, there is a tendency for individuals to find any risk of a serious adverse event unacceptable compared with an apparently small personal benefit from immunization.[25]

Case reports linking whole-cell pertussis vaccine with neurologic illness began to appear in the 1930s, shortly after the introduction of early single products.[27] Although DTP vaccine has been the preparation of choice for the delivery of pertussis vaccine since the 1950s,[28] safety questions have centred on the pertussis component.[2] The most serious concerns

relate to reported associations with acute neurologic illness and death,[2,29] although no pathognomonic clinical syndrome has been identified.[2] Other conditions which have been linked with pertussis vaccine include anaphylaxis, very high fever, excessive somnolence, seizures, hypotonic-hyporesponsive state, and Reye's syndrome.[2] Oral poliovaccine (OPV) has been associated with the development of paralytic poliomyelitis, among both recipients and their contacts.[3,7]

Several research projects were launched in the mid-1970s, prompted by increased reports suggesting an association between pertussis vaccine and permanent brain damage.[30,31] The study with the greatest impact was the British National Childhood Encephalopathy Study (NCES) whose preliminary findings, released in 1979, appeared to support the link between vaccine and illness.[32] The 1980s saw a general loss of confidence in pertussis vaccine,[33,34] and immunization levels fell dramatically in most countries. The effect was particularly marked in Britain and Japan, where publicity concerning the vaccine's alleged dangers was widespread; large epidemics of pertussis occurred with significant morbidity and mortality among infants and young children.[35]

Various study designs were subsequently employed as researchers in a number of countries attempted to clarify

the nature of the temporal links between pertussis vaccine and adverse events. Since, in North America, ethical considerations precluded the use of randomized controlled trials to study licensed vaccines,[36] studies using traditional prospective cohort designs concentrated on the outcome differences between varying numbers of DTP doses or between the use of DTP and DT vaccines.[37-44] Even when large cohorts were used, however, these studies had insufficient power to detect genuine differences in the occurrence of rare or uncommon events.[2] A number of case-control studies with alternate methodologies also failed to find an increased risk of acute neurologic illness after DTP immunization.[32,45-52] Evidently the neurological events are, if they occur, so rare that even studies of considerable size have limited statistical power to detect significant occurrences. The conclusions, taken over all the studies, were limited: there is *some* evidence for a true temporal association between the administration of vaccine and the occurrence of an adverse event *only* for OPV and paralytic poliomyelitis[3,7] and for DTP/DT vaccines and febrile seizures.[42,46] Although risk estimates for these events were calculated, no accurate quantification of risk was possible[2] owing either to design factors, to data inaccuracies or to uncontrolled systematic bias. What is more, the population rates of incidence of the uncommon

or rare, serious adverse events - the so-called "background" rates of these events - remain unknown.[53]

Debate over the use of pertussis vaccine continued in the 1980s and litigation over alleged vaccine injury increased[33,34] A number of commercial manufacturers withdrew DTP vaccine from the market; periodic instances of vaccine shortage resulted and the product price increased more than 100-fold. The search for a safer pertussis vaccine has dedicated resources to the development of "acellular" vaccines; these have been shown to produce good levels of immunity and to have a relatively low frequency of minor side effects and are currently undergoing efficacy trials.[33] Pre-licensure testing, however, cannot detect rare and serious vaccine sequelae.[53] As with other new products, the marketing of acellular pertussis vaccines will raise inevitable questions about safety.

In 1988, re-analyzed NCES data were released in Britain when a massive legal review of the evidence regarding brain damage after pertussis immunization (the "Loveday trial") resulted in the dismissal of a claim for such damage.[54] In the original NCES report, estimates of risk were based on the condition of seven previously healthy infants who had neurologic illness within seven days of DTP immunization and were categorized as impaired or dead one year later. A case-by-case review showed to

the judge's satisfaction that three of these children had in fact been healthy and that four had alternative causes for their illness.

Since that time, the data concerning pertussis vaccine have been meticulously re-examined. Several eminent investigators and professional organizations have concluded that a causal association between the administration of DTP/DT vaccine and permanent neurological damage has not been demonstrated (although it cannot be dismissed);[2,55-57] pertussis vaccine either is not associated with an increased risk of permanent brain damage or the magnitude of the risk is so small as to be virtually unmeasurable.[4,53,57,58] Even more recently, a very large population-based case control study was designed to assess the feasibility of a full-scale evaluation of pertussis-vaccine related adverse events in the United States.[59] Using the basic NCES design, the study analyzed the association between recent DTP exposure in young children and the risk of acute onset of neurologic illness by comparing the frequencies of recent DTP immunization in children with such illness and in healthy controls. In doing so, the study addressed criticisms raised against the NCES, which actually analyzed the time relationship of immunization and the neurologic event since both children with neurologic illness and controls were immunized.[2] No

statistically significant increased risk of serious neurologic illness following DTP immunization was found in the U.S. study. The authors concluded that precise quantification of the risk of serious neurologic illness following pertussis vaccine will require very large and expensive investigations and that, given the rarity of the events and the expected shift to the use of acellular vaccines, the public health benefit of such undertakings is questionable.

These judgments, reassuring to users of whole-cell pertussis vaccine, highlight the fact that years of detailed study using traditional methodologies have produced little convincing evidence that the temporal associations noted between immunizations and adverse events are actually real; there are no population-based measurements of vaccine-related risk and no proven techniques for assessing the risks of newly-released vaccines. In addition, regardless of the approach used, studies of adverse events face methodological difficulties related to a number of potential sources of bias,[60,61] addressed in Section 5.11.

The comprehensive review of the medical literature concerning adverse events following the administration of the immunizing agents routinely used in childhood appears in Appendix 2.

2.2 REVIEW OF THE LITERATURE: MEDICAL RECORD LINKAGE

Record linkage studies are both possible and practical in Manitoba, using the universal provincial health insurance database (the Manitoba Health database).[62] Different health care files can be linked using unique, enduring identification numbers and other variables included in each record in all files, to provide individual-based data. Statistics (such as those related to hospital admissions and immunization events) can then be compiled according to the number of individuals concerned, rather than simply to the number of events. Record linkage has been successfully used in Manitoba to conduct retrospective cohort analyses of common surgical procedures, to expand data collected for other purposes, and with various combinations of information such as survey, clinical, claims and mortality data.[63-65]

The Manitoba Health database provides the opportunity 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, for birth cohorts of children, the immunization and hospital files (Section 5.4). Immunization and hospitalization histories can then be examined simultaneously, and the relationship in time between their immunization and hospital experiences

determined.

A full review of the medical and health services literature concerning medical record linkage appears in Appendix 3.

2.3 PREVIOUS WORK

A preliminary study examined the feasibility of using linked data from the Manitoba Health database to implement an active surveillance system for immunization-related adverse events.(Roberts 1991, unpublished)

The study used the population-based data routinely collected in the computerized registry, hospitalization and immunization files. The registry file defined the study cohort: members of the 1988 Manitoba birth cohort whose enrolment with Manitoba Health was continuous from birth to the first birthday. The hospitalization and immunization files described, respectively, the hospitalization and immunization experiences of the study cohort in the first year of life.

The records in the hospitalization and immunization files of the study cohort were linked, and it was confirmed that record linkage techniques can be used to examine hospitalization and immunization experiences simultaneously. It was also determined that ICD-9-CM diagnostic codes can be used to identify immunization-

associated adverse events which lead to hospitalization. The study demonstrated the feasibility of using this methodology to establish an active surveillance system for adverse events temporally associated with routine immunization in the total population of Manitoba children.

3. STUDY OBJECTIVES

In general, for the total population of Manitoba children, the study sought to: describe immunization and hospitalization experiences; assess the nature of the temporal association between routine immunization and adverse events; demonstrate the application of the findings to routine immunization surveillance.

Specifically, for the 1987, 1988 and 1989 Manitoba birth cohorts, the study sought to:

- Develop immunization profiles of the cohorts in the first year of life.
- Develop hospitalization profiles of the cohorts in the first year of life.
- Determine population-based rates of incidence in the first year of life of serious adverse events leading to hospitalization.
- Assess the nature of the temporal associations between immunization in the first year of life and

serious adverse events leading to hospitalization.

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

The Manitoba recommended routine childhood immunization schedule 1986-1990 (Table 1) recommends that all children in the first year of life receive routine immunization with preparations containing the following agents: diphtheria toxoid, tetanus toxoid, pertussis vaccine and poliomyelitis vaccine. The administration of combined diphtheria-tetanus-pertussis (DTP) vaccine is recommended at each of two, four and six months of age, and that of separate oral poliomyelitis vaccine (OPV) is recommended at each of two and four months of age.

The 1986-1990 schedule did not recommend the administration of *Haemophilus influenzae* type b (HIB) vaccine in the first year of life. It was revised, in July, 1992, to recommend the administration of this vaccine at each of two, four and six months of age.

5. STUDY METHOD

5.0 SOURCES OF DATA

For the administration of Manitoba's universal health insurance plan, Manitoba Health maintains a computerized population registry on which have been constructed hospitalization, medical and immunization files. These files use information taken from the registry file and from routinely processed health insurance service claims.

The population registry includes, for each individual, a unique and enduring personal identification number. This number is confidential, providing a mechanism by which files can be matched, and is scrambled when used for research purposes. The file also includes other individual identifiers (including names, gender, date of birth), the date of enrolment with Manitoba Health, and the date of enrolment termination (migration or death). The currency of the population registry is maintained by registration of migrations from and into the province, and through regular, automatic updates from Manitoba Vital Statistics concerning births and deaths. The high quality of the Manitoba data has been confirmed through extensive investigation over the past fifteen years.[66-68]

Non-participation in the Manitoba plan is minimal, as residents are not required to pay any premiums to

register for insured benefits, and no limitations are placed on the choice of provider or use of the services. All hospital and medical care, with a few minor exceptions (such as private hospital room, cosmetic surgery and some out of province care) is available to all provincial residents registered with Manitoba Health. The database contains information on all registrants, regardless of where they receive care.

The hospitalization file includes all registrants, and contains all data from the abstract filed for claim purposes with Manitoba Health following each hospital separation, including individual identifiers, admission/separation dates and accompanying diagnoses by ICD-9-CM code. The medical file includes billings for physician visits, including physician claims for all immunization services.

The immunization (MIMS) file records immunization information for the Manitoba Immunization Monitoring System (MIMS). The MIMS file contains, for each child, individual personal identifiers (as above), date of birth, date of termination (migration or death), and the immunization records of the individual. Each immunization record includes a code which identifies the vaccine administered, its sequence in the immunization schedule, the service date, and restrictions (this category is provided to enable the recording of

contraindications to the use of any vaccine).

5.1 THE MANITOBA IMMUNIZATION MONITORING SYSTEM (MIMS)

The Manitoba Immunization Monitoring System is described in Figure 1. Children born on or after January 1, 1980, are automatically entered into MIMS at birth or following transfer into the province and registration with Manitoba Health. Each child is assigned to the public health office in the area of residence, using municipal codes and postal codes to identify the correct health office. Address changes recorded in the population registry are used to update MIMS automatically.

Immunization delivery in Manitoba occurs through three levels of government - municipal (City of Winnipeg), provincial, and federal (serving persons with Indian status) - and two types of provider - physicians (80 per cent) and public health nurses (20 per cent). Twenty-two MIMS terminals are located throughout Manitoba, at public health offices in all jurisdictions and at the Winnipeg Children's Hospital. Information concerning immunizations given by public health nurses is entered directly through public health office terminals, while physician immunization data are taken directly from physician billing claims submitted to the Manitoba Health

and transferred electronically to the MIMS file.

MIMS captures four-digit codes (identical to the immunization tariff codes used by physicians) for the specific immunizing agents recommended at each point in the recommended provincial schedule (Table 1). Also captured are codes for appropriate alternate vaccines as well as those used under special circumstances.

A low cost method of monitoring immunization status has been selected whereby, in the month of the first, second, fifth, and sixth birthdays, the MIMS record is compared with the provincial schedule. Missing or incorrectly coded immunizations detected at the first, second, and sixth birthdays stimulate the production of a letter to the provider of last record, requesting correction and/or completion. This "reminder" letter takes the form of an individual record which lists any scheduled immunization(s) not recorded in MIMS and is distributed (as is all correspondence) through the public health office in the area of residence; physicians return amended records to the office for data entry. At the fifth birthday, the family receives a letter which lists all immunizations given to date and flags those missing or incorrectly coded, requesting correction and/or completion. This letter provides the required proof of measles immunization at school entry and serves as a reminder that the preschool booster is due. At the

sixth birthday, the family receives an immunization certificate listing all immunizations given to date. Children whose records remain incomplete after any step in the monitoring process are actively followed by public health and offered immunization.

The records of children whose enrolment terminates are kept in MIMS for two years, then removed and stored in a historical file which will be maintained for twenty five years.

MIMS immunization records are available to families and providers at any time, from any terminal site. Summary lists, by public health area or by school, of children who have (or have not) received a particular immunization can be requested through the terminals. In addition, MIMS produces quarterly reports for each health office, documenting the number of immunizations recorded in that area, by service provider, and an annual report which includes, for each health region and the province: the census of children in each birth cohort back to 1980; the number of doses of each vaccine administered, by birth cohort and by service provider; the proportion of children with no immunizations recorded; and summary information regarding age at immunization, immunization rates, and agents, for each birth cohort.

By 1988, MIMS was in full use by all providers except those in the federal jurisdiction (serving

Indians), whose participation commenced in 1990 and remains incomplete.

5.2 MIMS DATA QUALITY

To examine data quality, several studies were conducted both before and after the implementation of MIMS.

Immunization records kept by parents and physician claims for immunizations were compared for a random sampling of 2,000 urban children, of whom the vast majority were immunized by physicians.(Manitoba Health: Johnson 1987, unpublished) In the absence of a clear "gold standard", the parents' records were assumed to be correct. The frequency of miscoding of immunizations by physicians ranged from 1.9 per cent (for the first dose of diphtheria-tetanus-pertussis vaccine [DTP]) to 4.0 per cent (for the third dose of DTP vaccine). Missing physician billing claims averaged 3 per cent -4 per cent for each immunization in infancy. Service dates agreed exactly in 85 per cent of cases. This degree of accuracy was considered sufficient to implement MIMS province-wide.

The studies conducted following implementation are detailed in Appendix 4. The first of these examined the agreement (before monitoring of the MIMS records) between

physician and MIMS records for infant patients of two large group practices, one rural (N = 122) and one urban (N = 131). Excellent agreement was found with respect to tariff codes and service dates; two per cent or fewer immunizations were coded incorrectly; service dates agreed 98 per cent of the time, with all mis-matched dates recorded within 6 days of each other. Immunizations unrecorded because of physician failure to submit a billing claim were also detected, the rate being estimated at 0.2 per cent (urban) and 6.6 per cent (rural).

To directly examine the efficacy of the monitoring process, a study was conducted at an urban public health office serving a population of approximately 2,500 one- and two-year olds (Appendix 4). For six months, all monitoring records (reminder letters) produced at first (N = 35) and second (N = 41) birthdays were logged at the times of their distribution and return; amended records were kept on file following data entry. Eight months from the start of data collection, the log was examined and the amended records reviewed; explanations for the missing immunizations were categorized; rates of complete age-appropriate immunization before and after monitoring were estimated. Among this population of one- and two-year olds, it was estimated that only 8 per cent were not fully immunized for their age prior to

monitoring at the first/second birthdays. Physicians amended and returned 97 per cent of the incorrect/ incomplete records distributed. "Missing" immunizations were explained as follows: physician failure to bill (43 per cent); coding error (27 per cent); terminated enrolment or change in provider (20 per cent); immunization not given (10 per cent). Monitoring led directly to increases in recorded schedule completion rates of approximately 6 per cent (from 92 per cent to 98 per cent) for both age groups.

The completeness of the immunization record depends to some extent on the child's age and residence. Although MIMS has enrolled all children born on or after January 1, 1980, physician billing claims have been captured only since November, 1987. Consequently, in major urban areas, primarily in the city of Winnipeg where 98 per cent of immunizations are administered by physicians, children born before 1987 are likely to have incomplete MIMS records.

A preliminary study of the quality of first year of life MIMS data for the 1987 birth cohort (N = 14,331) was therefore undertaken (Appendix 4). Two cohort subgroups were defined by immunization status: received at least one immunization in the first 160 weeks of life (N = 13,966); and, received no immunizations of any kind in the first 160 weeks of life - MIMS records blank (N =

365). For members of the first subgroup (in receipt of at least one immunization in the first 160 weeks of life) for whom first-year data were missing, there was no evidence of selection. That is, there was no evidence that these children represented a select group in which factors associated with avoidance or delay of immunization may have been associated with an increased risk of adverse-event-type medical outcomes. The use of the incomplete immunization data set for the 1987 birth cohort would underestimate overall immunization rates and the total number of hospitalizations before/after immunization, but was not likely to bias our findings concerning adverse events by tending to underestimate any real risks associated with immunization. For members of the second subgroup (in receipt of no immunizations of any kind in the first 160 weeks of life), there was some evidence to suggest that such children with blank MIMS records represented a select group, requiring characterization and separate data analysis.

Status Indian children are immunized by federal public health nurses. MIMS was not implemented in federal health offices until 1990, and the reliability of data for status Indian children born before this year is considered low and the data is not yet monitored. For this reason, status Indian children (approximately 2,000 children in each cohort) were excluded from the study.

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.[67]

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 for children born in 1987, 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 for children born in 1987, 1988 and 1989 was analyzed in several ways. Birth date (year-month-day) was complete in all cases but one. In 298 cases immunization date (service date) or death date preceded birth date. As registry checks are conducted routinely and regularly, the errors may be assumed to be in immunization date. Service date was coded zero intentionally by Manitoba Health in 224 cases. Such coding indicates a deliberate restriction on use of the immunization data. The release, for example, of data entered prior to adoption is prohibited by provincial law; such data must be transferred at the time of adoption when a new file is created.

5.3 IMMUNIZATION RATES - 1988 MANITOBA BIRTH COHORT

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:[69]

- 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 was

therefore difficult to analyze adverse outcomes by age and dose.

- 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 was not therefore 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.
- 87 per cent of children had received first doses, and 85 per cent of children had received second doses, of DT, pertussis and poliomyelitis vaccines by the time of their first birthday. Eighty per cent of children had received third doses of DT by this time, while 79 per cent had received a third dose of pertussis vaccine and 45 per cent a third dose of polio vaccine.

In summary, the MIMS data indicated that only 77 per cent of these infants met the recommended immunization schedule. This low figure is explained when the data are

compared with the findings on immunization status at the time of first birthday for the defined subgroup of the 1988 study cohort (Roberts 1991, unpublished). This subgroup of all children born in 1988 was selected by excluding those with inconsistent death and service dates (N = 66) and those with immunization records known in advance to be incomplete - those whose enrolment with the provincial health plan was interrupted in the first year of life by death or migration (N = 1,055) and status Indian children (approximately 2,000). Rates of completion of the infancy series by the first birthday for excluded groups ranged from only two per cent (for children who were born in Manitoba but died before the first birthday) to an estimated 67 per cent for status Indian children.

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,[69] 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.[70] 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.

5.4 DATA ORGANIZATION AND SOFTWARE

Registry, hospital and MIMS files containing the records of Manitoba children born in 1987, 1988 and 1989 were examined.

Three files were linked:

- The MIMS file. This file included all children born in the relevant year. 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 contraindications). The file was generated after all the children had passed the first birthday and records had been monitored at least once. Current registry information was contained in the MIMS file, including date of death (regardless of whether that death occurred in or out

of hospital) or termination.

- The Manitoba Health hospital file for the years 1987 through March 1991. This file included all children born in 1987, 1988 and 1989. 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[71]), and scrambled individual patient identifiers (PHIN) were included.
- The Manitoba Health registry file. This file provided a check on mortality, migration out of province, and the quality of the personal identifiers.

For each remaining child, linkage was carried out using the scrambled personal identifier. The resulting file contained, for each child, the scrambled personal identifier and other identifiers and the attached records (hospitalization and immunization).

As described in Section 5.5, from each birth cohort a study cohort was selected: that subgroup of children whose enrolment with Manitoba Health was continuous from birth until at least the first birthday. Exclusion of children whose enrolment with Manitoba Health was

interrupted during the first year of life maximized MIMS data quality. The records of children who died or transferred out of the province were available for study.

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 analyzed using the wide range of SAS procedures.

5.5 SELECTION OF THE STUDY COHORTS

The flow diagrams describing the selection of the three study cohorts (children born in 1987, 1988 and 1989) are set out in Appendix 6.

Children whose enrolment with Manitoba Health was interrupted, by migration (N = 5,477) or death (N = 45), or whose enrolment began after the first birthday (N = 862) or for whom analysis of the internal consistency of the MIMS file revealed incorrect death or service dates (N = 298), were excluded. Exclusions represented 12 per cent of the total non-Indian birth cohorts. The final study cohorts selected numbered 43,499 in total (children born in 1987, 1988 and 1989). Of these children, 42,612 received at least one and 887 received no immunizations (any type) in the first year of life.

5.6 DEFINITION OF VARIABLES

Since serious adverse clinical events were expected to lead to hospital admission, hospitalization 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,[32,47] children whose hospitalizations may be 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[69] 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 cohorts had therefore been subjected to at least 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.[3,32,46,47] 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 and so on). 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 sequence in the immunization series. The previous study of the 1988 Manitoba cohort (Section 5.4) looked at dose not by tariff code but by generic (or chronological) occurrence. This was done to avoid anticipated problems due to miscoding. The miscoding rate was found, however, to be under three per cent for each dose. Consequently, for the 1988 and 1989 birth cohorts, immunization sequence was sought by generic occurrence, as it will be in future studies. However, for the 1987 cohort, immunization sequence was

more accurately determined by tariff code (Appendix 4) and was sought by this means.

Hospital discharge diagnoses were represented by the ICD-9-CM code assigned to them in the Manitoba Health 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.[72] In this study, all available diagnoses were used.

The date of enrolment with Manitoba Health, included in the MIMS file, was used to categorize enrolment status as follows: enrolment began at birth and continued at least to the first birthday; enrolment began at birth and terminated before the first birthday; enrolment began after birth and before the first birthday; enrolment began after birth and after the first birthday. The date of death, included in the MIMS file, was used to further categorize children whose enrolment began at birth and terminated before the first birthday into two groups: those whose enrolment terminated in the first year of life due to death and those whose enrolment terminated in the first year of life due to migration from the province.

The MIMS file includes, for each child, the

municipal code. Municipal code "A" designates children with Treaty Indian status; children with all other municipal codes were designated to be without Indian status.

The MIMS file includes the postal code of residence. The postal code recorded for the time closest to the first immunization recorded was used to establish residence. Place of residence was categorized as Winnipeg/non-Winnipeg. Winnipeg residence was then categorized into two groups: Winnipeg residence in the core geographic area served by the City of Winnipeg Health Department (designated "inner Winnipeg") and Winnipeg residence in other geographic areas of the city (designated "outer Winnipeg").

5.7 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 was discussed in Section 4.1. It 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.[2,55-57] 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 all of the events listed in Appendix 5, including serious neurological events and death (both SIDS and non-SIDS).

Some evidence exists for a true association between DTP/DT immunization and other major adverse events:[2] 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.[2] 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.[3,7] The ranges of the estimates of incidence of these adverse events following DTP/DT and OPV administration are summarized in Table 2.

5.8 DATA ANALYSES

Data from the MIMS file was used to describe the immunization experiences of each cohort in the first year of life. Immunization rates, by vaccine and by dose, and the distribution of age at immunization, both in days and in four-week age groups, were determined. For the total 1989 birth cohort, rates of completion of the infancy immunization schedule (three DTP/DT and two OPV/IPV) were calculated by enrolment status, by Indian status and by place of residence.

Overall hospitalization rates by four-week age group were calculated for the first year of life. In addition, 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 were grouped into the 17 ICD-9-CM Classification of Diseases and Injuries categories.[71] The distribution of these categories among first year of life admissions was determined.

A list of the diagnostic codes (ICD-9-CM) which apply to serious events considered to be either major reactions to immunizing agents or major events having a temporal relationship with immunization 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 7 (which also provides

the time periods within which these events would reasonably be expected to occur following immunization). 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". Designated codes were sought among all recorded discharge codes and overall rates of hospitalization calculated for each code.

Length of hospital stay (in days) was determined for all admissions in the first year of life, both for those occurring on the day of birth and those occurring after the day of birth.

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. The following analysis was performed for each cohort: the numbers of hospitalizations, regardless of reason (any discharge diagnostic code), were counted for 28 day intervals before and after immunization as well as on the day of immunization. Within these specific intervals, eligible hospitalizations were those which occurred between the ages of five and 56 weeks. Separate calculations were done for each vaccine, not only for each dose but adding all doses together. 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 being compared. Therefore, children for whom hospitalizations were recorded in both "before" and "after" time periods, as well as children who were immunized during a hospital stay, were excluded from analysis; the total number of such admissions was determined and subtracted from the totals, producing adjusted totals. Results for the three study cohorts were aggregated. Potential differences in hospitalization rates between the time period prior to immunization and the corresponding time period following immunization hospitalization were then tested.

The above analysis was repeated for the subset of hospitalizations where at least one of the designated ICD-9-CM codes was recorded among the discharge diagnostic codes and admission occurred within the allocated time interval for each of those codes.

5.9 STATISTICAL METHOD

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.[73] When expected values fell below a minimum value of two,[74] a binomial approach was used to calculate exact probabilities of significance.[73]

The review of the literature indicated that, in the absence of a pertussis outbreak during the study period, 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.

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 per cent.

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 per cent while maintaining the level of Type I error at 5 per cent, 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).

Rates from the 1988 cohort, determined from the previous study, were used in the advance power calculations. It was estimated that, with a sample size of approximately 40,000 children and 120,000 first year immunizations, the study would be able to detect a

relative increase of around 10 per cent, if present, in hospitalizations regardless of reason and an increase of the order of ten-fold in the occurrence of code 780.3 (representing non-epileptic convulsions), over all three doses with 90 per cent power while controlling Type I error at 5 per cent. It was further estimated that, at the same levels, relative increases of 20 per cent in hospitalizations regardless of reason and twelve-fold increases in the occurrence of hospitalization with code 780.3 could be detected, if present, around each dose. The analysis would however, be less sensitive to the increased occurrence of other, less common codes.

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

5.10 DIAGNOSTIC DATA QUALITY

The interpretation of increased rates of hospitalization with one or more of the designated diagnostic discharge codes following immunization depended directly on the quality of the diagnostic data. Since the diagnostic information contained in the Manitoba Health database is routinely collected for administrative rather than research purposes, the design

of its collection and the expertise of the collectors are beyond the study's control.[75] The meaning of increased rates of hospitalization with the designated study codes therefore depended upon our knowledge of the reliability and the accuracy of the diagnostic information in the database.

Data reliability concerns the degree to which results are consistent across repeated measurements, reflecting reproducibility and precision.[76] Accuracy, or validity, concerns the degree to which results reflect the true state of affairs. In research, accuracy refers not only to the measuring indicator but, more importantly, to the interpretation of the data arising from the measurement process (that is, to its use).[76,77]

Reliability in diagnostic coding requires that the translation by medical records clerks of diagnoses on medical records to codes on claims and computerized records be consistently reproducible regardless of coder. Coding accuracy requires that each diagnosis be recorded in a form for which a code reflecting the true condition of the patient exists and that coders make the correct coding selections.[78-80]

For diagnostic information to be reliable, physicians should consistently have the same interpretation of, and use the same terminology for, the same medical conditions. Diagnostic accuracy, however,

is not easily established. For clinical observations that can be measured by physical means, the observed measurement can be compared to some accepted standard (the "gold" standard) - the accuracy of a physical finding, for example, can be established by the results of surgery or autopsy. Generally, for claims-based diagnoses, no standard of accuracy exists.[78-80]

There is good evidence that, in Manitoba, hospital diagnoses are reliably and accurately coded on discharge abstracts.[68,80-82] Analysis of admission/separation forms for a number of specific diagnoses has shown that the occurrence of simple coding errors is minimal. Manual reliability checks at each step in the transfer of information from hospital medical record to hospital abstract to hospitalization file have shown excellent correspondence among the various stages.

Checking diagnostic reliability, however, involves more than looking for simple recording and logical errors. Checks performed in Manitoba have shown that while intraphysician agreement on diagnoses is good, different physicians often disagree as to diagnosis; the reliability of diagnoses varies considerably according to the organ system and particular medical problem involved.

Checks of diagnostic validity in Manitoba, performed by checking diagnoses on hospital claim forms against hospital records, have shown a high level of

agreement.[68,80-82] There remains, however, the question of what is a valid diagnosis. For some conditions at least (such as acute myocardial infarction[83]), problems arise with diagnostic coding due to imprecision in the terminology used by physicians and imprecision in ICD-9-CM nomenclature and coding rules.

In claims data, diagnostic data quality problems are greatest when the diagnosis, ICD-9-CM code and tariff code are non-specific. Single diagnoses may be misleading; it has been suggested that it is often more helpful to group ICD-9-CM diagnostic information than to attempt fine diagnostic distinctions.[78,80]

Since many research subjects present both data reliability and validity concerns, additional methods of assessing Manitoba data quality have been used. Checking that the data make sense, for example, has been done in a number of ways - by identifying logically time-sequenced relationships, by looking for the association of certain diagnoses with certain procedures, and by seeking constellations of related diagnoses. Patterns in Manitoba have confirmed the general validity of the claims data.[78,80]

To assess the quality of the diagnostic information captured through the study techniques, an individual examination of all data in the hospitalization file record was conducted for each child whose record included

the appearance of one or more of the designated diagnostic discharge codes within the relevant time period(s) following DTP/DT or OPV/IPV immunization. The hospitalization file record contained individual hospital record numbers; corresponding hospital-held records were also identified and reviewed to assess the quality of coding and diagnostic data.

5.11 BIAS CONSIDERED

5.11.1 INDEPENDENT ASCERTAINMENT OF EVENTS

Prominent among sources of bias in studies of immunization-related adverse events is the problem of ensuring that adverse events are ascertained independently of immunization history. Failure to control for this factor may lead to the creation or overestimation of an association between administration of a vaccine and an adverse event.[60,61] In this study, immunization and hospitalization events separated by time and place were ascertained independently from the respective files. Since each child could be traced across all Manitoba Health database files, linked records permitted the simultaneous examination of these events. Hospitalizations with diagnoses indicative of immunization-related adverse events were identified by ICD-9-CM codes and their temporal association with

immunization assessed. Since incidence was measured directly, rates of occurrence were calculated for those adverse events showing a true temporal association with immunization.

5.11.2 SELECTION

A second major problem was the possibilty of confounding between the risk factor (immunization) and the outcome measure (adverse event) of interest. Many factors known to be associated with either avoidance or delay of immunization may themselves be associated with an increased risk of adverse-event-type medical outcomes. Studies which do not control adequately for this form of confounding by indication will tend to underestimate any real risks associated with immunization.[60,61]

Separate analyses were done for selected subsets of children with special experiences in the first year of life who may differ systematically from those fully immunized.

Children With Incomplete Immunizations In the First Year Of Life

Further immunizations may 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, rates of hospitalization regardless of reason were calculated as above for children who received fewer than the recommended number of immunizations in the first year of life (only two doses or one dose of DTP or only one dose of OPV.

Children Immunized In Hospital

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. Therefore, 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.

Children Who Died

The records of children who died within 28 days of DTP/DT or OPV/IPV immunization in the first year of life were examined individually.

Children With No Immunizations In the First Year Of Life

Examination of the MIMS database prior to study, in a review which included all Manitoba children born in 1988,[69] showed zero immunizations on record for 10.4 per cent of all children born in 1987, 8.5 per cent of all children born in 1988 and 8.6 per cent of all children born in 1989.

For members of the study cohorts who received no immunizations of any kind and might represent special groups of infants, the hospitalization experiences were determined as above in order to describe this group.

5.11.3 THE EFFECT OF AGING

Decreasing overall rates of hospitalization over the first year of life represent a potential source of systematic bias against finding differences in hospitalization rates before and after immunization. This was considered by calculating, for each study cohort, overall hospitalization rates in the first year

of life, by four-week age group, for (1) all study cohort members, (2) all study cohort members in receipt of at least one immunization in the first year of life, and (3) all study cohort members in receipt of no immunizations in the first year of life.

5.11.4 THE EFFECT OF SERVICE DATE ERRORS

The quality of MIMS data with respect to service dates was examined in a study (described in Section 5.2) which, using the physician record as the standard, found excellent agreement (98 per cent) between the service dates recorded by MIMS and physicians. One per cent of service date disagreements involved a difference of one day and one per cent a difference of between two and six days.

Service date discrepancies are random errors occurring during physician documentation or during claim preparation or input. The present study did not depend on the reliability of physician documentation. In addition, the larger the sample size, the smaller will be the effect of such random errors, particularly on the search for the uncommon events sought between days 7-28 following immunization.

To analyze the possible effects of service date errors, the study results were recalculated assuming the

worst effect: the misclassification (in the wrong time category) of one per cent of adverse events anticipated to occur on or between days 0-7 following immunization.

6. RESULTS

6.0 DESCRIPTIVE FINDINGS

6.0.0 IMMUNIZATION PROFILE, STUDY COHORTS

The immunization status of the 1987, 1988 and 1989 study cohorts at the time of the first birthday is shown in Figure 2 (cohorts combined) and in Figures 3-5 (cohorts separately). Immunization rates by vaccine and by dose for the first year of life are shown in Table 3.

Recorded completion of the recommended immunization schedule in infancy was defined as documentation of the receipt of at least three doses of DTP/DT and at least two doses of OPV/IPV by the first birthday. Recorded rates of infancy schedule completion were 85.4 per cent for the combined cohorts, and 75.9 per cent, 89.0 per cent, and 91.3 per cent for the 1987, 1988, 1989 cohorts respectively.

DT and DTPT vaccines were infrequently recorded as alternatives to DTP (under one per cent for each dose); IPV vaccine was recorded for only 23 of 101,682 poliovaccine doses given. Accordingly, all future references to these vaccines will be as DTP and OPV. The administration of OPV on the same day as DTP was recorded more than 98 per cent of the time for each dose. Forty eight per cent of all study children received three OPV, even though the schedule no longer recommended the third dose.

Of 1,942 children with neither DTP nor OPV recorded in their first year, 1,055 had records indicating the receipt of at least one immunization of another type in that period while 887 had no immunizations of any kind on record. These groups are discussed in Section 6.4.

The frequencies of immunization by dose and by age at immunization (four week age groups) were very similar for each vaccine and for each of the three study cohorts. The results for DTP immunization for the combined cohorts are summarized in Figure 6. The majority of each of the doses 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.

6.0.1 IMMUNIZATION PROFILE, TOTAL 1989 BIRTH COHORT

Table 4 shows, for the 1989 birth cohort, the recorded rates of infancy schedule completion for all children enrolled with Manitoba Health in the first year of life, by Indian status, enrolment status and place of residence. The overall recorded rate was 79.4 per cent. Among those continuously enrolled (from birth to at least one year of age), the recorded rate was 90.8 per cent for non-Indian children and 44.5 per cent for Indian children. Recorded rates for children whose first year enrolment was interrupted by migration (N = 1,119) or by

death (N = 119) were 40.0 per cent and 20.3 per cent for non-Indian and Indian children respectively.

The vast majority of children (93.1 per cent) were continuously enrolled, the proportions being somewhat lower in the inner city section of Winnipeg (non-Indians 90.6 per cent, Indians 92.5 per cent) than elsewhere (non-Indians 93.3 per cent, Indians 96.9 per cent). For continuously enrolled non-Indian children, those living in the inner city had the lowest recorded rate of completion of the recommended schedule (87.3 per cent) (Table 4). For continuously enrolled Indian children, this rate was lowest among those living outside Winnipeg (38.6 per cent).

Table 5 gives, for each vaccine, the number of doses recorded by the first birthday for the subgroup of continuously enrolled non-Indian children and for all children enrolled any time in their first year. Of continuously enrolled non-Indian children, 91.0 per cent had at least three doses of DTP vaccine (98.1 per cent had at least one dose recorded) and 95.4 per cent at least two doses of OPV vaccine by one year of age. Of all children enrolled any time in their first year, 82.5 per cent had at least three doses of DTP vaccine by one year of age (94.1 per cent had at least one dose recorded) and 88.3 per cent received at least two doses of OPV vaccine.

DTP and OPV vaccines were almost always administered on the same day. Among children receiving up to three doses of DTP, fewer than one per cent received DT for any dose. IPV accounted for only nine of the 35,216 doses of poliovaccine administered, while 45.8 per cent of the group received three doses of OPV. Calculation of the frequencies of immunization by dose and by age at immunization (four week age groups) produced a distribution which, for each vaccine, closely resembled those produced for each of the study cohorts (Section 6.0.0).

6.0.2 HOSPITALIZATION PROFILE, STUDY COHORTS

Hospitalization Rates, All Members of the Study Cohorts

Hospitalization rates in the first 56 weeks of life were calculated, by age, for each study cohort, regardless of the immunization status of its members. Results for each of the three cohorts were very similar and Figure 7 shows the hospitalization rates, by four week age group, per 1,000 members for the combined study cohorts (N= 43,499). Birth hospitalizations (N = 42,908) were excluded from the 0-4 week age group.

The rate was highest in the 0-4 week age group at 57.2 per 1,000 cohort members, declined sharply to 20.9 per 1,000 cohort members for the 5-8 week category, and remained below 20.0 per 1,000 cohort members between nine

and 56 weeks of age. Overall, the hospitalization rate for immunized cohort members in the first 56 weeks of life was 246.5 per 1,000 cohort members (birth hospitalizations excluded).

Hospitalization Status, Study Cohort Members Receiving At Least One Immunization in the First Year of Life

Hospitalization rates in the first 56 weeks of life were similarly calculated for cohort members receiving at least one immunization in the first year of life. Results for each of the three study cohorts were again very similar and Figure 8 shows the hospitalization rates, by four week age group, per 1,000 such members of the combined study cohorts (N = 42,612).

The rate declined sharply from 57.5 per 1,000 cohort members in the 0-4 week age group to 21.0 per 1,000 for the 5-8 week category, and remained below 20.0 per 1,000 between nine and 56 weeks of age. Overall, the hospitalization rate for immunized cohort members in the first 56 weeks of life was 245.0 per 1,000 cohort members (birth hospitalizations excluded).

The cohort subsets receiving at least one immunization in the first year of life were compared with those receiving no immunizations in the first year of life on the basis of length of hospital stay and primary discharge diagnoses.

Length of stay (in days) was calculated for each hospitalization in the first 56 weeks of life. Figure 9 shows, for cohort members receiving at least one immunization in the first year of life, the proportions of hospitalizations involving stays of more than six days duration; it compares categories of length of stay for hospitalizations which occurred on the day of birth, called day 0, (N = 45,500) with those which occurred after the day of birth (N = 10,044). Children hospitalized after the day of birth experienced a higher proportion of stays 7-28 days in duration than those hospitalized on the day of birth; relative to such children, their risks of experiencing hospital stays of more than six days duration were 2.2 for stays of 7-13 days, 1.9 for stays of 14-27 days, and 0.9 for stays over 28 days.

For all hospitalizations in the first 56 weeks of life, the primary discharge diagnosis (that most responsible for the hospitalization) was established and categorized according to the ICD-9-CM Classification of Diseases and Injuries (seventeen possible categories). The distribution of categories of primary diagnosis by age (four week age group) was determined. The category most frequently responsible for hospitalization in the 0-4 week age group was Category 15 (Certain Conditions Originating in the Perinatal Period, describing illnesses

specific to the neonatal period of life), encompassing the primary discharge diagnosis in 34 per cent of hospitalizations (Table 6). Respiratory diseases represented the most frequently responsible diagnoses in hospitalizations overall (28 per cent), between the ages of five and 56 weeks (34 per cent), and in each four week age group between five and 56 weeks of age.

Figure 10 shows hospitalization rates in the first 56 weeks of life by the four categories of primary diagnosis most often associated with overall hospitalization; rates were calculated by four week age group per 1,000 immunized members of the combined study cohorts (N= 42,612). Rates of hospitalizations related primarily to respiratory disease were high throughout the period, while steadily increasing rates were seen for hospitalizations in which the primary diagnosis was categorized among "Diseases of the Nervous System and Sense Organs".

Hospitalization Status, Study Cohort Members Receiving No Immunizations in the First Year of Life

The hospitalization status of these subsets of the study cohorts is described in Section 6.5.0.

6.1 HOSPITALIZATION WITH DIAGNOSTIC DISCHARGE CODES INDICATIVE OF SERIOUS ADVERSE EVENTS

6.1.0 ALL MEMBERS OF THE STUDY COHORTS

There were 754 appearances of designated ICD-9-CM codes among all codes (N = 104,304) for hospitalizations (N = 8,321) between the ages of five and 56 weeks among members of the combined study cohorts, regardless of immunization status.

Designated codes most frequently associated with such hospitalizations were codes 780.3 (convulsions, excluding epileptic and newborn), and 780.6 (pyrexia of unknown origin); they appeared for 34.0 and 33.5 respectively of every 1,000 hospitalizations between five and 56 weeks of age. Other designated codes were far less frequent; the next most commonly occurring were 348.0 (cerebral cysts) and 999.9 (other and unspecified complications of medical care, not elsewhere classified), which appeared for 3.4 and 3.0 respectively of every 1,000 hospitalizations.

6.1.1 STUDY COHORT MEMBERS RECEIVING AT LEAST ONE IMMUNIZATION IN THE FIRST YEAR OF LIFE

Table 7 presents the frequencies of designated ICD-9-CM codes (N = 710) among all codes (N = 101,493) for hospitalizations (N = 7,893) between five and 56 weeks of age in members of the combined study cohorts receiving at least one immunization in the first year of life.

The designated codes most frequently associated with such hospitalizations were again codes 780.6 and 780.3, which appeared for 34.2 and 34.1 respectively of every 1,000 hospitalizations in immunized children between five and 56 weeks of age. The next most commonly occurring codes, 348.0 and 999.9, appeared for 3.4 and 2.9 respectively of every 1,000 such hospitalizations. Codes 320.0 (*Haemophilus* meningitis), 322.9 (meningitis, unspecified) and 345.6 (infantile spasms) each appeared for 2.4 of every 1,000 hospitalizations, while codes 047.9 (unspecified viral meningitis) and 781.0 Abnormal involuntary movements) each appeared for 2.3 of every 1,000 hospitalizations.

Figure 11 shows rates of hospitalization with codes 780.6, 780.3 and 345.6 among the discharge diagnostic codes, by age, for this group of children between birth and 56 weeks of age. Rates were calculated by four week age group per 1,000 combined immunized cohort members (N = 42,612). For code 780.6, rates were highest in the period between birth and eight weeks of age and changed little between the ages of 17 and 56 weeks. For hospitalization with code 780.3, rates were at their lowest between 21 and 28 weeks of age and rose steadily thereafter, peaking at between 49 and 52 weeks of age. Rates with codes 345.6 were highest between 17 and 32 weeks of age.

6.1.2 STUDY COHORT MEMBERS RECEIVING NO IMMUNIZATIONS IN THE FIRST YEAR OF LIFE

Hospitalization with designated diagnostic codes is described for this subset of the study cohorts in Section 6.5.1.

6.2 THE TEMPORAL RELATIONSHIP BETWEEN HOSPITALIZATION AND IMMUNIZATION

6.2.0 IMMUNIZATION AND HOSPITALIZATION REGARDLESS OF REASON

For the combined study cohorts, children receiving at least one immunization in the first year of life, the adjusted numbers of hospitalizations (any diagnostic codes), between five and 56 weeks of age in the relevant time periods around immunization, are shown for DTP in Table 8. The results for OPV were virtually identical.

Since the analysis did not concern individuals who were hospitalized in both time periods, the adjusted totals were derived by reducing the total number of hospitalizations in each of the two time periods accordingly. The number of children hospitalized in both time periods included children who experienced hospitalizations during each time period (totals: DTP N = 45, OPV N = 39), and children hospitalized in the "before" time period who were immunized during a hospital stay which was then prolonged into the "after" period (totals: DTP N = 33, OPV N = 27).

For each vaccine, over all three doses considered together, hospitalization regardless of reason between five and 56 weeks of age was no more likely to occur in the period from the day of to 28 days after immunization than in the 28 days before. Power calculations showed that the study could detect an 11 per cent relative increase in hospitalizations, if present, over all three doses with a power of 90 per cent while controlling type I error at 5 per cent.

When each dose of vaccine was considered separately, there was a modest but statistically insignificant rise in hospitalizations after the third DTP. This analysis was less sensitive, able to detect relative increases in hospitalizations of from 16 per cent for the first DTP to 22 per cent for the third DTP, at 90 per cent power.

6.2.1 IMMUNIZATION AND HOSPITALIZATION WITH DESIGNATED DIAGNOSES

Table 9 shows, for DTP immunization, the adjusted number of hospitalizations and code appearances in the relevant time periods.

Statistically significant increases in the appearances of codes 345.6 (infantile spasms) and 780.3 (non-epileptic convulsions) occurred following the second DTP (Chi-square, with 1 df, one-tailed test: 3.0 for code 345.6, $p<0.05$; and 5.0 for code 780.3, $p<0.025$) and

in the appearance of code 780.3 following the third DTP (Chi-square, with 1 df, one-tailed test: 3.0, $p<0.05$). The increased occurrences of codes 345.6, 780.3, 780.6 (pyrexia of unknown origin) 999.5 (other serum reaction) and 999.9 (complications of medical care, not elsewhere classified) over all three doses considered together were also statistically significant (Chi-square, with 1 df, one-tailed test: 5.0 for code 345.6, $p<0.025$; 4.0 for code 999.5, $p<0.025$; 9.1 for code 780.3, $p<0.001$; 7.0 for code 780.6, $p<0.005$; and 6.0 for code 999.9, $p<0.01$). Hospitalization between five and 56 weeks of age with these codes was therefore more likely to occur in the relevant time periods following the day of DTP immunization than in those before. Calculated over all three DTP doses, the incidences of hospitalization per 100,000 doses were: with code 345.6 in the 28 day post-immunization period, 4.2; with code 999.5 in the 28 day post-immunization period, 3.4; with code 780.3, in the seven day post-immunization period, 9.2; with code 780.6, in the two day post-immunization period, 5.9; with code 999.9, in the two day post-immunization period, 2.5.

The frequencies of 14 additional codes found in the post-DTP immunization period were not statistically significant (Table 10). The study could, with 90 per cent power, detect nine-fold increases, if present, in

hospitalizations with these codes over all three doses combined and in hospitalizations occurring around each of the first, second and third DTP.

Over three doses of OPV considered together, four designated codes appeared once in the 28 days post-immunization: 344 (other paralytic syndromes), 781.0 (abnormal involuntary movements); 781.3 (lack of coordination); and E949 (other vaccines and biological substances). The frequencies did not reach statistical significance.

6.2.2 ANALYSIS OF THE EFFECT OF SERVICE DATE ERRORS

The potential for errors in service dates recorded on MIMS to bias the study findings was considered in Section 5.10.4. Accordingly, the results presented in Sections 6.2.0 and 6.2.1 were recalculated assuming the worst effect, that one per cent of events detected on or between days 0-7 following immunization were classified in the wrong time category. This analysis showed no difference in outcome.

6.2.3 THE EFFECT OF IMMUNIZATIONS GIVEN IN HOSPITAL

A total of 167 immunizations were administered during hospital stays: first DTP (N = 65); first OPV (N = 63); second DTP (N = 17); second OPV (N = 15); third DTP (N = 6); third OPV (N = 1).

A discharge date was available for each study child hospitalized in the first 56 weeks of life, 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.

6.3 STUDY COHORT MEMBERS WITH INCOMPLETE IMMUNIZATIONS IN THE FIRST YEAR OF LIFE

A slight decrease (from 31 to 24) in the number of hospitalizations regardless of reason occurred after immunization for the subset of children receiving only one DTP (N = 1,444) in the first year (Table 10). A slight increase after the second immunization (from 47 to 50) occurred for the subset receiving only two DTP (N = 2,623). These changes were not statistically significant. Three designated code appearances (780.3, 999.5 and 999.9) were recorded for hospitalizations following the second DTP in children receiving only two doses; no designated codes appeared following immunization in children receiving only one dose.

6.4 STUDY COHORT MEMBERS RECEIVING NO DTP OR OPV BUT AT LEAST ONE IMMUNIZATION OF ANOTHER TYPE IN THE FIRST YEAR OF LIFE

As mentioned in Section 6.0.0, 1,055 study cohort

members received no DTP or OPV but at least one immunization of another type in the first year of life. For this group, MIMS recorded the administration of 25 immunizations in the first year of life, involving the use of *Haemophilus influenzae* type b, MMR (measles-mumps-rubella) and BCG (Bacillus Calmette-Guérin) vaccines.

This group of children was included in the study population. Preliminary data analysis (Section 5.2) for its 929 members born in 1987 showed that, in the second year of life, MIMS recorded the administration of 837 doses of DTP which had been assigned the tariff code for the fourth DTP in the primary series. This suggested that the vast majority of the children born in 1987 were appropriately immunized in the first year of life. MIMS's incomplete operational status in 1987 was accepted as a reasonable explanation of the missing first-year data.

It was, in addition, believed that the group included children living near Indian reserves. Such children, although without Treaty status, are known to receive immunization services through Medical Services Branch (MSB) whose participation in MIMS is incomplete. At the time of study, MSB's first-year immunization schedule included BCG, *Haemophilus influenzae* type b and MMR, although these vaccines are not recommended provincially for administration in the first year of

life.

6.5 STUDY COHORT MEMBERS RECEIVING NO IMMUNIZATIONS OF ANY KIND IN THE FIRST YEAR OF LIFE

6.5.0 HOSPITALIZATION PROFILE

Children receiving no immunizations of any kind during the first year of life numbered 887. For this group, the database recorded 925 hospitalizations in the first 56 weeks of life, of which 711 occurred between 0-4 weeks of age.

Missing Data

For 207 children, no hospitalizations of any kind (including birth hospitalizations) were recorded. This observation may be explained by the occurrence of births outside Manitoba hospitals and of adoptions in the first year of life. 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 (Dr. K. Brown: personal communication). In 1988, Manitoba Child and Family Services completed 65 adoption placements of children under one year of age, and estimated that a similar number of Manitoba children were placed by private arrangement.(Manitoba Child and Family Support:

personal communication) While agency placements occur at varying ages, private placements almost always occur at less than ten days of age. The record of the adopted child's birth hospitalization, listed under the Manitoba Health registration number of the birth mother, may be lost when the child's registration is erased (as required by provincial law) at the time of adoption; subsequent records of health care contacts are then listed under the registration number of the adopting family, with Manitoba Health coverage back-dated to birth. Similarly, for children adopted at ages in excess of the recommended ages for immunization, immunization records may be lost unless a deliberate transfer of such information is made at the time of registration changeover.

Hospitalization Status

Hospitalization rates in the first 56 weeks of life were calculated, by age, for cohort members receiving no immunizations of any kind during the first year of life. Figure 8 shows the rates, by four week age group, per 1,000 such members of the combined study cohorts (N = 887). Birth hospitalizations (N = 680) were excluded from the 0-4 week group. Overall, the hospitalization rate for unimmunized children in the first 56 weeks of life was 285 per 1,000 cohort members (birth hospitalizations excluded). The rates were comparable to

those of children receiving at least one immunization in that period (N = 42,612). The small number of unimmunized children precluded statistical comparison with the immunized group.

Length of stay (days) was calculated for each hospitalization in the first 56 weeks of life. Figure 12 shows those involving stays of more than six days duration; it compares categories of length of stay for hospitalizations which occurred on the day of birth, called day 0, (N = 662) with those which occurred after the day of birth (N = 263). Among unimmunized (as among immunized) children, those hospitalized after the day of birth experienced a higher proportion of stays 7-28 days in duration than those hospitalized on the day of birth. Unlike immunized children, however, unimmunized children hospitalized after birth were far more likely to experience a very long hospital stay (over 28 days) than those hospitalized at birth; their risks, relative to the group hospitalized at birth, of experiencing hospital stays of more than six days duration were 1.6 for stays of 7-13 days, 2.2 for stays of 14-27 days, and 5.6 for stays over 28 days.

The most informative comparisons, however, were those between unimmunized and immunized children. For hospitalizations on the day of birth, the relative risks of the various categories of stay for unimmunized over

immunized children were 1.5 for stays 7-13 days, 1.3 for stays of 14-27 days and 1.6 for stays of over 28 days. For hospitalizations after birth, the risks were 1.6 for stays of 7-13 days, 2.7 for stays of 14-27 days, and 7.8 for stays over 28 days.

Table 11 shows the distribution of categories of primary diagnosis (the seventeen ICD-9-CM Classification of Diseases and Injuries categories) for hospitalizations in unimmunized children between birth and 56 weeks of age. Comparison with Table 6 shows that the same general categories of disease occasioned most of the hospitalizations among both immunized and unimmunized children. Category 15 (Certain Conditions Originating in the Perinatal Period) was again the leading category in the 0-4 week age group, but whereas it led to 34.3 per cent of hospitalizations among immunized children it was responsible for 64.5 per cent of hospitalizations in unimmunized children. The category responsible for the highest proportion of hospitalizations overall and in each age category between five to 56 weeks of age (among immunized and unimmunized children) was, as among immunized children, Category 8 (Diseases of the Respiratory System).

In Figure 13, hospitalization rates are given for the first 56 weeks of life calculated by age and by the four categories of primary diagnosis most often

associated with overall hospitalization, per 1,000 unimmunized members of the combined study cohorts (N= 887). The trend noted (Figure 10) among immunized children for rates of hospitalizations primarily attributed to diseases of the nervous system to increase with age was not seen among unimmunized children. Again, rates primarily attributed to respiratory disease were high and sustained throughout the period.

6.5.1 HOSPITALIZATION WITH DIAGNOSTIC DISCHARGE CODES INDICATIVE OF SERIOUS ADVERSE EVENTS

Table 12 shows the frequencies of designated ICD-9-CM codes (N = 44) among all codes (N = 2,811) for hospitalizations (N = 214) between five and 56 weeks of age in members of the combined study cohorts receiving no immunizations in the first year of life.

Code 780.3 was associated with 65.4, and code 780.6 with 28.0, of every 1,000 hospitalizations in unimmunized children between the ages of 5 and 56 weeks. Code 345.9 (epilepsy, unspecified) appeared at a rate of 23.4 per 1,000 hospitalizations.

6.6 CHILDREN WHO DIED IN THE FIRST YEAR OF LIFE

6.6.0 STUDY COHORT MEMBERS RECEIVING AT LEAST ONE IMMUNIZATION IN THE FIRST YEAR OF LIFE

The deaths of 23 children born in Manitoba were

recorded within 30 days of DTP or OPV immunization in the first year of life. Re-examination by the College of Physicians and Surgeons of Manitoba of the rulings of its Pediatric Death Review Committee showed that, for 22 children, death was not considered causally associated with immunization; one child could not be matched on birth date to the College file.

6.6.1 STUDY COHORT MEMBERS RECEIVING NO IMMUNIZATIONS OF ANY KIND IN THE FIRST YEAR OF LIFE

Of 1,099 children born in Manitoba whose enrolment with MHSC did not endure to the first birthday and who received no immunizations in the first year of life, 259 (24 per cent) died and 840 (76 per cent) migrated from Manitoba before the first birthday.

Individual record examination showed that 240 deaths occurred prior to the recommended age for the first immunization. Of these, 114 occurred on the day of birth (termed day 0 of life), 95 between days 1-27 of life, and 31 between days 28-60 of life.

6.7 HOSPITAL RECORD ANALYSIS

6.7.0 HOSPITALIZATION FILE EXAMINATION

The hospitalization file record was examined individually for each child whose record included the appearance of one or more of the designated diagnostic

discharge codes within the relevant time period(s) following DTP/DT or OPV/IPV immunization. This examination showed that 57 designated code appearances related to the hospitalizations of 48 children; each child had only one relevant hospitalization.

Forty four children had designated codes (a total of 53) amongst their hospital discharge codes following DTP/DT immunization; designated codes appeared only once among the discharge codes for 38 children, and more than once for six children. One designated code was recorded for each of four hospitalizations following OPV immunization. Definitions of the designated diagnostic codes and the time periods around immunization in which they were sought are given in Appendix 7.

The distributions of the designated diagnostic codes among the 48 hospitalizations following immunization are shown, by time period following immunization, in Table 13 (following DTP/DT) and in Table 14 (following OPV). These tables also give the distributions and descriptions of accompanying non-designated codes.

6.7.1 HOSPITAL-HELD RECORD EXAMINATION

Individual identifiers in the hospitalization file record were used to locate the hospital-held records of children whose hospitalizations were described in section 6.7.0. Forty four hospital-held records, of children

hospitalized in Manitoba, were examined individually to assess the quality of coding and diagnostic data; four records were inaccessible (three related to out-of-province hospitalizations and one to a hospitalization in a northern Indian reserve nursing station).

Twenty six of the Manitoba hospitalizations examined took place in Winnipeg teaching hospitals, six in an urban district hospital (Brandon General Hospital), and 12 in various rural hospitals. In every case, identifiers in the hospitalization file (hospital record number, Manitoba Health registration number, and dates of birth, admission and separation) matched perfectly with those in the hospital-held record.

The forty four hospitalizations recorded the appearance of 55 designated codes, of which 52 were related to DTP/DT vaccine and three to OPV vaccine.

Physician Diagnoses

Physician diagnoses indicated the occurrence of 13 possible immunization-related adverse events, all of which followed DTP/DT vaccine. Table 15 shows, for these 13 hospitalizations, the diagnostic discharge codes and physician diagnoses by time period following immunization.

Ten of the 13 hospitalizations occurred between days 0-3 post-DTP. Seven were documented as purely febrile

episodes (temperature equal to or greater than 39°C); six of these children were hospitalized between days 0-2 post-DTP and one on day three post-DTP. For three hospitalizations, screaming episodes were documented; the final diagnoses were "allergic reaction to vaccine", "post-immunization episode - not likely toxic or seizure" and "reaction to second immunization - most likely due to pertussis component of vaccine"; two of these children were hospitalized between days 0-2 post-DTP and one on day three post-DTP. Between days 0-7 post-DTP/DT, there were three seizure events in which review of the physician documentation showed that vaccines were considered as possible etiologic agents - two of these events were associated with the use of DTP and one with the use of DT vaccine.

Among the seven hospitalizations with physician diagnoses of possible post-DTP febrile events, two followed the first dose, two the second and three the third; of the three hospitalizations with physician diagnoses of possible post-DTP/DT screaming episodes, all followed the second dose; among the three hospitalizations with physician diagnoses of possible post-DTP/DT convulsion events, one followed the first dose of vaccine and two the second.

For 31 hospitalizations, physicians did not implicate vaccines in the disease process. The

diagnostic discharge codes and physician diagnoses related to these hospitalizations are listed in Appendix 8.

Diagnostic Data Quality

Although the accuracy of physician diagnoses could not be measured, final diagnoses documented in the hospital record were in all cases congruent with the constellation of physical signs and with the sequencing of clinical events. Physicians were consistent in their interpretatation of clinical findings and in their use of terminology for medical conditions.

The procedure used by coding clerks calls for the direct translation of diagnostic data to claims abstracts from the physicians' statements of "final diagnoses" to claims abstracts. Final diagnostic statements were available for approximately two-thirds of the hospitalizations; for the remaining hospitalizations, the coders culled diagnostic information from the chronological record of hospital stay. Diagnoses for which a specific code existed (otitis media and diaper rash, as examples) were reliably coded. There was, however, marked variation in the codes used to represent diagnoses when the available codes were non-specific in nature and when the coding rules were unclear, as was the case when the physician diagnosis indicated the

occurrence of immunization-related adverse events. In these instances, there was little consistency in the choice of code(s) to represent the physician diagnosis and in the selection of the single code to represent the primary diagnosis ("that which describes the most significant condition for which the patient is hospitalized"[72]).

Four broad categories of code were used. These denoted the disease entity (such as 382.9 for otitis media), the predominant physical sign (such as 780.6 for pyrexia), the occurrence of a complication (such as 999.9 for complications of medical care), and the explanatory codes (E to denote an external cause and V to denote factors influencing health status). When the physician diagnoses indicated immunization-related adverse events, the coders used "sign" and/or "complication" codes. The use of the E code was variable. Coding procedures were amended in 1990, deleting the requirement for its use in the presence of a complication code. The practice of qualifying complication codes with E codes has, however, been continued in some hospitals (such as the Health Sciences Centre) but not in others (such as St. Boniface Hospital).(Personal communication: S. Wadsworth, Director, Health Records, St. Boniface Hospital)

"Sign" and "disease entity" codes were highly accurate, reflecting in all cases the true conditions of

the patients. All post-DTP/DT appearances of designated codes 345.6 (5), 780.3 (11) and 780.6 (7) were validated. "Complication" were also accurately used; all (4) post-DTP/DT appearances of designated code 999.5 and four (of 6) appearances of code 999.9 were validated and represented physician diagnoses of possible immunization-related adverse events.

Three of five E codes used, however, were inaccurate. In one case, the E code relating to OPV vaccine was used instead of that for DTP vaccine - receipt of both vaccines was documented and the diagnosis read simply "post-immunization episode"; in this case, review of the hospital-held record changed the status of the potential immunization-related adverse event from one possibly related to OPV vaccine (Table 14) to one possibly related to DTP/DT vaccine (Table 13). In two instances, totally incorrect explanatory E codes were entered on the discharge abstract.

Evaluation of the Process of Using Only Designated Codes Listed in the Primary Position To Identify Hospitalizations Associated With Possible Immunization-Related Adverse Events

As described in Section 5.6, the study used all of the available diagnostic discharge codes (up to 16) listed in the hospitalization record to seek hospitalizations associated with the designated codes.

The record review showed that when the designated codes appeared, they were most often listed in the primary position; they described "the most significant condition for which the patient was hospitalized" in 32 of the 44 hospital-held records examined. When the clinical data were reviewed, they suggested that for eight children the occurrence of an immunization-related adverse event was an unreasonable supposition; these eight hospitalizations were among the 12 where the designated codes were listed in a subsidiary position (Table 16).

These observations suggested the possibility of detecting hospitalizations with suspected immunization-related adverse events by seeking only those designated codes listed in the primary position. To evaluate this process, the following were determined from the 44 records examined: the presence/absence of a designated code in the primary position; and the presence/absence of clinical data which allowed a reasonable possibility that an immunization-related adverse event had occurred. This information was used to assess the sensitivity, specificity and predictive values of the process of using only primary designated codes to detect hospitalizations associated with possible adverse events (Figure 14).

The following definitions were used: for *sensitivity*, the proportion of hospitalizations where the occurrence of an immunization-related adverse event was

possible and a designated code was listed in the primary position; for *specificity*, the proportion of hospitalizations where the occurrence of an immunization-related adverse event was unreasonable and a designated code was not listed in the primary position; for *positive predictive value*, the probability of a possible immunization-related adverse event when a designated code was listed in the primary position; for *negative predictive value*, the probability of not having a possible immunization-related adverse event when a designated code was not listed in the primary position.

The results (Figure 14) suggested that, when clinical data were used as the "gold standard", finding a designated code in the primary position was a highly specific "test" for possible immunization-related adverse events; designated codes did not appear in the primary position when the diagnosis of adverse event was unreasonable. The sensitivity of the "test", however, was somewhat lower; 11 per cent of clinically possible adverse events were misclassified as non-events. Consequently, while a positive "test" result (that is, finding a designated code in the primary position) predicted a possible adverse event 100 per cent of the time, a negative result was useful only 67 per cent of the time since one-third of negative "test" results were actually false negatives.

Incidence of Hospitalization With Immunization-Related Adverse Events

When clinical data were used as the "gold standard", the incidences of hospitalization with possible immunization-related adverse events were (calculated per 100,000 DTP/DT doses): with a febrile event in the two day post-immunization period, 5.1; with a screaming episode in the two day post-immunization period, 2.7; with a convulsion event in the seven day post-immunization period, 2.5.

Figure 1. The Manitoba Immunization Monitoring System.

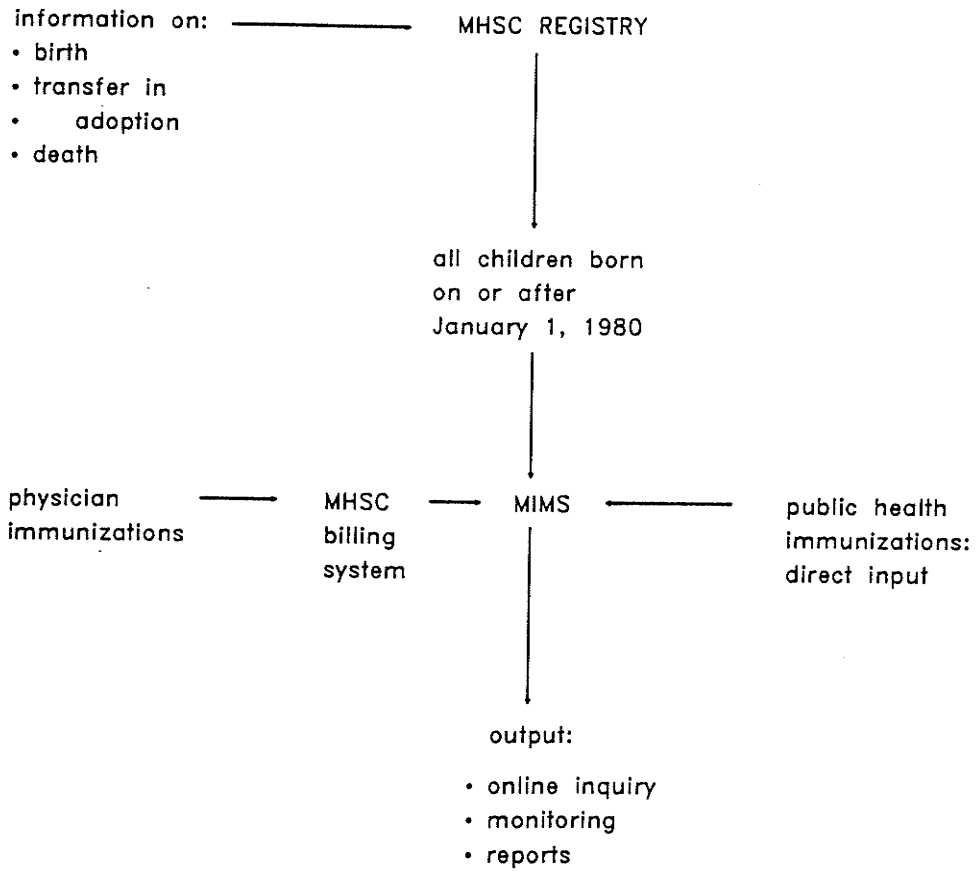


Figure 2. Combined 1987, 1988 and 1989 Study Cohorts: Immunization Status At the First Birthday.

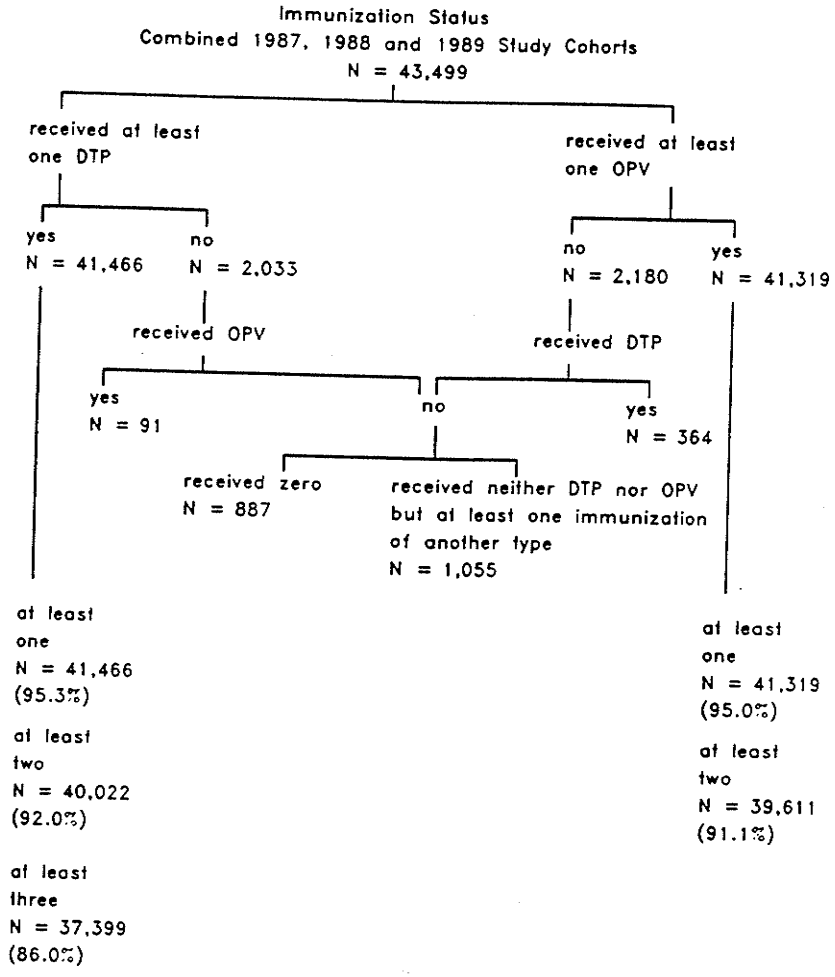


Figure 3. 1987 Study Cohort: Immunization Status At the First Birthday.

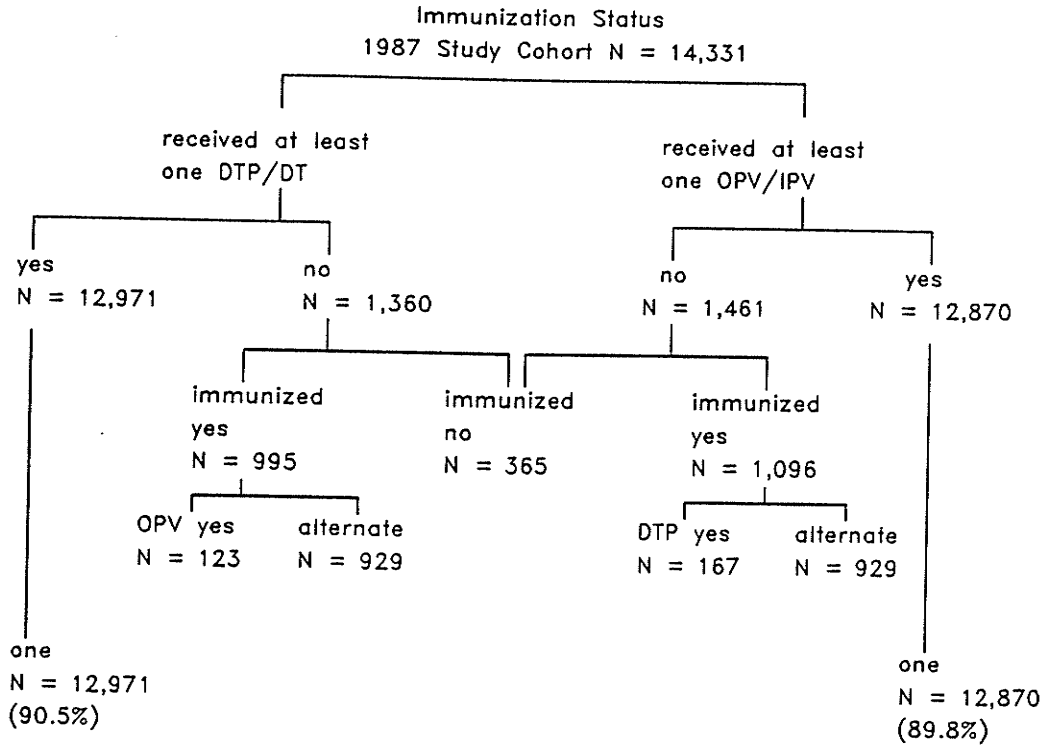


Figure 4. 1988 Study Cohort: Immunization Status At the First Birthday.

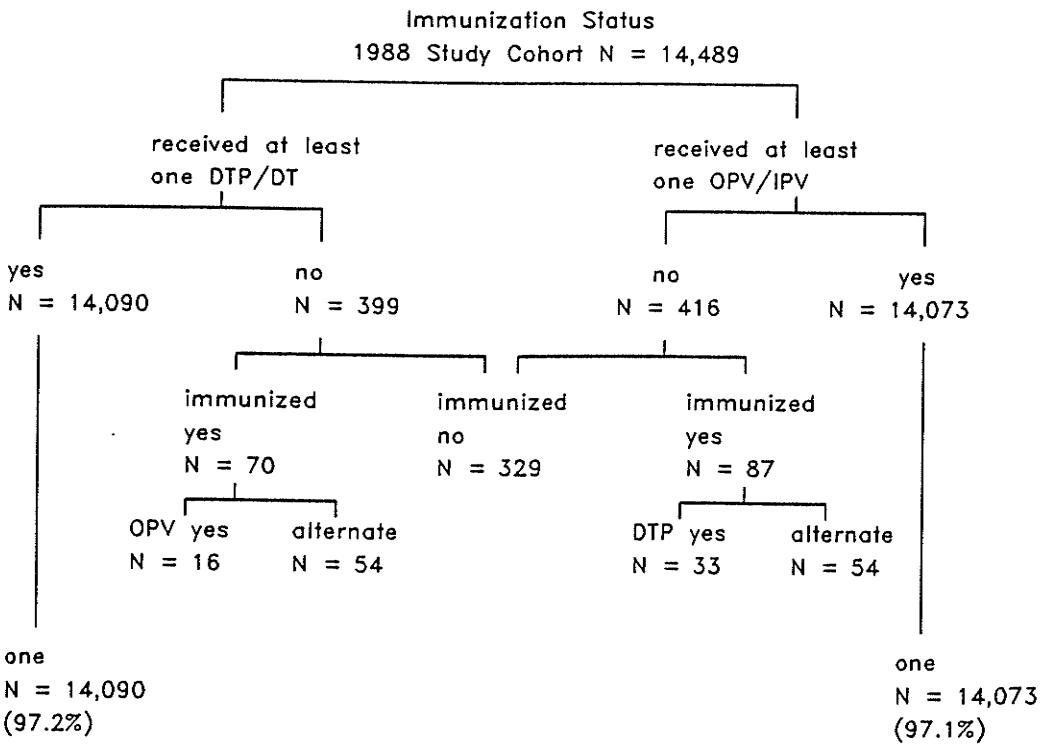


Figure 5. 1989 Study Cohort: Immunization Status At the First Birthday.

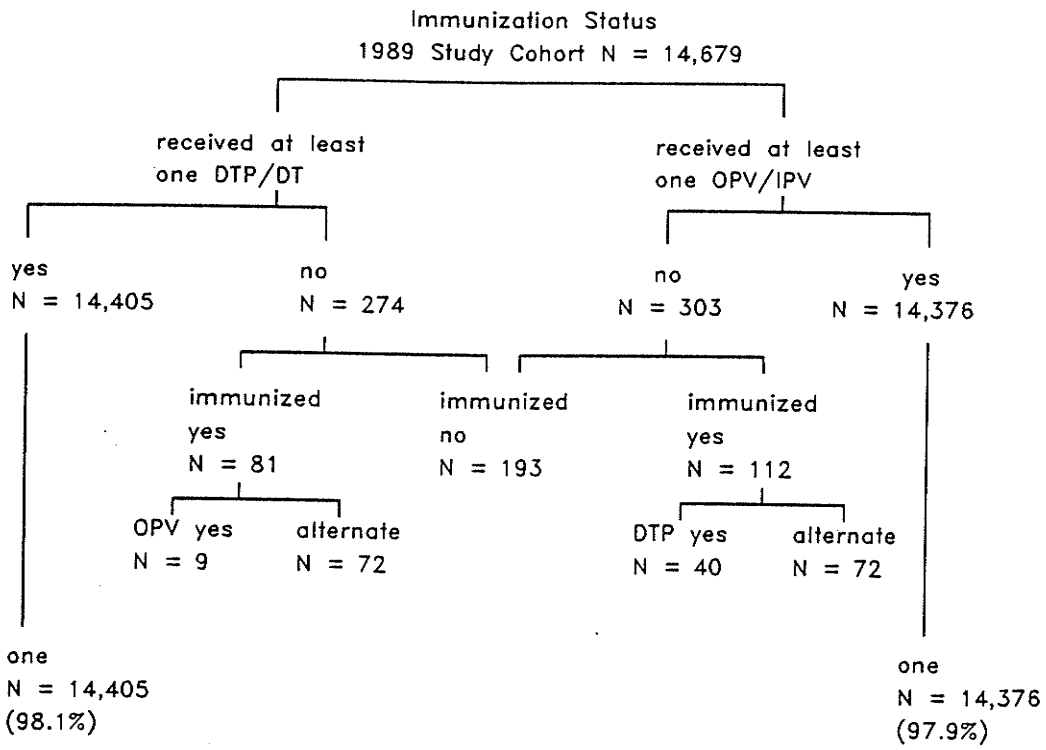


Figure 6. Combined 1987, 1988 and 1989 Study Cohorts: Age At DTP Immunization In the First Year of Life.

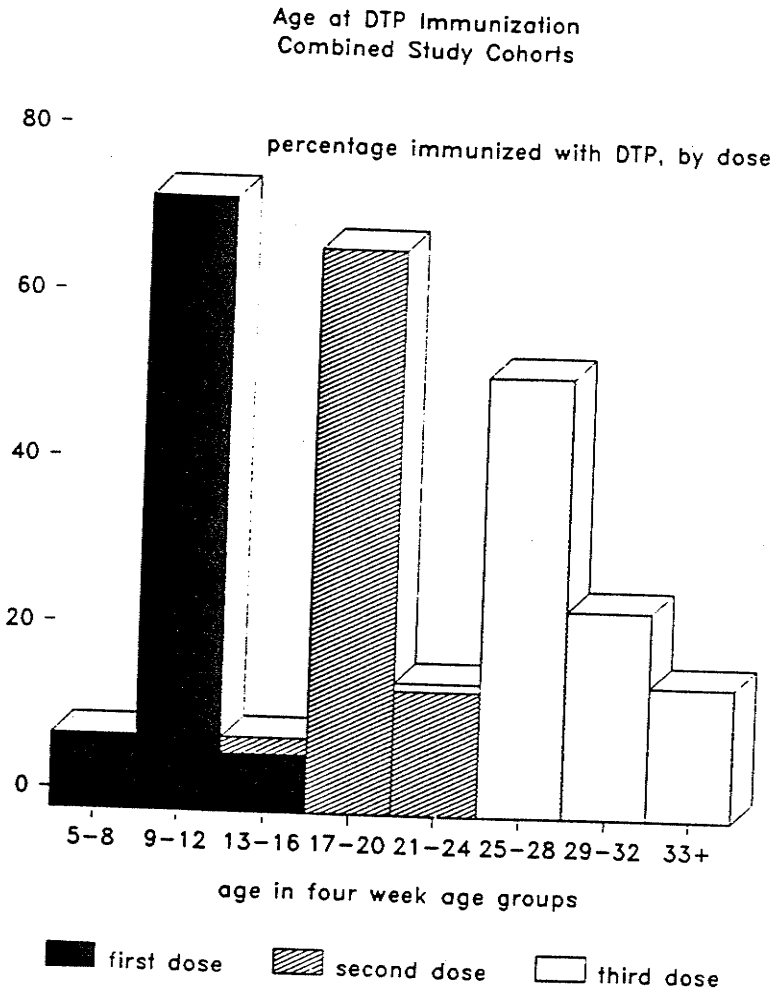
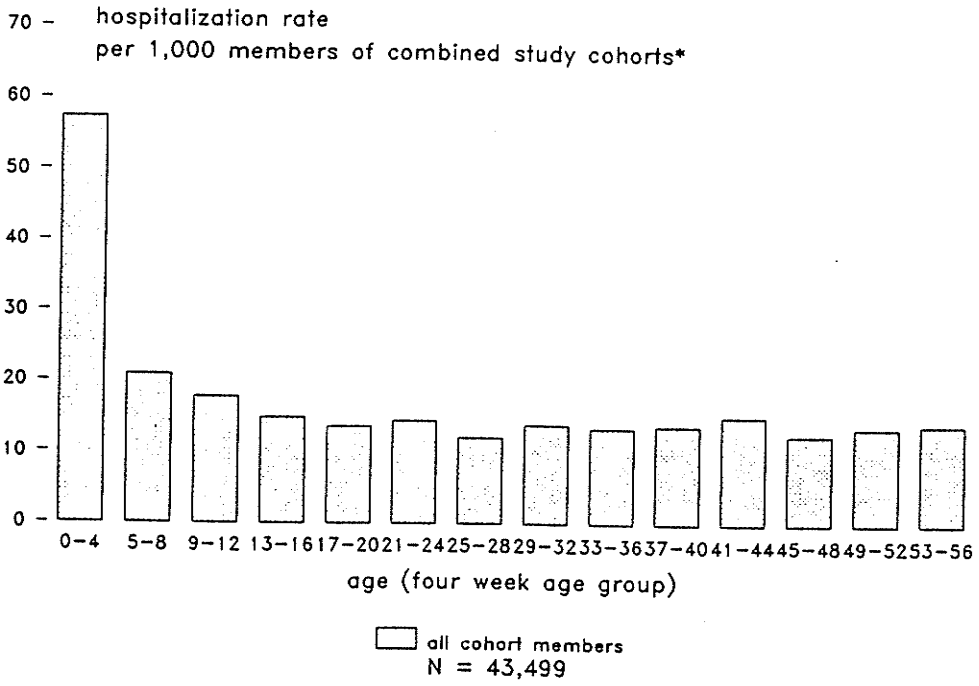
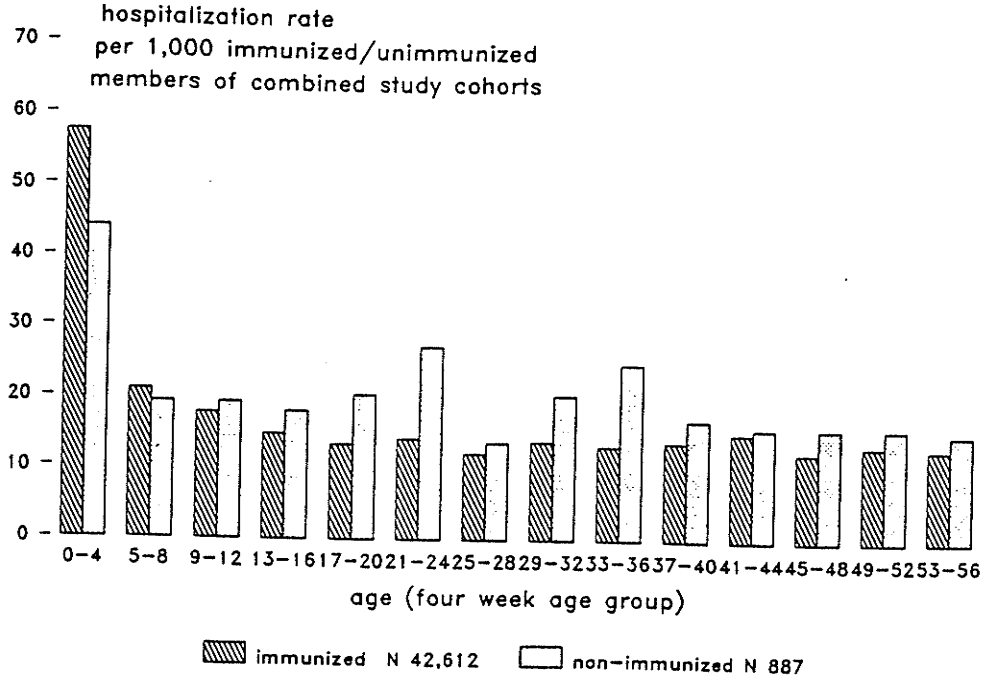


Figure 7. Combined 1987, 1988 and 1989 Study Cohorts: Hospitalization Rates By Age For the First 56 Weeks Of Life.



*birth hospitalizations excluded from 0–4 week category

Figure 8. Immunized and Unimmunized Members Of the Combined 1978, 1988 and 1989 Study Cohorts: Hospitalization Rates By Age For the First 56 Weeks Of Life.



*birth hospitalizations excluded from 0-4 week category

Figure 9. Members of the Combined 1987, 1988 and 1989 Study Cohorts Receiving At Least One Immunization In the First Year of Life: Proportion of Hospitalizations With Length of Stay Greater Than Six Days, By Age (Days) At Hospitalization.

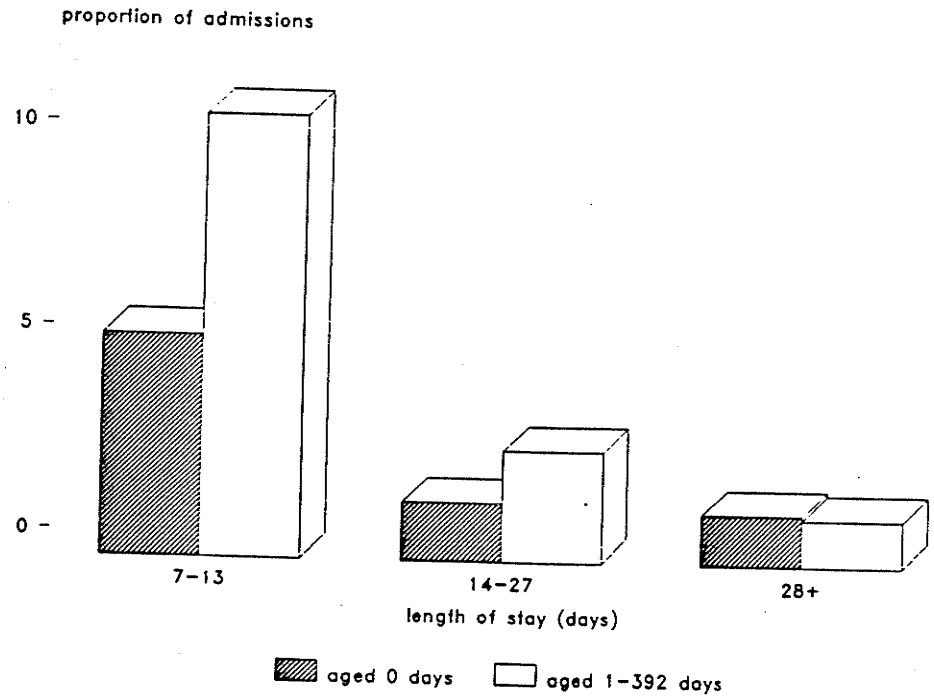


Figure 10. Members of the Combined 1987, 1988 and 1989 Study Cohorts Receiving At Least One Immunization In the First Year of Life: Hospitalization Rates By Age and By Principal Categories of Primary Diagnosis.

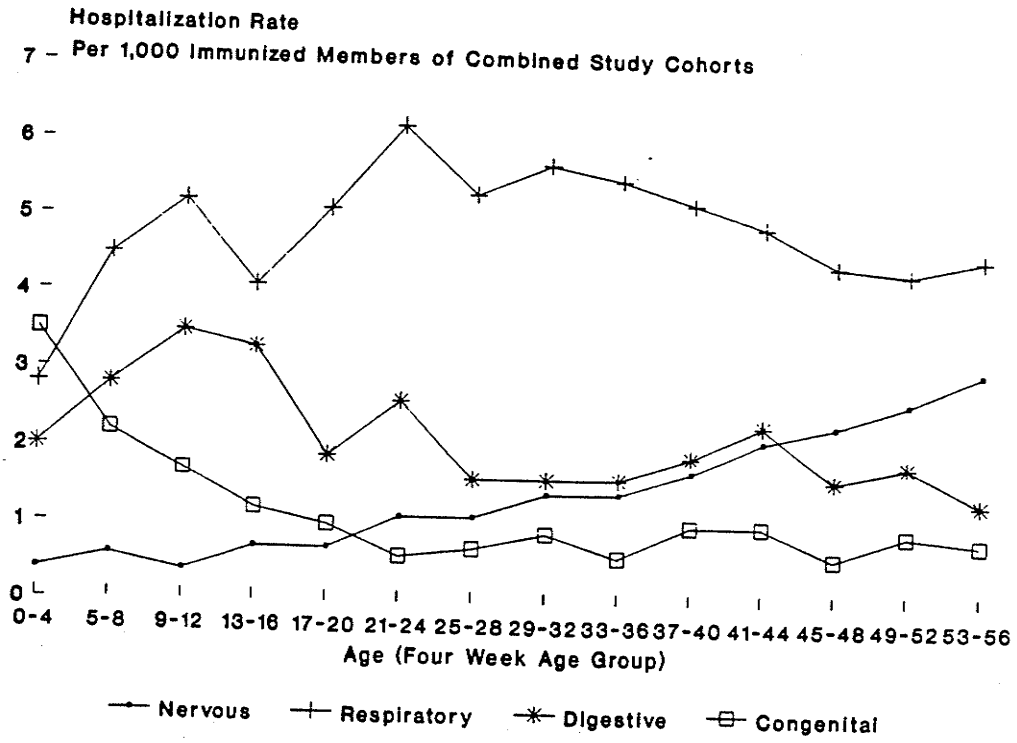


Figure 11. Members of the Combined 1987, 1988 and 1989 Study Cohorts Receiving At Least One Immunization In the First Year of Life: Rates of Hospitalization With Codes 780.3, 780.6 and 345.6 Among the Discharge Diagnoses Between Birth and 56 Weeks of Age, By Four Week Age Group.

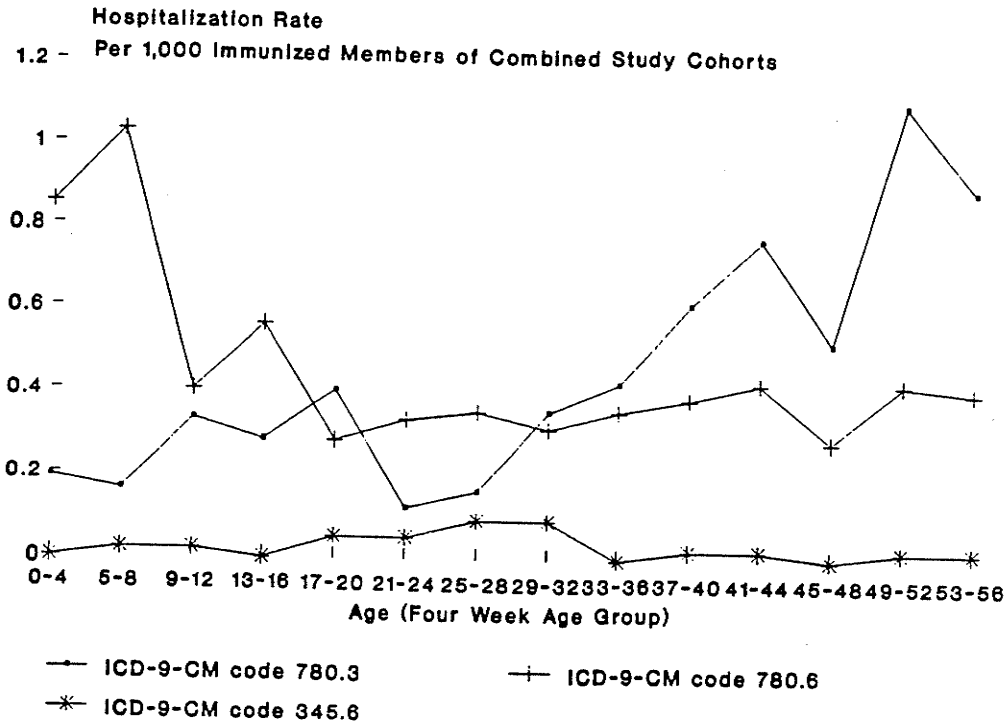


Figure 12. Members of the Combined 1987, 1988 and 1989 Study Cohorts Receiving No Immunizations In the First Year of Life: Proportion of Hospitalizations With Length of Stay Greater Than Six Days, By Age (Days) At Hospitalization.

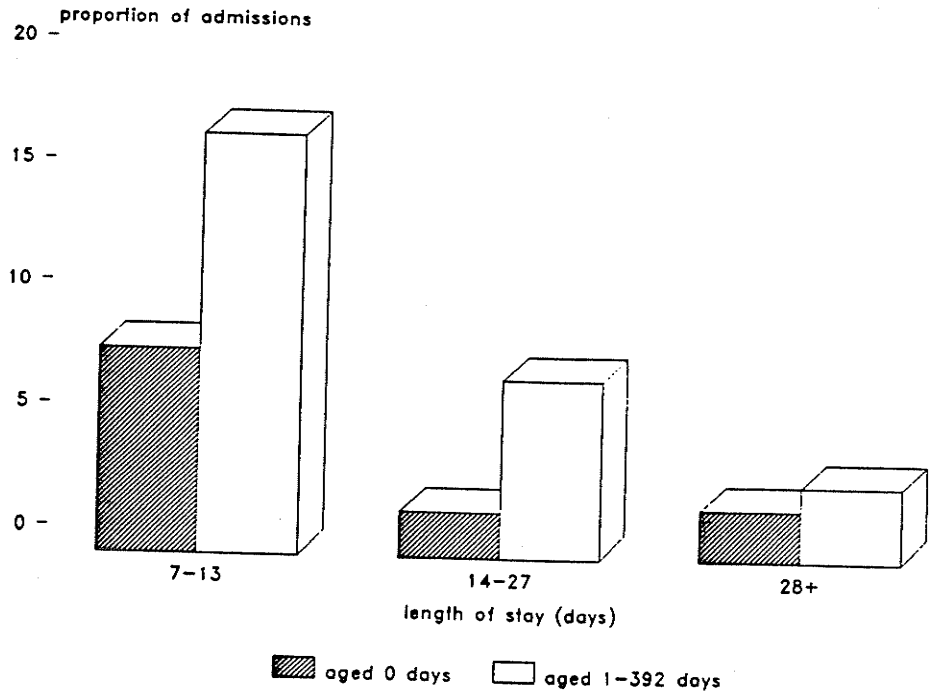


Figure 13. Members of the Combined 1987, 1988 and 1989 Study Cohorts Receiving No Immunizations In the First Year of Life: Hospitalization Rates By Age and By Principal Categories of Primary Diagnosis.

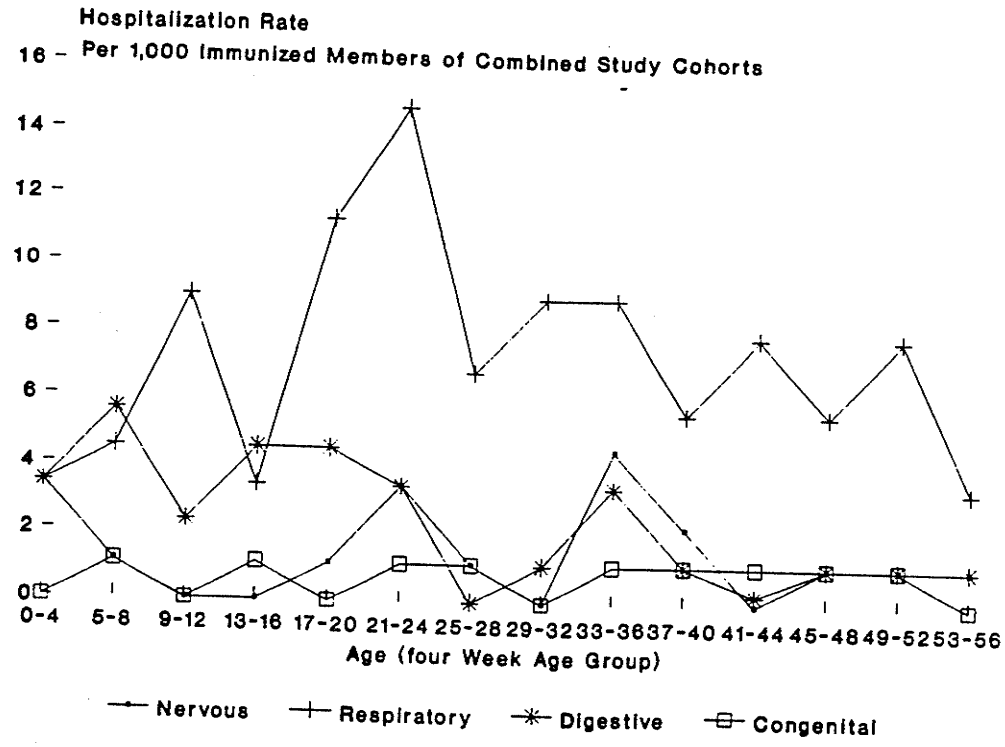


Figure 14. Sensitivity, Specificity and Predictive Values of the Process of Using Only Designated Codes Listed in the Primary Position To Identify Hospitalizations Associated With Possible Immunization-Related Adverse Events.

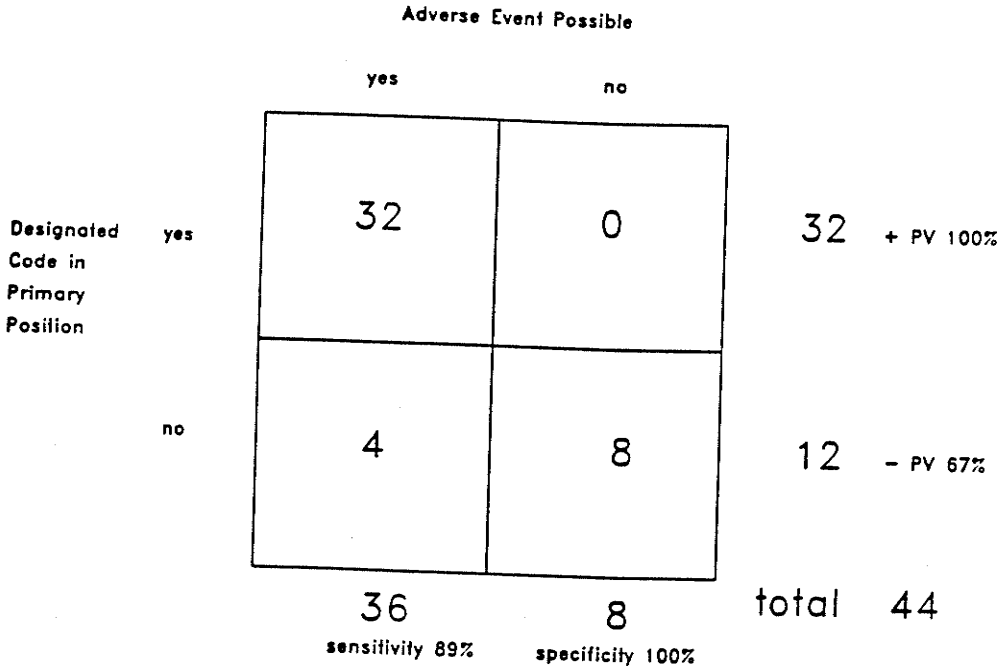


Table 1. Manitoba Recommended Routine Childhood Immunization Schedule 1986-1990 •

Age	Immunization Against			
2 months	diphtheria	pertussis	tetanus	poliomyelitis
4 months	diphtheria	pertussis	tetanus	poliomyelitis
6 months	diphtheria	pertussis	tetanus	poliomyelitis+
12 months	measles	mumps	rubella	
18 months	diphtheria	pertussis	tetanus	poliomyelitis
5 years	diphtheria	pertussis	tetanus	poliomyelitis
14-16 years	diphtheria++		tetanus++	poliomyelitis+

• MIMS accepts diphtheria-tetanus (DT) and diphtheria-pertussis-tetanus-polio (DPTP) as alternatives to DTP, and DPTP and inactivated poliovaccine (IPV) as alternatives to OPV.

+ Omitted if OPV is used exclusively.

++ Diphtheria and tetanus toxoid (Td) adsorbed.

Table 2. Ranges of Expected Incidence Rates of Adverse Events Following DTP/DT and OPV Vaccine Administration.

Expected Incidence Rates Of Adverse Events

Adverse Event	Expected Incidence Rates*	Time Period Of Interest Following Immunization
very high fever	>40°C: 15 per 1,000 doses[41,85] >40.5°: 3 per 1,000 doses[41,85]	48 hours
unusual high pitched crying or screaming	11 per 1,000 doses[41,85]	48 hours
excessive somnolence	no rate available	48 hours[2]
seizure	7 per 10,000 doses[2,86]	7 days
hypotonic/ hyporesponsive state	6 per 10,000 doses[41,85]	24 hours
anaphylaxis	1 per 50,000 doses to 5 per 1 million doses[2,46]	24 hours
vaccine-associated poliomyelitis	1 per 500,000 doses to 1 per 12 million doses[3,7]	7-30 days

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

Table 3. Combined 1987, 1988 and 1989 Study Cohorts: Immunization Rates By Vaccine and By Dose For the First Year of Life.

Immunization Rates

Study Cohort	Vaccine	Number of Doses	Proportion (per cent)
1987	DTP/DT	one	90.5
		two	84.4
		three	75.9
	OPV/IPV	one	89.8
		two	83.1
1988	DTP/DT	one	97.2
		two	95.2
		three	89.3
	OPV/IPV	one	97.1
		two	94.4
1989	DTP/DT	one	98.1
		two	96.3
		three	92.6
	OPV/IPV	one	97.9
		two	95.6
combined	DTP/DT	one	95.3
		two	92.0
		three	86.0
	OPV/IPV	one	95.0
		two	91.1

Table 4. 1989 Manitoba Birth Cohort: Recorded Rates Of Infancy Schedule Completion In the First Year Of Life By Indian Status, By Enrolment Status and By Place of Residence.

Children Born In 1989	Per Cent With Infancy Schedule Recorded As Complete			
	Outside Winnipeg (N)	Winnipeg		TOTAL
		Inner City (N)	Other Parts Of City (N)	
NON-INDIAN				
Continuous Enrolment From Birth To At Least First Birthday	90.3 (6,120)	87.3 (3,723)	93.6 (5,460)	90.8 (14,853)
Interrupted Enrolment In First Year Of Life	42.3 (442)	33.5 (340)	43.8 (377)	40.0 (1,159)
INDIAN				
Continuous Enrolment From Birth To At Least First Birthday	38.6 (1,519)	65.2 (368)	62.9 (70)	44.5 (1,957)
Interrupted Enrolment In First Year Of Life	12.8 (47)	30.0 (30)	50.0 (2)	20.3 (79)

Table 5. 1989 Manitoba Birth Cohort: Number of Doses of DTP/DT and Poliomyelitis Vaccine Recorded By the First Birthday.

Number of Doses Received	Proportion of Children Receiving DTP/DT Vaccine (Per Cent)	Proportion of Children Receiving Poliomyelitis Vaccine (Per Cent)
Non-Indian Children Born in 1989 With Continuous Health Plan Enrolment From Birth To At Least the First Birthday		
zero	1.9	2.2
at least 1	98.1	97.8
at least 2	96.1	95.4
at least 3	91.0	—
All Children Born in 1989 and Enrolled During the First Year of Life		
zero	5.9	6.6
at least 1	94.1	93.4
at least 2	89.6	88.3
at least 3	82.5	—

Table 6. Members Of the Combined 1987, 1988 and 1989 Study Cohorts Receiving At Least One Immunization In the First Year Of Life: Distribution Of Primary Discharge Diagnoses.

ICD-9-CM Category Of Diseases	N (%) All Admissions	N (%) 0-4 Week Admissions	N (%) 5-56 Week Admissions
8. Respiratory	2859 (27.5)	118 (4.9)	2741 (34.2)
9. Digestive	1279 (12.3)	86 (3.6)	1193 (14.9)
15. Perinatal	946 (9.1)	823 (34.3)	123 (1.5)
16. Ill-Defined	848 (8.1)	102 (4.3)	746 (9.3)
6. Nervous	824 (7.9)	17 (0.7)	807 (10.1)
14. Congenital	714 (6.9)	154 (6.4)	560 (7.0)
1. Infectious	531 (5.1)	42 (1.8)	489 (6.1)
10. Genitourinary	351 (3.4)	48 (2.0)	303 (3.8)
17. Injury	291 (2.8)	21 (0.9)	270 (3.4)
12. Skin	168 (1.6)	17 (0.7)	151 (1.9)
2. Neoplasms	80 (0.8)	4 (0.2)	76 (0.9)
4. Blood	42 (0.4)	0 (0)	42 (0.5)
3. Endocrine	43 (0.4)	12 (0.5)	31 (0.4)
7. Circulatory	20 (0.2)	6 (0.3)	14 (0.2)
13. Musc/skeletal	22 (0.2)	1 (0.04)	21 (0.3)
Factors Not Causing Current Illness (V Codes)	1397 (13.4)	947 (39.5)	450 (5.6)
TOTAL	10415 (100)	2398 (100)	8017 (100)

Table 7. Members Of the Combined 1987, 1988 and 1989 Study Cohorts Receiving At Least One Immunization In the First Year Of Life: Frequencies Of Designated Codes Among All Diagnostic Discharge Codes For Hospitalizations Between Birth and 56 Weeks Of Age.

Designated ICD-9-CM Code	Code Frequency	Designated ICD-9-CM Code	Code Frequency
047.8	1	348.3	1
047.9	18	348.5	1
048	3	348.8	16
049.9	4	349.8	4
320.0	19	349.9	1
320.1	1	351.0	2
320.2	6	352.6	6
320.3	2	354.8	1
320.7	1	682.3	2
320.8	5	682.6	7
320.9	1	682.9	1
322.9	19	780	4
323.9	1	780.0	3
331.9	4	780.2	1
342.9	1	780.3	269
343.0	1	780.6	273
344.6	10	781.0	18
344.8	2	781.3	13
345.0	3	781.4	2
345.1	10	785.5	9
345.3	6	978.6	1
345.4	2	995.1	3
345.5	8	995.2	2
345.6	19	995.3	1
345.7	1	999.3	5
345.9	14	999.5	5
348.0	27	999.9	23
348.1	5	E948	1
348.2	3	E949	1

TOTAL NUMBER OF CODES	101,493
TOTAL NUMBER OF DESIGNATED CODES	710
TOTAL NUMBER OF NON-DESIGNATED CODES	100,783

Table 8. 1987, 1988 and 1989 Study Cohorts. Hospitalization Regardless of Reason: DTP/DT Immunization In the First Year of Life.

Immunization Sequence	Time Period	Adjusted Number of Admissions in Time Interval*	Number of Children Eligible
first	before	607	41,466
	after	529	
second	before	457	40,022
	after	397	
third	before	331	37,399
	after	382	
TOTAL	before	1,395	
	after	1,308	

* "Before" interval includes admissions which occurred in the 28 day period before the day of immunization; "after" interval includes admissions which occurred both on the day of, and in the 28 day period after, the day of immunization

Table 9. 1987, 1988 and 1989 Study Cohorts.

Hospitalization With Designated Diagnoses: DTP/DT

Immunization In the First Year Of Life.

Immunization Sequence	Time Period*	Time Interval (Days)	Adjusted Number Of Occurrences	ICD-9-CM Code**
first	before	0-28	4	047.9
			2	048
			1	049.9
			1	320.3
			1	348.3
			1	348.8
	after	0-28	3	047.9
			1	320.0
			1	323.9
			1	345.1
			1	345.6
		0-7	2	780.3
		0-2	2	780.6
second	before	0-28	2	047.9
			1	320.0
			1	323.9
			1	345.3
			2	345.9
			1	352
	after	0-28	1	320.0
			1	331.9
			1	345.5
			3	345.6+a
			1	345.7
			1	348.8
			1	352.6
			1	978.6
			2	999.5
			1	E948.6
		0-7	5	780.3+b
			1	322.9
		0-2	2	780.6
			1	995.2
			1	999.3
			3	999.9

...Continued Page 105b

Table 9 Continued.

Immunization Sequence	Time Period*	Time Interval (Days)	Adjusted Number Of Occurrences	ICD-9-CM Code**
third	before	0-28	1	047.8
			1	047.9
			1	320.0
		0-7	1	780.3
	after	0-28	2	320.0
			1	322.9
			1	345.6
			1	351.0
			2	999.5
		0-7	4	780.3+c
		0-2	3	780.6
			3	999.9
TOTAL	before	0-28	1	047.8
			7	047.9
			2	048
			1	049.9
			2	320.0
			1	320.3
			1	323.9
			1	345.3
			2	345.9
			1	348.3
			1	348.8
			1	352
		0-7	1	780.3
	after	0-28	3	047.9
			4	320.0
			1	322.9
			1	331.9
			1	345.1
			1	345.5
			5	345.6+d
			1	345.7
			1	348.8
			1	351.0
			1	352.6
			1	978.6
			4	999.5+e
			1	E948.6
		0-7	11	780.3+f
			1	322.9
		0-2	7	780.6+g
			1	995.2
			1	999.3
			6	999.9+h

...Continued Page 105c

Table 9 Continued.

* "Before" category includes hospitalizations which occurred in the time period of interest before the day of immunization; "after" category includes hospitalizations which occurred both on the day of and in the time period of interest after the day of immunization.
** For code definitions, see Appendix 7.
+ Statistically significant, McNemar's Paired Test, with 1 df, one-tailed test.
a Chi-square 3.0, $p<0.05$
b Chi-square 5.0, $p<0.025$
c Chi-square 3.0, $p<0.05$
d Chi-square 5.0, $p<0.025$
e Chi-square 4.0, $p<0.025$
f Chi-square 9.0, $p<0.001$
g Chi-square 7.0. $p<0.005$
h Chi-square 4.0, $p<0.01$

Table 10. 1987, 1988 and 1989 Study Cohorts: Children With Incomplete Immunizations. Hospitalization Regardless of Reason: DTP/DT Immunization In the First Year of Life.

Immunization & Sequence	Time Period	Adjusted Number of Admissions in Time Interval*	Number of Children Eligible
first DTP/DT	before	31	1,444
	after	24	
second DTP/DT	before	47	2,623
	after	50	

* "Before" interval includes admissions which occurred in the 28 day period before the day of immunization; "after" interval includes admissions which occurred both on the day of, and in the 28 day period after, the day of immunization

Table 11. Members Of the Combined 1987, 1988 and 1989 Study Cohorts Receiving No Immunizations In the First Year Of Life: Distribution Of Primary Discharge Diagnoses.

ICD-9-CM Category Of Diseases	N (%) All Admissions	N (%) 0-4 Week Admissions	N (%) 5-56 Week Admissions
8. Respiratory	89 (36.3)	3 (9.7)	86 (40.2)
9. Digestive	29 (11.8)	3 (9.7)	26 (12.2)
15. Perinatal	24 (9.8)	20 (64.5)	4 (1.9)
16. Ill-Defined	12 (4.9)	3 (9.7)	9 (4.2)
6. Nervous	17 (6.9)	2 (6.5)	15 (7.0)
14. Congenital	12 (4.9)	0 (0)	12 (5.6)
1. Infectious	16 (6.5)	1 (3.2)	15 (7.0)
10. Genitourinary	4 (1.6)	0 (0)	4 (1.9)
17. Injury	7 (2.9)	1 (3.2)	6 (2.8)
12. Skin	11 (4.5)	0 (0)	11 (5.1)
2. Neoplasms	2 (0.8)	4 (0)	2 (0.9)
4. Blood	0 (0)	0 (0)	0 (0)
3. Endocrine	10 (4.1)	0 (0)	10 (4.7)
7. Circulatory	2 (0.8)	0 (0)	2 (0.9)
13. Musc/skeletal	1 (0.4)	0 (0)	1 (0.5)
Factors Not Causing Current Illness (V Codes)	3 (1.2)	0 (0)	3 (1.4)
TOTAL	245 (100)	31 (100)	214 (100)

Table 12. Members Of the Combined 1987, 1988 and 1989 Study Cohorts Receiving No Immunizations In the First Year Of Life: Frequencies Of Designated Codes Among All Diagnostic Discharge Codes For Hospitalizations Between Birth and 56 Weeks Of Age.

Designated ICD-9-CM Code	Code Frequency	Designated ICD-9-CM Code	Code Frequency
320.0	1	345.5	1
320.1	1	345.9	5
320.3	1	348.0	1
322.2	1	348.1	1
322.9	2	348.8	2
336.9	1	780.3	14
342.9	1	780.6	6
345.1	1	995.2	1
345.3	2	999.9	2

TOTAL NUMBER OF CODES	2,811
TOTAL NUMBER OF DESIGNATED CODES	44
TOTAL NUMBER OF NON-DESIGNATED CODES	2,767

Table 13. Hospitalization File Analysis. Distribution Of Designated Diagnoses Among Hospitalizations Following DTP/DT Immunization, By Time Period; Distribution and Description Of Accompanying Non-Designated Codes.

Time Period Following Immunization (Days)	Designated Codes Appearing	Non-Designated Codes Appearing	Description Of Non-Designated Codes
0	780.6*	691.0	diaper rash
	780.6	465.9* 382.9	acute URTI otitis media
	780.3	382.9	otitis media
	978.6* E948.6 999.9 780.6		
	999.5*		
	999.5*	E879.8	blood transfn
	999.9*		
	320.0*	285.9	anemia unspec
0-1	999.5*	E879.8	blood tranfn
	780.6*		
	780.3*		
	780.6* 999.5		
	780.3	519.8*	respiratory disease
	780.6* 999.5		

...Continued Page 109b

Table 13 Continued.

Time Period Following Immunization (Days)	Designated Codes Appearing	Non-Designated Codes Appearing	Description Of Non-Designated Codes
0-2	780.3*	599.0	urinary infn
	345.5* 345.7 999.3	251.0 945.32 958.3 682.7 E874.1 008.6 465.9	hypoglycemic coma skin loss wound infn cellulitis foot infusion viral enteritis acute URTI
0-7	780.3	345.9* 518.81 507.0 382.404 518.0 530.1 783.4 599.0 599.7 596.8 465.9 718.31 779.8 V017 280.9 754.89	unspecified nervous system disorder resp failure aspiration otitis media pulmonary collapse esophagitis fail to thriv urinary infn hematuria bladder disorder acute URTI joint dislocn perinatal conditions viral dis anemia congenital anomaly
	780.3*		

* primary diagnosis

Table 14. Hospitalization File Analysis. Distribution of Designated Diagnostic Codes Among Hospitalizations Following OPV Immunization, By Time Period; Distribution and Description of Accompanying Non-Designated Codes.

Time Period Following Immunization (Days)	Designated Codes Appearing	Non-Designated Codes Appearing	Description of Non-Designated Codes
0	995.2* E949.9		
0-28	781.3	782.4*	jaundice pneumonia
	781.0*	754.51	deformity feet
	344.61	997.5* 741.03	urinary complicns spina bifida, lumbar, + hydroceph.

* Primary code

Table 15. Hospital-Held Record Review. Hospitalizations Following Immunization: Diagnostic Discharge Codes and Physician Diagnoses, By Time Period, For Children With Physician Diagnoses Indicative Of Possible Immunization-Related Adverse Events.

Time Interval Following Immunizn (Days)	Diagnostic Discharge Codes 1-4 1 2 3 4	Physician Diagnoses
0	780.6 691.0	hyperthermic reaction to DTP immn.
	999.5	allergic reaction to vaccine
	999.5 E879.8	fever after immunizn.
	978.6 E948.6 999.9 780.6	pyrexial reaction to DTP
	995.2 E949.9	post-immn. episode, not likely toxic or seizure
0-2	780.6 999.9	hyperpyrexia secondary to DTP
	780.6	fever and irritability possibly secondary to DTP shot
	780.6 999.5	febrile reaction to DTP

...Continued Page 111b

Table 15 Continued.

Time Interval Following Immunizn (Days)	Diagnostic Discharge Codes 1-4 1 2 3 4	Physician Diagnoses
0-7	999.9	reaction to 2nd immn., most likely due to pertussis component of vaccine
	999.5 E879.8	post-immn. fever
	999.9 999.9 780.3 754.1	possible adverse reaction to DTP/OPV
	780.3 994.7 E913	seizures, unknown etiology - possibly suffocation less likely aspiration, even less likely reaction to DTP
	780.3	possible seizure disorder; similar episode day after prior DTP/OPV imm

Table 16. Hospital-Held Record Review. Description of Hospitalizations For Which the Designated Diagnostic Discharge Codes Detected Were Listed In a Subsidiary Position.

Designated Code	Clinical Data	Adverse Event Reasonable	Time Period Following Immunizn. (Days)
344.61	Spina bifida with myelomeningocele	no	18
781.3	Hypotonia noted shortly after birth	no	28
047.9	Bacterial meningitis due to E. coli infection (laboratory confirmed)	no	13
352.6	Congenital syndrome including cranial nerve palsies	no	20
351.0	Multiple congenital anomalies involving central nervous system	no	28
780.3	Myeloradiculopathy; hypotonia noted one month after birth	no	7
780.3	Zelwieger's syndrome	no	7
331.9	Hydrocephalus & cerebral atrophy	no	28
780.3	Apneic spells, at-risk for SIDS	yes	1
780.3	URTI & otitis media	yes	0
780.3	Otitis media	yes	0
780.6	Apneic spell probably due to otitis media causing fever & febrile convn.	yes	7

7. DISCUSSION

No vaccine has inspired the controversy generated by whole-cell pertussis vaccine. Its safety has been at issue through the many years since the first reports associated its use with permanent brain damage.[27,84]

However, although the potential of pertussis vaccine to cause serious neurological illness remains controversial, concern over its use has abated in recent years. Meticulous re-examination of the data from the National Childhood Encephalopathy Study and other investigations has concluded that a causal association between the administration of DTP vaccine and permanent neurological damage has not been demonstrated, although it cannot be dismissed. Pertussis vaccine either is not associated with an increased risk of permanent brain damage or the magnitude of the risk is so small as to be virtually unmeasurable.[53,57] To accurately quantify pertussis vaccine-related risk may require investigations of such magnitude that the public expense may well outweigh the public health benefit, given that the events are rare and that the terms "acellular" and "safer" may prove synonymous.[59]

But how certain are we about the risks of poliovaccine? What about newly-released vaccines, such as Hib and acellular pertussis? Even after years of traditional study, there is little convincing evidence

that any of the temporal associations noted between the routinely-used vaccines and serious adverse events are actually real. We have no accurate risk measurements for the common vaccines nor do we know the "baseline" incidences of the relevant adverse events in the childhood population. We need an effective and efficient method of evaluating and monitoring marketed vaccines for the occurrence of very rare but devastating adverse events.

This study was designed to assess the use of the population-based Manitoba Health database in addressing the crucial shortcomings in vaccine-related adverse events research. The database structure facilitated the design of a retrospective cohort study: it allowed the assembly of consecutive birth cohorts of children, the definition of study populations at risk for immunization-related adverse events, the accurate determination of the period of observation, and the ascertainment of all immunization and adverse events.

The study achieved its first objectives by demonstrating that data from computerized registries of health care contacts can be used in Manitoba to develop population profiles of immunization and hospitalization, and to calculate population-based rates of immunization (vaccine-specific), of hospitalization (diagnosis-specific) and of the occurrence of adverse events of

sufficient severity to warrant hospitalization in the first year of life.

The inclusion of the unique identifier on all records in each database file allowed the linking of records between files and the simultaneous examination of immunization and hospitalization events, independently ascertained, despite their being separated by time and place. Hospitalizations with diagnoses indicative of immunization-related adverse events were identified by ICD-9-CM codes and the timing of their occurrence around immunization determined. The use of these techniques achieved the final study objective, the assessment the nature of the temporal associations between immunization and adverse events; incidence rates were calculated for those events showing a true temporal association with immunization.

The Manitoba Immunization Profile

First-year immunization rates were high for most members of the 1987, 1988 and 1989 Manitoba birth cohorts; that is for children, with the exception of status Indians, whose Manitoba Health enrolment was continuous from birth to at least one year of age. Of the combined cohorts, 95 per cent were on record as receiving at least one dose of DTP/DT, 92 per cent at least two, and 86 per cent at least three. For the 1988

and 1989 cohorts, these rates averaged respectively 98 per cent, 96 per cent and 91 per cent. Rates for the 1987 cohort reflected missing immunization data, at 91 per cent, 84 per cent and 76 per cent respectively. DTP/DT immunization rates were closely approximated by those for poliovaccine, which was almost always given on the same day.

Recommended ages for immunization appeared to be quite closely followed, with the majority of each of the doses given in the four week period immediately following the recommended age. However, age at immunization exceeded the recommended age more frequently with successive doses.

Compliance with the recommended provincial immunization schedule was also high. Levels recorded for the 1988 and 1989 cohorts showed that, on average, 90 per cent were completely immunized, according to the schedule, by the first birthday; compliance recorded for the 1987 cohort was 76 per cent.

With respect to immunization practices, the analysis showed that DT and IPV were rarely used as alternatives to DTP and OPV vaccines and that almost half of the study children received three doses of poliovaccine, although the third dose is no longer recommended.

The immunization profile, by subgroup, for the total 1989 Manitoba birth cohort demonstrated that for the

majority (those resident in the province for the full first year of life) compliance with the recommended schedule was 91 per cent. This rate was consistent across all parts of the province, with only minor differences detected by geographic location. On the other hand, compliance levels for groups whose members had Indian status, died in the first year of life, or moved into or from Manitoba during that period ranged from only 13-42 per cent; for these groups, incomplete immunization records were of course expected. Residence in the core area of Winnipeg was associated with lower levels of schedule completion than residence in outer Winnipeg or rural areas, reflecting the core area's relatively high proportions of migrant residents and of those with Indian status. Record completion in children with Indian status was markedly lower for rural than for urban residents, reflecting the earlier and more complete participation in MIMS of Medical Services Branch's South Zone Office (located in Winnipeg and serving accessible reserves) than of the North Zone Office (located in Thompson and serving remote reserves).

The Manitoba Hospitalization Profile

Hospitalization rates calculated for the study cohorts in first 56 weeks of life showed that the highest rate occurred in the newborn period, averaging 57 per

1,000 cohort members after the exclusion of birth hospitalizations. The rate fell sharply after four weeks of age, and, at any time thereafter, the chance of being hospitalized remained fairly constant (at or below 20 per 1,000 cohort members).

When hospitalizations were categorized by discharge diagnoses, the majority occurring in the neonatal period were related to specific perinatal conditions, whereas the principal group of diseases leading to hospitalization between five and 56 weeks of age were respiratory in nature.

Leading causes and rates of hospitalization were used to compare children receiving at least one immunization in the first year of life with those receiving none in that period, and detected no measurable differences between the two groups.

Characterization of hospitalizations by length of stay showed that, for both groups, children readmitted to hospital after birth were more likely to have relatively long hospital stays (of 7-28 days duration) than those experiencing only birth hospitalizations. Completely unimmunized children, however, were clearly more prone to protracted hospital stays and, in particular, to very long stays (in excess of 28 days). The most likely explanation of this observation is that, due either to the nature or the severity of illness among children with

prolonged hospital stay, immunizations were withheld. Although unimmunized children did not exhibit the steady increase in rates of hospitalizations primarily due to diseases of the nervous system that was seen among immunized children, their hospitalization rates with other leading causes of admission (respiratory and digestive disease) were higher. It may also be that, among immunized children, health crises are prevented to some extent through contact with the health care system at immunization. Further characterization of immunized and completely unimmunized children is indicated since the possibility of a systematic difference between the groups cannot be excluded.

Population-based incidence rates were calculated for adverse events temporally-related to immunization with DTP/DT and OPV vaccines and serious enough to lead to hospitalization in the first 56 weeks of life. Of such events, the most frequent were non-epileptic convulsions (code 780.3) and pyrexia of unknown origin (code 780.6), which occurred for 31 and 29 respectively of every 1,000 hospitalizations in the time period. Although it was impossible to discriminate statistically between children receiving at least one immunization and those receiving none, the higher incidences of both events among the latter again suggested that the groups may systematically differ. Regardless of immunization status, the incidence

of hospitalization with non-epileptic convulsions rose, between the ages of 5-8 weeks, to an actual rate of just over 1.0 per 1,000 members of the combined study cohorts; the rate fell to a low of 0.1 per 1,000 such members between 21-24 weeks of age then rose again, reaching a peak incidence of 1.2 per 1,000 members between 49-52 weeks of age. Regardless of immunization status, the incidence of pyrexia of unknown origin, at its lowest between 5-8 weeks of age at just under 0.2 per 1,000 members of the combined study cohorts, remained fairly steady (at around or below 0.4 per 1,000 such members) through the remaining first 56 weeks of life.

For Manitoba children in the first year of life, the hospitalization profile provided new information concerning hospitalization rates, length of stay and hospitalization by diagnosis and illustrated the potential of using the database to examine pediatric hospital utilization and to monitor trends in utilization and illness rates. The information produced allowed the characterization and comparison of groups of children with different immunization experiences. The analysis yielded population-based incidence rates for serious adverse events which have been temporally associated with routine childhood immunization.

The Nature of Temporal Associations Between Immunization and Hospitalization

Assessment of the nature of the temporal association between routine DTP/DT/polio immunization and hospitalization yielded results of both statistical and clinical significance.

There was no increase in overall hospitalization rates following routine first-year immunization. This finding did not appear to be influenced by the overall trend in hospitalization rates, which remained steady as the cohort aged from five to 56 weeks. Hospitalization rates by dose, however, included children over a range of ages while rates calculated by age included children over a range of doses. Possible influences on overall hospitalization rates of age and the dose sequence or the cumulative number of doses were not captured. Definitive conclusions will require a larger study with the power to detect smaller rate increases and to permit rate analyses by age and by dose.

Statistically significant increases occurred in hospitalizations with ICD-9-CM codes 780.3 (non-epileptic convulsions) and 345.6 (infantile spasms) in, respectively, the seven and 28 days following the second DTP, and with code 780.3 in the seven days following the third DTP. When all doses were considered together, the increased occurrences of five codes in the relevant time

periods following DTP immunization were also statistically significant: 780.3, 345.6, 780.6 (pyrexia of unknown origin), 999.5 (other serum reaction) and 999.9 (other and unspecified complications of medical care, not elsewhere classified). Overall, the incidences of hospitalization per 100,000 doses of DTP were: with code 345.6 in the 28 day post-immunization period, 4.2; with code 999.5 in the 28 day post-immunization period, 3.4; with code 780.3, in the seven day post-immunization period, 9.2; with code 780.6, in the two day post-immunization period, 5.9; with code 999.9, in the two day post-immunization period, 2.5.

The 53 ICD-9-CM codes which appeared in the relevant post-immunization time periods were validated by individual review of hospital-held records. Codes 780.3, 345.6 and 780.6 accurately described the clinical conditions present; codes 999.5 and 999.9 represented diagnoses of possible immunization-related adverse events. Among the 48 post-immunization hospitalizations recording designated codes were 13 which recorded physician diagnoses of possible DTP/DT-related adverse events; these 13 possible events likely represented the maximum number captured by the passive reporting system. Overall, when physician diagnoses were used as the "gold standard", the incidences of hospitalization with immunization-related adverse events were (calculated per

100,000 DTP/DT doses): with a febrile event in the two day post-immunization period, 5.1; with a screaming episode in the two day post-immunization period, 2.7; with a convulsion event in the seven day post-immunization period, 2.5.

The comparison between rates of events before and after immunization is a valid approach when there are very few unimmunized individuals in the population.[60] Levels of immunization coverage in the study population were high; codes indicative of adverse events were not concentrated among children with less than the full series of immunizations. The methodology does provide for the eventual comparison of incidence rates of events between immunized and unimmunized individuals once cohorts of sufficient size have been assembled.

The effect of missing data was considered. Manitoba hospitalization data are of generally high quality,[68,78-80] and unlikely to have been missing to an extent which invalidated the findings. Although immunization information for the 1987 birth cohort was incomplete, preliminary data analysis found no evidence that members missing immunization data represented a select group in which factors associated with avoidance or delay of immunization may have been associated, producing an increased risk of adverse-event-type medical outcomes. There were no appreciable post-immunization rate

differences, either in overall hospitalization or in hospitalization with designated diagnoses, between the three study cohorts. The rate of immunization data loss to MIMS through physician failure to bill appears not to exceed seven per cent, while the high immunization rates recorded for the 1988 and 1989 study cohorts suggested little immunization data loss. Overall, given the very low numbers of adverse events detected in temporal association with immunization, the impact of missing data on the study findings was deemed minimal.

Although temperature elevations greater than 39°C have been reported in 3-8 per cent of DTP recipients[2,43,46,85] and persistent crying or screaming in 0.1-3 per cent,[2,85] there were no reports of post-DTP hospitalization rates with febrile or screaming episodes in the medical literature. However, the study's hospitalization rates calculated for the seven day period following overall DTP immunization with the convulsion code and with physician diagnosis of possible immunization-related convulsion event were lower than post-immunization rates previously reported.[45,46,85,86]

Hospitalization rates with convulsions may have been artificially low, reflecting the effect of random error. The considerable and unpredictable influence of random variation on rates calculated from very small numbers of adverse events is illustrated by comparing the rates of

hospitalization with the convulsion code 780.3 produced by the preliminary and present studies. The former detected seven post-DTP hospitalizations with code 780.3 and used a denominator of 40,825 DTP doses to calculate a rate of 17.2 such hospitalizations per 100,000 DTP doses in the seven days following immunization. The present study might have been expected to detect considerably more post-DTP hospitalizations with code 780.3, yet it detected only 10; using 118,887 DTP doses as its denominator, it produced a rate of 8.4 hospitalizations with code 780.3 in the seven day post-immunization period, less than half the rate of the preliminary investigation. Clearly, the determination of accurate incidence rates of adverse events following immunization will require a substantial increase in sample size.

The low convulsion rate may also reflect the fact that only events of sufficient severity to warrant hospitalization were considered (although similar techniques could be used to examine physician visit rates and diagnoses following immunization). It may also be partly explained by the common use of prophylactic antipyretics over recent years with an actual reduction in the incidence of post-immunization febrile events.

Population rates of hospitalization in infancy with convulsion code 780.3 increased with age. The fact that the children were older in the week after immunization

than in the week before could at least partially account for the temporal association between overall DTP immunization and hospitalization with convulsions; on the other hand, the association could account in part for the increase in admissions with age. These explanations are at best partial. A statistically significant increase in hospitalizations with code 780.3 was also found in the seven days following the second dose of DTP; 90 per cent of such second doses were given between 17-24 weeks of age, when hospitalization rates with code 780.3 were generally at their lowest. Among the three children hospitalized with physician diagnoses of convulsion events possibly following DTP/DT immunization, one had received the first dose of vaccine and two the second.

The statistically significant increase in hospitalization with code 780.6 (pyrexia of unknown origin) in the two day period following overall DTP vaccination did not appear to be influenced by age; the rate of hospitalization with this code among the diagnoses was fairly constant between the ages of five and 56 weeks. Among the seven children hospitalized with physician diagnoses of febrile events possibly following DTP/DT immunization, two had received the first dose, two the second and three the third.

The evidence disputing a causal link between infantile spasms and DTP vaccine[32,87,88] has been

described as "overwhelming".[89] Almost all cases of infantile spasms have an onset in the first year of life, most in the age range within which primary DTP vaccine is given.[2] It has been calculated that, by chance alone, about 12 per cent of all cases that occur between the ages of two and seven months will have their onset within seven days of DTP immunization.[2] Among all hospitalizations in the first 56 weeks of life, 72 per cent of all appearances of code 345.6 (infantile spasms) were between nine and 32 weeks of age, the age range within which 82 per cent of all DTP/DT immunizations were given. The study detected five hospitalizations with code 345.6 within 28 days of immunization, all confirmed by record review as the first admission with the condition. Of those which followed immunization and had their onset between nine and 32 weeks of age, one (5 per cent of all appearances of code 345.6) occurred within seven days of DT immunization and three (16 per cent of all appearances) occurred between seven and 28 days following DTP immunization. The findings support previous evaluations of the data concerning the temporal association between DTP immunization and the onset of infantile spasms which, finding no evidence for a causal relationship, have concluded that it is an age-related phenomenon.[2,8,57,90]

The record linkage techniques described in this

study could be applied not only to data for successive birth cohorts of children but for successive life-years of observation. They could be used to conduct population-wide post-marketing surveillance in Manitoba for rare and serious adverse events related to the use of established and newly-introduced vaccines in childhood. Such a surveillance system would, by accumulating data over many years, allow more detailed scientific assessments: of the temporal associations between each dose of vaccine and each code of interest; of the relationship between low immunization levels and adverse events; and of the effects on hospitalization rates, with specific diagnoses, of age and the number of preceding doses. Population-based incidence rates of serious adverse events could be calculated and vaccine-related risk quantified. Children who may differ systematically from those fully immunized[60] - those who die, receive no immunizations or fail to complete schedules, in whom factors common to both the increased risk of adverse events and avoidance or delay of immunization may operate - could be identified and described. Separate analyses could be done for subgroups receiving limited numbers of doses.

The review of hospital-held records suggested that the quality of the diagnostic claims data was high. Simple coding errors were minimal. The considerable

variation among the codes chosen to represent diagnoses indicative of immunization-related adverse events was related to the non-specific nature of the codes available and to the lack of clarity in coding rules. With the exception of codes representing supplementary diagnostic explanations (the E codes), discharge codes were highly accurate and truly represented the clinical conditions. Although a more complete validation is beyond the scope of this study, it is recommended that further research establish the properties of the process of using each code as a "test" to predict the probability of an adverse event; that is, to determine the positive predictive value (*the probability of having an immunization-related adverse event when a specific code is found among the discharge codes*), and the negative predictive value (*the probability of not having an immunization-related adverse event when a specific code is not found among the discharge codes*).[75]

Information from the record review also suggested that when a designated code did appear it was likely to be listed in the primary diagnostic position, whereupon its presence was an excellent predictor of a clinically possible adverse event. The converse situation, however, in which a designated code was present in a subsidiary position, did not, with any confidence, predict that an adverse event had been clinically ruled-out. Since, in

the surveillance situation, the need to detect all suspected adverse events greatly exceeds the need for diagnostic accuracy, it is recommended that the system continue to scan all of the available discharge codes for those which were designated.

Policy Implications

Immunization policies have evolved within the context of overall health care decision-making. In recent years, policies governing general health care and its delivery have been strongly implicated as key factors underlying low immunization coverage and poor communicable disease control in developed countries[12,91,92] particularly in the United States.[93] In fact, coverage levels appear to be very closely tied to policies which direct the delivery of preventive health services to children; immunization is regarded as an important indicator of child health and of the success (or failure) of associated programs.[93] Policies which lower the many financial and administrative barriers to health care access are those most likely to be associated with high coverage levels.[94] Policy decisions made centrally are likely to coordinate well and to produce not only high immunization rates but systems which measure coverage effectively and monitor levels in an ongoing manner; in countries which lack a national locus

of decision-making, coverage measurement tends to be inconsistent and incomplete.[93,95-97]

In Canada, health care is funded by a system run cooperatively by the federal and provincial governments.[98] The federal government has limited constitutional authority over health but has strongly, although indirectly, influenced provincial immunization policy by lowering fiscal barriers to immunization. This has been accomplished by setting standards to which each provincial health plan must conform in order to qualify for federal contributions - including those of universality, comprehensiveness and accessibility.[99]

However, since primary authority over health matters rests with provincial government,[100] the immunization policies of each Canadian province represent separate conclusions reached in the absence of national decision-making or policy coordination. Nevertheless, provincial policies have a number of uniform features advantageous to high immunization coverage. The provision of vaccines and immunization services is publicly-funded in all jurisdictions,[100] and the Canadian Medicare system has allowed each provincial public health agency to devote a relatively high proportion of its resources to childhood immunization.[101]

A lack of uniformity is seen, however, among the provinces with respect to other crucial immunization

policies. One of the most significant factors adversely affecting immunization programs is the failure to incorporate appropriate methods of surveillance[97,102] at the three essential levels: surveillance of communicable disease, of immunization levels, and of immunization-related adverse events. While all provinces maintain centralized disease surveillance systems,[100] few have made policy commitments to surveillance for immunization coverage. Only Manitoba has implemented a computerized immunization registry with tracking capabilities, a system which, similar in principle to those operating in Britain, the Netherlands and Finland,[103-105] combines individual-based immunization and population data to measure and continuously monitor coverage levels population-wide. Since, of the remaining provinces, only Ontario, Saskatchewan and Alberta are able to accurately estimate coverage,[106-108] only rough calculations of national immunization rates are possible. With respect to the surveillance of immunization-related adverse events, Ontario alone has legislation requiring providers to report such events; surveillance is otherwise limited to the passive participation of providers in the system operated by the federal government.[109]

Clearly, this study's elaboration of the capabilities of the Manitoba Immunization Monitoring System should be of great interest to other provinces.

The present situation in Canada has led to a call by the federal government for a nation-wide system of electronic immunization surveillance,[92,110] not yet possible since not all provinces have committed to high-quality population registries. Nevertheless, the favourable features of the Canadian immunization delivery system, together with universal entitlement and universal registration, lend themselves admirably to the construction of systems similar to MIMS. With the adoption of a standardized system of unique identification, nation-wide population-based surveillance would indeed become feasible. Without change, the measurement of immunization coverage in Canada will remain incomplete.

MIMS should also capture the attention of policy-makers in the United States, where the present immunization delivery system has been labelled "a conglomeration of complex and often uncoordinated efforts in both the public and private sectors". Immunization rates recorded in that country in 1990 were, for children aged two years and younger, lower than those in many developing countries.[111] The Clinton Administration has pledged support for higher immunization coverage, and federal funds have been directed to computerized surveillance systems.[112] The Robert Wood Johnson Foundation has funded the establishment of computerized

immunization registries in 23 cities and their integration into a national system.[112]

Immunization registries in the United States will face far greater problems related to population mobility and inner-city access than does MIMS; American family relocation rates are higher than those of almost all Western societies and the poor are particularly likely to move. The multiple provider system will also present difficulties (although standardized recording will help), as will software incompatibilities and jurisdictional issues - these can be expected, as in Canada, to be especially marked in the coordination of services to the American Indian population. Finally, unless a unique, nation-wide identifier is adopted, local registries will find it very difficult to keep track of children moving between states and to integrate into larger registry systems.

The concept of an immunization registry/monitoring system run from a population registry/claims payment structure should be of particular interest to American states considering single payer systems (as permitted by the Clinton health plan and suggested for hospital market areas with relatively small populations). The population-based approach appears to offer substantial economies over the provider-based system. MIMS' direct operational costs are approximately 150 thousand dollars

annually, less than $2.00 per child aged six years or under.(Manitoba Health: personal communication) These costs include those associated with separately capturing data on publicly-provided immunizations, merging such information with that recorded on physician payment claims, maintaining the resulting file in a form which permits users to extract immunization data, and sending out reminders.

For Manitoba, the study findings reinforce the wisdom of past policy decisions which led to the organization of an effective immunization program and to the development and implementation of MIMS. They strongly discourage any policy reversals which endanger coverage, by placing financial and/or administrative barriers in the way of immunization, or limit coverage measurement, by reducing investment in the MIMS program.

Although immunization coverage levels in Manitoba prior to the implementation of MIMS are not known, the province now has valid data against which to measure future trends. Nevertheless, the study indicated the need for several changes to provincial immunization policy.

Based on the findings, it is recommended that the full integration of Medical Services Branch into MIMS proceed without further delay; database analyses will only be truly-population-based when all children in the province are included, that is when the immunization

records of children with Indian status have been entered and can be considered complete. In fact, once this has been achieved, actual and recorded coverage rates for continuously enrolled status Indians and for the province overall should rise.

In addition, the study provided information on population sub-groups, often neglected by traditional immunization research. Data analysis for the total 1989 birth cohort described the Manitoba population of children by Indian status, enrolment status and place of residence and calculated immunization rates according these variables, which indicate a number of known influences on immunization uptake - level of urbanization, access to health service, and mobility.[113-115] The effect of migration on recorded immunization rates was quantified. These analyses demonstrated not only the extent to which changes in the denominator used in rate calculations influence reported coverage, but the limitations imposed on rate comparisons with other jurisdictions by the lack of general agreement concerning denominators and the way in which rate variations should be interpreted. Since provincial immunization rates clearly conceal what is actually happening in Manitoba, it is recommended that MIMS in future routinely calculate rates by the subgroups defined in the total 1989 cohort analysis. This will give direction to the province's

immunization program; subgroups recording low coverage (Indian, migrant and/or inner city children) can be actively tracked and targeted for completion of the immunization series and/or for completion of the record.

The key policy recommendation arising from this study is that its techniques be used to implement an active surveillance system for immunization-related adverse events in Manitoba. As described, this population-based system would eventually allow the calculation of vaccine-related risk and risk-benefit ratios for each existing and newly-introduced vaccine, something the present surveillance systems - passive and hospital-based active - cannot do. While the risks associated with the routinely-used vaccines are certainly low, their quantification would have substantial policy implications for Manitoba. Truly "informed" consent to immunization would become possible, allowing providers (including Manitoba Health) to fulfill their ethical obligations to recipients and to considerably reduce their statutory liability. Public and professional confidence in vaccines would rise; the resultant increase in vaccine uptake in the province would help to move coverage towards elimination levels for the common childhood diseases and to increase the cost-effectiveness of the overall immunization program. Governments (federal and provincial) would be in a position to make

informed policy decisions around vaccine compensation. The estimated implementation and operational costs of the active surveillance system are low: routinely-produced Manitoba Health data are used; additional resources are not required.

It is further recommended that Manitoba Health consider the possibility of striking an agreement with Health Canada for the joint conduct of active surveillance. While neither party would see a real cost advantage, both would profit if Health Canada could support the establishment of compatible systems in other provinces; a coordinated national surveillance system would have greatly enhanced analytic capabilities. This recommendation is conditional on a simultaneous agreement for common data ownership and access, to protect Manitoba's present advantage with respect to research.

Expanding the System's Applications

Interest in the Manitoba Immunization Monitoring System has led to speculation concerning the application of registry/monitoring systems to other program areas. A prime candidate for the incorporation of such a system is the Manitoba influenza immunization program, which is targeted to persons at high risk for the complications of influenza - primarily to the elderly but also to children and adults with chronic diseases.[116] Present levels of

coverage with influenza vaccine in Manitoba are unknown, but are estimated to fall well below those needed to meet the program's objective - the population-wide prevention of adverse health effects from the disease during outbreaks.

The program could expect to benefit from an immunization registry and monitoring system in several ways. The registry alone would allow the calculation of accurate coverage, the correlation of vaccine distribution with use to calculate wastage (currently estimated at between 10-300 per cent),(Manitoba Health: personal communication) and the linkage of data between the registry and other database files to study outcomes in population subgroups. To capture influenza immunizations, the registry would be expanded to include all Manitoba Health registrants (not only, as in MIMS, those born since 1980) and the follow-up period (currently 25 years) extended indefinitely. Monitoring could, by improving compliance with recommended immunizations, increase vaccine coverage to levels sufficient to prevent the majority of complications. There are some key differences, however, between the influenza and routine childhood immunization programs and their monitoring needs.

The vaccine-preventable diseases of childhood present a constant threat to health from the time of

birth; DTP/polio immunizations provide virtually life-long protection and are routinely recommended, at optimum ages early in life, for all infants and children as a single series of immunizations. MIMS monitoring, which very effectively increases compliance with early childhood immunizations, has two separate components. In the first, a check of the registry retrospectively identifies individuals lacking immunizations in the series, using age as the key indicator, and generates reminder letters to providers or recipients. In the second monitoring component, the reminder system is supplemented by a process of active follow-up through the public health system.

Influenza, however, is not only a seasonal illness but is caused by a constantly changing virus; it poses a renewed threat to vulnerable children and adults every year.[117] The influenza program therefore recommends that high-risk persons be immunized annually, prior to the onset of the influenza season. Monitoring would prospectively check the registry each year, select the target population, and attempt to influence compliance through client reminders; since the immunization delivery period is short, the MIMS approach (of reminding and following-up defaulters) would be of little benefit. In family practice settings, letter reminders to patients have been found to improve compliance with recommended

influenza immunization, although their use has not produced meaningful increases in overall coverage levels.[118-120] Nevertheless, it has been suggested that influenza immunization rates may improve over time in patient populations reminded annually.[121] However, whereas the majority of the target population (the elderly) can be readily identified in the registry by age, the real challenge facing influenza monitoring is the identification of younger adults and children for whom immunization is recommended on the basis of health status. In the absence of accurate, claims-based indicators of health status, their selection would rely on the use of such devices as proxy indicators, viz. the registry documentation of the previous receipt of influenza vaccine.

Clearly, the task of "expanding" MIMS to accommodate the needs of other programs is not a simple one. In the case of the influenza immunization program, expansion would involve the use of the entire population registry, indefinite follow-up, and a program-specific recall system designed (but not guaranteed) to reach an entire, large target population each year. While there is little doubt that influenza immunization is a cost effective intervention,[122-124] we should perhaps hesitate before assuming that applying a registry/monitoring system to the program would significantly increase levels of

vaccine coverage among risk groups. The potential benefits of the application, however, are enormous[125] and suggest that the feasibility and cost effectiveness of such a system should be explored in Manitoba, regardless of the difficulties presented. Contributing research could include the assessment of the impact on compliance of patient reminder letters distributed on a population basis.

Further Research

Ongoing study concerning the occurrence of adverse events in the first year of life will use Manitoba Vital Statistics data to expand the cause-of-death information concerning immunized children who die, and accumulate years of data to enable more powerful analyses. Further investigation of the quality of diagnostic data in the hospitalization file will, potentially, maximize the effectiveness of surveillance.

The techniques described may be used to study vaccines scheduled for administration later in childhood, such as measles-mumps-rubella and DTP/DT/polio vaccines in the second year of life, and newly-introduced vaccines, such as *Haemophilus influenzae* type b vaccine.

Similar techniques may be used to investigate physician visit rates and diagnoses following vaccine use and provide a more complete picture of the nature of

adverse events following immunization.

Conclusion

Immunization is not only one of disease prevention's most powerful and cost effective weapons but a critical investment in our nation's health. As recent analyses in the United States have shown, the inability to measure and augment immunization levels across whole populations can have drastic results, particularly in the presence of shortcomings and contradictions in health care policy. It has become increasingly apparent, in fact, that immunization levels parallel those of total health care and that coverage is an important index of the achievements of child health programs.

This province has the fortune to operate within a health care system which removes many of the impediments to efficient vaccine delivery. Manitoba is now able to monitor immunization levels population-wide, to identify and target groups exhibiting low coverage, and to influence compliance with immunization recommendations. Through the Manitoba Immunization Monitoring System, the province can fully expect to achieve immunization rates high enough to prevent most of the common childhood diseases.

The Manitoba Health database offers the possibility of applying similarly-structured registry and monitoring

systems to other program areas. It facilitates population-based research and provides a methodologically-sound, workable, and relatively inexpensive method of evaluating vaccines (old and new) and of monitoring for serious and rare adverse events. Given the unquestioned value of immunization programs and the importance of maintaining confidence in and acceptance of vaccines, this health database offers an alternate strategy for assuring vaccine safety that promises enormous public health benefits.

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. The transfer of any data out of the province will proceed only after confidentiality review and with the permission of Manitoba Health. Any papers or reports prepared for publication or distribution will be submitted to Manitoba Health for confidentiality review to ensure that the anonymity of individuals is preserved.

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