V·2

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

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

DOCTOR OF PHILOSOPHY

Department of Community Health Sciences
University of Manitoba
Winnipeg, Manitoba

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

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

DOCTOR OF PHILOSOPHY

APPENDIX 1

SURVEILLANCE IN THE CONTROL OF VACCINE-PREVENTABLE DISEASES

LIST OF TABLES

TABLE OF CONTENTS

1. SURVEILLANCE

Public health surveillance has been defined as "...the ongoing systematic collection, analysis, and interpretation of health data essential to the planning, implementation, and evaluation of public health practice, closely integrated with the timely dissemination of these data to those who need to know..." (Centers for Disease Control, Atlanta[1]) As noted by Thacker and Berkelman in their comprehensive review,[2] surveillance systems are usually designed to monitor trends, to detect and describe problems, and to establish hypotheses to be tested in more refined research designs. Surveillance systems are ongoing, and collect limited data on each case, and data analysis is traditionally straightforward. They differ from special studies, which are usually designed to test specific hypotheses, are time-limited, and involve more complex data collection and more sophisticated analyses.

With regard to immunization programs, surveillance systems not only monitor trends in the reporting of communicable diseases, but monitor vaccine coverage and the occurrence of adverse events associated with immunization.[3,4] Recently, the Division of Immunization, Centers for Disease Control (Atlanta) also established a surveillance system to monitor lawsuits against

manufacturers of diphtheria and tetanus toxoids and pertussis vaccine (DTP).[5]

2. PHASES OF IMMUNIZATION SURVEILLANCE

Immunization programs go through a series of phases from preprogram planning, to early implementation, to more extensive implementation, and are finally directed to the elimination or eradication of disease. To ensure that correct decisions are made, the system designed to provide information to the program must be tailored to each phase. At all times both surveillance and special studies are needed. However, the sophistication required of both types of information generally increases with each step.[5]

Clinical testing of previously untested vaccines usually consists of three separate phases.[6] Initial testing in humans (Phase I) begins with short-term studies in a small number of normal subjects to test the properties of the vaccine (classified as a biologic), levels of toxicity, and, when appropriate, metabolism and pharmacological effects. After basic information concerning the biologic has been obtained, larger and more detailed studies are performed (Phase II) to obtain preliminary information about the biologic's effectiveness and relative safety. Finally, more extensive testing using randomized clinical trials is

performed (Phase III), to more completely assess safety and effectiveness.

Once vaccines are licensed, information is needed to monitor program impact and to detect program problems. Data requirements include disease levels (changes in disease incidence and characteristics of remaining cases), vaccine coverage levels (the proportion of the target population immunized and the characteristics of populations not immunized), and the occurrence of adverse events following immunization.[5] Monitoring conducted following licensure is referred to as post-marketing (Phase IV) surveillance. Each set of data demands its own surveillance system.

3. DISEASE SURVEILLANCE

The ultimate purpose of immunization is the prevention of disease and its complications. Surveillance data on reported cases are critical to determine the impact of the immunization program, to assess reasons for continued disease occurrence, to evaluate the need for new strategies, and to detect problem areas and populations.

Each Canadian province and territory, and each U.S. state, has a list of diseases which physicians, laboratories and other health care providers are required to report by law. At the present time, among the

vaccine-preventable diseases, cases of measles, mumps, rubella, diphtheria, pertussis, tetanus, polio and invasive *Haemophilus influenzae* type b (Hib) disease are officially reportable to Manitoba Health, thence to the Laboratory Centre for Disease Control, Ottawa. In Manitoba, provider reports are complemented by the active monitoring of laboratory results from the centralized testing facility, Cadham Provincial Laboratory.

Orenstein and Bernier have described the surveillance process.[5] Cases are defined by laboratory and/or clinical diagnosis. Case definitions vary with the goals of the surveillance program. For example, prior to the commencement of an immunization program, all physician reports are usually accepted (the case definition is physician diagnosis). However, as incidence decreases, and a greater degree of disease control is achieved, individual cases are investigated by the health department and case definitions become more precise. In Canada, the clinical case definition for measles includes all three terms: fever greater than 38.3°C; cough, coryza or conjunctivitis, followed by; generalized rash for at least three days.[7] This definition is very sensitive in that it detects the majority of cases, and, though not very specific, is useful for evaluating case reports and in outbreak situations (when early action depends on high sensitivity

and rapid reporting). In order to establish the existence of an outbreak, a highly specific definition is also needed, and confirmation of the measles case requires laboratory evidence or epidemiological linkage to another case meeting the same clinical criteria. In the same way, clinical information from reported suspected cases of poliomyelitis must now be reviewed by a panel of experts before being accepted as a case.

Minimal disease surveillance data include date of onset or report, age and place of residence. Such limited data have been useful in demonstrating the marked impact of vaccination on disease incidence, and for analyzing how best to reduce remaining morbidity. For example, Manitoba's early strategy for dealing with rubella, introduced in the 1970s, targeted women of child-bearing age (through pre-marital and pre-natal testing) and, later, girls 10-14 years of age (through immunization). Surveillance has demonstrated the shortcomings of that program and the strength of the strategy introduced in 1981, when MMR became available, which targets the entire population of children for immunization. Manitoba averaged only five reported rubella cases annually between 1980 and 1991, but an outbreak in 1992 recorded 345 cases between January 1 and August 31. Only six occurred in children under ten years of age (three of these in children under one), while 81

per cent of cases were in males.(personal communication: Manitoba Health)

As programs mature and cases become less common, surveillance tends to move from the simple passive collection of limited data on cases to more sophisticated individual case investigations by health department personnel. During these investigations, staff generally collect relevant clinical and laboratory data as well as information on disease complications, hospitalizations, immunization status and other information such as potential sources and contacts of the case. Such investigations address the key issue in the control of vaccine-preventable diseases, that is whether a given case represents a failure of implementation of the vaccine strategy (a preventable case), or failure of the strategy (a non-preventable case). For example, a preventable case of measles occurs in an individual who was eligible for vaccine but was not immunized. Reports of outbreaks in immunized populations frequently lead to special investigations of vaccine efficacy.

4. BIOLOGICS SURVEILLANCE

In Canada, the Bureau of Biologics, Health Protection Branch, Ottawa, receives data from vaccine manufacturers concerning the number of doses distributed and the number of doses returned. In the United States,

similar monitoring is conducted by the Centers for Disease Control (CDC), Atlanta.

Data on biologics distribution have been helpful in a number of instances. In the United States, the distribution of various types of measles vaccine has been tracked since 1963, when both killed and live attenuated vaccines were licensed.[5] In 1965, further attenuated strains became available. By 1968, the distribution of killed vaccine had ceased, and by 1975 only further attenuated strains were being distributed. These data were used to recommend reimmunization of persons immunized prior to 1968 with a vaccine of unknown type, since the killed vaccine was ineffective.[8] The biologics surveillance system provides limited information, but is inexpensive and data are rapidly available.

5. MONITORING VACCINE COVERAGE

Optimum Immunization Levels

As part of the policy for achieving health for all by the year 2000, the World Health Organization European Regional Committee has adopted the goal of eliminating indigenous measles, poliomyelitis, neonatal tetanus, diphtheria and congenital rubella.[9] At the second World Health Organization Conference on Immunisation Policies in Europe (1984), the target was set of a 90 per cent

primary immunization rate for all children under two years of age by the year 1990.

World-wide, morbidity and mortality from diphtheria, polio and neonatal tetanus are at an all-time low. Because of the seriousness of these diseases, reporting is considered reliable. In Manitoba, only twelve cases of diphtheria and five of tetanus (at any age) have been reported since 1980; there were no cases of polio in that period.[10] Global concern centres on measles, congenital rubella syndrome and pertussis. The elimination of measles and congenital rubella has been estimated to require sustained vaccine uptake levels of 95 per cent in populations of children under the age of two.

Pertussis presents a rather different problem. Studies conducted both in Britain and the United States have calculated attack rates with pertussis during community outbreaks, and compared those in immunized children with those in children incompletely or never immunized. These studies have been reviewed by Cherry,[11] and indicate that the efficacy of three or more doses of pertussis vaccine in protecting children against clinical disease during outbreaks is, at most, 80-90 per cent. Moreover, a British study has found that pertussis vaccine efficacy decreases from 100 per cent in the first year after immunization to 52 per cent in the fifth year

after immunization. Neither does childhood pertussis provide lifelong immunity to the disease. However, studies have shown that when children with incomplete immunization and older children and adults with declining immunity are exposed to pertussis, the disease is likely to be atypical and milder, and complications far less frequent.[12,13] Prior to the introduction of pertussis vaccine in the 1950s, pertussis was endemic in Britain and North America. The endemic nature of disease has been altered by immunization, and the dominant feature of pertussis epidemiology is a cyclic pattern of epidemics.[13] Reported pertussis cases are considered the tip of the iceberg, with only the most serious or laboratory-confirmed cases documented. In Figure 1, the reported rate in Manitoba between 1980 and 1991 shows a sustained elevation from 1989 to 1991.(personal communication: Manitoba Health) Although social and economic factors may play a role, herd immunity, a phenomenon that varies among different infectious diseases and is difficult to measure, undoubtedly explains these cycles. Following an outbreak, several years are required for the proportion of susceptible persons to increase to a level that facilitates continuing spread within a population.[12] Pertussis immunization appears to maintain the proportion of susceptible individuals in the population below the level

necessary for widespread transmission. However, even with 100 per cent vaccine coverage, rapidly waning pertussis immunity and suboptimal vaccine efficacy makes it unlikely that the cyclic pattern can be significantly altered.

Measuring Vaccine Coverage

Vaccine coverage (knowledge of the proportion of any population immunized against a particular disease) is needed to plan and evaluate communicable disease control and to determine the rate of vaccine-associated adverse events. While the number of doses distributed are often known, the number of doses actually delivered and the demographic characteristics of the immunized and non-immunized populations usually remain unknown. Ideally, coverage information is produced by tracking of each dose of vaccine administered to each individual in the population.

Direct Measurement of Immunization Levels

Direct measurement of immunization levels is complicated by a number of factors, including the size of the target population, the variety of immunization providers, different recording systems and population movement.

Many jurisdictions therefore use surveys of population samples to estimate the immunization status of children at key ages. In the United States, an annual survey of households was conducted between 1959 and 1985 by the Bureau of the Census, to determine immunization levels for all key age groups (United States Immunization Survey, or USIS).[14] Most of the answers were based on parental recall during telephone interview, and concerns with the survey's accuracy, and cost, led to its abandonment after 1985. Other approaches to measuring pre-school levels in the United States have included a statewide follow-up at two years of age of a sample of children selected from state birth certificates.[15] This technique was also abandoned because response rates were frequently less than 50 per cent, casting concerns on the validity of the results.

To retrospectively assess immunization levels among school-aged children, CDC is conducting surveys of immunization levels among children entering school, in Kindergarten or the first grade, in the 60 largest U.S. cities.[16] The survey design included a random selection of school health records within a random selection of schools. Using date-specific information, immunization levels for children entering school were calculated, by dose and antigen type, as of the dates of their first and second birthdays. The results of surveys in nine cities

have been published.[16] The summary results from twenty cities and one rural area are shown in Table 1 (personal communication: Dr. Walter A. Orenstein). A similar approach has been taken by a number of U.S. states to calculate immunization levels for children entering school as of the date of their second birthday.[14,17] While helpful in evaluating preschool immunization levels in the past and in monitoring trends, the method is not useful in estimating immunization coverage of current preschoolers.

Vaccine coverage was estimated in Ontario (Table 2) by examining the computerized database used by 30 of the 43 public health agencies in that province to retrospectively record immunization histories at school entry.[18] This method also produced out of date information. In addition, not all histories were verified by written records and were thus subject to recall error, and large urban areas were less likely to participate in the data system used.

In the United States, national immunization levels have been assessed at school entry since 1978. Each state health department reports the results of its assessment to CDC, where a national estimate is calculated.[5] These levels represent a census of the immunization status of all children entering school, rather than a sample survey. Census results 1980-1990

are shown in Table 3. Each school must review the immunization status of each new child due to laws requiring specified immunizations prior to admission to school. State immunization program personnel perform sample validation surveys to confirm the school reports. The major advantage of this approach is that coverage levels are based on records rather than parental recall, and that the potential bias from sampling is removed. Its major disadvantage is that immunization levels are measured several years after the immunizations were due to be administered. Other problems relate to record validity, since even physician confirmation of immunization status may be based on parental recall, and the lack of precision in both numerator and denominator data permitting only the estimation of coverage levels. In addition, levels can be measured only for those antigens required by legislation.

CDC, Atlanta, also receives information on the number of doses administered by public sector providers, by age group.[5] This information has been used to monitor the proportion of the population served by the public sector, and in the calculation of adverse events following immunization in this select group. In Alberta, virtually all immunization delivery occurs through public health. Highly accurate numerator data are therefore available in that province, but denominator data are

incomplete as population estimates are based on 1986 federal census data. Immunization rates calculated are therefore regarded only as an index of Alberta coverage (Table 4, personal communication: Alberta Health).

In England and Wales, computerized preschool child registers which incorporate the immunization history of resident children are being used to measure coverage. The system used, COVER (Cover of Vaccination Evaluated Rapidly) measures the cumulative per cent of immunizations completed by certain ages in specified birth cohorts.[19] Coverage for 1988 determined by this system is shown in Table 5. By 1990, 146 of the 199 district health authorities in England and Wales were operating the nationally available National Health System Child Health System, and most others had alternative computer systems.[20] Children are entered at birth into a computerized register maintained by each district health authority, which must, by law, be notified of every child born to a resident family. The Child Health System produces an appointment invitation for the parents, based on the immunization schedule and the child's age. Information on immunizations given at community health clinics and general practices is fed back into the child health computing system.[21]

The British government proposed (1987) to link remuneration of general practitioners to the provision of

services such as immunization. This focussed interest on the accuracy and completeness of immunization records and on the accuracy of the population registers on which immunization registers are based: age-sex registers of general practice populations and the population registers of district health authorities. A wide degree of variation in the reliability and validity of age-sex registers in different practices was noted by Fraser and Clayton[22] and confirmed by Sheldon and colleagues.[23] In two areas, the register was deemed likely to be too inaccurate to be acceptable - inner city renewal areas and practices with a large proportion of the population in the 20-40 years age group. Several studies have compared various sources of immunization records. Mant et al[24] compared, for five general practices representing about one third of the population of a health district, sources of immunization numerator data (child health computer records and practice records) and sources of denominator data (age-sex register, practice record and child health computer record). The findings led them to believe that the major error in accuracy of immunization records lay with the denominator, and resulted from population movement into and from an area, a factor affecting both the health authority and age-sex registers. However, Pennington and Wilcox,[25] comparing four sources (practice notes, practice computer, district

health authority records and parental records) for a cohort of children found, using all sources, a rate for completed immunization schedules of 72 per cent while the rate recorded by the district health authority was only 40 per cent. This study was conducted before the health authority adopted the child health computing system, but highlighted a number of the problems presented by a dual system of immunization provision and a triplicate system of recording immunization data. All record sources were defective because the systems for exchange of data were dysfunctional. A single, well-maintained system of data storage was recommended.

Li and Taylor[21] found immunization uptake in Britain to be higher in general practices than in child health clinics. Alberman et al[26] suggested that the difference in uptake between immunization locations might reflect socioeconomic factors affecting the choice of provider. Other British studies have also reported the disparity in uptake among various minority ethnic groups[27] and among different social classes.[28]

In the Netherlands, the national immunization program couples municipal population records with a computerized database of individual immunization records at the provincial level. Registration of the birth stimulates the production of a set of punch cards with directions for use. Following immunization, the card is

returned to the Provincial Immunization Administration and information entered into the database. Up to two reminders are sent to the family if an immunization is late, and the district nurse visits if they still fail to comply. Verbrugge reports very high national immunization rates among Dutch children under this system (Table 6),[29] but states that low rates are found among certain population groups, including religious sects and children of foreign workers. Information concerning data quality and rates for population subgroups is not available in the English literature.

In the United States, a national computerized immunization registry is considered difficult to implement because of the need for participation by providers from both the public and private sectors. Nevertheless, at a preschool immunization assessment workshop convened in 1991 by the CDC, 86 per cent of consultants thought that a national immunization registry should be created.[30]

Nicol et al [31] have listed the requirements for computerized registries of immunization and other data relating to children (Table 7). The Manitoba Immunization Monitoring System (MIMS) is an immunization registry which provides a measure of the proportion of the population immunized by age (as in the U.S. school entry census) and also measures the cumulative proportion

of immunizations completed by key ages in each birth cohort (as does the COVER system). Rates are determined by population subgroup (region, service area, treaty status). MIMS has a valid numerator, as it tracks each dose of vaccine administered to each individual in the total population; it has a valid denominator, as it is based on an accurate and reliable population registry which can account for population migration and death. In addition, because individuals can be identified and located, a monitoring component is included. This not only reminds parents and providers that immunizations have been missed but also detects recording errors, so that it functions to improve both coverage and data quality. Reminder letters are augmented by the active follow-up of defaulters by public health staff.

Computer-generated reminders to physicians, patients or both have been shown to improve adherence to preventive services recommendations in primary care settings. Chambers[32], Tierney[33] and McDonald[34] have demonstrated that physicians will follow computer-generated prompts for preventive services. Computer-generated patient reminders have been shown to be effective for improving adherence to recommendations for tetanus booster immunization,[35] influenza immunization,[36] and Papanicolaou testing.[37] A study comparing computer-generated physician and patient reminders for

Papanicolaou tests found patient reminders to be more effective,[38] while Ornstein[39] found that reminders to both physician and patient improved adherence to cholesterol measurement and tetanus booster recommendations. McPhee[40] showed that computer-generated physician reminders increased patient compliance with six of seven cancer screening procedures.

The Comparison of Measured Immunization Rates

Several authors have noted that the comparison of immunization coverage rates within and between countries is almost impossible.[9,26,41] Wide variation exists in the collection of data disease incidence and coverage levels. The frequency and criteria for measuring coverage are not standardized. In areas of high mobility, population movement into and from an area between birth and the age of measurement may substantially affect coverage rates, yet there is no agreement on the denominator used and little attention paid to the effects of its variation. Rates are customarily reported by country or political division, without characterization of population subgroups exhibiting low coverage. Immunization schedules vary in agents recommended, the timing of their administration, and the number of doses. Data compared are often not

from the same year so the rate differences may be exaggerated.

The World Health Organization Conference on Immunisation Policies in Europe recommended all countries report target diseases in a standardized format, using agreed definitions, and that the methods used in calculating immunization coverage rates be stated.[9]

Explaining Low Coverage

Regardless of the difficulties involved in measuring coverage, there is evidence that levels of protection against vaccine-preventable diseases are low for certain population subgroups in developed countries, primarily in association with low socioeconomic status and urban residence.[26,27,29,41,42]

The organization and financing of well child care undoubtedly has an influence. Williams,[41] noting that western European countries report markedly higher immunization rates in preschool children than the United States (Table 8), points out that these countries all offer publicly funded health surveillance and immunization service. In the United States, both public and private health insurance have been found to increase the participation of children in preventive care,[43,44] but many children are not insured and many others have insurance policies which exclude preventive services.

While U.S. legislation requires specified immunizations prior to school admission,[5] only France has enacted legislation for the immunization of preschoolers.[41]

Other factors incriminated in poor coverage are inaccessibility of services, lack of parental awareness of the importance of immunization, misconceptions about immunizations (both parental and provider), and mobility (aggravated by incompletely coordinated recording systems and the absence of comprehensive reminder systems.[20,42]

6. SURVEILLANCE FOR ADVERSE EVENTS ASSOCIATED WITH THE USE OF PRESCRIPTION DRUGS

Introduction

The disaster which followed the distribution of the drug Thalidomide was a turning point in the history of drug safety. Until it occurred, adverse drug effects, while recognized as sometimes severe and occasionally even fatal, had been of relatively little concern to doctors or patients.[45] A public and professional outcry for closer drug regulation resulted, worldwide, in tighter and more specific government monitoring of the process of drug development and marketing.[46]

Surveillance for adverse drug reactions has many features in common with that for vaccine-associated adverse events, particularly in relation to the search for rare events, their often non-specific nature, and the

difficulty of ascertaining events in a manner independent of drug history. Adverse drug reaction surveillance is however distinguished by the severity of the problem of confounding by indication. The reasons for the choice of any specific medication - "the indication" - are many and complex. Unlike immunization, no assumptions re indication can be made when studying drug-disease associations. The natural history of the disease under treatment, its non-pharmacologic complications, and chance may all be easily confused with unwanted side-effects. Nevertheless, in principle, adverse event surveillance for drugs and for vaccines are very similar, and the manner in which the former has been approached deserves discussion.

Phases of Drug Surveillance

The development of new drugs is now governed by complex national and international regulatory processes, and addressed through equally complex and rigorous scientific approaches.

As with vaccines (which are classified not as drugs but as biologic products), newly-developed prescription drugs are subject to phases of scrutiny and surveillance.[6] Phase I begins with initial testing in humans in which short-term studies of a small number of normal subjects test the properties of the drug, levels

of toxicity and its metabolism and pharmacological effects. In Phase II, larger and more detailed studies are performed to obtain preliminary information about its effectiveness and relative safety. In Phase III, proof of safety and efficacy prior to marketing demands the testing of the product in randomized, blinded, controlled clinical trials.

Not everything is known about a drug's safety at the time of marketing. The costs of conducting clinical research have increased enormously, producing great economic pressures to streamline, as Tilton says: "the research process to its irreducible minimum compatible with such good science. The result is highly targeted, carefully calculated studies directed at highly focused endpoints. It is not unusual that a new drug will be marketed with experience in 2,000 patients or less".[46] In addition, clinical trials restrict the complexity of the patients tested, the endpoints procured, and the duration of therapy and monitoring. Many persons likely to receive the new medication are not included in testing - the chronically and severely ill, the very young and very old, women in the child-bearing years, and the fetus in utero.

Phase IV or post-marketing drug surveillance therefore begins once the new drug is licensed. Tognoni offers the following definition: "the identification and

evaluation of the effects of current, acute, or chronic use of pharmacological therapies in the population as a whole or in subgroups of patients exposed to specific types of therapy".[45]

Post-marketing Drug Surveillance

Passive Reporting

Historically, the first form of post-marketing surveillance was the passive, voluntary reporting by physicians of unsuspected drug effects. This method, exemplified by the British "yellow card" system of notification by physicians[47] and the spontaneous voluntary adverse reactions report monitoring system in the United States,[46] continues to be an important source of adverse experience information. Another is the pharmaceutical manufacturer. In the United States (and other countries) the manufacturer, unlike the practitioner, is obligated under federal regulation to report all adverse drug experiences; over 85 per cent of all spontaneous reports in the U.S. enter the surveillance system through the manufacturer, through direct reports and interaction with physicians and drug information pharmacists. Systems for passive reporting by physicians and drug companies exist in the United States, Europe, Australia and Japan. The World Health

Organization maintains a spontaneous adverse reactions reports registry.[46]

Passive reporting remains the mainstay of post-marketing adverse drug event surveillance, and is particularly useful for signalling problems. In Britain, early reports of thromboembolism in women using oral contraceptives influenced investigation of this potentially important event.[47] In the U.S., nephrotoxicity associated with the use of suprofen was signalled by sporadic physician reports of flank pain in 1986; transmitted to physicians by the manufacturer, this news resulted in a deluge of further reports and voluntary market withdrawal of the drug.[46]

Unfortunately, adverse events are rarely reported In voluntary reporting systems, and incidence cannot be reliably estimated. Various additional techniques have been developed over the past 15 years to actively monitor adverse drug effects.

Intensive, Active Hospital Monitoring Schemes

These have the advantage of recording all adverse events, whether perceived as due to drugs or not, and permitting accurate estimates of incidence. They can, however, only give information about relatively common and early drug reactions and exclude important events, such as sudden death, which do not result in admission.[47]

The Boston Collaborative Drug Surveillance Program (BCDSP), which began in 1966, has been the most successful intensive hospital monitoring scheme.[48] In its basic design, nurse monitors collected data on all patients regarding drug use, the occurrence of events and diagnoses. It has provided descriptive studies of patterns of drug use and toxicity and of particular adverse reactions, and detailed studies of drug interactions and of factors influencing the occurrence of particular adverse events. For example, the Special Study of 1972 provided confirmatory evidence of the inverse relationship between myocardial infarction and prior regular aspirin use. The BCDSP ceased its original data collection in 1981, but a similar method is being used to study newly marketed drugs in inpatient populations.[47]

Little success has been achieved in monitoring adverse events in outpatient populations. The best known system was set up in 1969 by the Kaiser-Permanente group in San Francisco, but its complexity did not allow its development beyond the experimental stage.[47]

Prescription Event Monitoring

By 1980, concern over the effectiveness of post-marketing surveillance methods had been expressed in many countries. The U.S. Joint Commission on Prescription

Drug Use (JCPDU) recommended that the spontaneous reporting system and the existing epidemiologic intelligence component be strengthened, and that the structured epidemiologic study be added to the standard approach to surveillance.[49] These recommendations have not been implemented in the United States.[47]

In Britain, however, Inman established the Drug Surveillance Research Unit (1980),[47,50] and the first new post-marketing surveillance scheme developed became known as Prescription Event Monitoring (PEM).[47,50,51] Inman has described the scheme.[50] It brings together two concepts: the monitoring of prescriptions and the reporting of events. In Britain, all prescriptions flow through a central National Health Service agency. Those received for newly-marketed drugs stimulate the mailing to the prescribing physician of a questionnaire, in which the occurrence of a clinical event rather than an adverse drug reaction is sought. No causal inference (thought to inhibit reporting) is required of the physician. PEM is usually a hypothesis-generating method, but it can also be used to test hypotheses. This is illustrated by the studies of Non-Steroidal Anti-inflammatory Drugs (NSAIDs), which showed no increases in the rates of serious gastrointestinal side effects during or after the use of seven NSAIDs,[50] and those of the drug enapralil,

which failed to uncover unexpected effects of the drug.[52,53]

Pharmaceutical Company Post-marketing Surveillance

Some pharmaceutical companies have undertaken post-marketing studies. These have generally been Phase IV clinical trials to assess efficacy, and usually include data on adverse events occurring during the study. However, some studies have been performed in the post-marketing phase which have neither the features of post-marketing surveillance (patients are often enlisted and are fully informed) nor those of a properly conducted trial (the studies are usually uncontrolled because competitors are unwilling to agree to the use of their products in potentially adverse comparisons).[47,50] In addition, some companies are perceived to have performed studies for promotional purposes, and this has tended to diminish the credibility of all company post-marketing research.[47]

Structured Epidemiologic Studies

Structured epidemiologic observational (non-experimental) studies of drug-disease associations greatly contribute to drug safety monitoring. They use case-control and cohort/followup methods.[46]

For example, the Slone Epidemiology Unit in Boston implemented, in 1976, a system known as case-control surveillance. This operates in 15 hospitals in the U.S., Canada and Israel, with the objectives of discovering serious drug-induced illnesses and providing for the rapid testing of hypotheses. Patients with a wide variety of conditions are interviewed by nurse monitors, who record lifetime drug histories, patient characteristics and behaviours. Diagnoses are later recorded. In this way, a number of drug-disease relationships have been investigated, including those between maternal drug exposure and birth defects and the role of oral contraceptives and other factors in the etiology of premature myocardial infarction.[47]

Medical Record Linkage

The most noteworthy development in post-marketing surveillance has been the development and use of large, automated, multipurpose computerized databases, as envisaged in the JCPDU Report.[49] These provide detailed and structured data on all drugs and medical events in defined populations.[45]

In recent years, a vast body of data has been accumulated in the claims payment files of major third party health insurance plans in Canada and the United States, and in the accounting systems of major U.S.

medical care programs such as the health maintenance organizations (HMOs). Since the mid-1970s, large data sets regarding prescriptions in populations have become available thanks to the automation of claims payment for pharmaceuticals and of pharmacy systems themselves.

In computerized billing systems (such as Medicaid and Blue Cross in the U.S., and the Saskatchewan Health Plan in Canada) and in several HMOs, data regarding all prescriptions can be attributed, through a unique patient-identifying number, to an individual.[46,54-56] Therefore, the individual's entire drug exposure experience over time can be assembled into a single computer record. This permits the automated development of patient medication profiles and checks for possible undesirable drug interactions. With the proper arrangement, records of pharmaceutical exposure can be linked with computerized data from other sources, such as hospital billings (Medicaid, Saskatchewan) or information from hospital discharge summaries (HMOs).

The large Medicaid database known as COMPASS (Computerized On-line Medicaid Pharmaceutical Analysis and Surveillance System), involves 10 states and over 10 million persons. It links patient characteristics, details of outpatient drugs prescribed, disorders and procedures.[47,57] This and other Medicaid databases have been successfully used to study the occurrence of adverse

events following the use of prescription drugs and childhood immunizing agents.[57-59]

In Saskatchewan, universal insurance for pharmaceutical, medical and hospital care has been available to the total provincial population (approximately one million) since 1976.[54] Claims data recorded in the linkable database of the Saskatchewan Prescription Drug Plan, Hospital Services Plan and Medical Care Insurance Commission make possible both population surveillance and pharmacoepidemiologic studies. This database has been used to develop a population profile of prescription drug use in the province[60] and to study adverse outcomes following the use of NSAIDs and adverse birth outcomes following the use of anticonvulsant drugs.[60,61]

In several large HMOs in the United States, such as the Group Health Cooperative of Puget Sound, between 300,000 and 2 million persons can be followed for all prescription-linked major medical events.[46,51,55] In addition, large medical practices in the United States (such as the Harvard Community Health Plan) and Britain (Value Added Medical Products or VAMP system) have automated recording systems and capture large volumes of clinical practice information, including medical events

and drug exposures, in potentially analyzable data sets.[46]

Similar large databases in hospitals with wholly automated hospital pharmacy dispensing and discharge data (including procedures and diagnoses) also permit linkage to ascertain the unexpected or unusual occurrence of important medical events among hospitalized patients.[62] These may permit the computer variant of the intensive hospital inpatient monitoring described above.

Record linkage techniques are therefore very powerful research tools for both case-control and cohort epidemiologic studies, and also have a role in population monitoring and signal generation. They present the possibility of "combing the databases" for possible signals of excesses in the ratio of adverse experiences (such as hospitalizations) in association with exposure to newly approved medications. Tilson[46] expresses the concern that new epidemiological standards and statistical practices will be needed to protect against premature alarm over chance associations.

Discussion

Since drugs work by exerting chemical change within the body, the problem of undesired side effects will remain an inevitable component of pharmacologic therapy. To again quote Tilson: "The target of

pharmacosurveillance is not to make the risk go away, but to recognize it so that those involved may address it".[46]

The application of scientific methods of surveillance to the field of pharmacology is already making a substantial contribution to the protection of the public's health. In their review of post-marketing surveillance and the many the difficulties faced by workers in this field, Lane and Rawson conclude: "We believe that record linkage systems will be the most important source of (post-marketing surveillance) study populations in the future...They raise the exciting possibility that, in the future, everyday clinical practice may well no longer be unmonitored".[51]

7. SURVEILLANCE FOR VACCINE-ASSOCIATED EVENTS

Introduction

Paradoxically, the control of many infectious diseases through the use of vaccines has led to increasing awareness of vaccine-related problems. In the virtual absence of these diseases, it has been recognized that severe but infrequent (ranging from one in every 100,000 to one per several million immunizations) adverse events may occur in association with the vaccines routinely used in childhood.[63-70] Such infrequent events are usually called adverse events temporally related to immunization rather than adverse reactions, since the

word reaction implies a known causal relationship with vaccine. Often these events are not clinically distinguishable from events that occur in the absence of receipt of vaccine. Such adverse events must be considered when the risks and benefits of routine immunization programs in populations from which the diseases in question have been almost or entirely eliminated are weighed.[71]

Surveillance of Immunizing Agents

Common adverse reactions caused by vaccine can usually be detected in prelicensure (Phase III) randomized, double-blind, placebo-controlled clinical trials.[72] However, since these are relatively short-term in nature and are conducted under controlled conditions using study groups not necessarily representative of the Canadian population, findings may differ from those in real life. The relationship of an uncommon or rare event to the receipt of vaccine therefore usually needs to be evaluated through local post-marketing (Phase IV) surveillance following licensure.

Post-Marketing Vaccine Surveillance

The general objectives of the post-marketing surveillance of adverse events temporally related to immunization have been described:[72,73]

- To identify adverse events of infrequent occurrence that may be caused by immunizing agents.
- To monitor for unusually high rates of previously-described adverse events.
- To monitor for the occurrence of unusual and unexpected adverse events.
- To develop accurate estimates of rates of occurrence of serious adverse events temporally related to immunization, by type of vaccine.
- To identify hypotheses which require more detailed epidemiological investigation and special study.

Canada and the United States both rely on passive surveillance systems for the detection of uncommon or rare adverse events temporally related to the administration of immunizing agents.[72,73] Passive reporting systems rely upon unsolicited reports from health care providers to public health authorities concerning events considered by those providers to be due to the administration of immunizing agents.[73] In Canada, reports from immunization providers are collated and analyzed by the Laboratory Centre for Disease Control, Ottawa. In the United States, the Vaccine Event

Reporting System (VAERS) takes reports from vaccine providers, but allows for direct reporting by consumers.[5] In addition, in the U.S., the National Childhood Vaccine Injury Act (1988) requires providers to report certain events following the use of selected vaccines.[5] No such federal legislation exists in Canada.

Passive adverse events monitoring is most useful in signalling potential vaccine problems and in identifying hypotheses for more detailed investigation in special studies. For example, in 1986, a number of case reports from Germany,[74] Sweden,[75] Canada[76-78] associated mumps meningoencephalitis with mumps immunization containing the Urabe Am9 strain of mumps virus. The vaccine was voluntarily withdrawn by its manufacturer from commercial distribution in Canada late in 1987,[79] Subsequent laboratory studies from Britain[80] and Japan[81] have provided sound evidence that the mumps virus strains isolated from the CSF of recipients of vaccine containing the Urabe strain were indeed related to the Urabe vaccine strain. Reports of a cluster of cases of Guillain-Barré syndrome, particularly within 2-3 weeks following immunization with the A/New Jersey influenza vaccine (swine flu), led to careful epidemiologic studies implicating this vaccine as a cause of the syndrome.[82] Studies of subsequent vaccines have failed to show such relationships.[83].

The limitations of passive reporting systems have been described in detail,[84] and include temporal reporting bias, underreporting, and the lack of baseline rates and accurate denominator data. More importantly, passive reporting systems cannot measure the true incidence of adverse events nor can they provide evidence of a causal association between the temporally related event and immunization. Even if reporting were complete and a denominator provided, passive systems do not allow measurement of the incidence of the event in the absence of immunization.

Active surveillance systems have to date involved the periodic solicitation of case reports by public health authorities from reporting sources such as physicians. Such active systems, though likely to produce more reports per patient seen than passive systems, are more expensive. In addition, they cover smaller populations, since limited numbers of physicians participate, and are less likely to detect relatively rare clinical events.[72] In Newfoundland, the Laboratory Centre for Disease Control and the College of Family Physicians of Canada have piloted an active surveillance system for adverse events following immunization with new agents, using a network of sentinel family physicians. Also in Canada, a pilot study of hospital-based active surveillance for vaccine-associated adverse events is

being conducted in five pediatric hospitals, by the Canadian Pediatric Society. This system is very timely, and ensures that diagnoses of serious adverse events leading to hospitalization are validated. It cannot however measure true incidences of adverse events or provide evidence of causal association between the temporally related events and immunization. Passive reporting systems have therefore remained the only practical means of conducting surveillance of large populations and identifying uncommon or rare adverse events temporally related to immunization.

Structured Epidemiologic Studies

To determine causation epidemiologically, it must be demonstrated that adverse events are attributable to immunization. Two approaches may be used.[5,85] The first, the cohort design, compares incidence rates of the event in question between cohorts of immunized and non-immunized individuals. If there are very few non-immunized individuals in the population, the comparison may be between (age-specific) rates of events before and at successive intervals after immunization. The alternative approach, case-control design, involves comparisons of the frequency of a history of recent immunization between individuals experiencing adverse events and appropriate controls.

Passive reporting systems do not have built-in control groups to allow measurement of the incidence of the event in the absence of immunization. Therefore, true determination of causation usually requires special studies. Causation may be accepted in the absence of special studies if the event is clinically distinctive (for example, vaccine-associated poliomyelitis) or if organisms are cultured from normally sterile body sites (for example, BCG-induced osteomyelitis).

Over the past 30 years, many special studies have examined the relationship between adverse events and the administration of DTP/DT vaccine. These studies have been conducted in different countries, using different research designs. While they have produced evidence of a temporal association with immunization for some events, such as febrile seizures,[86,87] they have failed to show a relationship between DTP/DT immunization and the events causing the greatest concern to the public and providers - those leading to permanent brain damage.[63,65,66,69]

As described in Appendix 2, several investigators have used record linkage techniques to examine the association between DTP/DT immunization and adverse events.

Walker looked at the temporal association between neurological events and DTP/DT immunization, using information from the database of the Group Health

Cooperative of Puget Sound.[88] Linked hospital discharge, medical, pharmacy and death records were examined retrospectively for some 35,000 children who had received DTP immunization over an 11 year period. Walker also conducted a case-control study, comparing 29 cases of Sudden Infant Death Syndrome (SIDS) with 262 age-matched controls drawn from linked immunization and mortality records in the database over the same period.[89]

Griffin[90] conducted a retrospective study in which hospital and medical files were linked with the immunization and pharmacy records of 38,171 Tennessee Medicaid children, who received 107,154 DTP immunizations in their first three years of life. ICD-8 codes, claims for an electroencephalogram, and prescriptions for anticonvulsant medication within seven days of a hospitalization were used to screen for neurological outcomes of interest. Griffin also linked birth, death and immunization records to follow 129,834 infants born between 1974-1984 and recorded as having received at least one dose of DTP vaccine. The relative risks of SIDS in successive intervals after receipt of DTP vaccine were calculated and compared with the risk of SIDS occurring more than 30 days after immunization.[91]

Fine and Chen have examined the influence of two major potential sources of bias in studies of immunization-associated adverse events.[85] The first is

the problem of ensuring that adverse events are ascertained independently from immunization history. Failure to control for this factor may lead to creation, or overestimation, of an association between administration of a vaccine and an adverse event. The second is the problem 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.

Discussion

The preliminary study (Section 2) has shown that it is uniquely feasible in Manitoba to implement a population-based active surveillance system for adverse events temporally related to routine childhood immunization. All adverse events leading to hospitalization can be captured, and their ascertainment is quite independent of immunization history. Non-immunized children and those receiving fewer than the recommended number of doses can be examined separately

from immunized children. Age-specific rates of the events of interest can be calculated for all groups.

Population data can be accumulated over many years. Powerful analyses are then possible of the temporal relationships between routine immunization and potentially adverse events and incidence rates can be calculated. In addition, descriptive studies can be used to complement the assessment of the effects on admission rates, with specific diagnoses, of the number of prior vaccine doses and of age.

The time delay involved in data analysis and diagnostic validation will however require the system's continued supplementation by the surveillance methods currently in use - the passive system (Laboratory Centre for Disease Control, Ottawa) and the hospital-based active system described above.

8. CONCLUSIONS

To support its immunization program, Manitoba has developed a comprehensive information system. This records data on all immunizations received for the entire population of children in such a way that immunization status is under constant surveillance. Coverage levels can be directly and accurately measured, by vaccine, age and area of residence. The system incorporates a means of increasing overall coverage, by increasing

individuals' compliance with the recommended immunization schedule. Variations in population coverage can be explained through identification and description of population subgroups, and, because individuals can be located, groups with low coverage can be targeted for immunization. The system facilitates both descriptive and longitudinal research. Special studies have shown ways in which the surveillance system can be enhanced and have demonstrated its use in the active surveillance of vaccine-associated adverse events.

In the words of Dr. Walter Orenstein, "There is no substitute for surveillance....any immunization program worth instituting is worth monitoring."[5]

9. REFERENCES

1. Centers for Disease Control. Comprehensive plan for epidemiologic surveillance. Atlanta: Centers for Disease Control, August, 1986:ii.
2. Thacker SB, Berkelman RL. Public health surveillance in the United States. Epidemiol Rev 1988; 10:164-190.
3. Eddins DL. Immunization status of the nation's 2-year-old children. In: Proceedings of the 21st Immunization Conference. Louisiana, June 8-11: New Orleans, 1987:63-66.
4. Stetler HC, Mullen JR, Brennon JP, et al. Monitoring system for adverse events following immunization. Vaccine 1987; 5:169-174.
5. Orenstein WA, Bernier RH. Surveillance in the Control of Vaccine-Preventable Diseases. In: Halperin W, Baker EL,Jr., eds. Public Health Surveillance. New York: Van Nostrand Reinhold, 1992:76-101.
6. Hopps HE, Meyer BC, Parkman PD. Regulation and Testing of Vaccines. In: Plotkin SA, Mortimer EA, eds. Vaccines. Toronto: W.B. Saunders Company, 1988:576-586.
7. Subcommittee of the Advisory Committee on Epidemiology. Guidelines for Measles Control in Canada. Can Dis Wkly Rep 1987; 13-49:219-224.

8. Centers for Disease Control. Recommendations of the Immunization Pracrices Advisory Committee (ACIP): measles prevention. M M W R 1987; 36:409-418-423-425.

9. Begg NT, Noah ND. Immunisation targets in Europe and Britain. Br Med J 1985; 291:1370-1371.

10. Annual Statistical Reports, Communicable Disease Control. Winnipeg: Manitoba Health, 1980-1991.

11. Cherry JD. The epidemiology of pertussis and pertussis vaccine in the United Kingdom and the United States: a comparative study. In: Lockhart JD, ed. Current Problems in Pediatrics. Chicago: Year Book Medical Publishers, 1984.

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

13. Thomas MG. Epidemiology of pertussis. Rev Infect Dis 1989; 11:255-261.

14. Eddins DL. Indicators of Immunization Status, 47-55. In: 17th Immunization Conference Proceedings, Atlanta, Georgia, May 18-19. 1982.

15. Centers for Disease Control. Guidelines for assessing immunity levels. Atlanta: USDHEW, PHS, CDC, Immunization Branch, 1972.

16. Anonymous. Retrospective assessment of vaccination coverage among school-aged children - selected U.S. cities, 1991. M M W R 1992; 41:103-107.

17. Eddins DL. Present systems that provide indicators of immunization status of preschool children, 83-84. In: 18th Immunization Conference Proceedings, Atlanta, Georgia, May 16-19. 1983.

18. Carter AO, Tostowaryk W, Lewis C, Carlson JAK. Estimation of Vaccine Coverage in Ontario Children. Can J Public Health 1988; 79:461-462.

19. Begg NT, Gill ON, White JM. COVER (Cover of Vaccination Evaluated Rapidly): Description of the England and Wales Scheme. Public Health 1989; 103:81-89.

20. Goodwin S. Preventive Care for Children: Immunization in England and Wales. Pediatrics 1990; (Suppl)86:1056-1060.

21. Li J, Taylor B. Comparison of immunisation rates in general practice and child health clinics. Br Med J 1991; 303:1035-1038.

22. Fraser RC, Clayton DG. The accuracy of age-sex registers, practice medical records and family practitioner committee registers. J R Coll Gen Pract 1981; 31:410-419.

23. Sheldon MG, Rector AL, Barnes PA. The accuracy of age-sex registers in general practice. J R Coll Gen Pract 1984; 34:269-271.

24. Mant D, Phillips A, Knightley M. Measles immunsation rates and the good practice allowance. Br Med J 1986; 293:995-998.

25. Pennington E, Wilcox RML. Immunization, practice records and the white paper. J R Coll Gen Pract 1988; 38:515-516.

26. Alberman E, Watson E, Mitchell P, Day S. The development of performance and cost indicators for preschool immunisation. Arch Dis Child 1986; 61:251-256.

27. Baker MR, Bandaranayake R, Schweiger MS. Differences in rate of uptake of immunization among ethnic groups. Br Med J 1984; 288:1075-1078.

28. Jarman B, Bosquanet N, Rice P, Dollimore N, Leese B. Uptake of immunisation in district health authorities in England. Br Med J 1988; 296:1775-1778.

29. Verbrugge HP. The National Immunization Program of the Netherlands. Pediatrics 1990; (Suppl)86:1060-1063.

30. Cutts FT, Zell ER, Mason D, Bernier RH, Dini EF, Orenstein WA. Monitoting progress toward US

Preschool immunization goals. J A M A 1992; 267(14):1952-1955.

31. Nicoll A, Elliman D, Begg NT. Immunisation: causes of failure and strategies and tactics for success. Br Med J 1989; 299:808-812.

32. Chambers CV, Balaban DJ, Carlson BL, Ungemack JA, Grasberger DM. Microcomputer-generated reminders: Improving the compliance of primary care physicians with mammography screening guidelines. J Fam Pract 1989; 29:273-280.

33. Tierney WM, Hui SL, McDonald CJ. Delayed feedback of physician performance versus immediate reminders to perform preventive care: effects on physician compliance. Med Care 1986; 24:659-666.

34. McDonald CJ, Hui SL, Smith DM, et al. Reminders to physicians from an introspective computer medical record: a two-year randomized trial. Ann Intern Med 1984; 100:130-138.

35. Rosser WW, Hutchison BG, McDowell I, Newell C. Use of reminders to increase compliance with tetanus booster vaccination. Can Med Assoc J 1992; 146(6):911-917.

36. Brimberry R. Vaccination of high-risk patients for influenza: a comparison of telephone and mail reminder methods. J Fam Pract 1988; 26:397-400.

37. Robertson AJ, Reid GS, Stoker CA, et al. Evaluation of a call programme for cervical cytology screening in women aged 50-60. Br Med J 1989; 299:163-166.

38. McDowell I, Newell C, Rosser W. Computerized reminders to encourage cervical screening in family practice. J Fam Pract 1989; 28:420-424.

39. Ornstein SM, Garr DR, Jenkins RG, Rust PF, Arnon A. Computer-generated physician and patient reminders: tolls to improve population adherence to selected preventive services. In: Yearbook of Medical Informatics. 1992:73-81.

40. McPhee SJ, Bird JA, Jenkins CNH, Fordham D. Promoting cancer screening: a randomized, controlled trial of three interventions. Arch Intern Med 1989; 149:1866-1872.

41. Williams BC. Immunization Coverage Among Preschool Children: The United States and Selected European Countries. Pediatrics 1990; (Suppl)86:1052-1056.

42. Hinman AR. Immunizations in the United States. Pediatrics 1990; (Suppl)86:1064-1066.

43. Gemperline P, Brockert J, Osborn LM. Preventive health care utilization. Prenatal and the first 3 years in a Utah population. Clin Pediatr (Phila) 1989; 28:34-37.

44. Newacheck PW, Halfon N. Access to ambulatory care services for economically disadvantaged children. Pediatrics 1986; 78:813-819.

45. Tognoni G. Drug use and monitoring. In: Hollard WW, ed. Evaluation Of Health Care. Toronto: Oxford University Press, 1983:207-225.

46. Tilson HH. Pharmacosurveillance: Public Health Monitoring of Medication. In: Halperin W, Baker EL, eds. Public Health Surveillance. New York: Van Nostrand Reinhold, 1992:206-229.

47. Rawson NSB. Post-marketing Surveillance. In: Hansch C, Sammes PG, Taylor JB, eds. Comprehensive Medicinal Chemistry. Volume 1: General Principles. Oxford: Pergamon Press, 1990:625-655.

48. Drug Effects in Hospitalized Patients: Experiences of the Boston Collaborative Drug Surveillance Program, 1966-1975. New York: Wiley, 1976.

49. Joint Commission on Prescription Drug Use . Final Report. Washington, D.C.: Joint Commission on Prescription Drug Use, 1980.

50. Inman WHW. Prescription-Event Monitoring: An Example of Total Population Post-Marketing Drug Surveillance. In: Gelijns AC, ed. Modern Methods of Clinical Investigation. Washington, D.C.: National Academy Press, 1990:68-77.

51. Lane DA, Rawson NSB. Inferential Problems in Postmarketing Surveillance. In: Berry DA, ed. Statistical Methodology in the Pharmaceutical Sciences. New York: Dekker, 1990:531-556.

52. Inman WHW, Rawson NSB, Wilton LV, Pearce GL, Speirs CJ. Postmarketing surveillance of enalapril. I: Results of prescription-event monitoring. Br Med J 1988; 297:826-829.

53. Speirs CJ, Dollery CT, Inman WHW, Rawson NSB, Wilton LV. Postmarketing surveillance of analapril. II: Investigation of the potential role of enalapril in death with renal failure. Br Med J 1988; 297:830-832.

54. West R. Saskatchewan Health Data Bases: A Developing Resource. Am J Prev Med 1988; (Suppl)4:25-27.

55. Rawson NSB, D'Arcy C. 'Validity' and Reliability: Idealism and Reality in the Use of Computerized Health Care Databases for Pharmacoepidemiological Research. In: Post Marketing Surveillance. Elsevier Science Publishers, 1991:3155.

56. Federspiel CF, Ray WA, Schaffner W. Medicaid records as a valid data source: the Tennessee experience. Med Care 1976; XIV:166-172.

57. Jones JK, Van de Carr SW, Rosa F, Morse L, LeRoy A. Medicaid drug-event data: an emerging tool for

evaluation of drug risk. Acta Med Scand 1984; 683(Suppl):127-134.

58. Griffin MR, Ray WA, Fought RL, Foster MA, Hays A, Schaffner W. Monitoring the Safety of Childhood Immunizations: Methods of Linking and Augmenting Computerized Data Bases for Epidemiologic Studies. Am J Prev Med 1988; (Suppl)4:5-13.

59. Carson JL, Strom BL, Morse ML, et al. The relative gastrointestinal toxicity of the non-steroidal anti-inflammatory drugs. Arch Intern Med 1987; 147:1054-1059.

60. Quinn K, Baker MJ, Evans B. A population-wide profile of prescription drug use in Saskatchewan, 1989. Can Med Assoc J 1992; 146:2177-2186.

61. West R, Sherman GJ, Downey W. A record linkage study of valproate and malformations in Saskatchewan. Can J Public Health 1985; 76:226-228.

62. Platt R, Stryker WS, Komaroff AL. Pharmacoepidemiology in hospitals using automated data systems. Am J Public Health 1988; 4(Suppl):39-47.

63. Cherry JD, Brunell PA, Golden GS, Karzon DT. Report of the Task Force on Pertussis and Pertussis Immunization 1988. Pediatrics 1988; 81(Suppl):938-984.

64. Varughese PV, Carter AO, Acres SE, Furesz J. Eradication of Indigenous Poliomyelitis in Canada: Impact of Immunization Strategies. Can J Public Health 1989; 80:363-368.

65. Cherry JD. 'Pertussis Vaccine Encephalopathy': It Is Time to Recognize It as the Myth That It Is. J A M A 1990; 263:1679-1680.

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

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

68. Nkowane BM, Wassilak SG, Orenstein WA, et al. Vaccine-Associated Paralytic Poliomyelitis: United States: 1973 Through 1984. J A M A 1987; 257:1335-1340.

69. Howson CP, Fineberg HV. Adverse Events Following Pertussis and Rubella Vaccines: Summary of a Report of the Institute of Medicine. J A M A 1992; 267:392-396.

70. Sutter RW, Onorato IM, Patriarca PA. Current poliomyelitis immunization policy in the United States. Pediatr Ann 1990; 19:702-706.

71. Chin J. Communicable Disease Control. In: Last JM, ed. Maxcy-Rosenau Public Health and Preventive

Medicine. 12th ed. Norwalk, Connecticut: Appleton-Century-Crofts, 1986:103-127.

72. Orenstein WA, Bernier RH. Surveillance: Information for Action. Ped Clin North Am 1990; 37:709-734.

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

74. Ehrengut W. Mumps vaccine and meningitis. Lancet 1989; ii:751.

75. Bottinger M, Christenson B, Romanus V, et al. Swedish experience of two dose vaccination programme aiming at eliminating measles, mumps and rubella. Br Med J 1987; 295:1264-1267.

76. McDonald JC, Moore DL, Quennec P. Clinical and epidemiologic features of mumps meningoencephalitis and possible vaccine-related disease. Pediatr Infect Dis J 1989; 8:751-755.

77. Champagne S, Thomas E, Furesz J. A case of mumps meningitis: a post immunization complication. Can Dis Wkly Rep 1987; 13:155-157.

78. Azzopardi P, Hockin JC. Mumps meningitis, possibly vaccine-related: Ontario. Can Dis Wkly Rep 1988; 14:209-211.

79. Waters JR. Mumps Meningitis Following Measles,Mumps and Rubella Vaccine. Epidemiologic Notes and Reports, Alberta Health 1989; 13:119-121.

80. Forsey T, Mawn JA, Yates PJ, Bently ML, Minor PD. Differentiation of vaccine and wild mumps viruses using the polymerase chain reaction and dideoxinucleotide. J Gen Virol 1990; 71:987-990.

81. Takahasi M, Ono S, Shimizu T, et al. MMR vaccine considered as the cause of aseptic meningitis. Jpn J Med 1990; No.3441:43-45.

82. Schonberger LD, Bregman DJ, Sullivan-Bolyai JZ, et al. Guillain-Barré syndrome following vaccination in the national influenza immunization program, United States 1976-1977. Am J Epidemiol 1979; 110:105-123.

83. Kaplan JE, Katona P, Hurwitz ES, Schonberger LB. Guillain-Barré syndrome in the United States, 1979-1980 and 1980-1981: lack of an association with influenza vaccination. J A M A 1982; 248:698-700.

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

85. Fine PEM, Chen RT. Confounding in studies of adverse reactions to vaccines. Am J Epidemiol 1992; 136(2):121-135.

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

87. Ellenburg JH, Hirtz DG, Nelson KB. Age at Onset of Seizures in Young Children. Ann Neurol 1984; 15:127-134.

88. Walker AM, Jick H, Perera DR, et al. Neurological Events Following Diphtheria-Tetanus-Pertussis Immunization. Pediatrics 1988; 81:345-349.

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

90. Griffin MR, Ray WA, Mortimer EA, et al. Risk of Seizures and Encephalopathy After Immunization With the Diphtheria-Tetanus-Pertussis Vaccine. J A M A 1990; 263:1641-1645.

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

Table 1. Percent Immunized by Vaccine and Age: Survey of 21 areas in the United States, 1990-1991.

Category	Percent Immunized (median/range)
3 doses DTP/DT and 2 doses OPV, first birthday	67.2 (45.0-80.0)
3 doses DTP/DT and 2 doses OPV, second birthday	80.7 (63.3-90.6)
3 doses OPV, second birthday	75.1 (54.3-83.4)
4 doses DTP/DT and 3 doses OPV, second birthday	48.2 (12.0-62.5)
MMR, second birthday	70.0 (52.5-81.1)

Table 2. Immunization Coverage with DPTPolio (Diphtheria, Tetanus, Pertussis and Polio) For 1981 Birth Cohort Of Children In 30 Health Units, Ontario.[18]

Number of doses of an acceptable combination	Age of child	Percent of Cohort Number
3	12 months	91.0
3	15 months	92.4
3	24 months	94.7
4	24 months	74.6
4	72 months	86.1
Complete immunization*	4-6 years	73.7
Booster due*	4-6 years	15.5
Booster overdue*	4-6 years	7.6
Incomplete immunization	4-6 years	0.7
No immunization	4-6 years	2.5

*For diphtheria, tetanus and polio only

Table 3. Percent Immunized By Antigen: Kindergarten/1st Grade Immunization Status, 1980-90, United States.[5]

Year	Measles	Mumps	Rubella	Polio	DTP/DT
1980/81	96	92	96	95	96
1981/82	97	95	97	96	96
1982/83	97	96	97	97	96
1983/84	98	97	98	97	97
1984/85	98	97	98	97	97
1985/86	97	96	97	96	96
1986/87	97	97	97	97	97
1987/88	98	98	98	97	97
1988/89	98	98	98	97	97
1989/90	98	98	98	97	97
1990/91[1]	98	98	98	97	97

[1]Provisional data as of 4/22/91

Table 4. Index Of Immunization Coverage, Alberta, 1989.

DTP/DT COVERAGE

By age of one	ACTUAL / TOTAL	34920 / 39987	=	87.33%
By 2 years of age	ACTUAL / TOTAL	2539 / 41036	=	93.52%
By school age	ACTUAL / TOTAL	1314 / 165259	=	94.32%
By age of one	ACTUAL / TOTAL	34920 + (485) / 39987	=	88.54%
By 2 years of age	ACTUAL / TOTAL	2539 + (129) / 41036	=	95.04%
By school age	ACTUAL / TOTAL	1314 + (137) / 165259	=	95.92%

POLIO VACCINE COVERAGE

By age of one	ACTUAL / TOTAL	37339 + (137) / 39987	=	93.96%
By 2 years of age	ACTUAL / TOTAL	934 + (30) / 41036	=	96.31%
By school age	ACTUAL / TOTAL	771 + (25) / 165259	=	96.79%

Table 5. Cover Of Vaccination Evaluated Rapidly: May 1988.[19]

Region	Number of children in study cohort	% had 3rd diphtheria by evaluation date	% had 3rd pertussis by evaluation date
England:			
Northern	5950	86	75
Yorkshire	6823	84	73
Trent	4045	83	74
E Anglia	4143	89	79
NW Thames	12223	81	72
NE Thames	12914	75	66
SE Thames	8691	81	72
SW Thames	1963	95	83
Wessex	3669	88	79
Oxford	6596	90	82
S Western	7141	88	76
W Midlands	9511	86	73
Mersey	3070	85	69
N Western	10638	86	71
Wales:	9362	87	66
England & Wales:	106739	84	73

Table 6. National Immunization Program In the Netherlands: Percentage Vaccination Rate Per Cohort.[29]

Cohort	DTP-Polio 1st revaccination infants (4 injections)	DT-Polio 4y	DT-Polio 9y
1970	90.8		92
1971	91.7	93	92
1972	90.5	93	92
1973	88.7	95	92
1974	89.8	94	93
1975	92.7	93	93
1976	93.4	92	94
1977	93.9	93	94
1978	94.1	92	93
1979	94.1	93	
1980	94.5	92	
1981	94.5	93	
1982	94.8	93	
1983	95.0	93	
1984	95.1		
1985	93.8		
1986	94.1		

Values given are percentages

Table 7. Requirements For Computerized Child Health Systems.[31]

- Regular supply of uptake figures and default lists for all levels of the organisation - general practitioner, health visitor, clinic, school, school nurse, sector, district.
- Linkage with birth notifications, hospital, and family practitioner systems.
- A complete register of all children resident in a health district, limked to other child registers - for example, special needs.
- Replacement rather than duplication of manual records.
- On line updating with facility for this to be done by peripheral terminals.
- Capacity to incorporate new procedures swiftly.
- Rapid turnaround of data.
- Compatibility with surrounding authorities to allow for electronic transfer of information.
- Facility for local scheduling of appointments.

Table 8. Immunization Coverage Rates For Preschool Children In the United States and Selected Countries, Most Recent Available Year.[41*]

Country	Year	DTP[abc]	Measles[d]	Polio[e]
United States	1985	64.9	60.8	55.3
Denmark	1987	94.0[f]	82.0	100.0
France[g]	1986	97.0	55.0	97.0
West Germany[g]	1987	95.0	50.0	95.0
Netherlands	1987	96.9	92.8	96.9
Norway	1987	80.0	87.0	80.0
England and Wales	1987	87.0[h]	76.0	87.0

* Source: United States Public Health Service, World Health Organization Expanded Program on Immunization, National Statistics Offices (Denmark, Netherlands, England, and Wales).
[a]Diphtheria-tetanus-pertussis.
[b]Three doses or more.
[c]US rates are for children 1-4 y of age; European figures are for children less than 3 y of age.
[d]US rates are for children 1-4 y of age; European figures are for children less than 2 y of age.
[e]US rates are for children 1-4 y of age; European figures are for children 1-3 y of age.
[f]Rate is for combined diphtheria, tetanus, and polio immunizations (IPV). Pertussis (coverage = 89.0%) and oral polio vaccine are given at separate visits; sequential immunization against polio by both injectable and oral vaccines is recommended.
[g]Estimated.
[h]Rate is for diphtheria and tetanus; rate for pertussis immunization is 73%.

APPENDIX 2

THE CURRENT STATE OF KNOWLEDGE CONCERNING ADVERSE EVENTS FOLLOWING ADMINISTRATION OF IMMUNIZING AGENTS ROUTINELY USED IN CHILDHOOD

TABLE OF CONTENTS

1. IMMUNIZATION

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

In active immunization, "an attempt is made to replace the natural primary contact with a hostile organism by a safer artificial contact so that any subsequent natural contact takes place in a state of heightened immunity".[2] The body is stimulated to develop an active immunologic defense (antibodies) in preparation for meeting the challenge of future natural exposure. This is done through the administration of a vaccine or toxoid prior to natural contact with a hostile organism.[1,3] The introduction and widespread use of active immunization has resulted in the global eradication of smallpox, the near elimination of poliomyelitis, rubella, measles, diphtheria and tetanus from Canada[4] and the United States,[1] and dramatic reductions in the incidence rates of other communicable diseases.[1,4]

Passive immunization is the provision of temporary immunity through the administration of preformed human or animal antibodies to individuals already exposed, or about to be exposed, to certain infectious agents.[1,2]

Passive immunization is indicated only in the following circumstances:[2]

- In individuals deficient in synthesis of antibody as a result of congenital or acquired B-lymphocyte cell defects.
- When no vaccine for a given disease is available and prevention or modification is possible by antibody.
- When time does not permit adequate protection by active immunization alone.
- When a specific toxic effect of venom is best managed by antibody administration.
- Therapeutically, when a disease already is present and antibody may ameliorate or aid in suppressing the effects of a toxin.

Edward Jenner demonstrated in 1796 that inoculation of an uninfected human with pustular material from a human lesion caused by cowpox produced a similar infection, and that the inoculated individual was protected from inoculation with smallpox after recovery.[5] Jenner termed this process vaccination, and this term has been used since that time to describe the process of inoculating humans against smallpox with strains of vaccinia virus. In modern medical literature, the terms immunization and vaccination are used interchangeably to describe all active immunization processes.

The best means of reducing the occurrence of vaccine-preventable communicable diseases is the establishment of a highly immune population, resulting in the interruption of person to person spread of disease in the community and the provision of protection to those who are not themselves immunized. This indirect protection is often called herd immunity.[6] Tetanus is the one vaccine-preventable disease which is not communicable but acquired through environmental exposure.[7]

2. APPROACHES TO ACTIVE IMMUNIZATION

Two major approaches to active immunization have been used and two major types of vaccines are in current use: live and killed.[1,5] The pathogenicity of the intact organism must be reduced by either creating an attenuated (meaning weakened and less likely to cause clinical illness than the natural disease-causing agent[8]) living organism, or by killing the agent.

Live vaccines contain a small dose of infectious agents - generally attenuated. Attenuation has been successful for immunization against poliomyelitis, measles, mumps, rubella, smallpox, tuberculosis and typhoid fever.[5] The organisms multiply in the recipient, and antigen production generally increases until it is checked by the onset of the immune response that it is

intended to produce. Following this, the immune system can be exposed to a large dose of antigen without the host becoming ill.[1]

Killed or inactivated vaccines are of two types:[5] killed whole organisms, as in whole cell pertussis and inactivated poliomyelitis vaccines, or purified components of the whole organism containing protective antigens, as in tetanus and diphtheria toxoids and polysaccharide vaccines (such as *Haemophilus influenzae* type b vaccine).

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

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

The specific nature and content of immunobiological agents may differ because of the inclusion by various manufacturers of differing active and inert ingredients, including suspending fluids, preservatives, culture proteins, stabilizers, antibiotics, and adjuvants.[1] Measles and mumps vaccines are prepared in chicken embryo

tissue culture,[9,10] the antibiotic neomycin is used in the production of both these vaccines,[9,10] and inactivated poliomyelitis vaccine contains trace amounts of streptomycin and neomycin.[11]

The factors which influence recommendations concerning the age at which vaccines are administered include the age-specific risks of disease, age-specific risks of complications of disease, the ability of individuals to respond to the vaccine(s), and the potential interference with the immune response by passively transferred maternal antibody.[1] In general, the approach is to administer vaccine at the earliest possible age at which the vaccine is reliably effective.[6]

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

3. HISTORY OF THE DEVELOPMENT OF IMMUNIZING AGENTS

The history of smallpox vaccination dates at least from the time of Edward Jenner's demonstrations with

cowpox virus in 1796, and in 1885 the first human rabies vaccine was used successfully by the Pasteur group in Paris.[12] Passive immunization for tetanus treatment and for prevention following wounds became common practice in World War I, using antitoxin prepared in large animals.[7]

These early agents were known to cause neurological complications and anaphylactic reactions. The reactions associated with these active and passive immunizing techniques were generally inflammatory in nature and associated with demyelination.[13]

Smallpox vaccines

The differing incidence across the world of encephalopathy and encephalitis following smallpox vaccination (in those without known contraindications to vaccination) appears to have been related to the pathogenicity of the many differing strains used in vaccination.[5] The world was declared free of smallpox in 1980, ending the need for routine vaccination.[6]

Rabies vaccines

The solution to the problem of the safety of rabies vaccine lay in the development, in the early 1960s, of vaccines prepared from rabies virus grown in tissue culture free of brain tissue. During the seventy years for which only rabies vaccines containing nervous tissue

were used, not only did neurological reactions attributed to that tissue occur, but cases of paralysis after vaccination were caused by imperfectly inactivated vaccine virus.[14]

Tetanus Vaccines

Tetanus Immune Globulin (human) became available early in the 1960s to replace equine antitoxin and permit passive immunization without the frequent allergic and serum sickness reactions which were experienced with the former agent, and with greater clinical efficacy. Tetanus toxoid became commercially available in 1938, but was not widely administered until the military services began routine prewound prophylactic inoculation in 1941.[7]

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

Pertussis Vaccine

The first era of production of pertussis vaccine began prior to World War II, when killed whole cell vaccines, which were "produced by rather hit-or-miss methods",[15] were clinically tested. After World War II, a reproducible laboratory test was devised to measure the potency and protective efficacy of whole cell pertussis

vaccines, and permit their standardization. The current era of pertussis vaccine development, toward less reactogenic vaccines, has seen the separation of the antigens responsible for clinical immunity from other components of the organism in purified, 'acellular' pertussis vaccines.[13,16,17]

The pertussis immunization regimens and the vaccines used in the early days of pertussis immunization were different from those in use today. For example, some children received repeated doses of vaccine with undoubtedly high concentrations of endotoxin through a short period of time.[13] Some of these children may have experienced subsequent illness secondary to iatrogenically prolonged endotoxemia.

Diphtheria Toxoid

Diphtheria toxin was discovered and its antitoxin developed in the last part of the 19th century.[18] It was subsequently discovered that balanced mixtures of toxin and antitoxin successfully immunized humans. The current immunizing preparation, diphtheria toxoid, came into being in the early 1920s, when Ramon showed that diphtheria toxin, when treated with heat and formalin, lost its toxic properties but retained its ability to produce serologic protection against the disease diphtheria.

Toxoid gradually replaced the toxin-antitoxin preparation for primary immunization in the United States and Canada over the next fifteen years. In 1926 Glenny found that alum-precipitated toxoid was more immunogenic.[18]

Tetanus Toxoid

The purification of tetanus toxoid and its successful chemical inactivation without loss of immunogenicity led to the commercial availability of tetanus toxoid in 1938.[7] It was not widely administered until the military services began routine prewound pr ophylactic inoculation in 1941.[7]

Because of the success of active immunization, the universal risk and high death-to-case ratio of disease, and frequent reactions and incomplete efficacy of equine antitoxin, routine tetanus toxoid inoculation in childhood was recommended in 1944 by the American Academy of Pediatrics.[7]

Combined Diphtheria, Tetanus and Pertussis Vaccines

In the mid 1940s, diphtheria toxoid, tetanus toxoid and pertussis vaccine were combined (as DTP), which permitted administration of all three antigens in a single injection.[7] Adsorption of all three onto an aluminum salt followed shortly thereafter. In 1951, the

American Academy of Pediatrics recommended routine use of DTP in infancy,[7] and its universal use in infancy and childhood is currently recommended unless contraindications exist.[3,4] The current preparation, combined diphtheria and tetanus toxoids and pertussis vaccine, adsorbed (DTP), became available in the 1970s and has been used routinely in Canada since 1981.[19]

Poliomyelitis Vaccines

The inactivated poliovirus vaccine (IPV) was first licensed in the United States and Canada in 1955,[11,20] and licensing and routine use of live attenuated poliovirus vaccine (OPV) began in many countries in 1960. In Canada, OPV was licensed in 1962, while DPT-Polio, DT-Polio and the tetanus-inactive poliovirus combination vaccine T-Polio had been licensed in 1959.[20]

Measles Vaccines

Live attenuated measles vaccine was licensed in the United States in 1963.[9] A killed measles vaccine was also licensed in the United States in 1963 and used in North America until 1967, when it became apparent that it produced short-lived immunity and placed many recipients at risk for atypical measles infection.[9] Further-attenuated live measles vaccines derived from the initial virus strain were later licensed, of which the Moraten

vaccine is now the only measles vaccine used in North America.[9]

Rubella Vaccines

Three live rubella virus vaccines from strains prepared in animal tissue culture were licensed in the United States in 1969-70, and in 1979 the vaccine strain RA27/3, prepared in human tissue culture, was licensed there.[21] The other vaccines have been withdrawn in North America, leaving RA27/3 as the only licensed vaccine, and this strain is the most widely used throughout the world.

Mumps Vaccines

An inactivated mumps vaccine became available in 1950, but its use was finally discontinued in 1976, as it induced only short-term immunity and had a relatively low protective efficacy against clinical mumps in susceptible individuals. Since 1967, live attenuated mumps virus vaccine has been available (Jeryl Lynn strain) - other strains (Leningrad-3-Parkow and Urabe Am9) have more recently been developed in the Soviet Union and Japan respectively.[10]

Haemophilus influenzae Vaccines

Haemophilus b polysaccharide vaccine (PRP), a type b polysaccharide conjugate vaccine against *Haemophilus influenzae* disease, was licensed in the United States in 1985, and the conjugate vaccine (PRP-D) was licensed in the United States in 1987,[22] and in Canada in 1988,[23] for children eighteen months and older. *Haemophilus* b Conjugate Vaccines (Diphtheria CRM_{197} Protein Conjugate or HbOC, and Meningococcal Protein Conjugate or PRP-OMP) for routine use in infancy were licensed in Canada in 1991 and added to the Manitoba recommended immunization schedule in 1992.

4. AGENTS CURRENTLY USED IN ACTIVE IMMUNIZATION

While measles, mumps and rubella vaccines are each available as a single live attenuated vaccine, in Canada and the United States immunization against measles, mumps and rubella is most often accomplished with combined live vaccines containing attenuated measles, mumps and rubella viruses (measles-mumps-rubella, or MMR vaccine).[9,24] The live, attenuated measles, mumps and rubella virus vaccine administered as a single injection induces the same response and protection as each vaccine administered individually at different sites at the same or at different times.[10]

Diphtheria and tetanus toxoids and pertussis vaccine adsorbed (DTP vaccine) and diphtheria and tetanus toxoids adsorbed for pediatric use (DT vaccine) are combinations of antigens used for the immunization of infants and children under seven years of age. Tetanus and diphtheria toxoids adsorbed for adult use (Td) is for administration in those seven years of age and older because it contains less diphtheria toxoid.[7]

Immunization against poliomyelitis may be achieved using live attenuated poliomyelitis vaccine, given orally (oral poliomyelitis vaccine, or OPV - also known as Sabin vaccine), or, less commonly, inactivated poliomyelitis vaccine (IPV - also known as killed or Salk vaccine) constituted singly or in combination with diphtheria, tetanus and pertussis vaccines (as DPT-Polio or DT-Polio).[20]

In Manitoba, it is currently recommended that all children receive DTP, OPV, and MMR vaccines, unless contraindications exist.[4] It is recommended that primary series be complete by eighteen months of age. The primary series of DTP consists of four doses; the primary series of OPV consists of three doses. A fifth dose of DTP is recommended at four to six years of age, with tetanus and diphtheria toxoids adsorbed for adult use (Td) boosters administered every ten years thereafter. A fourth dose of OPV is also recommended at four to six

years of age. A single dose of MMR vaccine is recommended shortly after the first birthday. The current Manitoba provincial immunization schedule is reproduced in Appendix I.

PRP-D is the conjugate vaccine against *Haemophilus influenzae* disease currently licensed for use in Canada. The peak incidence of invasive disease caused by *Haemophilus influenzae* type b occurs in children six to eighteen months of age. In the absence of the vaccine's proven protective efficacy in this age group,[22] it is licensed only for use in children eighteen months of age and older, and is not recommended for routine administration.[23]

5. VACCINE RECOMMENDATIONS

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

Hinman[6] describes the process by which vaccine schedules and recommendations are developed and publicized in the United States. Recommendations concerning civilian groups who should receive a vaccine and the schedule of vaccination have been developed in that country by two advisory bodies: the Immunization Practices Advisory Committee (ACIP) of the Public Health

Service, whose recommendations have been directed primarily toward public sector immunization, and the Committee on Infectious Diseases of the American Academy of Pediatrics, with recommendations primarily directed towards private sector immunization. Recommendations of the ACIP are published as issued in *Morbidity and Mortality Weekly Report*, while those of the American Academy of Pediatrics are published in the *Report of the Committee on Infectious Diseases* (the Red Book), which is regularly revised. New or revised recommendations of the American Academy of Pediatrics developed between editions of the Red Book are published as issued in *Pediatrics*.

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

6. ADVERSE EVENTS - BACKGROUND

Given the uncertain nature of early immunizing agents, it is not surprising that temporal associations between vaccines and adverse events have been considered and documented, and that causal associations between immunization and adverse outcomes sought and even

assumed. Cherry, writing about pertussis vaccine, says that "the major problem has been the failure of observers to separate sequences from consequences. The two are not synonymous".[25]

An adverse event or experience associated with a drug or biological agent has been defined as one "...associated with the use of a drug, whether or not it is considered drug-related, and any side effect, injury or toxicity, or sensitivity reaction or significant failure of pharmacological action" (United States Code of Federal Regulations 21:310.310.b).[26]

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

Adverse Reactions Caused by Inactivated Vaccines

These include immediate and delayed type hypersensitivity and Arthrus reactions.

Potential predisposing conditions may be injection of vaccines, such as DTP, into the subcutaneous rather than muscular tissue (this is believed to predispose to local inflammation, and abscess and granuloma formation),

or hyperimmunization with toxoids such as tetanus (this is believed to lead to severe local reactions).

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

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

Adverse Reactions Caused by Live Vaccines

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

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

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

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

"To epidemiologically prove causation requires that the incidence of the event after vaccination is significantly greater than the incidence of the disease in the absence of vaccination".[3] Even then, finding a statistically significant association between two independent variables at the 5 per cent level does not necessarily mean that one event caused the other. Additional evidence concerning the illnesses of interest which would support a causal association would be that they were:[27]

- Clinically distinctive.
- Restricted to immunized children.
- Closely related in time to immunization.
- Associated with a biologically plausible pathogenesis.
- Without alternative explanation.

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

Adverse events which have been associated in time with immunization but whose etiology and causal relationship with immunization is uncertain are generally termed in the medical literature 'adverse events temporally associated with immunization'. This temporal association may occur for a number of reasons:[13]

- There may be a direct cause-and-effect relationship due to a property of the vaccine.
- There may be an indirect cause and effect relationship due to an idiosyncrasy of the host.
- There may be no causal relationship with the vaccine, but rather with a preexisting, unrelated host problem. In this case, the association with the immunization may occur completely by chance, or the event may be moved forward in time by the immunization and would have occurred regardless of immunization.

7. CLASSIFICATION OF ADVERSE EVENTS

Apparent reactions associated with the use of immunizing agents must be considered with respect both to

their frequency and severity, and to the likelihood that they are due to the vaccine.

The classification of adverse events used here will therefore be that employed by the Task Force on Pertussis and Pertussis Immunization,[13] which divided all reported vaccine reactions into two categories, as follows.

7.0 TRANSIENT LOCAL AND SYSTEMIC REACTIONS

The nature and frequency of common (defined as occurring with a frequency of the order of 1 in 100 doses), mild, transient local and systemic reactions to DTP, live measles vaccine (alone and in combination with mumps and rubella vaccines), inactivated and live poliomyelitis vaccines, and PRP-D *Haemophilus influenzae* type b polysaccharide vaccine are well documented.

Pertussis Vaccine

Despite the fact that reactions occurring in association with pertussis immunization have been noted for more than fifty years, there have been virtually no placebo-controlled studies from which quantitative data are available.[13] Early studies in the United States and Britain included control populations, but these studies were primarily concerned with vaccine efficacy, and quantitative and qualitative reaction data were not

obtained.[15,28] DTP immunization has been a routine part of well baby care for some decades, precluding on ethical grounds the inclusion of a placebo group in a vaccine study to differentiate vaccine caused events from temporally associated events due to other causes. However, in the past fifteen years relatively large controlled prospective studies have been carried out in the United States which give quantitative and qualitative data concerning the occurrence of common reactions to DTP.[29-34] In addition, similar data have been gathered in the past ten years from studies comparing reaction rates in recipients of DTP vaccines containing whole cell and acellular pertussis components.[35-37]

Measles, Mumps and Rubella Vaccines

A number of studies have compared, quantitatively and qualitatively, common adverse reactions occurring in recipients of each of measles, mumps and rubella vaccines and the combined MMR vaccine and controls.[38-47] Similar data have also been gathered comparing reaction rates in recipients of varying combinations of live vaccines.[48-51] Reactions following receipt of these live vaccines are usually mild and limited to susceptible vaccinees.

Poliomyelitis Vaccines

A very large controlled trial of inactivated poliomyelitis vaccine was conducted in 1954,[11,52] and large scale field trials of live attenuated poliomyelitis vaccine were conducted in many countries, under a variety of conditions, between 1955 and 1959.[53,54] Mild transient local and systemic reactions have been reported in these and subsequent studies.[55]

PRP-D Haemophilus influenzae Vaccine

Several controlled double-blind clinical trials in humans have examined not only the protective efficacy of the *Haemophilus influenzae* type b polysaccharide conjugate vaccines but also their safety, and have provided quantitative and qualitative data concerning common adverse reactions.[56-58] Mild transient local and systemic reactions have been reported.

7.1 MAJOR REACTIONS AND TEMPORALLY RELATED EVENTS

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

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

- The infrequency of these events. The background rates of these illnesses are not insignificant, and studies with the power to detect statistically significant differences between the frequencies of illnesses occurring before and after immunization required very large study populations followed over long periods of time.
- The need to include a control group in the study population. Prospective, randomized and controlled trials are not possible, on ethical grounds, following the licensure of vaccines.
- The clinical nonspecifity of the illnesses of interest. Neurological events, such as seizures, occurring in young children are associated with many different etiologic possibilities.[13,59] 'Encephalopathy' and 'encephalitis' encompass a broad group of etiologies. The term encephalopathy, meaning in its broadest sense 'illness of the brain', is generally used when an illness clinically resembles an encephalitis but no inflammatory response within the brain (or within the meninges - meningoencephalitis) is evident.[13]

In addition, the developing nervous system displays a limited range of responses to insults of various kinds. Impairment most commonly involves the motor system, special senses (vision and hearing), language, higher cognitive function, or any combination of these problems. Not only is the assessment of the integrity of the infant nervous system a difficult task, but an abnormality or pattern of abnormalities can rarely be used to implicate a specific cause.[13]

Damage to the brain may first manifest in early infancy as nonspecific abnormalities in feeding, responsiveness, sleep patterns, or interpersonal contact.[13] In many instances there is a latent interval, during which the infant appears to be progressing well, before the processes of maturation call for the functional use of damaged areas and clinical abnormalities become apparent.

Other complicating issues include the frequency of these uncommon or rare events, greatest during the period of life at which children normally receive immunizations, and the demonstration that deficits of motor function found during the first year of life may disappear, leaving a child who is unimpaired.[60]

8. MAJOR REACTIONS AND ADVERSE EVENTS TEMPORALLY RELATED TO SPECIFIC VACCINES

8.0 DTP AND DT VACCINES

Attempts to establish a causal association between the administration of pertussis vaccine and serious acute sequelae date back to 1933 with the report by Madsen[61] of two infant deaths following the administration of the vaccine. Golden[62] notes that, since the collation by Berg[63] in 1958 of 107 reports citing neurological complications temporally associated with the administration of pertussis vaccine, "there has been prolonged and often acrimonious debate concerning the existence of a causal relationship between pertussis immunization and neurologic disease".

High Fever

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

As described in the Report of the Task Force on Pertussis and Pertussis Immunization,[13] the UCLA study, prospectively evaluated 16,536 immunizations. A total of 15,752 DTP and 784 DT immunizations were given to children, zero to six years of age and routinely scheduled for immunization, who were then evaluated for reactions that occurred within 48 hours of vaccine

administration. During the study, a substudy, which was a double-blind comparison of DTP vs DT in 305 children, was carried out to assess the reliability of the results of the total study. As the rates of common reactions in the double-blind portion of the study were similar to the rates in the overall study, it was thought by the investigators that parent or study worker bias had little effect on the overall findings.

The degree of temperature elevation was evaluated in the UCLA study.[13,29] Temperature was elevated following 7,753 DTP and 292 DT immunizations. 6.1 per cent of DTP recipients had a temperature of ·39°C, whereas only 0.7 per cent of DT recipients had a similar temperature elevation. 1.5 per cent and 0.3 per cent of the DTP recipients had temperatures ·40°c and ·40.5°C respectively, while none of the DT recipients had temperatures of a similar magnitude.

Long and colleagues[64] conducted a longitudinal prospective study which evaluated immunogenicity and adverse reactions to DTP in 538 children given 1553 doses of DTP. Subjects were randomized to the standard four dose immunization schedule or to a three dose schedule (with a saline injection substituted for DTP at 6 months of age). Parents and study personnel were unaware of the assignment of injection at 6 months of age. High fever (temperature >39.4°C) occurred within 48 hours of

immunization with 2.7 per cent of doses overall, in significantly more DTP than placebo subjects at 6 months, and no temperature exceeded 40.5°C.

Two studies in Britain noted fever in only 3-8 per cent of children immunized with DTP and in none of the children was the temperature elevation marked.[65,66] In one of these studies,[66] axillary rather than rectal or oral temperatures were taken and the temperature was determined only at 4 and 24 hours after immunization. In the other study,[65] fever was determined by the parents by palpation. It seems likely that the study techniques may explain some of the discrepancies in rates between the two British studies and the others.

Persistent Crying and Unusual High Pitched Crying or Screaming

Persistent crying has been commonly noted after DTP immunization and would appear to be a reaction to immunization.[13] In the UCLA study, 3.1 per cent of DTP immunizations resulted in persistent crying of greater than one hour duration occurring within 48 hours of immunization, whereas only 0.7 per cent of DT recipients had similar crying.[13,29]

Unusual high-pitched crying has been characterized as screaming or "a cerebral cry",[13] usually described by the parents as a high-pitched scream, and distinguished

by the parents as one they have never heard their child produce before.[29] In the UCLA study, the parents of 0.11 per cent of DTP recipients reported such unusual crying occurring within 48 hours of immunization. Valid statistical comparison between DTP and DT recipients was not possible. In this study an attempt was made to record children with unusual screaming, but evaluators were unable to differentiate the cry on a representative tape of one screaming child from the cry of an unvaccinated child.[67]

In a British study,[66] neither persistent crying nor high pitched screaming were more common in DTP (adsorbed vaccine) than DT (adsorbed vaccine) recipients, with rates for both similar to those in the UCLA study. Long[64] also reported similar rates. However in the British study, persistent crying and screaming attacks were both significantly more common in recipients of plain (unadsorbed) DTP vaccine.

No long term adverse effects have been observed in children who have had either persistent crying or unusual high pitched cry.[13]

Excessive Somnolence

Drowsiness is a common response to DTP immunization. In the UCLA study, drowsiness within 48 hours of immunization was noted in 31.5 per cent of DTP recipients

but in only 14.9 per cent of DT recipients.[13] Long reported drowsiness or sleepiness within 48 hours of immunization in 42.9 per cent of DTP recipients.[64]

Excessive somnolence is difficult to quantitate and separate from the drowsiness which commonly occurs. In the UCLA study one of the immunizations was associated with excessive somnolence, defined as prolonged unnatural drowsiness.[29]

Seizures

In studies of the relationship between seizures and immunization adverse events, a clinical classification of seizures similar to that used by Hauser and Kurland[68] is usually employed - Griffin and associates used the following clinical classification:[69]

- neonatal seizures - those occurring within the first 28 days of life.
- febrile seizures - defined below.
- afebrile seizures - those unaccompanied by fever or an acute neurological illness.
- symptomatic seizures - those associated with an acute neurological illness.

Febrile seizures are one of the most common neurological disorders in clinical pediatrics.[59] The Consensus Statement on Febrile Seizures defines a febrile

seizure as "an event in infancy or childhood, usually occurring between 3 months and 5 years of age, associated with fever but without evidence of intracranial infection or defined cause".[70] Seizures in children who have suffered a previous nonfebrile seizure are excluded from the definition. "Complex" febrile seizures are defined as those with one or more of the following characteristics: more than 15 minutes duration, more than one seizure in 24 hours, or focal features.[71] "Simple" febrile seizures lack all of the preceding characteristics. Febrile seizures must be distinguished from epilepsy, which is characterized by recurrent nonfebrile seizures.[70] Reported prevalence rates of febrile seizures range from 0.1 to 15.1 per hundred, with an average prevalence of 5.3 per hundred.[59] The wide variation is due to the use of different methods of case ascertainment and definitions of febrile seizures. Studies in which populations of children have been followed longitudinally and standard definitions used have yielded prevalence rates of between 2.4 and 4.2 per hundred.[59,71-73]

Prospective and retrospective studies indicate that convulsions after DTP immunization are relatively common. These seizures have the clinical characteristics, in most cases, of febrile seizures, and there is no evidence that they produce central nervous system injury, indicate the

onset of epilepsy, or worsen preexisting neurological disease. Although there is an increased risk of postimmunization seizures in children with a personal or family history of convulsions, there is no evidence of an increased risk that other neurological problems will develop after immunization.

The National Collaborative Perinatal Project enrolled 52,360 pregnant women, and followed 91 per cent of children born live to these women for one year and 75 per cent for seven years. It was found that 616 of the children born to these women had a seizure that occurred between one month and one year of age.[74] Therefore it can be estimated that, by chance alone, seven infants per 10,000 will have a convulsion within one week of DTP immunization, and two per 10,000 will have a convulsion within two days of DTP immunization.[13] In the study, eight children (1.5/10,000) were noted to have had a convulsion within two days of DTP immunization. Data analysis combined the data on all children, so the role of the different vaccines administered cannot easily be determined. As a group, however, the seizures almost always occurred in the presence of fever and were brief. More than half of the children had a personal or family history of convulsions. No child developed epilepsy, and the authors concluded that the immunization-related seizures closely resembled febrile seizures.

In the UCLA study,[29] there were nine instances overall of convulsions occurring within 48 hours of immunization (all occurred within 24 hours), giving a rate of one seizure per 1,750 immunizations (or 5.7 per 10,000). Seven of the nine children were febrile, a finding similar to that of Strom[75] and others,[76,77] and seven of the nine children had no previous history of convulsions or neurologic disorders, and two had prior febrile convulsions. Five were examined by a pediatric neurologist, and in all cases the examination was normal.

Pollock and Morris[76] conducted a seven year longitudinal, prospective cohort study of disorders attributable to immunization in the North West Thames region in Britain. During the study period, 134,000 children received three doses of DTP vaccine and 133,500 children completed courses of DT vaccine. A voluntary reporting system was established, and all children identified were examined within four weeks. A convulsion without evidence of neurological damage occurred within 48 hours of immunization in fifteen children in the DTP group (one per 26,800 immunizations) and in one child in the DT group (this event was associated with intercurrent infection). None of the children had a close personal or family history of convulsions. A hospital activity analysis was made on records for 1979 of children under two years of age admitted to hospital with relevant

neurological diagnoses. The febrile convulsion rate for admissions in these children was found to be 6.6 per 1,000. The denominator for children receiving immunizations during this year was underestimated, but, of 64 children admitted to hospital within 28 days of immunization, 16 had received DTP (15 febrile convulsions) and 18 had received DT (all febrile convulsions).

Walker, in a study of neurological events following DTP immunization, used information from a large HMO database in Seattle, Washington, in which hospital discharge records were linked to medical, pharmacy and death records.[78] The records of 35,581 children over 30 days of age who had received DTP immunization over an 11 year period were examined. Children with uncomplicated first febrile seizures were not likely to have been hospitalized or treated with drugs, and the study objective was not to seek these events but to search for new, serious neurological events by identifying hospitalizations for neurological disease. The study found that the incidence of first seizures occurring at any time within 29 days following DTP immunization was no greater than that expected by chance alone. The incidence of six hospitalizations for first seizure in the 29 days following the approximately 106,000 immunizations included in this study was similar to the

count of four cases following approximately 51,000 DTP immunizations and three cases following 54,000 DT immunizations reported by Pollock and Morris[76] in Britain. One child in the Seattle study had the onset of a seizure disorder three days after immunization, but this was to be expected on the basis of chance alone. The cumulative incidence of idiopathic postneonatal seizures in this population of healthy children was 3.1 per 1,000. The closest corresponding figure from the National Collaborative Perinatal Project[74] was 170 such seizures in approximately 40,000 children followed to age seven years (4.3 per 1,000). An analysis showed that the incidence of recorded febrile seizures in the immediate postimmunization period was 3.7 times (95 per cent confidence interval 1.4 to 10) that in the period 30 days or more after immunization, after adjustment for age.

Griffin[69] conducted a retrospective study in which hospital and medical files were linked with the immunization and pharmacy records of 38,171 Tennessee Medicaid (predominantly poor, nonwhite) children, who received 107,154 DTP immunizations in their first three years of life. ICD-8 codes, claims for an electroencephalogram, and prescriptions for anticonvulsant medication within seven days of a hospitalization were used to screen for neurological outcomes of interest. Of 1,187 children with such

outcomes, records were available for review in 70 per cent, and 358 children finally met the case definitions. The study found the risks of febrile seizures which generated hospital-based medical contact in the 0-7 day and 0-29 day intervals following DTP immunization to be 1.1 (95 per cent confidence interval 0.6 to 2.2) and 1.0 (95 per cent confidence interval 0.7 to 1.5) respectively times that of the period 30 or more days following DPT immunization. The corresponding risks for afebrile seizures which generated a medical contact were 1.8 (95 per cent confidence interval 0.5 to 6.3) and 1.1 (95 per cent confidence interval 0.4 to 2.6). This study probably underestimated the risk of seizures following DTP immunization in at least two important ways: it is possible that some of the highest-risk children did not receive immunization or did not receive hospital-based care in the event of a seizure; and 359 children identified as possible cases did not have their records reviewed because non-hospital-based outpatient records were not sought.

Shields[79] conducted a retrospective study examining the relationship between the time of onset of neurological disorders with the time of pertussis immunization in two cohorts of Danish children aged one month to two years who received pertussis immunization at different ages because of a change in the immunization

schedule. A significant statistical association between first febrile seizures and the scheduled age of administration of pertussis vaccine was found. The peak in first febrile seizures in Denmark changed from age 15 months to age 10 months corresponding to the change in age of scheduled pertussis immunization, while a similar shift in timing of these seizures was not observed with the simultaneous change in pertussis immunization from the age of 4-8 months to the age of 1-3 months. This finding is consistent with the observation that febrile seizures most often begin after three months of age.[59] No relationship was found between the age of onset of epilepsy and the vaccine administration schedule.

Hunt[80] examined the relationship between immunization (with DPT or DT vaccine), the onset of seizures, and the severity of cognitive deficit in children with tuberous sclerosis. There was no evidence that the vaccine precipitated seizures. The profoundly affected children all had seizures before seven months of age, and more of these children had never been immunized, or had been immunized after the first seizure, than had received the vaccine before the first seizure occurred. There was also no evidence that the vaccine caused additional brain damage; children with severe convulsions were in the groups that had not been immunized or had received only DT vaccine.

Children with either febrile or nonfebrile convulsions are more likely to have a personal or family history of convulsions. 2,062 reports of adverse neurological events from the Monitoring System for Adverse Events Following Immunization (Centers for Disease Control) were reviewed.[81] In children with a neurological event after DTP immunization, the likelihood of a personal or family history of convulsions was 7.2 and 4.5 times higher respectively than in those with a non-neurological adverse event. In the great majority of cases the neurological event was a convulsion. Febrile seizures after immunization were more likely to occur in children with a family history of convulsions. Children with either febrile or nonfebrile convulsions were more likely to have a personal history of convulsions. Baraff[33] found the rate of febrile seizures in siblings of children who experienced either convulsions or hypotonic-hyporesponsive episodes to be 16 per cent. Hirtz[77] reported a prenatally ascertained family history of febrile or nonfebrile seizures in 23 per cent of children with immunization-associated seizures, and in 14 per cent of children with febrile seizures. Hauser[82] reported an 8 per cent rate and van den Berg[83] an 11.5 per cent rate of seizures among siblings of children with febrile seizures.

Baraff[84] carried out follow-up examinations of nine children who had convulsions and nine who had hyptonic-hyporesponsive episodes within 48 hours of DTP immunization. Sixteen children were available for follow-up six or seven years later, and in each case the parents considered the child normal. Neurologic and psychometric examinations were performed in 13 cases. Neurological findings were essentially normal, and psychometric testing revealed normal performance IQ scores but low verbal IQ scores (explained by the high proportion of bilingual children in the sample. There is agreement that simple convulsions following DTP immunization are not followed by neurological sequelae in the majority of cases.[85-87]

To date, only the study of Pollock and Morris[76] has had both DPT and DT recipients in numbers sufficient to permit a statistically valid comparison of the two groups. This study was carried out in Britain between 1975 and 1981, during which time pertussis vaccine was the subject of much unfavourable discussion in the lay media. Consequently, the investigators believed the comparison to be biased by overreporting of reactions to DTP vaccine relative to DT vaccine.

Hypotonic-hyporesponsive State (Collapse, Shock)

This illness has its onset between one and twelve hours after immunization.[13] Most children are initially febrile and irritable, then become pale, limp and unresponsive. Respirations are shallow and cyanosis is frequently noted. The duration of illness may be minutes or a day or more. No adverse long-term effects have been reported.[13]

This illness was noted in six immunized children by Hopper[88] in 1961, and has been observed repeatedly since that time.[29,75,76]

In the UCLA study,[29] nine children were noted with this reaction (one per 1,750 immunizations). Because the control group (DT recipients) was small, the relationship between pertussis vaccine and this illness could not be examined. It has, however, been the belief of many experts that it is a specific pertussis vaccine reaction. The study by Pollock and Morris[76] suggests that a similar illness may also occur following DT immunization. In this study, in which approximately equal numbers of children received DTP and DT vaccines, five DTP recipients and four DT recipients had episodes consistent with this diagnosis.

Neurologic Illness and Death

Encephalopathy, Encephalitis

Pertussis vaccine has long been implicated in the etiology of severe neurological illness and brain damage. Epidemiological studies using several designs have failed to document a causal relationship between pertussis immunization, DTP immunization or DT immunization and brain damage.[62]

The most widely quoted epidemiological study on the possible adverse effects of pertussis vaccine is the National Childhood Encephalopathy Study (NCES).[89] This was a case control study of all severe, acute neurological illnesses leading to hospital admissions in children aged from 2 to 36 months in England, Scotland and Wales during a three year period between 1976 and 1979. The initial results[27] of this study suggested a risk of permanent brain damage from pertussis immunization of 1 per 330,000 vaccine doses and a risk of encephalopathy of 1 per 140,000 vaccinations. No causal association was found between pertussis immunization and infantile spasms. Recent analyses of the NCES data indicate that both of these rate estimates are incorrect.[25]

Golden[62] describes the intensive reanalysis of the NCES study in the form of a legal trial. The case of Loveday v Renton and the Wellcome Foundation was heard in

the High Court of Justice in London in 1987 and 1988. The review of the primary data led to the exclusion of many of the subjects included by the authors in the original analysis. The critical findings were reviewed by Griffith.[90] No patient had encephalopathy with characteristics similar to those in anecdotal case reports. No child who was previously normal sustained permanent brain damage. All children who had prolonged febrile convulsions were found to be normal on follow-up examination. MacRae[91] found that the increased relative risk that was observed within seven days of immunization was offset by a decreased relative risk over the subsequent three week period. This indicates, therefore, not a cause and effect relationship, but perhaps a redistribution of events over time similar to that observed with the occurrence of infantile spasms.[25] In an analysis of the cases that led to the calculated rate of 1 per 140,000 for all encephalopathy, Stephenson[92] has shown that this is an artefact caused by the inclusion of nine children with febrile convulsions. The final verdict was that the probability that pertussis vaccine could cause permanent brain damage could not be supported.[93]

Pollock and Morris[76] found 12 instances of neurologic disorders following DTP and two following DT immunization. In six of the twelve neurological

disorders that followed DTP immunization, the interval between the immunization and the onset of the disorder was eight days or longer (eight weeks in one case). Of the six cases following DTP immunization, one child had infantile spasms, four had evidence of viral infection at the time of illness, and one had petit mal seizures. In the Hospital Activity Analysis, no neurological disorders other than convulsions were noted. The authors concluded that no convincing evidence indicated a causal relationship between DTP and DT immunization and neurological damage. They also noted that, despite the administration of over 400,000 doses of DTP vaccine, no cases of the syndrome associated with "pertussis encephalopathy" were seen.

Walker[78] and Griffin[69] detected no cases of unexplained encephalopathy within 29 and 14 days respectively of DTP immunization.

Infantile Spasms

Infantile spasms represent a seizure disorder in which almost all cases have an onset in the first year of life, and 77 per cent have their onset in the six months from two to seven months of age.[94,95] Most cases of infantile spasms therefore have their onset at the age when primary DTP immunization is given, and by chance alone about 12 per cent of all cases of infantile spasms

that occur between two and seven months of age will have their onset within seven days of DTP immunization, and 5 per cent will have their onset within 72 hours of DTP immunization.[13]

A link between pertussis immunization and infantile spasms was proposed 25 years ago.[96]

Fukuyama[97] studied 110 cases of infantile spasms: a total of five cases met the authors' criteria for possible vaccine association, but they stated that this number could be explained on the basis of chance association.

Melchior[95] studied the occurrence of infantile spasms in Denmark in the period 1970 to 1975, during which pertussis immunization was given at ages 5 weeks, 9 weeks, and 10 months. Results were compared with the occurrence of infantile spasms noted in a previous study, when pertussis vaccine was administered at 5, 6, 7 and 15 months of age. No significant difference in the time of onset of infantile spasms in the two series was demonstrated. In each series, 42 per cent of the cases had their onset before the age of 5 months.

The Danish data of Shields[79] showed no association between the onset of infantile spasms and the time of pertussis immunization.

The data from the NCES were used to examine the relationship between infantile spasms and DTP vaccine.[89]

Case control analysis showed no relationship within the 28 days after immunization. There did appear to be a clustering of new cases in the seven days after immunization, but this was balanced by a deficit of new cases during the following 21 days.

Sudden Infant Death Syndrome (SIDS)

There have been suggestions in the medical literature and the lay media that DTP vaccine may cause some cases of SIDS. These suggestions arise from small, uncontrolled clinical experiences.[98,99]

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

The Cooperative Epidemiological Study of Sudden Infant Death Syndrome Risk Factors (National Institute of Child Health and Human Development) is a multi-centre, population-based case control study.[100] A total of 757 case infants who, after pathologic examination, were classified as definitely or probably having died of SIDS, were matched with 1515 control infants. There were two living control subjects for each research subject. Analysis indicated that the infants with SIDS were less likely to have received any DTP vaccine than the control infants.

An eight year study including 222 cases of SIDS was conducted in Norway.[101] There were 53 SIDS cases which occurred within one month of DTP immunization. The observed dates of occurrence were compared with the expected frequency distribution, and there was no evidence that DTP immunization was an etiological factor in SIDS.

Griffin[102] studied a cohort of 129,834 Medicaid children from a defined geographic area of Tennessee to examine the relationship between DTP immunization and SIDS. Each child had received at least one dose of DTP vaccine from a public health clinic or Medicaid provider. Immunization records were linked with death records, and 109 cases of SIDS were found. The relative risk of SIDS was determined by comparing the first 30 days after immunization with the period beginning 31 days after immunization. The relative risk in the first three days after immunization was 0.18. Subsequent periods gave a relative risk at 4 to 7 days of 0.17; 8 to 14 days of 0.75; 15 to 30 days of 1.0. A multivariate analysis of several important demographic factors also failed to support a relationship between immunization and SIDS.

Walker conducted a case control study in which the relationship of DTP immunization and 29 SIDS cases was investigated for a twelve year period in a health maintenance organization in Washington.[103] In this

study, the relative risk for the occurrence of SIDS within three days of immunization in the first year of life was 7.3 (95 per cent confidence limits 1.7 to 31), suggesting a causal association. Two points concerning this study should be noted: the small sample size (and there were only four cases of SIDS within three days of immunization); in addition, nonimmunized SIDS cases and their controls were eliminated from the analysis because of the authors' belief that delayed immunization represents a known risk factor for SIDS. In this study, the mortality rate from SIDS in nonimmunized infants was 6.5 times that of immunized infants of the same age (95 per cent confidence limits 2.2 to 19).

Non-SIDS Death

Madsen[61] first noted the occurrence of death in temporal association with pertussis immunization when he reported the deaths of two babies in 1933. Since that time, there have been scattered reports of deaths associated with pertussis vaccine and its combinations. These reports have been reviewed,[13,86,104] and it is clear that many of the non-SIDS deaths occurring soon after DTP immunization are due to other causes. There is little evidence to support an association between DTP immunization and non-SIDS temporally related deaths.[13]

Neuropathy

There have been a number of case reports of polyneuropathy occurring hours to weeks following tetanus toxoid administration. These reports and laboratory findings have been reviewed by Rutledge,[105] who summarized reports of 19 published cases. These cases had an age range of 9 to 54 years, and 85 per cent had received more than one injection.[106] In the majority of cases, the onset of polyneuropathy occurred within 14 days of the last injection,[105] and ranged in severity from a single nerve palsy,[107] profound sensorimotor neuropathy,[105] to extensive involvement of the central nervous system including cord and cortex.[108,109] Recovery was usually complete, although the degree of recovery correlated with the interval between the administration and the onset of symptoms. One patient had relapsing signs and symptoms after repeated doses of toxoid.[110] The estimated incidence of these reactions is 0.4 per million doses of vaccine.

These case reports are anecdotal, and do not demonstrate proof of a cause and effect relationship between tetanus toxoid and polyneuropathy, mononeuropathy, myelopathy, or encephalopathy.[105] The reports are, however, consistent with neuropathy as a manifestation of immune complex disease, similar to that following administration of equine tetanus antitoxin.[7]

Other neurological events, including seizures, have been reported following tetanus toxoid administration.[109,111]

Anaphylaxis

There have been case reports suggesting anaphylactic reactions to DTP vaccine[112] and to tetanus toxoid[113-115] and although these reactions appear to be rare, there are few data available.[116]

During the Monitoring System for Adverse Events Following Immunization surveillance period from 1979 to 1982,[116] the rate of allergic reactions attributed to DTP vaccine was five per million doses of administered vaccine.[13] Eight instances of anaphylaxis associated with DTP were noted.

In the North West Thames region study of Pollock and Morris,[76] anaphylaxis/collapse was noted eight times in association with DTP immunization (one per 50,000 doses), and twice in association with DT immunization (one per 200,000 doses).

Other

There have been rare case reports of hemolytic anemia, thrombocytopenic purpura and conditions affecting the skin and soft tissues occurring in association with DTP immunization.[13]

8.1 MEASLES, MUMPS AND RUBELLA VACCINES

Neurological Events

Encephalitis and Encephalopathy

Landrigan and Witte[117] used data from 1963 to 1971 and estimated the risk of either encephalitis and encephalopathy occurring within 30 days of measles immunization was approximately one in one million doses of vaccine.

During the period 1979 to 1984, five cases of encephalitis and encephalopathy were reported to the Centers for Disease Control, after administration of 18.1 million doses of measles antigen-containing vaccine, giving a rate of occurrence of these events of one in 3.6 million doses, or 0.3 per one million doses.[118] This rate is lower than that noted for severe neurological disorders of unknown etiology in unimmunized children of the same age range, suggesting that chance temporal association rather than cause and effect accounts for some, if not most, cases.[119]

To date, there has been only one report of a vaccine isolate recovered from the cerebrospinal fluid of an otherwise normal individual.[120] Another report describes isolation of a further attenuated measles strain from the cerebrospinal fluid of an immunocompromised patient.[121]

The risk of illness following mumps immunization is clearly less than that following natural infection.[122]

Between 1960 and 1968, encephalitis, meningoencephalitis and meningitis were reported to the Centers for Disease Control in the United States at a rate of two to four cases per 1,000 cases of mumps.[123] The term meningoencephalitis is now considered by the Centers for Disease Control as the appropriate term for central nervous system illness occurring in natural mumps infection; the distinction between aseptic meningitis and encephalitis in reporting is regarded as an arbitrary one.[10]

A number of case reports have associated mumps meningoencephalitis with mumps immunization. Ehrengut[124] recorded 27 cases of neurological events temporally associated with MMR vaccine from West Germany, in which the mumps component was either the Jeryl Lynn strain or the Urabe Am9 strain. Böttinger[125] reported 19 cases of "serious neurological sequelae" probably or possibly associated with the Jeryl Lynn mumps strain in Sweden between 1982 and 1984. One British report[126] recorded the isolation of the vaccine strain of virus, Urabe Am9, from the cerebrospinal fluid 21 days after immunization. Eight cases of mumps meningoencephalitis were reported from Canada,[127-129] all with mumps virus isolated from the cerebrospinal fluid but indistinguishable from natural mumps virus. The eight cases occurred within four weeks of MMR immunization with a vaccine (Trivirix^{R})

introduced into Canada in 1986 and containing the Urabe Am9 strain of mumps virus rather than the Jeryl Lynn strain. All cases recovered quickly and without sequelae.

It was concluded in Canada that mumps vaccine, particularly the Urabe strain, seems capable of producing the full range of symptoms associated with natural mumps infection, including neurological involvement.[122] However, the Jeryl Lynn strain is satisfactorily immunogenic, and appears to have a considerably lower risk of symptomatic infection. Mumps meningitis was observed in recipients of Trivirix^{R} vaccine with a frequency of one case per 62,000 doses distributed.[130] Never used in Manitoba, Trivirix^{R} vaccine was voluntarily withdrawn by its manufacturer from commercial distribution in Canada late in 1987,[122] and, effective May 1990, is no longer licensed for sale in Canada.[130]

Furesz[130] reports that recent laboratory findings from the United Kingdom[131] and Japan[132] have provided sound evidence that the mumps virus strains isolated from the CSF of recipients of vaccine containing the Urabe strain were indeed related to the Urabe vaccine strain. British[131] and Canadian investigators (Brown EG, et al, unpublished data)[130] have shown that the mumps viruses isolated from Canadian Trivirix^{R} vaccine recipients were identical to the Urabe vaccine virus and differed from

'wild' mumps virus strains isolated in Canada in 1967 and 1982.

In the USA, where the Jeryl Lynn strain of vaccine virus is used, the Immunization Practices Advisory Committee estimates that the frequency of encephalitis within 30 days of receiving a mumps-containing vaccine is 0.4 per one million doses, no higher than the observed background incidence for central nervous system dysfunction in the normal population.[133]

Subacute Sclerosing Panencephalitis (SSPE)

SSPE is a progressive, fatal disease of the central nervous system that affects children and young adults and is thought to be secondary to measles virus infection, especially when infection occurs before two years of age.[105,134] The mean age of onset is generally about seven years.[134] Between 1981 and 1986, only 20 new cases were registered in the United States.[134] The association between natural measles infection and SSPE has led to concern that vaccine virus could also cause a persistent central nervous system infection.

A review of cases based on subacute sclerosing panencephalitis surveillance from 1969 to 1981 included 368 cases.[135] Fourteen percent of cases had a history of measles immunization and a history negative for natural infection. The frequency of illness associated with

natural measles infection was 8.5 per million, and that associated with vaccine was 0.7 per million vaccine recipients who had not had measles.

Polyneuropathy

Polyneuropathy is a complication of natural rubella infection, and has been reported as an unusual complication of rubella immunization. Schaffner[136] reviewed 299 reports of polyneuropathy following rubella immunization, but none were associated with immunization using the RA27/3 vaccine.[105] Serious events following immunization with the RA27/3 rubella vaccine have been reported rarely.

Other Neurological Events

There have been a number of other reported adverse events involving the nervous system.

Acute Guillain-Barré syndrome, Reye's syndrome, ocular motor palsy, optic neuritis, retinitis, hearing loss, myelitis and cerebellar ataxia have all been documented as individual case reports, occurring in temporal association with the administration of MMR vaccine or its components.[9,21]

Arthritis

Arthritis is part of the disease caused by rubella virus, at least in adults, and arthralgia and arthritis are well recognized vaccine associated side effects. Up to 40 per cent of vaccinees in large field trial have experienced joint pain,[137] while 10-15 per cent of adult women have been reported to have arthritis-like signs and symptoms with RA27/3 vaccine.[138,139] While up to 3 per cent of susceptible children have been reported to have arthralgia, arthritis has rarely been reported in these vaccinees.[47,139]

Other Adverse Events

There have been case reports of thrombocytopenia and reactions involving the skin and soft tissues with these vaccines.[9,21]

In the United States, with more than 170 million doses of measles vaccine distributed, five cases of immediate allergic reactions to measles vaccine have been reported among children who have had histories of anaphylactic reactions to egg ingestion.[140] Serious neomycin allergy is a theoretical possibility, but no case reports have been found.

8.2 POLIOMYELITIS VACCINE

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

From the experience in many countries, it is evident that paralytic poliomyelitis due to wild poliovirus can be eliminated using either IPV or OPV.[141]

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

under 40 years of age had received three or more doses of IPV.

OPV was licensed in Canada in March, 1962, and Manitoba commenced an immunization program using OPV in April of that year. In Manitoba, 85 per cent of children under one year of age born in 1988 and registered with the Manitoba Immunization Monitoring System (MIMS) had received two doses of poliovaccine by their first birthday.[142] Of almost 70,000 doses of poliovirus vaccine administered in 1989 to the population of Manitoba children registered with MIMS and born on or after January 1, 1980, only 18 were doses of IPV.[143]

Canadian vaccine coverage is currently estimated to exceed 90 per cent for school-aged children, and between 1965 and 1988 only 51 cases of paralytic poliomyelitis were reported.[20] The United States experienced a shift from the IPV to an OPV program in 1961,[144] and, by 1969, only about a dozen cases were reported in the entire country.[144] In 1990, the Pan American Health Organization reported a doubling in OPV coverage in the Region of the Americas (the U.S. and Latin America) for children one year of age, to 73 per cent in 1989.[145] Reported cases of paralytic disease have fallen from an average of 16,000 cases per year, for the four years prior to the introduction of IPV in 1955, for the U.S.

alone[146] to 130 confirmed cases in the Americas in 1989.[145]

Inactivated Poliomyelitis Vaccine (IPV)

No serious side effects of currently available IPV have been documented. Trivalent IPV caused some early problems.[147] Material from one manufacturer, in which formalin treatment had not inactivated the viruses, caused 192 cases of paralytic poliomyelitis.[148] With purification of the virus before formalin treatment, and improved testing, there have been no further cases of paralysis attributed to IPV, nor any other serious adverse reactions.[141]

Since IPV contains trace amounts of streptomycin and neomycin, a theoretical possibility of hypersensitivity reactions in individuals sensitive to these antibiotics exists.[11]

Live Attenuated Poliovirus Vaccine (OPV)

The occurrence of paralytic poliomyelitis in OPV recipients and contacts of recipients has been recognized in recent years in the light of the enormous decline in the incidence of the wild disease.[20]

From the beginning of experimental trials in humans, extensive excretion of virus, both pharyngeal and fecal, by vaccinees had been documented, as had spread of virus

to close contacts.[149] Poliovirus vaccines must multiply in the alimentary tract in order to immunize, and all strains, regardless of how highly attenuated, retain the ability to multiply and exert neurotropic effects.[149] Laboratory techniques are such that different degrees of neurotropism, even among attenuated strains, can be readily detected, and licensed attenuated strains are those which exhibit, simultaneously, maximum immunogenic and minimum neurotropic effects.[149]

Nevertheless, as stated in report of the WHO Expert Committee on Poliomyelitis, "virus excreted in the stools can be more neurotropic than that which was fed".[150] The general view is that OPV strains, mainly type 2 or type 3, do occasionally cause paralytic poliomyelitis.[147] Results of genetic manipulations of the OPV seed strains, especially type 3, promise that a more stable mutant may be developed, with preservation of immunogenicity but loss of the potential for reversion to neurovirulence.[144]

In order to establish the possible role of OPV in the development of paralytic poliomyelitis, a thorough assessment must be taken into account in each case, taking into consideration all clinical, laboratory, and epidemiological data.[20] Cases are epidemiologically classified into two groups: non vaccine-associated (caused by wild polioviruses, endemic or imported) and suspected as vaccine-associated.

In Canada, the classification criteria for each case are those recommended by the WHO Consultative Group.[151] These criteria define a "vaccine recipient" case as one in which the illness began within 7-30 days after the patient received vaccine. A "contact/possible contact" case is one in which the patient was known to have been in contact with a vaccine recipient, and became ill within 7-60 days after the vaccine recipient had taken the vaccine.[20] In recipients of OPV, poliovirus persists in the throat for one to two weeks, and is excreted in the feces for several weeks and, rarely, for more than two months.[3] Recipients are potentially contagious as long as fecal excretion persists. A committee established in Canada in 1989 by the National Advisory Committee on Immunization to review the four poliovirus-associated cases identified in Canada in 1987-88 extended the upper limit of 60 days to 80 days for a case deemed a vaccine-associated contact/possible contact case.[152]

Of the 51 reported cases of paralytic poliomyelitis reported in Canada between 1965 and 1988, 16 were suspected to be vaccine-associated.[20] Four cases, ranging in age from 2 to 8 months, occurred in OPV recipients, and twelve cases occurred among contacts of OPV recipients (five of these were under age 5, and the remaining seven were between 19 and 40 years of age). The estimated number of trivalent OPV doses distributed

in Canada between 1965 and 1988 was 38 million, leading to an estimated risk of vaccine-associated paralysis of one case per 9.5 million doses distributed for recipients, and one case per 3.2 million doses distributed for contacts. These figures are similar to those reported by the WHO Consultative Group from six countries in 1970-1979.[151]

In the United States, Nkowane et al[146] estimated the incidence of paralytic poliomyelitis following OPV at one case per 500,000 first doses given to infants, and one case per 12 million subsequent doses. The overall rates for recipient and contact cases were estimated to be one recipient case to 7.8 million doses distributed, and one contact case to 5.5 million doses distributed, respectively.

A small proportion (under 10 per cent) of vaccine-associated cases occur in individuals with severe immunodeficiency disorders.[144]

8.3 *Haemophilus influenzae* TYPE b VACCINE

The leading cause of bacterial meningitis in North America and Europe is *Haemophilus influenzae*.[153]

PRP vaccine (designated "*Haemophilus* b polysaccharide vaccine") was licensed in the United States (though not in Canada) in 1985, and recommended there for use in children 24 months of age or older.[154]

The Advisory Committee on Immunization Practices of the Centers for Disease Control further recommended its use at 18 months of age for children in daycare or otherwise at increased risk.[155]

Subsequent to the vaccine's licensure in the United States, it became apparent[23] that its protective efficacy was likely less than that assessed in the only prospective study which had established that efficacy. This was a large clinical trial, involving children 3 to 71 months of age, conducted in Finland in 1974.[156,157]

The only serious adverse event documented in temporal association with the administration of PRP vaccine has been the occurrence of invasive *Haemophilus influenzae* (Hib) disease within one week of vaccine administration.[157]

Haemophilus influenzae infection is transmitted by the respiratory route, and invasive disease is characterized by the dissemination of bacteria, almost always *H. influenzae* type b, from the nasopharynx to the bloodstream and subsequently to other body sites.[157] Invasive Hib disease occurs endemically, and its most important epidemiological feature is its age-related incidence. Approximately 85 per cent of all invasive Hib disease occurs in children under five years of age, due almost exclusively to type b strains. While less than 15 per cent of invasive disease occurs in children under six

months of age, immunizing children by this age could theoretically prevent 85 per cent of invasive disease in childhood.

Each form of invasive disease has a characteristic age occurrence. The incidence of meningitis is greatest in infants six to twelve months of age, and declines markedly after two years of age. Hib cellulitis tends to occur during the first year of life, and epiglottitis tends to occur in children over two years of age.

American active surveillance studies have found the native Alaskan populations of Inuit, Indians, mixed Inuit, mixed Indians, and Aleuts to be at high risk for *Haemophilus influenzae* type b infections.[158] A Manitoba study[159] found a markedly increased risk of *Haemophilus influenzae* meningitis among Inuit in the Keewatin District, NWT, and suggested an increased risk of the disease among the overall Indian population of Manitoba. Attendance at daycare centres and household overcrowding also increase the risk of invasive *Haemophilus influenzae* disease.[157]

Following licensure of the vaccine, prospective randomized and controlled trials ceased to be an option in the United States for assessing vaccine efficacy and safety, and researchers used alternative study designs.[157] Five post-licensure case control studies were conducted,[160-163] detecting 373 cases of invasive

Hib disease in children older than 18 months. 12 of these cases occurred within one week of Hib immunization. Interpretation of these findings has been controversial. Some authors expressed concern that this number was excessive.[164,165] Ward et al[155] pointed out that a disproportionate number of the 12 children had experienced a recent exposure to Hib disease (a reason for vaccine administration), were more likely to develop Hib disease (attended daycare), or may have had increased susceptibility to Hib disease (sickle cell disease, Down syndrome, recurrent Hib disease), rendering their fair comparison with the general population invalid.

PRP-D, the first of the so-called second-generation conjugate vaccines, was developed to overcome the poor immunogenicity of PRP, particularly in infants.[166] Studies of PRP-D conjugate vaccine with children aged two to thirty months[56-58,167,168] have essentially demonstrated enhanced immunogenicity of PRP-D over PRP vaccine and no major concerns about safety. Its protective efficacy in the age group six to eighteen months was not satisfactorily demonstrated in these studies however,[22] and it was licensed in the United States in 1987[169] and in Canada in 1988,[23] for use in children eighteen months of age and older, and is not recommended for routine administration in Manitoba.[23] Only 196 doses of PRP-D vaccine were administered in 1989

to the population of Manitoba children registered with MIMS and born on or after January 1, 1980.[143]

Late in 1990, two vaccines were licensed in the United States for use with infants: *Haemophilus* b Conjugate Vaccine (Diphtheria CRM_{197} Protein Conjugate) (HbOC) and *Haemophilus* b Conjugate Vaccine (Meningococcal Protein Conjugate) (PRP-OMP). These vaccines, licensed in Canada in 1991, have been recommended for routine use in infants, beginning at two months of age, by the Immunization Practices Advisory Committee (ACIP), based on the following considerations.[170]

A recent study of HbOC vaccine was conducted among 60,000 infants who were enrolled in the Northern California Kaiser Permanente Health Plan and who were immunized at 2, 4, and 6 months of age. Approximately one-half of these infants received HbOC vaccine. Twelve of the unvaccinated children and none of the children who had received a full series of vaccine (i.e. three doses) subsequently had Hib disease, an efficacy of 100 per cent (lower 95 per cent confidence limit 68 per cent). Three children who had received one dose of the vaccine and none of the children who had received two doses had Hib disease.[171] Although children were not randomly assigned to vaccine and comparison groups, analysis of the results suggested that the observed efficacy was not due to lack of comparability between the two groups.

A randomized, placebo-controlled, double-blind trial of PRP-OMP vaccine was performed among Navajo infants immunized at 2 and 4 months of age. Vaccine efficacy was evaluated for 3,486 infants who completed the primary two-dose regimen. Fourteen cases of invasive Hib disease occurred in the placebo group compared with one case in the vaccine group, an efficacy of 93 per cent (95 per cent confidence limits 45-99 per cent).[170] Among infants who received only one dose of vaccine or placebo, eight cases of Hib disease occurred in the placebo group, compared with none in the vaccine group (p=0.008).

9. REFERENCES

1. Bart KJ, Orenstein WA, Hinman AR. The current status of immunization principles: recommendations for use and adverse reactions. J Allergy Clin Immunol 1987; 79:296-315.
2. Zimmerman B, Gold B, Lavi S. Adverse effects of immunization. Is prevention possible? Postgrad Med 1987; 82:225-232.
3. Committee on Infectious Diseases AAP. Report of the Committee on Infectious Diseases. 21st ed. Illinois: American Academy of Pediatrics, 1988.
4. National Advisory Committee on Immunization. Canadian Immunization Guide. 3rd ed. Ottawa: Minister of Supply and Services Canada, 1989.
5. Henderson DA. Smallpox and Vaccinia. In: Plotkin SA, Mortimer EA, eds. Vaccines. Toronto: W.B. Saunders Company, 1988:8-30.
6. Hinman AR. Public Health Considerations. In: Plotkin SA, Mortimer EA, eds. Vaccines. Toronto: W.B. Saunders Company, 1988:587-611.
7. Wassilak SGF, Orenstein WA. Tetanus. In: Plotkin SA, Mortimer EA, eds. Vaccines. Toronto: W.B. Saunders Company, 1988:45-73.
8. Ellis RW. New Technologies for Making Vaccines. In: Plotkin SA, Mortimer EA, eds. Vaccines. Toronto: W.B. Saunders Company, 1988:568-575.

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

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

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

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

13. Cherry JD, Brunell PA, Golden GS, Karzon DT. Report of the Task Force on Pertussis and Pertussis Immunization 1988. Pediatrics 1988; 81(Suppl):938-984.

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

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

16. Edwards KM, Lawrence E, Wright PF. Diphtheria, tetanus and pertussis vaccine: a comparison of the immune response and adverse reactions to

conventional and acellular pertussis components. Am J Dis Child 1986; 140:867-871.

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

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

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

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

21. Plotkin SA. Rubella Vaccine. In: Plotkin SA, Mortimer EA, eds. Vaccines. Toronto: W.B. Saunders Company, 1988:235-262.

22. Ward JI. Commentary: Results of efficacy trials in Alaska and Finland of *Haemophilus influenzae* type b conjugate vaccine. Pediatrics 1990; 85(Suppl):667.

23. Manitoba Health Communicable Disease Control. *Haemophilus influenzae* - PRP-D (Conjugate) Vaccine. Epidemiologic Notes 1988; 124:1.

24. Subcommittee of the Advisory Committee on Epidemiology. Guidelines for measles control in Canada. Can Dis Wkly Rep 1987; 49:219-224.

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

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

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

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

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

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

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

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

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

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

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

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

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

37. Pichichero ME, Badgett JT, Rodgers GC. Acellular pertussis vaccine: immunogenicity and safety of an acellular pertussis vs. a whole cell pertussis vaccine combined with diphtheria and tetanus toxoids

as a booster in 18- to 24- month old children. Pediatr Infect Dis J 1987; 6:352-363.

38. Krugman S, Giles JP, Jacobs AM, Friedman H. Studies with a further-attenuated live measles virus vaccine. Pediatrics 1963; 31:919-928.

39. Medical Research Council. Vaccination against measles: a study of clinical reactions and serological responses of young children. Br Med J 1965; 1:817-823.

40. Schwarz AJF, Anderson JT, Ramos-Alvarez M, et al. Extensive clinical evaluations of a highly-attenuated live measles vaccine. J A M A 1967; 199:84-88.

41. Isozaki M, Kuno-Sakai H, Hoshi N, et al. Effects and side-effects of a new trivalent combined measles-mumps-rubella (MMR) vaccine. Tokai J Exp Clin Med 1982; 7:547-550.

42. Just M, Berger R, Glueck R, Wegmann A. Evaluation of a combined vaccine against measles-mumps-rubella produced on human diploid cells. Dev Biol Stand 1986; 65:25-27.

43. Hilleman MR, Weibel RE, Villarejos VM, et al. Combined live virus vaccines. Radiology 1971; 226:397-400.

44. Weibel RE, Stokes J, Buynak EB, et al. Live attenuated mumps virus vaccine. N Engl J Med 1967; 276:245-251.

45. Böttinger M, Heller L. Experiences from vaccination and revaccination of teenage girls with three different rubella vaccines. J Biol Stand 1976; 4:107-114.

46. Menser MA, Forrest JM, Bransby RD, Collins E. Rubella vaccination in Australia: experience with the RA27/3 rubella vaccine and results of a double-blind trial in schoolgirls. Med J Aust 1978; 2:85-88.

47. Peltola H, Heinonen OP. Frequency of true adverse reactions to measles-mumps-rubella vaccine. A double-blind placebo-controlled trial in twins. Lancet 1986; 1:939-942.

48. Lerman SJ, Bollinger M, Brunken JM. Clinical and serological evaluation of measles, mumps, and rubella (HPV-77:DE-5 and RA27/3) virus vaccines, singly and in combination. Pediatrics 1988; 81:779-784.

49. Brunell PA, Novelli VM, Lipton SV, Pollock B. Combined vaccine against measles, mumps, rubella, and varicella. Pediatrics 1988; 81:779-784.

50. Vesikari T, Eija-Liisa A-L, Heikkinen A, et al. Clinical trial of a new trivalent measles-mumps-

rubella vaccine in young children. Am J Dis Child 1984; 138:843-847.

51. Popow-Kraupp T, Kundi M, Vanura H, Kunz C. A controlled trial for evaluating two live attenuated mumps-measles vaccines (Urabe Am 9-Schwarz and Jeryl-Lynn-Moraten) in young children. J Med Virol 1986;18:69-79.

52. Francis TMJr., Korns RF, Voight RB, et al. An Evaluation of the 1954 Poliomyelitis Vaccine Trials. (Summary Report). Am J Public Health 1955; 45(5.pt.2).

53. Pan American Sanitary Bureau: Live Poliovirus Vaccines. 44th ed. Special Publication of the Pan American Sanitary Bureau, 1959.

54. Pan American Health Organization: Live Poliovirus Vaccines. 50th ed. Special Publication of the Pan American Health Organization, 1960.

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

56. Berkowitz CD, Ward JI, Meier K, et al. Evaluation of the safety and immunogenicity of *H. influenzae* type b polysaccharide and polysaccharide diphtheria toxoid conjugate vaccines in children 15 to 24 months of age. J Pediatr 1987; 110:509-514.

57. Lepow ML, Samuelson JS, Gordon LK. Safety and immunogenicity of *H. influenzae* type b polysaccharide-diphtheria toxoid conjugate vaccine in infants 9 to 15 months of age. J Pediatr 1985; 106:185-189.

58. Eskola J, Käyhty H, Peltola H, et al. Antibody levels achieved in infants by a course of *H. influenzae* type b polysaccharide/diphtheria toxoid conjugate vaccine. Lancet 1985; 1:1184-1186.

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

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

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

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

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

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

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

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

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

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

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

70. Consensus Statement on Febrile Seizures. National Institutes of Health Consensus Development Conference Summary. In: Nelson KB, Ellenberg JH, eds. Febrile Seizures. New York: Raven Press, 1981:301-306.

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

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

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

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

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

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

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

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

79. Shields WD, Nielsen C, Buch D, et al. Relationship of pertussis immunization to the onset of

neurological disorders: A retrospective epidemiologic study. J Pediatr 1988; 113:801-805.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

100. Hoffman HJ, Hunter JC, Damus K, et al. Diphtheria-tetanus-pertussis immunization and sudden infant death: results of the National Institute of Child Health and Human Development Epidemiological Study

of Sudden Infant Death Syndrome Risk Factors. Pediatrics 1987; 79:598-611.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

117. Landrigan PJ, Witte JJ. Neurologic disorders following live measles-virus vaccination. J A M A 1973; 223:1459-1462.

118. Anonymous. Adverse events following immunization: Surveillance report No.2, 1982-1984, December. Atlanta: Centers for Disease Control, 1986.

119. Bloch AB, Orenstein WA, Wassilak SG, et al. Epidemiology of measles and its complications. In: Gruenberg EM, Lewis C, Goldston SE, eds. Vaccinating Against Brain Syndromes: The Campaign Against Measles and Rubella. New York: Oxford University Press, 1986.

120. Forman ML, Cherry JD. Isolation of measles virus from the cerebrospinal fluid of a child with encephalitis following measles vaccination. Abstract 13, April 26-29: Presented at the 77th Annual Meeting of the American Pediatric Society, 1967.

121. Valmari P, Lanning M, Tuokko H, Kouvalainen K. Measles virus in the CSF in postvaccination immunosuppressive measles encephalopathy. Pediatr Infect Dis J 1987; 6:59-63.

122. Waters JR. Mumps meningitis following measles, mumps and rubella vaccine. Epidemiologic Notes and Reports, Alberta Health 1989; 13:119-121.

123. Anonymous. Mumps Surveillance, Report No.2, September. Atlanta: Centers for Disease Control, 1972.

124. Ehrengut W. Mumps vaccine and meningitis. Lancet 1989; ii:751.

125. Böttinger M, Christenson B, Romanus V, et al. Swedish experience of two dose vaccination programme aiming at eliminating measles, mumps and rubella. Br Med J 1987; 295:1264-1267.

126. Gray JA, Burns SM. Mumps vaccine meningitis. Lancet 1989; ii:927.

127. McDonald JC, Moore DL, Quennec P. Clinical and epidemiologic features of mumps meningoencephalitis and possible vaccine-related disease. Pediatr Infect Dis J 1989; 8:751-755.

128. Champagne S, Thomas E, Furesz J. A case of mumps meningitis: a post immunization complication. Can Dis Wkly Rep 1987; 13:155-157.

129. Azzopardi P, Hockin JC. Mumps meningitis, possibly vaccine-related: Ontario. Can Dis Wkly Rep 1988; 14:209-211.

130. Furesz J, Contreras G. Vaccine-related mumps meningitis - Canada. Can Dis Wkly Rep 1990; 16:253-254.

131. Forsey T, Mawn JA, Yates PJ, Bently ML, Minor PD. Differentiation of vaccine and wild mumps viruses using the polymerase chain reaction and dideoxinucleotide. J Gen Virol 1990; 71:987-990.

132. Takahasi M, Ono S, Shimizu T, et al. MMR vaccine considered as the cause of aseptic meningitis. Jpn J Med 1990; No.3441:43-45.

133. Anonymous. Mumps prevention. Recommendations of the Immunization Practices Advisory Committee (ACIP). M M W R 1989; 38:388-400.

134. Gibbs CJJr. Chronic Neurological Diseases. In: Evans AS, ed. Viral Infections of Humans: epidemiology and control. 3rd ed. New York: Plenum Publishing Corporation, 1989:781-806.

135. Anonymous. Subacute Sclerosing Panencephalitis Surveillance: United States. M M W R 1982; 31:585.

136. Schaffner W, Fleet WF, Kilroy AW, et al. Polyneuropathy following rubella immunization: A follow-up study and review of the problem. Am J Dis Child 1974; 127:684-688.

137. Preblud SR. Some current issues relating to rubella vaccine. J A M A 1985; 254:253-256.

138. Polk BF, White JA, DeGirolami PC. A controlled comparison of joint reaction among women receiving one of two rubella vaccines. Am J Epidemiol 1982; 115:19-25.

139. Tingle AJ, Allen M, Petty RE, et al. Rubella-associated arthritis. I. Comparative study of joint manifestations associated with natural rubella infection and RA 27/3 rubella immunization. Ann Rheum Dis 1986; 45:110-114.

140. Measles Prevention: Recommendations of the Immunization Practices Advisory Committee (ACIP). M M W R 1989; 38:1-18.

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

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

143. Manitoba Immunization Monitoring System. Report of Immunizing Agents by Provider and Type, March 22. Winnipeg: Manitoba Health Services Commission, 1990.

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

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

146. Nkowane BM, Wassilak SG, Orenstein WA, et al. Vaccine-associated paralytic poliomyelitis: United

States: 1973 through 1984. J A M A 1987; 257:1335-1340.

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

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

149. Melnick JL. Live Attenuated Poliovaccines. In: Plotkin SA, Mortimer EA, eds. Vaccines. Toronto: W.B. Saunders Company, 1988:115-157.

150. World Health Organization. Expert Committee on Poliomyelitis: Second Report. WHO Tech Rep Ser 1958; No.145:1-83.

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

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

153. Schlech WF, Ward JI, Band JD, et al. Bacterial meningitis in the United States, 1978 through 1981. J A M A 1985; 253:1749-1754.

154. *Haemophilus influenzae* Type b Prevention. Epidemiology Notes, New York State Department of Health 1989; 4:1-2.

155. Ward J, Broome CV, Harrison LH, et al. *Haemophilus influenzae* Type b Vaccines: lessons for the future. Pediatrics 1988; 81:886-892.

156. Makela PH, Peltola H, Käyhty H, et al. Polysaccharidevaccines of group A *Neisseria meningitidis* and *H.influenzae* type b: a field trial in Finland. J Infect Dis 1977; 136(Suppl):S43-S50.

157. Ward JI, Cochi S. *Haemophilus influenzae* vaccines. In: Plotkin SA, Mortimer EA, eds. Vaccines. Toronto: W.B. Saunders Co., 1988:300-332.

158. Wilfert CM. Epidemiology of *Haemophilus influenzae* type b Infections. Pediatrics 1990; 85(Suppl):631-635.

159. Hammond GW, Rutherford BE, Malazdrewicz R, et al. *Haemophilus influenzae* meningitis in Manitoba and the Keewatin District, NWT: potential for mass vaccination. Can Med Assoc J 1988; 139:743-747.

160. Harrison LH, et al. Case-control efficacy study of the polysaccharide *Haemophilus influenzae* type b (Hib) vaccine. Program and Abstracts of the 27th Interscience Conference on Antimicrobial Agents and Chemotherapy, Oct. 1-4, Abstract 319. New York: 1987.

161. Black SB, Shinefield HR. Efficacy of *Haemophilus influenzae* type b (b-CAPSA 1) polysaccharide vaccine in 87,541 children. Pediatr Res 1987; 21:322a.

162. Murphy TV, et al. The protective efficacy (PE) of *Haemophilus influenzae* type b (Hib) polysaccharide vaccine (PV). Program and Abstracts of the 27th Interscience Conference on Antimicrobials and Chemotherapy, Abstract 317. New York, Oct. 1-4, 1987.

163. Osterholm MT, et al. Lack of protective efficacy and increased risk of disease within 7 days after vaccination associated with *Haemophilus influenzae* type b (Hib) polysaccharide (PS) vaccine use in Minnesota (MN). Program and Abstracts of the 27th Interscience Conference on Antimicrobial Agents and Chemotherapy, Abstract 318. New York, Oct. 1-4, 1987.

164. Murphy TV. *Haemophilus* b polysaccharide vaccine: need for continuing assessment. Pediatr Infect Dis J 1987; 6:701-703.

165. Granoff DM, Osterholm MT. Safety and efficacy of *Haemophilus influenzae* type b polysaccharide vaccine. Pediatrics 1987; 80:590-592.

166. *Haemophilus influenzae* Type b Conjugate Vaccine. Statement of the Committee on Infectious Diseases. Pediatrics 1988; 81:908-911.

167. Eskola J, Peltola H, Takala AK, et al. Efficacy of *Haemophilus influenzae* type b polysaccharide-

diphtheria toxoid conjugate vaccine in infancy. N Engl J Med 1987; 317:717-721.

168. Ward JI, Brenneman G, Lepow M, et al. *Haemophilus influenzae* Type b anticapsular antibody responses to PRP-pertussis and PRP-D vaccines in Alaska native infants. J Infect Dis 1988; 158:719-723.

169. Update: Prevention of *Haemophilus influenzae* type b disease. M M W R 1988; 37:13-16.

170. Recommendations of the Immunization Practices Advisory Committee (ACIP). *Haemophilus influenzae* Conjugate Vaccines for Prevention of *Haemophilus influenzae* type b Disease Among Infants and Children Two Months of Age and Older. M M W R 1991; 40:1-7.

171. Black SB, Shinefield RA, Hiatt B, Fireman B, Polen M, Lampert D. Efficacy of HbOC conjugate *Haemophilus influenzae* type b vaccine in a study population of 48,000 infants. In: Program and Abstracts of the 30th Interscience Conference on Antimicrobial Agents and Chemotherapy, Oct.21-24. Atlanta, Georgia: 1990.

APPENDIX 3

AN OVERVIEW OF MEDICAL RECORD LINKAGE

TABLE OF CONTENTS

1. INTRODUCTION

The idea of linking records is simply the bringing together of information from two independent source records that are believed to relate to the same individual or family.[1] Such records are said to be "linked" and may be treated as a single record for one individual or family. With successive linkings, the information may take on the characteristics of a collection of personal or family histories.

2. HISTORY

The term "medical record linkage" was first used in 1946 by H.L. Dunn, Chief of the United States National Bureau of Vital Statistics.[2] As Acheson describes in his classic text *Medical Record Linkage*,[1] Dunn introduced the new term to a group of Canadian vital statisticians in this way: "Each person in the world creates a book of life. This book starts with birth and ends with death. Its pages are made up of the records of the principal events in life. Record linkage is the name given to the process of assembling the pages of this book into a volume."

This literature review is concerned with record linkage as it relates to the health care system's need for information about the whole population, but the same principles may be applied to any field in which it is

necessary to bring together information recorded about persons in different places or at different times.[1] Acheson has outlined the historical development of medical record linkage.[1] Concern with the correlation of community information had risen during the eighteenth and nineteenth centuries, as populations became more mobile, and life and the fiscal requirements of the State became more complex. With twentieth century medicine came the view of the cumulative personal file of health data as a tool to advance knowledge of chronic disease and genetics. The trend toward illness documentation by all agencies delivering health care produced what Bothwell termed, in 1965, an "epidemic of medical records",[3] and the definition of a new type of medical problem: that "where the data to solve the problem exist in part or in full, but are inaccessible".[1] The lack of continuity of health records maintained by physicians, hospitals, and local health and education authorities was emphasized in 1967 by Godber,[4] who said "we are stuck with a record in its most primitive manuscript form that is almost useless for later reference".

Dunn, in 1946, first envisaged the assembly of health records into personal files over a lifetime, with linkage implying that records are brought together by means of common identification data (for example names, date of birth) which ensure that the records are assigned

to the correct file.[1] By 1957, Canadian geneticist H.B. Newcombe had recognized the full implications of extending the principle to the arrangement of personal files in family groups,[5] and the year 1959 saw the application in Britain of the computer to the problems of sorting and matching personal records with discrepant identification data.[1] Commenting on the first use of computerized medical records by a government medical officer in Britain, Godber noted:[4] "It is not coincidental that he is about the only Medical Officer of Health in the country...who manages to get about 90 per cent. of the children immunized".

The National Health Service in Britain, under which a single system provided virtually all health care, presented an ideal opportunity to British researchers to examine for the first time the practical application of prospective record linkage for a whole population.[1] In 1962, a regional pilot study, the Oxford Record Linkage Study, was begun.[6] The early pilot study was later described by Godber[4] as "pioneer work" and "a pretty primitive example of record linkage", but in its fully developed form the Oxford Record Linkage Study was highly influential outside the region, and laid the foundation for the Office of Population Censuses and Surveys (OPCS) Longitudinal Study in England and Wales, and for the Scottish national system of medical record linkage.[6]

The definition of medical record linkage used by the Oxford Record Linkage Study remains appropriate: "A system of linked health records which brings together selected data of biological interest for a whole population commencing with conception and ending in death, in a series of personal cumulative files, the files being organized so that they can be assembled in family groups. The term record linkage may apply specifically to the techniques of assembling the files in spite of errors and omissions in the identifying particulars, or may be used in a more general sense to apply to the organization involved".[1]

Both the idea and technique of family record linkage were developed in Canada, by Newcombe.[1] This work began in 1957, and was possible because vital statistics identifying data collected in Canada surpassed that of any other country, and because material was already collected in a form accessible to computers.[1] Early studies by Newcombe linked British Columbia health and vital records, and strongly supported the case that linkage and integration of various source records could be used in health care administration, demographic studies, the provision of health statistics, and for medical research.[7] Over more than 20 years, Newcombe and his colleagues carried computer techniques of linking records to a high level of sophistication,[1] and since

that time Statistics Canada has contributed definitively to the mathematical theory of record linkage, and has developed an exceedingly flexible computer system for handling all aspects of a linkage operation.[8]

Record linkage systems are currently in operation in a number of centres throughout the world,[9,10] including Britain, Northern Ireland, Canada and the United States. In North America, record linkage and long-term follow-up have generally been carried out centrally at Statistics Canada for Canadian mortality data, and at the National Center for Health Statistics for American mortality data.[10] During the past decade, Statistics Canada has made available, to medical investigators, automated facilities for follow-up studies.[11] Two such centralized follow-up facilities, the Canadian Mortality Data Base and the National Cancer Incidence Reporting System, have been used to monitor very large study populations for delayed effects on health, and consist of provincial records converted into a standardized format under the custody of Statistics Canada.[12] The U.S. National Center for Health Statistics reported 122 users of the National Death Index in the November 1981-December 1985 period, with studies involving exposure cohorts, disease cohorts, lifestyle and risk factors, clinical trials, and general population cohorts.[10]

Roos and Nicol[13] point out that, while Statistics Canada data have received considerable attention, an alternative non-centralized data processing approach has also been taken in Canada. Provincial databases, developed from data routinely collected as part of administering Canada's national health insurance within each province, have also been successfully used in a similar fashion in several provinces.[10,12]

3. CONCEPTS

The task of keeping a population-wide file of general health histories up-to-date requires a computer-based information processing system.[9] When presented with a new health record, this system must be capable of determining to which individual in the master health history file the record should be attributed, following which the process of incorporating the new health information into the master history by linkage is relatively simple.

There are two principal steps prior to any linking operation.[8,9,14,15] The first is the searching step, in which potentially linkable pairs of records are sought, narrowing interest to a small number of records in the main health file which seem to have special relevance to the new record. In this step, it is essential to reduce the number of failures to bring potentially linkable

records together for comparison, and this must be done without resort to excessive amounts of additional searching. The second step is the matching step, in which pairs of records are compared to determine whether they should be linked. This entails detailed comparison of the new record with each of the existing records in the group or block. In the automated process, the machine must apply in numerical form the rules of judgment by which a human clerk would decide whether or not a pair of records relates to the same person when some of the identifying information agrees and some disagrees.[14] Linking is the process by which pairs of correctly matched records are brought together in such a way that they may be treated as a single record for one individual.[15]

Newcombe[14] describes the optimization of the searching step, in which errors in the form of failure to bring potentially linkable pairs of records together for comparison must be minimized. These errors could be reduced to zero by comparing each incoming record with all of the records already present in the master file, but, where the files are large, this procedure entails enormous numbers of wasted comparisons of pairs of records that are unlinkable. For this reason, the file is arranged in an orderly sequence, using identifying information that is common to both the incoming records

and those already present in the master file. Detailed comparisons need then be carried out only within the small portions of the master file for which the sequencing information is the same as that on the incoming records. Any kind of identifying information available on all the records may be used for sequencing the files, and the identifier should subdivide the file with the greatest efficiency and an acceptably low level of wasted comparisons.

Gill and Baldwin describe the practical aspects of matching and linking.[15] The fundamental requirement for correct matching is that there should be a means of uniquely identifying the individual (or episode or family) on every document to be linked. Where records include unique identifiers, matching is a relatively simple process, and is "all-or-none" matching since the pairs of records compared either do or do not match. Where no unique identifier is available, matching depends on achieving the closest equivalent to unique identification by using several matching variables, each of which is only a partial identifier, but which in combination provide a match which is sufficiently accurate for the intended uses of the linked data. The use of several identifiers to match records is called "probability matching" since the object is to estimate the probability that the records in each pair refer to

the same individual. Based on the discriminating power and reliability of each identifier, numerical values can be calculated for the amount of agreement or disagreement and expressed as weights which indicating the likelihood that a pair of records belong to the same individual.

4. RECORD LINKAGE IN MANITOBA

Roos and colleagues[10,16] describe the health insurance database in the province of Manitoba. The Manitoba Health Services Commission (MHSC) computer registry or master enrolment file has been constructed from individual histories generated from the population registry and from health insurance claims filed routinely with MHSC. The MHSC data are population-based, and are designed to cover all the individuals in the province. All hospital and medical care, with a few minor exceptions (such as private room, cosmetic surgery and some out-of-province care) is available to all provincial residents registered with MHSC. Non-participation in the Manitoba health plan is minimal, as residents are not required to pay any premiums to register for insured benefits, and no limitations are placed on provider or use. The health database contains information on all registrants, regardless of where care was received.

The MHSC enrolment file includes a unique individual patient identification number (the PHIN, personal health

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

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

Wajda and Roos[10] report that record linkage has proven both possible and practical in Manitoba, and in several other Canadian provinces, particularly Saskatchewan. In Manitoba, different health care files can currently be linked using the identification numbers and other variables to form individual-based data which permits statistics (such as those relating to hospital admissions) to be compiled according to the number of individuals involved rather than simply the number of events. These researchers, outlining the need for simpler and less expensive methods of carrying out record linkage, demonstrated the use of advanced software in the linkage of 1979-1984 information from the MHSC registry file with the Canadian Mortality Data Base. In Manitoba, retrospective cohort analyses of the outcomes of common

surgical procedures have also been conducted,[17-19] and record linkage has also been successfully used to expand data collected for other purposes and with various combinations of data, such as survey, clinical, claims, and mortality data.[10]

The Manitoba Immunization Monitoring System (MIMS)[20] file is also built on the MHSC population registry. Children born on or after January 1, 1980 are automatically entered into MIMS at birth or after transfer into the province. Children who die or move out of the province are automatically removed from the monitoring system, but remain in the MIMS database until their file has been inactive for two years. The MIMS file contains the individual patient identifier (the PHIN), the date of birth, the sex, date of termination (death or migration), and the attached immunization records (including immunization tariff code, service date, and restrictions).

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

5. REFERENCES

1. Acheson ED. Medical Record Linkage. London: Oxford University Press, 1967.
2. Acheson ED. In: Acheson ED, ed. Record Linkage in Medicine. Proceedings of the International Symposium, Oxford, July 1967. Edinburgh: E. & S. Livingstone, 1968.
3. Bothwell PW. A New Look at Preventive Medicine. London: Pitman Medical Publishing, 1965.
4. Godber G. In: Acheson ED, ed. Record Linkage. Proceedings of the International Symposium, Oxford, July 1967. Edinburgh: E. & S. Livingstone, 1968:1-4.
5. Newcombe HB. Detection of Genetic Trends in Public Health. In: Effect of Radiation on Human Heredity. Geneva: WHO, 1957.
6. Acheson ED. In: Baldwin JA, Acheson ED, Graham WJ, eds. Textbook of Medical Record Linkage. Toronto: Oxford Medical Publications, 1987:1-12.
7. Newcombe HB. Early Stages of Linked Records. In: Acheson ED, ed. Record Linkage in Medicine. Proceedings of the International Symposium, Oxford, July 1967. Edinburgh: E. & S. Livingstone, 1968:7-34.
8. Newcombe HB. Handbook of Record Linkage. Toronto: Oxford Medical Publications, 1988.

9. Hassard TH. Writing the Book of Life: Medical Record Linkage. In: Brook RJ, et al., eds. The Fascination of Statistics. New York: Marcel Dekker, 1986:25-46.

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

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

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

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

14. Newcombe HB. Record Linking: The Design of Efficient Systems for Linking Records Into Individual and Family Histories. In: Baldwin JA, Acheson ED, Graham WJ, eds. Textbook of Medical Record Linkage. Toronto: Oxford Medical Publications, 1987:15-38.

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

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

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

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

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

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

APPENDIX 4

MIMS DATA QUALITY

POST-IMPLEMENTATION STUDIES

COMPARISON OF THE MANITOBA IMMUNIZATION MONITORING SYSTEM RECORDS AND CLIENT IMMUNIZATION RECORDS OF A GROUP OF URBAN PEDIATRIC PRACTICE PATIENTS

J.D. Roberts

November, 1991

ABSTRACT

The physician client immunization records and the computerized Manitoba Immunization Monitoring System (MIMS) records of a birth cohort of 131 infant patients of a large urban group pediatric practice were examined and compared. 98% of all immunizations given to the cohort were provided by the clinic physicians. There was excellent agreement between the two record sources with respect to data on personal identification, service provider and vaccine type. The study showed a miscoding rate equivalent to 5 errors per 1,000 pairs of DTP/OPV immunizations administered. The rate of failure to successfully claim for immunization service was equivalent to 8 per 1,000 pairs of DTP/OPV immunizations administered. Clinic physicians documented all immunizations for which they billed. Service dates agreed 98% of the time, with the MIMS-recorded date of immunization differing from the actual date by more than one day for only one in every 100 immunization events, when physician records were used as the standard. Compliance with the provincial immunization schedule by age twelve months was 98.5%.

ACKNOWLEDGEMENTS

The willingness of the Manitoba Clinic, Winnipeg, Manitoba, to help with this investigation is greatly appreciated. I wish to thank the clinic's administrative and pediatric staff for their cooperation and assistance. It is expected that the study, which demonstrates a highly efficient immunization system to be in operation at the clinic, will also lead to a considerable streamlining of the MIMS system. I am grateful to Mrs. Lynn Heise, Manitoba Health, who provided valuable technical assistance.

LIST OF TABLES

TABLE OF CONTENTS

1. INTRODUCTION

The Manitoba Immunization Monitoring System (MIMS) of the Province of Manitoba completed its first year of full service in 1990. All children born in, or moving into, Manitoba since January 1, 1980, have an immunization file in this computerized system. MIMS captures immunizations given to all children either automatically, through physician claims to the provincial health insurance system, or manually, through public health units. Manitoba is now unique in its ability to provide immunization rates and other immunization-related data on a population basis. This study addresses the question of MIMS data quality.

2. MANITOBA IMMUNIZATION MONITORING SYSTEM

The Manitoba Immunization Monitoring System (MIMS) is described in the Manitoba Immunization System User Manual.[1]

The essential elements of MIMS are shown in Appendix 1. MIMS is built on the computerized population registry of the Manitoba Health Services Commission (MHSC). Children are automatically entered into MIMS at birth, or after transfer into the province, if they were born on or after January 1, 1980. Children who die or move out of the province are automatically removed from the

monitoring system, but remain in the MIMS database until their file has been inactive for two years.

MIMS is a mainframe system, with terminals in all the public health regions of the province. The MIMS database is shared by all public health units, including federal and municipal units, and can be updated by anyone with access to the terminal. Address changes recorded in the MHSC registry are used to update the MIMS file automatically, so that each child is assigned to the correct regional health unit.

Information regarding immunizations given by public health nurses is entered directly at the health unit. Physician immunizations have been captured directly from the tariff codes on their billing cards since November, 1987. The Manitoba provincial immunization schedule and the tariff codes which MIMS recognizes (regardless of whether they are part of the regular immunization schedule) are shown in Appendices 2 and 3.

The records in MIMS are subjected to monitoring activities, which can be seen in Appendix 4. The quality of the information in the database is improved by the monitoring system, which, at specific ages, checks each child's record for completeness. If the record indicates that the child has not had one of the scheduled immunizations, a letter (Follow-up Record, Appendix 5) is produced which is sent to the health care provider of

last record, requesting that they update the record if possible.

During the monitoring process, MIMS looks for the tariff codes specific to each dose of vaccine. Thus, if a child has been given three doses of DPT but the tariff code for the first dose has been used for all three, a letter will be generated, allowing the coding errors to be corrected. Where an obvious coding error has occurred (for example, a third DTP given at the correct age but coded as a first dose), regional staff are permitted to make the correction directly. Monitoring is conducted in the month of the child's first, second and sixth birthdays. The quality of the data therefore improves with the age of the child.

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

The Manitoba provincial immunization schedule (Appendix 2) calls for all children in the first year of life to receive routine immunization with preparations containing the following agents: diphtheria toxoid, tetanus toxoid, pertussis vaccine and poliomyelitis vaccine. The diphtheria and tetanus toxoids are administered in a combined preparation (DT vaccine) and most children receive these toxoids in a preparation which also contains pertussis vaccine (DTP vaccine). The

schedule calls for DTP/DT vaccine administration at each of two, four and six months of age. Poliomyelitis vaccine is administered separately, almost always as the live vaccine (oral poliomyelitis vaccine or OPV) and uncommonly as the killed vaccine (inactivated poliomyelitis vaccine or IPV). The schedule calls for poliomyelitis vaccine administration at each of two and four months of age. Analysis of the MIMS database has shown that a high proportion of children continue to receive poliomyelitis vaccine at six months of age.

4. IMMUNIZATION IN MANITOBA

Approximately half of the province's children live in the city of Winnipeg, where a large number of family physicians and pediatricians provide about 97% of all immunizations[2] to a highly mobile population. In contrast, in rural areas of Manitoba, provision of immunization is divided almost equally overall between family physicians and public health nurses. The rural population is relatively stable, and patient movement between medical practices is limited.

5. MIMS DATA QUALITY

Unpublished studies conducted for Manitoba Health have examined the reliability and validity of the MIMS

data, and indicate excellent agreement between the computerized MIMS data and physician-patient immunization records.

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

To provide a more complete picture of MIMS data quality, information concerning the agreement between MIMS records and physician immunization records from the city of Winnipeg is required. In addition, further research requires knowledge of agreement between MIMS records and physician immunization records with respect to immunization service dates.

6. STUDY OBJECTIVES

The general objective of the study is to provide additional information concerning provincial MIMS data quality. Specifically, the study examines the extent of agreement between the computerized MIMS immunization records and the client immunization records of children

immunized by the pediatricians working at a large Winnipeg clinic with respect to personal identification data (MHSC number, name, date of birth) and immunization data (immunization type, service date and service provider).

7. SAMPLE

The sample was drawn from the "newborn" registers maintained by the seven individual pediatricians at a large Winnipeg clinic. These registers record all infants attended and enrolled as clinic patients at birth, and provide date of birth, name, and assigned clinic record number. Children born on or after January 1, 1990, who remained clinic patients for at least one year after birth were included. The final sample contained the clinic records of 131 eligible infants, with approximately equal numbers attended by each of the seven clinic pediatricians. All infants had passed the first birthday by the study date.

8. METHOD

The clinic records provided personal identification data (name of the infant and parents/guardians, MHSC number, date of birth) and immunization data. These were examined manually and the relevant information noted for each study subject.

For each subject, the personal identification data provided by the clinic record were used to retrieve the individual computerized MIMS immunization record.

For each individual, the clinic and MIMS records for the first year of life were compared, and the number and nature of disagreements noted. Comparisons were made on the following items: personal identification data (MHSC number, name, date of birth) and immunization data (immunization type, service date and service provider for each of the five recommended immunizations for the first year of life, and the six-month dose of poliovaccine and MMR vaccine). Disagreements were examined by tariff codes, by source of record and by provider. Immunization rates for the study group were calculated.

9. RESULTS

9.0 Personal Identification Data

Names, MHSC numbers (including alternate last names and altered MHSC numbers), and birth dates were identically recorded by both record sources in all instances.

9.1 Immunization Data

9.1.0 Immunizations Administered

The clinic documented the administration of 871 immunizations to the study group of 131 children, between birth date and study date. Table 1 summarizes the 871 immunizations by vaccine, dose, and distribution to the study group.

MIMS documented the receipt of 856 immunizations by the study group, between birth date and study date. Table 2 summarizes these 856 immunizations by vaccine, dose, and distribution to the study group.

9.1.1 Service Dates

All children who received OPV vaccine received both DTP and OPV on the same day. Identical service date discrepancies occurred for immunizations administered on the same day. The study found 10 service date discrepancies in a total of 490 individual clinic immunization events (immunizations given on the same day were considered together as immunization events).

Table 3 summarizes the distribution of service date discrepancies. Six discrepancies placed the MIMS service date within one day of the clinic service date. Four discrepancies placed the MIMS service date 2-6 days from the clinic service date. Overall, using the physician record as the gold standard, for approximately one in

every 50 immunization events the actual date of immunization fell not on the MIMS-recorded date but within 6 days of this date, with one in every 100 actual dates falling within one day of the MIMS-recorded date.

This rate should be generalized with caution. Service date discrepancies can only arise through human error during the recording of service dates, either by the physician during record documentation, the billing clerk during claim preparation, or the terminal clerk during claim data input. While it can be assumed that the rate of random errors made by billing clerks and terminal operators will be fairly constant in other clinic situations, the sample size in this study was small and the true service date error rate will, if anything, be lower in large studies which do not depend upon the reliability of physician documentation.

9.1.2 Service provider

Service provider was accurately recorded by physician and physician number on MIMS for all immunizations administered by clinic physicians.

9.1.3 Vaccine Type and Tariff Code

The vaccine types recommended in the provincial schedule (DTP, OPV, MMR) were recorded by clinic physicians in all cases, and the MIMS tariff codes

represented the appropriate vaccine types. Table 4 (page 14) shows the number of incorrect tariff codes contained in the MIMS records, by dose. The overall miscoding rate was 1.3 per 100 immunizations given. Since DTP and OPV immunizations are usually miscoded in pairs, the study showed a miscoding rate equivalent to 5 errors per 1,000 pairs of DTP/OPV immunizations administered.

9.1.4 Missing Records

Of the 871 immunizations recorded at the clinic, 18 failed to appear in the MIMS records (Table 5, page 14). For all 12 missing MMR immunizations, service date preceded study date by less than one month. The time usually allowed for the processing of a physician service claim and generation of a MIMS record is three months.

The study therefore calculated, for the three recommended doses of DTP/OPV in the first year of life, a rate of failure to successfully claim for immunization service equivalent to 8 per 1,000 pairs of DTP/OPV immunizations administered.

MIMS recorded 19 immunizations which did not appear in the clinic records. These were administered by non-clinic physicians. Clinic physicians therefore documented all immunizations for which they billed. None of the study children were immunized by public health nurses.

9.1.5 Immunization Rates

Immunization rates were calculated from each source, by dose, and are shown in Table 6 (page 16). Both the clinic and the MIMS records showed very high rates for each of the first recommended three doses (first DTP/OPV, second DTP/OPV and third DTP).

Clinic records showed that, of children who received a third DTP, 84% simultaneously received a third OPV. This figure reflects physician practice style - five clinic physicians administered a third OPV to 100% of children to whom they administered a third DTP. Using clinic records as the standard for MMR administration, 9% of the study children remained unimmunized. All were over 365 days of age, with only three under 400 days of age.

Table 6 also shows the rates of full immunization, according to the provincial schedule, by age 12 months (three doses DTP, two doses OPV). The rate taken from the clinic records was 96.2%, from the MIMS records 97.7%, and when the immunization information from both sources was combined the fully immunized rate was 98.5%.

10. DISCUSSION

The results show a very high level of agreement between clinic records and MIMS records with respect to personal identification and immunization information.

Personal data, vaccine type and service provider were represented on MIMS with 100% reliability.

Agreement between service dates was high. This new information is relevant to further research in which MHSC and MIMS data is used in situations where knowledge of the date of immunization in relation to the occurrence of clinical events is crucial.

Only a small number of immunizations were billed with incorrect tariff codes. This finding is consistent with those of other studies, and, given the high quality of MIMS data concerning vaccine type and service date, supports the current practice of having MIMS staff make on-line corrections to illogical tariff codes.

All immunizations billed by the clinic were clearly documented in the clinic record, and very few documented immunizations failed to generate a billing claim and MIMS record.

The MIMS monitoring process, in examining each computerized immunization record in the month of a child's first birthday, would have flagged the DTP/OPV immunizations of 10 children as unacceptable to the system. Clinic physicians would have received enquiries regarding 10 patients concerning missing immunizations (documented but not billed 3, not given 2) and miscoded immunizations (5). Instructing the monitoring process to ignore miscodes would have resulted in only one enquiry

to each of five physicians during the infancy of 131 patients. These enquiries would have called attention to the fact that immunization services at three visits were not remunerated.

Immunization rates for the first three doses of DTP/OPV were found to be very high, and even higher when information from the two sources was combined. MIMS records produced an MMR immunization rate for the group which was artificially lowered by the slow turnaround time for processing billing claims. Clinic records also showed a less than ideal MMR immunization rate for age. This might have its cause in inter-physician differences in practice style with regard to age at MMR immunization, or in an overall decrease in health consciousness and the number of physician office visits after infancy.

11. SUMMARY

The clinic studied demonstrated a very high degree of immunization efficiency with respect to immunization rates, documentation and billing. The MIMS data concerning the immunization of children who attended this clinic throughout infancy was extremely accurate and reliable. The study provides further evidence that, while the provision of a distinct tariff code for each vaccine type has resulted in highly accurate MIMS vaccine coverage data, the monitoring of the accuracy of the

separate codes for each dose of vaccine administered is probably no longer necessary. Further study should include the investigation of MIMS data concerning Winnipeg children who receive immunizations from multiple physicians and medical facilities.

12. REFERENCES

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

2. Manitoba Immunization Monitoring System. Report of Immunizing Agents by Provider and Type. Winnipeg: Manitoba Health Services Commission, 1990.

Table 1
Clinic Records: Immunization Summary

dose and vaccine	number of children receiving	proportion of children receiving
first DTP	129	98.5%
first OPV	129	98.5%
second DTP	131	100.0%
second OPV	131	100.0%
third DTP	126	96.2%
third OPV	106	90.8%
MMR	119	90.8%
TOTAL	871	-

Table 2
MIMS Records: Immunization Summary

dose and vaccine	number of children receiving	proportion of children receiving
first DTP	128	97.7%
first OPV	128	97.7%
second DTP	131	100.0%
second OPV	131	100.0%
third DTP	129	98.5%
third OPV	104	79.4%
MMR	105	80.2%
TOTAL	856	-

Table 3
Source Comparison: Service Date Discrepancies

number of records (N = 10)	number of days by which MIMS record differed from clinic record
1	+6
1	+3
4	+1
2	−1
2	−3

Table 4
Source Comparison: Tariff Codes

dose, vaccine and tariff codes	number of tariff code errors	nature of tariff code errors
first DTP/OPV (8601/8611)	0	–
second DTP/OPV (8602/8612)	1	coded as 8601/8611
	1	coded as 8603/8613
third DTP/OPV (8603/8613)	1	coded as 8601/8611
	2	coded as 8602/8612
TOTAL	5	–

Table 5
Source Comparison: Missing MIMS Records

dose and vaccine	number of immunizations documented on clinic records	number of immunizations missing on MIMS records
first DTP	129	3
first OPV	129	3
second DTP	131	0
second OPV	131	0
third DTP	126	0
third OPV	106	0
MMR	119	12
TOTAL	871	18

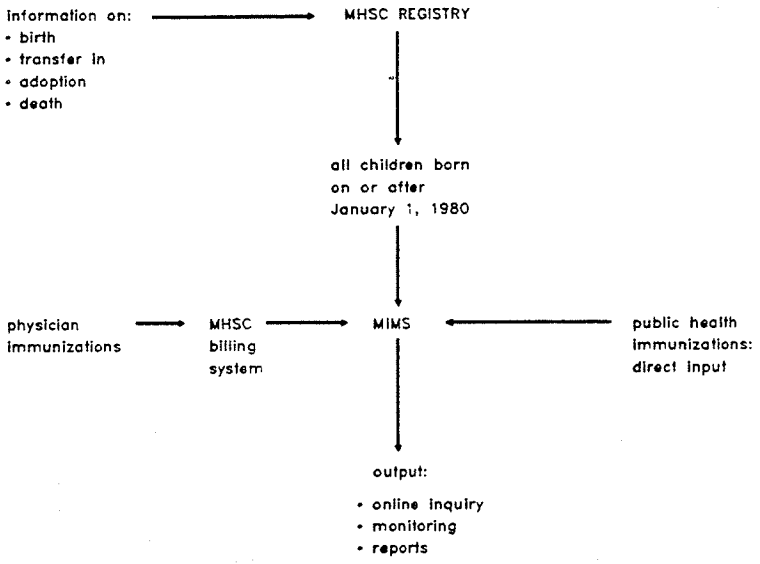
Table 6
Immunization Rates

dose	proportion immunized		
	source: clinic record	source: MIMS record	source: combined records
first DTP/OPV	98.5%	97.7%	100.0%
second DTP/OPV	100.0%	100.0%	100.0%
third DTP	96.2%	98.5%	98.5%
third OPV	80.9%	79.4%	80.9%
MMR	90.8%	80.2%	92.4%
fully immunized*	96.2%	97.7%	98.5%

* fully immunized by the first birthday, according to the provincial immunization schedule (DTP three doses, OPV two doses)

APPENDIX 1

The Essential Elements of MIMS


information on:
• birth
• transfer in
• adoption
• death
MHSC REGISTRY
all children born on or after January 1, 1980
physician immunizations
MHSC billing system
MIMS
public health immunizations: direct input
output:
• online inquiry
• monitoring
• reports

APPENDIX 2

Manitoba Provincial Immunization Schedule

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.

APPENDIX 3

Immunization Alternatives

IMMUNIZATION ALTERNATIVES

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

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

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

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

APPENDIX 4

MIMS Monitoring Activities

		MIMS MONITORING PROCESS			
		FOLLOW-UP	REMINDER	IMMUNIZATION	FOLLOW-UP
PRESCHOOL	1 YEAR	SERVICE PROVIDER			
	2 YEARS	SERVICE PROVIDER			
	5 YEARS		PARENT		
SCHOOL	6 YEARS	SERVICE PROVIDER		PARENT	HEALTH OFFICE
	12 YEARS			PARENT	HEALTH OFFICE
	14 YEARS			PARENT	HEALTH OFFICE
	15 YEARS		PARENT		
	17 YEARS			PARENT	

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

APPENDIX 5

MIMS Follow-up Record

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

MHSC NO.  CHILD SURNAME        GIVEN      SEX  BIRTHDATE
XXXXXX    XXXXXXXXXXXXXXXXXX  XXXXXXXXX  X     XX/XX/XX
ALTERNATE SURNAME XXXXXXXXXXXXXXXXXXX            YY MM DD
RES    XXXXXXXXXXXXXXXXXXXXXXXX  MAIL XXXXXXXXXXXXXXXXXXXX
ADDR. XXXXXXXXXXXXXXXXXXXXXX    ADDR. XXXXXXXXXXX XXX XXX

PARENT/GUARDIAN: XXXX XXXXXXXXXXXXX  HOME PHONE: XXX XXXX
                                     WORK PHONE: XXX XXXX

SERVICE PROVIDER: XXXX   HEALTH UNIT: XX XXX PH: XXX XXXX
XXXXXXXXXXXXXXXXXXXXXXXX   XXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
XXXXXXXXXXXXXXXXXXXXXX     XXXXXXXXXXXXXXXXXXXXXX
XXXXXXXXXXXXXXXXXXXXXX     XXXXXXXXXXXXXXXXXXXXXX
XXXXXXXXXXXXXXX XXX XXX    XXXXXXXXXXXXXXXXXXXXXX XXX XXX
```

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

IMMUNIZATIONS NOT ON OUR RECORD AS OF XXXXXXXXXXX

RECOMMENDED AGE/MTHS	CODE	DESCRIPTION	SERVICE DATE	PROVIDER
XX XXXX	XXXX	XXXXXXXXXXXXX XXXXXXXXXXXXXXXXXX	__/__/__	________
XX XXXX	XXXX	XXXXXXXXXXXXX XXXXXXXXXXXXXXXXXX	__/__/__	________
XX XXXX	XXXX	XXXXXXXXXXXXX XXXXXXXXXXXXXXXXXX	__/__/__	________
XX XXXX	XXXX	XXXXXXXXXXXXX XXXXXXXXXXXXXXXXXX	__/__/__	________
XX XXXX	XXXX	XXXXXXXXXXXXX XXXXXXXXXXXXXXXXXX	__/__/__	________
XX XXXX	XXXX	XXXXXXXXXXXXX XXXXXXXXXXXXXXXXXX	__/__/__	________
XX XXXX	XXXX	XXXXXXXXXXXXX XXXXXXXXXXXXXXXXXX	__/__/__	________

COMMENTS:

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

COMPARISON OF THE MANITOBA IMMUNIZATION MONITORING SYSTEM RECORDS AND CLIENT IMMUNIZATION RECORDS OF A GROUP OF RURAL FAMILY MEDICAL PRACTICE PATIENTS

J.D. Roberts

November, 1991

ABSTRACT

The physician client immunization records and the computerized Manitoba Immunization Monitoring System (MIMS) records of a cohort of 122 infant patients of a large rural group practice were examined and compared. 76% of all immunizations given to the cohort were provided by the practice physicians. There was excellent agreement between the two record sources on personal identification data. The overall rate of immunizations incorrectly coded at input by the clinic was 2.1%. 6.6% of immunizations documented on the client record as given were not billed to the provincial health insurance system and produced no MIMS record. 4.7% of immunizations billed to the provincial health insurance system and recorded on MIMS were not documented in the client record. Compliance with the full provincial immunization schedule was 87.7% at the time of examination.

ACKNOWLEDGEMENTS

The willingness of the Steinbach Family Medical Centre, Steinbach, Manitoba, to help with this investigation is greatly appreciated. Thanks are extended to the administrative and medical staff, and to Ms. Alison Logan who provided valuable medical and technical assistance.

TABLE OF CONTENTS

LIST OF TABLES

1. INTRODUCTION

The Manitoba Immunization Monitoring System (MIMS) of the Province of Manitoba completed its first year of full service in 1990. All children born in, or moving into, Manitoba since January 1, 1980, have an immunization file in this computerized system. MIMS captures immunizations given to all children either automatically, through physician claims to the provincial health insurance system, or manually, through public health units. Manitoba is now unique in its ability to provide immunization rates and other immunization-related data on a population basis. This study addresses the question of MIMS data quality.

2. MANITOBA IMMUNIZATION MONITORING SYSTEM

The Manitoba Immunization Monitoring System (MIMS) is described in the Manitoba Immunization System User Manual.[1]

The essential elements of MIMS are shown in Appendix 1. MIMS is built on the computerized population registry of the Manitoba Health Services Commission (MHSC). Children are automatically entered into MIMS at birth, or after transfer into the province, if they were born on or after January 1, 1980. Children who die or move out of the province are automatically removed from the

monitoring system, but remain in the MIMS database until their file has been inactive for two years.

MIMS is a mainframe system, with terminals in all the public health regions of the province. The MIMS database is shared by all public health units, including federal and municipal units, and can be updated by anyone with access to the terminal. Address changes recorded in the MHSC registry are used to update the MIMS file automatically, so that each child is assigned to the correct regional health unit.

Information regarding immunizations given by public health nurses is entered directly at the health unit. Physician immunizations have been captured directly from the tariff codes on their billing cards since November, 1987. The Manitoba provincial immunization schedule and the tariff codes which MIMS recognizes (regardless of whether they are part of the regular immunization schedule) are shown in Appendices 2 and 3.

The records in MIMS are subjected to monitoring activities, which can be seen in Appendix 4. The quality of the information in the database is improved by the monitoring system, which, at specific ages, checks each child's record for completeness. If the record indicates that the child has not had one of the scheduled immunizations, a letter (Follow-up Record, Appendix 5) is produced which is sent to the health care provider of

last record, requesting that they update the record if possible.

During the monitoring process, MIMS looks for the tariff codes specific to each dose of vaccine. Thus, if a child has been given three doses of DPT but the tariff code for the first dose has been used for all three, a letter will be generated, allowing the coding errors to be corrected. Where an obvious coding error has occurred (for example, a third DTP given at the correct age but coded as a first dose), regional staff are permitted to make the correction directly. Monitoring is conducted in the month of the child's first, second and sixth birthdays. The quality of the data therefore improves with the age of the child.

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

The Manitoba provincial immunization schedule (Appendix 2) calls for all children in the first year of life to receive routine immunization with preparations containing the following agents: diphtheria toxoid, tetanus toxoid, pertussis vaccine and poliomyelitis vaccine. The diphtheria and tetanus toxoids are administered in a combined preparation (DT vaccine) and most children receive these toxoids in a preparation which also contains pertussis vaccine (DTP vaccine). The

schedule calls for DTP/DT vaccine administration at each of two, four and six months of age. Poliomyelitis vaccine is administered separately, almost always as the live vaccine (oral poliomyelitis vaccine or OPV) and uncommonly as the killed vaccine (inactivated poliomyelitis vaccine or IPV). The schedule calls for poliomyelitis vaccine administration at each of two and four months of age. Analysis of the MIMS database has shown that a high proportion of Manitoba children continue to receive poliomyelitis vaccine at six months of age.

4. IMMUNIZATION IN MANITOBA

Approximately half of the province's children live in the city of Winnipeg, where a large number of family physicians and pediatricians provide about 97% of all immunizations[2] to a highly mobile population. In contrast, in rural areas of Manitoba, provision of immunization is divided almost equally overall between family physicians and public health nurses. The rural population is relatively stable, and patient movement between medical practices is limited.

5. MIMS DATA QUALITY

The high quality of the MHSC registry data has been confirmed through extensive investigation over the past fifteen years.[3,4,5] Consequently, information contained in MIMS and derived from the registry has been validated.

A review of the validity of physician billing codes was carried out prior to the implementation of the present MIMS system.(Johnson, Manitoba Health, 1986) Parental immunization records and physician billing claims for immunizations were compared for a random sample of urban children, the vast majority of whom are known to be immunized by physicians. The frequency of miscoding by physicians (assuming the parental record to be correct) ranged from 1.9% (for the first dose of DTP) to 4.0% (for the third dose of DTP). The frequency of missing physician billing claims was 3-4% for each immunization. Service dates agreed exactly in 80% of cases. This degree of accuracy was considered sufficient to implement the province wide immunization recording and monitoring system.

The monitoring process provides the means to improve data quality by checking record completeness at specified ages and encouraging record additions and alterations. Although MIMS will accept repeated tariff codes if they are recorded on different dates, the monitoring process will assess the true tariff code as missing and generate

a follow-up letter for correction. This process will also detect immunizations which are unrecorded because administration was not followed by the submission of a physician billing claim.

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, it has captured physician billing claims only since November, 1987. Consequently, in major urban areas, primarily Winnipeg City, where 98% of immunizations are administered by physicians, children born before 1987 are likely to have incomplete MIMS records. Children served by federal public health nurses also have incomplete records, since federal health office access to MIMS was not possible until 1990. Since federal records are known to be incomplete, monitoring is not carried out in these jurisdictions. This problem will correct itself over time as MIMS matures.

To provide a more complete picture of MIMS data quality, information concerning the agreement between MIMS records and physician immunization records is required.

6. STUDY OBJECTIVES

The general objective of the study is to provide information concerning provincial MIMS data quality.

Specifically, the study examines the extent of agreement between the computerized MIMS immunization records and the client immunization records of children immunized by the family physicians working at a large rural clinic. Agreement is compared with respect to personal identification data (MHSC number, name, date of birth) and immunization data (immunization type and service provider).

7. SAMPLE

The sample was drawn from a computerized list of all children born on or between January 1, 1990, and June 30, 1990. Children who received care from any of the physicians in the group between birth and the study date (January 18, 1991) were included. The final sample contained the clinic records of 125 infants.

8. METHOD

The clinic records provided personal identification data (name of the infant, MHSC number, date of birth) and immunization data. These were examined manually and the relevant information noted for each study subject.

For each subject, the personal identification data provided by the clinic record were used to retrieve the individual computerized MIMS immunization record.

For each individual, the clinic and MIMS records for the first year of life were compared, and the number and nature of disagreements noted. Comparisons were made on the following items: personal identification data (MHSC number, name, date of birth) and immunization data (immunization type and service provider, for each of the five recommended immunizations for the first year of life, and the six-month dose of poliovaccine). Disagreements were examined by tariff codes, by source of record and by provider. Immunization rates for the study group were calculated.

MIMS records found to be incomplete on initial record examination were re-examined for completeness three months after the initial examination.

9. RESULTS

9.0 Personal Identification Data

MHSC numbers were unavailable on the clinic records for two children, and their MIMS records could not be accessed using the other identifiers alone. One other child received a new MHSC number through adoption and transferred out of the area prior to the age of the first immunization. These three children were excluded from further analysis.

A further five children had experienced a change of MHSC number since birth and their new numbers were recorded at the clinic. For the 122 children remaining to study, MHSC numbers, names and dates of birth were identically recorded by both record sources in all instances.

9.1 Immunization Data

9.1.0 Immunizations Administered

The clinic recorded documented the administration of 439 immunizations to the 122 children, between birth date and study date. Seven clinic physicians administered some or all of the immunizations received to date by 105 children and all recorded immunizations received by 81 children. Table 1 summarizes the 439 immunizations by vaccine, dose, and distribution to the study group.

MIMS documented the receipt of 573 immunizations by the 122 children (432 from clinic physicians, 46 from other physicians, and 95 from regional public health nurses) between birth date and study date. Table 2 summarizes these immunizations by vaccine, dose, and distribution to the study group.

9.1.1 Service provider

Service provider was accurately recorded on MIMS, by physician and physician number, for all immunizations administered by clinic physicians.

9.1.2 Vaccine Type and Tariff Code

None of the children had a clinic or MIMS record of MMR (or alternate) vaccine. The vaccine types recommended in the provincial schedule (DTP and OPV) were recorded by clinic physicians in all cases, and the MIMS tariff codes represented the appropriate vaccine types. Table 3 shows the number of incorrect tariff codes contained in the MIMS records, by dose. For one child, the second doses of DTP and OPV were both miscoded. The overall miscoding rate by clinic physicians was 2.1 per 100 immunizations given. On this basis alone, MIMS monitoring would define eight children (6.6% of the study group) as having incomplete immunization records.

9.1.3 Missing Records

Of the 439 immunizations recorded at the clinic, 29 (given to 17 children) failed to appear in the MIMS records (Table 4). This indicates that clinic physicians failed to bill for 6.6% of all immunizations provided to the study group. On this basis alone, MIMS monitoring

would define 17 children (13.9% of the study group) as having incomplete immunization records.

22 immunizations (for 22 children) were recorded on MIMS but not at the clinic, indicating that clinic physicians billed but failed to document 4.7% of all immunizations given to the study group (Table 5). This resulted in incomplete clinic records for 18% of the group.

9.1.4 Immunization Rates

Table 6 (page 17) shows the immunization rates, by dose, for the study group. At the study date, 111 children were aged between six and twelve months and eleven children had passed the first birthday. Observations suggest that age at immunization tends to increasingly exceed the recommended age with successive doses. This probably explains the relatively low study rates calculated for the third DTP dose and completion of the recommended immunization schedule for the first year of life (three doses of DTP and two doses of OPV).

Combined record sources showed that, of children who received a third DTP, 21% simultaneously received a third OPV, despite the fact that the provincial schedule no longer recommends the third dose of OPV.

9.2 Three-month Follow-up of MIMS Records

The MIMS records of 34 children were incomplete at the time of initial examination. Review of these records three months later showed the following: three children had transferred out of the province; the records of ten children had achieved completion; the records of 21 children remained incomplete. Seven incomplete records were amenable to clerical correction as they contained only coding errors.

10. DISCUSSION

The results show a high level of agreement between clinic records and MIMS records with respect to personal identification and immunization information despite the fact that the records of these infants had not been monitored by MIMS.

Personal data, vaccine type and service provider were represented on MIMS with 100% reliability.

Only a small number of immunizations were billed with incorrect tariff codes. MIMS data concerning vaccine type is of high quality, and the calculation of coverage rates is not dependent on the accuracy of tariff coding by specific dose. The current practice of making online corrections to illogical tariff codes is reasonable.

The proportion of immunizations billed but not documented in the clinic record was low (4.7%), as was that of immunizations which failed to generate a billing claim/MIMS record (6.6%).

The initial findings anticipated the flagging of 34 children with incomplete records during the first round of MIMS monitoring. This round can be considered complete three months after the first birthday. Review of the incomplete MIMS records three months after the study date (but still prior to effective MIMS monitoring) showed that, by this time, only 14 children had incomplete records which were dependent on the immunization provider for correction/ completion.

Immunization rates for the first two doses of DTP/OPV were high when information from the two sources was combined. Lower coverage rates for the third DTP dose and completion of the recommended immunization schedule for the first year of life were calculated before all cohort members had passed the first birthday and may be artificially low.

11. SUMMARY

The clinic studied demonstrated a high degree of immunization efficiency with respect to immunization rates, documentation and billing. The MIMS data concerning the immunization of children who attended this

clinic in infancy was accurate and reliable. The study suggests that, while the provision of a distinct tariff code for each vaccine type has resulted in highly accurate MIMS vaccine coverage data, the monitoring of the accuracy of the separate codes for each dose of vaccine administered may not be necessary.

The findings of this study give insight into MIMS data quality for immunizations given to rural children. Further study should investigate the quality such data for immunizations given to urban children, particularly in the city of Winnipeg.

12. REFERENCES

1. Manitoba Immunization Monitoring System User Manual. Manitoba Health, Winnipeg, Manitoba, 1988.

2. MIMS Annual Report. Manitoba Health, Winnipeg, Manitoba, 1991.

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

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

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

Table 1
Clinic Records: Immunization Summary

dose and vaccine	number of children receiving at clinic	proportion of children receiving at clinic
first DTP	96	78.7%
first OPV	97	79.5%
second DTP	85	69.7%
second OPV	85	69.7%
third DTP	73	59.8%
third OPV	3	1.6%
TOTAL	439	-

Table 2
MIMS Records: Immunization Summary

dose and vaccine	number of children receiving at clinic	total number of children receiving	total proportion of children receiving
first DTP	93	117	95.9%
first OPV	93	117	95.9%
second DTP	78	107	82.5%
second OPV	78	107	82.5%
third DTP	75	102	83.6%
third OPV	15	23	18.9%
TOTAL	432	573	-

Table 3
Source Comparison: Tariff Codes

dose, vaccine and tariff codes	number of tariff code errors	nature of tariff code errors
first DTP (8601)	0	
first OPV (8611)	1	coded as 8612
second DTP (8602)	2	coded as 8601
second OPV (8612)	1	coded as 8611
third DTP (8603)	2	coded as 8602
	1	coded as 8613
	1	coded as 8619
third OPV (8613)	1	coded as 8619
TOTAL	9	-

Table 4
Source Comparison: Missing MIMS Records

dose and vaccine	number of immunizations documented on clinic records	number of immunizations missing on MIMS records
first DTP	96	4
first OPV	97	4
second DTP	85	7
second OPV	85	7
third DTP	73	5
third OPV	3	2
TOTAL	439	29

Table 5
Source Comparison: Missing Clinic Records

dose and vaccine	number of clinic immunizations documented on MIMS records	number of immunizations missing on clinic records
first DTP	93	1
first OPV	93	0
second DTP	78	0
second OPV	78	0
third DTP	75	7
third OPV	15	14
TOTAL	432	22

Table 6
Immunization Rates

dose	proportion immunized		
	source: clinic record	source: MIMS record	source: combined records
first DTP/OPV	79.5%	95.9%	99.2%
second DTP/OPV	69.7%	82.5%	93.4%
third DTP	59.8%	83.6%	87.7%
third OPV	1.6%	18.9%	20.5%
fully immunized*	–	–	87.7%

* fully immunized, according to the provincial immunization schedule (DTP three doses, OPV two doses)

APPENDICES

AS FOR PREVIOUS STUDY

FOLLOW-UP RECORDS GENERATED BY THE MIMS MONITORING PROCESS: A SIX MONTH SURVEY AT AN URBAN PROVINCIAL HEALTH UNIT

J.D. Roberts

February, 1992

Abstract

A six month survey of reminder letters to providers, concerning missing immunizations in one and two year old children and generated by the Manitoba Immunization Monitoring System, was conducted at a suburban provincial health unit.

High rates (92%) of initial age-appropriate immunization schedule completion were estimated for children served by the health unit. Monitoring at each of one and two years of age generated reminder letters to physician providers for approximately eight per cent of children. Monitoring improved immunization levels by approximately six per cent for each age group. Most immunizations regarded as missing by the computerized system had in fact been given but inadequately recorded; failure of physicians to claim for this service accounted for 42% of all missing immunizations. However, physicians showed a high level of compliance with the record completion process.

LIST OF TABLES

TABLE OF CONTENTS

INTRODUCTION

In November, 1987, Manitoba Health Services Commission (MHSC) implemented the process which automatically captures immunization data from physician claim forms and enters them into the computerized Manitoba Immunization Monitoring System (MIMS) file.

In Winnipeg, where over one half of the province's births occur, physicians perform almost all early childhood immunizations. The immunization records of children born on or after January 1, 1988, and served by municipal and provincial (though not federal) health jurisdictions are therefore considered to be essentially complete. Since that date, all records have all been subject to routine monitoring procedures designed to improve immunization levels through a reminder system.

One suburban provincial health unit has conducted a survey of reminder letters (follow-up records) generated by the MIMS monitoring process.

OBJECTIVE

The objective of the survey was to describe the number, nature and outcome of follow-up records generated over a six month period for children born since January 1, 1988, and resident in the area served by the health unit.

METHOD

MIMS Monitoring

Virtually all Manitoba children are registered with MHSC; those born on or after January 1, 1980, are included in the MIMS file. Monitoring is conducted in the month of the child's first, second and sixth birthdays. The child's MIMS record is compared with the acceptable provincial immunization schedule. Immunizations noted as missing (not given or the correct code absent) generate a letter (follow-up record) to the last recorded provider (public health nurse or physician) requesting record completion or correction. All follow-up records are distributed to providers by the local health unit.

The records of adoptees and of children who die or leave the province are transferred to an inactive file and no longer monitored. This transfer is dependent upon registry notification of the changes.

Study Population

The 1990 MIMS Annual Statistical Report provided the census of children who resided in the area served and were registered on MIMS, as of June, 1990. The census is summarized in Table 1.
Only children born since January 1, 1988 (aged one or two years at monitoring) were included.

Data Collection

All follow-up records received by the health unit in the six month period September, 1990, through February, 1991, inclusive were collected. Those received in 1990 represented children born in the corresponding months of 1988 and 1989 and aged two and one years respectively. Those received in 1991 represented children born in the corresponding months of 1989 and 1990 and aged two and one years respectively.

The MIMS monitoring protocol calls for the return of corrected or completed follow-up records to the health unit, where MIMS clerk makes the appropriate on-line record alterations. This procedure was followed. In addition, the clerk noted those follow-up records which included incorrectly coded entries.

RESULTS

Children for whom follow-up records were received are described, by month and year of birth, in Table 2. Seventy six follow-up records in total were received in the six month period; all were distributed to physicians. By early April, 1991, 74 follow-up records had been returned; physicians had either corrected the records or given reasons for their inability to do so.

Table 3 describes the explanations for immunizations regarded by MIMS as missing. These were categorized as

follows: immunization not given; immunization given but no physician claim submitted; adoption (with failure to transfer immunization data to new record); migration into the province (some or all immunizations given out-of-province) or from the province (migration before the immunization series completed); no explanation (change of provider before the immunization series completed or no response from provider).

Of 41 children aged two at monitoring, 31 were missing immunizations scheduled for the second year of life. Missing first year immunizations for these children were explained as follows: change in registration status (8), change in provider (1), no response (1).

From the results, it is estimated that, of children served by this health unit, approximately 8% (aged one or two years) had incomplete immunization records at the time of monitoring, regardless of birth year. Physicians had failed to claim for immunizations given to 42% of children with incomplete records and had incorrectly coded immunizations given to a further 26%. Migration accounted for about 14% of record incompletion, while for only 9% was it established that the immunizations in question had not been given.

The effect of monitoring on immunization rates for this service area can be estimated from the data and is

described in Table 4. Rates given for one year-olds are the averages of those calculated for children with the first birthday in 1990 and 1991, with the census totals for children born in 1989 and 1990 as denominators; rates given for two year-olds are the averages of those calculated for children with the second birthday in 1990 and 1991 with the census totals for children born in 1988 and 1989 as denominators. Immunization coverage at one and two years of age was high, with 92% of both age groups estimated to have completed the age-appropriate schedules. Following monitoring, the completion rate at one year of age is estimated to have increased by 6% and that at two years of age by 7%.

DISCUSSION

The findings estimate high rates of full immunization amongst one and two year olds served by the health unit. Follow-up records were generated for approximately 8% of children following each of the first and second rounds of monitoring; it is estimated that elimination of coding errors would lower this proportion to 5%.

Monitoring substantially improved immunization levels. Most immunizations regarded as missing had in fact been given. Migration and provider change were readily established. Failure of physicians to bill for

immunizations given accounted for a high proportion of missing immunizations, but physicians showed a high level of compliance with the record completion process. It is likely that rates of failure to bill will diminsh over time.

Table 1. MIMS Census by Birth Year, Study Health Unit.

Year of Birth	Children With Active Records	Children With Inactive Records	Total
1988	1022	53	1075
1989	796	30	826
1990	745	26	771

Table 2. Numbers of Children For Whom Follow-up Records Were Received During the Study Period, by Month and Year of Birth.

Month of Birth	Year of Birth		
	1988	1989	1990
September	11	10	
October	5	3	
November	8	7	
December	6	3	
January		6	5
February		5	7

Table 3. Summary of Explanations Determined for Missing MIMS Immunization Records, By Age at the Time of Monitoring.

Age at Monitoring (years)	Explanation for Missing MIMS Immunization Records							N
	Given, No Claim	Not Given	Coding Error	Adoption	Migration Into/From Province	None		
						No Response	Provider Change	
one	20	0	10	0	2	0	3	35
two	12	7	10	1	8	2	1	41
TOTAL	32	7	20	1	10	2	4	76

Table 4. Service Area Immunization Rates With and Without Monitoring, By Age At Monitoring.

Age (Years)	Proportion Completely Immunized For Age, Without Monitoring	Proportion Completely Immunized For Age, With Monitoring
one	92%	98%
two	92%	99%

THE QUALITY OF MIMS DATA FOR THE 1987 MANITOBA BIRTH COHORT IN THE FIRST YEAR OF LIFE

J.D. Roberts

June, 1993

ABSTRACT

Although the Manitoba Immunization Monitoring System (MIMS) has enrolled all children born on or after January 1, 1980, physician billing claims have been captured only since November, 1987. Consequently, since physicians administer about 80 per cent of early childhood immunizations in Manitoba and approximately 98 per cent of those given in the city of Winnipeg,{206} children born before 1987 are likely to have incomplete MIMS records. In many instances, however, the MIMS monitoring process has allowed the back-entry of immunization information taken from physician and client records.

MIMS data for the 1987, 1988 and 1989 Manitoba birth cohorts will be used to study the relationship between routine immunization and the occurrence of adverse events in the first year of life. Since many members of the 1987 birth cohort are known to be missing first-year immunization data, it must first be determined if these children represent a select group.

A preliminary study of the quality of first year of life MIMS data for the 1987 birth cohort (N = 14,331) was therefore undertaken. 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.

LIST OF FIGURES

Page

LIST OF TABLES

TABLE OF CONTENTS

1. INTRODUCTION

Although the Manitoba Immunization Monitoring System (MIMS) has enrolled all children born on or after January 1, 1980, physician billing claims have been captured only since November, 1987. Consequently, since physicians administer about 80 per cent of early childhood immunizations in Manitoba and approximately 98 per cent of those given in the city of Winnipeg,[1] children born before 1987 are likely to have incomplete MIMS records. In many instances, however, the MIMS monitoring process has allowed the back-entry of immunization information taken from physician and client records.

MIMS data for the 1987, 1988 and 1989 Manitoba birth cohorts will be used to study the relationship between routine immunization and the occurrence of adverse events in the first year of life. Since many members of the 1987 birth cohort are known to be missing first-year immunization data, it must first be determined if these children represent a select group. If so, their inclusion in the study cohort will tend to underestimate any real risks associated with immunization, since factors known to be associated with either avoidance or delay of immunization may themseves be linked to an increased risk of adverse-event-type medical outcomes.

This preliminary study assessed the quality of first-year-of-life MIMS data for the 1987 Manitoba birth

cohort by examining immunization and hospitalization data for defined subgroups.

2. OBJECTIVES

The general objective of the study was to assess the quality of MIMS data for the 1987 Manitoba birth cohort in the first year of life.

Specifically, the study sought to:

- Determine the immunization status of defined subgroups of the 1987 birth cohort.
- Determine the hospitalization status of defined subgroups of the 1987 birth cohort.
- Quantify missing immunization data.
- Describe the subgroup with complete immunization data.
- Describe the subgroup with incomplete immunization data.

3. METHOD

3.0 Data Sources

The study used population-based data routinely collected in the computerized registry, hospitalization and immunization files of the Manitoba Health database. Sections 5.1-5.3 of the thesis fully describe data sources and data quality, while the Manitoba provincial recommended immunization schedule 1986-1990 is set out in

Table 1.

3.1 Data Organization

Files containing the records of the 1987 Manitoba birth cohort were examined. The linkage of three files was required:

- The MIMS file included all children born in 1987. Status Indian children were excluded. The file contained the individual patient identifier (PHIN), the date of birth, the sex, the date of termination, and the attached immunization records (with tariff code, service date and restrictions). The file was generated after all the children had passed their second birthday and had been monitored twice. Registry information current to June 30, 1990, was contained in the file.
- The hospital file for the years 1987 through 1990. This file included all children born in 1987. Status Indian children were excluded. The file contained all hospitalizations, and the date of hospital admission, the occurrence of death during hospitalization, accompanying diagnoses and scrambled individual patient identifiers (PHIN) were included. Linkages also used the individual patient identifiers as noted above on the MIMS file.
- The Manitoba Health registry file. This file

provided a check on mortality, migration out of province, and the quality of the personal identifiers.

3.2 Selection of the Study Cohort

The registry and MIMS files defined the study cohort (N = 14,331) as those members of the 1987 birth cohort who were enrolled with Manitoba Health as of June 30, 1990, did not have Indian status, and had continuous Manitoba Health enrolment from birth to the first birthday. Two cohort subgroups were defined by immunization status (Figures 1 and 2: received no immunizations of any kind in the first 160 weeks of life [MIMS records blank] (N = 365); and received at least one immunization in the first 160 weeks of life (N = 13,966).

3.3 Data Analyses

The immunization and hospitalization files described, respectively, the immunization and hospitalization experiences of the study cohort in the first 160 weeks of life.

Immunization rates for the entire study cohort (considering together the experiences of the immunized and unimmunized subgroups) were calculated, by vaccine type and by generic dose (first, second, third).

The MIMS file defined two subsets of children within the subgroup which received at least one immunization in the first 160 weeks of life (Figure 3): received no DTP/DT in the first year but at least one immunization (any kind) in the first 160 weeks of life (N = 976); received at least one DTP/DT in the first year of life (N = 12,990).

The immunization status of the immunized subset in receipt of at least one DTP/DT in the first year of life was described. For each vaccine, in the first year of life, the following distributions were determined: of generic doses (first, second, third, and so on); of tariff codes by generic dose; of tariff codes by age at immunization (in four week age groups), for each generic dose; of age at immunization (in four week age groups) by calendar and month in which immunization took place, for each generic dose.

The immunization status of the immunized subset with zero recorded DTP/DT immunizations for the first year of life but at least one immunization (any kind) in the first 160 weeks of life was described. For each vaccine, in the first year of life, the following distributions were determined: of tariff codes by age at immunization (in four week age groups) over the first 160 weeks of life; of age (in four week age groups) as of November 1, 1987.

Hospitalization status was determined for the immunized and unimmunized subgroups in the first year of life. Rates of hospitalization in the first year of life, regardless of reason, were calculated by four-week age group for both subsets of the immunized subgroup and for the unimmunized subgroup.

4. RESULTS

4.0 Immunization Status: Total Cohort

The immunization status of the total birth cohort is shown in Figure 3. MIMS recorded that 75 per cent of the total study cohort had completed the infancy immunization schedule (three DTP/DT and two OPV/IPV) by the first birthday. Children receiving poliovaccine received DTP/DT vaccine on the same day 99 per cent of the time.

4.1 Immunization Status: Immunized Subset in Receipt of At Least One Dose of DTP/DT in the First Year of Life

MIMS recorded that 82 per cent of children who received at least one DTP/DT in the first year of life had completed the infancy immunization schedule by the first birthday.

For the following distributions, only the results for DTP/DT vaccine are given; those for OPV/IPV vaccine were almost identical.

Counting doses generically showed that, by the first

birthday, 91 per cent of the subset received a first dose, 85 per cent a second, and 75 per cent a third (Figure 3). Counting doses by tariff code, however, showed that 82 per cent of doses were coded as the first in the schedule, 84 per cent as the second, and 84 per cent as the third.

Table 1 shows the distribution of DTP tariff codes by generic dose. The generic first (or second) dose was coded as a second (or third) dose 5-7 per cent of the time, while the generic second (or third) dose was coded as first (or second) 1 per cent or less of the time.

Tables 2, 3, and 4 give, for each generic dose, the distribution of tariff codes by age at immunization. When the first (or second) generic dose was recorded with the tariff code for the second (or third) dose, age at immunization was most often appropriate for the second (or third) dose. However, when the second (or third) generic dose was recorded with the tariff code for the first (or second) dose, age at immunization was most often appropriate for the actual generic dose on record.

Tables 5, 6, and 7 give, for each generic dose, age at immunization for immunizations which were given before and after the automatic capture of physician data began. It can be seen that, for immunizations recorded as the first (or second) generic doses in the series, those given after November 1, 1987, were more likely to have

been administered at an age appropriate to a second (or third) dose. On the other hand, for third generic doses, age at immunization was hardly that ever appropriate for a preceding dose.

4.2 Immunization status: Immunized Subset in Receipt of No DTP/DT in the First Year of Life But At Least One Immunization (Any Kind) in the First 160 Weeks of Life

For this subset (N = 976), MIMS recorded the receipt of 3,256 immunizations by age 160 weeks.

Table 8 shows the age at immunization for each dose of DTP/DT and OPV/IPV (identified by tariff code). Of all immunizations received by the subset by age 160 weeks, 1,939 were DTP/DT/poliovaccine given between ages 53-160 weeks; 837 DTP/DT and 842 OPV/IPV were coded as the fourth in the series. Of the remainder, 913 were measles-mumps-rubella (MMR) and 385 were *Haemophilus influenzae* type b vaccine, both recommended for administration in the second year of life. Thirty four immunizations were recorded for the first year of life, including nine OPV and 19 MMR (given within eight weeks of the first birthday).

Table 9 shows the age of the subset at November 1, 1987; 77 per cent were over 32 weeks of age by this date, and 95 per cent were over 25 weeks of age.

4.3 Hospitalization Status

Hospitalization rates in the first 0-56 weeks of life, by four week age group, were calculated. Rates were expressed as the number of admissions in each age group per 1,000 group members.

Figure 4 compares rates of admission, between five and 56 weeks of age, for the two immunized subsets and the unimmunized subgroup. Rates for the group receiving at least one DTP/DT in the first year of life (N = 12,990) were steady at around 10 per 1,000 group members throughout the period. For the group receiving no DTP/DT in the first year of life but at least one immunization by age 160 weeks (N = 976), rates were somewhat higher but also remained steady throughout the first year, at around 15 per 1,000 group members. Both rates were consistent with the rate for immunized children born in 1988. (Roberts 1991, unpublished) For the group with no immunizations recorded in the first 160 weeks of life (N = 365), rates were higher throughout the first year.

Admissions in the 0-4 week age group included live births. Admission rates were calculated for each group, both before and after live birth admissions were subtracted from the 0-4 week age group total. For the subset receiving at least one DTP/DT in the first year of life, the rates including and excluding live births were 1049.7 and 7.4 per 1,000 group members respectively. For

those receiving no DTP/DT in the first year of life but at least one immunization before age 160 weeks, the respective rates were 1032.8 and 12.3 per 1,000 group members. For those with no recorded immunizations in the first 160 weeks of life, the respective rates were 813.7 and 82.2 per 1,000 group members; the low "before" rate for this subgroup is partly explained by the absence of live birth admission records for 27 per cent of its members.

Statistical comparison of rates between groups was not possible because of the disparate sample sizes.

5. DISCUSSION

MIMS records that 75 per cent of the total cohort completed the infancy immunization schedule by the first birthday. However, of children who received any DTP/DT at all in the first year of life, 82 per cent completed the schedule.

For children born in 1988, the miscoding rate for first year immunizations has been found to range from 1 per cent (for the first) to 3 per cent (for the third) generic doses.(Roberts 1991, unpublished) However, for children born in 1987 who received at least one DTP/DT in the first year of life, first and second generic doses were coded to subsequent positions in the series 5-7 per cent of the time. Second and third generic doses were

rarely coded to preceding positions. When generic doses carried the tariff codes for subsequent doses, age at immunization was most often appropriate for the subsequent dose; this tendency was far more marked when the immunization was given after automatic claims capture was implemented.

These findings strongly suggest that for children who received any DTP/DT at all in the first year of life, most missing immunizations were not the second and third in the infancy series, as inferred from the distribution of generic doses, but the first and second doses, given by physicians and not automatically recorded. For children born in 1987, the tariff code is a far more reliable index of the immunization's sequence in the series than is its generic occurrence.

Almost one thousand children had no record of DTP/DT immunization in the first year of life but did have a record of some form of immunization in the first 160 weeks of life. The system documented only 34 first year immunizations for these children, including nine poliovaccine. However, 847 DTP/DT (and a similar number of OPV) were recorded, and were coded as the fourth in the series and given after the first year of life. The vast majority of these children were at or beyond the recommended age for the third DTP/DT when automatic physician claims capture began. These findings strongly

suggest that over 90 per cent of the subset had received the infancy series but that no records were produced. Hospitalization rates for this subset over the first 56 weeks of life parallel those for children born in 1987 and 1988 for whom MIMS records of first year immunizations exist. These findings indicate that this immunized subset does not differ systematically from the immunized subset of children who received any DTP/DT at all in the first year of life. Postulating infancy schedule completion for children with a fourth DTP/DT on record after age 52 weeks but no DTP/DT on record before 53 weeks increases the schedule completion rate for the 1987 study cohort to 89 per cent, equivalent to the completion rate calculated for the 1988 study cohort.(Roberts 1991, unpublished)

Whereas 10.4 per cent of all children born in 1987 had completely blank MIMS records at June 30, 1990,{206} exclusion of status Indian children and those with interrupted enrolment lowered this proportion to 2.5 per cent; the equivalent proportion calculated for the 1988 study cohort was 2.3 per cent. Other results for this unimmunized subset were similar to those for its 1988 counterpart: hospitalization rates remained higher over the first 5-56 weeks of life than those for immunized children; approximately 30 per cent had no record of a birth hospitalization. While the occurrence of births

outside hospital and out-of-province could explain the absence of some birth records, adoptions during the first year of life could explain the simultaneous absence of both birth and early immunization records; the potential for loss of all records at the time of adoption exists. There is no ready explanation for the high rate of admissions not associated with live births between 0-4 weeks of age for this subgroup. The findings suggest that the subgroup with blank records may in fact differ systematically from the immunized subsets.

Of 14,331 1987 study cohort members, 9.4 per cent had no DTP/DT recorded for the first year. MIMS incorporates a mechanism whereby data on immunizations given but not recorded are sought and back-entered. The analysis has confirmed the effectiveness of the monitoring process. Automatic claims capture began only in November, 1987, so that physicians producted no MIMS records January-October, 1987, yet provided 80 per cent of immunizations. Assuming a steady birth rate and a schedule completion rate of 89 per cent, it can be estimated that, by the end of 1987, MIMS had recorded approximately 13,000 DTP/DT for the study cohort. By June 30, 1990, however, 35,790 DTP/DT had been recorded.

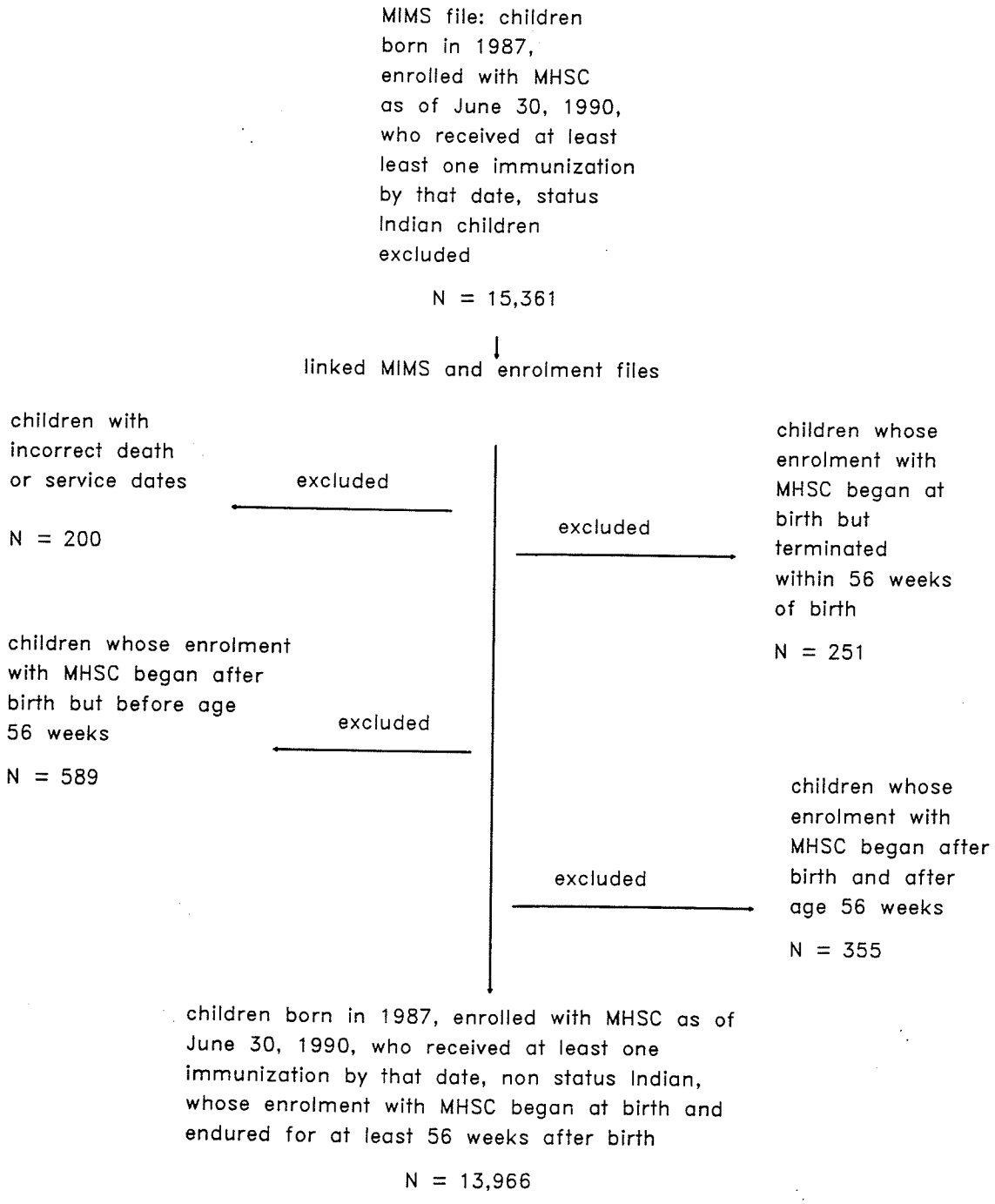
In summary, the results are in keeping with our previous observation that children with any immunizations recorded on MIMS tend to have all, or almost all,

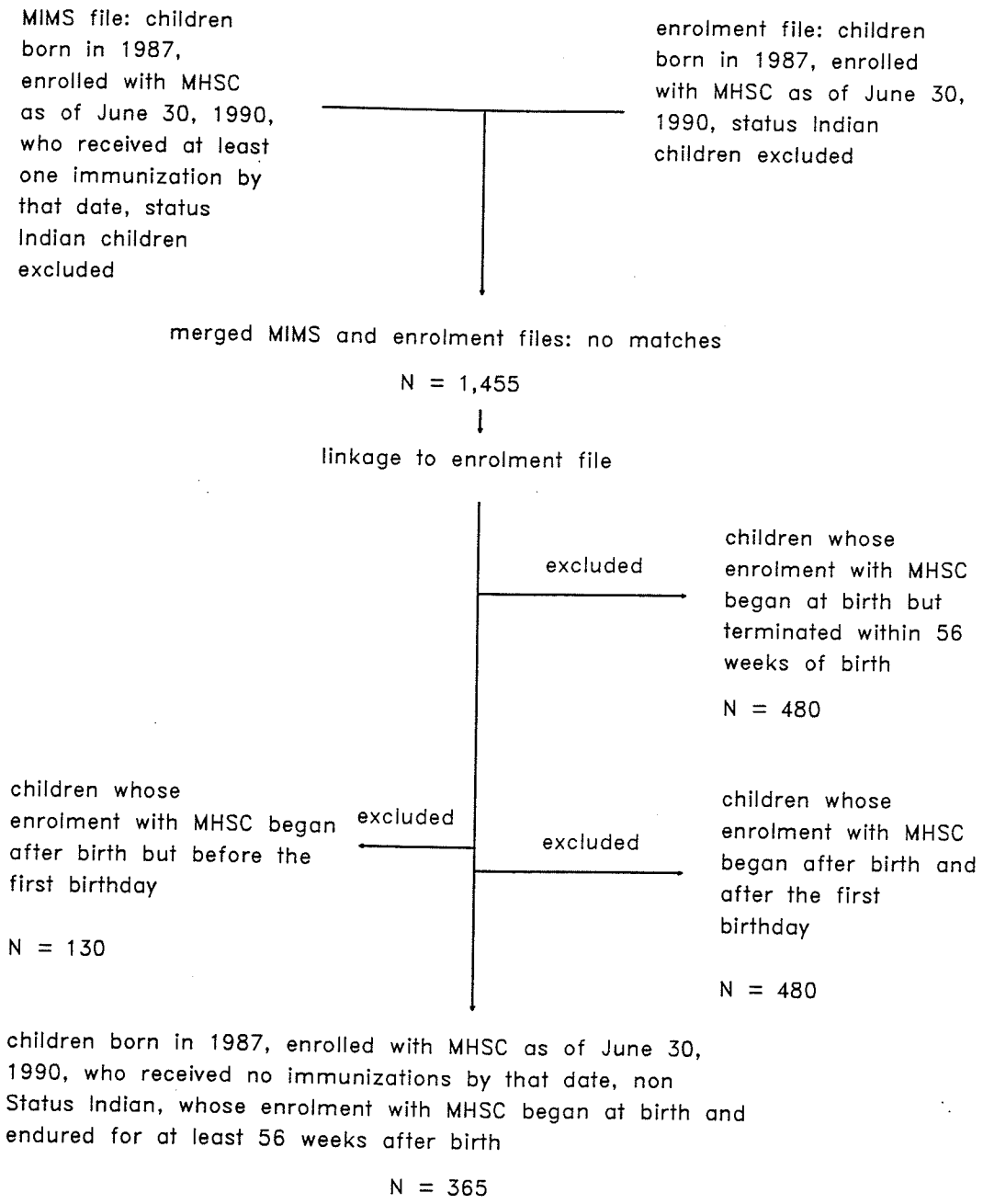
immunizations recorded. It is reasonable to assume that children born in 1987 with DTP/DT documented after but not during the first year of life do not represent a select group of children. Excluding them from the immunized group when first-year adverse events are studied will underestimate immunization rates and the total number of hospitalizations before/after immunization, but will not underestimate any real risks associated with immunization.

There is evidence, however, that children with blank records are a select group. They should again be considered separately and efforts made to obtain a more detailed description of their characteristics.

6. REFERENCES

1. Manitoba Immunization Monitoring System. Report of Immunizations By Provider and Type. Manitoba Health, March 22, 1990.


MIMS file: children born in 1987, enrolled with MHSC as of June 30, 1990, who received at least least one immunization by that date, status Indian children excluded
N = 15,361
linked MIMS and enrolment files
children with incorrect death or service dates
excluded
N = 200
children whose enrolment with MHSC began at birth but terminated within 56 weeks of birth
excluded
N = 251
children whose enrolment with MHSC began after birth but before age 56 weeks
excluded
N = 589
children whose enrolment with MHSC began after birth and after age 56 weeks
excluded
N = 355
children born in 1987, enrolled with MHSC as of June 30, 1990, who received at least one immunization by that date, non status Indian, whose enrolment with MHSC began at birth and endured for at least 56 weeks after birth
N = 13,966


MIMS file: children born in 1987, enrolled with MHSC as of June 30, 1990, who received at least one immunization by that date, status Indian children excluded
enrolment file: children born in 1987, enrolled with MHSC as of June 30, 1990, status Indian children excluded
merged MIMS and enrolment files: no matches
N = 1,455
linkage to enrolment file
excluded
children whose enrolment with MHSC began at birth but terminated within 56 weeks of birth
N = 480
children whose enrolment with MHSC began after birth but before the first birthday
N = 130
excluded
excluded
children whose enrolment with MHSC began after birth and after the first birthday
N = 480
children born in 1987, enrolled with MHSC as of June 30, 1990, who received no immunizations by that date, non Status Indian, whose enrolment with MHSC began at birth and endured for at least 56 weeks after birth
N = 365

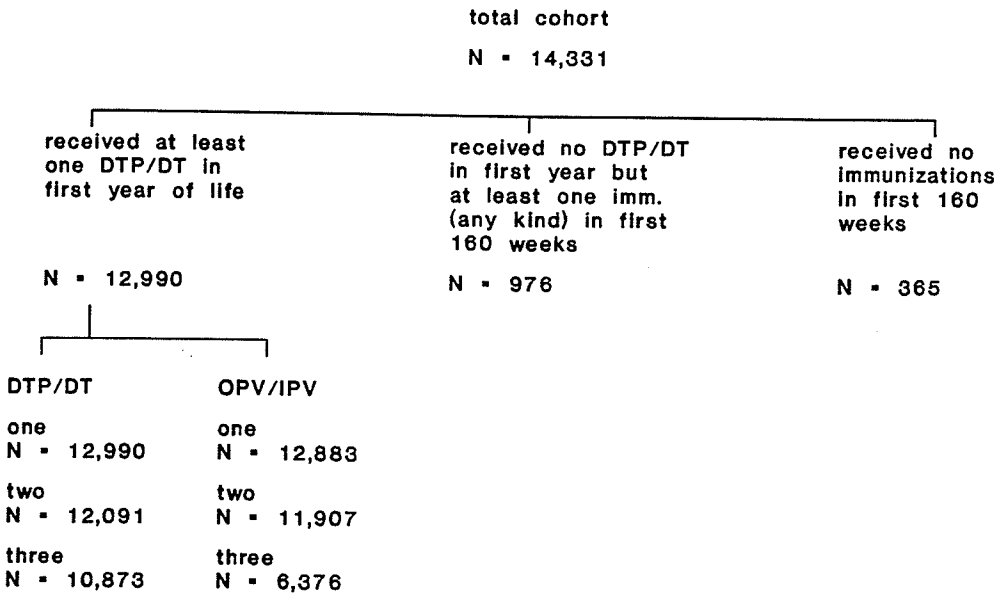

total cohort
N = 14,331
received at least one DTP/DT in first year of life
N = 12,990
received no DTP/DT in first year but at least one imm. (any kind) in first 160 weeks
N = 976
received no immunizations in first 160 weeks
N = 365
DTP/DT
one
N = 12,990
two
N = 12,091
three
N = 10,873
OPV/IPV
one
N = 12,883
two
N = 11,907
three
N = 6,376

Figure 4. 1987 Manitoba Birth Cohort. Hospitalization Rates In the First Year Of Life, By Age.

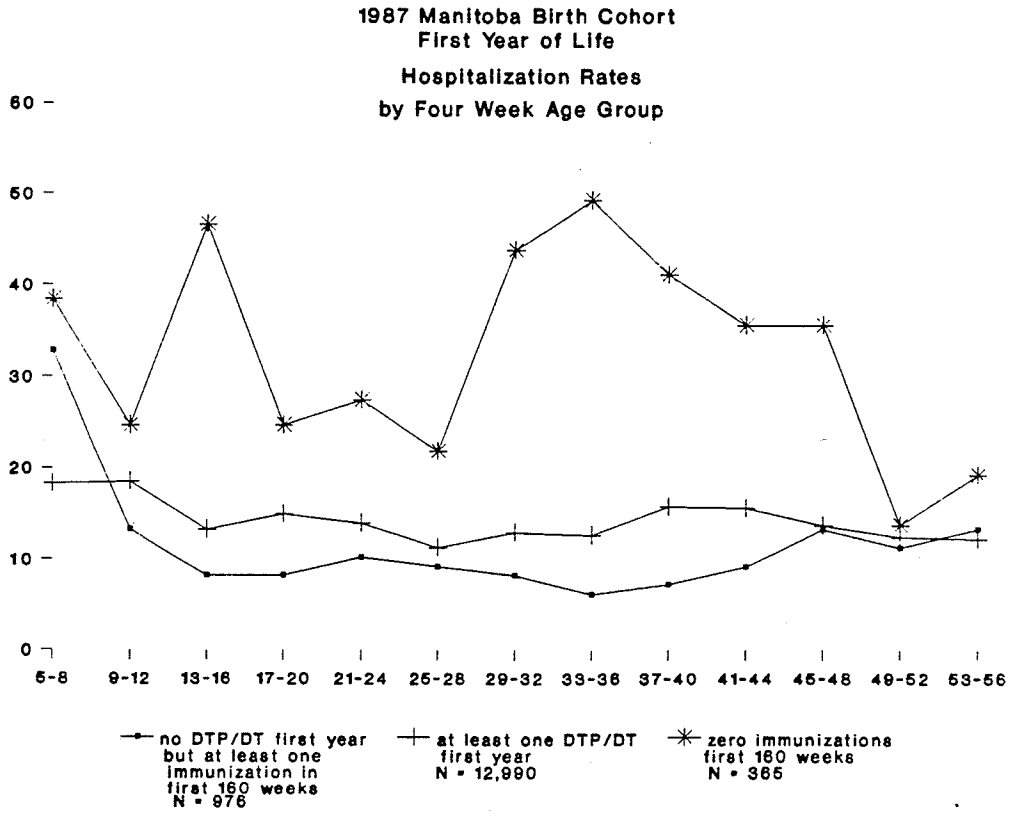


Table 1. 1987 Manitoba Birth Cohort. Distribution of DTP Tariff Codes By Generic Dose.

Generic Dose	Percentage With Tariff Codes For: First DTP/DT	Second DTP/DT	Third DTP/DT
First DTP/DT N = 12,990	89.4	5.9	4.7
Second DTP/DT N = 12,091	0.9	92.1	7.0
Third DTP/DT N = 8,649	0.4	1.2	98.4

Table 2. 1987 Manitoba Birth Cohort, Immunized Subset in Receipt of At Least One Dose of DTP/DT in the First Year of Life. Distribution of Tariff Codes By Age At Immunization: First Generic DTP Dose.

Tariff Code	Age At Immunization		
	5-16 weeks	17-24 weeks	25-32 weeks
First DTP/DT N = 11,608	96.8%	2.1%	0.5%
Second DTP/DT N = 770	8.1%	82.1%	9.1%
Third DTP/DT N = 612	1.8%	2.5%	75.8%

Table 3. 1987 Manitoba Birth Cohort, Immunized Subset in Receipt of At Least One Dose of DTP/DT in the First Year of Life. Distribution of Tariff Codes By Age At Immunization: Second Generic DTP Dose.

Tariff Code	Age At Immunization		
	5-16 weeks	17-24 weeks	25-32 weeks
First DTP/DT N = 107	27.0%	55.1%	8.4%
Second DTP/DT N = 11,132	2.9%	88.8%	6.4%
Third DTP/DT N = 852	0.5%	5.4%	74.1%

Table 4. 1987 Manitoba Birth Cohort, Immunized Subset in Receipt of At Least One Dose of DTP/DT in the First Year of Life. Distribution of Tariff Codes By Age At Immunization: Third Generic DTP Dose.

Tariff Code	Age At Immunization		
	5-16 weeks	17-24 weeks	25-32 weeks
First DTP/DT N = 40	0	12.5%	75.0%
Second DTP/DT N = 134	2.5%	37.3%	49.3%
Third DTP/DT N = 10,669	0.01%	1.0%	81.8%

Table 5. 1987 Manitoba Birth Cohort, Immunized Subset in Receipt of At Least One Dose of DTP/DT in the First Year of Life. Age at Immunization For Immunizations Given Before and After the Commencement Of Automatic Capture of Physician Data: First Generic Dose.

Age At Immunization (Weeks)	Percentage of Doses Administered:	
	Before Nov.1, 1987 N = 7,202	After Nov.1, 1987 N = 5,788
5-16	96.1	75.7
17-24	2.9	11.9
25-32	0.8	9.2

Table 6. 1987 Manitoba Birth Cohort, Immunized Subset in Receipt of At Least One Dose of DTP/DT in the First Year of Life. Age at Immunization For Immunizations Given Before and After the Commencement Of Automatic Capture of Physician Data: Second Generic Dose.

Age At Immunization (Weeks)	Percentage of Doses Administered:	
	Before Nov.1, 1987 N = 4,891	After Nov.1, 1987 N = 8,002
5-16	4.2	1.9
17-24	90.7	69.4
25-32	4.5	14.1

Table 7. 1987 Manitoba Birth Cohort, Immunized Subset in Receipt of At Least One Dose of DTP/DT in the First Year of Life. Age at Immunization For Immunizations Given Before and After the Commencement Of Automatic Capture of Physician Data: Third Generic Dose.

Age At Immunization (Weeks)	Percentage of Doses Administered:	
	Before Nov.1, 1987 N = 2,714	After Nov.1, 1987 N = 7,995
5-16	0	0.02
17-24	2.1	1.3
25-32	91.6	79.2

Table 8. 1987 Manitoba Birth Cohort, Immunized Subset in Receipt of No DTP/DT in the First Year of Life But At Least One Immunization (Any Kind) in the First 160 Weeks of Life. Age At Immunization For Each Dose of DTP/DT and OPV/IPV

Tariff Code	Number of Doses Recorded By Age (Weeks)		
	0-53	53-104	105-160
First DTP/DT	0	21	9
First OPV/IPV	3	16	8
Second DTP/DT	0	38	12
Second OPV/IPV	3	39	12
Third DTP/DT	0	41	16
Third OPV/IPV	3	37	11
Fourth DTP/DT	0	758	79
Fourth OPV/IPV	0	761	81
TOTAL	9	1,711	228

Table 9. 1987 Manitoba Birth Cohort, Immunized Subset in Receipt of No DTP/DT in the First Year of Life But At Least One Immunization (Any Kind) in the First 160 Weeks of Life. Age Of Subset At November 1, 1987.

Age (Weeks)	N (%)
0-16	29 (2.9)
17-24	18 (1.8)
25-32	178 (18.2)
>32	751 (77.0)
TOTAL	976 (100.0)

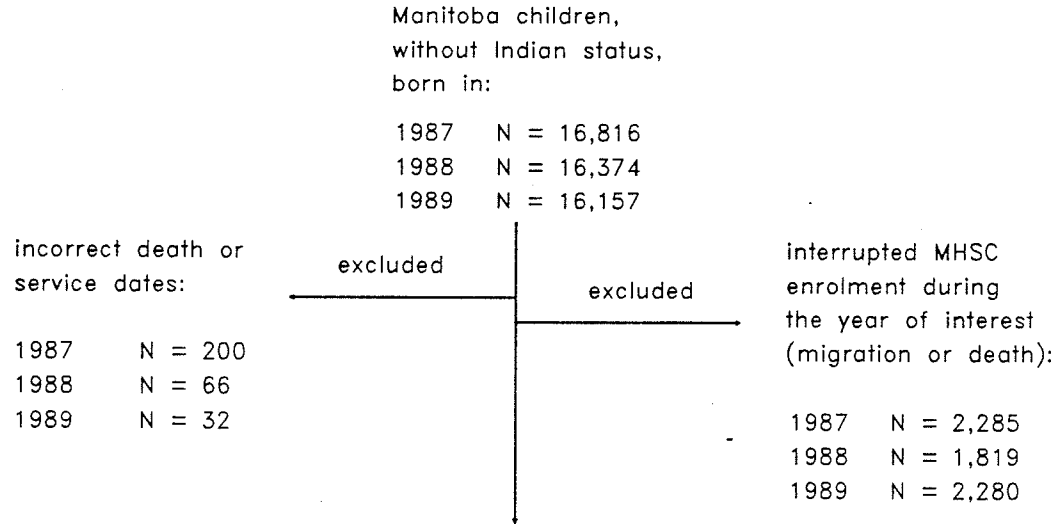
APPENDIX 5

MAJOR ADVERSE EVENTS SOUGHT IN THE STUDY

Vaccine	Major Adverse Event
DTP/DT	anaphylaxis
	encephalitis
	encephalopathy
	excessive somnolence
	high fever
	hypotonic-hyporesponsive state (collapse, shock)
	infantile spasms
	non-SIDS death
	persistent crying and unusual high pitched crying or screaming
	polyneuropathy
	seizures
	sudden infant death syndrome (SIDS)
OPV	paralytic poliomyelitis

APPENDIX 6

FLOW DIAGRAMS DESCRIBING THE SELECTION OF THE 1987, 1988 AND 1989 STUDY COHORTS



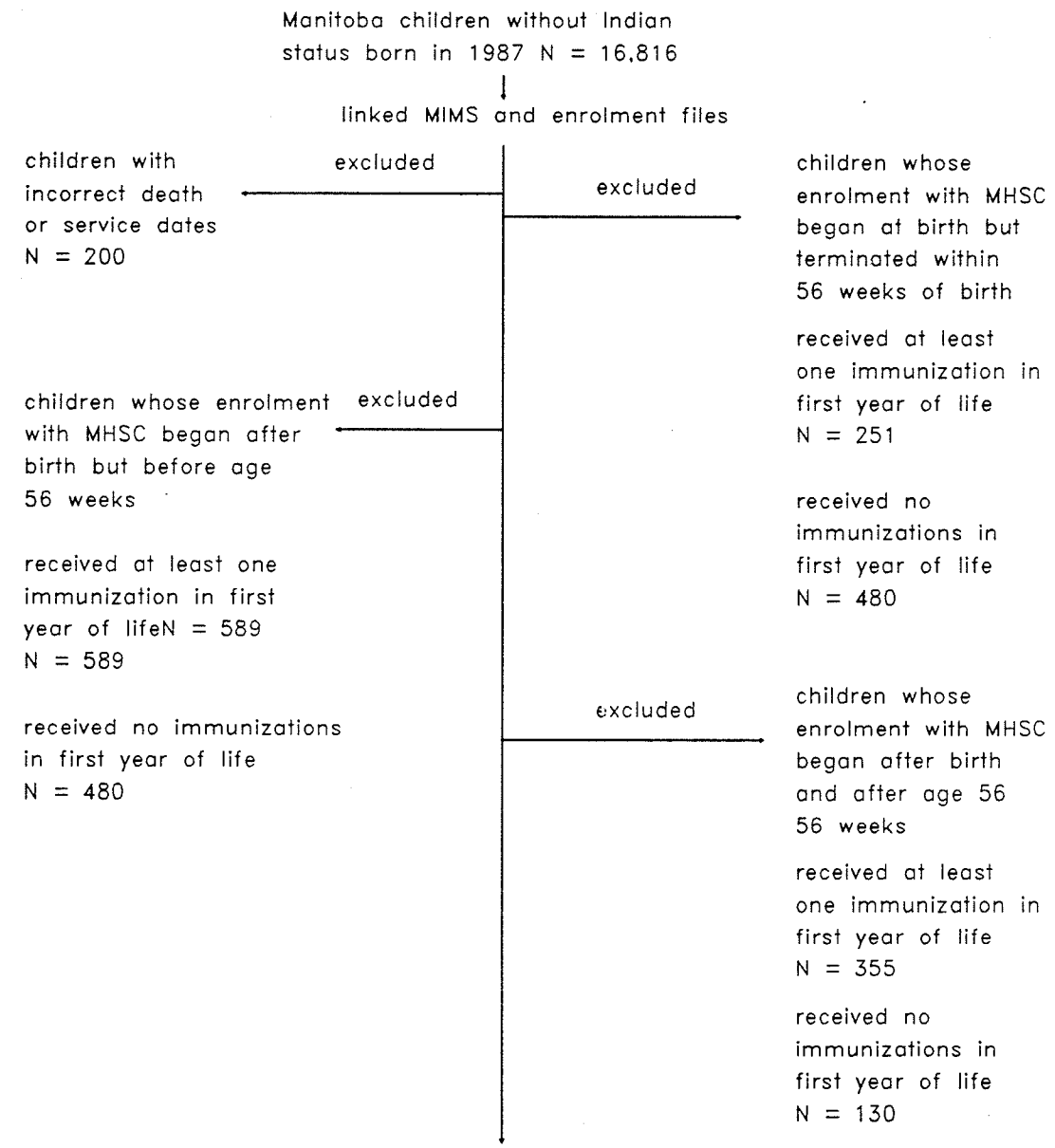
1987, 1988 and 1989: N = 43,499
received at least one immunization in first year of life:
N = 42,612
received no immunizations in first year of life:
N = 887

1987 N = 14,331
received at least one immunization in first year of life:
N = 13, 966
received no immunizations in first year of life
N = 365

1988 N = 14,489
received at least one immunization in first year of life:
N = 14,160
received no immunizations in first year of life:
N = 329

1989 N = 14,679
received at least one immunization in first year of life:
N = 14,486
received no immunizations in first year of life:
N = 193

Flow Diagram of 1987 Study Cohort Selection

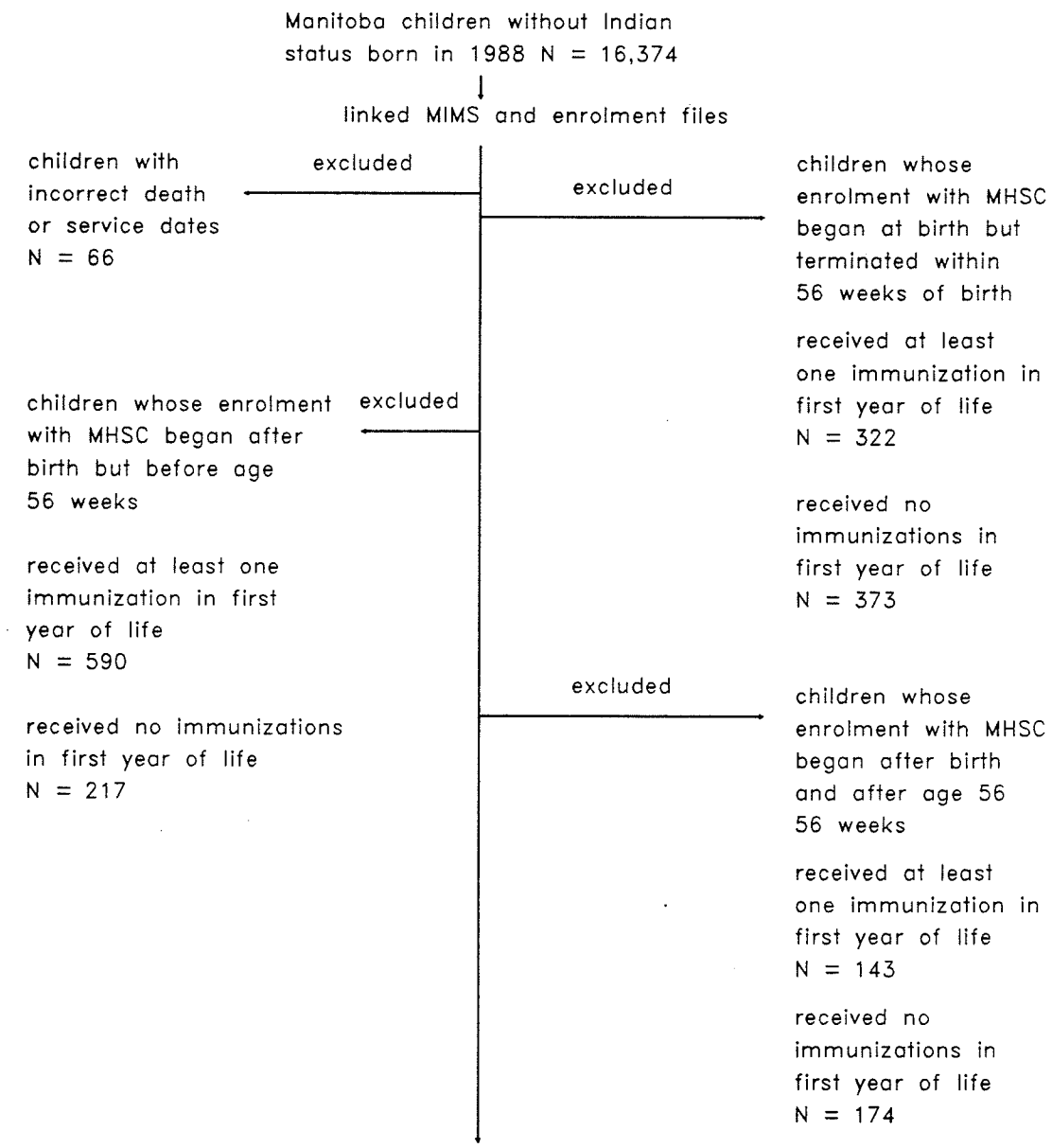


Manitoba children without Indian status, with consistent death and service dates and uninterrupted MHSC enrolment during the first year of life, born in 1987: N = 14,331

received at least one immunization in first year of life N = 13,966

received no immunizations in first year of life N = 365

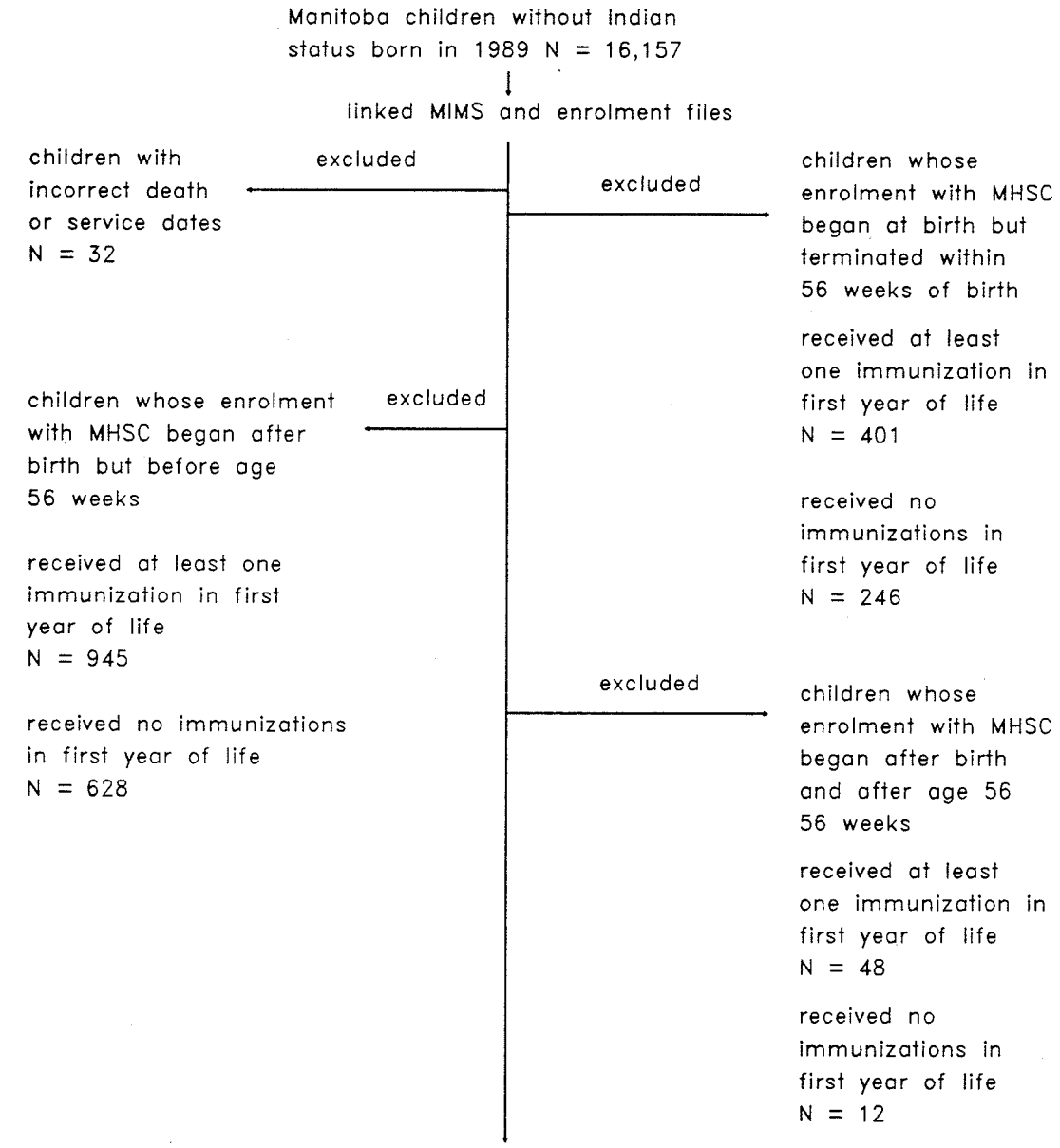
Flow Diagram of 1988 Study Cohort Selection



Manitoba children without Indian status, with consistent death and service dates and uninterrupted MHSC enrolment during the first year of life, born in 1988:

received at least one immunization in first year of life
N = 14,160
received no immunizations in first year of life
N = 329

Flow Diagram of 1989 Study Cohort Selection



Manitoba children without Indian status, with consistent death and service dates and uninterrupted MHSC enrolment during the first year of life, born in 1989:

received at least one immunization in first year of life
N = 14,486
received no immunizations in first year of life
N = 193

APPENDIX 7

LIST OF ICD-9-CM CODES APPLICABLE TO THE ADVERSE EVENTS SOUGHT IN THE STUDY, INCLUDING THE TIME PERIODS OF INTEREST AROUND IMMUNIZATION

Vaccine	ICD-9-CM Code	Description	Allocated Post-Immunization Time Interval (Days)
DTP/DT	780.0	coma and stupor	0-1
	780.2	syncope and collapse	
	785.5	shock without mention of trauma	
	799.9	other unknown and unspecified cause of morbidity and mortality	
	995.0	anaphylactic shock	
	995.1	angioneurotic edema	
	780.6	pyrexia of unknown origin	0-2
	995.2	unspecified adverse effect of drug, medicinal and biological substance	
	995.3	allergy, unspecified	
	999.3	other infection	
	999.9	other and unspecified complications of	

	medical care, not elsewhere classified	
342	hemiplegia	0-7
680.3	carbuncle and furuncle, upper arm and forearm	
680.6	carbuncle and furuncle, leg, except foot	
682.3	other cellulitis and abscess, upper arm and forearm	
682.6	other cellulitis and abscess, leg, except foot	
682.9	other cellulitis and abscess, unspecified site	
780.3	convulsions	
047	meningitis due to enterovirus, including:	0-28
047.8	other specified viral memingitis	
047.9	unspecified viral meningitis	
048	other enterovirus diseases of central nervous system	

049	other non-arthropod-borne viral diseases of central nervous system, including:
049.9	unspecified non-arthropod-borne viral diseases of central nervous system
320	bacterial meningitis, including:
320.0	*Haemophilus* meningitis
320.1	Pneumococcal meningitis
320.3	Staphylococcal meningitis
320.7	meningitis in other bacterial diseases classified elsewhere
320.8	meningitis due to other specified bacteria
320.9	meningitis due to unspecified bacterium
321	meningitis due to other organisms
322	meningitis of unspecified cause, including:
322.2	chronic meningitis
322.9	meningitis, unspecified
323	encephalitis, myelitis and encephalomyelitis,

	including:
323.9	unspecified cause of encephalitis
330.9	unspecified cerebral degeneration in childhood
331.8	other cerebral degeneration
331.9	cerbral degeneration, unspecified
336.8	other myelopathy
336.9	unspecified disease of spinal cord
341.9	demyelinating disease of central nervous system, unspecified
345	epilepsy, including:
345.0	generalized nonconvulsive epilepsy
345.1	generalized convulsive epilepsy
345.3	grand mal status
345.4	partial epilepsy with impairment of consciousness
345.5	partial epilepsy, without mention of impairment of

	consciousness
345.6	infantile spasms
345.7	epilepsia partialis continua
345.9	epilepsy, unspecified
348	other conditions of brain, including:
348.0	cerebral cysts
348.1	anoxic brain damage
348.2	benign intracranial hypertension
348.3	encephalopathy, unspecified
348.5	cerebral edema
348.8	other conditions of brain (cerebral calcification, fungus)
349	other and unspecified disorders of the nervous system, including:
349.8	other specified disorders of nervous system
349.9	unspecified disorders of nervous system
350	trigeminal nerve disorders
351	facial nerve disorders,

	including:
351.0	Bell's palsy
352	disorders of other cranial nerves, including:
352.6	multiple cranial nerve palsies
353	nerve root and plexus disorders
354	mononeuritis of upper limb and mononeuritis multiplex, including:
354.8	other mononeuritis of upper limb
355	mononeuritis of lower limb
356.9	hereditary and idiopathic peripheral neuropathy, unspecified
357.0	acute infective polyneuritis
357.6	polyneuropathy due to drugs
357.8	inflammatory and toxic neuropathy, other
357.9	inflammatory and toxic neuropathy, unspecified
798.0	sudden infant death

		syndrome	
	978.4	poisoning by bacterial vaccines: tetanus	
	978.5	poisoning by bacterial vaccines: diphtheria	
	978.6	poisoning by bacterial vaccines: pertussis vaccine, including combinations with a pertussis component	
	979	poisoning by other vaccines and biological substances: poliomyelitis vaccine	
	999.5	other serum reaction	
	E948	external cause, bacterial vaccines	
	any	death	
OPV	045	acute poliomyelitis	0-28
	342	hemiplegia, including:	
	342.9	hemiplegia, unspecified	
	343	infantile cerebral palsy, including:	
	343.0	infantile cerebral palsy, diplegic	
	343.2	infantile cerebral palsy, quadriplegic	
	343.9	infantile cerebral	

	palsy, unspecified
344	other paralytic syndromes, including:
344.6	cauda equina syndrome
344.8	other specified paralytic syndromes
357.0	acute infective polyneuritis
357.6	polyneuropathy due to drugs
357.8	inflammatory and toxic neuropathy, other
357.9	inflammatory and toxic neuropathy, unspecified
781.0	abnormal involuntary movements
781.2	abnormality of gait
781.3	lack of coordination
781.4	transient paralysis of limb
E949	external cause, other vaccines and biological substances

APPENDIX 8

HOSPITAL-HELD RECORD REVIEW

HOSPITALIZATIONS FOLLOWING IMMUNIZATION: DIAGNOSTIC DISCHARGE CODES AND PHYSICIAN DIAGNOSES, BY TIME PERIOD, FOR CHILDREN WITHOUT PHYSICIAN DIAGNOSES INDICATIVE OF IMMUNIZATION-RELATED ADVERSE EVENTS

Time Interval Following Immunizn. (Days)	Diagnostic Discharge Codes 1-4 1 2 3 4	Physician Diagnoses
0	465.9 780.6 382.9	viral infn. - URTI with otitis media
	382.9 780.3	febrile convulsion
	320.0 285.9	*H.influenzae* type b meningitis
0-2	519.8 780.3	apneic spells - at-risk for SIDS
	345.5 345.7 251.0 999.3	focal seizures; gastro-enteritis; burn to foot
	780.3 599.0 041.4	convulsion due to urinary infection
0-7	780.3 382.9	seizure dis. NYD and otitis media
	786.09 780.6 382.9 780.3	apneic spell prob. due to otitis media causing fever & febrile convulsions
	780.3 465.9	hyperpyrexia & febrile convulsions in presence of URTI

Time Interval Following Immunizn. (Days)	Diagnostic Discharge Codes 1-4 1	2	3	4	Physician Diagnoses
0-7	349.9	518.81	507.0	518.0	respiratory failure; hypotonia; congenital myeloradic-ulopathy; recurrent urinary infection
	759.8	780.3	783.4	754.51	Zelwieger's syndrome
	047.9	519.8	382.9	599.0	aseptic meningitis; URTI; otitis media; urinary infection
	320.0	038.41	599.0	041.4	*Haemophilus* meningitis; E. coli urinary infection
	345.6	558.9	465.9		intractable epilepsy
0-28	742.3	331.9			hydrocephalus & cerebral atrophy
	782.4	742.2	486	781.3	persistent jaundice; septo-optic dysplasia; pneumonia; long-standing hypotonia

Time Interval Following Immunizn. (Days)	Diagnostic Discharge Codes 1-4 1 2 3 4	Physician Diagnoses
0-28	781.0 754.51	possible seizure disorder; subluxable hips
	047.9	meningitis with negative cultures
	320.0 008.6 382.9 253.6	*Haemophilus* meningitis; rotavirus gastro-enteritis; otitis media; inappropriate ADH secretion
	320.0	*Haemophilus* meningitis
	038.42 047.9 599.0	bacterial meningitis due to E. coli
	345.6 754.1	afebrile seizures NYD; torticollis
	345.6	infantile spasms
	550.90 352.6	inguinal hernia; Moebius syndrome
	345.6 742.4	infantile spasms

Time Interval Following Immunizn. (Days)	Diagnostic Discharge Codes 1-4 1 2 3 4	Physician Diagnoses
0-28	345.9	?seizure disorder
	345.1	seizure disorder
	345.6	infantile spasms
	348.8 078.5	disconjugate eye movements NYD
	742.59 754.51 351.0 754.0	bilateral club feet; congenital spinal anomaly - tethered cord
	997.5 997.5 741.03 344.61	neurogenic bladder; vesicotomy; meningo-myelocele