Hepatitis B and Delta Hepatitis

in Nova Scotia:

Association with illicit injectable drug use.

By

Christiane Claire Poulin, M.D.

Department of Epidemiology and Biostatistics

McGill University, Montréal

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ABSTRACT

An epidemic of hepatitis B occurring in a rural area of Nova Scotia in 1988 and 1989 was investigated. Illicit injectable drug use (IIDU) was the major determinant of transmission. The epidemic was the first highly visible indication of IIDU in Nova Scotia. A contact-tracing approach was used to identify the cohort of IIDUs. Of 186 IIDUs, 78 had serological evidence of hepatitis B infection. Using epidemiological criteria, it was determined that 57 of these formed a definite cluster of hepatitis B infections. Age, the total number of IIDU-contacts named and the number of hepatitis B seropositive IIDU-contacts named were identified as risk factors for hepatitis B infection. Six cases of delta hepatitis coinfection were found among the cluster cases, with a secondary attack rate estimated at seven percent. Risk-reduction and immunization strategies for the prevention of viral illnesses associated with IIDU were recommended.

RESUME

Une épidémie d'hépatite B (HB) dans une région rurale de la Nouvelle Ecosse au cours des années 1988 et 1989 a été investiguée. L'injection de drogue illégale (IDI) a été identifiée comme étant le moyen de transmission principal. Cette épidémie était la première indication visible d'un grave problème avec l'IDI en Nouvelle Ecosse. Une méthode de recherche de contacts a été employée pour identifier les usagers. Parmi la cohorte de 186 usagers, 78 usagers avaient une preuve sérologique d'infection HB. Au moyen de critères épidémiologiques, on a demontré un groupe de 57 usagers infectés récemment. L'âge, le nombre total de contact d'IDI, et le nombre de contact d'IDI avec preuve sérologique d'infection, ont été identifiés comme facteur de risque pour l'infection HB. Six usagers étaient aussi atteints de l'hépatite delta. Un taux d'attaque secondaire approximatif de sept pourcent a été calculé pour l'hépatite delta. Des stratégies d'immunization et de réduction de risque vis-à-vis les maladies virales associées avec l'injection de drogue illégale ont été recommendées.

SUGGESTED SHORT TITLE

Hepatitis B, delta hepatitis and
illicit injectable drug use
in Nova Scotia

On the occasion of their retirement, I made for my parents a needlepoint depicting their country home, graced with a saying which captures our Beauceron heritage:

Quand je n'aurai plus rien a faire,
je vais pouvoir vraiement travailler.

A year later, my parents generously put aside their hobbies and hard-earned freedom. And that is how I--family physician, mother of two young children, wife of a family physician--was able to embark on a new career in epidemiology.

This thesis is dedicated to my parents,

Marie-Thérèse Rodrigue and Henri-Paul Poulin.

PREFACE

This thesis evolved from the author's involvement in the investigation of an epidemic of hepatitis B. As Field Epidemiologist in Nova Scotia for the Laboratory Centre for Disease Control, Health and Welfare Canada, the author had the opportunity to head the investigation. This role encompassed the development of a questionnaire for hepatitis B (subsequently adopted throughout the province); the development of objectives and the approach used in the investigation; the training of a team of interviewers; the coordination of laboratory services and of data collection; the recommendation and implementation of control measures; liaison between the Department of Health and Fitness and the medical staff in the outbreak area; data processing and analysis; and the writing of interim reports.

The investigation of the epidemic was requested and facilitated by Dr. Wayne Sullivan, Administrator of Community Health Division, and Dr. Leo MacCormick, Director of Cape Breton Health Unit, of the Nova Scotia Department of Health and Fitness.

Interviews of persons-at-risk in the epidemic region were conducted by public health nurses, Juanita MacPhee, Beverly Hannem, Janet Bickerton and Heather MacSween, from November 1988 to June 1989. Most blood samples were collected by the laboratory staff of the Northside General Hospital, under the direction of Dr. Hilda Tremblett. Most serology testing was done at the Provincial Pathology Laboratory under the supervision of Dr. Spencer Lee. Non-routine hepatitis B serology tests were done at the Laboratory of the National Viral Hepatitis Reference Centre, in Ottawa, under the direction of Dr. R.K.Chaudary.

The author obtained data on cases of hepatitis B in Atlantic Health Unit by reviewing the entire file of hepatitis B case notifications for that health unit from January 1986 to July 1989.

Data on hepatitis B vaccine distribution in the Cape Breton Health Unit were obtained from the Finance Division of the Nova Scotia Department of Health and Fitness, under the direction of Mr. Fred Canavan.

Data on substance abuse and treatment in Nova Scotia were obtained from Marvin M. Burke, Executive Director of the Nova Scotia Commission on Drug Dependency.

Data on reported cases of nepatitis B in Canada were obtained from Dr. Paul Varughese, Bureau of Epidemiology, Laboratory Centre for Disease Control, Ottawa.

This thesis makes several original contributions. This is the first study on the epidemiology of hepatitis B and illicit injectable drug use in Nova Scotia. The adoption of a province-wide hepatitis B questionnaire and the implementation of a case-definition for reportable hepatitis B are both new for the province. The delta hepatitis outbreak among illicit injectable drug users is the first reported outbreak of delta hepatitis in Canada. The estimation of a secondary attack rate of delta virus in hepatitis B delta hepatitis coinfection is another original contribution. Finally, the approach used by public health persons in interviewing illicit injectable drug users was unique and largely successful, and may be useful as a model for future interventions in this population.

It is hoped that this thesis will have some influence on public health policy in Nova Scotia. Specifically, illicit injectable drug use needs to be recognized as a major public health concern in Nova Scotia. Hepatitis B immunization policy and measures for the prevention of other viral illnesses in this high-risk group need to be re-examined.

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I am grateful to Dr. Walter Schlech, Associate professor in Medicine and Assistant Professor in Community Health and Epidemiology at Dalhousie University, who provided guidance during the investigation of the epidemic and subsequently as my supervisor at Dalhousie University.

Doctors Leo MacCormick and Wayne Sullivan, Community Health Division, Nova Scotia Department of Health and Fitness, helped sustain the momentum required for the investigation of an epidemic among illicit injectable drug users. Special thanks are extended to public health nurses Juanita MacPhee, Janet Bickerton, Beverley Hannem, and Heather MacSween. Their compassion and professionalism assured the success of the contact-tracing, education and follow-up of all persons at risk.

I appreciate the assistance provided by Dr. Spencer Lee and his staff at the Provincial Pathology Laboratory. The complexity of the hepatitis serology coupled with the realities of geography posed a real challenge for the investigation of the epidemic.

The Chief of Medical Staff, Dr. Paul Hickey, and the Executive Director, Mr. John Higgins, representing the medical and hospital staff of the Northside General Hospital, were very supportive of this study, through exceptionally trying times. Dr. Hilda Tremblett and her laboratory staff at Northside General Hospital played a vital role in the implemention of an efficient surveillance system.

I wish to acknowledge the guidance I received from Dr. David Kinloch, former Chief of Field Epidemiology, Dr. Jamie Hockin, Acting Chief of Field Epidemiology, and Dr. John Spika, Director of Communicable Disease Epidemiology, Laboratory Centre for Disease Control. The discussions regarding this and other projects provided excellent learning opportunities during my two-year term as Field Epidemiologist.

Thanks are extended to Doctors Theresa Gyorkos, Walter Schlech and Spencer Lee as well as to the Laboratory Centre for Disease Control for their financial assistance in my poster presentation at "The 1990 International Symposium on Viral Hepatitis and Liver Disease" in Houston, Texas. I am also grateful to the Nova Scotia Commission on Drug Dependency, the Nova Scotia Public Health Association and the Laboratory Centre for Disease Control for financial assistance in my presentation at the "Addictions in the 90's--Challenges and Responses" conference in St. John's, Newfoundland.

Finally, I received unfailing encouragement throughout all phases of this research work from my husband, Dr. David Elliott. David also provided invaluable technical assistance with the formatting of the manuscript. To my parents, Marie-Therese Rodrigue and Henri-Paul Poulin--I hope that the dedication of this work to them will reflect my gratitude.

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AFP	Alpha-fetoprotein
ALT	Alanine aminotransferase
anti-HBc	Hepatitis B core antibody
anti-HBe	Hepatitis B e antibody
anti-HBs	Hepatitis B surface antibody
AST	Aspartate aminotransferase
C.B.H.U.	Cape Breton Health Unit
CAH	Chronic active hepatitis
CMV	Cytomegalovirus
CPH	Chronic persistent hepatitis
EBV	Epstein-Barr virus
HAV	Hepatitis A virus
HBcAg	Hepatitis B core antigen
HBeAg	Hepatitis B e antigen
HBIG	Hepatitis B immune globulin
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDV	Hepatitis D virus (Delta hepatitis)
HEV	Hepatitis E virus
HIV	Human immunodeficiency virus
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IIDU	Illicit injectable drug use(r)
ORFs	Open reading frames

CHAPTER 1

INTRODUCTION

From January to November 1988, 20 serologically confirmed cases of hepatitis B were reported in Cape Breton Island, Nova Scotia. This compares with 11 cases which had been reported in 1987. Cape Breton Island has a population of 166,115 persons (Statistics Canada, 1986b). The 20 cases in a 48-week period represented an increase in incidence from a crude annual rate of 6.7 cases per 100,000 in 1987 to 13 cases per 100,000 in 1988. Fourteen of the twenty cases in the 48-week period in 1988 occurred in a rural area with a population of about 30,000 persons. In comparison with two cases reported in this area in 1987, the fourteen cases represented a dramatic increase in the crude rate from 6.7 to 51 cases per 100,000 persons.

Investigation of this outbreak included a review of all cases of hepatitis B reported in the Health Unit from 1986, with continued active case-finding until June 1989. Early in the investigation, it was found that the principal mode of transmission was percutaneous associated with the sharing of contaminated needles for injection of illicit drugs. Therefore, the on-going investigation and control strategy focused primarily on the illicit injectable drug user (IIDU) population.

On the island of Cape Breton, not only was this the first highly visible indication of the existence of a serious problem with illicit injectable drug use in rural Nova Scotia, but it also uncovered an unexpected occurrence of hepatitis B infection and disease as a result of this drug use. (Because of its magnitude, further reference to it will be, not as an outbreak, but as an epidemic (Last, 1988).)

The study of this epidemic led to the identification of a definite cluster of infection involving illicit injectable drug users and several non-users. The identification of a cluster of delta hepatitis occurring later in the epidemic suggested that the IIDU high-risk group was not a closed system, and that on-going recruitment into the group could potentially lead to exposure and concurrent epidemics of other viral illnesses.

The burden of suffering due to hepatitis B is considerable, including acute hepatitis, fulminant hepatitis, chronic active hepatitis, cirrhosis of the liver and hepatocellular carcinoma. The chronic carrier state provides a reservoir of virus. Coinfection and superinfection by other hepatotropic viruses often causes more severe and protracted illness. Delta superinfection of hepatitis B creates a reservoir of delta virus.

It has been noted that illicit injectable drug use itself can spread rapidly like an epidemic. The burden of suffering due to illicit injectable drug use is significant. The user is at risk of acute medical pathology such as cellulitis, viral hepatitis of several etiologies, and acute toxicity (over-dose), as well as chronic diseases such as AIDS and chronic liver disease. Illicit injectable drug users are at risk of epidemic viral illness and have the potential to transmit infection to the non-using population through sexual, or other, close contact. The burden of suffering experienced by the community as a whole is considerable, encompassing not only the medical consequences of illicit injectable drug use, but also the social pathology engendered by this high-risk behaviour.

There have been few studies describing the epidemiology of hepatitis B in Nova Scotia. Furthermore, the epidemiology of hepatitis B in Canada has not been extensively studied, especially in relation to illicit injectable drug use. In the United States, this risk group now accounts for the largest proportion of reported cases. The occurrence of an epidemic of hepatitis B within a geographically defined region

like Cape Breton, provided the opportunity to undertake an in-depth study of hepatitis B infection among illicit injectable drug users, a population generally difficult to study.

Prior to the start of this investigation, there had been no standardization either of investigational tools, or of a reporting definition for hepatitis B among the six health units of Nova Scotia. Subsequent adoption of a method of standardization assisted in inter-region comparisons.

The research work described here has important implications in terms of public health policy. Illicit injectable drug users comprise a major reservoir for hepatitis B, and the existence of delta hepatitis in this group is serious. The approach to investigation and prevention of hepatitis B in this study population may be useful to investigators and public health policy makers throughout Canada, particularly in Nova Scotia.

CHAPTER 2

LITERATURE REVIEW

2.0 Overview of viral hepatitis

Acute viral hepatitis is a general term referring to a group of at least seven different diseases caused by seven distinct viral agents. The best characterized are hepatitis A (previously known as infectious hepatitis) caused by hepatitis A virus (HAV), hepatitis B (previously known as serum hepatitis) caused by hepatitis B virus (HBV), and infectious mononucleosis caused by Epstein-Barr virus (EBV). Delta hepatitis is caused by coinfection or superinfection of hepatitis B infection with hepatitis D virus (HDV). Hepatitis C virus (HCV), likely the etiology for the majority of post-transfusion hepatitis, was recently isolated (Choo et al, 1989). The genome of hepatitis E virus (HEV), a non-A, non-B hepatitis virus which is transmitted enterically, was also recently characterized (Reyes, 1990; Tam et al, 1990).

These seven hepatitides have similar clinical, biochemical and epidemiological features. In addition, cytomegalovirus (CMV) infection is occasionally difficult to distinguish clinically from the viral hepatitides. The initial diagnosis of viral hepatitis is made on the basis of clinical presentation and/or liver function tests. Therefore, sensitive and specific serological tests are essential for accurate differentiation of etiology.

In general, recent hepatitis A infection is confirmed by the presence of IgM anti-HAV. Infectious mononucleosis is often confirmed with the "monospot" test, a sensitive and specific test for heterophilic antibodies. Recent EBV infection is also demonstrated with seroconversion to anti-Epstein-Barr nuclear antigens (anti-EBNA), or by

the presence of IgM anti-viral capsid antigens (IgM anti-VCA). An assay for anti-HCV has been developed (Kuo et al, 1989). To date, demonstration of HEV infection has been in the research setting by immune electron microscopy (Tsarev et al, 1990). CMV is demonstrated directly by culture or indirectly by a four-fold rise in CMV antibody titres.

The only commercial test currently available for HDV infection is an assay for total anti-HD, although several other tests exist in reference laboratories. Three serology tests using two different antigens (hepatitis B surface and core antigens), are usually used to confirm the diagnosis and the timing of infection with hepatitis B virus. Non-A, non-B hepatitis, caused by as-yet-unidentified virus(es) is a diagnosis of exclusion.

Multiple attacks of viral hepatitis may occur in the hepatitis B chronic carrier, defined as HB surface antigen positivity for more than six months, as a result of superinfection by the other hepatotropic viruses. However, the unexpected event of a serologically confirmed outbreak of hepatitis B in an area with a previously very low incidence of hepatitis B, suggested primary infection with hepatitis B virus in a susceptible population rather than superinfection. The mode of transmission and the particularly severe clinical course in several cases suggested involvement of the delta virus.

The literature review on viral hepatitis will therefore focus on hepatitis B and delta hepatitis.

2.1 Hepatitis B

2.1.1 Hepatitis B virus

In 1965, Blumberg discovered the Australian antigen, now called hepatitis B surface antigen (HBsAg) (Blumberg et al, 1965). Its

association with serum hepatitis was subsequently recognized in 1968 (Blumberg et al, 1966; Prince, 1968; Okochi and Murakami, 1968).

In 1970, Dane et al found HBsAg-positive virus particles of three forms in sera of hepatitis patients. The larger spherical particle of 42 nanometres (Dane particle) has since been shown to be the complete Hepatitis B virion. The more numerous filamentous and smaller spherical HBsAg-positive forms are thought to be incomplete viral coat protein.

The Dane particle consists of a lipoprotein envelope and a viral capsid, or inner core, 27 nanometres in diameter (Almeida et al, 1971). Embedded in the envelope are three related proteins, Pre-S1, Pre-S2 and HBsAg (Neurath et al, 1986; Pfarf et al, 1986). The viral capsid consists of 180 core proteins (Onodera et al, 1982), referred to as HB core antigen (HBcAg), and contains the viral DNA genome (Robinson et al, 1974).

The genome of hepatitis B virus, a circular DNA molecule approximately 3200 base pairs in length, has a very compact organization due to open reading frames (ORFs) with overlapping gene sequences, and regulatory signal sequences within protein-encoding sequences (Miller et al, 1989). The ORFs represent gene sequences encoding four major proteins--core, surface, X, and polymerase, as well as minor proteins--pre-core, pre-surface and X/core fusion proteins.

Three antigen-antibody systems are associated with HBV: HBsAg/anti-HBs, HBcAg/anti-HBc and HBeAg/anti-HBe.

HBsAg is a protein of molecular weight 24,000 daltons (Tiollais et al, 1981). Its presence in the serum is an indicator of active HBV infection, either acute or chronic, and of potential infectivity (Barker and Murray, 1972). HBsAg may appear as early as 6 days after exposure to HBV (Krugman et al, 1979), and is usually easily detectable by the time of clinical illness. There is a gradual decline to

undetectable levels within four to six months. Persistence of elevated HBsAg levels beyond 3 months after onset of illness is associated with increased risk of development of the chronic carrier state.

HBsAg consists of a group-specific antigen "a", and at least two subtype determinants, "d/y" and "w/r" (Le Bouvier, 1971; Bancroft et al, 1972), which usually are mutually exclusive. The four major subtype categories, **ayw**, **ayr**, **adw**, and **adr**, were thought to be the phenotypic expression of four major genotypes of HBV (Le Bouvier et al, 1972).

In 1972, Mosley et al demonstrated that epidemiologically linked cases of hepatitis B consistently had the same subtype as the index case, excluding from their series any secondary case suspected of illicit drug practices. Since then, subtyping has been considered a "gold standard" as an epidemiological tool to confirm links between cases. However, recent discoveries about hepatitis B virus may limit the usefulness of this tool in some circumstances.

Some complex subtypes such as **adywr** display both allelic determinants on the same particle. Due to more precise subtyping by mapping of the entire nucleotide sequence of the HBV genome, followed by transfection of cells, it has been found that compound subtypes are produced by phenotypic mixing during infection with two distinct genomes, rather than genomic recombination (Okamoto et al, 1987).

Also through comparison of complete nucleotide sequences of genomes, considerable divergence has been found in nucleotide sequences of the same subtype. For example, a subtype from American chronic carriers differed from the same subtype from Japanese chronic carriers, suggesting that Le Bouvier's four major antigenically defined subtypes may not reflect true genotypic variation of HBV (Okamoto et al, 1988).

Concomitant HBsAg and anti-HBs of differing subtypes can be found in association with hemodialysis (Foutch et al, 1983) and illicit injectable drug use (Stimmel et al, 1975). Concurrent heterotypic

HBsAg and antibody formation has also been demonstrated in chronic hepatitis B without a likely second exposure to HBV of a different subtype suggesting a disturbance in immune response (Shiels et al, 1987).

Although consistent transmission of an unusual subtype was demonstrated in an outbreak of hepatitis B among the patients of an infected oral surgeon (Reingold et al, 1982), the pattern of subtype transmission associated with multiple exposures has not been studied in an epidemiological context.

Therefore, the significance of subtypes may need to be re-examined. Specifically, 1) there may be significant genomic heterogeneity within subtype categories; 2) there is evidence of heterotypic antigen-antibody formation; and 3) single and multiple exposure transmission patterns may differ. Verification of epidemiological links using the conventional subtyping technologies (immunodiffusion and radio-immunoassay) may be limited in cases of multiple exposures (personal communication, H. Will).

In uncomplicated acute HBV infection, the disappearance of HBsAg and HBeAg antigenemia is followed by a window phase characterized by the presence of anti-HBc but the absence of both HB surface antigen and anti-HBs. The window phase ends with the appearance of hepatitis B surface antibody signalling recovery from overt or unapparent infection and lack of infectiousness (Lander et al, 1972; Aach et al, 1974). Up to 20 percent of cases who recover from hepatitis B infection may never produce anti-HBs; however, once produced, anti-HBs persists indefinitely in more than 80 percent of patients (Barker et al, 1973).

HBsAg and anti-HBs may be found concurrently. In one study, 32 percent of cases had concurrent HBs antigen and antibody, with greater frequency in patients with chronic active hepatitis (63 percent) than in those with acute hepatitis (34 percent), concurrence being

associated with evidence of viral replication and active inflammation (Shiels et al, 1987).

In nature, HBcAg is found only in the enveloped virus in serum, or in infected hepatocytes. Both serum and liver HBcAg contain a serologically distinct e antigen (HBeAg) (Magnius and Espmark, 1972). The exact nature of HBeAg and its relationship with HBcAg remained enigmatic until only recently. It is now known that HBcAg and HBeAg are produced by alternate translation from two different start codons at the 5' end of the pre-core or core open reading frames. Thus HBeAg is produced in vivo by a secretory mechanism involving the precore signal sequence rather than by denaturation of HBcAg (Ou et al, 1986).

In acute and chronic HBV infection, HBeAg is usually found during the phase of viral replication and is therefore associated with a high degree of infectivity (Alter et al, 1976; Andres et al, 1981). Persistence of HBeAg for more than ten weeks after incubation period is predictive for development of chronic infection (Norkrans et al, 1979).

Although HBcAg exists primarily in the liver and within HBV particles, anti-HBc antibody is produced by virtually all HBV-infected patients regardless of clinical disease. In contrast, antibody to HBeAg only inconsistently appears and is indicative of reduced viral replication and the beginning of resolution (Hoofnagle et al, 1981). In general, infectivity is considered limited in the presence of anti-HBe; however, some HBeAg-negative, anti-HBe-positive individuals may be positive for HBV-DNA, and be infectious (Krogsgaard et al, 1986).

Specific antibody in primary humoral response to viral infection is usually of the immunoglobulin M (IgM) class. IgM anti-HBc, indicative of recent infection, persists at high titres for approximately six months and at a much lower titre for a prolonged interval (Perrillo et al, 1983). Hence IgM anti-HBc is used to distinguish between recent and remote HBV infection (acute versus chronic HBsAg-positivity), and

between coinfection and superinfection by a second hepatotropic virus (Perrillo et al, 1983).

In summary, HBeAg, DNA polymerase, HBV-DNA, Dane particles in serum or HBcAg in hepatocytes, and high titres of HBsAg or IgM anti-HBc, are all associated with increased infectivity. In general, anti-HBe is associated with lower infectivity, IgG anti-HBc occurs in recovery, and anti-HBs signifies immunity.

2.1.2 Diagnostic profile of Hepatitis B

The diagnosis of hepatitis can be established clinically by symptoms and signs such as arthralgias and jaundice, and/or biochemically with hepatic damage demonstrated by liver function tests--elevated transaminases, bilirubin, alkaline phosphatase, lactic dehydrogenase, and prolonged prothrombin time. Viral etiologies such as Hepatitis A, EBV, HCV or HEV, can be ruled out by specific serology tests.

Depending on the purpose of testing (diagnosis, screening, immune status), various algorithms have been devised for the sequencing of HBsAg, anti-HBs and anti-HBc serology tests. The complexity of serological responses that occurs in HBV infection continues to make diagnosis difficult; however, the combined testing for all three yields high sensitivity for demonstration of HBV infection except during the early incubation period.

In the presence of HBsAg-positivity, IgM anti-HBc may be useful to differentiate between acute or chronic infection. Both positive and negative predictive values of IgM anti-HBc have been found to be above 90 percent (Perrillo et al, 1983; Hoofnagle et al, 1985). HBeAg and anti-HBe testing are generally reserved as indicators of infectivity in the chronic carrier or to determine the risk of perinatal transmission. HBV-DNA in serum is a more specific and sensitive indicator of infectivity than HBeAg/anti-HBe (Tassopoulos et al, 1987).

2.1.3 Clinical aspects of hepatitis B

About 50 to 65 percent of persons acutely infected with hepatitis B virus remain asymptomatic; 10 to 20 percent are symptomatic with flu-like illness but are anicteric; 20 to 30 percent of infected persons develop clinical disease (Hollinger, 1989). The subclinical to clinical ratio is even higher in children--HBV infections in young children are almost always asymptomatic.

The typical clinical course of acute hepatitis B is divided into four phases: incubation period, prodromal phase, icteric stage and convalescence. The virus burden and the potential for transmission are greatest during the incubation period, which is usually 45-180 days, with an average of 60-90 days. The prodrome is insidious with anorexia, nausea, malaise, myalgia, easy fatigability, vague abdominal pain, headache, and occasionally mild fever. Five to 15 percent of cases experience manifestations of immune complex disorder (serum-sickness) with rash, arthralgia, arthritis and vasculitis (Hollinger, 1989). Signs of liver damage include jaundice, dark urine, tender liver, and hepatomegaly; splenomegaly may also be present. HBsAg levels then decline, followed by a recovery phase of several months. Fulminant hepatic necrosis and fatality develop in about one percent o icteric cases.

Acute hepatitis B is not the most serious consequence of hepatitis B viral infection. Chronic carrier status can result, with the potential for transmission of infection even in the absence of clinical manifestations of disease. Ninety percent of infected newborns, 20 to 30 percent of infected preschool children, and six to 10 percent of children infected after age five or six, do not clear the virus and become chronically infected (Beasley et al, 1982; Beasley and Hwang, 1983). Age at infection is a major determinant of the chronic carrier status. Gender is also an important determinant of chronic carrier

status with persistence of HBsAg 1.5-2 times more frequent in men, for unknown reasons (Szmuness et al, 1978). A mean of one percent per year of HBsAg carriers clears the virus indefinitely (Alward et al , 1985). Intrinsic or iatrogenic immunosuppression is associated with a higher risk of persistent infection (Szmuness et al, 1978).

In the majority of chronic carriers, there is a paucity of symptoms and signs of liver disease, with mild non-specific symptoms such as easy fatigability, and, rarely, mild hepatosplenomegaly. In a series of 100 cases, biochemical tests of liver function revealed elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in nearly all cases; in fewer than 10 percent, serum albumin, bilirubin and prothrombin time were abnormal (Hoofnagle and Alter, 1984).

2.1.4 Sequelae of hepatitis B infection

The sequelae of persistent hepatitis B infection are chronic persistent and chronic active hepatitis, cirrhosis of the liver and hepatocellular carcinoma. Chronic hepatitis B carriers are also at risk of superinfection with the other hepatotropic viruses.

Chronic persistent hepatitis (CPH), chronic active hepatitis (CAH), and cirrhosis are histological diagnoses. In both CPH and CAH, there is biochemical evidence of liver dysfunction. However, in CPH, the lobular architecture is preserved with little or no fibrosis and no piecemeal necrosis, whereas in CAH, there is piecemeal necrosis with or without bridging necrosis and fibrosis. The prognosis in CPH is considered good, depending on duration of viral replication, superinfection and immunostatus. The prognosis of CAH is the eventual development of cirrhosis (Cooksley et al, 1986), with a high risk of subsequent hepatocellular carcinoma.

The period of viraemia without liver damage in the prodromal phase, and the existence of carriers with a high level of HBV replication with

normal hepatic histology support the theory that HBV is not directly cytopathic (Chu et al, 1985; Lok et al, 1985). In acute hepatitis, liver damage coincides with the appearance of IgM anti-HBc, suggesting that inflammation is caused by immune lysis of infected hepatocytes (Lok et al, 1985). Thomas et al (1988) hypothesize that, in adults, chronicity derives from deficient production of alpha interferon and suppression of host response to interferon, whereas in neonates, chronicity may be due to specific suppression of cell-mediated immune response.

Persistent infection with HBV is divided into replicative and non-replicative phases (Chu et al, 1985). During the first few years after acute infection, viral replication is active, with high levels of HBeAg and free HBV-DNA predominating in both hepatocytes and serum. This is followed by a low replicative phase in which either HBeAg or anti-HBe is present, with low concentrations of serum HBV-DNA, and overt histological chronic liver disease. Finally, viral replication ceases, no HBV-DNA is identified in serum, and there is no longer demonstrable liver inflammation. However, HBV-DNA persists in an integrated form in the genome of the hepatocyte. Cirrhosis, if it develops, usually starts during the replicative phase or during the transition to the nonreplicative phase (Hoofnagle, 1988,.

Reactivation of chronic hepatitis B refers to the reappearance of the serological markers of viral replication. Often mimicking an episode of acute viral hepatitis, this occurs principally in association with immunosuppressive disorders or therapy but may also occur spontaneously (Seeff and Koff, 1986).

Hepatocellular carcinoma, probably the commonest malignant tumor in males in the world, has an estimated annual incidence of one million cases, and a male-to-female ratio of about 3:1 (Tiollais et al, 1985). There is marked geographic variation in the incidence, with 150 cases per 100,000 population in China, Taiwan, Korea and sub-Saharan Africa,

in contrast with fewer than four cases per 100,000 in the United States (Rustgi, 1988).

The epidemiological evidence linking hepatocellular carcinoma with chronic hepatitis B virus infection is undisputed. First, there is a correlation between areas of high prevalence of hepatocellular carcinoma and areas where hepatitis B virus is hyperendemic. In China and most of Southeast Asia, virtually all adults have serologic evidence of hepatitis B virus infection with 10 to 15 percent being chronic carriers. The incidence of hepatocellular carcinoma ranges from 20 to 150 per 100,000 population per year. In contrast, in the United States and Western Europe, five to 15 percent of adults have serologic evidence of hepatitis B viral infection, fewer than one percent are carriers, and the incidence of hepatocellular carcinoma is from 1 to 5 cases per 100,000 population per year (Sandler et al, 1983).

Secondly, a high percentage of patients with hepatocellular carcinoma have chronic hepatitis B infection. In China and Korea, 85 to 95 percent of individuals with hepatocellular carcinoma are HBsAg-positive; in the United States and Western Europe, 10 to 26 percent of cases are chronic carriers (Rustgi, 1988). Thirdly, in family clusters of hepatocellular carcinoma, there is a high incidence of HBsAg-positivity, where cases of hepatocellular carcinoma are usually carriers, and maternal-infant transmission of infection is implicated (Sung and Chen, 1980).

Finally, two large prospective studies have provided evidence of the causal link between hepatitis B virus infection and hepatocellular carcinoma. In 1975, a prospective study of 22,707 males was started in Taiwan (Beasley et al, 1981). Follow-up in 1986 indicated a marked excess of deaths from hepatocellular carcinoma and cirrhosis in carriers of HBsAg with a relative risk of 94 (Beasley, 1988). This study also demonstrated a 1000-fold higher incidence of hepatocellular carcinoma in HBsAg-positive persons with known cirrhosis. A

prospective study among 150 Eskimo chronic carriers in Alaska documented the development of hepatocellular carcinoma in three males during the ten years of follow-up (Alward et al, 1985). This was a rate 307 times the expected rate for the general United States population with the same age and sex composition. Hepatocellular carcinoma arises in the long-term carrier state, usually after 20 to 40 years of chronic infection (Hoofnagle, 1988).

The demonstration of hepatitis B viral DNA incorporated into the DNA of hepatoma cells is further evidence linking hepatocellular carcinoma and hepatitis B viral infection (Imazeki et al, 1986). The exact mechanism of hepatocarcinogenesis by hepatitis B virus is unknown, but it is hypothesized that viral DNA may be a promoter sequence for oncogenes or may alter genes controlling cellular growth (Di Bisceglie, 1989).

Approaches to prevention and treatment of hepatocellular carcinoma include primary prevention of hepatitis B viral infection through vaccination or hepatitis B immune globulin, and early detection of tumor through screening strategies involving serum alpha-fetoprotein (AFP) and ultrasonography. As a single screening test in high-risk individuals, AFP has a sensitivity between 85-90 percent and a specificity between 70-80 percent (Regan, 1989). The mean 5-year survival rate after surgical resection has been calculated at 20 to 30 percent, with no evidence that adjuvant chemotherapy after hepatic resection increases cure rates (Lotze, 1988).

2.1.5 Mode of transmission of hepatitis B virus

The reservoir for human hepatitis B virus is man. Its mode of transmission is direct from person to person, through apparent or unapparent percutaneous or transmucosal exposure to virion present in infectious blood, semen, vaginal fluids and saliva.

Parenteral transmission has long been recognized in association with the transfusion of infectious blood or blood products (Pattison et al, 1973). This led to the mandatory HBsAg testing of all blood, blood products and plasma used in transfusion in most countries. A subsequent decrease in transfusion-related hepatitis B occurred. Recognition of common nosocomial risks such as needle-stick injury (Alter et al, 1976) has led to the development of post-exposure prophylaxis protocols. Infection due to unusual nosocomial risks such as percutaneous exposure to contaminated devices (Douvin et al, 1990) or medications (Alter et al, 1983) has been documented with infection control measures subsequently being implemented.

The major population at risk of parenteral transmission of hepatitis B infection in the United States is illicit injectable drug users, accounting for 27 percent of all reported hepatitis B infections in 1987 (Alexander et al, 1988). Patients with renal failure are also at high risk because of long-term hemodialysis (Pattison, 1973). The percutaneous mode of transmission of hepatitis B can be very efficient. An attack rate of 91 percent was reported in one study related to a multiple-dose vial used in a hemodialysis unit (Alter et al, 1983).

Transmucosal transmission associated with both homosexual and heterosexual sexual activity, first recognized in the early 1970's (Szmuness et al, 1975a; Wright, 1975), has since been well documented. A recent controlled study demonstrated an association between heterosexual activity with multiple partners and infection with hepatitis B (Alter et al, 1989). Infection resulting from heterosexual contact with a single acutely infected partner was estimated at 23 percent during one year (Koff et al, 1977). Among institutionalized mentally handicapped persons, where an average of 20 percent test positive for HBsAg, there is a great risk of nonpercutaneous transmission (Van Damme et al, 1989).

Household contacts of infected persons are at increased risk of infection, due to transmucosal or occult percutaneous transmission,

with secondary attack rates estimated at up to 30 percent for contacts of acutely ill patients (Boughton et al, 1982). The risk of acquiring hepatitis B from contact with chronically infected persons increases through time (Szmuness et al, 1975b).

The greatest contribution to the global burden of hepatitis B infection is due to perinatal transmission from infected mothers to newborns. This mode of transmission accounts for 40 percent of all chronic carriers in the world (Tong, 1989). An estimated 35 to 40 percent of chronic carriers are infected in the preschool years, presumably due to increased risk as a result of contact with other HBsAg-positive family members (Tong, 1989).

2.1.6 Epidemiology of hepatitis B

Hepatitis B occurs worldwide, with an estimated 200 million chronic carriers of hepatitis B virus. The estimated lifetime risk of death from cirrhosis and/or hepatocellular carcinoma among chronic carriers is 40 percent (Beasley and Hwang, 1984). HBV infection is thought to be responsible for at least 80 percent of cases of hepatocellular carcinoma worldwide (Beasley and Hwang, 1984).

The global distribution of hepatitis B infection is described in terms of low, intermediate and high endemicity based on prevalence rates. The level of endemicity reflects the interactive nature of host risk factors, properties of the virus including mode of transmission, and environmental conditions.

Australia, Western Europe, North America and parts of South America are areas of low endemicity, where the prevalence of HBsAg is estimated between 0.2 and 0.5 percent. Neonatal and childhood infection are infrequent (Maynard et al, 1989). High-risk groups include illicit injectable drug users, homosexual men, heterosexual persons with multiple sex partners, clients and staff of programs for the mentally

handicapped, prison inmates, health care workers, hemodialysis patients, recipients of certain blood products, sexual and household contacts of HBV carriers, children of carrier mothers, and persons from areas of higher HBV endemicity (Immunization Practices Advisory Committee, 1987).

Eastern Europe, Japan, the Middle East, the Union of Soviet Socialist Republics, and parts of South America are areas of intermediate endemicity, where the prevalence of HBsAg is between two and seven percent. There is frequent childhood infection, but infrequent neonatal infection. China, Southeast Asia, tropical Africa, and the Amazon Basin of South America are considered areas of high endemicity, where prevalence rates vary from eight to 20 percent. Neonatal infections are frequent and childhood infection is very frequent, virtually the entire population having experienced an infection episode by adult life (Maynard et al, 1989).

The epidemiology of hepatitis B in Canada is thought to be similar to that in the United States (Remis and Brazeau, 1985), and it is from the American literature that information is obtained about trends and risk factors. The incidence of HBV disease, based on the number of reported cases, increased from 6.9 to 11.5 cases per 100,000 population from 1978 to 1985, in the United States (Immunization Practices Advisory Committee, 1987). Although 25,000 cases of hepatitis B disease are reported to the Centers for Disease Control every year, it is thought that this number greatly underestimates the true incidence of infection. It is estimated that only 50 percent of acute hepatitis B cases are reported by the current passive surveillance system (Alter et al, 1987). After correcting for subclinical disease and under-reporting, it is estimated that there are actually about 300,000 hepatitis B infections per year (Immunization Practices Advisory Committee, 1987). In spite of the availability of hepatitis B vaccine since 1982, it is estimated that there has been a 50 percent increase in the number of infections per year, relative to the early 1980's (Kane et al, 1989).

The groups at risk of HBV infection have been changing in the United States. Prior to 1986, homosexual men comprised the single largest risk group. However, the proportion of cases reported in this group has decreased from 21 percent to nine percent since then, possibly due to changes in sexual behaviour related to the HIV epidemic (Alexander et al, 1988). Heterosexual transmission has increased from 18 percent to 24 percent of reported cases possibly because of heterosexual activity in populations with a high prevalence of HBV carriers such as illicit injectable drug users or certain ethnic groups (Alexander et al, 1988). Percutaneous transmission associated with illicit injectable drug use has increased from 15 percent to 27 percent of reported cases.

McGuillan et al (1989) conducted a study of the seroprevalence of HBV infection from 1976 to 1980, of the demographic and behavioural factors associated with risk of infection, in a group representative of the general United States population. Hepatitis B infection was estimated to be 3.2 percent among the white population in comparison with 13.7 percent among the black population. In both racial groups, there was a low prevalence in children, which began to rise between the ages of 12 and 18 years. Adult black Americans were at highest risk for HB infection. Other predictors of HBV positivity were male gender, residence in an urban area, certain geographic regions, living below the poverty level, serving in the armed forces, and a positive syphilis test.

The epidemiology of hepatitis B in Canada has not been as extensively studied. It has been estimated that 1.3 million Canadians are potentially at risk of hepatitis B (Coates and Rankin, 1983). (A group is considered at high risk of hepatitis B infection on the basis of a comparison of its prevalence rate of HB markers with that of adult volunteer blood donors who are considered at low risk.) The major recent hepatitis B seroprevalence studies in Canada are summarized in Table 2.1. Although the methodologies of these surveys vary markedly,

Table 2.1 Major recent hepatitis B seroprevalence studies in Canada

Author* (year)	Testing period	Setting	Number tested (% tested)**	Seroprevalence percent HBsAg+	Seroprevalence percent any marker
blood donors					
Nusbacher (1987)	6 months 1986***	Central Ontario	95,917 (100%)	0.04	n/a
	self-identified high-risk		627	0.48	13.9
prenatal screening					
Sekla (1988)	10 months 1987	Manitoba	13,099 (100%)	0.61	n/a
Waters (1989)	1985	Alberta	43,314	0.25	n/a
	1986		43,670	0.41	n/a
	1987		42,094 (100%)	0.45	n/a
Delage (1986)	1982-1984	Montréal	30,315 (100%)	3.40	n/a
Canadian Armed Forces					
Manley (1989)		recruits	1,848:anti-HBc 577:HBsAg	0.20	3.5
		HMSC crew (one acute case)	251:anti-HBc 251:HBsAg (100%)	0.80	6.8

* First author only
** Percentage actually tested in the group or population
*** Year of testing is assumed to be 1986
n/a not available

Table 2.1 Major recent hepatitis B seroprevalence studies in Canada (continued)

Author* (year)	Testing period	Setting	Number tested (% tested)** group****	Seroprevalence percent HBsAg+	any marker
dental professionals					
Epstein (1984)	1981-1982	national convention	713 volunteers	2.0	11.4
occupational health nurses					
Strickler (1987)	1985	Ontario convention	151 volunteers	0.7	8.6
anaesthesia personnel					
Malm (1986)	1986***	teaching hospital Vancouver	anaes. 83 resid. 27 aides 7 perfu. 5 (90%)	0 0 0 0	12.0 0 0 40.0
Chernesky (1984)	1978 & 1982	6 teaching hospitals Ontario	anaes. 71	n/a	16.9
mentally handicapped/day school					
Remis (1987)	1984	Montréal (one acute case)	stu. 505 staff 165 (81-84%)	7.3 1.2	26.9 13.0

* First author only

** Percentage actually tested in the group or population

*** Year of testing is assumed to be 1986

**** Abbreviations describing the groups: anaes.=anaesthetists; resid.=residents; perfu.=perfusionists; stu.=students.

n/a not available

Table 2.1 **Major recent hepatitis B seroprevalence studies in Canada** (continued)

Author* (year)	Testing period	Setting	Number tested (% tested)** group***	Seroprevalence percent HBsAg+	any marker*
mentally handicapped/institutionalized					
Poulin (1985)	1985	Québec (99%)	resid. 182 staff 194	11 0.5	61.0 17.0
Farley (1987)	1986	N.B.	resid. 288 (99%)	0.4	12.0
Lavigne (1983)	1983	N.S. 2 institutions	resid. 202 staff 239 resid. 168 staff 333 (68-100%)	0.5 0 0 0	15.8 11.3 11.6 5.5
immigrants from regions of high endemicity					
Chaudhary (1981)	1979-1980	all Indochinese refugees to Montréal	14,347	11.6	62.9
indigenous peoples of the Canadian North					
Larke (1987)	1983-1985	N.W.T.every community 51% of all Inuit 44% of all Dene 12% of all non-native	14,198	3.9 2.9	28.4 24.4
Minuk (1982)	1980	Baker Lake N.W.T.	720 (85%)	3.9	27.0

* First author only
** Percentage actually tested in the group or population
**** Abbreviations describing the groups: resid.=residents.

Table 2.1 **Major recent hepatitis B seroprevalence studies in Canada** (continued)

Author* (year)	Testing period	Setting	Number tested (% tested)**	Seroprevalence percent HBsAg+	Seroprevalence percent any marker
Indigenous peoples of the Canadian North					
Minuk (1985)	1984	Chesterfield N.W.T.	172 (78%)	2.3	22.0
Baikie (1989)	1986	Labrador Newfoundland 5 ethnic groups	2,156 (62%)		
			Inuit	6.9	26.4
			settler	1.9	10.0
homosexual/heterosexual with multiple partners illicit injectable drug use					
Willoughby (1986)	1982-1984	"Vancouver AIDS Study"-general practice-homosexual	576 (82%)	7.8	68.4
Romanowski (1983)	1983	Edmonton-STD clinic			
		homosexual	150	3.3	39.3
		heterosexual	150	0.7	9.3
Hankins (1989)	1989	Montréal, prison for women, volunteers 52% IIDU, 25% prostitution	248	n/a	45.0

* First author only
** Percentage actually tested in the group or population
n/a not available

and results are difficult to compare, these studies suggest that Canada is a region of low hepatitis B endemicity with infection concentrated in several definable high-risk populations.

A low prevalence of chronic hepatitis B carriers (0.04 percent) was found among blood donors in Central Ontario (Nusbacher et al, 1987). The prevalence of chronic hepatitis B carriers among blood donors in Canada had previously been reported as 0.15 percent (Varughese, 1985). Predictably, high prevalences of both hepatitis B infection and chronic carrier state were found among refugees from Indochina, an region of high endemicity (Chaudhary et al, 1981). High prevalences are well documented among the Inuit, ranging from 2.3 to 6.9 percent for the chronic carrier state, and 10 to 28 percent for past hepatitis B infection (Larke et al, 1987; Minuk et al, 1982; Minuk et al, 1985; Baikie et al, 1989). The age-specific pattern of infection among the Inuit is unusual: hepatitis B infection is rare among Inuit children, and prevalence rises steeply during adulthood. It has been suggested that this pattern, atypical of both industrialized and developing countries, is resulting from a loss in the "critical mass" of infectious individuals during the past 30 years (Minuk et al, 1982).

The prevalence of hepatitis B infection among Canadian health care workers is very variable, ranging from zero to 16.9 percent, based on positivity for any HBV marker. This variability reflects not only the study methodologies, but probably also variable levels in the risk of exposure due to the specific nature of the work and the patient populations. The prevalence of hepatitis B among the residents and staff of institutions for the mentally handicapped in Québec is similar to that reported in the American and European literature. In sharp contrast, institutions in the Maritime provinces have been found to have low prevalence rates. Farley et al (1987) speculated that the lower rates may be due to the smaller size of the Maritime institutions.

Actual rates of hepatitis B infection among Canadian illicit injectable drug users, homosexual men and heterosexuals with multiple partners are largely unknown. It is generally assumed that the epidemiology of hepatitis B in these risk groups in Canada is similar to that in the United States. Several Canadian studies support this hypothesis.

The Vancouver Lymphadenopathy AIDS-Study, based on a relatively unselected sample of homosexuals, demonstrated the hyperendemicity of hepatitis B in the male homosexual community in Vancouver (Willoughby et al, 1986). The HIV-1 study among inmates of a women's prison was not designed to determine the prison seroprevalence of HIV and HBV (Hankins et al, 1989). However, among the 245 female inmates studied, 45 percent had hepatitis B markers; illicit injectable drug use and prostitution were reported by 52 and 25 percent, respectively.

A study of 718 persons undergoing liver biopsy in six Toronto teaching hospitals provides information on risk factors for hepatitis B (Coates et al, 1986). Among the 65 percent on whom complete data were available, country of birth and race were risk factors most significantly and consistently related to HBV marker status. In this study, homosexuality was associated with HBV marker status and had the largest relative risk among males. In females, Oriental race and previous injectable drug use were significantly associated with HBV marker status.

In summarizing reported cases data from 1974 to 1983, Varughese (1985) noted a steady increase in the numbers of cases, and a considerable geographical variation in crude rates. In 1983, based on information provided on 40 percent of the reported cases, there was a male-to-female ratio of about 2:1 with the highest rates in males aged 20 to 29 years, and females aged 20 to 24 years. Very little epidemiological information was available and this age-gender distribution was presumed to be related to homosexual activity and drug abuse. Varughese (1985) concluded that reported cases underestimated the true incidence, that the source of infection was not documented or not reported to public

health authorities, and that the upward trend was in part due to improved awareness and laboratory testing.

Incident cases of hepatitis B must be reported by the provinces to the Notifiable Diseases Reporting System, Health and Welfare Canada. One of the greatest difficulties has been the lack of a national reportable case definition. Currently, there is great variation in how cases are reported by province, with respect to the definition of clinical disease, serological markers, and biochemical evidence of hepatic damage. Some provinces report only acute disease, others include newly identified chronic carriers. The standardization of a case definition is relatively new (personal communication, A. Carter). A case definition was recommended by the Advisory Committee on Epidemiology, in late 1988; however, it is unknown if provincial jurisdictions have implemented this definition. Furthermore, risk factor data are not reported, and age and sex data are inconsistently reported by some provinces.

2.1.7 Treatment and prevention of hepatitis B

Recovery from acute hepatitis B is usually spontaneous with supportive therapy required only in the more severely symptomatic cases. The goal of treatment of chronic hepatitis is two-fold: the reduction of infectivity, and the halting of progressive liver disease. A rational pharmacological approach to the treatment of chronic hepatitis would therefore comprise both antiviral and immunomodulating drugs. In a review of the treatment of chronic hepatitis, Garcie and Gentry (1989) concluded that single agent therapies were ineffective or associated with toxicity. The focus of research is now combination therapy. Orthotopic liver grafting is the only treatment for terminal liver disease, but is often complicated by recurrence of the original infection in the case of cirrhosis due to hepatitis B virus (Po..es et al, 1984).

Clearly, the prevention of infection through appropriate precautions and/or immunization is the most effective means of reducing the burden of disease related to hepatitis B virus. The screening of blood and blood products for HBsAg is mandatory in most countries and has resulted in marked reduction of transfusion-related hepatitis B infection. Universal precautions for preventing transmission of bloodborne pathogens have been recommended for health care facilities (Laboratory Centre for Disease Control, 1989). Hepatitis B immune globulin (HBIG) also provides significant post-exposure prophylaxis under certain circumstances (National Advisory Committee on Immunization, 1989). However, the most important means for the global control of hepatitis B infection is immunization.

The first vaccine against human hepatitis B virus, derived from HBsAg from the plasma of healthy carriers, became commercially available in the United States in 1982 and in Canada in 1983 (Hoofnagle, 1989a; Coates and Rankin, 1983). Recombinant hepatitis B vaccine, made from the hepatitis B surface antigen expressed in genetically manipulated yeast cells (Andre, 1989), was licensed in Canada in 1987 (Boucher, 1987). The characteristics of the hepatitis B vaccines as summarized by Maynard et al (1989) are:

1) extremely low frequency of adverse effects
2) high degree of immunogenicity even when administered at birth
3) high degree of pre- and post-exposure efficacy
4) no interference effect with maternal anti-HBs
5) no cross-interference with BCG, poliovirus, and DTP vaccines.

Strategies for the use of hepatitis B vaccine are predicated by the geographic patterns of the prevalence of hepatitis B. In regions of intermediate and high endemicity, immunization of infants would be essential to achieve control. Selective immunization of only infants born to HBsAg-positive mothers would be sufficient in countries where perinatal transmission is the principal contributor to the overall rate of HBV carriage. Mass immunization of all infants is argued to be

preferable because even in areas of high endemicity, no more than 50 percent of total HBV carriage may be attributed to perinatal transmission (Maynard et al, 1989). A focal approach also entails an expensive screening program. Although the characteristics of the vaccines would permit mass immunization programs, the cost of the vaccines has presented a major difficulty in the implementation of immunization strategies.

In countries of low hepatitis B endemicity, recommendations for the use of hepatitis B vaccine are targeted to high-risk groups, such as infants born to HBsAg-positive mothers, patients undergoing dialysis or recipients of multiple transfusions of blood or blood products, health care workers, residents and staff of institutions for the mentally handicapped, homosexually active men, illicit injectable drug users, sexual and household contacts of chronic carriers, embalmers and international travellers to endemic areas (National Advisory Committee on Immunization, 1989). Other high risk groups are inmates of long-term correctional facilities and heterosexuals with multiple sexual partners.

In spite of the availability of hepatitis B vaccine since 1982, there has been an increase in the number of reported cases of hepatitis B in the United States (Kane et al, 1989). The proportion of cases of health workers has decreased, possibly because 30 to 40 percent of health care workers have been immunized. Although the proportion of cases due to homosexual activity has declined since 1986, the proportion associated with heterosexual transmission and illicit injectable drug use has increased. These three high-risk groups accounted for 59 percent of reported cases in 1987 (Alexander et al, 1988). Kane et al (1989) concluded that because these groups cannot be effectively reached by even aggressive immunization programs, immunization of children or adolescents would be a more effective strategy than the targeting of high-risk groups.

The goal of post-exposure prophylaxis of the newborn is to prevent or modify the course of hepatitis B infection. Infants of HBsAg-positive mothers should be given intramuscular hepatitis B immune globulin (HBIG) immediately after birth, and three infant doses of hepatitis B vaccine, the first dose within 7 days of birth (National Advisory Committee on Immunization, 1989). This combination is the most effective means of preventing the chronic HBV carrier state, with efficacy rates ranging from 85 to 93 percent (Tong, 1989). In developing countries who are unable to afford HBIG, hepatitis B vaccine alone has been shown to prevent perinatal HBV transmission with efficacy rates ranging from 70 to 80 percent (Tong, 1989).

2.2 Delta hepatitis

2.2.1 Delta hepatitis virus

The delta antigen was first detected in 1977 as an antigenic determinant in the hepatocyte nuclei of HBsAg carriers (Rizzetto et al, 1977). The delta hepatitis virus (HDV) is a defective hepatotropic RNA virus which occurs only in the presence of hepatitis B virus on which it is dependent for its replication (Purcell et al, 1983). The virion is a spherical 36 nanometre particle, with a lipoprotein envelope of HBsAg, an internal delta antigen coded by the HDV genome, and a genome (Bonino and Smedile, 1986).

The HDV genome, a circular molecule of RNA 1,678 nucleotides in length, is the smallest RNA genome of any known animal virus (Wang et al, 1986; Rizzetto et al, 1980a). HDV-RNA contains six open-reading frames of more than 100 amino acids in both genomic and antigenomic strands, the largest antigenomic strand producing a protein which reacts with antibodies to hepatitis delta antigen (Wang et al, 1987).

2.2.2 Delta hepatitis serology

Acute delta hepatitis occurs either as a coinfection simultaneously with acute hepatitis B, or as a superinfection in which acute delta hepatitis is superimposed on a chronic hepatitis B infection. Delta superinfection of HBV carriers may be self-limited, or may progress to HDV chronicity. Acute delta coinfection only rarely leads to HDV chronicity. The timing of delta hepatitis markers--antigen in liver and serum, and antibody to HDV in the serum--is dependent on the expression of the underlying hepatitis B infection.

In acute delta hepatitis, coinfection may be distinguished from superinfection by the presence of IgM anti-HBc, the serological marker of acute hepatitis B infection. Because of the diagnostic accuracy of IgM anti-HBc, HDV markers can now be found in unapparent acute HBsAg-negative hepatitis B, contradicting the previous belief that HDV infection seldom occurs without concurrent HBsAg in serum (Caredda et al, 1989).

HDV-RNA and HDV antigen are first detectable during the incubation period, prior to the elevation of serum aminotransferase (Hoofnagle, 1989b). Serum HDV antigen and IgM anti-HD are the most sensitive markers (60 and 75 percent respectively) for the diagnosis of delta infection during the first two weeks after onset of symptoms. Both markers become undetectable one month later (Buti et al, 1987). Humoral response in HDV coinfection is variable, from the isolated expression of IgM or IgG antibody, to a complete response consisting of a primary IgM and a secondary IgG response (Aragona et al, 1987a). HDV-RNA is no longer detectable one month after acute illness, and its persistence in the serum may indicate progression to chronicity (Buti et al, 1988).

In contrast to delta hepatitis coinfection, delta hepatitis superinfection is marked by the elevation of serum aminotransferase levels and the rise of total anti-HD to high, sustained titres (Aragona

et al, 1987b). The IgM anti-HD response is initially brisk, persists over prolonged periods of time in chronic delta hepatitis, but declines or disappears in HBV carriers whose disease improves or resolves (Farci et al, 1986). A stable pattern of serum HDV RNA may identify a subpopulation in the chronic delta hepatitis group still in the replicative phase of infection (Smedile et al, 1987). The explosive replication of HDV during acute superinfection can suppress the synthesis of HBsAg to undetectable levels (Chen et al, 1988). Rarely, superinfection with HDV may induce termination of HBsAg carrier state with seroconversion to anti-HBs and clearance of both HBV and HDV infections (Chin et al, 1988).

2.2.3 Diagnosis of delta hepatitis

The diagnosis of delta hepatitis generally rests on the presence of total anti-HD in serum, predominately IgG, detectable by commercial radioimmunoassays. Because this antibody is often low in titre and short-lived in HDV coinfection, accurate diagnosis requires testing in the acute and convalescent phases. However, in illicit injectable drug users, a strong serologic response to HDV usually develops, and may be associated with severe liver damage (Aragona, 1987a). Typically, the clinical course of such an infection is biphasic hepatitis, with acute illness characterized by two peaks of serum transaminase, the first corresponding with the peak of HD viraemia, the second with the peak of HBV replication (Govindarajan et al, 1986; Caredda et al, 1985). The detection of IgM anti-HD in association with rising titres of total anti-HD confirms the diagnosis of delta coinfection (Aragona et al, 1987b).

Delta superinfection is readily diagnosed by detection of high titres of IgM anti-HD and total anti-HD at all but the earliest stages of infection. A titre of more than 1:1000 is usually considered diagnostic of delta superinfection (Rizzetto et al, 1979).

2.2.4 Clinical aspects of delta hepatitis

It is important to distinguish between HDV/HBV coinfection and superinfection because the severity and outcome of illness differ. Onset of illness occurs between one and eight weeks after delta coinfection; in delta superinfection, the incubation period is shorter (Bonino et al, 1988). Zanetti et al (1987) described HDV infection as invariably pathogenic. However, Shattock et al (1985) found evidence of simultaneously acquired HBV-HDV infection in four illicit injectable drug users among 29 who remained asymptomatic.

Acute delta hepatitis is generally similar clinically to acute hepatitis B and acute non-A, non-B hepatitis (Bonino et al, 1988). Coinfection and superinfection are indistinguishable clinically in acute delta hepatitis, except for biphasic hepatitis seen predominantly in drug addicts in coinfection (Caredda et al, 1985). However, for either the coinfection or the superinfection pathway, acute delta hepatitis is associated with an increased risk of fulminant acute hepatitis (Smedile et al, 1982; Caredda et al, 1985). Delta infection is also associated with an increased mortality rate ranging from two to 20 percent in comparison with less than one percent for acute hepatitis B (Hoofnagle, 1989b).

In HBV/HDV coinfection, the outcome in 90 percent of cases is complete recovery with seroconversion to anti-HBs (Caredda et al, 1985). Less than five percent of cases of acute delta coinfection develop chronic HBV/HDV infection (Caredda et al, 1987).

In contrast, HDV chronic carrier state is the most common sequela of acute delta superinfection, resulting in chronic delta hepatitis in more than 80 percent of patients (Caredda et al, 1987; Hadler et al, 1984). Chronic delta hepatitis is more severe than chronic hepatitis B alone, with 70 to 80 percent developing cirrhosis in contrast with 15 to 30 percent seen in chronic hepatitis B (Hoofnagle, 1989b). In a series of 176 consecutive patients with chronic delta hepatitis, 14

percent died within three years from acute hepatitis, with the cumulative number of deaths about three times higher in comparison with HBV chronic carriers with liver disease (Bonino et al, 1987).

Delta superinfection has been implicated in 30 to 60 percent of cases of fulminant hepatitis (De Cock et al, 1984; Smedile et al, 1982). All types of fulminant hepatitis in northern South America, including Labrea and Santa Marta hepatitis, represent the same histological and clinical entity, usually due to delta superinfection of HBV carriers (Bensabath et al, 1987). In the Venezuelan Yucpa Indian outbreak, delta superinfection of chronic HBV carriers was responsible for a high rate (17 percent) of fatal fulminant hepatitis (Hadler et al, 1984).

Rarely, acute delta hepatitis results in hepatitis B virus clearance (Chin et al, 1988). HDV infection does not appear to increase the risk of hepatocellular carcinoma above that of HBV infection alone (Bonino et al, 1987). Chronic delta infection is not always associated with clinically overt liver disease. One study in an endemic community in Greece identified a high prevalence (27 percent) of HDV infection among oligo- or asymptomatic hepatitis B carriers, often with florid histological hepatitis (Hadziyannis et al, 1987). The prognosis of chronic HDV hepatitis seems unrelated to the original morphologic lesion. Piecemeal necrosis, bridging necrosis or the extent of lobular inflammation are not predictive of the clinical course (Verme et al, 1986).

2.2.5 Mode of transmission of hepatitis D virus

Like the hepatitis B virus on which it is dependent, transmission of the delta hepatitis virus is from person to person through apparent or unapparent percutaneous or transmucosal pathways. Transmission of HDV in endemic areas likely occurs through unapparent percutaneous inoculation. Although the mode of delta transmission could not be ascertained in the delta hepatitis epidemic among the Yucpa Indians of

Venezuela, the villages with severe outbreak were characterized by poor socioeconomic conditions, overcrowding, and 100 percent prevalence of skin disease among children (Hadler et al, 1984). Cultural practices such as acupuncture may also have facilitated the epidemic (Hadler et al, 1984).

Transmucosal transmission associated with heterosexual activity has been documented in sexual contacts of infected illicit injectable drug users (Lettau et al, 1987), and accounts for some transmission in family clusters of HDV infection (Bonino et al, 1985). Delta virus is less efficiently transmitted sexually than parenterally, in both heterosexual and homosexual activity (Lettau et al, 1987; De Cock et al, 1988a; Weisfuse et al, 1989). An association was found between HIV and HDV infection in homosexual men with both acute and chronic hepatitis B in a large study at a hepatitis clinic in Los Angeles (De Cock et al, 1988b). It was postulated that, as in HIV infection, a high level of promiscuity may be a risk factor for delta infection in homosexual males.

Direct parenteral inoculation with contaminated blood or blood products is a very efficient mode of delta hepatitis virus transmission, as evidenced by the development of high endemicity among illicit injectable drug users in some areas within a ten-year interval (Gust and Dimitrikakis, 1987; Hansson et al, 1982). In contrast to the high risk of HDV infection from uncontrolled blood, or for HBsAg carrier haemophiliacs receiving coagulation factors made from pooled plasma (Rizzetto et al, 1982), the overall risk of acquiring HDV from transfusion of blood screened for HBsAg is estimated at 1 in 3,000 transfusions (Rosina et al, 1985).

The efficiency of percutaneous versus transmucosal transmission may be related to the mode of delta hepatitis infection, whether coinfection or superinfection. Experimental studies of delta hepatitis in chimpanzees revealed that a smaller inoculum of HDV is needed to initiate infection in established chronic hepatitis B, than for

coinfection (Purcell et al, 1983). Coinfection may require appropriate quantities of both agents, whereas chronic HBV infection promotes rescue of the defective delta hepatitis virus.

Perinatal transmission of HDV appears to be rare, primarily because of the low HDV prevalence in HBV-infected mothers, and possibly also because lower fertility is associated with chronic HDV infection (Craig et al, 1986). Vertical transmission of HDV is presumed to be a minor contributor to the reservoir of chronic HDV infection. The majority of patients with delta infection has antibody to HBeAg, and perinatal transmission of HBV occurs virtually only in the presence of HBeAg (Smedile et al, 1981; Zanetti et al, 1982).

2.2.6 Epidemiology of hepatitis D virus

Although first discovered in 1977, delta hepatitis is not a new disease. "Santa Marta" hepatitis is an unusually severe hepatitis occurring in northern Colombia. First recognized in 1930, it is now thought to be fulminant hepatitis associated with delta superinfection of hepatitis B. This conclusion was based on the epidemiologic features of the disease and on the histopathology of stored liver specimens (Buitrago et al, 1986). Further evidence of the existence of HDV prior to 1977 comes from anti-HD found in a lot of immune serum globulin prepared from plasma collected in 1944 from United States Army soldiers. A decrease in the prevalence of anti-HD in immune serum globulin lots coincided with the start of routine HBsAg screening of blood and plasma in 1972 (Ponzetto et al, 1984).

Since delta hepatitis virus is inextricably linked to hepatitis B virus, its epidemiology and mode of transmission are also similarly linked. Chronic hepatitis B carriers are the reservoir and major source of HDV infection. Delta infection is found worldwide but occurs in three distinct epidemiologic patterns: as an endemic disease occurring in a large proportion of chronic hepatitis B carriers, as an

epidemic disease in isolated communities of chronic hepatitis B carriers, and as a disease that occurs only in certain high-risk populations (Hoofnagle, 1989b).

Its geographical prevalence is difficult to interpret because of a lack of standardization of its measurement (Zanetti et al, 1987). However, the Amazon Basin, parts of Africa, the Middle East and the Islands in the South Pacific, are thought to be areas of high endemicity, where 30 to 90 percent of HBsAg carriers with liver disease are also infected with HDV (Ponzetto et al, 1985). In Europe, HDV infection is predominantly found in the Mediterranean Basin, the Balkan Peninsula and the European Soviet Union. The highest rates are reported in Romania where 95 percent of HBsAg carriers with liver disease are HDV-infected (Ponzetto et al, 1985). In Northern Europe and the British Isles, HDV is rare in the general HBsAg-positive population, but has an endemic-epidemic pattern in the illicit injectable drug user population (Hansson et al, 1983; Shattock et al, 1982; Weller et al, 1983). In Asia, despite the high endemicity of hepatitis B, HDV in patients with chronic liver diseases and hepatocellular carcinoma is rare (Chen et al, 1984).

In the United States, HDV prevalence is thought to be low in the general HBsAg-positive population. A 3.8 percent anti-HD prevalence was found in one large series of asymptomatic HBsAg-positive volunteer blood donors (Nath et al, 1985). A five percent anti-HD prevalence was found in a diverse referral population of HBsAg-positive patients Shiels et al, 1985). Prevalence rates in Los Angeles are among the highest reported in the United States (De Cock et al, 1988a).

A high rate of HDV infection was reported among haemophiliacs treated with commercial clotting factor produced in the United States from pooled plasma (Rizzetto et al, 1980b). Widespread HDV infection was recently recognized in nine geographically dispersed facilities for the developmentally disabled in Illinois, with a prevalence of HDV

infection ranging from 15 to 75 percent in hepatitis B carriers (Hershow et al, 1989).

HDV is thought to be an infrequent cause of viral hepatitis in male homosexuals in several geographic regions of the United States, with the low prevalence (two percent) suggesting non-endemicity in this high-risk population (Weisfuse et al, 1989). However, in a large series of unselected cases at a hepatitis clinic in Los Angeles, HDV infection was found in 14 percent of homosexual men with chronic hepatitis B (De Cock et al, 1988a).

In the United States, the highest prevalences of HDV infection have been found in illicit injectable drug users. Among illicit injectable drug users in Los Angeles, 73 percent who had chronic hepatitis B infection and eight percent who had acute hepatitis B infection also had antibody to HDV (De Cock et al, 1988a). Investigation of an unusually large and severe outbreak of hepatitis B in Worcester, Massachusetts, led to the conclusion that HBV and HDV had been endemic among Worcester drug abusers and that the outbreak resulted from concurrent spread of HBV and HDV among a susceptible pool of new needle users (Lettau et al, 1987).

Several seroprevalence studies have been done in Canada. Of 326 HBsAg-positive blood samples submitted to the National Viral Hepatitis Reference Centre, Laboratory Centre for Disease Control, one homosexual among 25 males considered at high risk, and seven among 216 persons from regions of hepatitis B endemicity, tested positive for delta antibody (Parker and Chaudhary, 1985). A seroprevalence study of 186 Indian, Inuit and non-native HBsAg-positive residents of Newfoundland and Labrador, regions of high hepatitis B endemicity relative to southern Canada, revealed no HDV antibody (Ratnam et al, 1986). Of 123 HBV-infected Manitoba residents during the period 1974 to 1986, four had delta coinfection and one had delta superinfection; three delta infections were associated with illicit injectable drug use (Hannan et al, 1988). Of 245 HBsAg-positive sera collected between 1982 and 1985

in Alberta, Yukon and the Northwest Territories, one had delta coinfection and three had delta superinfection (Cheng et al, 1986).

These studies indicate that delta hepatitis has been present in Canada since at least 1974, with high risk groups including illicit injectable drug users, homosexuals and immigrants from regions of high hepatitis B endemicity. It is not possible from these studies to estimate the average prevalence rates in these high-risk groups or in the general population.

There is a lack of both provincial and national delta hepatitis incidence statistics. Delta hepatitis is not included in the Notifiable Diseases Reporting System of the Laboratory Centre for Disease Control, Ottawa (Carter, 1988). It may, however, be reported under the "Hepatitis other and unspecified viral" designation, by some provinces. Reporting of delta hepatitis to public health authorities is not mandatory in Nova Scotia.

2.2.7 Treatment and prevention of delta hepatitis

Acute HBV/HDV coinfection usually resolves spontaneously with only supportive therapy required in the more severely symptomatic cases. There have been few studies on the treatment of chronic HDV infection. Small pilot studies with alpha-interferon have yielded decreased serum levels of HDV antigen and HDV-RNA during therapy, with recurrence of viral replication on cessation of therapy (Garcia and Gentry, 1989).

Delta hepatitis coinfection can be prevented by immunizing susceptible persons with hepatitis B vaccine. Passive antibodies do not prevent infection after exposure (Fields and Hadler, 1986). Pending the development of an HDV vaccine, the prevention of delta hepatitis superinfection is difficult and rests on measures such as exposure-reduction strategy.

2.3 Overview of illicit injectable drug use

2.3.1 Implications of illicit drug use

The concern regarding illicit drug use, from the local to international levels, is four-fold (Hughes et al, 1983). First, illicit drug use has a tendency to spread in an epidemic manner. Secondly, illicit drug use involves young people and causes major disruption in the most productive period of life. Thirdly, illicit drug use is associated with local and international criminality. Finally, there is a necessity for international treaties and a secretariat for global narcotics control to ensure licit supplies of raw substances for medical use while controlling illicit traffic.

Illicit drug use refers to nine types of drugs: opium, heroin, other opiates, cocaine, cannabis, hallucinogens, amphetamines, barbiturates (including sedatives and tranquillizers) and volatile solvents. Licit drugs are prescribed by physicians or are available legally without prescription. Illicit refers to the initially illegal source of drugs (Bureau of Dangerous Drugs, 1988). Licit drugs may be diverted to the illicit market. The pattern of multiple drug use is well recognized, especially among regular narcotics users (Hartnoll et al, 1989).

2.3.2 Methodological issues concerning the epidemiology of illicit injectable drug use

For illicit drug use, incidence refers to first-time drug users per unit time, and prevalence refers to active users at a given time. An underlying difficulty in the methodologies used to estimate prevalence of illicit drug use is the variability among users of frequency and intensity of use. Further complicating the concept of prevalence is the existence of attrition from drug use, and cycles of abstinence and relapse among chronic regular users. Estimates of incidence and

prevalence are necessary for policymakers for allocation of resources for treatment and law enforcement. There are four methods of estimating the prevalence of illicit drug use: surveys, indirect indicators, direct counts, and inferential estimates.

There have been numerous surveys of the general and special populations with respect to drug use. Although this method is probably reliable for describing patterns of use of common drugs such as alcohol, tobacco, cannabis or medicines, surveys are not useful for assessment of illicit injectable drug use. A survey must be based on a probability sample. However, in the case of illicit injectable drug users, there is no method for enumeration of the population. Intuitively, the usual surrogate enumerations (telephone directories and households) may not be representative of the illicit injectable drug user population. Not only may illicit injectable drug users not have a telephone or a stable address, but there tends to be a pattern of clustering among illicit injectable drug users (Hunt, 1977).

Indirect estimates are based on indicators reflecting the medical, social and legal consequences of illicit drug use. Accuracy presumes knowledge of the relationship between the indicator and illicit injectable drug use. These relationships may not be spatially or temporally generalizable. However, this method may be useful for the monitoring of trends once the indirect indicators are validated. Often-used medical indicators are drug-related deaths (subject to underreporting); treatment statistics (limited by the possible non-comparability of treated versus non-treated illicit drug users); and viral hepatitis notifications (also subject to underreporting). Law enforcement statistics and illicit market indicators are subject to the variability of police activity and the functioning of the criminal justice system.

The comparative epidemiology of indirect indicators was recently evaluated in a multi-city European study (Hartnoll et al, 1989). It was emphasized that comparability was dependent on a clear definition

of 1) who or what was being counted as a case or event, 2) the population base to which the data referred (per 1,000 population in specific age ranges), and 3) the time period involved. Furthermore, first-hand information from ethnographic studies was considered essential for the interpretation of agency-based indicators. In their particular setting, of the eight indicators studied, the demand for treatment from medical and social facilities (especially first-treatment demand), and police arrests for offenses involving illegal drugs, were considered to be of particular value. Other indicators potentially important were drug-related deaths, illicit market indicators and viral hepatitis. Viral hepatitis was considered a useful indicator, specifically of injectable drug use.

Direct counts of illicit drug users are derived from medical, law enforcement and social service registers. These data are necessarily incomplete and biased. Direct counts may also be obtained through intensive case-finding studies. Although time-consuming and expensive, this method provides a better assessment of the prevalence of illicit injectable drug use as well as a means to validate indirect indicators. Ethnographic studies provide some information about prevalence, but are especially useful for information on drug use patterns and incidence rates.

Inferential estimates result from the statistical manipulation of direct counts. The principal inferred estimates are based on the capture-recapture method. Initially, a number of users is identified from prison, treatment programs, etc. Subsequently, random samples are taken from this group of users. It is then possible to estimate the total number of users. This method requires assumptions which do not reflect the complexity of illicit injectable drug use in the real world. For example, the second sample may not be random (individuals with a previous arrest may be subject to more surveillance), and there is attrition from and recruitment into the pool of users.

2.3.3 Epidemiology of illicit injectable drug use

Illicit drug use has been documented world-wide. The World Health Organization (WHO) classifies regions into extensive or minimal illicit drug use based on prevalence rates of one or more per 1,000 population versus less than one per 10,000 population. Regions with intermediate prevalences are classified as moderate (Hughes et al, 1983). There are distinctive regional patterns of illicit drug use, with different rates and populations affected. For example, in Asian countries, heroin is generally smoked, whereas in the Americas and Europe, injection is the predominant means of administration (Hughes et al, 1983). In Peru, coca leaf is chewed by the Andean Indian population, whereas coca paste is smoked by urban youth. In North America, cocaine is smoked, sniffed or injected. In their review spanning 1977 to 1980, Hughes et al (1983) reported cocaine use as extensive in only four countries, all in the Americas.

Based on two documents from the Commission on Narcotic Drugs, the Division of Narcotic Drugs of the United Nations Secretariat (DND-UNS) (1987) concluded that there was an escalation of heroin and cocaine use, with a number of countries reporting epidemic proportions. In the Americas, cocaine and cannabis were the major illicit drugs used, and combinations of two or more drugs, often involving alcohol, were common.

Estimates of the numbers of heroin and cocaine users in Canada are very variable. In a 1983 report, the Royal Canadian Mounted Police estimated 20,000 heroin and 250,000 cocaine users Canada-wide, based on intelligence and information derived from data gathered by the operational statistical reporting system and the automated drug system (Stamler et al, 1983).

Illustrating the methodological difficulties in estimating prevalence, WHO reports 10,126 known heroin and 2,559 known cocaine users throughout Canada in 1980 (Hughes et al, 1983); whereas, DND-UNS cites

3,275 and 5,813 known heroin users Canada-wide in 1985 and 1983 respectively (Division of Narcotic Drugs of the United Nations Secretariat, 1987).

In 1985, Health and Welfare conducted a Canada-wide health promotion survey which included questions about marijuana, hashish and cocaine use (Health and Welfare Canada, 1988). The target population for this telephone survey was all persons 15 years of age or older.

This survey revealed that 0.9 percent of Canadians had used cocaine, and 5.6 percent had used cannabis in the twelve months prior to the survey. Overall, cocaine use in Canada was found to be more prevalent among the young, males, students and those looking for work, singles, and residents of British Columbia. Nearly all cocaine users had also used cannabis in the previous twelve months. The prevalence of cocaine use was two percent in the 15-24 age group for both sexes, and in males aged 25-34 years. The gender-specific prevalence of cocaine use was 1.3 and 0.6 percent among males and females respectively.

Approximately three percent of households in Canada did not have telephones. Data collected in 1984 on persons in these households indicated marked differences from the general population. They tended to be young, male, single and less educated than the general population.

In this survey, zero percent of Nova Scotians reported cocaine use, whereas reported marijuana and hashish use was 5.4 percent. However, the Annual Report(s) of the Nova Scotia Commission on Drug Dependency, for 1984 and 1986, stated that cocaine use and its availability had continued to climb and that cocaine as part of multiple-drug use was not uncommon in Nova Scotia. No actual counts or prevalence rates were reported in the latter two publications.

Given the fundamental difficulty of reaching the cocaine-user population, the discrepant conclusions from these two sources may be

due to lack of access to the user population in a telephone survey. Although non-telephone owners accounted for only three percent of the Canadian population, their demographic profile--male, single and less educated--suggests the survey may not have included a very relevant subgroup. If this were the case, then the prevalence of drug use in Nova Scotia and in the country as a whole would be underestimated.

The Nova Scotia Commission on Drug Dependency is an agency of the government of Nova Scotia. The Commission delivers services through five regional programs. Treatment and rehabilitation services include primary care (detoxification, assessment and treatment orientation), and aftercare (inpatient and outpatient components). Extended care is offered through a long-term sheltered workshop for the chronically ill. The Commission also has employee assistance, prevention and community education programs (Burke, 1988).

During 1987-1988, of 6,851 individuals treated through the Nova Scotia Commission on Drug Dependency, approximately 50 percent of patients were poly-drug users, generally alcohol and minor tranquillizers or cannabis. The Commission knew of 120 opiate users in the province. There had been a marked increase in the number of injectable-cocaine users requesting treatment (no counts provided) (Burke, 1988).

In the three fiscal periods, 1984, 1985-1986, and 1987, the age distribution of all patients treated in facilities from the five regions, for substance abuse of any kind, was similar and stable (Nova Scotia Commission on Drug Dependency, 1984; 1986; 1987). Approximately 15 percent of persons treated were between 11 and 24 years of age; 50 to 60 percent were between 25 and 44 years of age. The male-to-female ratio of 4:1 was similarly stable in all regions in these fiscal periods. Unemployment was reported in 24 to 39 percent of patients of all regions in these fiscal periods.

Available age and gender data for patients admitted during the twelve-month period starting November 1, 1988, at Cape Breton and Metro drug

dependency centres, are summarized in Table 2.2. Cocaine use was reported by five and 27 percent of patients treated at the Cape Breton and Metro centres respectively. The male-to-female ratio of persons who reported cocaine use was 4.6:1 in Cape Breton and 3.2:1 in Metro. The difference may be due to the small numbers of cases in Cape Breton. The extent to which treated cocaine users are representative of all cocaine users in these two regions is not known. However, the pattern of mostly male, mostly young, users seen at these treatment centres is consistent with that reported in the literature.

The age-specific prevalence rates of cocaine use calculated on the basis of the Cape Breton drug dependency centre data are lower than the rates revealed by the Canadian health-promotion survey. This may reflect failure to seek treatment or an actual lower prevalence of cocaine use. Differences between the two treatment centres may reflect different tendencies to seek treatment, or actual differences in prevalence of cocaine use.

An indirect indicator of the prevalence of illicit drug use in Canada is the steady increase in the number of convictions for all federal drug related legislation from 1979 to 1988 (Bureau of Dangerous Drugs, 1988). Convictions related to cocaine have also increased steadily, with the proportion of convictions related to cocaine increasing from 15 percent in 1979 to 61 percent in 1988. (Bureau of Dangerous Drugs, 1988). However, in May, 1987, the Government of Canada announced a comprehensive program on illicit drug use. Considerable emphasis was placed by the Royal Canadian Mounted Police on reinforcing and expanding the Anti-Drug Profiteering Program (Royal Canadian Mounted Police, 1987). The contribution of increased police activity to the observed upward trend in convictions and to the changing relative importance of cocaine is therefore difficult to assess.

Table 2.2 Enumeration data and age-specific minimum prevalence rates of cocaine users admitted to Cape Breton and Metro Drug Dependence Centres, for the twelve-month period starting November 1, 1988*

Age in years	Number of patients admitted (number per 1,000)	
	Cape Breton	Metro
15 - 20	6 (0.4)	38 (1.4)
21 - 30	37 (1.4)	221 (3.1)
31 - 40	27 (1.2)	127 (2.1)
41 - 50	2 (0.1)	10 (0.2)
51 - 60	1 (<.1)	0
total cocaine users	73	396

* Data provided by the Nova Scotia Commission on Drug Dependency

In summary, estimating the prevalence rate of illicit injectable drug use is problematic. Currently, there exists no reliable estimate of the extent of illicit drug use, except perhaps for cannabis, in Canada and Nova Scotia. Indirect indicators suggest cocaine use is increasing in Nova Scotia.

2.5 Hepatitis B: Eight-year experience in Canada, Nova Scotia and Cape Breton Health Unit

Population figures and reported hepatitis B cases for Canada, Nova Scotia and Cape Breton Health Unit (C.B.H.U.) are tabulated in Appendices 1, 2 and 3. Table 2.3 summarizes the incidence data of cases of hepatitis B from 1981 to 1988.

There was a gradually increasing trend in Canada in the crude rate of reported cases of hepatitis B, from 4.4 to 12.1 cases per 100,000 population during this period. The trend in Nova Scotia (up to the time that the present investigation was initiated in C.B.H.U.) showed more variability, but in general, Nova Scotia had a lower crude rate of hepatitis B than did Canada. The crude reported rate of hepatitis B in C.B.H.U. was, until 1987, lower than those of Canada and Nova Scotia. The marked increase in the reported rate of hepatitis B in C.B.H.U. from January to November 1988, from 6.7 to 13.0 cases per 100,000 population, prompted investigation.

A better indication of the sharp increase of hepatitis B disease in C.B.H.U. and in Nova Scotia is obtained by comparison of age-standardized rates (Table 2.4). Age-standardization is based on the two most recent years in which there were sufficient data for comparison. In 1987 and 1988, age and gender were specified in 71 and 74 percent of reported cases (Appendix 2).

Table 2.3 Reported incidence of hepatitis B in Canada*, Nova Scotia and Cape Breton Health Unit (C.B.H.U.), 1981 to 1988

	year	number of cases	population	incidence per 100,000 population
CANADA	1981	1065	24,343,200	4.4
	1982	1301	24,631,800	5.3
	1983	1914	24,889,800	7.7
	1984	1894	25,127,900	7.5
	1985	2194	25,358,600	8.7
	1986	2389	25,309,300	9.4
	1987	3005	25,625,100	11.7
	** 48 wks 88	3001	25,923,300	12.5
	1988	3132	25,923,300	12.1
NOVA SCOTIA	1981	10	847,440	1.2
	1982	60	851,800	7.0
	1983	27	858,900	3.1
	1984	21	869,900	2.4
	1985	24	880,700	2.7
	1986	35	873,180	4.0
	1987	47	878,900	5.4
	** 48 wks 88	82	883,900	10.1
	1988	103	883,900	11.7
C.B.H.U.	1981	1	170,000	0.6
	1982	6	169,900	3.5
	1983	2	170,900	1.2
	1984	1	172,400	0.6
	1985	2	173,200	1.2
	1986	1	166,000	0.6
	1987	11	165,000	6.7
	** 48 wks 88	20	166,115	13.0
	1988	37	166,115	22.3

* HB data provided by Laboratory Centre for Disease Control, Ottawa

** Data as recorded for the first 48 weeks of 1988, separately. Intensive case-finding efforts started in late November, 1988. After the initiation of investigation, C.B.H.U. data was no longer comparable to the rest of Nova Scotia or Canada.

Table 2.4 Age-standardized rates of reported hepatitis B disease per 100,000 population in 1987 and 1988 in Canada, Nova Scotia and Cape Breton Health Unit (C.B.H.U.)

1987

	Nova Scotia	Canada excluding Nova Scotia	C.B.H.U.	Nova Scotia excluding C.B.H.U.
male	6.82	10.91	4.77	6.63
female	3.40	5.55	7.57	1.98

1988*

	Nova Scotia	Canada excluding Nova Scotia	C.B.H.U.	Nova Scotia excluding C.B.H.U.
male	11.12	11.36	15.40	9.34
female	7.91	6.36	8.68	7.83

* Age-standardized annual rates are based on reported cases for the 48-week period ending November 15, 1988. Intensive case-finding efforts started in late November, 1988. After the initiation of investigation, C.B.H.U. data was no longer comparable to the rest of Nova Scotia or Canada.

Age-standardization was calculated by the direct method, using age-specific rates in each population group. The standard population used was that of Canada, 1986 census.

The age-standardized rate of reported hepatitis B in 1987 was lower in Nova Scotia than in the rest of Canada, for both males and females. The male-to-female ratio (approximately 2:1) in Nova Scotia was similar to that in the rest of Canada. In 1987, the age-standardized rate of hepatitis B in C.B.H.U. males was lower than that of the rest of Nova Scotia. Among females, the higher observed rate in C.B.H.U. may be due to small numbers and the inclusion of two elderly newly-identified chronic carriers.

By November 1988, the age-standardized rate for males in Nova Scotia had caught up to that of the rest of Canada, and among females, had exceeded that of the rest of Canada. In sharp contrast with 1987, the age-standardized rate of hepatitis B among males in C.B.H.U. had increased more than three-fold, and had increased 1.6 times relative to the rate among males in the rest of Nova Scotia. An increase was also observed among C.B.H.U. females. Clearly, there existed an outbreak of hepatitis B, all the more unexpected because of the rural setting.

CHAPTER 3

METHODOLOGY

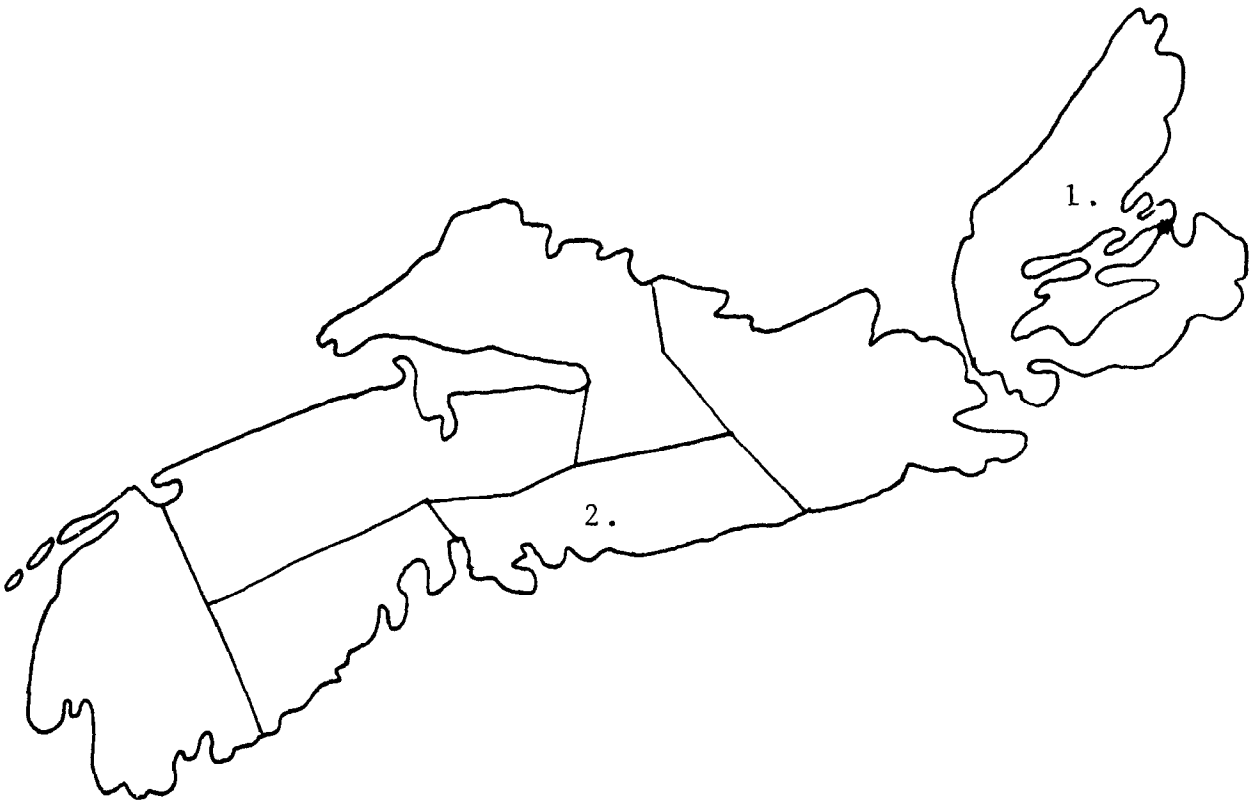
3.0 Introduction

This chapter details the epidemiological and laboratory methods used in investigating the occurrence of hepatitis B in relation to illicit injectable drug use in two Health Units of Nova Scotia. Health Units are geographic regions defined by the Nova Scotia Department of Health for the delivery of public health services. Health Unit authorities are individually or collectively referred to as Public Health in this study. Figure 3A presents a map of Nova Scotia highlighting the two Health Units.

The covert nature of illicit injectable drug use imposes constraints on the design of epidemiological studies in this population. In Cape Breton Health Unit, an epidemic of hepatitis B in a circumscribed geographic area brought to light the existence of a loosely defined group of "buddies" who engaged in the activity. The epidemic area involved two contiguous towns and, to a lesser extent, five small communities in close proximity. The existence of an epidemic among the illicit injectable drug users was an event recognized by members of the group. These circumstances determined a study design based on the enumeration of a cohort of illicit injectable drug users through effective contact-tracing.

In contrast, the Atlantic Health Unit serves a largely metropolitan population, including Nova Scotia's largest urban centres, the cities of Halifax and Dartmouth. The potential for effective contact-tracing is limited. Basic descriptive epidemiology of the incidence of reported cases of hepatitis B is presented for that Health Unit.

Figure 3A **Map of Nova Scotia Cape Breton Health Unit and Atlantic Health Unit**



1. Cape Breton Health Unit

   * The epidemic area:

     Communities of: North Sydney, Sydney Mines, Bras d'Or, Florence, Georges River, Alder Point, Point Aconi

2. Atlantic Health Unit

3.1 Objectives

The objectives of this research work are threefold:

1) to investigate the occurrence of hepatitis B in relation to illicit injectable drug use in two health units in Nova Scotia;

2) to identify risk factors predictive of hepatitis B infection in the illicit injectable drug user population in the epidemic area;

3) to review hepatitis B prevention strategies and make recommendations on policy in Nova Scotia based on the findings in these two health units.

3.2 Cape Breton Health Unit

3.2.1 Setting

The Cape Breton Health Unit offers public health services to a population of approximately 166,000 persons in four counties located on an island linked to the mainland of Nova Scotia by a causeway.

Sociodemographic information on Cape Breton County obtained from the most recent census indicated that it had a population of 123,625 persons, 63 percent of single ethnic origin, predominantly of British descent (Statistics Canada, 1986a). Among the 94,590 persons 15 years of age or older, 19 percent had attained a level of schooling less than grade 9; 37 percent attained a level between grades 9 and 13; eight percent had obtained their high school leaving certificate; and six percent had a university degree. The remaining 30 percent had a trade, university or non-university diploma.

Two indices of labour force activity used by the Statistics Canada census are the participation rate and the unemployment rate. The participation rate is the labour force as a percentage of the population aged 15 years or older. The unemployment rate is the percentage of unemployed persons in the labour force. At the time of the 1986 census, the participation rates for males and females in Cape Breton County were 66 and 44 percent respectively; the unemployment rates were 22 and 23 percent, respectively.

Low income was defined by Statistics Canada on the basis of the 1978 Family Expenditure Survey updated to the 1985 Consumer Price Index. The cut-offs are based on size of family unit and population size of the area of residence. Among 31,525 families in Cape Breton County at the time of the 1986 Census, the prevalence rate of low income was 20 percent.

The hepatitis B epidemic occurred in Cape Breton County in two towns and five small communities in close proximity. The towns of North Sydney and Sydney Mines have a combined population of about 15,500 persons (Statistics Canada, 1986a). Bras d'Or, Florence, Georges River, Alder Point and Point Aconi have a combined population of about 14,000 persons. For North Sydney and Sydney Mines, the proportions for the levels of schooling, labour force activity indices, and prevalence rates of low income were similar to those of Cape Breton County (Statistics Canada, 1986a).

3.2.2 Rationale for study design

From January to November 1988, 20 serologically confirmed cases of hepatitis B were reported in the Cape Breton Health Unit. Of these, 11 were in the epidemic area. In comparison with 1987 when 11 cases of hepatitis B had been reported in the entire Cape Breton Health Unit, the 20 cases represented an increase in incidence, from a crude rate of 6.7 cases per 100,000 in 1987 to 13 cases per 100,000 in 1988. In the

epidemic area, the crude rate was 51 cases per 100,000 in 1988. The temporal distribution of reported cases from 1986 to November 1988 is illustrated as an epidemic curve based on the 4-weekly reports to the Department of Health and Fitness (Figure 3B).

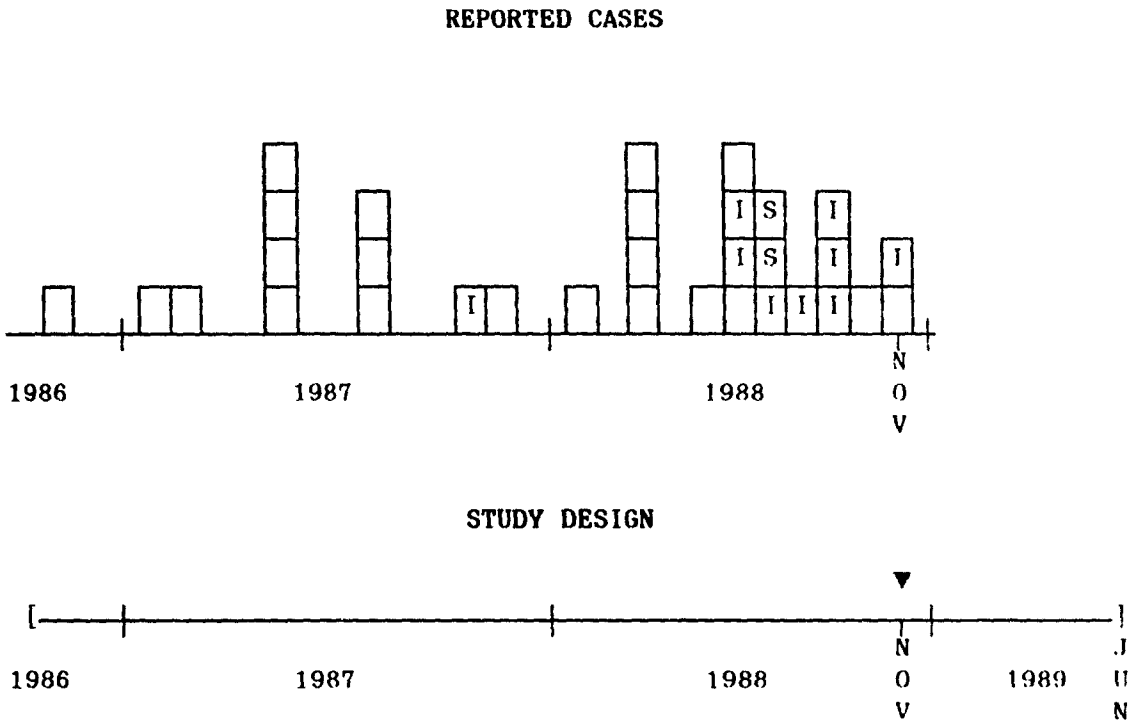
Three features of the epidemic were noted in the preliminary assessment, and determined the study design. The first was that although there was clear indication of the existence of an outbreak in the circumscribed geographic area in 1988, the increase in cases reported in the Cape Breton Health Unit started as early as 1987. The second was the identification of illicit injectable drug use as a mode of transmission in eight of the 14 cases in the epidemic area. Finally, there existed a cluster of hepatitis B infections: ten of the 14 cases were linked with a case reported in late 1987 through contact-tracing.

3.2.3 Study design

The study design is represented as a diagram (Figure 3B). The investigation was initiated in late November, 1988. The first concern was addressed by including a retrospective component in the study design. Public Health documentation of all cases reported in the Cape Breton Health Unit starting from 1986 were reviewed, with supplemental information sought from the treating physician in unclear cases. Reports were reviewed specifically to ascertain the mode of transmission and establish possible epidemiological links with the epidemic. All hepatitis B serology requests in 1988 at the community hospital in the epidemic area were reviewed. Supplemental information on patients with positive results was obtained from the treating physician or through Public Health follow-up.

A prospective component was included in the study design. Active surveillance of hepatitis B and intensive efforts to identify illicit injectable drug users were made from November 1988 to June 1989.

Figure 3B Reported cases of hepatitis B in Cape Breton Health Unit from 1986 to November 1988, per 4-weekly intervals, and study design



i) Retrospective to 1986

ii) Prospective to June 1989

iii) Illicit injectable drug use

iv) Cluster

Legend

□ : Reported case of hepatitis b

I : Illicit injectable drug use

S : Sexual transmission

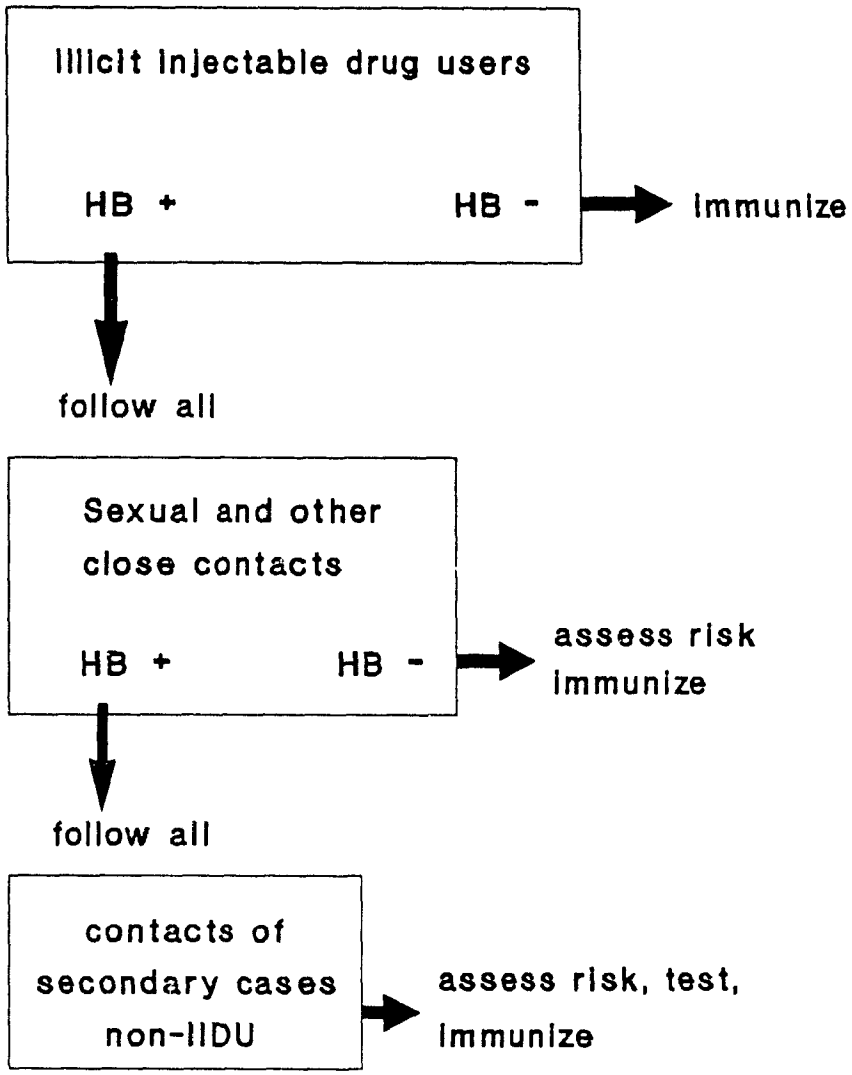
▼ : Study started in November 1988

Illicit injectable drug use as a risk factor and mode of transmission of hepatitis B had direct consequences in the choice of strategy for case-finding and epidemiological investigation. Surveys, distributions of questionnaires, and absenteeism records were rejected because none of these strategies could reach the population of illicit injectable drug users due to the covert nature of the activity. The circumscribed geographic area of the reported cases of hepatitis B suggested there existed a cohort of illicit injectable drug users. For users who were sharing injection apparatus, the potential for transmission was great and rendered them all at risk of infection. In order to prevent further occurrences of hepatitis B, it was essential to identify the cohort of illicit injectable drug users through contact-tracing, determine the extent of infection among them through serological testing, and immunize the susceptibles. Contact-tracing would also serve to identify illicit injectable drug users' sexual or other close contacts.

The contact-tracing scheme is represented in Figure 3C. Contact-tracing focused on identification of the cohort of illicit injectable drug users and their sexual or other close contacts. Contacts of secondary cases of infection not due to parenteral transmission were also followed. Immunization was offered to illicit injectable drug users, and to sexual or close contacts when appropriate. The limitations of contact-tracing were recognized. Contact-tracing is time-consuming and limited to persons identified through others at risk. Illicit injectable drug users may be reluctant to cooperate in follow-up. Furthermore, the results of a study using this method are usually not generalizable since the extent of completeness is unknown.

Finally, a cluster is a group of cases with a clearly-defined association. Methods were chosen to establish the epidemiological links and the timing of infection in order to define the cluster of hepatitis B infections among illicit injectable drug users and their close contacts. This enabled the subsequent estimation of a secondary attack rate for delta hepatitis.

Figure 3C Diagrammatic representation of contact-tracing scheme



3.2.4 Case definitions

A **person-at-risk** was defined as a temporary or permanent resident in the epidemic area between 1 October 1987 and 30 June 1989, with identifiable epidemiological links to a person(s) infected with hepatitis B as established through contact-tracing. Persons-at-risk were at risk of hepatitis B infection through one or more potential modes of transmission. These included percutaneous (through illicit injectable drug use, direct contact with contaminated blood through a wound, needle-stick injury in a health-care worker, unapparent means in family contact), transmucosal (through sexual or family contact), and perinatal transmission.

Three definitions were used for cases of hepatitis B to characterize the epidemic. Because one of the purposes of investigation was to find persons-at-risk and immunize the susceptibles, a **serological** definition was specified for a case of hepatitis B infection. Prior to the investigation, there had been no standardized definition of a reportable case of hepatitis B in Nova Scotia. A **reportable** case definition was implemented during the investigation for surveillance of hepatitis B disease. This definition was based on the one provided by the Advisory Committee on Epidemiology at the October 1988 meeting. Finally, in order to show the dynamics of transmission, the **cluster** case of hepatitis B infection was defined. The relationship among these three classes of cases and persons-at-risk is represented as a diagram (Figure 3D).

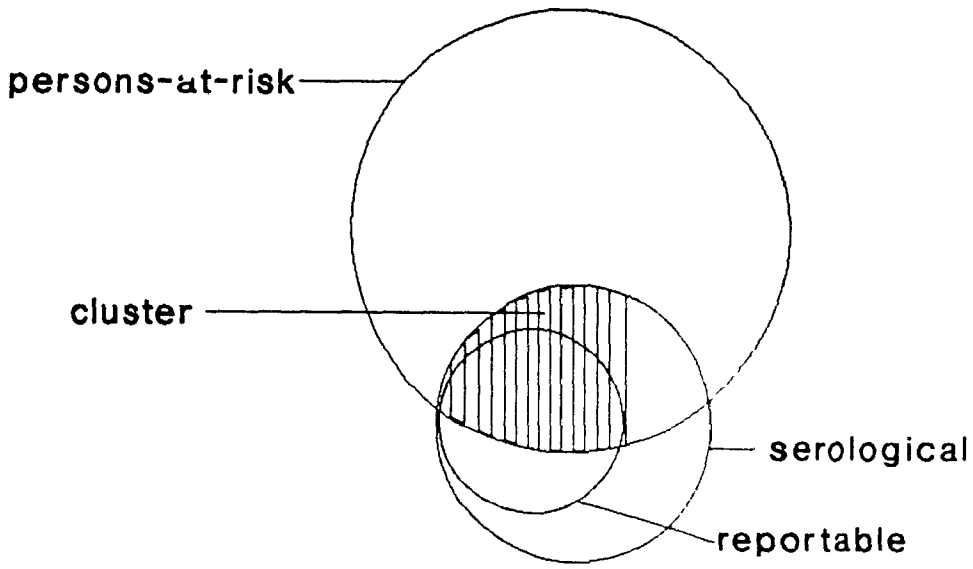
1) A **serological** case of hepatitis B in the Cape Breton Health Unit was defined as serological

   - positivity for HBsAg and/or anti-HBc,

   OR

   - positivity for both anti-HBs and anti-HBc.

Figure 3D Persons-at-risk
and
Serological, Reportable and Cluster
cases of hepatitis B



2) A **reportable** case of hepatitis B infection in the Cape Breton Health Unit was defined as:

- clinical and/or laboratory evidence of recent hepatic inflammation or infection;
- and serologic evidence of recent hepatitis B infection;
- and no evidence of any non-infectious causes;

OR

- confirmed chronic carrier of hepatitis B, not previously reported.

3) A **cluster** case of hepatitis B infection was defined as a serological case of hepatitis B infection with all of the following conditions:

- infection occurring between 1 October 1987 and 30 June 1989 (except for index cases and chronic carriers);
- permanent or temporary residence in the epidemic area;
- definite identifiable epidemiological links with other cluster cases;
- all information consistent with membership in the cluster.

The cluster case definition was divided into three categories:

Definite: symptom-complex compatible with Hepatitis B with onset of symptoms during the cluster period

OR

asymptomatic with positive IgM anti-HBc or evidence of serological progression establishing the timing of infection as during the cluster period.

Probable: asymptomatic with history of exposure establishing the timing of infection as during the cluster period.

Chronic carrier: HBsAg-positivity for six or more months, or HBsAg-positivity and IgM anti-HBc negativity. Contribution to the dynamics of infection within the cluster was demonstrated for inclusion into this class.

Hepatitis B infection results in a continuum of symptomatology. In the absence of proof of hepatic damage by liver enzyme elevation, there was potential for recall bias, especially in persons who had a mild course or who did not consult their physician at the time of illness. The definition of hepatitis B disease, as opposed to simple infection, was based on the group of symptoms reported on the questionnaire. Considered sufficient for labelling as symptomatic were:

1) the presence of jaundice

2) in the absence of jaundice:

a) illness severe enough for hospital admission;

OR

b) presence of at least two of the following six symptoms: arthritis, dark urine, rash, pruritus, anorexia, weight loss.

OR

c) a combination of the remaining symptoms (flu-like illness) ONLY with demonstrated serological progression in keeping with the onset of symptoms.

Finally, delta hepatitis was suspected because of an especially severe and protracted course of hepatitis B in one patient. A case of **delta hepatitis** was defined as anti-HDV positivity in the presence of serological hepatitis B. The unexpected event of a serologically-confirmed epidemic of hepatitis B in an area with a previously very low incidence of hepatitis B suggested primary infection with hepatitis B and coinfection with hepatitis D virus in a susceptible population.

3.2.5 Methods

3.2.5.1 Questionnaire

The questionnaire entitled "Hepatitis B--Case report and follow-up" (Appendix 4) was adopted as the standard epidemiological tool for investigating and reporting cases of hepatitis B in Nova Scotia. An important feature of the questionnaire was the inclusion of elements necessary to identify a reportable case of hepatitis B, based on symptomatology. A requirement of proof of liver enzyme elevation was considered too restrictive for Nova Scotia's reportable case definition. The questionnaire was also used to determine risk factors, mode of transmission, possible sources of infection, and persons at risk.

3.2.5.2 Interviewing technique

The sensitive nature of illicit drug use as the primary suspected risk factor and mode of transmission of hepatitis B in a small community was recognized as problematic at the outset. Concern for confidentiality was paramount among those at risk; gaining their confidence and cooperation was essential for contact-tracing.

During the first week, reported cases of hepatitis B were interviewed by the field epidemiologist accompanied by one of three Public Health nurses. The roles were then reversed, with each Public Health nurse taking charge of one or two interviews in the presence of the field epidemiologist. Invaluable to the process was the nurses' considerable knowledge of the region and population. Through trial, error and discussion, an approach was developed which was refined into an interview technique with the following "Golden Rules". (Comments on the rationale follow the rules.)

Golden Rules

1. At the beginning of the interview, emphasize that we will ask NO drug names, NO traffickers' names;
2. Never divulge the source of a contact's name;
3. Incomplete information about contacts is noted exactly as given;
4. The questionnaire is not only a record but also an aide-memoire;
5. Education integrated in the dialogue is our most powerful tool to foster cooperation;
6. The person being interviewed has the courage to help us, his contacts and himself, and deserves our respect.

Although the majority of contacts were found through active Public Health efforts, as word got out about Rules 1 and 2, several persons who knew themselves at risk through illicit injectable drug use or sexual contacts, sought out counselling and testing regarding hepatitis B at the Public Health office. The small loss of information about potential hepatotoxicity of certain drugs was more than adequately countered by the increased cooperation of the high risk group. Among the illicit injectable drug users who volunteered the information, cocaine was frequently mentioned.

Confidentiality was ensured at the start of the interview, and was reinforced by the nurses' refusal to divulge confidential information, in spite of occasional insistence by the person being interviewed.

To ensure that confidentiality would not be broken, and that information would not be prejudiced by the interviewer's broad knowledge of needle-sharing networks, incomplete information was noted

exactly as given. In this small community, incomplete information (such as a nickname) was often adequate for successful contact-tracing.

Although the nurse's authority was established by the simple effort of the first phone call to a contact, authority offered no guarantee of a successful interview. The interrogative nature of interviewing about sexuality and drug activity was minimized by nurturing dialogue, rather than adhering to the strict sequence of the questionnaire.

Education about the disease was found to be an effective means of overcoming the very sensitive questions. For example, explaining the risks of HB in the newborn was often sufficient to elicit the names of sexual contacts in the high-risk group of child-bearing age.

The last rule is self-explanatory.

3.2.5.3 Interaction among Public Health, community physicians and laboratories

An initial meeting with the physicians at the Northside General Hospital, North Sydney, served to confirm diagnoses, establish the existence of an epidemic, and inform physicians of the investigation.

Each contact interviewed was asked for the name of his family physician. Family physicians were notified by a form letter concerning contact-tracing and tests ordered (Appendix 5) and by a second form letter for follow-up and immunization recommendations (Appendix 6). There was occasionally additional communication by telephone and letter concerning the management of specific cases.

Because of the likelihood that some illicit injectable drug users would be naturally immune, immunization at Public Health's expense was recommended pending serological proof of susceptibility. Actual immunization was carried out by family physicians. This strategy was

adopted to lessen the heavy demands on Public Health human resources, and to encourage a visit to the family doctor to initiate treatment for illicit drug use.

The nature of the epidemic, although suspected by the medical community at the outset, was nonetheless largely unexpected in rural Nova Scotia. The preliminary findings were made available to physicians at a formal meeting at the Northside General Hospital prior to a report released through Canada Disease Weekly Report (Poulin, 1989).

The Northside General Hospital laboratory does not have the facility for hepatitis B serological testing, but sends sera to the Provincial Pathology Laboratory. To ensure timely reporting of results of all persons-at-risk, a system was organized for the efficient requisitioning and reporting of hepatitis B tests. The Northside General Hospital laboratory made their log available to Public Health and photocopied reports on receipt from the Provincial Pathology Laboratory. One of the Public Health nurses, designated official liaison with the laboratory, then gathered this information, initially on a daily basis, then weekly as the number of cases started to wane.

Persons-at-risk tested at Public Health's request were told to make an appointment with their family physician seven days after their test. Since all serology requests made by the Public Health nurses were annotated with the family physician's name, the dual reporting ensured that all persons-at-risk would be notified as soon as possible and appropriate follow-up arranged. The partially computerized log at the Provincial Pathology Laboratory was periodically reviewed for missing or incomplete reports.

3.2.5.4 Serology

Prior to the investigation, sera submitted from the Northside General Hospital to the Provincial Pathology Laboratory for hepatitis B testing were, in general, first screened for HBsAg, and if negative, tested for anti-HBc. By agreement with the Provincial Pathology Laboratory, from the start of the investigation until the end of June 1989, all sera submitted from the epidemic area were tested for HBsAg (Abbott Ausyme), anti-HBs (Abbott Ausab-EIA), and IgG anti-HBc (Abbott Corzyme).

Tests to rule out other etiologies of viral hepatitis (except for delta hepatitis) were not ordered and a stipulation of serological evidence of hepatitis B infection was included in the hepatitis B case definitions. One case actually reported to Public Health as hepatitis B was suspected as not being hepatitis B on epidemiological grounds. This was confirmed by an existing high EBV titre, and the case was deleted.

Additional tests were performed on selected sera. These included IgM anti-HBc (Abbott Corzyme-M rDNA), hepatitis B antigen subtyping by immunodiffusion or radioimmunoassay, HBeAg and anti-HBe (Abbott HBe rDNA-EIA), and anti-HDV (Abbott anti-delta EIA).

Because it was likely that most HBsAg-positives were primary infections rather than chronic carriers, IgM anti-HBc was ordered mostly as an epidemiological tool on asymptomatic individuals found to be immune at first testing. IgM anti-HBc was not easily available in Nova Scotia, nor routinely done at Laboratory Centre for Disease Control. The first IgM anti-HBc was done at St. Joseph's Hospital in Hamilton, Ontario. A limited number of IgM anti-HBc tests subsequently became available and were carried out by the Provincial Pathology Laboratory in Halifax.

As many HBsAg-positives as possible were tested for antigen subtype at the Laboratory of the National Viral Hepatitis Reference Centre, Bureau of Microbiology, Ottawa. Subtyping was done either by immunodiffusion,

or if not typeable by that method, by a second test using the radioimmunoassay technique developed at that laboratory (Chaudhary and Knelsen, 1987).

HBeAg and anti-HBe testing were done on a case suspected of being a chronic carrier. Testing was performed by the Laboratory of the National Viral Hepatitis Reference Centre.

Anti-HDV testing was initially done on one case with an especially severe clinical course of hepatitis B. The existence of delta infection was established and as many as possible of the hepatitis B-infected illicit injectable drug users associated with this case were tested. The sexual partners of the delta hepatitis cases, and one case of hepatitis B resulting in fulminant hepatitis and death, were also tested for anti-HDV.

3.2.5.5 Chart review

Hospital charts of all cases of hepatitis B admitted between 1 October 1987 and 30 June 1989 at the Northside General Hospital were reviewed for duration of hospital stay, symptoms, clinical course, and biochemical results. Charts of cases admitted to other hospitals were not reviewed. Values for liver enzymes were made available by the family physician for cases suspected or known to be chronic carriers.

3.2.5.6 Immunization records

In Nova Scotia, all hepatitis B vaccine is dispensed by Public Health. The amount of vaccine issued for free by Public Health is a direct consequence of defined high-risk exposures to hepatitis B. The amount of vaccine purchased by individuals or groups reflects the risk of infection as perceived by those persons, usually in an occupational setting. The amount of vaccine dispensed by Public Health was

determined for each month from January 1987 to June 1989, for Cape Breton Health Unit, from immunization records. The monthly amounts were divided into "free-issue" vaccine or vaccine "purchased" by individuals or groups of employees.

3.2.5.7 Data review

Data processing of information from the questionnaires and laboratory results was undertaken using the "Epi Info, version 3" program produced by the Epidemiology Program Office, Centers for Disease Control, Atlanta, Georgia. During the active case-finding and contact-tracing efforts, data were updated daily, enabling timely decisions regarding immunization or further follow-up.

The timing of infection was ascertained entirely by serological results in those classified as definite cluster cases. For those classified as probable cluster cases, the timing of infection was ascertained by review of drug-use history and by repeatedly cross-referencing contacts with their serological status. At the conclusion of active case-finding and contact-tracing, the group of persons-at-risk was completely reviewed. Any contacts initially followed but subsequently found to be not genuinely at risk of infection were excluded. A secondary attack rate for delta hepatitis was estimated based on knowledge of illicit injectable drug users' contacts and timing of infection.

3.2.5.8 Data analysis

The data were summarized using descriptive statistics. Cluster cases were treated as a sub-sample of serological cases.

Six potential risk factors were evaluated as predictors of hepatitis B infection in illicit injectable drug users. These included two

categorical variables, gender and employment status. The remaining four were continuous variables--age, the total number of illicit injectable drug user contacts (IIDU-contacts) named, the number of seropositive IIDU-contacts, and the number of sexual partners who themselves were illicit injectable drug users (sexual-IIDU contacts).

The total number of IIDU-contacts reflects the risk of exposure to hepatitis B whereas the number of seropositive IIDU-contacts reflects the number of potential sources of inoculum. The number of sexual-IIDU contacts reflects an additional risk of exposure and potential mode of transmission. Age was used as a proxy for the number of years with a risk of exposure and the cumulative number of times receiving an inoculum. Employment status was used as a proxy for socioeconomic status.

Comparisons between infected and uninfected illicit injectable drug users were made in two ways. In the first instance, seropositive cases were taken as a positive outcome. In the second instance, only cluster cases were taken as a positive outcome. Risk factors for both prevalent and incident cases of hepatitis B infection were therefore assessed.

The statistical significance of the observed differences was initially documented using univariate analysis. Univariate analysis using logistic regression with a single independent variable was done for each variable. As well, univariate analysis of the categorical variables was done using the Fisher's exact test or chi-square test. For the continuous variable of age, univariate analysis was also done using the Student's t test. For the three continuous variables involving the numbers of contacts, the Mann-Whitney U non-parametric test was used because of non-normal distributions.

Multivariate analysis was done using logistic regression. A first model included five independent variables, whether significant or not on univariate testing. The five variables were gender, employment

status, age, the number of sexual-IIDU contacts, and either the total number of IIDU-contacts, or the number of seropositive IIDU-contacts. Because the latter two variables are highly interactive (the number of seropositive IIDU-contacts is a subset of the total number of IIDU contacts), these were assessed separately. A second model included only those independent variables which were significant on univariate analysis or in the full logistic model.

For risk factor assessment of incident cases of hepatitis B, the index case(s) and seropositive users not classified as infected during the cluster period were excluded from the analysis.

Logistic modelling, odds ratios and the 95-percent confidence limits of the odds ratios were done with "Logress", a program using an iterative maximum likelihood method, produced by Dan McGee, Centers for Disease Control, Atlanta Georgia.

An estimate of the secondary attack rate for hepatitis D virus was based on the number of anti-HDV seropositives divided by the number of hepatitis B seropositive IIDU contacts. These hepatitis B seropositive IIDU contacts were presumed to be susceptible to hepatitis D virus for a six month period. The hepatitis B seropositive IIDU contacts known to have seroconverted to immune status during that period were excluded from the denominator.

The correlation between the amount of "free-issue" vaccine and the amount of vaccine purchased from January 1987 to June 1989 was established by Pearson's correlation coefficient.

3.3 Atlantic Health Unit

3.3.1 Setting

The Atlantic Health Unit offers public health services to a population of 306,400 persons in Halifax County. The County includes the cities of Halifax and Dartmouth which have a combined population of 168,820 persons. (Statistics Canada, 1986a and 1986b).

There were 241,130 persons 15 years of age or older in Halifax County at the most recent census (Statistics Canada, 1986a and 1986b). Eleven percent had attained a level of schooling less than grade 9; 28 percent had completed between grades 9 and 13; nine percent had obtained their high school leaving certificate; and 14 percent had a university degree. The remaining 38 percent had a trade, university or non-university diploma.

The participation rates in labour force activity for males and females were 80 and 59 percent, respectively; the unemployment rates were eight and 11 percent, respectively. The overall prevalence rate of low income was 12 percent.

For the population 15 years of age or older residing in Halifax or Dartmouth, the overall participation rate in labour force activity was 70 percent; the overall unemployment rate was nine percent. The prevalence rate of low income was about 14 percent in these two cities.

3.3.2 Study design

The Atlantic Health Unit provided an important comparison for the Cape Breton Health Unit regarding the reported incidence and mode of transmission of hepatitis B. From 1986 to 1988, a report form with age, sex, some clinical information, and mode of transmission had been

used. The "Hepatitis B case report and follow-up" questionnaire, used in the Cape Breton Health Unit, was adopted in the Atlantic Health Unit in late 1988.

Existing documentation of all reported cases in this health unit from 1986 to July 1989 was reviewed, applying the reportable case definition stated in section 3.2.4. Demographic and mode of transmission data were summarized using descriptive statistics.

CHAPTER 4

RESULTS AND PRELIMINARY DISCUSSION

4.0 Introduction

This chapter describes the study results with discussion of specific findings. Chapter 5 presents more general discussion on study design and prevention measures in the illicit injectable drug user population.

Cape Breton Health Unit results are presented in ten sections. The first four relate to the entire population at risk: the results of contact-tracing, the classification of serological cases and serology results, and the occurrence of hepatitis B infection and disease attributable to illicit injectable drug use. The next four sections relate to the cohort of illicit injectable drug users in the epidemic area: the dynamics of the hepatitis B epidemic, the risk factors for hepatitis B infection, and the occurrence of delta hepatitis. The final two sections describe the impact of the epidemic in terms of morbidity and immunization.

Hepatitis B reported in Atlantic Health Unit is summarized in one section detailing the population rates, the demographic characteristics and the changing trend in the mode of transmission of the reported cases of hepatitis B.

4.1 Cape Breton Health Unit

4.1.1 Contact-tracing

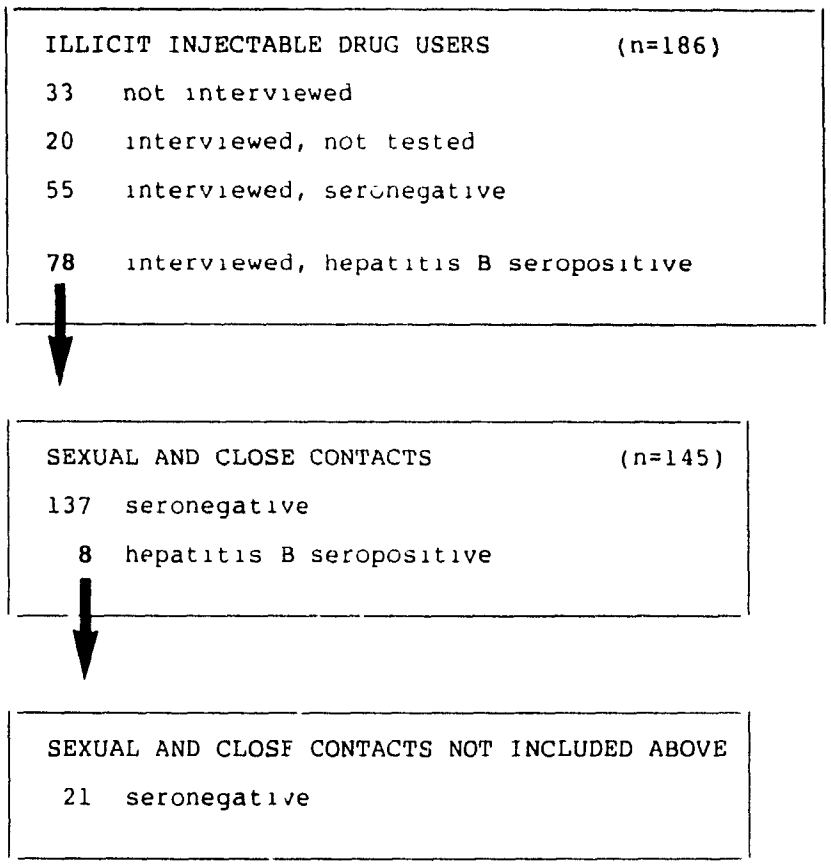
Early in the investigation of the epidemic, the principal mode of transmission was found to be percutaneous associated with illicit injectable drug use. The focus of contact-tracing therefore evolved to identify the cohort of illicit injectable drug users and the sexual or other close contacts of the infected users. Information was obtained on all reported cases of hepatitis B as well as on all cases of hepatitis B infection which were not reported, but were found retrospectively or prospectively through the community hospital laboratory serology requests.

Figure 4A summarizes the contact-tracing results. Of a total of 386 cases and contacts entered in the computer database, 34 were excluded because the epidemiological links were judged remote. The remainder had a demonstrable risk of infection due to illicit injectable drug use or through sexual or close contact with epidemiologically linked cases. These 352 were considered persons-at-risk.

Of the 186 illicit injectable drug users identified, 153 (82 percent) were interviewed and 133 (72 percent) also underwent serological testing. Of the 20 users who were interviewed but refused serological testing, only one had an illness with jaundice and other symptoms compatible with viral hepatitis. Onset of illness was in January 1989, and the user had shared needles with known seropositive users. Although his clinical course and the epidemiological circumstances suggested acute hepatitis B related to the epidemic, he was not considered as infected with hepatitis B due to lack of serological proof. Thirty-three illicit injectable drug users identified were not interviewed. It is not known to what extent these 33 differ from those interviewed.

Figure 4A **Contact-tracing results of all persons at risk of hepatitis B infection during the epidemic**

352 PERSONS-AT-RISK



Contact-tracing of the 78 seropositive illicit injectable drug users led to identification of 145 persons-at-risk who were not illicit injectable drug users. The eight secondary cases among these non-users exposed a further 21 persons, all of whom were found to be seronegative.

Table 4.1 summarizes the nature of contact among the 352 persons-at-risk. Contact-tracing specifically sought to identify illicit injectable drug users and therefore the relative risk due to the various types of contact cannot be assessed. Among the 166 persons-at-risk who were not illicit injectable drug users, most had family or sexual contact with cases of hepatitis B.

The nature of risk posed by family contact with a case of hepatitis B was variable. The assessment of risk of infection through family contact was often done jointly by Public Health and the family physician. In some instances, the risk was considered high due to poor housing, hygienic conditions or health, including poor dental health. There were several family situations where more than one infected illicit injectable drug user resided with children or elderly persons. Most persons-at-risk identified through family contact were offered immunization at Public Health's expense.

The greater number of females at risk through sexual contact is a reflection of the greater number of male infected illicit injectable drug users. Most infected illicit injectable drug users named a single sexual partner; only one user admitted to a sexual relationship with a person of the same sex. Although contact-tracing specifically sought to identify illicit injectable drug users, the role of multiple sexual partners or homosexuality seems to have been of minor importance in the dynamics of the epidemic spread of hepatitis B in this community.

The remaining contacts were at risk through perinatal, wound or other types of contact. Of 13 pregnant women at risk of infection through illicit injectable drug use or through their partner's illicit

Table 4.1 Nature of contact of all persons-at-risk, by gender

Nature of contact	Number of males	Number of females	Total
IIDU	117	13	130
IIDU S*	30	26	56
Subtotal	147	39	186
Sexual	4	41	45
Family	47	59	106
Perinatal	1	1	2
Wound	3	0	3
Other**	5	5	10
Subtotal	60	106	166
Total	207	145	352

* IIDU S Illicit injectable drug user whose sexual partner is an illicit injectable drug user.

** Other includes law enforcement or health professionals through needle-stick or mucous membrane exposure to a case of hepatitis B.

Classes are mutually exclusive.

injectable drug use, three were seropositive. Two of these females were HBsAg-positive at delivery resulting in two newborns at perinatal risk of infection. Three males suffered wounds and exposure to blood during altercations with two illicit injectable drug users. One of the users was known to be infectious (HBsAg-positive); the other was not tested but was epidemiologically linked to three cases of hepatitis B. Ten law enforcement or health professionals were offered immunization as a result of percutaneous or mucocutaneous exposures to known infectious cases of hepatitis B.

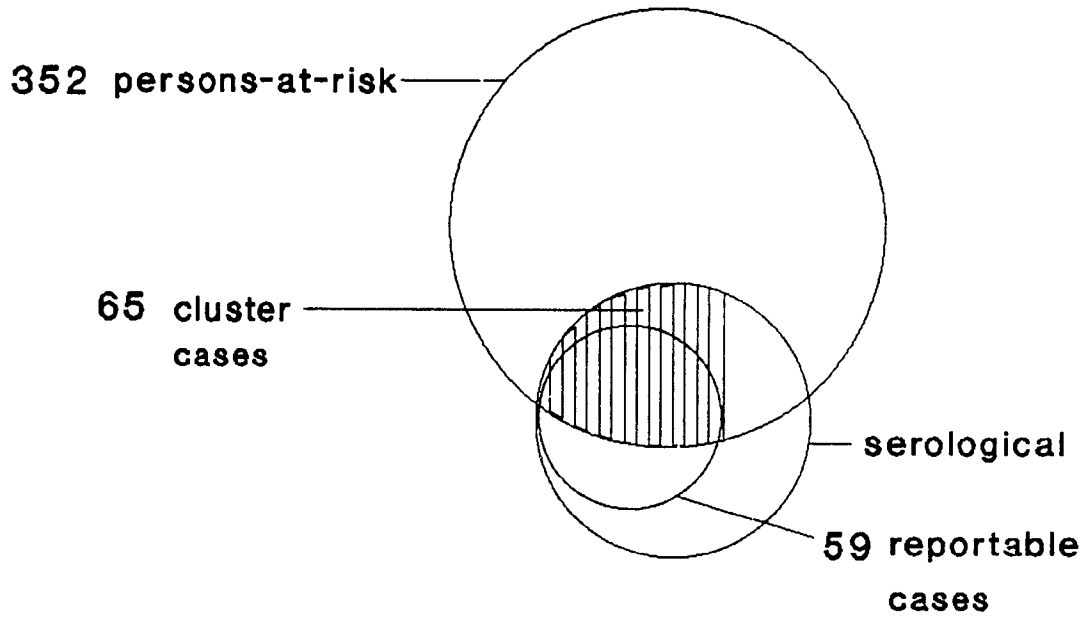
4.1.2 Classification of serological cases

Figure 4B presents the numbers of persons-at-risk, and serological, reportable and cluster cases of hepatitis B, from 1 October 1987 to 30 June 1989. The 352 persons-at-risk have been described in the Section 4.1.1. Serology results, including the limitations of the classification of serological cases in the cluster case definition, are presented in this section.

Serological cases of hepatitis B who were also persons-at-risk totalled 86. A further 16 serological cases of hepatitis B infection which were not reported were found retrospectively or prospectively through the community hospital laboratory serology requests. These were subsequently classified as unrelated to the epidemic. Thirteen had been infected through transfusions or dialysis, or were older than 60 years of age with no known risk factors. The mode of transmission was not ascertained for the remaining three serological cases. These three were entered in the computerized database temporarily and subsequently excluded after review failed to demonstrate an epidemiological link with the epidemic.

The case-finding and active surveillance system implemented for the study provided the number of serologically-proven cases of hepatitis B infection in the epidemic area. Information concerning hepatitis B

Figure 4B Persons-at-risk
and
Serological, Reportable and Cluster
cases of hepatitis B ,
From 1 October 1987 to 30 June 1989



serology requests is only partially computerized at the Provincial Pathology Laboratory. It was not possible to obtain the total number of hepatitis B infections in the entire Cape Breton Health Unit for the study period. The total number of serological cases is therefore not reported in Figure 4B.

Of the 86 persons-at-risk who were also serological cases, 21 had evidence of naturally-acquired immunity to hepatitis B (positivity for both anti-HBs and anti-HBc) but the timing of infection could not be ascertained or was determined to be prior to October 1987. These 21 were illicit injectable drug users of more than three years' duration.

The remaining 65 serological cases were classified as cluster cases of hepatitis B infection. There are two concerns with the false labelling of a serological case as a cluster case. The first is that this would result in an overestimate of the extent of the epidemic. The second is that the a priori assumption of symptomatic cases being primo infections would lead to lack of diagnosis of superinfection and underestimation of the incidence of disease due to other hepatotropic viruses. This finding would be especially important in the illicit injectable drug user population.

The accuracy of labelling as a cluster case depends on the specificity of the components of the cluster case definition. The definite cluster case is based on symptomatology, serological progression of hepatitis B markers, or positivity for IgM anti-HBc. Serological progression demonstrated on serum samples drawn on two (or more) different occasions, and the presence of IgM anti-HBc, are highly specific. In the absence of these two kinds of serological evidence, symptoms of viral hepatitis with seropositivity for hepatitis B, while specific for the existence of hepatitis B infection, does not conclusively rule out the possibility of superinfection. However, in the context of a community with a low incidence of reported hepatitis B prior to an outbreak of clinically significant disease, the specificity of this component is probably acceptable. The specificity of the probable

cluster case definition is lower because it is limited by the accuracy of drug-use history information. The greatest uncertainty would be in the case of the asymptomatic chronic carrier.

Eight cluster cases were acquired through sexual, family or wound contact, in the absence of illicit injectable drug use (Table 4.2). Six persons were HBsAg-positive on presentation with clinically significant disease; one asymptomatic case was IgM anti-HBc-positive. One case was an asymptomatic child with serological evidence of naturally-acquired immunity to hepatitis B. Both parents were newly infected, as evidenced by serological progression of hepatitis B markers. It is likely that these eight cases were true recent infections and correctly classified as cluster cases.

Among the 57 cluster cases directly attributable to illicit injectable drug use, two were apparent index cases, and two were confirmed to be chronic carriers infected prior to October 1987 (Figure 4C). Fifty-three were considered infections acquired during the epidemic period.

Forty-seven of these were classified as definite cluster cases. Thirty-three had evidence of serological progression, being either initially seronegative and becoming seropositive, or, in an early or infectious stage of infection then developing immunity. Four cases were IgM anti-HBc-positive (three of them were asymptomatic). Ten cases were HBsAg-positive and/or anti-HBc positive at clinical presentation.

The remaining six cases were asymptomatic and classified as probable cluster cases. However, in addition to drug-use history, four of these had sexual partners whose timing of infection was based on evidence of serological progression. The remaining two were classified as probable cluster cases only on the basis of firm drug-use and contact histories. These two, tested late in the epidemic, were HBsAg-positive and IgM anti-HBc negative. Both were considered potential new chronic carriers, pending repeat HBsAg testing.

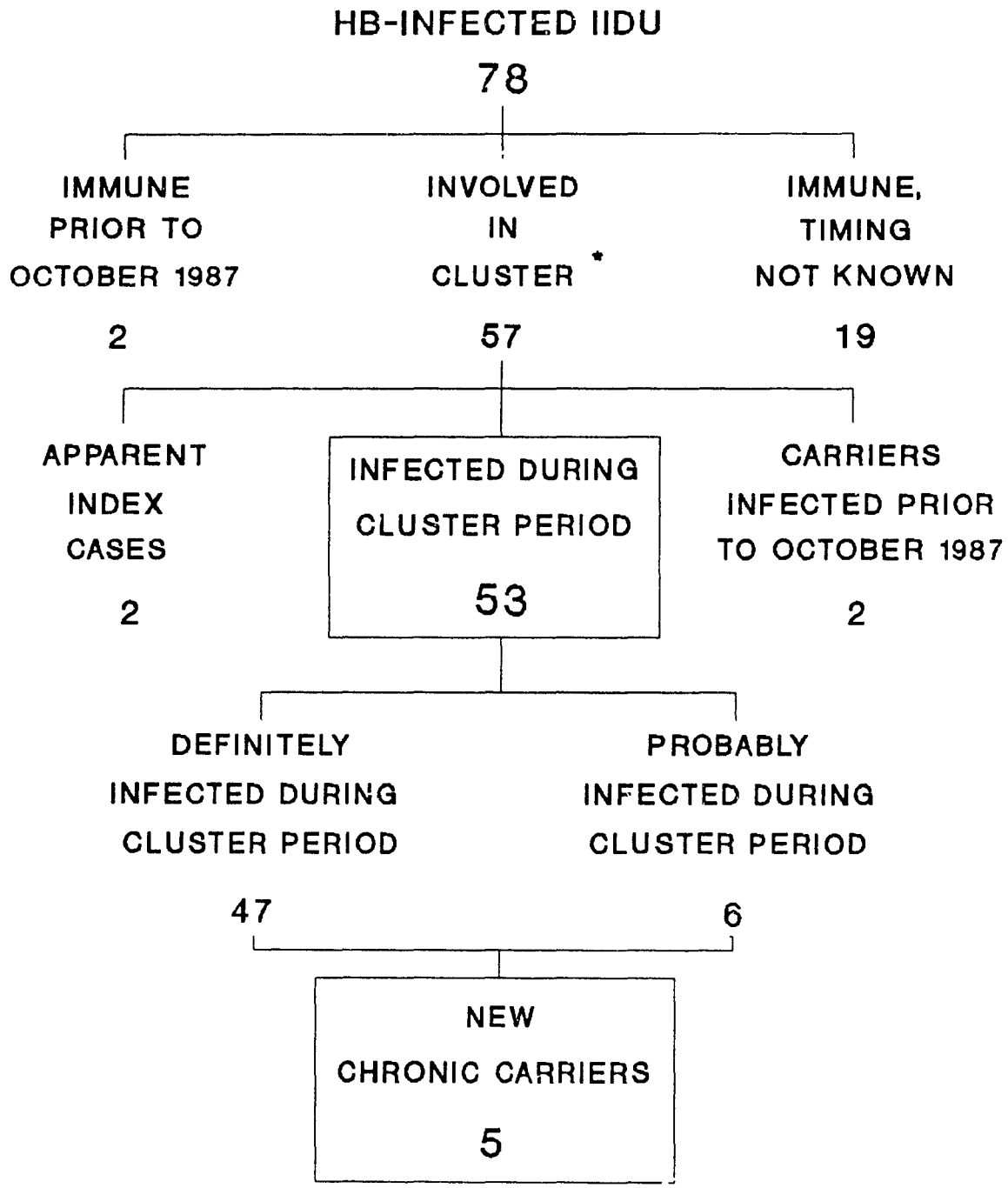
Table 4.2 Cluster cases of hepatitis B infection, by mode of transmission and gender

Mode of transmission	Number of males	Number of females	Total
IIDU	29	2	31
IIDU S*	15	11	26
Sexual	1	5	6
Family	1	0	1
Wound	1	0	1
Total	47	18	65

* IIDU S Illicit injectable drug user whose sexual partner is an illicit injectable drug user.

Classes are mutually exclusive.

Figure 4C Algorithm of hepatitis B seropositive IIDU,s
In the epidemic area in Cape Breton Health Unit



* Cluster of cases occurred from October 1987 to June 1989

Thirty-three illicit injectable drug users were HBsAg-positive on initial testing (excluding the two chronic carriers). Twenty-two (67 percent) had serological evidence of primary hepatitis B infection: 20 subsequently seroconverted to HBs-Ag-negativity or anti-HBs positivity; two were IgM anti-HBc positive. Of the remaining 11, only three were retested six or more months after their initial test. These three were still HBsAg-positive and were considered new chronic carriers (one had been IgM anti-HBc-positive; the other two had been symptomatic with symptomatic sexual-IIDU partners who seroconverted). The large proportion of seroconversion among those initially HBsAg-positive supports the a priori assumption of general hepatitis B susceptibility in the illicit injectable drug user population.

4.1.3 Hepatitis B antigen subtypes

Subtyping was possible on the HBsAg-positive sera of 32 persons. The results are summarized in Table 4.3, according to laboratory technique used and mode of transmission. Twenty-nine sera were reported as subtype **ay**; three were subtype **ad**. The finding of more than one subtype among serological cases classified as cluster cases was unexpected. The 32 persons were considered persons-at-risk on the basis of identifiable links established through contact-tracing.

Case 1 with subtype **ad** was an illicit injectable drug user whose sexual-IIDU contact was subtype **ay**. Both had links with other illicit injectable drug users who were subtype **ay**. Case 2 was an illicit injectable drug user who had links with other users with subtype **ay**. Case 3 had no history of illicit injectable drug use and his sexual partner was seronegative. His infection was attributed to lacerations and exposure to blood during an altercation with an illicit injectable drug user. This illicit injectable drug user was not tested but was closely linked with three cluster cases of hepatitis B infection, one of whom was Case 2.

Table 4.3 Hepatitis B antigen subtyping results, by 1) laboratory technique and 2) mode of transmission

1) by laboratory technique

Subtype	Number of cases ad	ay	Total
immunodiffusion	2	22	24
radioimmunoassay	1	7	8
Total	3	29	32

2) by mode of transmission

Subtype	Number of cases ad	ay	Total
IIDU	2	27	29
sexual		2	2
wound	1		1
Total	3	29	32

There are two possibilities explaining these findings. One is that the three cases with subtype **ad** are in fact not part of the cluster of infections. This possibility seems unlikely in view of the links established through contact-tracing.

The second is that subtyping using the immunodiffusion and radioimmunoassay (RIA) techniques may be neither sensitive nor specific enough to establish the source of infection. The "gold standard" for RIA is immunodiffusion, a method with a sensitivity of only 0.32. Not only is the sensitivity of the RIA method higher, but it is higher for subtype **ad** (0.97) than for subtype **ay** (0.62) (Chaudhary and Knelsen, 1987). The higher sensitivity of the RIA method precludes the use of immunodiffusion as a "gold standard" against which to assess specificity. Furthermore, the methods used in this study tested for only one subtype determinant, "**d/y**", but not "**w/r**", resulting in a further decrease in specificity.

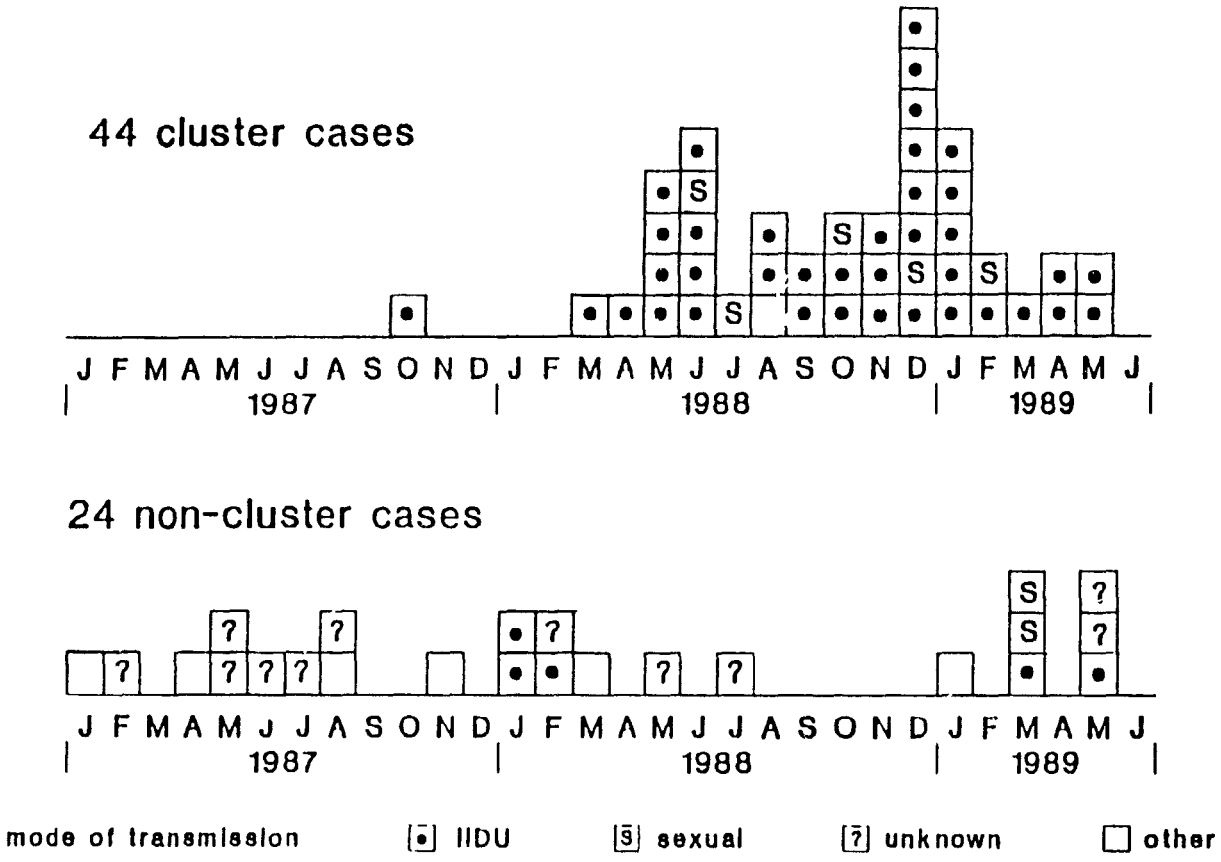
With the advent of nucleotide-sequence mapping of hepatitis B subtypes, the limitations of the latter two laboratory techniques have been recognized, especially in the presence of multiple exposures (Okamoto et al, 1987; Okamoto et al, 1988). It was concluded that the best available information for the determination of the potential source of infection was that obtained through contact-tracing. The subtype results were not considered useful for either exclusion nor for confirmation of linkage between cases.

4.1.4 Hepatitis B disease and infection related to illicit injectable drug use

The impact of illicit injectable drug use as a mode of transmission of hepatitis B in Cape Breton Health Unit is demonstrated by:
1) hepatitis B disease (reportable cases), and, 2) hepatitis B infection (cluster cases). Figure 4D presents epidemic curves for cluster and non-cluster cases from January 1987 to 30 June 1989.

Figure 4D

Cape Breton Health Unit
Reportable cases of hepatitis B
by month of onset



In all, 43 (63%) of 68 cases reported were directly attributable to illicit injectable drug use.

This diagram also illustrates the six secondary cases of hepatitis B disease among the cluster cases, which were indirectly attributable to illicit injectable drug use. Five of these were related to sexual contact with an infected illicit injectable drug user; one was attributed to exposure to blood during an altercation with an illicit injectable drug user.

The investigation of the epidemic and the contact-tracing method probably brought to light some cluster cases among illicit injectable drug users, which may otherwise have gone undiagnosed or unreported. This would result in an overestimation of the role of illicit injectable drug use in the overall burden of hepatitis B disease in Cape Breton Health Unit. However, 20 reportable cluster cases with onset of illness before December 1988 were illicit injectable drug users. Most of these had illness important enough to consult a physician prior to the initiation of investigation. Of the 18 cluster cases due to illicit injectable drug use reported from December 1988 to 30 June 1989, four would likely not have been diagnosed without Public Health's efforts. Of the remainder, five required hospitalization, and nine had jaundice or serum-like illness and consulted a physician. Furthermore, among the entire group of 44 reportable cluster cases, 18 required hospitalization.

The degree of morbidity among the reportable cluster cases is indirect evidence that illicit injectable drug use was a real contributor to disease rather than an association found due to investigation bias. Not only was there an epidemic of hepatitis B among illicit injectable drug users, but illicit injectable drug use indirectly caused significant morbidity among non-users. The burden of hepatitis B disease in Cape Breton Health Unit from January 1987 to 30 June 1989 was, directly or indirectly, mostly attributable to illicit injectable drug use.

Among the 65 cluster infections, the mode of transmission was attributed to needle-sharing and illicit injectable drug use in 57 cases (Table 4.2). The remaining eight cluster cases were secondary infections among sexual or close contacts of infected illicit injectable drug users. Among the six cases infected through sexual contact, all had a single sexual partner who was an infected illicit injectable drug user. The greater number of females infected through sexual contact is a reflection of the greater number of infected male illicit injectable drug users. Among the 65 cluster cases of hepatitis B infection, 72% were male. The overall age distribution ranged from 5 to 44 years of age, with a mean age of 28.9 years among males and 25.9 years among females (Table 4.4). Because of the study design, age and gender as possible determinants of infection are meaningful only in the context of illicit injectable drug use.

4.1.5 Characteristics of illicit injectable drug users

Table 4.5 presents the age and gender characteristics of the 186 illicit injectable drug users identified. Among those interviewed, the male to female ratio was 3.4:1 The age distribution ranged from 15 to 44 years, with a mean age of 28.0 years among males and 26.5 years among females. The observed age and gender distributions may be a function of the contact-tracing strategy. However, the preponderance of young male users is compatible with the literature on illicit injectable drug use and with distributions observed by the Nova Scotia Commission on Drug Dependency. The observed age pattern has also been documented in the literature in relation to drug type (cocaine rather than heroin). The interview approach adopted precluded specific verification of drugs used. However, it was surmised from several sources that poly-drug use including cocaine was common in this Nova Scotian population.

The ratio of uninfected to unapparent infected to symptomatically infected users was 11:9:6.6. The ratio of asymptomatic to symptomatic

Table 4.4 Cluster cases of hepatitis B infection, by age and gender

Age (years)	Number of males	Number of females	Total
5 - 9	1	0	1
10 - 14	0	0	0
15 - 19	3	1	4
20 - 24	7	3	10
25 - 29	11	11	22
30 - 34	16	3	19
35 - 39	7	0	7
40 - 44	2	0	2
Total	47 (72%)	18 (28%)	65 (100%)
Mean age	28.9	25.9	
Standard deviation	6.8	4.0	

Table 4.5 Illicit injectable drug users, by age and gender

Age (years)	Number of males	Number of females	Total
unknown	29	4	33
15 - 19	5	2	7
20 - 24	28	10	38
25 - 29	38	14	52
30 - 34	34	8	42
35 - 39	9	0	9
40 - 44	4	1	5
Total	147 (79%)	39 (21%)	186 (100%)
Mean *	28.0	26.5	
Standard deviation	5.3	5.0	

* for IIDU's whose age is known.

infection cited in the literature is 6:4. The observed ratio and the age-gender similarities suggest that contact-tracing was not a priori skewed towards the identification of easily-labelled (jaundiced) users. Thirty-three illicit injectable drug users were not interviewed. Only one of these underwent serological testing and was found to be seronegative. Of the 33, 20 were identified by only one admitted illicit injectable drug user. In this group, there remains some uncertainty about illicit injectable drug use, needle-sharing practices, and actual risk of hepatitis B infection.

Inclusion of the 33 users not interviewed would result in a low estimate of the prevalence rate of hepatitis B infection among the cohort of illicit injectable drug users. Exclusion of the 33 would result in a high estimate of the prevalence. The low and high estimates of prevalence of hepatitis B infection are 42 and 51 percent, respectively. Illicit injectable drug users identified but not interviewed were necessarily excluded from the calculation of age-specific period prevalence rates of illicit injectable drug use (Table 4.6).

The age-specific period prevalence rates for illicit injectable drug use in the epidemic area represent underestimates. The principal source of error stems from the failure of contact-tracing to identify infrequent users or users with few needle-sharing partners, or users known to be fugitives from law enforcement. Furthermore, among the 33 users identified but not interviewed, at least those identified by more than one admitted illicit injectable drug user were more likely to be truly illicit injectable drug users.

The age-specific minimum period prevalence of illicit injectable drug use ranged from 3.5 to 33.3 per 1000 population among males. Among females, the minimum age-specific period prevalence ranged from 1.0 to 12.0 per 100 population. The peak period prevalence for both males and females occurred in the group 25-29 years of age. There was a preponderance of males, with the male:female ratio increasing from the

Table 4.6 **Minimum period prevalence rate* of injectable drug use in the epidemic area, 1 October 1987 to 30 June 1989, by age and gender**

Age (years)	Prevalence rate for Males	Prevalence rate for Females	Male:Female ratio
15 - 19	3.5	1.5	2.3 : 1
20 - 24	21.1	7.7	2.7 : 1
25 - 29	33.3	12.0	2.8 : 1
30 - 34	29.8	6.8	4.4 : 1
35 - 39	9.4	0	
40 - 44	4.2	1.0	4.2 : 1
Overall prevalence rate	17.0	5.2	3.3 : 1

* Prevalence rate per 1,000 population in the specified age-group, based on a total population of 30,000 in the epidemic area

younger to older age groups, and ranging from 2.3:1 to 4.4:1. The increasing over-representation of males with increasing age may be due to the contact-tracing strategy or reflect very small numbers among females. Alternatively, as they grow older, females may be less subject to recruitment or more subject to attrition than are males.

Clearly, however, for both males and females, the prevalence of illicit injectable drug use exceeds the one per 1000 population rate used by the World Health Organization in classifying a region as an area of extensive illicit drug use prevalence.

In Cape Breton County, the overall unemployment rate at the time of the most recent census was about 22 percent (Statistics Canada, 1986). To be a risk factor of illicit injectable drug use, employment status among users would have to be significantly different from that among non-users. Employment statistics were not available for the population in the epidemic area over the time-frame of the hepatitis B epidemic. The definitions of employment status and methods used in the census may differ from those of the present study. The reliability of employment status as a proxy for socioeconomic status in the region is not known.

Therefore, this study provides only indirect evidence of a possible association between poor socioeconomic status and illicit injectable drug use in the epidemic area. Forty-three percent of the illicit injectable drug users interviewed were unemployed. Thirty-seven percent were employed (full- or part-time); ten percent were homemakers; five percent were disabled. The remaining five percent were unstated or other (for example, students) status.

4.1.6 The dynamics of the hepatitis B epidemic

A summary of the timing of hepatitis B infection among seropositive illicit injectable drug users is presented diagrammatically in Figure 4C. Of 78 seropositive illicit injectable drug users, 57 formed a

demonstrable cluster of infections. Therefore, among the cohort of 186 illicit injectable drug users, at least 42 percent were seropositive, with 68 percent (53/78) of these infections occurring as a cluster in approximately 18 months. This illustrates the very efficient percutaneous transmission of hepatitis B, reinforced by complex needle-sharing activity among the users. Of public health importance is the subsequent development of five new chronic carriers during the epidemic. Continued needle-sharing activity by chronic carriers potentiates further occurrence of infection and the endemicity of hepatitis B among the illicit injectable drug users in the area.

The dynamics of the hepatitis B epidemic are partially represented in Figure 4D (the epidemic curves of the reportable cases in Cape Breton Health Unit from January 1987 to 30 June 1989).

The apparent index case and an asymptomatic infected sexual partner acquired the infection in another province and returned to Cape Breton at the onset of clinically-significant illness in October 1987. Two months later, a third illicit injectable drug user, an asymptomatic chronic carrier diagnosed through contact-tracing efforts, also returned to Cape Breton. These three infected users quickly integrated themselves into the cohort, sharing needles with numerous illicit injectable drug users. The complex needle-sharing patterns and susceptibility to hepatitis B of the cohort of illicit injectable drug users were very favourable for the epidemic spread of infection.

The shape of the epidemic curve supports person-to-person spread. Onset of illness of the first secondary case associated with needle-sharing occurred five months after the index case. With an average incubation period of 60 to 90 days, infection has apparently been propagated six to eight generations. The epidemic continued with new cases among illicit injectable drug users definitely related to the cluster becoming symptomatic in late 1989. An illicit injectable drug user in a town close to the epidemic area was symptomatic and diagnosed with hepatitis B in late 1989. The continuation of the epidemic with

possible extension to illicit injectable drug users outside the area would depend on needle-sharing patterns, and susceptibility to hepatitis B of long-time users or of newly-recruited users.

It is possible that some non-cluster cases were linked to cluster cases. Two non-cluster cases attributed to illicit injectable drug use likely acquired their infections outside the province and were not identified by any member of the cohort of users. The remaining three and most non-cluster cases with an unknown mode of transmission were residents outside the epidemic area, and were similarly not identified by any member of the cohort. Due to the covert nature of illicit injectable drug use, and the uncertain history among those with an unknown mode of transmission, it may be that epidemiological links with cluster cases do in fact exist. If this were the case, then the epidemic may have commenced in early 1987. This possibility would be relevant only in as much as uncertainty existed in those assumed to be primary infections without complete serological confirmation of the timing of infection.

4.1.7 Risk factors of hepatitis B infection among the cohort of illicit injectable drug users

Six variables were evaluated as potential predictors of prevalent and of incident hepatitis B infection in illicit injectable drug users. Data for each variable were summarized for the 153 interviewed illicit injectable drug users according to serological status, and are presented in Tables 4.7 to 4.12. A summary of the results of univariate analysis for prevalent infection is presented in Table 4.13.

No statistically significant difference in the frequency of gender was observed between seropositive and seronegative illicit injectable drug users (Tables 4.7 and 4.13). No statistically significant difference in the frequency of employment status was observed between seropositive and seronegative illicit injectable drug users (Tables 4.8 and 4.13).

Table 4.7 Gender among all interviewed illicit injectable drug users, by hepatitis B serological status

Gender	Number of seropositive IIDU	Number of seronegative IIDU	Number of IIDU not tested	Total
Male	60	46	12	118
Female	18	9	8	35
Total	78	55	20	153

Chi-square for gender
between seropositive and seronegative = 0.53; p = 0.47

Fisher's exact test for gender
between all tested and not tested, 2-tailed p = 0.08

Table 4.8 **Employment status among all interviewed illicit injectable drug users, by hepatitis B serological status**

Employment	Number of seropositive IIDU	Number of seronegative IIDU	Number of IIDU not tested	Total
Unemployed	31	25	9	65
Employed	29	22	5	56
All other*	18	8	6	32
Total	78	55	20	153

Chi-square for employment status
between seropositive and seronegative = 1.52; p = 0.47

Chi-square for employment status
between tested and not tested** = 0.82; p = 0.36

* includes homemaker, disabled, student and not stated

** classes regrouped to unemployed versus all the rest due to small numbers

Table 4.9 Age in years among all interviewed illicit injectable drug users, by hepatitis B serological status

Age group	Number of seropositive IIDU	Number of seronegative IIDU	Number of IIDU not tested	Total
15 - 19	3	4	0	7
20 - 24	13	19	6	38
25 - 29	24	20	8	52
30 - 34	27	11	4	42
35 - 39	8	1	0	9
40 - 44	3	0	2	5
Total	78	55	20	153
Mean age	28.9	25.9	27.8	
Standard deviation	5.4	4.5	5.8	

Student's t test for age between seropositive and seronegative

$t_{131} = 3.416$ $p < .001$

Student's t test for age between tested and not tested

$t_{151} = 0.13$ $p = 0.89$

Table 4.10 **Total number of IIDU-contacts among all interviewed illicit injectable drug users, by hepatitis B serological status**

Total # of IIDU-contacts	Number of seropositive IIDU	Number of seronegative IIDU	Number of IIDU not tested	Total
1 - 2	19	21	12	52
3 - 7	33	29	6	68
8 - 34	26	5	2	33
Total	78	55	20	153
Range	1-25	1-34	1-8	
Median	4	2.9	1.9	

Mann-Whitney U for total number of IIDU-contacts between seropositive and seronegative = 8.520; p = .004

Mann-Whitney U for total number of IIDU-contacts between tested and not tested = 7.205; p = .007

The data are presented as grouped data.
Mann-Whitney U test was done on the individual data.

Table 4.11 Number of seropositive IIDU-contacts among all interviewed illicit injectable drug users, by hepatitis B serological status

Number of seropositive IIDU-contacts	Number of seropositive IIDU	Number of seronegative IIDU	Number of IIDU not tested	Total
0 - 2	30	39	15	84
3 - 7	35	15	5	55
8 - 20	13	1	0	14
Total	78	55	20	153
Range	1-20	1-16	1-8	
Median	2.9	1.7	1	

Mann-Whitney U for number of seropositive IIDU-contacts between seropositive and seronegative = 16.434; $p < .001$

Mann-Whitney U for number of seropositive IIDU-contacts between tested and not tested = 5.004; $p = .025$

The data are presented as grouped data.
Mann-Whitney U test was done on the individual data.

Table 4.12 **Number of sexual partners who are themselves users, among all interviewed illicit injectable drug users, by hepatitis B serological status**

Number of sexual IIDU-contacts	Number of seropositive IIDU	Number of seronegative IIDU	Number of IIDU not tested	Total
0	43	42	15	100
1	28	10	3	41
2-5	7	3	2	12
Total	78	55	20	153
Range	0-5	0-3	0-3	
Median	0	0	0	

Mann-Whitney U for number of sexual IIDU-contacts between seropositive and seronegative = 5.816; p = .016

Mann-Whitney U for number of sexual IIDU-contacts between tested and not tested = 0.606; p = 0.44

The data are presented as grouped data.
Mann-Whitney U test was done on the individual data.

Table 4.13 **Summary of univariate analysis of six potential risk factors predictive of prevalent cases of hepatitis B infection among 133 interviewed and tested illicit injectable drug users**

Variable	Chi-square or Student's t or Mann-Whitney U	Logistic regression	
		odds ratio	95% CI
Gender	X^2=0.53; p=0.47	1.53	0.63-3.73
Employment status	X^2=1.52; p=0.47	1.17	0.84-1.64
Age	t_{131}=3.42; p=0.001	1.13	1.05-1.22
Total # IIDU-contacts	M-W=8.52; p=0.004	1.10	1.01-1.20
# seropositive IIDU-contacts	M-W=16.43; p<0.001	1.31	1.12-1.53
# sexual-IIDU-contacts	M-W=5.82; p=0.016	1.64	0.97-2.77

Furthermore, no statistically significant difference was found for these two factors between those tested and those not tested (Tables 4.7 and 4.8). These findings suggest that male gender and unemployed status may be associated with illicit injectable drug use per se rather than with infection.

A statistically significant difference ($p < .001$) in age distribution was observed between seropositive and seronegative illicit injectable drug users (Table 4.9). Seropositive illicit injectable drug users were, on average, three years older than seronegative users. Univariate analysis using logistic regression showed increasing risk of infection (odds ratio = 1.13) with increasing age (Table 4.13). No significant difference in age distribution was found between users who were tested and those not tested (Table 4.9).

The association between increasing age and the presence of hepatitis B markers has been noted in a study of a representative sample of the general population of the United States (McQuillan et al, 1989). The increase in prevalence with increasing age starting at puberty was thought to be due to sexual transmission and illicit injectable drug use as the principal modes of transmission.

In the present study, the association between age and seropositivity may be confounded by the variables concerning contacts, since a user may come to have numerous IIDU-contacts with increasing age. The association may also be confounded by several other variables for which data were not consistently collected. These include the frequency and duration of use, the needle-sharing practices, and periods of abstinence. Furthermore, an epidemic of hepatitis B is an event which occurs in a population of susceptibles. The net effect of an epidemic would be to dilute the association between increasing age and prevalent hepatitis B infection.

The total number of IIDU-contacts ranged from 1 to 34 among seronegative users, 1 to 25 among seropositive users, and 1 to [illegible] among

those not tested (Table 4.10). The observed frequencies of the total number of IIDU-contacts were significantly different ($p < .004$) between seropositive and seronegative users. Univariate analysis using logistic regression showed a small increasing risk of infection (odds ratio = 1.10) with an increasing number of IIDU-contacts (Table 4.13).

The association between the total number of IIDU-contacts and seropositivity was expected. Potential confounders of the association are the frequency, the timing and the order of needle-sharing practices, and the possible tendency of providing "safe" IIDU-contact names (users who were jaundiced and already known to Public Health). No data were available on these potential confounders. Comparison of users tested with those not tested showed a statistically significant difference in the number of IIDU contacts (Table 4.10). Therefore, the subsequent inclusion of users not tested could influence the association.

The range of the number of seropositive IIDU-contacts was 1 to 20 among the seropositives, 1 to 16 among the seronegatives, and 1 to 8 among those not tested (Table 4.11). There was a significant difference ($p < .001$) between seropositive and seronegative illicit injectable drug users in the observed frequencies of the number of seropositive IIDU-contacts. Univariate analysis using logistic regression showed an increasing risk (odds ratio = 1.31) with an increasing number of seropositive IIDU-contacts (Table 4.13).

A potential bias would be the tendency of users to preferentially name easily-labelled (jaundiced) IIDU-contacts. However, the observed ratio of uninfected to unapparently infected to symptomatically infected (11:9:7) of the 133 tested did not support this possibility. There were significant differences ($p = 0.025$) in the observed frequencies of the number of seropositive IIDU-contacts between users tested and those not tested (Table 4.11). The subsequent inclusion of users not tested could therefore have an effect on the association between seropositivity and the number of seropositive IIDU-contacts.

On non-parametric testing, there was a statistically significant difference ($p = 0.016$) between seropositive and seronegative users in the number of sexual-IIDU-contacts (Table 4.12). Using logistic regression, there was an increased risk of seropositivity with an increasing number of sexual-IIDU-partners (odds ratio = 1.64) (table 4.13). However, the confidence interval of the odds ratio was broad and included the value of one (95% CI of odds ratio 0.97-2.77). The lack of association could be due to a lack of power to detect a difference using logistic regression. There was no statistical difference between users tested and those not tested in the number of sexual-IIDU-contacts (Table 4.12).

In order to assess the ability of these six variables to predict infection, logistic regression modelling was done. Gender, employment status and the number of sexual-IIDU-contacts did not achieve significance in these models and were excluded.

Logistic regression modelling was done with age and either the total number of IIDU-contacts or the number of seropositive IIDU-contacts. The independent association of these two variables with seropositivity was confirmed in both models (Table 4.14). Therefore, among the 133 illicit injectable drug users tested, the risk factors for prevalent hepatitis B infection were age and either the total number of IIDU-contacts or the number of seropositive IIDU-contacts.

Univariate analysis and logistic regression modelling of the six variables were repeated to determine potential risk factors for incident hepatitis B infection. Of the 133 illicit injectable drug users tested, the timing of infection in 21 could not be ascertained. These were presumed to be immune prior to the epidemic and were therefore excluded from this analysis. Similarly, the two apparent index cases and two chronic carriers infected prior to October 1987 were excluded. Therefore, analyses were based on 55 seronegative and 53 newly-infected illicit injectable drug users.

Table 4.14 Risk factors for hepatitis B seropositivity among 133 tested illicit injectable drug users

A. Model 1

Logistic regression with age and the total number of IIDU-contacts as independent variables

	odds ratio	95% confidence limits	p-value
Age	1.13	1.04 - 1.22	.001
Total # of IIDU-contacts	1.09	1.01 - 1.19	.017

B. Model 2

Logistic regression with age and the number of seropositive IIDU-contacts as independent variables

	odds ratio	95% confidence limits	p-value
Age	1.11	1.03 - 1.21	.004
Number of seropositive IIDU-contacts	1.28	1.09 - 1.50	.001

Table 4.15 summarizes the results of univariate analysis of the six variables. The results revealed the same associations between each of the six variables and new infection as were demonstrated between the variables and prevalent hepatitis B infection. Logistic regression modelling was then done with age and either the total number of IIDU-contacts or the number of seropositive IIDU-contacts. The independent association of the two variables with new infection was confirmed in both models (Table 4.16). Therefore, among the 108 illicit injectable drug users presumed to be susceptible prior to the epidemic, risk factors for infection were increasing age and an increasing number of either the total number of IIDU contacts or the seropositive IIDU-contacts.

An increasing number of IIDU-contacts or seropositive IIDU-contacts results in a greater risk of, or actual exposure to, an infected person. Since the percutaneous mode of transmission is very efficient, the number of IIDU-contacts as a risk factor is evident for both incident and prevalent hepatitis B. Increasing age, as a proxy for duration of habit, is intuitively recognized as a risk factor for prevalent hepatitis B infection.

Increasing age as an independent risk factor for incident hepatitis B infection is less easily interpreted. Several confounders may influence the association. For example, the frequency of injection and of needle-sharing (due to economic reasons or due to withdrawal-avoidance) may increase as the drug-use habit becomes more firmly established. An attitude of fatalism resulting in less regard for risk-reduction measures may develop through the years. If such were the case, and the group of illicit injectable drug users was largely susceptible, then the older users would be more exposed to infection through deleterious needle-sharing practices acquired through time. Conversely, an association between increasing age and incident hepatitis B supports the contention of a largely-susceptible population of illicit injectable drug users.

Table 4.15 **Summary of univariate analysis of six potential risk factors predictive of incident cases of hepatitis B infection among 108 interviewed illicit injectable drug users presumed to be susceptible prior to the epidemic**

Variable	chi-square or Student's t or Mann-Whitney U	Logistic regression	
		odds ratio	95% CI
Gender	X^2=0.34; p=0.56	1.50	0.57-3.91
Employment status	X^2=2.51; p=0.28	1.25	0.87-1.80
Age	t_{106}=2.86; p=0.005	1.12	1.03-1.21
Total # IIDU-contacts	M-W=9.79; p=0.002	1.11	1.01-1.21
# seropositive IIDU-contacts	M-W=15.10; p<0.001	1.33	1.12-1.57
# sexual-IIDU-contacts	M-W=5.75; p=0.016	1.66	0.91-3.05

Table 4.16 Risk factors for hepatitis B infection in 108 illicit injectable drug users presumed to be susceptible prior to the epidemic

A. Model 1

Logistic regression with age and the total number of IIDU-contacts as independent variables

	odds ratio	95% confidence limits	p-value
Age	1.13	1.04 - 1.23	.002
Total # of IIDU-contacts	1.11	1.02 - 1.21	.008

B. Model 2

Logistic regression with age and the number of seropositive IIDU-contacts as independent variables

	odds ratio	95% confidence limits	p-value
Age	1.10	1.01 - 1.20	.016
Number of seropositive IIDU-contacts	1.29	1.09 - 1.53	.002

4.1.8 Delta hepatitis

Six hepatitis B serological cases were also positive for total anti-HDV. All six were illicit injectable drug users with identifiable epidemiological links identified through contact tracing. This cluster of delta hepatitis comprised five males with ages ranging from 24 to 34 years and one female 25 years of age. All were symptomatic; two were severely ill and hospitalized; all recovered. The apparent index case of delta hepatitis likely acquired his infection in another province, returning to Cape Breton early in his clinical course.

Only one serum sample was obtained from the apparent index case, six months after the onset of illness in June 1988. Serological testing was positive for IgG anti-HBc and negative for HBsAg, IgM anti-HBc, and anti-HBs. It is likely this case was in the recovery phase of HBV/HDV coinfection, although HBV/HDV superinfection with depletion of serum HBsAg cannot be ruled out entirely. The five secondary (or tertiary) cases had onsets of illness from three to six months after the apparent index case. All were HBsAg-positive on presentation. Two subsequently seroconverted to hepatitis B immunity, and were therefore likely HBV/HDV coinfections. Although repeat serology tests at six or more months were not available on the remaining three cases, these were considered HBV/HDV coinfections on the basis of drug-use and contact histories.

The secondary attack rate of HBV/HDV coinfection was estimated using the number of HB-seropositive IIDU contacts as the denominator. These HB-seropositives were presumed to be susceptible to hepatitis D virus infection for part of the six-month period starting June 1988. A reasonable upper estimate would be based on the assumption that the apparent index case led to five secondary cases. The six delta cases collectively had shared needles with 35 other illicit injectable drug users, of whom 26 were seropositive for hepatitis B, seven were seronegative and two, both asymptomatic, were not tested.

Among the 26 hepatitis B seropositive IIDU contacts, 19 tested negative for anti-HDV; five asymptomatic and two symptomatic were not tested for anti-HDV. The one chronic carrier in the group of 26 IIDU contacts tested negative for anti-HDV on two occasions. Error would be introduced in the estimate by falsely-negative anti-HDV test results, and in the case of the relatively rare event of asymptomatic HBV/HDV coinfection. (The onsets of illness of the two symptomatic cases not tested for anti-HDV preceded by two or more months that of the apparent delta hepatitis index case, and neither had a second episode of clinical hepatitis). The upper estimate of the secondary attack rate is therefore 16 percent (5/31).

A reasonable lower estimate of the secondary attack rate for HBV/HDV coinfection would be based on the complete IIDU-contact information of one original case-pair. Of 14 HB seropositive IIDU contacts, 11 tested negative for anti-HDV; three asymptomatic contacts were not tested for anti-HDV. Potential sources of error would be similar to the estimate of the upper limit. The lower estimate of the secondary attack rate is therefore 6.7 percent (1/15).

The estimated secondary attack rate for delta hepatitis coinfection may be compared with 1) the rate of percutaneous transmission of hepatitis B virus, and 2) the relative efficiency of hepatitis D virus in coinfection versus superinfection. The World Health Organization uses a transmission coefficient of 90 percent for the parenteral transmission of hepatitis B in the evaluation of strategies related to the testing of transfusion blood supplies (Ghendon, 1990). It has been demonstrated experimentally that hepatitis D virus is less efficiently transmitted than hepatitis B virus, and that hepatitis D virus transmission is less efficient in coinfection than in superinfection (Purcell et al, 1983). The estimated secondary attack rate of 7 to 16 percent for delta hepatitis coinfection is compatible with the literature.

Finally, the concern with delta hepatitis in this particular population

was three-fold. Firstly, both coinfection and superinfection with hepatitis D are associated with more severe disease than hepatitis B infection alone. Secondly, the apparent introduction of hepatitis D virus after the establishment of the hepatitis B epidemic indicated that the illicit injectable drug user population was not a closed system. Thirdly, there was now a potential for endemicity of hepatitis D virus in this population through the superinfection of known or newly developed chronic carriers in this population.

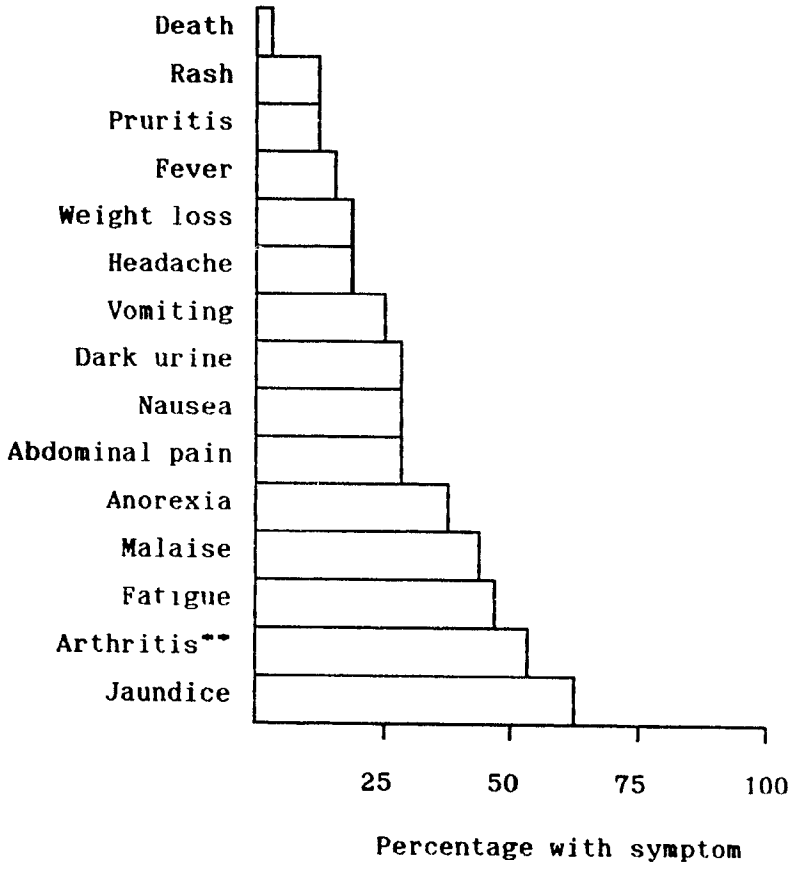
4.1.9 Morbidity associated with the epidemic

The morbidity associated with hepatitis B infection comprises acute and chronic illness. Excluding the two chronic carriers, 39 cluster cases were symptomatic, representing a rate of illness of 61 percent among the recently infected cluster cases. The frequency of symptoms among the 39 ill cluster cases is presented in Figure 4E.

The high rate of illness among cluster cases may in part be due to several factors: 1) the use of symptoms as a component of the cluster case definition; 2) the possible failure to demonstrate some asymptomatic hepatitis B serological cases as true cluster cases; 3) the possible existence of infection among the 19 asymptomatic illicit injectable drug users who were not tested; and 4) the presence of delta hepatitis.

Eighteen of the cluster cases were hospitalized a total of at least 139 days. (Hospital charts of two cases admitted to other hospitals were not reviewed.) The duration of hospital stay ranged from 3 to 29 days, with a median duration of 8.5 days. Of the eighteen cases, 14 cases had acquired their infection through illicit injectable drug use; three were through sexual transmission; and one was through wounds and exposure to blood during an altercation. This latter case progressed

Figure 4E Frequency of symptoms among all cluster cases*



* The two chronic carriers infected prior to October 1987 are excluded. Percentages are based on 39 cluster cases.

** Arthritis denotes painful joints (arthralgia) or inflamed joints (arthritis).

to fulminant hepatic necrosis and was the only cluster case to result in a fatality. Serological testing for total anti-HDV was negative on two occasions.

Among the 61 cluster cases with recently-acquired hepatitis B, three illicit injectable drug users were confirmed to be new chronic carriers nine or more months after an initial HBsAg-positive test. Two illicit injectable drug users were considered potential new chronic carriers, pending repeat HBsAg testing. (A case of acute hepatitis B in late 1989 was attributed to one of the latter two.)

Of the two illicit injectable drug users whose infection and chronic carrier status preceded the epidemic, one has confirmed chronic active hepatitis. There was no histological diagnosis available for the second who has persistent elevation of liver function enzymes.

In summary, the acute morbidity resulting from this epidemic was considerable. The development of new chronic carriers constitutes a larger reservoir of HBV in the illicit injectable drug user population. The chronic carriers are themselves at risk of superinfection and of the sequelae associated with the chronic carrier state.

4.1.10 Hepatitis B immunization as a result of the epidemic

In Nova Scotia, all hepatitis B vaccine is dispensed by Public Health. The amount of vaccine issued for free ("free-issue") by Public Health is a direct consequence of defined high-risk exposures to hepatitis B. In contrast, vaccine purchased by individuals or groups is a consequence of the evaluation of risk to those persons, usually in an occupational setting. The amount of "purchased" vaccine therefore reflects very variable levels of risk in the community.

One hundred and sixty-five persons-at-risk were offered immunization at Public Health's expense. Table 4.17 summarizes the number of persons

Table 4.17 **Number of persons for whom "free-issue" hepatitis B immunization was recommended, and number of persons actually immunized at Public Health's expense, by the nature of contact in Cape Breton Health Unit**

	Number of persons recommended	Number of persons immunized	Percent immunized
IIDU	56	31	55
Sexual	19	17	89
Family	77	67	87
Perinatal	2	2	100
Other*	11	6	55
Total	165	123	75

* Other includes law enforcement or health professionals through needle-stick or mucous membrane exposure to a case of hepatitis B.

Classes are mutually exclusive.

recommended for "free-issue" immunization and the number actually immunized at Public Health's expense, by the nature of contact. All 56 susceptible illicit injectable drug users were considered at high risk and were offered "free-issue" immunization.

Of the 166 persons at risk through all other types of contact (Table 4.1), 109 were offered "free-issue" immunization for variable levels of risk. Education about hepatitis B prevention was considered sufficient for the remainder with a low risk of infection. Of the 56 illicit injectable drug users recommended, 55 percent presented to their family physician for the first dose. Hepatitis B vaccine was variably provided by Public Health as one-, two- or three- dose supplies. Physician records were not reviewed for the actual administration of vaccine. The timeliness of subsequent doses and the extent to which illicit injectable drug users received a partial or full course were therefore not verified.

Public awareness about hepatitis B and the existence of a major outbreak was heightened by widespread media coverage starting in November 1988. The community's perceived risk of infection was assessed by correlating the amount of "free issue" vaccine and the amount of "purchased" vaccine dispensed by Public Health, from January 1987 to June 1989.

Figure 4F presents scatter diagrams of the amounts of "free issue" and "purchased" vaccine from January 1987 to June 1989. Regardless of the source of funding for hepatitis B vaccine, the amount dispensed started to increase in late 1988. From November 1988 to June 1989, the amount of "purchased" vaccine very rapidly progressed to large amounts, 4.5 times greater than the amount dispensed as "free-issue".

Figure 4G is a scatter diagram of the amount of "free-issue" versus the amount of "purchased" vaccine. The degree of linear association between these two variables is high ($r = 0.77$, 95% CI 0.56, 0.88). The correlation between "free issue" and "purchased" vaccine is not

Figure 4F Scatter diagrams of the amounts (mls) of vaccine dispensed as "free-issue" or "purchased" vaccine per month from January 1987 to June 1989 in Cape Breton Health Unit

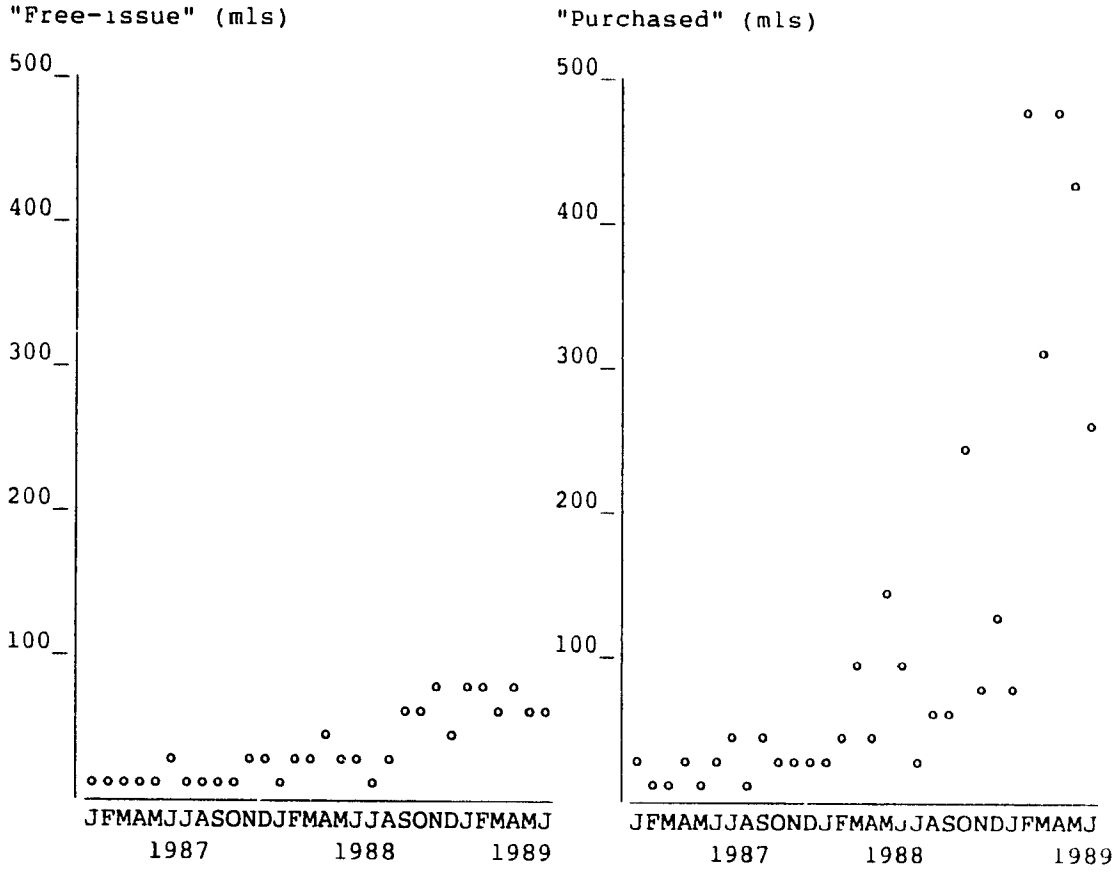
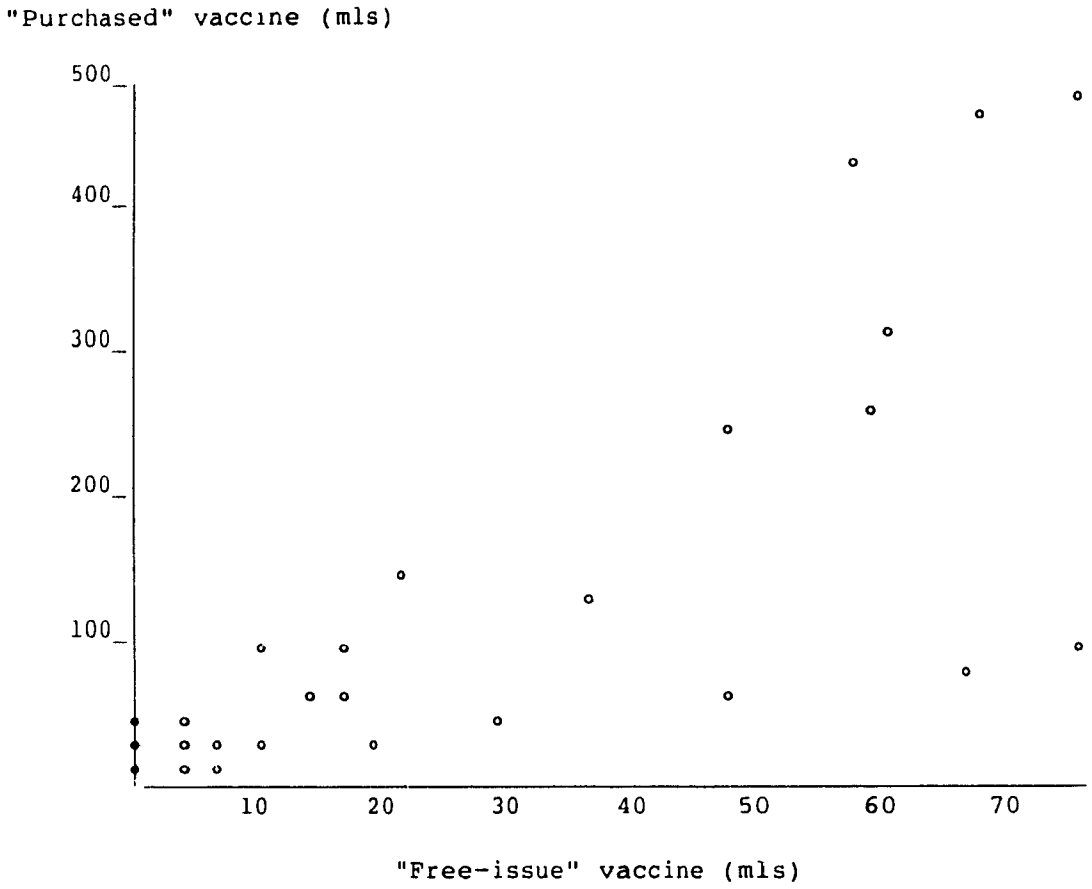


Figure 4G Scatter diagram of the monthly amounts (mls) of "free-issue" versus "purchased" vaccine in Cape Breton Health Unit from January 1987 to June 1989



merely by chance. Decisions were made by several groups on Cape Breton Island to immunize their entire membership because of occupational risk. These groups included hospital maintenance personnel, health care professionals, firefighters, law enforcers, and incinerator workers. In Cape Breton Health Unit, from November 1988 to June 1989, hepatitis B vaccine was purchased to immunize approximately 716 persons, at a total cost of about $60,860.

The Cape Breton Health Unit experience with hepatitis B vaccine is similar to that reported in the United States. There, it was estimated that more than 85 percent of distributed vaccine was used by persons who work in health-care professions and have exposure to blood, staff and clients of institutions for the developmentally disabled, and staff and patients in hemodialysis units (Immunization Practices Advisory Committee, 1987). These risk groups accounted for nine percent of the number of reported cases of hepatitis B from 1982 to 1985 (Alexander et al, 1988). Furthermore, members of the highest risk groups, such as illicit injectable drug users, were the least likely to be reached by immunization programs (Hoofnagle, 1989).

Several factors may in part explain the low rate of presentation by the group of illicit injectable drug users offered "free-issue" vaccine. Firstly, some may have decided to discontinue or modify their high-risk behaviour and/or perceived themselves no longer at risk. Secondly, some may have perceived the risk of hepatitis B as not unacceptably high because infection usually results in recovery. Thirdly, the necessity for numerous visits to health care providers (Public Health interview, blood test, the three-dose regime) over six months may be an important deterrent.

Finally, "free-issue" vaccine was made available in the epidemic area to the cohort of illicit injectable drug users as a post-exposure prophylactic measure. However, four illicit injectable drug users knew themselves at risk in October 1987, tested negative but were not immunized at that time, and subsequently became infected. These

infections may have been prevented with a policy of "free-issue" immunization for lifestyle risks.

4.2 Atlantic Health Unit

4.2.1 Incidence and mode of transmission of reported hepatitis B

Table 4.18 summarizes the reported cases of hepatitis B in the Atlantic Health Unit. From 1986 to July 1989, assuming the population age distributions remained stable, the rate of reported cases of hepatitis B increased nine-fold among males and three-fold among females. From 1986 to 1988, the male-to-female ratio was approximately one, whereas in 1989, there were more than twice as many males as females reported with hepatitis B. Ages ranged from children to the elderly in all years; however, in 1989, there were also two cases of perinatal transmission of hepatitis B. The median age for the entire period of time ranged from 25 to 30 years among females and 30 to 37 among males.

The proportion of reported cases who were acutely ill (with jaundice or hospitalized) increased from 19 percent in 1986 to 34 percent in 1988, and 58 percent in 1989. The proportion of chronic carriers or asymptomatic cases who were reported decreased from 62 percent in 1986 to 46 percent in 1988 to 40 percent in 1989. The increasing proportion of acutely ill patients suggests that the increasing population rates were due to a true increase in incidence rather than due to a change in reporting or contact-tracing practices.

The increasing male-to-female ratio may be related to the changing trend in risk factors or mode of transmission. Table 4.19 summarizes the percentage of the reported risk factors or mode of transmission. From 1986 to July 1989, the percentage of cases reported with an unknown mode of transmission was relatively stable, ranging from 22 to 32 percent overall. The percentage of cases attributed to infection

Table 4.18 **Population rates and demographic characteristics of reported cases of hepatitis B in Atlantic Health Unit, from 1986 to 1989*, by gender****

	1986		1987		1988		1989	
	M	F	M	F	M	F	M	F
Number of cases	9	12	17	9	25	25	45	20
Rate per 100,000 population	6.0	7.7	11.4	5.8	16.7	16.0	55.7	23.7
Age range (years)	8-39	6-64	14-80	3-56	19-89	17-82	<1-64	18-51
Median age (years)	34	27	37	27	33	28	30	25

* Reported cases for the 28-week period from 25 December 1988 to 8 July 1989

** M = male; F = female

Table 4.19 **Percentage of hepatitis B cases with illicit injectable drug use reported as the mode of transmission in Atlantic Health Unit, from 1986 to 1989*, by gender****

PERCENTAGE OF REPORTED CASES WITH MODE OF TRANSMISSION

	1986		1987		1988		1989	
Mode of transmission	M	F	M	F	M	F	M	F
Endemic region***	34	25	53	44	16	12	16	5
Homosexual activity	22	0	0	0	0	0	0	0
Heterosexual activity	11	0	0	34	12	28	0	25
Perinatal	0	16	0	0	0	0	2	0
IIDU	11	17	17	11	28	16	49	45
Other****	0	7	6	11	12	16	4	0
Unknown	22	25	24	0	32	28	29	25

* Reported cases in the 28-week period ending 8 July 1989
** M = male; F = female
*** Unspecified mode of transmission in a person from a region of HB endemicity
**** Other includes hemodialysis, transfusion and tattooing

acquired in an endemic country fluctuated from 16 to 53 percent among males and 5 to 44 percent among females. Sexual transmission through homosexual activity was rarely reported. Sexual transmission associated with heterosexual activity was reported more among females, accounting for 25 to 34 percent of cases.

Hepatitis B infection associated with illicit injectable drug use was increasingly reported from 1986 to July 1989, among both males and females. Furthermore, during the 28-week period in 1989, more than 45 percent of cases were attributed to this mode of transmission. Assuming that unreported cases have a similar distribution of risk factors, then this trend suggests that illicit injectable drug use was an increasingly important contributor to hepatitis B disease in the Atlantic Health Unit.

Among those whose mode of transmission was attributed to illicit injectable drug use in 1989, ages ranged from 20 to 45 years among males (median age 29 years), and 18 to 40 years among females (median age 25 years). The male-to-female ratio was 2.4:1. The preponderance of youthful males is comparable to that in the literature and that observed in the epidemic area in Cape Breton Health Unit.

CHAPTER 5

GENERAL DISCUSSION

5.0 Introduction

The occurrence of hepatitis B in two health units of Nova Scotia was largely related to illicit injectable drug use in 1988 and 1989. The limitations in study design due to the nature of the illicit injectable drug user population are discussed in the first section of this chapter. The limitations of the study methods and the usefulness of risk factor identification in the epidemic setting are discussed in the next two sections. Finally, the prevention of viral illnesses associated with illicit injectable drug use is discussed, with emphasis on immunization and risk-reduction strategies. Discussion of specific study findings is presented in Chaper 4.

5.1 Contact-tracing as part of the study design

The recognition of illicit injectable drug users as a population has been a gradual phenomenon resulting from work in many disciplines. Insight into the nature of substance abuse and addiction has been provided largely through persons in the field of treatment and rehabilitation. The commonality of experiences and observations in treatment centres has led to formal psychosocial modelling for both the condition and its treatmert. Illicit injectable drug use has been extensively studied as a risk factor for several viral illnesses, with users being considered an important reservoir of these viruses in some regions.

However, a population defined by an activity rather than by demographic characteristics is problematic, all the more so if the activity is covert with potential legal and socioeconomic repercussions. Illicit injectable drug users are thought to be a heterogenous population with complex drug-use and sexual behaviours that vary according to socioeconomic status and racial or cultural background (Schoenbaum et al, 1989). An analogous situation exists in the case of prostitution. Furthermore, persons engaging in these activities often constitute overlapping and interdependent populations, and pose similar problems for the delivery of social and medical programs and for epidemiological study.

Most information on these populations has been obtained from studies of the accessible subgroups--those with medical problems, those in treatment programs for drug addiction, or those incarcerated. However, each of these subgroups may not be representative of the population being studied. One approach to this limitation has been to recruit large numbers of volunteers among those engaging in the activity(ies) in several cities through street and educational outreach programs (Weddington et al, 1990; Khabbaz et al, 1990). Again, the potential lack of generalizability of the results to non-volunteers or to other geographic regions is recognized.

Clearly, the major limitation in studying behaviour and disease among illicit injectable drug users has been access to the population. This fundamental difficulty has imposed constraints on case-finding strategies and on study designs. It may be argued that any subgroup amenable to study is not representative of the population of illicit injectable drug users. However, the contribution by this population to the burden of disease in a region creates an imperative for epidemiological study, notwithstanding design limitations.

In Cape Breton Health Unit, gaining access to the illicit injectable drug user population was instigated by the event of a hepatitis B epidemic among users in a circumscribed geographic area. The long

incubation period for hepatitis B, the existence of post-exposure prophylaxis through immunization, and the possibility of modifying behaviour to reduce the risk of infection, provided the impetus for adoption of a contact-tracing strategy. Inherent to this strategy was the lack of knowledge of the completeness or representativeness of the identified group. In an attempt to overcome these problems, a contact-tracing method was developed which aimed at the exhaustive identification of all those at risk and promoted successful interviews.

Other than the estimate of 200 users provided by one frequent male user, no reliable estimate of the number of illicit injectable drug users was available for the epidemic area. The completeness of the enumeration of the cohort of illicit injectable drug users in the present study is therefore difficult to assess. However, contact and interviewing were effected by Public Health in 82 percent of the 186 IIDU-contacts named. In comparison with published results of contact-tracing efforts for viral hepatitis among illicit injectable drug users, the Cape Breton experience seems successful. For example, in a London, England, health district, only 67 percent of hepatitis B cases and of named contacts were interviewed, drug addicts being the most difficult to reach (Munday et al, 1983). In a recent outbreak of hepatitis A associated with illicit injectable drug use in Vancouver, only 3 of 20 cases could be contacted by the public health staff (Jin and Bardsley, 1990).

The extent to which the interviewed group is representative of all injectable drug users in the area or of those in other regions is similarly difficult to judge. The ratio of non-infected to asymptomatic infected to symptomatic infected users among those interviewed suggests there was no a priori bias toward identification of easily labelled users. This ratio, coupled with the successful completion of interviews, and the non-judgemental interviewing method that was employed suggest that the results of the contact-tracing efforts may be similar to recruitment of volunteer study subjects through outreach programs. In this regard, the present study provides

useful information particularly for other rural regions in Nova Scotia and possibly in Canada.

5.2 Study methods

The questionnaire was designed as an instrument for general use by Public Health authorities in the reporting and follow-up of cases of hepatitis B, regardless of the implicated mode of transmission. This questionnaire was adequate for the expedient purpose of the study in Cape Breton Health Unit which was control of the hepatitis B epidemic. Priority was given to fostering the trust and cooperation of the illicit injectable drug user population rather than obtaining formal insight into the high-risk behaviours related to their addiction. Administration of a second questionnaire concerning these aspects of illicit injectable drug use was therefore deferred. This non-judgemental and unobtrusive approach stressing confidentiality has been cited as a key component in a successful program among illicit injectable drug users (Bardsley et al, 1990).

A frustrating limitation of the study methods was the lack of general availability of IgM anti-HBc testing. The triad of tests for HBsAg, IgG anti-HBc and anti-HBs was a sensitive means of diagnosis of hepatitis B infection. In the epidemic context with demonstrable epidemiological links, this group of tests was also specific. However, current epidemiological studies present IgM anti-HBc positivity as the standard evidence of recent hepatitis B infection. The general availability of IgM anti-HBc testing would have offered immediate confirmation of the timing of infection, independently of retesting or drug-use and contact histories. The increasing incidence of reported hepatitis B associated with illicit injectable drug use in two health units now renders this serological test indispensable in Nova Scotia.

5.3 Identification of risk factors for hepatitis B infection

The hepatitis B epidemic was the first highly visible indication of a serious problem with illicit injectable drug use in rural Nova Scotia. The contact-tracing strategy served to partially expose the extent of the latter problem in the epidemic area. Although risk factors for hepatitis B infection among illicit injectable drug users may be population-specific, the identification of risk factors in the epidemic area was important for two reasons.

Firstly, the identification of increasing age as a risk factor for incident hepatitis B infection was a useful adjunct to the study methods. In the absence of complete serological evidence, this association offered independent (indirect) evidence of the general susceptibility to hepatitis B of the illicit injectable drug user population.

Secondly, the association of hepatitis B infection and the number of IIDU-contacts confirms our understanding of the spread of hepatitis B through this mode of transmission. Regardless of certain knowledge of the infectious status of IIDU-contacts, an increasing number of IIDU-contacts poses an increased risk of hepatitis B infection for the individual. By implication, an infected IIDU with numerous IIDU-contacts is an efficient contributor to the dissemination of disease. The presence of IIDU's with numerous IIDU-contacts in a defined cohort represents a condition very favourable for the rapid spread of a newly-introduced bloodborne virus. Knowledge of the needle-sharing potential among illicit injectable drug users in a small community may be useful in determining appropriate control strategies for hepatitis B and other viruses in the rural setting.

5.4 Strategies for the prevention of viral illnesses associated with illicit injectable drug use

The most effective means of preventing viral illnesses associated with illicit injectable drug use would be prevention of the behaviour which engenders the risk. Fundamental to this goal is an understanding of the underlying reasons for drug use and subsequent drug dependency and of the societal circumstances which promote substance abuse. The prevention of substance abuse, of illicit injectable drug use, of the associated high-risk behaviours and the ensuing viral infections necessitate a comprehensive, long-term approach through coordinated community programs.

Several pathogenic viruses including HIV and at least three of the viral hepatitides-- HBV, HCV and HDV--, are commonly transmitted percutaneously through the sharing of contaminated injection apparatus during illicit injectable drug use. Transmission of hepatitis A has also been documented in association with illicit injectable drug use. Of these, hepatitis B and delta hepatitis coinfection are preventable diseases through hepatitis B immunization. Hepatitis A may be prevented by the timely administration of immunoglobulin; furthermore, several candidate vaccines against hepatitis A are currently being tested (Purcell, 1990). Prevention of HIV and HCV infection and delta hepatitis superinfection rests entirely on modifying behaviour and risk-reduction.

5.4.1 Hepatitis B immunization strategy

The single most important limitation in hepatitis B immunization strategy has been the cost of the vaccine itself, resulting in recommendations targeting several high-risk groups. A second important limitation has been the difficulty of vaccine delivery to certain high-risk groups, especially illicit injectable drug users.

In the United States, the incidence of hepatitis B has steadily increased during the past decade (McQuillan et al, 1989). This trend is attributed to a lack of programs to immunize persons in all high-risk groups. Hepatitis B occurs principally in young adults due to lifestyle-related exposure. Because these groups cannot be effectively reached by even aggressive immunization programs, selective or universal immunization of infants or adolescents is now being proposed (Krugman, 1990; Kane et al, 1989). This strategy would eliminate problems of vaccine delivery to future members of high-risk hard-to-reach groups.

The incidence of hepatitis B disease in Nova Scotia has dramatically increased in the past two years, with the majority of disease directly attributed to illicit injectable drug use. A universal immunization program has not been considered necessary or desirable because of the cost of vaccine and because hepatitis B has been perceived as an uncommon disease occurring in defined high-risk groups. The cost of an immunization program targeting those at high-risk through lifestyle choices has similarly been considered prohibitive.

However, the failure to prevent disease through immunization programs also entails some costs. Firstly, a post-exposure immunization strategy must rely on contact-tracing which is labour-intensive and which necessitates the serological testing of numerous contacts. This approach is not assured of success especially in the urban regions and vaccine delivery to members of the high-risk group remains problematic. Secondly, the increasing incidence of hepatitis B results in major costs for the treatment of acute and chronic disease. The presence of delta hepatitis adds to the burden of acute disease with a serious consequence of chronicity in the case of superinfection. Thirdly, persons may unknowingly be at risk through interaction with those at remote or immediate risk of infection. The potential for unapparent intection is especially of concern in the obstetric population. The value of screening questions to detect high-risk women has been demonstrated to be unacceptably low (McQuillan et al, 1987). The

National Advisory Committee on Immunization recommends that all pregnant women be routinely screened for HBsAg (National Advisory Committee on Immunization, 1989). Thus, the increasing incidence of hepatitis B disease in Nova Scotia lends urgency to the implementation of a pre-natal serological screening program, also costly.

A partial, temporary solution in Nova Scotia would be to make free vaccine available to the accessible illicit injectable drug users--those seeking help in medical or drug treatment programs. Illicit injectable drug users who are incarcerated are another accessible segment of the population. Immunization programs for this group may be available through Correctional Service Canada (personal communication, J. Roy).

However, a selective or universal hepatitis B immunization program for infants or adolescents in Nova Scotia needs to be considered. At the current price per dose, the cost of such a program is prohibitive. Large-scale procurement through the pooling of orders from several jurisdictions provides the means for obtaining the production scale necessary to effect a major reduction in cost per dose. Working examples of this principle exist in the provincial, national and international (Expanded Programme on Immunization) immunization programs for childhood diseases. Models for large-scale affordable hepatitis B vaccine production are considered feasible (Mahoney, 1990) and several mass hepatitis B immunization programs have been implemented successfully (Chen, 1990; Bergamini et al, 1990; Al-Faleh et al, 1990). The worrisome trend in incidence of hepatitis B and delta hepatitis in Nova Scotia warrants exploring the application of this economic principle, for example, by participation in or initiation of joint provincial/federal studies and programs.

5.4.2 High risk behaviour

In the absence of vaccines or treatment, prevention and control of viral illnesses related to illicit injectable drug use rest entirely on the reduction of high-risk behaviours. Two behaviours associated with a high risk of transmission of infectious diseases among illicit injectable drug users are sexual activity with numerous partners and the sharing of injection apparatus. In Cape Breton Health Unit, the latter behaviour was the predominant concern.

Needle-sharing among users is thought to be common, with proportions ranging from 68 to 88 percent in studies of various subgroups of illicit injectable drug users (Friedland et al, 1985; Black et al, 1986; Weddington et al, 1990). The determinants of needle-sharing were studied in a group of illicit injectable drug users in a methadone treatment program (Magura et al, 1989). Sharing was found to be directly related to peer group behaviour, attitudes conducive to sharing (such as withdrawal avoidance), economic motivation to share, not owning injection equipment, and fatalism about developing AIDS. Needle-sharing may also be related to the drug injected. The effect from cocaine is of a much shorter duration than that from heroin, with an almost immediate craving causing a phenomenon called "binging": users get high constantly for up to 48 hours without eating or sleeping (Friedman et al, 1989).

Two studies reported that the majority of needle-sharing users did so with friends or relatives rather than with strangers (Black et al, 1986; Weddington et al, 1990). The tendency to share with persons well known to a user as opposed to sharing with strangers may itself differ between regions and between cultural and racial groups. In a study identifying risk factors for HIV infection, whites were more likely to report sharing with friends and relatives whereas blacks and Hispanics were more likely to report sharing with strangers (Schoenbaum et al, 1989). Drug users who shared needles with strangers were at high risk

of HIV infection compared with those sharing needles with friends or relatives.

The tendency to share injection apparatus with persons well known to the user has been interpreted as evidence of caution among illicit injectable drug users regarding the health risks of needle sharing. However, in the context of a defined cohort, once a bloodborne virus is introduced, not only does this behaviour cease to be protective, it then becomes a very efficient mechanism for the transmission of viral infections. This is likely to be the situation in the case of rural or small communities. The Cape Breton Health Unit experience was therefore important not only because of the occurrence of hepatitis B, but also as a demonstration of the potential for epidemic spread of other viral infections among illicit injectable drug users in a small community.

5.4.3 HIV infection

In 1985 and 1986, several conditions were stipulated by the Nova Scotia Department of Health and Fitness for HIV serological testing. These conditions include: 1) the requirement of pre- and post-test counselling to be conducted by a physician; 2) the mandatory nominal reporting of HIV-seropositivity (and not HIV-seronegativity); and 3) the non-availability of anonymous testing. Therefore, neither numerator nor denominator data about initial or repeat HIV test results among illicit injectable drug users were available in either health unit.

The mandatory nominal reporting of HIV-seropositivity may have discouraged serological testing of persons at risk through illicit injectable drug user and sexual activity. Consideration is now being given to the mandatory non-nominal reporting of HIV-seropositivity.

5.4.4 Risk reduction measures

The coordinated community programs reported in the literature stress the importance of a holistic, culturally sensitive, non-judgemental approach towards prevention of illicit injectable drug use and the associated high-risk behaviours and diseases (Bardsley et al, 1990; Comella et al, 1989; Flynn et al, 1989; van den Hoek et al, 1989). These programs include components of education for the prevention of drug use, treatment and rehabilitation for drug dependency, voluntary HIV testing and counselling, and health education concerning sexual and drug-related risk-reduction measures. Drug-related risk-reduction measures include the promotion of effective needle hygiene, the liberalizing of legal access to sterile injection, and needle exchange programs.

To date, there have been no government-sanctioned needle-exchange programs or pilot projects in Nova Scotia. The perception has been that the vaccine-preventable viral illnesses associated with illicit injectable drug use may be addressed by post-exposure immunization. The other viral illnesses such as HIV and HCV infection are perceived to be uncommon.

Even if HIV prevalence is currently low, the experience with hepatitis B in two health units exemplifies the vulnerability of the illicit injectable drug user population. No illicit injectable drug user population can be considered a closed society--there is active recruitment into the ranks; there is sufficient travel to other regions and mixing with other populations. Once a virus is introduced, the potential for endemicity is great in the illicit injectable drug user population.

Regardless of certain knowledge of the HIV-seroprevalence, the prevalence of illicit injectable drug use and the needle-sharing patterns in one region of Cape Breton Health Unit underscore the urgency of the implementation of HIV-prevention strategies. During the

hepatitis B epidemic in that region, communication was established among various community agencies. Furthermore, illicit injectable drug users proved themselves remarkably motivated and cooperative. A needle-exchange project within a comprehensive community program may be a viable option in that setting.

CHAPTER 6

SUMMARY

The study of the occurrence of hepatitis B in relation to illicit injectable drug use in two health units in Nova Scotia has provided some insight into this difficult-to-reach population. Clearly, illicit injectable drug use is an significant contributor to the burden of disease in Nova Scotia. The identification of age and the number of IIDU-contacts as risk factors for hepatitis B infection was useful in understanding the dynamics of transmission of viral infection in a rural population of illicit injectable drug users. The contact-tracing strategy in that setting proved successful, and provided a means of obtaining an estimate of the secondary attack rate in delta hepatitis coinfection.

The following recommendations for the prevention of hepatitis B and other viral illnesses among illicit injectable drug users resulted from the findings in Cape Breton and Atlantic Health Units and a review of prevention strategies.

1) The epidemic of hepatitis B associated with illicit injectable drug use is known to have resulted in the development of new chronic carriers in Cape Breton Health Unit. The increased incidence of hepatitis B among illicit injectable drug users in Atlantic Health Unit likely has similarly resulted in an increased number of chronic carriers. The potential for superinfection with other hepatotropic viruses renders essential the accurate diagnosis of recent versus chronic hepatitis B infection. It is therefore recommended that IgM anti-HBc testing be routinely available in Nova Scotia. Serological testing for delta hepatitis is recommended for cases of hepatitis attributed to illicit injectable drug use.

2) As a partial, temporary solution to the increased incidence of hepatitis B among illicit injectable drug users, it is recommended that free hepatitis B immunization be available to users seeking help in medical or drug treatment programs. In addition, an immunization program for incarcerated illicit injectable drug users may be available through Correctional Service Canada.

3) Hepatitis B is an entirely preventable disease by immunization. A selective or universal hepatitis B immunization program for infants or adolescents would eliminate problems of vaccine delivery to future members of high-risk hard-to-reach groups. Large-scale procurement through the pooling of orders from several jurisdictions provides the means for obtaining the production scale necessary to effect a major reduction in cost per dose. The potential for cost-effective hepatitis B immunization programs needs to be seriously explored by active participation in or initiation of joint provincial/federal studies or programs.

4) Illicit injectable drug use is an important risk factor and mode of transmission of several viral illnesses. Formal study into the details of drug use needs to be undertaken, for both urban and rural populations of users in Nova Scotia.

5) The prevention of substance abuse, of illicit injectable drug use, of the associated high-risk behaviours and viral infections, necessitates a comprehensive approach through coordinated community programs. Because of the prevalence of illicit injectable drug use and the needle-sharing patterns, a pilot needle-exchange program in Cape Breton Health unit warrants serious discussion and consideration.

CHAPTER 7

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Appendix 1 Population figures for Canada, Nova Scotia and Cape Breton Health Unit in 1986, by age and gender*

AGE (years)	CANADA	NOVA SCOTIA	CAPE BRETON HEALTH UNIT
Males			
<1	186,280	6,210	
1- 4	741,500	24,575	5,900**
5- 9	920,105	31,025	6,300
10-14	916,750	34,080	7,200
15-19	985,255	37,150	7,900
20-24	1,131,450	41,470	7,200
25-29	1,164,985	38,875	6,300
30-39	2,094,815	69,255	11,700
40-59	2,680,705	86,210	16,900
60+	1,663,800	61,715	12,500
total	12,485,645	430,565	81,900
Females			
<1	177,345	5,835	
1- 4	705,070	23,515	5,500**
5- 9	874,870	30,005	6,200
10-14	870,050	32,120	6,700
15-19	939,600	34,735	7,300
20-24	1,121,895	40,075	6,900
25-29	1,176,520	39,2[illegible]	6,300
30-39	2,117,000	70,41[illegible]	11,700
40-59	2,682,430	87,355	17,400
60+	2,158,920	79,355	15,900
total	12,823,700	442,605	83,900

* Statistics Canada (1986a, 1986b)

** For Cape Breton Health Unit only, age <1 is included in the age class 0-4 years.

Appendix 2 **Hepatitis B cases reported in 1987 and 1988 in Canada*, Nova Scotia** and Cape Breton Health Unit**, by age and gender**

1987	CANADA		NOVA SCOTIA		CAPE BRETON HEALTH UNIT	
Age (years)	Male	Female	Male	Female	Male	Female
<1	6	3	0	0	0	0
1- 4	15	9	1	0	0	0
5- 9	16	8	1	0	0	0
10-14	12	9	0	0	0	0
15-19	55	74	2	0	1	0
20-24	192	150	2	4	0	2
25-29	288	133	5	3	0	2
30-39	407	170	9	1	1	0
40-59	294	110	4	3	1	0
60+	66	36	3	2	1	2
unknown	45	37	3	0	0	0
not specified	870				1	
Total	3005		43		11	

1988	CANADA		NOVA SCOTIA	
Age (years)	Male	Female	Male	Female
<1	7	2	0	0
1- 4	8	17	0	0
5- 9	12	10	0	0
10-14	14	18	0	0
15-19	69	97	2	3
20-24	211	150	8	10
25-29	306	150	13	7
30-39	412	196	22	10
40-59	297	138	8	4
60+	92	47	5	3
unknown	33	27	6	3
not specified	810			
Total	3132		104	

* Statistics Canada, Notifiable Diseases, Annual Report (1987, 1988)
** Data from Nova Scotia Department of Health and Fitness

Appendix 3 Reported hepatitis B cases for Nova Scotia and Cape Breton Health Unit for the 48-week period ending November 15, 1988, by age and gender

Age (years)	Male	Female	Male	Female
<1	0	0	0	0
1- 4	0	0	0	0
5- 9	0	0	0	0
10-14	0	0	0	0
15-19	1	3	0	0
20-24	5	8	1	2
25-29	11	6	3	3
30-39	15	9	6	0
40-59	7	3	3	0
60+	4	3	0	1
unknown	5	3	0	1
Total	82		20	

Nova Scotia

Department of
Health and Fitness
Community Health Services

HEPATITIS B

CASE REPORT AND FOLLOW-UP

patient _____ sex ___ date of birth ___/_____/___
address _____ occupation _____
phone _____

family physician _____ phone _____

reason for initial serological testing:
[ ] clinical hepatitis
[ ] contact with known/suspected HBV (name) _____
[ ] high-risk behavior
[ ] pregnancy
[ ] other _____

symptoms [ ] yes (underline) malaise, fatigue, jaundice, headache
[ ] no anorexia, nausea, vomiting, abd pain
dark urine, rash, itching, arthritis

date onset of illness ___/_____/___ date hospitalized ___/_____/___

date first serology ___/_____/___ HBsAG ___ HBsAB ___ HBcAB ___

underlying medical problem [ ] none [ ] pregnancy EDC ___/_____/___
[ ] hemophilia
[ ] cirrhosis [ ] other _____

physicians in past 6-12 months _____

procedures in past 6-12 months: transfusion, dialysis, surgery, other __
_____

dental care in past 6-12 months: dentist _____
procedure _____

plans for surgical or dental care in next 6 months? _____

blood/sperm donation in past year [ ] no [ ] yes date ___/_____/___

Do you use IV needles? [ ] no [ ] yes First time when ___/____/___

Regular sexual partner _____

serology ordered by Public Health __/____/__

CONTACTS

HOUSEHOLD MEMBERS	relationship	serology date	vaccine date	HBIG date
_____	_____	__/__/__	__/__/__	__/__/__
_____	_____	__/__/__	__/__/__	__/__/__
_____	_____	__/__/__	__/__/__	__/__/__
_____	_____	__/__/__	__/__/__	__/__/__
_____	_____	__/__/__	__/__/__	__/__/__

SEXUAL CONTACTS in past 6-12 months	address	phone	pregnant?
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____

IV NEEDLE CONTACTS	address	phone	pregnant?
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____

FURTHER COMMENTS

_____
_____
_____
_____

Education on Hepatitis B to be provided to patient, family and other contacts by CHN ___ family doctor ___ other _____

Form completed by _____ ___/_____/___.

Nova Scotia
Department of Health and Fitness

NOTIFICATION OF HEPATITIS B
CONTACT TRACING

____/____/____

Dear Doctor _____:

Through contact tracing in the current HEPATITIS B outbreak, your patient _____

has sought medical attention and will be undergoing serological testing at the request of the Nova Scotia Department of Health and Fitness.

Counselling was provided by _____ on ____/____/____.

As part of our follow-up, if _____'s current serology indicates infection (HBsAg positive or HBcAB positive) but not immunity (HBsAB negative), we will contact you in _____/1989 to ascertain the patient's immune status.

_____

_____

_____

The Department of Health and Fitness emphasizes the need for HBsAg screening of pregnant women at risk of HBV infection. The investigation of this outbreak may lead the Department to recommend routine prenatal HBsAg screening of all pregnant women in this area for a period of time.

According to normal Department procedure, the utmost effort is made to maintain confidentiality. The detailed case/contact report will be kept at the Cape Breton Health Unit. Your request for further information may be addressed to Doctor Leo MacCormick.

For your information, enclosed is a photocopy of the Nova Scotia Department of Health and Fitness "Recommendations for post-exposure prophylaxis of HEPATITIS B", sections relating to perinatal, sexual and household exposure. (A photocopy of the complete "Recommendations ...." is available at the Northside General Hospital Library.

Please let us know if we may be of further assistance.

Christiane Poulin, M. D.
Field Epidemiologist for Nova Scotia

and _____
Community Health Nurse
SYDNEY MINES, Nova Scotia

CP:dh

Nova Scotia
Department of
Health and Fitness

RECOMMENDATION FOR HEPATITIS B IMMUNIZATION

-----/-----/-----

Dear Doctor ----------:

Through contact tracing in the current Hepatitis B outbreak, your patient

---

---

has undergone serological testing at the request of the Department of Health and Fitness.

Serology results on -----/-----/----- *were sAg negative, sAb negative and cAb negative, indicating he has not been infected. However,* ---------- *continues to be exposed to infection through* ---------- *and we therefore recommend immunization.*

Recombivax vaccine is available through Dr. Leo MacCormick, Director of the Cape Breton Health Unit, Sydney (tel: 563-2400).

If you require further information, please do not hesitate to contact us.

Sincerely,

Christiane Poulin, M.D.
Field Epidemiologist