Viral Hepatitis and Emerging Bloodborne Pathogens in Canada

Health Canada　Santé Canada

Canada

*Our mission is to help the people of Canada
maintain and improve their health.*

Health Canada

Viral Hepatitis and Emerging Bloodborne Pathogens in Canada

Table of Contents

Preface

The Community Acquired Blood-Borne Infections Section (CABBI) of the Blood-Borne Pathogens Division at Health Canada is responsible for the federal coordination of surveillance, prevention, and control of viral hepatitis and emerging bloodborne pathogens. This supplement constitutes the first annual report on the current status of these diseases and pathogens in Canada. Several experts were also asked to provide their research results on important issues related to the surveillance, prevention, and control of these diseases and pathogens.

The first two articles in the supplement provide a general overview of the surveillance systems in place to monitor viral hepatitis and emerging bloodborne pathogens, and the various strategies aimed at preventing and controlling these infections. The next four articles provide the reader with a summary of the current status of hepatitis A, B, C, and G in Canada. These are followed by several articles synthesizing the available knowledge on both emerging bloodborne pathogens, such as SEN virus and herpesvirus 6, 7, and 8, and "hot" issues, such as xenotransplantation and xenozoonoses. The final three articles examine the effectiveness of targeted prevention and control strategies, including hospital infection control strategies, germicide inactivation, and harm reduction strategies.

Surveillance, prevention, and control of viral hepatitis and emerging bloodborne pathogens, as with other health threats, require multi-disciplinary and multi-organizational effort. Other units within Health Canada, such as the Division of Surveillance of the Bureau of Infectious Diseases and the

Hepatitis C Division of the Centre for Infectious Disease Prevention and Control, provincial/territorial public health agencies, and health professional groups across the country all contribute to this effort. Without their collaboration and support this report would not have been possible. Similarly, without the support of the Scientific Publication and Multimedia Services unit the report would not have been possible.

Staff in CABBI have been working diligently to provide essential information for risk assessment and policy formulation towards the prevention and control of viral hepatitis and emerging bloodborne pathogens. Leslie Forrester and Marina Kanabe coordinated the preparation of this report. The collective contribution of all participants will go a long way towards providing Canadians with current information to help them maintain and improve their health. In this regard, the continuous support from our partners and collaborators at all levels and from all aspects is greatly appreciated.

If there are questions or comments, please contact me by phone at (613) 957-1789 or by e-mail at <antonio_giulivi@hc-sc.gc.ca>, or contact Dr. Shimian Zou, Chief of the CABBI Section, at (613) 946-8819 or at <shimian_zou@hc-sc.gc.ca>.

Antonio Giulivi, MD, FRCPC
Chief, Blood-Borne Pathogens Division
Associate Director
Bureau of Infectious Diseases
Centre for Infectious Disease Prevention and Control
Health Canada

Surveillance for Viral Hepatitis and Emerging Bloodborne Pathogens in Canada

Shimian Zou, Antonio Giulivi

Surveillance for viral hepatitis and emerging bloodborne pathogens is coordinated by the Blood-Borne Pathogens Division, Bureau of Infectious Diseases, Centre for Infectious Disease Prevention and Control, Population and Public Health Branch of the realigned Health Canada (HC). Viral hepatitis includes hepatitis A, B, C, D, and E, though current surveillance activities in Canada cover mainly hepatitis A, B, and C. Hepatitis D is caused by hepatitis D (delta) virus, which is a satellite agent of hepatitis B virus. Effective control of hepatitis B controls hepatitis D. Hepatitis E is not currently a major public health threat in Canada.

Emerging bloodborne pathogens include new and re-emerging agents that can be transmitted through blood, blood products, body fluids, and biological therapeutic products, including cells, tissues, and organs. Hepatitis G virus, transfusion-transmitted (TT) virus, TT virus-like viruses, and SEN virus are examples of recently identified bloodborne agents. More novel bloodborne agents will likely be identified, since there are cases of chronic hepatitis in which infectious agents have not yet been identified. The availability of more sensitive, new technologies will also allow the identification of new agents from the blood. Further, the introduction of preventive or treatment measures could bring about new agents, such as hepatitis B viral mutants induced by hepatitis B vaccination, and possible emergence of virus strains resistant to chemotherapy. Although no

xenotransplantation practice is currently being conducted in Canada, clinical trials are under way elsewhere in the world. This leaves room for the potential emergence of new pathogens in the human populations targeted.

Surveillance systems

Surveillance for viral hepatitis and emerging bloodborne pathogens in Canada includes routine, sentinel and targeted surveillance as well as research[1]. Routine surveillance comprises the reporting of viral hepatitis A, hepatitis B, and hepatitis C through the National Notifiable Disease Reporting System and analysis of other routinely collected data[2]. Hepatitis A, B, and C are reportable across the country. Provincial and territorial ministries of health receive reports of identified cases and submit data to HC, which compiles national data and disseminates them periodically through the *Canada Communicable Disease Report* and the Health Canada Surveillance On-line web site at http://www.hc-sc.gc.ca/hpb/lcdc/webmap/index.html[3]. Other routinely collected data include mortality, morbidity, and hospital discharge data as well as laboratory-based surveillance data. Routine surveillance provides essential data on hepatitis A, B, and C; however, in itself it is not sufficient to support evidence-based decision making in public health.

Sentinel surveillance is the selection of health units or population groups and the monitoring of events and associated

factors in those units or groups. Because it involves smaller population groups, sentinel surveillance can be conducted in more depth, with more consistency among different population groups, and in a more timely manner. Currently, an enhanced surveillance system consisting of Vancouver-Richmond, Edmonton, Calgary, Winnipeg, Ottawa-Carleton, and New Brunswick has been established for acute hepatitis B and acute hepatitis C. In addition, a special surveillance system for emerging bloodborne pathogens is being developed in collaboration with public health agencies, professional groups, and health care providers across the country. Lastly, a viral hepatitis network of hospital centres is being established, one of whose functions will include surveillance of viral hepatitis and emerging bloodborne pathogens.

The enhanced surveillance was started in Edmonton and Ottawa-Carleton in October 1998, was joined by Calgary and Winnipeg in January 1999, by Vancouver-Richmond in April 2000, and by New Brunswick in August 2000. Consensus case definitions and an operating protocol are used in all participating health regions. Each reported case of hepatitis B or hepatitis C is investigated to obtain relevant clinical information, medical history, and laboratory data so that acute cases can be identified. Further, risk factors are collected from each case through telephone interview. Data from the enhanced surveillance provide national estimates of incidence and transmission patterns and possible changes in such patterns over time[4].

The surveillance for emerging pathogens, through a rapid response surveillance system, is designed to establish databases of participants and banks of blood specimens from these participants, together with informed consent for testing or contact for future testing if there are new or re-emerging bloodborne pathogens. Each time a new pathogen emerges, all participants will be contacted for consent to testing, and the risk of the new pathogen can be assessed promptly[5].

The hepatitis network of hospital-based centres is currently being developed by Canadian hepatologists and infectious disease experts with support from both the Hepatitis C Division and the Blood-Borne Pathogens Division of HC. In addition to providing care and treatment to hepatitis patients it will carry out surveillance for new bloodborne pathogens, follow-up of hepatitis cases to study the natural history of the disease, and education of both professionals and the public.

Targeted surveillance refers to surveillance in specific population groups, locations, or physician practices, for example, among recipients of blood, blood products and transplants; Aboriginal populations; at-risk groups, such as injection drug users, street youth, and inmates; and pregnant women. Since these special population groups are either at increased risk of other diseases, such as AIDS, or are of particular relevance to the mandates of other functions of the government, activities targeting them are often initiated or carried out jointly with different units within and outside of HC. For instance, the Divisions of HIV Epidemiology, Blood-Borne Pathogens, and Hepatitis, Population and Public Health Branch, and the First Nations and Inuit Branch of HC are collaboratively working on surveillance among Aboriginal populations. HC and Correctional Service Canada are working together to propose surveillance activities of bloodborne pathogens among inmates.

Research

The research component of surveillance comprises some activities that do not fall under the above categories but provide important information for risk assessment as well as the prevention and control of bloodborne pathogens. Such activities may include prediction of disease burden, assessment of vertical and sexual transmission of hepatitis C, and cost-benefit analysis of intervention options. The research activities are either carried out by staff from the Blood-Borne Pathogens Division, such as the burden analysis of hepatitis C[6], conducted by university researchers with support from HC, such as the transmission of hepatitis C (in progress), or coordinated by HC but performed by external expert working groups, such as the project on transfusion-transmitted hepatitis C infections[7] and the analysis of hepatitis A vaccination strategies (in progress).

Dissemination

Results from surveillance activities are usually disseminated through reports to collaborators and provinces/territories and through articles either in HC publications or in peer-reviewed journals. The reports in this supplement provide updated information on viral hepatitis and emerging bloodborne pathogens in Canada as well as other issues of particular relevance. Summaries of several expert review articles and a workshop report are also included to aid in the prevention and control practices for viral hepatitis and emerging bloodborne pathogens in this country.

References

1. LCDC. *Hepatitis C – prevention and control: a public health consensus.* CCDR 1999;25S2:1-23.

2. Zou S, Tepper M, Giulivi A. *Current status of hepatitis C in Canada.* Can J Public Health 2000;91(Suppl 1):S10-S15.

3. Doherty J. *Establishing priorities for national communicable disease surveillance.* Can J Infect Dis 2000;11(1):21-4.

4. Zou S, Zhang J, Tepper M et al. *Enhanced surveillance of acute hepatitis B and acute hepatitis C in four health regions in Canada.* Can J Infect Dis 2001 *(in press)*.

5. Zou S, Forrester L, Giulivi A, and the Working Group on Emerging Bloodborne Agents. *Surveillance and risk assessment for emerging bloodborne agents in Canada.* Presented at the 10th International Symposium on Viral Hepatitis and Liver Disease in Atlanta, Georgia, USA (abstract: Antiviral Therapy 2000;5(Suppl 1):G.5).

6. Zou S, Tepper M, El Saadany S. *Prediction of hepatitis C burden in Canada.* Can J Gastroenterol 2000;14(7):575-80.

7. Remis RS, Hogg R, Krahn M et al. *Estimating the number of blood transfusion recipients infected by hepatitis C virus in Canada, 1960-85 and 1990-1992.* Report to the Bloodborne Pathogens Division, Health Canada, 1998 (available on the Health Canada web site at http://www.hc-sc.gc.ca/hpb/lcdc/bid/bbp/annexe.pdf).

Prevention and Control of Viral Hepatitis and Emerging Bloodborne Pathogens in Canada

Shimian Zou, Lianne Vardy, Antonio Giulivi

As with other communicable diseases, prevention and control of viral hepatitis, specifically hepatitis A, B, and C, includes measures for the infected individuals and the pathogen they excrete or carry, interruption of the transmission routes, protection of susceptible individuals, and modification of the social or natural factors that influence these elements. Provinces and territories are responsible for the direct delivery or implementation of such measures, and all jurisdictions have guidance documents governing procedures for investigating identified cases and for other necessary public health responses. HC assists in the formulation of such measures and coordinates activities at the national level.

Prevention and control

In collaboration with the provinces and territories, HC held a consensus conference for hepatitis C in 1998, and recommendations from the conference for prevention and control of hepatitis C were published in 1999[1]. In addition, HC has prepared a series of guidelines for prevention and control of bloodborne pathogens in health care and other settings[2-6]. Professional groups have also issued guidelines, often with support from HC, for matters relevant to the prevention and management of bloodborne infections. These include guidelines from the Canadian Association for Study of the Liver (CASL) on the management of viral hepatitis[7], guidelines from the Society of Obstetricians and Gynecologists of Canada (SOGC) on the management of hepatitis C in pregnant women[8], and the soon to be published guidelines on management of hepatitis C virus (HCV) and HIV co-infection, a joint effort by CASL and the Canadian Infectious Disease Society[9].

Individual measures

Measures for infected individuals involve identification, isolation if necessary, and appropriate treatment and care, which not only help the recovery of the infected but may also reduce the risk of the pathogen being spread to others. For hepatitis B, jurisdictions across the country have introduced prenatal screening. Once a mother is identified as infected, her baby is given hepatitis B immunoglobulin and hepatitis B vaccine immediately after birth[10]. Counseling of infected individuals to prevent further transmission is another component of primary prevention[1].

Targeting the pathogen

Measures targeting the pathogen or the materials that may be contaminated by the pathogen consist of proper handling of contaminated materials and adequate disinfection as well as appropriate hospital infection control practices. These measures are generally part of normal medical and health care procedures. HC, provincial/territorial health authorities, and professional organizations issue guidelines or recommendations from time to time to improve existing practices or initiate new ones

whenever necessary[2-6]. Two articles in this supplement (Germicide Inactivation of Hepatitis B and C Viruses, by Dr. Sattar et al, and Hospital Infection Control and Bloodborne Infective Agents, by Dr. Diaz-Mitoma et al) discuss some of these measures in more detail.

Interrupting transmission

For interruption of hepatitis A transmission, food and water safety is the most important factor. However, prevention of infection during travel or through sharing of contaminated needles for drug injection is also essential[11]. More details can be found in the next article in this supplement, Hepatitis A and its Control. For both hepatitis B and hepatitis C, preventing the initiation of drug injection and establishing harm reduction practices among injection drug users hold the key to effective control of transmission. Furthermore, adequate attention should be paid to sexual and perinatal transmission of hepatitis B and potentially hepatitis C. Details can be found in the articles of this supplement specifically dealing with these diseases.

Nosocomial and occupational transmission of bloodborne pathogens such as hepatitis B and C has been recognized as an important risk to health care workers and patients. Various interventions have been implemented to reduce such risks. Examples include the use of disposable medical instruments, such as needles and syringes, sterilization of non-disposable equipment, routine practices and additional precautions (universal precautions) in the handling of materials potentially contaminated with blood or body fluids, as well as vaccination of health care workers against hepatitis B. HC recently issued a series of guidelines for the prevention and control of nosocomial and occupational transmission of bloodborne pathogens[2-4,6].

Transmission of bloodborne pathogens through blood, blood products, other biological drugs, tissues, and organs is a special type of nosocomial transmission. Although the risk of such transmission has been reduced dramatically thanks to the effective implementation of various measures, including donor selection and blood screening, continuous vigorous safeguarding of these products can never be overemphasized.

Protecting susceptible individuals

Susceptible contacts of infected individuals should be identified through the public health responses (contact tracing), and appropriate measures need to be taken to protect them. Individuals susceptible to hepatitis A[11,12] and hepatitis B[10,13] infection can be protected by passive as well as active immunization. Immunoglobulin preparations specific to hepatitis A or hepatitis B virus are effective against the respective

pathogen and can be used immediately after exposure to obtain prompt, though short-term, protection. Safe and effective vaccines are also available for individuals susceptible to these two pathogens, and various programs exist in different jurisdictions across the country. For instance, universal pre-adolescent vaccination against hepatitis B has been implemented across the country, and HC has initiated a study that is being carried out by an expert working group to assess various strategies for hepatitis A vaccination. In the case of hepatitis C, support for education and harm reduction measures and prevention of injection drug use initiation contribute to the prevention of infection.

Public health responses

Investigation and control of outbreaks or unusual clusters of viral hepatitis are an essential part of public health intervention activities. For hepatitis A, in addition to epidemiologic investigation, vaccination of contacts or community members with or without immunoglobulin is recommended[12].

Measures for the prevention and control of emerging bloodborne pathogens mainly focuses on the development of rapid risk assessment capacities. Once a new or re-emerging bloodborne pathogen is identified and its risk assessed, appropriate public health responses can be taken accordingly to prevent and control its spread. Two articles in this supplement, SEN-V and the Rapid Response Surveillance System, and Cytomegalovirus, Herpesvirus 6, 7 and 8, and Parvovirus B19 in Canada, describe preliminary data or work in progress on new or re-emerging bloodborne pathogens; as well, the potential challenges of xenotransplantation are discussed by Dr. Laderoute.

In addition to primary prevention measures, prevention of disease progression and management of infected cases are also important. For example, hepatitis patients are strongly encouraged to eliminate or reduce the consumption of alcohol[7].

At the population level, various health promotion activities, such as public education and awareness, are essential to effective prevention and control of viral hepatitis and emerging bloodborne pathogens. To know how a disease is caused, transmitted, and influenced and how to prevent or control it is necessary but not sufficient. Equally important is the application of this knowledge for the prevention and control of diseases. For example, there is enough knowledge about hepatitis A virus, its transmission, the risk factors associated with transmission, and the means to protect susceptible individuals; there are also effective and safe immunoglobulin preparations and vaccines for hepatitis A infection. Nevertheless, outbreaks occur yearly in communities and among those exposed to contaminated food or water. For hepatitis C and to a lesser degree hepatitis B,

sharing of contaminated needles through injection drug use is known to account for the majority of infections. However, how to prevent transmission of hepatitis B, hepatitis C, and other bloodborne infections through injection drug use remains a major challenge, which is a current focus.

Nosocomial and occupational exposure to bloodborne pathogens has been reduced significantly in recent years, but the risk is far from eliminated: education of health care professionals

and vigilance on their part are still warranted. More effort is needed in this area to improve the effectiveness of prevention and control activities aimed at viral hepatitis and emerging bloodborne infections. Recently, HC released a supplement issue addressing various aspects of hepatitis C prevention and control[14]. This will serve to assist professionals and the public alike in the fight against the virus, which is already the number one reason for liver transplantation in this country.

References

1. Health Canada. *Hepatitis C – prevention and control: a public health consensus*. CCDR 1999;25S2:1-23.

2. Health Canada. *An integrated protocol to manage health care workers exposed to bloodborne pathogens*. CCDR 1997;23S2:1-16.

3. Health Canada. *Proceedings of the consensus conference on infected health care workers: risk for transmission of bloodborne pathogens*. CCDR 1998;24S4:1-28.

4. Health Canada. *Infection control guidelines: hand washing, cleaning, disinfection and sterilization in health care*. CCDR 1998;24S8:1-55.

5. Health Canada. *Infection control guidelines: infection prevention and control practices for personal services: tattooing, ear/body piercing, and electrolysis*. CCDR 1999;25S3:1-82.

6. Health Canada. *Infection control guidelines: routine practices and additional precautions for preventing the transmission of infection in health care: revision of isolation and precaution techniques*. CCDR 1999;25S4:1-142.

7. Canadian Association for the Study of the Liver. *Canadian consensus conference on the management of viral hepatitis*. Can J Gastroenterol 2000;14(Suppl B):5B-20B.

8. Society of Obstetricians and Gynecologists of Canada. *Clinical guidelines regarding the reproductive care of women living with hepatitis C infection*. Health Canada, 2000.

9. CASL and Canadian Infectious Disease Society. *Management guidelines for the HCV/HIV co-infected adults – recommendations of a multidisplinary expert panel*. Health Canada 2000.

10. National Advisory Committee on Immunization. *Hepatitis B vaccine*. In: *Canadian immunization guide*, 5th edition. Ottawa: Health Canada, 1998:90-102 (Minister of Public Works and Government Services Canada, Cat. No. H49-8/1998E.)

11. National Advisory Committee on Immunization. *Hepatitis A vaccine*. In: *Canadian immunization guide*, 5th edition. Ottawa: Health Canada, 1998:83-89 (Minister of Public Works and Government Services Canada, Cat. No. H49-8/1998E.)

12. National Advisory Committee on Immunization. *Supplementary statement on hepatitis A vaccine*. CCDR 2000;26(ACS-4):12-8.

13. National Advisory Committee on Immunization. *Statement on alternate adolescent schedule for hepatitis B vaccine*. CCDR 2000;26(ACS-5):19.

14. Hepatitis C Division, Health Canada. *Hepatitis C: Canadian perspectives*. Can J Public Health. 2000;91(Suppl 1):S1-S44.

Hepatitis A and Its Control

Jun Wu, Shimian Zou and Antonio Giulivi

Introduction

Infection with the hepatitis A virus (HAV) results in inflammation of the liver and is an important cause of acute jaundice in some age groups. HAV is one of the main causes of hepatitis in humans, accounting for 20%-40% of acute hepatitis in adults. Presentation of hepatitis A infection typically includes flu-like symptoms, which cannot be distinguished from other types of acute hepatitis. The distribution of hepatitis A is geographically related to socioeconomic conditions. Increasing number of studies from around the world suggest that the epidemiologic pattern of hepatitis A is changing where hygienic and socioeconomic conditions are improving. Different countries are responding to these changes by adopting different immunization strategies against HAV. Thus, vaccination programs may be targeted at specific high-risk groups or the entire population. This article reviews recent information on hepatitis A in Canada and in other countries.

Transmission routes

The most common mode of transmission of hepatitis A is via the fecal-oral route, either directly through interpersonal contact or indirectly through ingestion of contaminated food or water. The latter is more common when an outbreak occurs. Risk factors for hepatitis A transmission vary in importance around the world. In developing countries, food-borne or water-borne infections are common, whereas in North America the most commonly identified risk factor is household or sexual exposure to a recent case[1-3]. Overall, individuals at increased risk include residents of communities with high rates of infection, children and staff of day-care centres, staff and residents of long-term care facilities, injection drug users, gay men, and international travellers.

Incidence and prevalence

Hepatitis A may occur either in epidemics or as sporadic cases. In developing countries, the incidence of hepatitis A in adults is relatively low because of exposure to HAV in childhood. In areas of low endemicity, the incidence of HAV infection among young children is low, and the proportion of susceptible individuals, especially young adults, is high. Hepatitis A is the seventh most commonly reported infectious disease in the United States and accounts for as many as 65% of all viral hepatitis cases identified each year. It has been estimated that approximately 150,000 people become infected with HAV and more than 28,000 hepatitis A cases are reported each year in the United States. Data collected over several decades show that hepatitis A incidence peaks cyclically about every 10 years[2]. The highest incidence of hepatitis A is in children: nearly 30% of reported cases occur in children younger than 15 years of age. The risk for susceptible travellers to developing countries

has been estimated at 3-5 per 1,000 per month, higher in those who eat or drink in places with poor hygienic conditions.

Hepatitis A is reportable in Canada. Like most industrialized countries, Canada has a relatively low incidence of hepatitis A: each year 1,000-3,000 cases are reported. It is generally accepted that the true incidence of HAV infection is considerably underestimated as a result of under-reporting of clinical illness and the occurrence of subclinical infections in children[3]. The reported hepatitis A rates vary with age group and sex, rates among males being higher than among females. Since there is no evidence indicating that males are more susceptible to hepatitis A than females[4], differences in exposure factors could be responsible for these higher rates. The rates of reported hepatitis A infection in Canada vary significantly among provinces and territories, the highest rates being observed in British Columbia. Geographic and sex differences suggest the need to determine related risk factors and population subgroups with higher risk of hepatitis A, and to develop vaccination options for particularly "at-risk" groups.

As already indicated, HAV infection is closely associated with socioeconomic and hygienic conditions. As living standards improve, the incidence and prevalence of hepatitis A decline, but at the same time the average age of exposure and subsequent infection increases. These changes in epidemiologic pattern have been taking place around the world in recent decades[5,6] and are important, because clinical severity is directly related to the age of infection. Older age groups experience more severe and prolonged clinical illness. On the other hand, natural immunity in the population as a whole decreases, particularly in children, adolescents, and young adults. As a result, the overall number of susceptible individuals in the population increases, creating the potential for hepatitis A outbreaks to occur.

Studies indicate that immunity to HAV infection occurs in about 3% of Canadian-born pre-adolescents but increases with age, and is over 60% for those 60 years of age and older. The most dramatic increase in the rate of HAV seropositivity has been noted between the 20-29 and 30-39 year age groups, increasing from 25% to 46%[7].

Prevention

Intervention measures include early detection of infected individuals, interruption of transmission, and protection of the susceptible population. The most important prevention measure is interrupting HAV fecal-oral transmission by promoting good personal hygiene, proper food handling practices, and provision of clean drinking water and effective sanitary facilities. Other prevention measures include active immunization with hepatitis A vaccines and passive immunization with immune globulin.

Hepatitis A vaccines contain a killed or inactivated virus. The immunologic response takes about 4 weeks to become established, and antibodies persist for at least 1 year after the first dose. Booster doses, given at 6 months or later, confer long-term immunity[8]. Studies to date indicate that antibodies are sustained for at least 3 years after vaccination[9]. Patients with suppressed immune systems may require more doses of the vaccine than a person with a healthy immune system in order to develop an immunological response.

In Canada, hepatitis A vaccine is currently recommended by the National Advisory Committee for Immunization (NACI) for individuals at increased risk[1]. These include travellers to countries where hepatitis A is endemic; residents of communities with high endemic rates or recurrent outbreaks of HAV; members of the armed forces; emergency relief workers and others likely to be posted abroad at short notice to areas with high rates of HAV infection; residents and staff of institutions for the developmentally challenged, where there is an ongoing problem with HAV transmission; inmates of correctional facilities, in which there is an ongoing problem with HAV infection; people with lifestyle-determined risks of infection, such as intravenous drug use, and men who have sex with men; people with chronic liver disease who may not be at increased risk of infection but are at increased risk of fulminant hepatitis A; and others, such as patients with hemophilia A or B receiving plasma-derived replacement clotting factors, zoo-keepers, veterinarians, certain researchers who handle non-human primates, and certain workers involved in research on hepatitis A virus or production of hepatitis A vaccine.

According to the supplementary statement on hepatitis A vaccine by NACI, in 2000[10], HAV vaccine without immune globulin is the preferred method of post-exposure immunoprophylaxis against this disease, because immune globulin is unlikely to be more effective than HAV vaccine, and is sometimes difficult to obtain. For example, when an outbreak of hepatitis A occurs, an epidemiologic investigation may be initiated to define the scope and cause of the outbreak, and immunization is administered to close contacts of cases as soon as possible to prevent the further spread of infection.

If rapid protection is needed, or active immunization is not suitable or available, human immune globulin is recommended. The efficacy of immune globulin has been shown to be up to 80% to 90% when the product was administered within 2 weeks of exposure[11]. Immune globulin is still the recommended immunoprophylaxis for infants and those who may not

respond fully to the vaccine, e.g. immunocompromised patients.

Future challenges

With the changing epidemiologic pattern of hepatitis A, it is not certain whether vaccination of higher risk groups alone will be sufficient to prevent the transmission of HAV in the general population. The changing dynamics of HAV infection in different populations indicate that continuous study and surveillance are needed to provide evidence for further decision making.

Universal childhood vaccination is not currently recommended in Canada. Before a recommendation for universal vaccination is made, it will be necessary to determine the cost-effectiveness of such a program. This should take into account the effectiveness of the implementation of universal hepatitis B vaccination in all provinces and territories and the availability of combined hepatitis A and hepatitis B vaccines in Canada. A project, initiated and funded by Health Canada, is currently being carried out by an expert working group. The results from this study will contribute to the assessment of whether universal immunization against hepatitis A would provide a cost-effective strategy for preventing infection in Canada.

References

1. *Canadian immunization guide*, 5th edition. Ottawa: Health Canada, 1998 (Minister of Public Works and Government Services Canada, Cat. No. H49-8/1998E).

2. Shapiro CN, Coleman PJ, McQuillan GM et al. *Epidemiology of hepatitis A: seroepidemiology and risk groups in the USA*. Vaccine 1992;10(suppl 1):S59-62.

3. Gust ID. *Epidemiological patterns of hepatitis A in different parts of the world.* Vaccine 1992;10(suppl 1):S56-58.

4. Barros H, Oliveiri F, Miranda H. *A survey on hepatitis A in Portuguese children and adolescents.* J Viral Hepat 1999;6(3):249-53.

5. Sawayama Y, Hayashi J, Ariyama I et al. *A ten year serological survey of hepatitis A, B and C viruses infections in Nepal.* J Epidemiol 1999;9(5):350-54.

6. Beran J, Douda P, Rychly R. *Seroprevalence of viral hepatitis A in the Czech Republic*. Eur J Epidemiol 1999;15(9):805-8.

7. LCDC. *Seroprevalence of hepatitis A antibodies in travellers at the Edmonton travellers' health clinic — Alberta*. CCDR 1995;21(8):65-76.

8. Furesz J, Scheifele DW, Palkonyay L et al. *Safety and effectiveness of the new inactivated hepatitis A virus vaccine.* Can Med Assoc J 1995;152(3):343-8.

9. Berger R, Just M. *Vaccination against hepatitis A: control 3 years after the first vaccination.* Vaccine 1992;10(suppl 1):S295-99.

10. National Advisory Committee of Immunization. *Supplementary statement on hepatitis A vaccine*. CCDR 2000;26(ACS-4):12-18.

11. Mosley JW, Reisler DM, Brachott D et al. *Comparison of two lots of immune serum globulin for prophylaxis of infectious hepatitis*. Am J Epidemiol 1968;87:539-550.

Hepatitis B in Canada

Jun Zhang, Shimian Zou, Antonio Giulivi

The magnitude of hepatitis B infection

Hepatitis B is an important vaccine-preventable infectious disease in Canada. The incidence rate of clinically recognized acute hepatitis B has been estimated to be 2.3 per 100,000, indicating approximately 700 cases a year. The rate is higher among males (3.0 per 100,000) than females (1.5 per 100,000) and peaks for those aged 30-39 (6.1 per 100,000) followed by those aged 15-29 (2.7 per 100,000) and 40-59 (1.8 per 100,000)[1]. Acute hepatitis B virus (HBV) infection is asymptomatic in 90% of infants and young children and in 50% to 70% of adolescents and adults[2]. Infection in infancy and early childhood is strongly associated with progression to chronic HBV infection, contributing to a significant proportion of chronic liver diseases. The prevalence of hepatitis B has been estimated to be between 0.5% and 1.0% with substantial variation due to the heterogeneity of the population[3]. The prevalence of hepatitis B surface antigen (HBsAg) has been reported to be high in immigrant populations (7.4%) and the Inuit (6.9%)[4,5]; intermediate among First Nations (0.3%), adolescents (0.4%), STD clinic visitors (0.3%), and residents of long-term care facilities (0.6%)[6-9]; and low in the general population[10].

Transmission patterns and risk factors

HBV is transmissible through several routes: 1) percutaneous — injection drug use, exposure to contaminated blood or body fluid; 2) sexual — heterosexual or male homosexual activities; 3) vertical — from mother to infant; and 4) horizontal —
between children and household contacts through skin lesions or sharing of blood-contaminated toothbrushes and razors[11].

In Canada, the major risk factors associated with acute hepatitis B infection include injection drug use (IDU) (34%) and heterosexual activities such as having multiple heterosexual partners (24%) and sex with HBV-infected individuals (12%). Drug snorting (2.4%), receipt of blood products (2.4%), male homosexual activity (7.3%), a hepatitis B carrier in the family (2.4%), association with an institution (2.4%), history of hospitalization (7.3%), and surgery (2.4%) or dental visit (2.4%) also account for a proportion of acute cases. In about 27% of acute hepatitis B cases there is failure to identify any risk factor[1]. For remote hepatitis B cases, a high proportion report a history of blood transfusion (10.0%), body piercing (13.8%), and occupational blood contact (5.0%). In comparison with acute cases, a much smaller proportion (11.2%) report IDU as a risk factor.

A recent study conducted by Roy et al[12] showed that injection drug use increased the risk of acquiring hepatitis B by a factor of 4.5 (95% confidence intervals [CI] 1.5-8.3). Although reported as risk factors, tattooing and body piercing did not show a statistically significant association with risk (for tattooing, odds ratios [OR] = 1.6, 95% CI 0.6-4.2; for body piercing, OR = 1.6, 95% CI 0.8-3.6).

Co-infection with other bloodborne pathogens

Co-infection of HBV with other bloodborne pathogens, such as hepatitis C virus (HCV), hepatitis delta virus (HDV), and human immunodeficiency virus (HIV), may affect the natural history or clinical severity of HBV infection[13]. HBV-HCV coinfection seems to increase the severity of chronic hepatitis B, especially the risk of development of hepatocellular carcinoma. HDV infection among hepatitis B patients increases not only the risk of fulminant liver disease but also the risk and severity of chronic hepatitis B. On the other hand, IDUs infected with HIV and HBV are more likely to be asymptomatic but also more likely to become chronic hepatitis B carriers. Hepatitis B carriers infected with HAV are more likely to have fulminant hepatitis.

Public health surveillance

Hepatitis B has been reportable through the National Notifiable Disease Reporting system since 1969[14]. Physicians and laboratories are required to report clinically diagnosed or laboratory-confirmed hepatitis B cases to their local health authority. Cases that meet the hepatitis B surveillance case definition[15] are officially reported to provincial/territorial public health authorities. However, the inconsistent reporting practices across jurisdictions and the lack of information on risk factors have limited the usefulness of the data.

To address the surveillance needs and the information gaps, an enhanced surveillance system for hepatitis B and C has been established in six health units (region or province) and covers about 15% of the Canadian population[1]. The objective is to identify acute hepatitis B and C cases in order to estimate the incidence, monitor incidence trends, and examine risk factors associated with transmission of these acute cases. A consensus protocol and standardized case definitions and questionnaire were developed and are used by all six health regions. Each of the health regions assigns one or more public health nurses as investigator(s). Information on demographic factors, clinical characteristics, and laboratory test results are collected through contact with physicians and laboratories while information on potential risk factors are obtained from a telephone interview with hepatitis B patients. Data from each health unit are sent to HC on a monthly basis to update the estimates of incidence and to evaluate the risk factors.

Prevention and control

To prevent hepatitis B in Canada, a comprehensive strategy has been developed and carried out through various federal/ provincial/territorial programs[16-18]. To prevent vertical transmission, all pregnant women are required to undergo testing for HBsAg during prenatal visits or at the time of delivery. Infants born to HBV-infected mothers should receive hepatitis B immune globulin (HBIg) within 48 hours after birth and a course of three doses of hepatitis B vaccine within 6 months after birth[16], measures that reduce the risk of vertical transmission by more than 90%[19].

HC has developed guidelines for prevention and control of nosocomial hepatitis B[17]. These include, for example, the prevention of HBV transmission from patients to health care workers through education and vaccination; the prevention of HBV transmission from patient to patient through blood donor screening and the use of single-use needles and syringes; and the prevention of HBV transmission from health care workers to patients through medical evaluation, risk assessment, and counselling.

Hepatitis B vaccination has been recommended for all individuals at increased risk, such as homosexual/bisexual men, persons with a recent history of STDs or multiple sexual partners, injection drug users, inmates of correctional facilities, household and sexual contacts of HBV-infected persons, and health care and emergency service workers[18]. A school-based universal hepatitis B vaccination program targeting pre-adolescents aged 9 to 13 has been implemented in all provinces and territories since the early 1990s[16]. The vaccination completion rates are high (91% to 93%)[20], and it is anticipated that the program may prevent 63% of all acute hepatitis B infections and 47% of chronic infections[21]. However, the current program, without complementary infant vaccination, will not prevent the proportion of chronic hepatitis B cases (10% to 15%) that occur as a result of infection in infancy or early childhood[22]. A recent study has suggested that a universal infant hepatitis B vaccination program may be more efficient and cost-effective in stable and low incidence regions than the universal pre-adolescent programs[23]. Currently, a few provinces/territories (including New Brunswick, Northwest Territories, Prince Edward Island and the Yukon Territory) have undertaken a universal infant plus pre-adolescent vaccination program[16].

Although hepatitis B vaccination is safe and effective, the duration of the protection induced by the vaccination is not clear. Increasing evidence, however, suggests long-term protection[24]. More specifically, the antibody response rate has been shown to be high in the general population (90% to 95%) and, as might be expected, is lower in immuno-compromised individuals such as those infected with HIV (50% to 70%), patients with diabetes mellitus (70% to 80%),

and seniors aged 60 and older (50% to 70%)[18]. It has been suggested that hepatitis B vaccine may induce hepatitis B surface antigen mutants or variants[25]. Such variants may not be detected by current test assays, and anti-HBs antibodies induced by HBV vaccine may not protect the host against the infection. It is suggested that such variants may not be detected by current screening methods or may infect individuals who have developed protective levels of anti-HBs after the vaccine[26].

Public health responses following identification of infected individuals may also play an important role in prevention and control. These include tracing and notification of sexual/household contacts and providing passive (HBIg) and active (vaccination) immunization. In addition, strategies that are aimed at public health education and promotion of behaviour change, such as reducing the number of sexual partners and discouraging initial drug use, are warranted.

References

1. Zou S, Zhang J, Tepper M et al. *Enhanced surveillance of acute hepatitis B and acute hepatitis C in four health regions in Canada 1998-1999.* Can J Infect Dis (in press).

2. Shapiro CN. *Epidemiology of hepatitis B.* Pediatr Infect Dis J 1993;12:433-37.

3. Sherman M. *The epidemiology of hepatitis B in Canada.* The Hepatitis Information Network Hepatitis Update. June 1996. http://www.hepnet.com/update5.html

4. Delage G, Montplaisir S, Remy-Prince S et al. *Prevalence of hepatitis B virus infection in pregnant women in the Montreal area.* Can Med Assoc J 1986;134:897-901.

5. Baikie M, Ratnam S, Bryant DG et al. *Epidemiologic features of hepatitis B virus infection in Northern Labrador.* Can Med Assoc J 1989;141:791-95.

6. Martin JD, Mathias RG. *HIV and hepatitis B surveillance in first nations alcohol and drug treatment centers in British Columbia, Canada.* Int J Circumpolar Health 1998;57(Suppl 1):280-84.

7. Dobson S, Scheifele D, Bell A. *Assessment of a universal school-based hepatitis B vaccination program.* JAMA 1995:274:1209-13.

8. Romanowski B, Campbell P. *Sero-epidemiologic study to determine the prevalence and risk of hepatitis B in a Canadian heterosexual sexually transmitted disease population.* Can J Public Health 1994;85:205-07.

9. Simor AW, Gordon M, Bishai FR. *Prevalence of hepatitis B surface antigen, hepatitis C antibody, and HIV-1 antibody among residents of a long-term-care facility.* J Am Geriatr Soc 1992;40:218-20.

10. Glasgow KW, Schabas R, Williams DC et al. *A population-based hepatitis B seroprevalence and risk factor study in a Northern Ontario town.* Can J Public Health 1997;88:87-90.

11. Tepper M, Gully P. *Hepatitis B.* Can Med Assoc J 1997;156:1033-34.

12. Roy E. Haley N, Lemire N et al. *Hepatitis B virus infection among street youths in Montreal.* Can Med Assoc J 1999;161:689-93.

13. Levine OS, Vlahov D, Nelson KE. *Epidemiology of hepatitis B virus infections among injecting drug users: seroprevalence, risk factors, and viral interactions.* Epidemiol Rev 1994;16:418-35.

14. Sockett PN, Garnett MJ, Scott C. *Communicable disease surveillance: notification of infectious disease in Canada.* Can J Infect Dis 1996;7:293-95.

15. Advisory Committee on Epidemiology and Bureau of Communicable Disease Epidemiology. *Canadian Communicable Disease Surveillance System: disease specific case definitions and surveillance methods.* CDWR 1991;17S3:16-7.

16. National Advisory Committee on Immunization. *Canadian national immunization report: program update.* Paediatr Child Health 1999;4(Suppl C):30c-33c.

17. LCDC. *Infection Control Guidelines: preventing the transmission of bloodborne pathogens in health care and public services settings.* CCDR 1997;23S3:1-43.

18. National Advisory Committee on Immunization. *Hepatitis B vaccine.* In: *Canadian immunization guide*, 5th edition. Ottawa: Health Canada, 1998:90-102 (Minister of Public Works and Government Services Canada, Cat. No. H49-8/1998E.)

19. Eleftheriou A, Kalakoutis G, Pavlides N. *Transfusion transmitted viruses in pregnancy.* J Pediatr Endocrinol Metabolism 1998;11:901-14.

20. Munroe V, Pielak K. *A school-based hepatitis B immunization program for British Columbia.* Can J School Health 1996;66:229-32.

21. Krahn M, Guasparini R, Sherman M et al. *Costs and cost-effectiveness of a universal, school-based hepatitis B vaccination program.* Am J Public Health 1998;88:1638-44.

22. Tepper ML. *Universal hepatitis B immunization: young adolescent immunization.* Vaccine 1998;16:S23-S26.

23. Wiebe T, Fergusson P, Horne D et al. *Hepatitis B immunization in a low-incidence province of Canada: comparing alternative strategies.* Med Decis Making 1997;17:472-82.

24. West DJ, Calandra GB. *Vaccine induced immunologic memory for hepatitis B surface antigen: implications for policy on booster vaccination.* Vaccine 1996;14:1019-27.

25. Carman WF, Zanetti AR, Kareylannis P et al. *Vaccine-induced escape mutant of hepatitis B virus.* Lancet 1990;336:325-29.

26. Zuckerman AJ, Zuckerman JN. *Molecular epidemiology of hepatitis B virus mutants.* J Med Virology 1999;58:193-95.

Hepatitis C in Canada

Shimian Zou, Martin Tepper, Antonio Giulivi

Gully and Tepper prepared a concise article on hepatitis C in 1997[1]. An update on the current status of the disease in Canada, based on a recent review by the authors[2] and on new information, is presented here.

It is estimated that approximately 3% of the world's population, or as many as 170 million persons worldwide, are infected with HCV. The virus is a member of the flaviviridae family with a genome of single-stranded RNA. Various genotypes exist in different regions of the world. So far, six major genotypes have been isolated: genotypes 1-3 have been described worldwide, genotypes 4 and 5 principally in Africa, and genotype 6 primarily in Asia. In Canada, the major genotypes are 1, 2, and 3, although genotype 1 is predominant.

A key feature of HCV infection is the high frequency (75% to 85%) with which acute infection progresses to chronic infection. Available studies of hepatitis C infection have shown that the disease has a protracted course and serious sequelae may not appear until decades after initial infection. Infection by HCV does not seem to induce a protective humoral response, but it is becoming clear that some infected individuals do recover from their infection.

Hepatitis C is transmitted through blood or body fluids contaminated with the virus. The most important risk factor associated with transmission of HCV is the sharing of drug injection equipment. Vertical and sexual transmission can occur but are inefficient. Inapparent parenteral exposure, such as tattooing, body piercing, and sharing of personal hygiene items, are presumed to be risk factors only if the instruments or items for such activities are contaminated with blood or body fluids. Although historically important, the risk associated with blood transfusion and the use of blood products has been markedly reduced in most developed countries through screening of blood donations.

Hepatitis C prevalence

In Canada, reporting of hepatitis C started in British Columbia in 1992, and gradually more provinces began to report the disease (data source: Division of Surveillance, Health Canada). Although there has been an exponential increase in the number of reported cases over time, this is primarily a result of increasing recognition and reporting of remotely acquired cases as opposed to an epidemic of new infections[2].

It has been estimated that the prevalence of anti-HCV positivity is approximately 0.8% (0.68% to 0.94%) in Canada, 0.96% in males and 0.53% in females[3]. According to seropositivity rates for first time blood donors in 1997 (Canadian Red Cross: unpublished data), there are evident differences among the provinces, B.C. having the highest seropositive rate (0.274%) and Newfoundland the lowest (0.0%).

The prevalence of HCV infection is much higher in certain at-risk population groups in Canada. For example, Strathdee et al[4] showed that 88% of 1,006 injection drug users in

Vancouver who had injected illicit drugs in the previous month were positive for anti-HCV. Inmates in prisons were found to have anti-HCV positive rates in the range of 28% to 40%[5,6]. A study of 437 street youth in Montreal indicated a prevalence of 12.6% (Roy et al, Hepatitis B and C among street youth in Montreal - final report, 1997) whereas another study of street youth in Ottawa showed a lower prevalence, of 4%[7]. Finally, in a northern Alberta dialysis population, the prevalence of hepatitis C infection was 6.5%[8].

According to data from the enhanced sentinel health unit surveillance in Edmonton, Calgary, Winnipeg, and Ottawa-Carleton in 1998-1999, the incidence rate of clinically recognized acute hepatitis C (with symptoms, elevated levels of liver enzymes, and positive anti-HCV test results) was 2.9 per 100,000 person years[9]. Males had higher incidence rates than females except in the 15-29 age group. The incidence of acute hepatitis C peaked at 30-39 years of age for males and 15-29 years for females.

Risk factors

A few Canadian studies have looked at transmission patterns and risk factors for hepatitis C. In a report by Scully et al[10] of a series of 63 consecutive patients, 43% of infections could be attributed to injection drug use (IDU) and 33% to blood use. Among 54 cases reported in Prince Edward Island from 1991 to 1995 and followed up by the Chief Medical Officer of Health, 46% were attributed to IDU, 39% to blood use, and 6% to both; for 9% a risk factor was not identified[11]. In the Capital Regional District, B.C., of 698 anti-HCV positive cases in the general population reported to the public health department in 1995 and 1996, 69.6% admitted to IDU and 16% to receipt of blood (Health Canada, unpublished data).

Enhanced surveillance in the four health units in 1998-1999 identified 102 acute cases of hepatitis C, of which 72 (71%) were asked about a history of risk factors during the 6 months before the onset of the disease[9]. Of the 57 acute hepatitis C cases reporting one or more risk factors, 36 (63%) revealed a history of IDU, among whom 28 (78%) reported sharing needles. Sex with HCV-infected individuals was identified as a risk factor for only 3.5% (2/57) of cases. Clearly, IDU is the single most important route of HCV transmission currently in Canada, accounting for at least 60% of all HCV transmissions.

Prevention and control

Modelling of the estimated increase in the burden of sequelae specifically related to HCV in Canada between 1998 and 2008 predicts that the number of prevalent cirrhosis cases will almost double (increasing by 92%); the number of prevalent cases of liver failure and hepatocellular carcinoma will increase by 126% and 102% respectively; and the number of liver deaths will increase by 126%[12]. These results highlight the importance of the control of disease progression in HCV-infected persons in addition to the primary prevention of hepatitis C infections in this country.

Prevention and control of hepatitis C involves prevention of HCV infection, slowing disease progression, and reducing the likelihood of premature death. In October 1998, Health Canada held a national consensus conference in Ottawa: *Hepatitis C - Prevention and Control: A Public Health Consensus,* and a report was published[13] that provides a general guide for activities to be used in the prevention and control of hepatitis C.

No vaccine has as yet been developed for this infection; hence, prevention relies primarily on the successful interruption of viral transmission. This mainly involves preventing very high-risk behaviours, such as the sharing of needles and other IDU gear. Prevention of transmission from blood or blood components, organs, tissues, or semen and through unsafe medical or health care practices and contaminated personal hygiene items is also important.

Efforts should be made on different fronts to reduce the transmission of HCV and other bloodborne pathogens among injection drug users[13]. These include prevention of initiation, harm reduction among illicit drug users, programs targeting special population groups at higher risk for IDU and hepatitis C, such as street youth, and research to explore new ways to contain the spread of HCV through illicit drug use.

Although the risk associated with blood, blood components and blood products is currently very low (< 1/100,000), ensuring the highest safety possible of these products is essential. Guidelines have been prepared for nosocomial, occupational, and other inapparent parenteral transmission routes of HCV[14-18]. Counseling of anti-HCV positive persons to prevent further transmission is another component of primary prevention. HCV-infected women of childbearing age should be informed that there is a risk of transmission to any infants born, that the risk increases if a woman is infected with both HIV and HCV, and that the infants should be tested for infection and managed appropriately[13]. HCV-infected persons should not share their personal hygiene items. Household contacts should take "common sense measures" to protect themselves from exposure to the blood of an HCV-infected person. Although the risk may be low, HCV can be transmitted through sexual activities, especially with risky

sexual behaviours such as unprotected sex with multiple partners.

Prevention of disease progression and management of hepatitis C cases include reduction of consumption of alcohol, consideration of vaccination against other hepatitis viruses such as HAV, and treatment with interferon and ribavirin. The CASL has prepared a guideline for the clinical management of hepatitis C cases[19].

References

1. Gully PR, Tepper ML. *Hepatitis C*. Can Med Assoc J 1997;156(10):1427-30.
2. Zou S, Tepper ML, Giulivi A. *Current status of hepatitis C in Canada*. Can J Public Health 2000;91(Suppl 1):S10-S15.
3. Remis R, Hogg R, Krahn MD et al. *Estimating the number of blood transfusion recipients infected by hepatitis C virus in Canada, 1960-85 and 1990-92*. Report to Health Canada, June 1998.
4. Strathdee SA, Patrick DM, Currie SL et al. *Needle exchange is not enough: lessons from the Vancouver injecting drug use study*. AIDS 1997;11(8):F59-F65.
5. Ford PM, White C, Kaufmann H et al. *Voluntary anonymous linked study of the prevalence of HIV infection and hepatitis C among inmates in a Canadian federal penitentiary for women*. Can Med Assoc J 1995;153(11):1605-09.
6. Prefontaine RG, Chaudhary RK. *Seroepidemiologic study of hepatitis B and C viruses in federal correctional institutions in British Columbia*. CDWR 1990;16:265-66.
7. Slinger R, El Saadany S, Tepper M et al. *Seroprevalence of and risk factors for hepatitis C and hepatitis B in street youth in Ottawa, Canada*. Paediatr Child Health 1999;4(Suppl B):48B.
8. Sandhu J, Preiksaitis JK, Campbell PM et al. *Hepatitis C prevalence and risk factors in the northern Alberta dialysis population*. Am J Epidemiol 1999;150(1):58-66.
9. Zou S, Zhang J, Tepper M et al. *Enhanced surveillance of acute hepatitis B and acute hepatitis C in four health regions in Canada*. Can J Infect Dis 2001 *(in press)*.
10. Scully LJ, Mitchell S, Gill P. *Clinical and epidemiological characteristics of hepatitis C in a gastroenterology/hepatology practice in Ottawa*. Can Med Assoc J 1993;148:1173-77.
11. Stratton E, Sweet L, Latorraca-Walsh A et al. *Hepatitis C in Prince Edward Island: a descriptive review of reported cases, 1990-1995*. Can J Public Health 1997;88(2):91-4.
12. Zou S, Tepper ML, El Saadany S. *Prediction of hepatitis C burden in Canada*. Can J Gastroenterol 2000;14:575-80.
13. Health Canada. *Hepatitis C – prevention and control: a public health consensus*. CCDR 1999;25S2:1-25.
14. Health Canada. *An integrated protocol to manage health care workers exposed to bloodborne pathogens*. CCDR 1997;23S2:1-16.
15. Health Canada. *Proceedings of the consensus conference on infected health care workers: risk for transmission of bloodborne pathogens*. CCDR 1998;24S4:1-28.
16. Health Canada. *Infection control guidelines: hand washing, cleaning, disinfection and sterilization in health care*. CCDR 1998;24S8:1-55.
17. Health Canada. *Infection control guidelines: infection prevention and control practices for personal services: tattooing, ear/body piercing, and electrolysis*. CCDR 1999;25S3:1-82.
18. Health Canada. *Infection control guidelines: routine practices and additional precautions for preventing the transmission of infection in health care: revision of isolation and precaution techniques*. CCDR 1999;25S4:1-142.
19. Canadian Association for Study of the Liver (CASL). *Current issues in the management of viral hepatitis*. Can J Gastroenterol 2000;14(Suppl B):5B-20B.

HGV and Implications for Blood Safety Policies in Canada

Steven Kleinman

Hepatitis G virus (HGV) was discovered in 1996, and the viral genome was cloned from a patient with chronic non-A-E hepatitis[1]. At about the same time, another group of investigators identified a similar agent from an African patient with acute non-A-E hepatitis, which they termed GBV-C[2]. Subsequently, numerous isolates have been cloned and sequenced. The virus is described in the literature by one of several names: HGV, GBV C, and HGV/GBV-C. For simplicity, this report will refer to the virus as HGV.

HGV is a single-stranded RNA (positive-stranded, 9300 nucleotides) virus belonging to the Flaviviridae family[3]. HGV RNA in plasma or serum is detected using a reverse transcriptase PCR (polymerase chain reaction) assay[1-4]. After HGV RNA PCR assays became available, a test to detect the host immune system response to HGV infection was developed. This assay detects antibody to an HGV envelope protein, E2[4]. It has now been well documented that anti-E2 is a marker that appears when the host successfully clears HGV infection[4-6].

HGV prevalence

The prevalence of HGV RNA in blood donors has been relatively consistent internationally, ranging from approximately 1% to 4% according to data reported from the U.S. and multiple countries in Europe and Asia[4]. Unpublished data indicate an HGV RNA positive rate of approximately 2% in Canadian blood donors (G. Sher, Canadian Blood Services, Ottawa: personal communication, 2000). This rate of HGV

viremia in blood donors in developed countries is much higher than that for known transfusion-transmitted pathogenic agents. Rates of anti-E2, indicating resolved HGV infection, are much higher, ranging from 3% to 14% in these same studies[4].

The HGV viremia rates in donors with normal and elevated levels of alanine aminotransferase are similar, suggesting that the large majority of HGV infections do not result in elevations of this liver enzyme[1,5,6]. The rate of HGV infection is higher in blood donors who are also positive for HCV, suggesting common risk factors and routes of transmission for these two viruses.

HGV transmission by transfusion of blood components has been definitively established. Studies also provide evidence of HGV transmission by transfusion of non-virally inactivated Factor VIII concentrate[4,7]. In contrast, HGV detection rates in recipients of virally inactivated Factor VIII concentrates have been very low or zero, indicating that viral inactivation methods are effective against HGV[4]. It appears that immunoglobulin given intravenously transmits HGV infrequently, if at all, and that lack of transmission is explained either by the partitioning of the virus into other plasma fractions during manufacture, the presence of HGV neutralizing antibody in immunoglobulin preparations, the effectiveness of viral inactivation techniques, or a combination of these factors. There are no reports of HGV transmission from intramuscular administration of immunoglobulin[8,9].

Very high rates of HGV infection (75% to 95%) have been demonstrated in injection drug users, indicating parenteral transmission through shared injection drug equipment[4,10]. Studies of patients in surgical and dialysis units suggest that nosocomial transmission can occur[4,11]. Vertical (maternal-child) transmission of HGV has been well documented. Transmission rates range from 60% to 80% in HGV RNA positive mothers infected with HGV alone as well as in mothers coinfected with HCV[12]. Although data concerning sexual transmission are more limited, studies provide evidence that such transmission occurs[13].

The high rate of maternal-infant transmission and the relatively high rate of sexual transmission may explain the fairly high prevalence of HGV among blood donors. Unlike HCV, specific parenteral risk factors (such as injection drug use or transfusion) are absent in many HGV positive donors[4].

HGV RNA appears shortly after infection with HGV, becoming detectable as soon as 2 to 3 weeks after exposure. In 50% to 75% of cases, the infected person successfully clears HGV infection. In these cases, HGV RNA disappears as anti-E2 becomes detectable over an interval of several months. Seroconversion to E2 is evidence of past HGV infection and confers immunity against further infection with HGV. In a minority of cases, HGV infection becomes persistent for many years. Several studies have suggested that younger age at time of infection and concurrent or ongoing immunosuppression may favour persistent infection[4,14].

HGV as a cause of liver disease

The role of HGV as an etiologic agent of liver disease and its possible role in exacerbating pre-existing or coexisting liver disease have been extensively investigated[4]. In each clinical situation studied, the overwhelming majority of evidence has established that HGV has no pathologic effects on the liver.

The available data suggest that HGV does not cause acute non-A-E viral hepatitis at all or, if it does, that this is a rare occurrence; HGV is not a significant cause of fulminant hepatic failure and appears to have no causative role in this condition; the extent and severity of liver disease in HGV-infected cryptogenic cases are no different than in cryptogenic cases without HGV infection; HGV infection is not a contributing agent to the development of hepatocellular carcinoma (HCC); pre-existing HGV infection or HGV infection acquired at the time of transplantation does not affect the incidence of post-transplant hepatitis or other clinical sequelae[4].

Numerous studies have documented that the clinical course, biochemical profile, and histopathology of HCV infected individuals with or without HGV coinfection are similar[4,15]. In addition, the response of HGV/HCV coinfected patients to interferon therapy is no different from that of HCV infected persons without HGV infection[4,15]. Interferon therapy for HCV infection results in suppression of HGV RNA, which tends to reappear when interferon therapy is discontinued.

It is well known that aplastic anemia may develop in association with viral hepatitis of unknown etiology. The available data indicate that HGV infection in patients with aplastic anemia is a result of treatment for aplastic anemia and that HGV is not the causative agent of this disease[4,7].

Because of the known association between HCV and mixed cryoglobulinemia, this phenomenon was studied with respect to HGV infection. The prevalence of HGV in this patient group was no higher than in controls, suggesting no role for HGV in the pathogenesis of mixed cryoglobulinemia[16].

Longitudinal studies with follow-up intervals in the range of 1 to 6 years in cohorts of patients with thalassemia, patients with hemophilia, other transfusion recipients, and hemodialysis patients have failed to demonstrate any adverse long-term sequelae of HGV infection[14,17-20]. Specifically, manifestations of liver disease in HGV-infected patients were no different from those in similar patients not infected with HGV.

HGV infection has not been associated with any adverse effects on graft or patient survival in patients undergoing liver transplantation; similar results have been obtained in renal and heart transplantation. Furthermore, neither patient category showed an increased incidence of post-transplant liver disease[21,22]. There is a single case report of a renal transplant recipient who tested HGV RNA positive and developed membranoproliferative glomerulonephritis with HGV deposition in glomeruli and tubules 7 years after transplantation[23]. In bone marrow transplantation, studies have shown that the rate of acute graft-versus-host disease (GVHD), chronic GVHD, veno-occlusive disease, and hepatic dysfunction are not influenced by the presence of HGV infection[4,24]. In studies of patients with primary immunodeficiency, HGV infection did not contribute to the development of chronic hepatitis[25]. Two studies have demonstrated that the rate of progression of HIV infection is slower in HIV-infected persons who are coinfected with HGV than in those who are not. There is as yet no biological explanation for this apparent protective effect of HGV on the progression of HIV disease[26,27].

In summary, there are numerous well-designed, controlled studies documenting that HGV does not cause any form of liver disease. In contrast, there are a few case reports and small studies suggesting a possible association of HGV with

liver pathology or clinical disease. Despite suggested associations, these studies have not established causation; furthermore, the findings have not been duplicated by other studies in similar population groups.

Similarly, there is now a large body of evidence that HGV does not cause other types of disease, even in immunosuppressed populations. However, since these studies are less numerous, this conclusion may be less definitive than the conclusion regarding liver disease. It is, of course, virtually impossible to conclusively prove that a specific infectious agent (e.g. HGV) does not cause or contribute to the development of any disease. Therefore, the more conservative conclusion based on the current data would be that if HGV does cause disease of the liver or other organ systems, it does so only in a very small number of infected persons[4].

Studies have been conducted to determine whether HGV infects and replicates in liver or other cells[28-35]. These data indicate that it is highly unlikely that HGV replicates in or infects hepatocytes. The site of HGV replication may be in mononuclear cells in bone marrow or spleen, but not in peripheral blood mononuclear cells. Candidate cell types for HGV replication include stem cells, B-cells, and monocytes/macrophages; T-cells, which are abundant in lymph nodes, have been excluded as the likely replication site. Further work will be needed to verify these findings.

HGV and issues of blood donor screening

HGV is common in blood donors (1% to 4% positive for HGV RNA) and in the general population. It is transmitted by transfusion. There is a high rate of HGV infection in heavily transfused patient populations. Although most of these infections are self-limited and are cleared by the infected person, a smaller number of infections are chronic and may persist for decades. Because of the high prevalence in blood donors and likely presence in the blood supply for several decades, it is likely that hundreds of thousands of people worldwide have acquired HGV infection by transfusion. Nevertheless, no adverse effects have been documented in the population of transfusion recipients at large or in specially studied populations of prospectively enrolled transfusion recipients, patients with thalassemia, and patients with hemophilia.

Despite extensive study, HGV has not been identified as a causative agent of any type of liver disease or any other known clinical condition. Although it is not possible to completely rule out any association between HGV infection and clinical disease, if such an association exists it must be extremely infrequent or it would have been recognized during this recent period of intense scrutiny. The molecular biology data showing lack of hepatotropism are consistent with the clinical data showing lack of hepatic disease, and this strongly supports the contention that HGV is not a hepatotropic virus and was inappropriately designated with the name of "hepatitis G virus".

These data have prompted almost all transfusion medicine experts to argue against the need for HGV screening of donated blood, and currently there are no countries that screen the blood supply for HGV[4].

References

1. Linnen J, Wages J, Zhang-Keck ZY et al. *Molecular cloning and disease association of hepatitis G virus: a transfusion-transmissible agent.* Science 1996;271:505-08.

2. Simons JN, Leary TP, Dawson GJ et al. *Isolation of novel virus-like sequences associated with human hepatitis.* Nat Med 1995;1:564-69.

3. Muerhoff AS, Simons JN, Leary TP et al. *Sequence heterogeneity within the 5'– terminal region of the hepatitis GB virus C genome and evidence for genotypes.* J Hepatol 1996;25:379-84.

4. Kleiman S. *Hepatitis G virus – a report to Health Canada.* Ottawa, 1999.

5. Nordbo SA, Krokstad S, Winge P et al. *Prevalence of GB virus C (also called hepatitis G virus) markers in Norwegian blood donors.* J Clin Microbiol 2000;38:2584-90.

6. Ross RS, Viazov S, Schmitt U. *Distinct prevalence of antibodies to the E2 protein of GB virus C/hepatitis G virus in different parts of the world.* J Med Virol 1998;54:103-06.

7. Alter HJ. *G-pers creepers, where'd you get those papers? A reassessment of the literature on the hepatitis G virus.* Transfusion 1997;37:569-72.

8. Cristiano K, Pisani G, Wirz M et al. *Hepatitis G virus in intramuscular immunoglobulin products manufactured in Europe* (letter). Transfusion 1999;39:428.

9. Cristiano K, Pisani G, Wirz M et al. *Do antibodies to the hepatitis G virus E2 antigen in immunoglobulin products reduce infectivity?* (letter) Transfusion 1999;39:1271-72.

10. Thomas DL, Vlahov D, Alter HJ et al. *Association of antibody to GB virus C (hepatitis G virus) with viral clearance and protection from reinfection.* J Infect Dis 1998;177:539-42.

11. Lunel F, Frangeul L, Chuteau C et al. *Transfusion-associated or nosocomial hepatitis G infection in patients undergoing surgery.* Transfusion 1998;38:1097-103.

12. Zanetti AR, Tanzi E, Romano L et al. *Multicenter trial on mother-to-infant transmission of GBV-C virus. The Lombardy Study Group on vertical/perinatal hepatitis viruses transmission.* J Med Virol 1998;54:107-12.

13. Yeo AE, Matsumoto A, Shih JW et al. *Prevalence of hepatitis G virus in patients with hemophilia and their steady female sexual partners.* Sex Transm Dis 2000;27:178-82.

14. Woelfe J, Berg T, Keller KM et al. *Persistent hepatitis G virus infection after neonatal transfusion*. J Pediatr Gastroenterol Nutr 1998;26:402-07.

15. Pawlotsky JM, Roudat-Thoraval F, Muerhoff AS et al. *GB virus C (GBV-C) infection in patients with chronic hepatitis C. Influence on liver disease and on hepatitis virus behavior: effect of interferon alpha therapy*. J Med Virol 1998;54:26-37.

16. Crovatto M, Mazzaro C, Mishiro S et al. *GBV-C/HGV and HCV infection in mixed cryoglobulinaemia*. Br J Haematol 1999;106:510-04.

17. Wang JT, Chen PJ, Liu DP et al. *Prevalence and infectivity of hepatitis G virus and its strain variant, the GB agent, in volunteer blood donors in Taiwan*. Transfusion 1998;38:290-95.

18. Hanley JP, Jarvis LM, Hayes PC et al. *Patterns of hepatitis G viremia and liver disease in haemophiliacs previously exposed to non-virus inactivated coagulation factor concentrates.* Thromb Haemost 1998;79:291-95.

19. Prati D, Zanella A, Rebulla P et al. *The incidence and natural course of transfusion-associated GB virus C/hepatitis G virus in a cohort of thalassemic patients. The Cooley Cooperative Group.* Blood 1998;91:774-77.

20. Desassis JF, Laperche S, Girault A et al. *Prevalence of present and past hepatitis G virus infection in a French haemodialysis centre.* Nephrol Dial Transplant 1999;14:2692-97.

21. Fabrizi F, Martin P. *GBV-C/HGV infection in end-stage renal disease*. J Nephrol 1999;12:131-39.

22. Kallinowski B, Janicki M, Seelig R et al. *Clinical relevance of hepatitis G virus (HGV) infection in heart transplant patients*. J Heart Lung Transplant 1999;18:190-93.

23. Berthoux P, Laurent B, Cecillon S et al. *Membranoproliferative glomerulonephritis with subendothelial deposits (type 1) associated with hepatitis G virus infection in a renal transplant recipient*. Am J Nephrol 1999;19:513-18.

24. Maruta A, Tanabe J, Hashimoto C et al. *Long-term liver function of recipients with hepatitis G virus infection after bone marrow transplantation*. Bone Marrow Transplant 1999; 24:359-63.

25. Morris A, Webster AD, Brown D et al. *GB virus C infection in patients with primary antibody deficiency*. J Infect Dis 1998;177:1719-22.

26. Yeo AE, Matsumoto A, Hisada M et al. *Effect of hepatitis G virus infection on progression of HIV infection in patients with hemophilia. Multicenter Hemophilia Cohort Study.* Ann Intern Med 2000;132:959-63.

27. Lefrere JJ, Roudot-Thoraval F, Morand-Joubert L et al. *Carriage of GB virus C/hepatitis G virus RNA is associated with a slower immunologic, virologic, and clinical progression of human immunodeficiency virus disease in coinfected persons.* J Infect Dis 1999;179:783-89.

28. Tucker TJ, Smuts HE, Eedes C et al. *Evidence that the GBV-C/hepatitis G virus is primarily a lymphotropic virus*. J Med Virol 2000;61:52-8.

29. Kao JH, Chen W, Chen PJ et al. *Liver and peripheral blood mononuclear cells are not major sites for GB virus-C/hepatitis G virus replication*. Arch Virol 1999;144:2173-83.

30. Laras A, Zacharakis G, Hadziyannis SJ. *Absence of the negative strand of GBV-C/HGV RNA from the liver*. J Hepatol 1999;30:383-88.

31. Kobayashi M, Tanaka E, Nakayama J et al. *Detection of GB virus-C/hepatitis G virus genome in peripheral blood mononuclear cells and liver tissue*. J Med Virol 1999;57:114-21.

32. Pessoa MG, Terrault NA, Detmer J et al. *Quantitation of G and C virus in the liver: evidence that hepatitis G is not hepatotropic.* Hepatology 1998;27:877-80.

33. Fan X, Xu Y, Solomon H et al. *Is hepatitis G/GB virus-C virus hepatotropic? Detection of hepatitis G/GB virus-C viral RNA in liver and serum*. J Med Virol 1999;58:160-64.

34. Radkowski M, Wang LF, Cianciara J et al. *Analysis of hepatitis G virus/GB virus C quasispecies and replication sites in human subjects.* Biochem Biophys Res Comm 1999;258:296-99.

35. Radkowski M, Kubicka J, Kisiel E et al. *Detection of active hepatitis C virus and hepatitis G virus/GB virus C replication in bone marrow in human subjects*. Blood 2000;95:3986-89.

SEN Virus and the Rapid Response Surveillance System

Leslie Forrester, Shimian Zou, Antonio Giulivi

Between 80% and 90% of all community-acquired or transfusion-associated viral hepatitis is caused by hepatitis viruses A, B, C, D, and E, leaving 10% to 20% currently unaccounted for. Hepatitis of unknown etiologic origin is typically referred to as non-A non-E, or NANE hepatitis, and researchers in the field are working to identify the cause(s). Recent advances in molecular biology have led to the discovery of several new viruses. In the past 5 years, three candidate viruses for NANE hepatitis have been discovered, namely, GB virus-C/hepatitis G virus (GBV-C/HGV), TT virus, and the more recently discovered SEN virus (SEN-V). The present article summarizes what is currently known about SEN-V and describes the surveillance system that HC has put in place to address new and re-emerging bloodborne pathogens.

The discovery of SEN-V by an Italian research group, led by Dr. Daniele Primi, was announced at a press conference in July 1999 without the support of any published empirical data[1]. To date, there is only one known published, peer-reviewed article on SEN-V[2]. Besides that, the only information available to the scientific community has been in the form of a few press releases and conference abstracts, and the supporting documentation for a patent application for the identification of SEN-V genotypes. Until such time as more data are published in the peer-reviewed scientific literature, the information on SEN-V contained in this and other reports should be considered preliminary.

SEN-V is named after the initials of the patient from whom the virus was isolated. SEN-V is a circular, single stranded DNA virus with an average length of 3,900 nucleotides[2]. Sequence and physical studies suggest that it is an unenveloped virus[3]. To date, standard sequencing procedures have revealed eight, highly divergent genotypes: SEN-V A through H. All eight members of the SEN-V family are encoded for at least three open reading frames (ORFs) that code for one protein each[4]. The length of the ORFs can vary with each SEN V genotype[4]. In terms of diagnostic methodology, general PCR primers able to detect the presence of any member of the SEN-V family as well as specific primers for each subtype have been developed[2-5]. Further to this, a specific PCR serum assay has been developed to obtain epidemiologic information on the prevalence and distribution of SEN-V in the general population as well as in specific patient population groups[2]. Studies employing PCR DNA detection indicate that SEN-V exists in the blood and is transmitted parenterally[2,3,6,7].

SEN-V and hepatitis

Preliminary results suggest that SEN-V is associated with transfusion-associated non-A to non-E hepatitis. In the first peer-reviewed publication on SEN-V, Umemura et al.[2] reported a significantly higher incidence of SEN-V infection among transfused (30%; 86 of 286) than non-transfused controls (3%; 3 of 97). Moreover, a significant association

was observed between the number of units transfused and transfusion risk, and donor-recipient linkage was confirmed by sequence homology[2]. In collaboration with the National Institutes of Health and others, the Italian research group has also tested blood samples from normal blood donors and patients, with or without hepatitis, followed prospectively after open-heart surgery[6]. The results showed a prevalence of 2.1% (5 of 243) among normal blood donors from the United States, and 3.8% (10 of 262) in patients prior to transfusion or surgery. Excluding those with prior infection, a significantly higher proportion of transfused (40.0%) than non-transfused patients (3.1%) developed SEN-V infection following surgery (p < 0.0001). Among transfused patients without pre-existing viremia, newly acquired SEN-V infection was detected in 83% of patients (10 of 12) who developed NANE hepatitis, 41% of patients (20 of 49) with chronic hepatitis C and 34% of patients (32 of 94) who did not develop hepatitis[6]. Although the incidence of SEN-V infection was significantly higher in the NANE patient group than among those patients who did not develop hepatitis (p < 0.003), this does not necessarily imply that SEN-V causes hepatitis. The fact remains that 34% of individuals who did not develop hepatitis were SEN-V positive. As a first step towards establishing causality, studies demonstrating intrahepatic replication are required[6].

In a study examining the incidence of SEN-V infection among 143 HIV positive and 80 HCV/HBV positive patients, Pirovano et al.[7] found a similar incidence of SEN-V in the two patient groups, with rates of 45% and 47% respectively. However, when examined closer, it was found that the prevalence of SEN-V was significantly higher (p < 0.0001) among injection drug users (IDUs) (68.6%) than homo/heterosexual HIV positive individuals (28.9%), suggesting the possibility of effective transmission through contaminated needles or syringes. It is still not known whether the virus can be spread through ways other than blood and injections, such as through nosocomial or sexual transmission.

Finally, in a cross-sectional study examining the seroprevalence of SEN-V in a sample of liver transplant recipients, Yoshida et al. found that SEN-V infection was common, with 51.7% or 30 of 58 patients testing positive[8]. No significant differences were observed with regard to the primary indication for transplantation. Further to this, no biochemical differences attributed to SEN-V were detected. The authors concluded that although SEN-V was highly prevalent among liver transplant recipients it did not appear to be associated with graft dysfunction[8].

Rapid Response Surveillance System

Since SEN-V exists in the blood and preliminary evidence indicates that it is prevalent in patients with liver diseases, the virus was determined to pose a potential threat to the health of Canadians. In response, HC formed a special working group to assess the risk of SEN-V in Canada. To assess the level of risk associated with a virus such as SEN-V, it is necessary to determine the level of infection in different population groups, to follow up the outcomes of infection, and to explore factors that may put Canadians at risk of infection. Timely risk assessment, however, usually requires the testing of blood specimens as soon as possible. Since it is not possible to test stored specimens for this purpose because of a lack of consent for the testing of any new pathogen, it became imperative to establish a Rapid Response Surveillance System for new and re-emerging bloodborne pathogens. Specifically, the system was designed to collect blood specimens for the identification of SEN-V as well as relevant clinical and epidemiologic information for the assessment of risk associated with the virus[9]. To ensure the confidentiality and anonymity of the information collected, HC does not receive any personal information on the patients recruited into the system through participating physicians. Rather, blood specimens are coded with a personal identification (PID) number, permitting specimens to be linked anonymously to the clinical and epidemiologic data collected by way of a questionnaire.

Two categories of individuals are the target population for the system: patients visiting family physicians for routine check-ups and/or the treatment of common conditions, and patients in special groups, such as those with viral hepatitis of unknown cause, patients with hemophilia, and other groups with risk factors that potentially put them at higher risk for bloodborne infection. Surveillance results from the first category of patients will be used to assess the risk of the new pathogen in the general Canadian population, whereas results from the latter category will be important for assessing the clinical relevance of the pathogen as well as the risk associated with specific subgroups.

The Rapid Response Surveillance System is composed of the Division of Blood-Borne Pathogens as the national coordinator, health care professional groups as collaborators and facilitators, members of these groups as investigators and recruiters, and provincial/territorial public health agencies as consultants. Currently, the surveillance network includes the Canadian Science Centre for Human and Animal Health in Winnipeg; the Liver Diseases Unit of the University of Manitoba; the Cadham Provincial Laboratory of Manitoba; the British Columbia Transplant Society; the Canadian Association of

Hepatologists (Canadian Association for Study of the Liver); the College of Family Physicians of Canada; and the Canadian Hemophiliac Physicians Association.

Although initiated in response to SEN-V, once fully established the system will be able to respond rapidly to determine the risk associated with any new or re-emerging bloodborne pathogen: in addition to the collection and testing of blood specimens (with specific consent for SEN-V) as well as the collection of relevant information, aliquots of the blood specimens are being stored in centralized laboratories (with consent) for future testing. Should a new bloodborne pathogen be identified, the individuals whose blood is in storage will be contacted through their physicians for specific consent for testing. If granted, their specimens will be tested immediately for the new pathogen.

To date, over 1,000 blood specimens have been collected. The collection of relevant clinical and epidemiologic data is ongoing. Of the specimens tested so far, preliminary Canadian results indicate that SEN-V is prevalent in patients with chronic hepatitis of unknown cause (31.3%), patients infected with hepatitis B (50.0%) and, as reported above, among liver transplant recipients (51.7%). It should be noted, however, that 18% of a sample of 50 community controls were also found to be SEN-V positive. The preliminary results also suggest that SEN-V positivity may be associated with a history of blood transfusion among those patients tested. However, more research, especially longitudinal epidemiologic studies following both SEN-V positive and negative individuals over time, are needed to clarify the clinical relevance of SEN-V. More specifically, evidence needs to be obtained to show that SEN-V positive individuals are more likely to develop a certain disease than are comparable control (SEN-V negative) individuals.

Acknowledgement

References

1. Allain J-P. *Emerging viruses in blood transfusion*. Vox Sanguinis 2000;78(suppl 2):243-48.
2. Umemura T, Yeo AET, Sottini A et al. *SEN virus infection and its relationship to transfusion-associated hepatitis*. Hepatology 2001;33(5):1303-11.
3. Primi D, Sottini A. *Identification and characterization of SEN virus, a family of novel DNA viruses*. Antiviral Therapy 2000;5(Suppl. 1):G.7.
4. Fiordalisi G, Bonelli M, Olivero P et al. *Identification of SENV Genotypes*. Requested Patent WO0028039, 18 May 2000.
5. Chan I, Diaz-Mitoma F. *SEN virus*. Report prepared for the Division of Bloodborne Pathogens, Health Canada, 2000.
6. Umemura T, Donahue P, Sottini A et al. *The incidence of SEN virus infection in transfusion-associated hepatitis*. Antiviral Therapy 2000;5(Suppl. 1):Abstract G.11.
7. Pirovano S, Sottini A, Bianchi V et al. *Incidence of the SENV-A subtype in different cohorts of patients*. Antiviral Therapy 2000;5(Suppl. 1):Abstract 81.
8. Yoshida EM, Buczkowski AK, Giulivi A et al. *A cross-sectional study of SEN virus in liver transplant recipients*. Liver Transplantation (in press).
9. Zou S, Forrester L, Giulivi A, and the Working Group on Emerging Bloodborne Agents. *Surveillance and risk assessment for emerging bloodborne agents in Canada*. Presented at the 10th International Symposium on Viral Hepatitis and Liver Disease in Atlanta, Georgia, and in Antiviral Therapy 2000;5(Suppl 1):G.5.

Cytomegalovirus, Herpesvirus 6, 7, and 8, and Parvovirus B19 in Canada

Zhiyong Hong, Shimian Zou, Antonio Giulivi

A large number of microbes (bacteria, rickettsiae, chlamydiae, viruses, fungi, parasites) have been identified within the last 20 years[1]. Human herpesvirus 6 (HHV-6), HHV-7, HHV-8, parvovirus B19, and cytomegalovirus (CMV) are examples of such new or re-emerging etiologic agents. Changes in human behaviour, industrial and economic development, travel and mass movement, civil unrest and war, medical treatment (especially transplantation and the widespread use of anti-microbial agents), and microbial change and adaptation result in their emergence or re-emergence. Surveillance and research activities are being carried out in Canada to monitor and study these pathogens[2]. A recent expert working group meeting summarized the findings on HHV-6 and HHV-7 from Canada and other countries[3].

Cytomegalovirus

Human CMV was first isolated in the 1950s[4]. The importance of human CMV as a pathogen has increased over the past 20 years as immunosuppressive states resulting either from post-transplantation therapies or AIDS and other immuno-deficiency states have come to the forefront in medicine. These conditions predispose individuals to primary CMV infection or to reactivation of latent infection. CMV is transmitted by blood transfusion, and a large reservoir of seropositive indi-viduals remains an important source of virus in many settings. Embil et al provided the first case report of cytomegalic inclusion disease in Canada in 1965[5]. During the 1960s and 1970s, a series of epidemiologic investigations were conducted on the prevalence of CMV infection in the normal population in Nova Scotia[6], Montreal[7], Hamilton[8], and the Northwest Territories[9]. In Nova Scotia, for example, 34% of infants possessed antibodies to CMV, presumably of maternal origin. There followed a decline until 2 years of age (4% with anti-bodies to CMV), and then a gradual increase up to 16% by age 20, and to 50% by age 40. Dene and Inuit women had a significantly higher prevalence of CMV antibodies than Edmonton women at all ages. The lower socio-economic status of the population was presumed to be a contributing factor in the higher CMV prevalence.

Ernst et al described the symbiosis of *Pneumocystis carinii* and cytomegalovirus in 1983[10], and CMV as an opportunistic pathogen in AIDS was investigated in 1983-1984[11]. Other studies have included CMV infection and survival in patients who have undergone liver transplantation[12], lung transplan-tation[13], and bone marrow transplantation[14]. Table 1 summarizes the relationship between CMV infection and transplantation in Canada from 1989 to the present. The data show that CMV infection among recipients has resulted in higher mortality.

Strategies have been developed to combat CMV infection[16]. Long-term ganciclovir prophylaxis may have the greatest benefit for lung transplant recipients, CMV-positive marrow transplant recipients, and any CMV-negative recipients of a CMV-positive donor; CMV-negative blood products are

Table 1
Cytomegalovirus infection and transplantation in Canada (1989-2000)

Type of transplantation	No.	Follow-up time	CMV incidence	Survival rate
Children				
Liver transplantation[12]	18	2 years	30% (4/12) infection 25% (3/12) CMV disease	New CMV infection: 25% Pretransplant immunity or CMV(-): 75%
Adults				
Lung transplantation[13]	95	1-5 years	24%-26% CMV disease	55%-61% for 5 years (3 CMV-related deaths)
Bone marrow transplantation[14]	103	1 year	3%	CMV(-): 76% for 1 year CMV(+): 52% for 1 year
Liver transplantation[15]	97	12 weeks	62.9% infection 21.6% CMV disease	Acute rejection: 47.6% in CMV disease 22.4% in no CMV disease

suitable for CMV-negative recipients of a CMV-negative donor. Pre-emptive ganciclovir therapy guided by detection of CMV or use of anti-lymphocyte antibody therapy may be best suited for CMV-positive patients receiving a renal, liver, or heart transplant.

Human herpesvirus 6

HHV-6 was identified as a causal agent for *Exanthema subitum* in 1988[17]. The basic epidemiology of HHV-6, with particular reference to its role in diseases in normal children and immuno-compromised patients, has been associated with the development of febrile syndrome, hepatitis, pneumonitis, and encephalitis after transplantation[18]. Acott et al observed a significant correlation between renal allograft and HHV-6 infection at a children's hospital in Halifax, Nova Scotia, during a 30-month period from February 1993 to August 1995[19]. Humar et al[20] observed the coexistence of HHV-6 and CMV in liver transplant recipients at The Toronto General Hospital. Additional Canadian data can be found in the recent summary by the expert working group[3].

Human herpesvirus 7

HHV-7 was discovered in 1990, when Frenkel and coworkers observed a cytopathic effect in culture of peripheral blood lymphocytes from healthy adults[21]. HHV-7 is highly preva-lent worldwide and is typically acquired during childhood. Infectious HHV-7 can easily be detected in the saliva of 75% of healthy adults[22] and in the peripheral blood of 83% of healthy adults[23]. HHV-7 has also been detected in cervical

swabs of pregnant women[24], raising the possibility of perinatal or congenital transmission. More details can be found in the recent expert working group report[3].

Human herpesvirus 8

HHV-8 was discovered in tissues from Kaposi's sarcoma lesions in 1994[25]. The prevalence of antibodies to HHV-8 varies internationally. It is lower in Northern Europe and the U.S. (0% to 10%), higher in Mediterranean countries such as Greece and Italy (4% to 35%), and highest in parts of Africa (10% to 60%). In the U.S. and Northern Europe, HHV-8 was found with highest frequency in homosexuals infected with AIDS, and sexual transmission is strongly indicated[26].

The general properties of the recently discovered herpesviruses (HHV-6, 7, and 8) are summarized by Dollard and Pellett[27] in Table 2.

Parvovirus B19

Parvovirus B19 was discovered in 1974, while healthy blood donors were being screened for hepatitis B[28]. The first dis-ease associated with parvovirus B19 was aplastic crisis in patients with sickle-cell disease[29]. Rodis et al investigated the management of parvovirus infection during pregnancy in the U.S. and Canada in 1997. They observed that approxi-mately one-third of the cases of parvovirus-produced nonimmune hydrops resolved spontaneously, whereas 83.5% of hydropic fetuses transfused survived[30].

Table 2
General properties of the recently discovered herpesviruses*

Virus	Mode of transmission			Seroprevalence		Principal clinical syndromes
	Casual contact	Intimate contact	Organ transplant	Young children	Healthy adults	
HHV-6A	Possible	Unlikely	Possible	?	> 50%	Febrile illness
HHV-6B	Yes	Possible	Possible	> 90%	99%	Roseola post-transplant disease
HHV-7	Yes	Unlikely	Possible	70%	80%-95%	Roseola post-transplant disease
HHV-8	Possible	Yes	Yes	?	0%-10%[†]	KS, MCD, PEL

* Source: Dollard and Pellett[27]

KS: Kaposi's sarcoma; MCD: multicentric Castleman's disease; PEL: primary effusion lymphoma.

† Does not include KS endemic regions or population at high risk for KS.

Many questions about parvovirus B19 infection remain unanswered: the normal route of transmission, the spread of the virus from the port of entry to the site of replication in the bone marrow, and the role of B19 in chronic arthritis, myocarditis, vasculitis, and neurologic diseases.

Prevention

The Centers for Disease Control and Prevention (CDC) in the U.S. have developed a plan to address emerging infectious disease threats[31]. The plan has four major goals: (a) surveillance and response, including detection, prompt investigation, and monitoring of emerging pathogens, the diseases they cause, and the factors that influence their emergence; (b) applied research, including integrated research of laboratory science and epidemiology to optimize public health practice; (c) prevention and control, such as enhanced communication of public health information about emerging diseases and prompt implementation of prevention strategies; (d) infrastructure, such as strengthened local, state, and federal public health infrastructure to support surveillance and implementation of prevention and control programs. Canada is also setting up surveillance for these agents, especially with regard to the safety of the blood supply, as described by Giulivi[2].

References

1. Satcher D. *Emerging infection: getting ahead of the curve*. Emerg Infect Dis1995;1(1):1-6.

2. Giulivi A. *Surveillance of the blood supply*. In: *Expert Working Group on HHV-6 and 7 laboratory diagnosis and testing*. CCDR 2000;26S4:24-25.

3. Health Canada. *Expert Working Group on HHV-6 and 7 Laboratory Diagnosis and Testing*. CCDR 2000;26S4:1-23.

4. Weller TH, Hanshaw JB. *Virologic and clinical observations on cytomegalic inclusion disease*. N Engl J Med 1962;266:1233-35.

5. Embil JA, Ozere RL Jr, van Rooyen CE. *Cytomegalic inclusion disease: a case report with isolation of virus*. Can Med Assoc J 1965;93:1268.

6. Embil JA, Haldane EV, Machenzie RAE et al. *Prevalence of cytomegalovirus infection in a normal population in Nova Scotia*. Can Med Assoc J 1969;101:78-81.

7. Montplaisir S, Martineau B. *Infection causée par le virus cytomégalique (VCM) dans la région de Montréal: étude épidémiologique*. Can J Public Health 1972;63:333-41.

8. Larke RPB, Wheatley E, Saigal S et al. *Congenital cytomegalovirus infection in an urban Canadian community*. J Infect Dis 1980;142;647-53.

9. Preiksaitis JK, Larke RPB, Froese GJ. *Seroepidemiology of cytomegalovirus infection in the Northwest Territories of Canada*. Arctic Med Res 1988;47:S701-04.

10. Ernst P, Chen MF, Wang NS et al. *Symbiosis of **Pneumocystis carinii** and cytomegalovirus in a case of pneumonia*. Can Med Assoc J 1983;128:1089-92.

11. Frappier-Davignon L, Walker MC, Adrien A et al. *Anti-HIV antibody and other serological and immunological parameters among normal Haitians in Montreal*. J AIDS 1990;3:166-72.

12. Superina RA, Pearl RH, Roberts EA et al. *Liver transplantation in children: the initial Toronto experience*. J Pediatr Surg 1989;24:1013-19.

13. Snell GI, Hoyos AD, Winton T et al. *Lung transplantation in patients over the age of 50*. Transplantation 1993;55:562-66.

14. Humar A, Wood S, Lipton J et al. *Effect of cytomegalovirus infection on 1-year mortality rate among recipients of allogeneic bone marrow transplant*. Clin Infect Dis 1998;26:606-10.

15. Humar A, Gregson D, Caliendo AM et al. *Clinical utility of quantitative cytomegalovirus viral load determination for predicting cytomegalovirus disease in liver transplant recipients.* Transplantation 1999;68:1305-11.

16. Winston DJ. *Prevention of cytomegalovirus disease in transplant recipient.* Lancet 1995;346:1380-81.

17. Yamanishi K, Okuno T, Shiraki K et al. *Identification of human herpesvirus-6 as a causal agent for exanthema subitum.* Lancet 1988;1:1065-67.

18. Yoshikawa T, Suga S, Asano Y et al. *A prospective study of human herpesvirus-6 infection in renal transplantation*. Transplantation 1992;54:879.

19. Acott PD, Lee SHS, Bitter-Suermann et al. *Infection concomitant with pediatric renal allograft rejection.* Transplantation 1996;62:689-91.

20. Humar A, Malkan G, Moussa G et al. *Human herpesvirus-6 is associated with cytomegalovirus reactivation in liver transplant recipient.* J Infect Dis 2000;181:1450-53.

21. Frenkel N, Schirmer EC, Wyatt LS et al. *Isolation of a new herpesvirus from CD4+ T cells*. Proc Natl Acad Sci USA 1990;87:748-52.

22. Wyatt LS, Frenkel N. *Human herpesvirus-6 is a constitutive inhabitant of adult human saliva*. J Virol 1992;66:3206-09.

23. Kidd IM, Clark DA, Ait-Khlaled M et al. *Measurement of human herpesvirus 7 load in peripheral blood and saliva of healthy subjects by quantitative polymerase chain reaction*. J Infect Dis 1996;174:396-401.

24. Okuno T, Oishi H, Hayashi K et al. *Human herpesvirus 6 and 7 in cervixes of pregnant women.* J Clin Microbiol 1995;33:1968-70.

25. Chang Y, Cesarman E, Pessin MS et al. *Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma.* Science 1994;266:1865-69.

26. Gao S-J, Kingsley L, Li M et al. *KSHV antibodies among Americans, Italians and Ugandans with and without Kaposi's sarcoma.* Nature Med 1996;2:925-28.

27. Dollard SC, Pellett PE. *Human herpesvirus 6, 7 and 8.* Rev Med Microbiol 2000;11(1):1-13.

28. Cossart YE, Field AM, Cant B et al. *Parvovirus-like particle in human sera*. Lancet 1975;1:72-3.

29. Pattison JR, Jone SE, Hodgson J et al. *Parvovirus infection and hydroplastic crisis in sickel-cell anaemia.* Lancet 1981;1:664-65.

30. Rodis JF, Borgida AF, Wilson M et al. *Management of parvovirus infection in pregnancy and outcomes of hydrops: survey of members of the Society of Perinatal Obstetricians*. Am J Obstet Genecol 1988;179:985-88.

31. Centers for Disease Control and Prevention. *Addressing emerging infectious disease threats: a prevention strategy for the United States*. Atlanta, Georgia: U.S. Department of Health and Human Services, Public Health Service, 1994.

Hepatitis B Viral Mutants and Their Relevance to the Health Care System

Gerald Y. Minuk, Antonio Giulivi

Over the past 10 years an increasing number of mutations in the HBV genome have been described. Although the majority of these mutations appear to be "silent" or not clinically relevant, some have been described in association with evasion of host immunologic surveillance mechanisms (S escape mutants), increased severity of disease (pre-core, core promoter, and core mutations), resistance to antiviral agents (DNA polymerase mutations), and hepatocellular carcinogenesis (X mutants). This review describes both the molecular events and their clinical consequences.

S Mutants

The target of the host's humoral response to HBV is the hydrophilic region of the HBsAg between amino acid residues 100 and 160. Thus, mutation(s) in this region would afford HBV variants a distinct survival advantage. One such mutation was first described in an Italian child who developed HBV despite vaccination and HBIg given at birth[1]. The mutation resulted in a glycine (G) to arginine (A) switch at amino acid 145. Other common mutations that have been described in this region include Asp-144-Ala, Met-133-Leu, Gln -129 - His and ILe/Thr - 126 – Ala[2]. HBsAg or S mutations have now been documented in many areas of the world but are most common in Asian infants (2% to 3% of vaccine recipients)[2]. High maternal viral loads and mutations elsewhere in the mother's HBV S gene appear to increase the risk of S mutations occurring in the offspring[3]. The same mutations also occur in liver transplant recipients receiving HBIg[2]. Less frequently, they develop spontaneously during the course of a chronic HBV infection[4,5].

Some of the S mutations have been described in association with other clinical events. For example, the Thr-126-Ala mutation has been identified in vaccinated infants who subsequently developed fulminant hepatic failure[6]. Of more diagnostic concern are nucleotide insertions in the area of amino acids 121-124, which can result in false-negative HBsAg testing and thereby represent a risk to the health of the undiagnosed patient and the safety of the blood transfusion system[4-7].

Currently, the clinical concerns associated with S mutants lie in four principal areas:

- Although uncommon, their failure to be detected by commercially available tests raises the possibility that carriers could enter the blood donor population[8]. In this regard, it is important to note that in greater than 95% of cases, antibody to hepatitis B core antigen (anti-HBc) is strongly positive[9]. Other diagnostic tests that can also serve to document HBV infection in this setting are HBV-DNA and hepatitis B e antigen (HbeAg)[9].
- Despite encouraging results in vaccinated chimpanzees, HBIg and HBV vaccination do not protect humans from S mutant infections[10].
- Like other forms of HBV, S mutants have the capacity to induce both acute and chronic liver disease as well as HCC[11,12].

Pre-core and core promoter mutants

Because a large region of the pre-core/core ORF is not overlapped by another ORF, more mutations of the viral genome are tolerated in this region. The most common and extensively studied of these is the G to A mutation at nucleotide 1896 of the pre-core region. This mutation transforms codon 23 from TGG to a TAG stop codon, which terminates transcription at this site and thereby abrogates the synthesis of HBeAg[13,14]. The same mutation also affords the viral genome increased stability, as the 1896 nucleotide site that is now occupied by A binds more avidly to the corresponding T nucleotide at position 1858, resulting in enhanced stability, pregenomic encapsulation and initiation of DNA synthesis[15]. Presumably, this feature has contributed to pre-core mutant infections being very, if not the most, common form of HBV in the Mediterranean, Africa, Southern Europe and Asia (50% to 60% of HBV carriers)[16,17]. Although common in these areas, precore mutants are less prevalent in North America and Northern Europe (10% to 50%), where the HBV genotype (type A) has a C rather than a T nucleotide at position 1858 required to stabilize the A base at the corresponding 1896 site[15,16].

Although initially described in association with histologically active liver disease, including fulminant hepatic failure, the pre-core mutant has more recently been identified in chronic HBV carriers without biochemical or histologic evidence of liver disease[16]. Indeed, in a recent population-based study of Canadian Inuit, none of approximately 35 pre-core mutant carriers had clinical or biochemical evidence of liver disease[17]. Moreover, there are data indicating that reactivation of disease is not associated with the emergence of pre-core mutants, and wild type virus is associated more with inflammation and fibrosis than pre-core mutants[18]. Finally, HBV-DNA levels are not increased in patients with pre-core mutant infections when compared with wild type infection[19,20]. Thus, in itself the mutation is not uniformly pathogenic. These findings have led to searches for co-mutations that might explain the more virulent forms of pre-core infections originally described.

The status of the 1858 nucleotide site may be clinically important in its own right, as studies have demonstrated that patients without 1896 mutations but a T rather than C nucleotide at 1858 have greater histologic activity/inflammation on liver biopsy[16,21]. On the other hand, those with 1896 mutations and T rather than C nucleotides at 1858 have more benign histologic findings[16]. G to A mutations at nucleotides 1898 and 1899 have also been reported to be associated with the severity of liver disease[13,22].

Other mutations that might explain the increased pathogenicity in patients with (or without) pre-core mutations include point mutations and short deletions or insertions in the core promoter region (nucleotides 1634-1782), which not only limit transcription of pre-core mRNA and thereby HBeAg synthesis but also enhance transcription of core-mRNA and, with it, HBcAg and polymerase enzyme synthesis[23]. The most frequently described mutations in this region are A to T nucleotide substitutions at 1762 and G to A at 1764. The frequency of mutations at these sites correlates with disease activity, rates of progression and perhaps hepatocarcinogenesis[24-27]. This increased pathogenicity is likely related to decreased synthesis of the immunotolerogen HBeAg and increased core protein synthesis and viral replication. However, not all studies have identified an association between 1762/1764 mutations and severity of liver disease[28]. Whether pre-core and/or core promoter mutations predispose to a rapidly progressive fibrosing, cholestatic form of liver disease in the post liver transplant period remains unclear[29-31].

In terms of therapeutic implications, initial reports suggested that if greater than 20% of the viral population within a patient consists of pre-core mutants, then a poor response to interferon therapy can be expected[32]. On the other hand, more recent data suggest that a high prevalence of pre-core mutants results in earlier responses to interferon therapy[33]. What is clear is that relapses are more common in patients with pre-core mutations when interferon (or nucleoside analogue) therapy is withdrawn, but once again this may be related to associated mutations in the core promoter or core rather than pre-core region[34,35]. Indeed, the importance of the core promoter in predicting the response to interferon therapy has recently been emphasized[36].

HBcAg mutants

The most immunodominant epitopes of HBcAg are between amino acids 50-69 and 61-85[37]. Mutations in this region have been described in HBV patients with chronic active hepatitis but not during the immune tolerant phase of the infection[35,38]. Deletions in the core region have also been described and shown to result in decreased cytotoxic T cell responses and viral replication[39]. Similar deletions may play a role in converting an immune tolerant to an immune intolerant state and in progression of acute to chronic HBV infection[40]. If the mutations, which likely occur as a result of B and T cell pressure on core antigen, are present prior to interferon therapy, response to treatment is less likely[36,38].

DNA polymerase mutants

Mutations in the catalytic domain of DNA-polymerase (DNA-P), the enzyme responsible for viral replication, tend not to occur naturally but have been described in association with nucleoside analogue therapy[41]. In the case of lamivudine, the first nucleoside analogue licensed for the treatment of HBV, a Met-552-ILE or Met - 552 - Val mutation was described in the conserved Tyr-Met-Asp-Asp' (YMDD) motif that is part of the active site (domain C) of the reverse transcriptase[42]. Famciclovir, another nucleoside analogue with anti-HBV properties, can induce Val-521-Leu and Leu- 528 - Met mutations within the B domain of DNA-P[43]. These mutations decrease but do not eliminate the affinity of nucleoside analogues for the DNA-P enzyme. As a result, viral replication increases but not to levels documented before treatment was initiated[44-46]. Because the mutant virus is replicatively compromised in the vital region of DNA-P activity, wild type virus returns on cessation of drug therapy[47,48].

Of interest is that the 'a' determinant of HBsAg is located in the variable linker region between the A (410-426) and B (498-528) domains of DNA-P. Thus, although YMDD mutations could result in HBsAg changes, they are unlikely to do so in the critical antigenic site of HBsAg. Nonetheless, patients with both YMDD and S escape mutations have been described[49].

HBX mutations

Data are only just emerging on mutations in the X ORF. Preliminary findings describe a novel class of HBX mutants in Asian patients with HCC[50]. These mutations were found to negate X- induced inhibition of clonal outgrowth and increased apoptosis. Thus, X - mutants increased clonal outgrowth and decreased apoptosis, suggesting a possible carcinogenic role.

Although this is intriguing, it should be noted that the HCC tissue sources for the HBX mutations detected also contained HBsAg mutations, which may have been relevant to HCC development[51].

Summary

Mutations have been described in all four ORFs of the hepatitis B virus. From a clinical perspective, the S escape mutant is the most worrisome, because in the absence of surveillance systems and/or a high index of suspicion the diagnosis can be difficult to establish. Undiagnosed cases can progress to liver failure and HCC. Transmission to others, including transmission via the blood transfusion route, might also occur. Fortunately, the prevalence of this mutation appears to be low and is not increasing, despite the widespread application of universal vaccination.

Pre-core mutant infections are less of a clinical concern than originally anticipated. Although they are associated with fulminant and active chronic hepatitis, that association is not universal and appears to be linked to coexisting mutations in the basic core promoter or core regions of the genome. Thus, isolated pre-core mutations more likely reflect the natural evolution of HBV infection from an active to relatively inactive replicative state.

Mutations in the basic core promoter region are worrisome, but it is hoped that their location in terms of overlap with other ORFs will render them relatively infrequent. If confirmed, preliminary findings that mutations to the X gene render the X protein more carcinogenic are disconcerting. Nonetheless, some consolation can be derived from the possibility of exploiting this finding for diagnostic and prognostic purposes in chronic HBV carriers.

References

1. Carman WF, Zanetti AR, Karayiannis P et al. *Vaccine-induced escape mutant of hepatitis B virus.* Lancet 1990;336:325-29.
2. Hunt CM, McGill JM, Allen MI et al. *Clinical relevance of hepatitis B viral mutations.* Hepatology 2000;31:1037-44.
3. Carman WF. *The clinical significance of surface antigen variants of hepatitis B virus.* J Viral Hepat 1997;4:11-20.
4. Yamamoto K, Horikita M, Tsuda F et al. *Naturally occurring escape mutants of hepatitis B virus with various mutations in the S gene in carriers seropositive for antibody to hepatitis B surface antigen.* J Virol 1994;68:2671-76.
5. Carman WF, Korula J, Wallace L et al. *Fulminant reactivation of hepatitis B due to envelope protein mutant that escaped detection by mono-clonal HBsAg ELISA.* Lancet 1995;345:1406-07.
6. Hou J, Karayiannis P, Waters J et al. *A unique insertion in the S gene of surface antigen-negative hepatitis B virus Chinese carriers.* Hepatology 1995;21:273-78.
7. Wallace LA, Carman WF. *Clinical implications of hepatitis B virus envelope protein variation.* Int J Clin Lab Res 1994;24:80-5.
8. Coleman PF, Chen YC, Mushahwar IK. *Immunoassay detection of hepatitis B surface antigen mutants.* J Med Virol 1999;59:19-24.
9. Hsu HY, Chang MH, Liaw SH et al. *Changes of hepatitis B surface antigen variants in carrier children before and after universal vaccination in Taiwan.* Hepatology 1999;30:1312-17.
10. Ogata N, Cote PJ, Zanetti AR et al. *Licensed recombinant hepatitis B vaccines protect chimpanzees against infection with the prototype surface gene mutant of hepatitis B virus.* Hepatology 1999;30:779-86.
11. Ogata N, Zanetti AR, Yu M et al. *Infectivity and pathogenicity in chimpanzees of a surface gene mutant of hepatitis B virus that emerged in a vaccinated infant.* J Infect Dis 1997;175:511-23.
12. Carman WF, Korula J, Wallace L et al. *Fulminant reactivation of hepatitis B due to envelope protein mutant that escaped detection by monoclonal HBsAg ELISA.* Lancet 1995;345:1406-07.

13. Brunetto MR, Stemler M, Schodel F et al. *Identification of HBV variants which cannot produce precore derived HBeAg and may be responsible for severe hepatitis.* Ital J Gastroenterol 1989;21:151-54.

14. Carman WF, Jacyna MR, Hadziyannis S et al. *Mutation preventing formation of hepatitis B e antigen in patients with chronic hepatitis B infection.* Lancet 1989;2:588-91.

15. Lok AS, Akara U, Greene S. *Mutations in the pre-core region of hepatitis B virus serve to enhance the stability of the secondary structure of the pre-genome encapsidation signal.* Proc Natl Acad Sci USA 1994;91:4077-81.

16. Lindh M, Horal P, Dhillon AP et al. *Hepatitis B virus carriers without precore mutations in hepatitis B e antigen-negative stage show more severe liver damage.* Hepatology 1996;24:494-501.

17. Minuk GY, Orr PS, Brown R et al. *Pre-core mutant infections in the Canadian Inuit.* J Hepatol (in press).

18. Loriot MA, Marcellian P, Talbodec N et al. *Low frequency of precore hepatitis B virus mutants in anti-hepatitis B e-positive reactivation after loss of hepatitis B e antigen in patients with chronic hepatitis B.* Hepatology 1995;21:627-31.

19. Knoll A, Rohrhofer A, Kochanowski B et al. *Prevalence of precore mutants in anti-HBe-positive hepatitis B virus carriers in Germany.* J Med Virol 1999;59:14-8.

20. Brunetto MR, Rodriguez UA, Bonino F. *Hepatitis B virus mutants.* Intervirology 1999;42:69-80.

21. Chan HLY, Leung NW, Hussain M et al. *Hepatitis B e antigen-negative chronic hepatitis B in Hong Kong.* Hepatology 2000;31:763-68.

22. Tillmann H, Trautwein C, Walker D et al. *Clinical relevance of mutations in the precore genome of the hepatitis B virus.* Gut 1995;37:568-673.

23. Li J, Buckwold VE, Hon MW et al. *Mechanism of suppression of hepatitis B virus precore RNA transcription by a frequent double mutation.* J Virol 1999;73:1239-44.

24. Fang ZL, Ling R, Wang SS et al. *HBV core promoter mutations prevail in patients with hepatocellular carcinoma from Guangxi, China.* J Med Virol 1998;56:18-24.

25. Baptista M, Kramvis A, Kew MC. *High prevalence of 1762T 1764A mutations in the basic core promoter of hepatitis B virus isolated from black Africans with hepatocellular carcinoma compared with asymptomatic carriers.* Hepatology 1999;29:946-53.

26. Tillmann H, Trautwein C, Walker D et al. *Clinical relevance of mutations in the precore genome of the hepatitis B virus.* Gut 1995;37:568-73.

27. Takahashi K, Aoyama K, Ohno N et al. *The precore/core promoter mutation of hepatitis B virus: clinical significance and an easy method of detection.* J Gen Virol 1995;75:3159-64.

28. Chan HLY, Hussain M, Lok ASF. *Different hepatitis B virus genotypes are associated with different mutations in the core promoter and precore regions during hepatitis B e antigen seroconversion.* Hepatology 1999;29:976-84.

29. McMillan JS, Bowden DS, Angus PW et al. *Mutations in the hepatitis B virus precore/core gene and core promoter in patients with severe recurrent disease following liver transplantation.* Hepatology 1996;24:1371-78.

30. Protzer U, Goergen B, Hopf U et al. *Pre-core mutants of hepatitis B virus in patients receiving immunosuppressive treatment after orthotopic liver transplantation.* J Med Virol 1996;50:135-44.

31. Naumann U, Protzer Knolle U, Berg T et al. *A pretransplant infection with precore mutants of hepatitis B virus does not influence the outcome of orthotopic liver transplantation in patients on high dose anti-hepatitis B virus surface antigen immunophrophylaxis.* Hepatology 1997;26:478-84.

32. Brunetto MR, Giarin M, Saracco G et al. *Hepatitis B virus unable to secrete e antigen and response to interferon in chronic hepatitis B.* Gastroenterology 1993;105:845-50.

33. Lok AS, Akarca US, Greene S. *Predictive value of precore hepatitis B virus mutations in spontaneous and interferon-induced hepatitis B e antigen clearance.* Hepatology 1995;21:19-24.

34. Naoumov NV, Thomas MG, Mason AL et al. *Genomic variations in the hepatitis B core gene: a possible factor influencing response to interferon alfa treatment.* Gastroenterology 1995;108:505-14.

35. Chuang Wl, Omata M, Ehata T et al. *Precore mutations and core clustering mutations in chronic hepatitis B virus infection.* Gastroenterology 1993;104:263-71.

36. Erhardt A, Reineke U, Blondin D et al. *Mutations of the core promoter and response to interferon treatment in chronic replicative hepatitis B.* Hepatology 2000;31:716-25.

37. Colucci G, Beazer Y, Cantaluppi C et al. *Identification of major hepatitis B core antigen determinant by using synthetic peptides and monoclonal antibodies.* J Immunol 1988;141:4376-80.

38. Bozkaya H, Ayola B, Lok AS. *High rate of mutations in the hepatitis B core gene during the immune clearance phase of chronic hepatitis B virus infection.* Hepatology 1996;24:32-7.

39. Ackrill AM, Naoumov NV, Eddleston ALWF et al. *Specific deletions in the hepatitis B virus core open reading frame in patients with chronic active hepatitis B.* J Med Virol 1993;41:165-69.

40. Akarca US, Lok AS. *Naturally occurring hepatitis B virus core gene mutations.* Hepatology 1995;22:50-60.

41. Locarnini S, Birth B. *Antiviral chemotherapy for chronic hepatitis B infection: lessons learned from treating HIV-infected patients.* J Hepatol 1999;30:536-50.

42. Allen MI, Deslauriers M, Andrews CW et al. *Identification and characterization of mutations in hepatitis B virus resistant to Lamivudine.* Lamivudine Clinical Investigation Group. Hepatology 1998;27:1670-77.

43. Aye TT, Bartholomeusz AI, Shaw T et al. *Hepatitis B virus polymerase mutations during famciclovir therapy in patients following liver transplantation.* Hepatology 1996;24:285A.

44. Lai CL, Chien RN, Leung N et al. *A one-year trial of lamivudine for chronic hepatitis B.* N Engl J Med 1998;339:61-8.

45. Dienstag J, Schiff E, Wright TL et al. *Lamivudine as initial treatment for chronic hepatitis B in the United States.* N Engl J Med 1999;341:1256-63.

46. Liaw YF, Chien RN, Yeh CT et al. *Acute exacerbation and hepatitis B virus clearance after emergence of YMDD motif mutation during lamivudine therapy.* Hepatology 1999;30:567-72.

47. Rosenberg PM, Dienstag JL. *Therapy with nucleoside analogues for hepatitis B virus infection.* Clin Liver Dis 1999;3:349-61.

48. Chayama K, Suzuki Y, Kobayashi M et al. *Emergence and takeover of YMDD motif mutant hepatitis B virus during long-term lamivudine therapy and re-takeover by wild type after cessation of therapy.* Hepatology 1998;27:1711-16.

49. Oon CJ, Chen WN, Lim N et al. *Hepatitis B virus variants with lamivudine-related mutations in the DNA polymerase and the 'a' epitope of the surface antigen are sensitive to ganciclovir.* Antiviral Res 1999;41:113-18.

50. Sirma H, Giannini C, Poussin K et al. *Hepatitis B virus X mutants, present in hepatocellular carcinoma tissue abrogate both the antiproliferative and transactivation effects of HBx.* Oncogene 1999;18:4848-59.

51. Oon CJ, Chen WN, Zhao Y et al. *Detection of hepatitis B surface antigen mutants and their integration in human hepatocellular carcinoma.* Cancer Lett 1999;136:95-9.

Hepatitis B and its Control in Southeast Asia and China

Zhiyong Hong, Shimian Zou, Antonio Giulivi

Hepatitis B is one of the major infectious diseases of mankind: of 360 million chronic carriers worldwide, 78% are in Asia, 16% in Africa, 3% in South America, and 3% in Europe, North America, and Oceania combined. HBV infection is the most common cause of chronic hepatitis, liver cirrhosis and HCC worldwide[1].

In order to combat HBV infection and subsequent carriage, most East Asian and Southeast Asian countries introduced mass vaccination programs during the late 1980s and mid-1990s, which have resulted in a drastic decline in the HBV carrier rate and the number of patients with HCC.

Although HBV prevalence is low in Canada, changes in the epidemiology of this disease in other parts of the world may have a significant impact on the health of Canadians. Therefore, it is important to closely and continuously monitor the status of the disease in the world, especially in areas where HBV is endemic.

Indonesia

The island of Lombok, east of Bali in Nusa Tenggara Barat Province, was the first to introduce a mass infant hepatitis B immunization project in Indonesia, which ran from November 1987 to October 1991[2]. The Lombok Project clearly demonstrated the feasibility of incorporating HBV vaccine into the Expanded Program on Immunization (EPI) in a way that can significantly reduce chronic HBV infection and strengthen the EPI. The success of the Lombok Project was the basis for a national program of universal infant immunization in Indonesia. Four provinces were added to the program in 1991-1992, and the program was further expanded to 10 provinces in 1992-1993, requiring 4.5 million annual vaccine doses. The overall reduction in the prevalence of HBsAg among fully vaccinated children (less than 4 years old) fell from 6.2% to 1.9%, for a reduction of 70%.

Malaysia

From February 1997 to July 1999, a total of 79,103 individuals, including university students, health care workers, and primary and secondary school students, participated in a prospective study of hepatitis B. In all, 92.9% were Chinese, 4.8% were Malays, 2.1% were Indians, and 0.1% were from other ethnic groups[3]. The age of the participants ranged from 5 to 60 years old. Demographic data and history of hepatitis B vaccination were obtained from each participant, and testing was carried out for HBsAg and anti-HBs. The overall prevalence of HBsAg was 1.5%. The rate among the Malays, Chinese, and Indians was 1.5%, 1.5%, and 0.3% respectively. Among all participants, 62.4% had been vaccinated with all three doses of HBV. Chinese participants were found to have the highest vaccination rate (64.5%), followed by Indians (37.8%), and Malays (32.7%). The rate of endemic HBV in Malaysia is now low, as its vaccination programs and possibly other

intervention measures have successfully reduced the incidence of the infection[4].

The Philippines

The prevalence of chronic HBV infection in the Philippines, as indicated by HBsAg positivity, has been found to range from 2.0% to 16.5%, with an average of 12.0%, in a study of rural villagers[5]. In a study assessing the feasibility and effectiveness of incorporating hepatitis B vaccine into the national EPI, HBsAg positivity decreased to 2% during the last 10-year period (1987-1996) in the Philippines[6].

The Republic of Singapore

In Singapore, the HBsAg carrier rate for the general population was 9% to 10% in 1980-1981. A national childhood hepatitis B vaccination program was formulated and implemented in phases, starting with babies born to carrier mothers on October 1, 1985, and finally extending to all newborns on September 1, 1987. During the period from 1994 to 1996, more than 90% of children completed the full schedule of immunization by 1 year of age, and 85% had evidence of vaccination at school entry at age 6. Follow-up of two cohorts of vaccinated children showed that perinatal transmission was reduced by 80% to 100%. Horizontal transmission also declined through other public health measures. The incidence of acute hepatitis B declined from 10.4 per 100,000 in 1985 to 4.8 per 100,000 in 1996[7]. The vaccination coverage in newborns reached 100%, and the HBsAg positive rate declined to 2% to 3% in 1997 and 1998 in randomized population groups and in new blood donors. The acute HBV morbidity had fallen continuously from 10.4 per 100,000 in 1985 to 4.5 per 100,000 in 1997, and the incidence of HCC continued to decline[8].

Thailand

In 1992, hepatitis B vaccine was included in the EPI on a nationwide scale in Thailand. Recent data on the immunization program against hepatitis B demonstrate a steady decline in the incidence of HBV carriers among the Thai population during the period from 1981 to 1991. For example, the prevalence of HBV carriers among blood donors and students decreased from 8.2% and 6.6 % in 1987 to 6.5% and 5.2% in 1991 respectively[9]. Current data from an epidemiologic survey in Songkhle Province in the south of Thailand demonstrated an overall prevalence of HBV carriers of 0.55% among children less than 15 years of age[10]. It has been clearly shown that hepatitis B immunization as part of the EPI is highly efficient in protecting newborns from infection.

Viet Nam

Blood donors from two cities in Viet Nam were tested for markers of HCV and HBV infection. Among 491 donors in Ho Chi Minh City and 499 donors in Hanoi City, HBsAg carrier rates were 3.1% and 3.0% respectively[11]. There is no report about the HBsAg carrier rate in the general population.

China (mainland)

HBV infection rates reported for university students ranged from 4.5% to 19.4% during the period from the mid-1980s to the early 1990s[12]. The HBsAg carrier rate in China showed a substantial decrease after the implementation of the WHO strategy. Zeng et al carried out a randomized two-stage household sampling survey at 112 disease surveillance points from 25 provinces, autonomous regions, and municipalities of China in 1996[13]. The results showed that the hepatitis B vaccination coverage rates among neonates were 96.7% in 1993 and 97.5% in 1994-1996 in urban areas, and 50.8% in 1993 and 73.9% in 1994-1996 in rural areas. Vaccination coverage rates among 7-9 year-old students in 1994 in urban and rural areas were 97.5% and 73.9% respectively. Lu et al conducted a sampled survey on hepatitis A, B, and C in Yunnan province, China, in 1998[14]. The prevalence of HBsAg was 2.0% in 452 serum samples collected from pupils aged 6-12 years old in three different counties. Zhang et al[15] determined the persistence of immunity in neonates born to HbsAg positive mothers following HB immunization with different schedules[15]. In total, 203 neonates were followed-up continuously for 6 years for anti-HBs and HBsAg. Anti-HBs in the neonates was maintained in greater than 90% of the children during those years. None of the children tested positive for HBsAg. A booster dose of vaccine after the primary immunization seemed unnecessary for children 6-10 years old. Zhu et al[16] reported the results of the status of hepatitis B vaccination in China from the 1999 National Coverage Study. A total of 25,878 children aged 18-34 months from 31 provinces were surveyed. The national hepatitis B vaccine coverage (receipt of three doses) was 70.7%.

Hong Kong

A campaign to promote screening and vaccination for hepatitis B in students at the University of Hong Kong was described by Marshall (1995)[17]. Of eligible students, 98% had the first dose of vaccine, and greater than 96% completed the full course of three doses. After vaccination, the prevalence of HBsAg was 3.6%; male students showed a significantly higher prevalence (4.5%) than female students (2.9%). These levels are

about one-third of the prevalence levels found in the same age group in the general population in Hong Kong. The author recommended that students at secondary schools and post-secondary educational institutions in Hong Kong should be offered serologic screening and vaccination for hepatitis B.

Taiwan

In the early 1980s, 15% to 20% of the population of Taiwan were estimated to be HBV carriers. A program of mass vaccination against hepatitis B was launched in 1984. In the first 2 years of the program, newborns of all HbsAg positive mothers were vaccinated. Since 1986, all newborns, and then pre-school children, primary school children, adolescents, young adults, and others have also been vaccinated. Vaccination coverage was greater than 90% for newborns, 79% of pregnant women being screened for HBsAg. The proportion of babies who were born to highly infectious carrier mothers and became carriers decreased from 86% to 96% to 12% to 14%, whereas the decrease was from 10% to 12% to 3% to 4% for babies of less infectious mothers. Between 1989 and 1993, the prevalence of HBsAg among children aged 6 years also fell, from 10.5% to 1.7%. The average annual incidence

of HCC among children aged 6-14 years decreased significantly, from 0.7/100,000 in 1981-1986 to 0.4/100,000 in 1990-1994. Similarly, the annual incidence of HCC among children aged 6-9 years declined from 0.5/100,000 for those born in 1974-1984 to 0.1/100,000 for those born in 1986-1988. These data demonstrate that the mass vaccination program has been effective in controlling chronic HBV infection and in preventing liver cancer in Taiwan. If a 90% coverage rate of hepatitis B vaccination in newborns can be maintained, the carrier rate of HBsAg in Taiwan is expected to decline to lower than 0.1% by year 2010[18].

Summary

The most recent data from Southeast Asia and China show that there have been substantial decreases in the incidence and prevalence of hepatitis B following the immunization strategies that have been implemented in that region. However, it should also be noted that the overall HBV prevalence rate is nevertheless high in the area, especially among children and adults born before the introduction of the current hepatitis B vaccination programs. Both aspects of the epidemic pattern in that area may have implications for decision making regarding the prevention and control of hepatitis B in Canada.

References

1. Kane MA. *World-wide epidemiology of hepatitis B.* Soz Preventivemed 1998;43:S24-6.
2. Ruff TA, Gertig DM, Otto BF et al. *Lombok hepatitis B model immunization project: toward universal infant hepatitis B immunization in Indonesia.* J Infect Dis 1995;171(2):290-96.
3. Ng KP, Saw TL, Baki A et al. *APASL Commemorative International Congress on Viral hepatitis prevention and Control.* Singapore, 16-19 February 2000:80.
4. Andre F. *Hepatitis epidemiology in Asia, the Middle East and Africa.* Vaccine 2000;18:S20-2.
5. Lansang MA. *Epidemiology and control of hepatitis B infection: a perspective from the Philippines.* Asia Gut 1996;38(S2):43-7.
6. Subida RD, Zhang ZW, Agetano MC et al. *Hepatitis B and C virus infection prevalence among women in Manila, the Philippines.* Southeast Asian J Trop Med Public Health 1997;28(4):683-88.
7. Goh KT. *Prevention and control of hepatitis B virus infection in Singapore.* Ann Acad Med Singapore 1997;26(5):671-81.
8. Oon CJ, Goh KT, Tan KL et al. *APASL Commemorative International Congress on Viral hepatitis prevention and Control.* Singapore, 16-19 February 2000:62.
9. Tanprasert S, Somjitta S. *Trend study on HBsAg prevalence in Thai voluntary blood donors.* Southeast Asian J Trop Med Public health 1993;24(Suppl 1):43-5.
10. Chub-uppakarn S, Panichart P, Theamboonlers A et al. *Impact of the hepatitis B mass vaccination program in the southern part of Thailand.* Southeast Asia. J Trop Med Public Health 1998;29(3):464-68.
11. Song P, Duc DD, Hien B et al. *Markers of hepatitis C and B virus infections among blood donors in Ho Chi Minh City and Hanoi.* Vietnam Clin Diagn Lab Immunol 1994;1(4):413-18.
12. Zhang S, Chen Y. *HBV serum marker detection and relative factor analysis of 2925 new students.* Public Health 1998;112(4):257-59.
13. Zeng X, Yang G, Liao S. *A study on the coverage, strategy and cost of hepatitis B vaccination in China, 1996.* J Chinese Epidemiology 1998;19(5):277-81.
14. Lu L, Ma Y, Xie Z et al. *A sampling survey on the epidemic status of hepatitis A, B, C among the pupils in the Yunnan province's countryside.* China Public Health 1998;14(11):647.
15. Zhang XC, Ying Y, Shen L et al. *Follow-up on hepatitis B immunized neonates born to HBsAg positive.* J Chinese Preventive Medicine 1998;32(2):97-99.
16. Zhu X, Zhang X, Wang L et al. *Status of hepatitis B vaccination in China: results from the 1999 national coverage study.* Antiviral Therapy 2000;5:S37.
17. Marshall IB. *Screening and vaccination for hepatitis B in Hong Kong university students.* J Am Public Health 1995;44(2):59-62.
18. Huang K, Lin S. *Nationwide vaccination: a success story in Taiwan.* Vaccine 2000;18(S1):S35-8.

Xenotransplantation Surveillance in Canada

Marian P. Laderoute

Xenotransplantation is the transplantation, implantation, or infusion into a human recipient of either (a) live cells, tissues, or organs from a non-human animal source or (b) human body fluids, cells, tissues, or organs that have had *ex vivo* contact with live, non-human animal cells, tissues, or organs[1]. Fixed pig heart valves that have been commonly used as medical devices in Canada do not qualify as xenotransplantation products or "xenografts", as this tissue is not alive and viruses have been destroyed by the fixation process.

A common animal species being explored worldwide for source materials for xenotransplantation is the pig, although in the past non-human primates and other sources have been occasionally tried. Mouse fibroblasts have been used in some cases in the U.S. as a feeder layer for supporting the expansion of human (autologous) skin for burn patients. This has prompted the inclusion of such products under the jurisdiction and the definition of xenotransplantation (given above) of the United States Public Health Service (PHS)[1]. Although some countries, such as the U.S., have authorized or allowed xenotransplantation clinical trials, to date such trials have not been authorized in Canada, nor are applications for xenotransplantation considered under the Special Access Program, even under extenuating circumstances[2].

Surveillance measures for xenotransplantation clinical trials

Efforts are under way to set up surveillance measures for xenotransplantation in Canada. HC is responsible for such surveillance, specifically through the Centre for Infectious Disease Prevention and Control within the Population and Public Health Branch, and the regulatory bodies within the Health Products and Food Branch.

Although xenotransplantation products would be subject to drug and/or medical device regulations, including the need for HC authorization to proceed with clinical trials, xeno-transplantation protocols are thought to present a biologic hazard meriting enhanced surveillance measures[3,4]. These risks have also been viewed as warranting the establishment of minimal operating criteria to deal with animal husbandry issues, source animal procurement, archiving of samples, etc. The draft standard on xenotransplatation is available for comment on the HC website[5]. Enhanced surveillance, however, goes well beyond the usual adverse event reporting and safety assessments required for all clinical trials. These additional concerns primarily relate to the largely unknown but theoretic risks of transmission of infectious agents from the non-human source, such as pigs, to human populations[6]. Many exogenous viruses that cause frank diseases in pigs can be screened or bred out of herds biologically sequestered from other animals, but there are three categories of virus that are more problematic. They are the endogenous, endemic and, as yet, unknown viruses of pigs.

Transmission of endogenous viruses

Endogenous viruses include porcine endogenous retroviruses (PERVs). All pig herds studied to date express one or more PERV subtypes, some which have been shown to infect

human cells *in vitro*[4]. Preliminary studies on human populations exposed to xenografts seem to suggest that transpecies infections do not commonly occur, if at all, although these trials did not evaluate transmission from transgenic sources, from which the risks are thought to be somewhat higher. However, in some cases pig DNA and pig PERV DNA have been found in human recipients, but without evidence of viremia or infection. This condition has been referred to as "microchimerism", in which it is assumed that pig cells have survived and are circulating in the host. Whether microchimerism actually represents free-floating pig cells in human recipients or not, the important question becomes, are these recipients at an increased or decreased risk of infection from PERVs and other infectious agents[6]? Furthermore, what are the risks of transmission of these viruses, if they become replication competent, to other humans?

Transmission of endemic viruses

Endemic pig viruses are detailed more extensively elsewhere in this supplement and have been recently reviewed[7]. Most endemic viruses are present in all herds, have little or no known disease association in pigs, but have the potential to be transmitted and cause disease in humans. This risk is probably increased if the host is immunosuppressed or other barriers to cross-species transmission are lacking, which occurs when transgenic pig materials are implanted. Although it is thought that these viruses can be bred out, details on the successes of such programs have yet to be published. For example, a porcine cytomegalovirus (pCMV)-free herd has not been described to date. Whether pCMV or any of the other pig endemic viruses will or can cause communicable diseases in humans remains to be established. There is a large gap in knowledge about the transmission of these endemic viruses and the potential for human diseases.

Screening for unknown viruses

A third category and the most contentious one is that of unknown viruses for which specific screening methods are currently not available. However, modern technology does allow the screening for certain types of viruses, even if the virus has not yet been characterized. For example, assays for reverse transcriptase activity in which the output is amplified by PCR (the PERT assay) provide a very sensitive means of detecting retroviruses (DNA or RNA). As well, primers for PCR can be designed that will detect most herpesviruses, including those that are unknown. Nevertheless, the challenge remains of how to protect Canadians from unknown pig infectious agents that theoretically could become new

emerging bloodborne pathogens. It is important to note that this risk is present regardless of whether xenotransplantation actually occurs on Canadian soil or not. In this regard, HC is currently considering adding xenograft recipients to blood donor exclusion criteria, despite the fact that xenotransplantation clinical trials are not under way in Canada.

Enhanced surveillance measures

To determine what enhanced surveillance measures may be appropriate or feasible, the Blood-Borne Pathogens Division, Centre for Infectious Disease Prevention and Control, held a 1-day workshop on xenotransplantation surveillance in March 2000[4]. An important problem to emerge was that any symptom or even no obvious symptom could be associated with a xenozoonosis (transmission of an infectious agent from one species to another associated with xenotransplantation). Thus, relying on clinical symptoms to decide whether to investigate for a known or unknown infectious agent was concluded to be likely relatively ineffective as an early warning system. No particular surrogate marker for a xenozoonosis was identified, although any abnormal laboratory test might provide the first hint of an infectious disease problem. From the analysis of the workshop survey, it was strongly suggested that active screening in xenograft recipients for viral agents known to be in pig herds, such as PERVs and endemic viruses, will be necessary to assess whether they cross the species barriers and/or have the potential to be associated with disease[4]. In the revised U.S. PHS guideline, a similar recommendation was made[1].

As well from the workshop, a full infectious disease investigation on major autopsy tissues for deceased xenograft recipients was judged to be very important in assessing the ability of endemic and endogenous pig viruses to cross the species barrier to human populations. To date these investigations, if conducted, have not been published, despite the fact that deaths have occurred within xenotransplantation clinical trials[4] and, at least for one individual, autopsy samples were taken[8]. A major conclusion of the workshop was the need for international collaboration, including the harmonization of definitions, the standardization of adverse event reporting and screening methods, and the sharing of data, experience, and outcomes. A similar conclusion and a specific call for enhanced xenotransplantation surveillance at the international level was recently reached at the OECD/WHO consultation meeting on xenotransplantation surveillance, held October 4-6, 2000, in Paris.

A number of activities to address xenotransplantation surveillance are in the works. Plans are being developed to first provide a science-based risk assessment on the potential for

cross-species transfer of endogenous and endemic pig infectious agents to humans. Several hundred high-risk individuals who are occupationally or medically exposed to pig blood or materials will be tested for the presence of the various known endogenous and endemic pig viruses using modern PCR technology and, when practical, for evidence of exposure by serologic means. The results will be compared with those of individuals at low risk who have not been exposed to pig blood, aside from the preparation and consumption of pork. In parallel, an attempt will be made to establish a sensitive method to determine whether a person has, in fact, been exposed to pig blood. It is hoped that all individuals showing the presence of pig infectious agents or previous exposure would all be positive for the pig blood exposure test. If this can be confirmed and demonstrated in the laboratory, then it is possible that this "pig blood exposure test" might be used as a surrogate marker for known and unknown pig viruses in the general population, for example in the screening of blood and organ donors. The development of a single screening assay rather than testing for a dozen or more specific pig viruses, is not only more cost-effective and plausible, but for blood donor screening, it would have the added benefit of reducing the risks from unknown viruses for which specific detection methods have not yet been developed.

Since the methods for screening for endogenous and endemic pig viruses along with non-specific tests for other viruses would be set up and validated on humans samples, this would help furnish HC with the testing capacity necessary to prepare for outbreaks in human populations associated with pig blood-borne pathogens, whether they were associated with a xenotransplantation clinical trial or not.

In summary, new developments in xenotransplantation and infectious disease risks potentially associated with the procedure are closely monitored by HC. The framework for international surveillance is being established and laboratory detection capacity is being developed for known and unknown pig infectious agents. HC is committed to its mandate to prevent and control infectious disease risks in the medical setting.

References

1. United States Public Health Service. *Guideline on infectious disease issues in xenotransplantation.* May 26, 2000. See Website http://www.fda.gov/cber/gdlns/xeno0500.pdf

2. Health Canada, Therapeutic Products Program. *Notice to hospitals from the Therapeutic Products Program, March 29, 1999: The clinical use of viable animal cells, tissues, or organs to treat patients.* See Website http://www/hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/btox/notices/noticetohospitals_e.html

3. Health Canada, Therapeutic Products Program. *National Forum on Xenotransplantation: Clinical, Ethical and Regulatory Issues,* November 1997. See Website http://www/hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/btox/reports/frmrptx_e.html

4. Health Canada, Centre for Infectious Disease Prevention and Control. *Xenotransplantation Surveillance Workshop I: Infection Control Database and Sample Archiving*, March 31, 2000 (submitted for the Population and Public Health Branch website).

5. *Proposed Canadian Standard for Xenotransplantation*, see Website http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/btox/Standard/xeno_std_e.html

6. Tackaberry ES, Ganz PR. *Xenotransplantation: assessing the unknown.* Can Med Assoc J 1998;159:41-3.

7. Yoo D, Giulivi A. *Xenotransplantation and the potential risk of porcine viruses for xenogeneic transmission.* Can J Veterinary Res 2000;64:193-203.

8. Deacon T, Schumacher J, Dinsmore J et al. *Histological evidence of fetal pig neural cell survival after transplantation into a patient with Parkinson's disease.* Nature Medicine 1997;3:350-53.

Swine Viruses and Xenozoonosis*

Dongwan Yoo, Antonio Giulivi

Recent advances in xenotransplantation technology as a therapeutic approach have the potential to benefit human health. Liver cancer and liver cirrhosis in humans may some day be treated by implantation of porcine liver, diabetes may be treated by pancreatic cell transplantation, and neuronal tissues may be implanted for treatment of neurodegenerative diseases. As a source of donor organs, primates are widely considered unsuitable, mainly because of ethical issues and the likely transmission of infectious agents. Swine is the animal species of prime interest in clinical xenotransplantation. Pigs are easy to breed and economic to produce, and the physiology of swine is similar to that of humans.

Risks of xenotransplantation

It is important to recognize, however, that xenotransplantation may put the human community at risk. Transplantation of animal organs to humans will allow microorganisms present in the donor organs to bypass the normal defence mechanisms of the recipient. After transplantation, prolonged contact with the human body may allow the microorganisms to adapt and transmit to the recipient, and an agent that is non-pathogenic in its natural host may become pathogenic in the recipient. Immunosuppressive drug therapy is common in transplant patients, and the xenograft recipient's immune-suppressed condition may result in unpredicted consequences.

Of the many microorganisms infecting swine, viruses are the major concern, since other microorganisms can be greatly suppressed by routine treatment with antibiotics. Pathogens known to produce apparent disease in pigs should be the primary target to eliminate from donor herds. This is a relatively easy task, and therefore these pathogens are of less concern in xenotransplantation. In contrast, viruses that do not produce obvious disease in swine and those that result in latent infection are more difficult to eliminate and thus are of more concern, because xenotransplantation may provide unique opportunities for species jumping of viruses from pigs to humans. To date, about 25 different viruses have been identified in pigs. Most of these viruses do not cause apparent disease in humans, with the exception of Nipha virus, which caused recent outbreaks and deaths in Malaysia[1]. Viruses with oncogenic potential, those that can be vertically transmitted, and those that are transmitted from semen are of particular concern and need to be carefully screened. Included in these categories are swine hepatitis E virus, porcine endogenous retrovirus, porcine cytomegalovirus, porcine circovirus types 1 and 2, and two newly identified herpesviruses[2]. With the exception of porcine circovirus type 2, all of these viruses are generally considered non-pathogenic in pigs.

Swine hepatitis E virus

Hepatitis E is one of several types of the recognized viral hepatitis in humans. Hepatitis E virus (HEV) is excreted in the feces of infected individuals, and contaminated feces are likely the primary source of transmission. The mortality rate is 1% to 3% but up to 20% higher among pregnant women[3]. Hepatitis E is traditionally found in countries where hygienic conditions are poor. In these countries two antigenic types of HEV, Asian type and Mexican type, have been recognized. A third type of human HEV has been isolated from HEV non-endemic countries, and this type appears to be distinct from the Asian or Mexican types.

Recently, an HEV-like virus has been discovered in swine and, surprisingly, this swine HEV appears to have remarkable similarity to the third type of human HEV[4]. The virus shows only a limited similarity to Asian or Mexican types. Evidence has accumulated indicating that swine HEV is likely a zoonotic agent and is able to infect primates and cause hepatitis[5]. Conversely, human HEV that is genetically similar to swine HEV infects pigs, but human HEV genetically distinct from swine HEV does not[6]. The transmission may occur by direct contact or through food or water contaminated with swine feces containing HEV. The cross-species infection from swine to humans may be dose-dependent.

The potential for cross-species infection by HEV raises a public health concern. Risk groups include swine practitioners, pig farmers and handlers, meat handlers, those involved in manure disposal, and others in close contact with swine. Since swine are of great interest for xenotransplantation, swine HEV is a major concern as a potential xenogeneic agent. Xenografts of swine organs to humans will allow the direct transmission of swine HEV. Although HEV infections in pigs and primates are asymptomatic[5], it is not known whether the virus will become pathogenic in humans, especially immunosuppressed recipients. This virus should be considered as a potential xenogeneic agent.

Circoviruses

Circoviruses are frequently found in birds and plants, but pigs are the only mammalian species from which the virus has been isolated to date. In pigs, two types of circovirus have been identified, type 1 and type 2. Porcine circovirus type 1 is believed to be ubiquitous in pig populations worldwide, but there is no associated disease in pigs[7]. In contrast, type 2 circovirus, first recognized in Western Canada, has been suggested to cause a post-weaning multisystemic wasting syndrome in pigs[8]. Both types are closely related to each other but distinct. Type 2 circovirus is widespread throughout the world. Circovirus has the potential to transform primary porcine cells, but the potential risk for human transmission via xenotransplantation remains unclear. Circovirus-specific antibodies have been demonstrated in humans, mice, and cattle, but neither the virus nor the viral genome has been detected yet in any of these species but pigs. There is no evidence that humans have been infected with circovirus during normal contact with swine and swine products. It therefore remains unknown whether immunosuppressed xenograft recipients will be at risk of infection by porcine circovirus. Nevertheless, swine herds should be screened for the virus and positive herds excluded from the xenotransplantation protocols.

Herpesviruses

Herpesviruses are widespread in nature and found in insects, reptiles, amphibians, and every species of birds and mammals, including humans and primates. A hallmark of herpesvirus infection is that the virus remains persistent in the infected host for life and is frequently reactivated and shed. In pigs, four herpesviruses have been identified: pseudorabies virus, porcine cytomegalovirus, and two recently identified lymphotrophic herpesviruses. Pseudorabies virus is an important veterinary pathogen. However, Canada has remained free of pseudorabies for many years, and since the infection in pigs is clinically apparent, its xenogeneic risk is diminished and of less concern in xenotransplantation.

Porcine cytomegalovirus (CMV) causes rhinitis in young pigs, and in older pigs the infection is subclinical. Similar to human CMV, porcine CMV crosses the placenta and infects fetuses, with resulting congenital infections. Porcine CMV is endemic worldwide, including Canada[9]. Porcine CMV may be secreted into semen. The ability of porcine CMV to infect lung macrophages raises some concern that it may modify host defence mechanisms and alter the pathogenic consequences in the host. Further studies need to be done on the pathogenic potential of the porcine CMV in humans. Despite its potential importance for xenogeneic infection, little is known about porcine CMV pathogenesis and cell tropisms. No data are available on human exposure to the virus.

Besides pseudorabies virus and CMV, two additional herpesviruses have recently been identified in pigs. The two sequences for herpesvirus found in pig spleen[10] were distinct from each other and furthermore were distinct from those of any known porcine herpesviruses sequences. The prevalence of the two new types is as high as 90% in domestic pigs. On the basis of the sequence information, these two new viruses have tentatively been designated porcine lymphotropic herpesvirus

types 1 and 2[11]. The viruses may replicate in lymphoblastoid cells with a specificity for either T or B lymphocytes. Despite the identification of the specific sequences, however, actual virus isolation has not yet been reported, and therefore their tropisms for other animal species, tissues, or lymphocytes are unclear.

Screening for swine viruses

Xenotransplantation may provide unique therapeutic benefits in modern medicine. A major concern, however, is the potential transmission of swine virus to humans and further transmission to the community from the xenograft recipient[2]. Therefore, viruses of concern need to be carefully screened. The list of tests available for known viruses in pigs should be comprehensive, and their sensitivity and specificity should be maximized. Research to detect unknown viruses of potential concern in xenotransplantation should be promoted. Development and use of animal models will provide the best opportunity to understand the basis for species jumping and viral pathogenesis. Policy development will be necessary to set up an appropriate national system for screening and monitoring animal sources and recipients for known viruses, discovery of new viruses, and development of new and better diagnostic methods. To provide reliable screening information, reference diagnostic laboratories need to be established for individual viruses. At a recent workshop organized by the Centre for Infectious Disease Prevention and Control of HC, general strategies for national surveillance and international coordination on xenotransplantation and xenozoonosis were discussed, and subsequently guidelines have been prepared. These guidelines will support the principles of xenogeneic safety with regard to individual and societal risks and benefits, as well as indicate future directions for xenotransplantation.

References

1. Herrera JL, Hill S, Shaw J et al. *Outbreak of Hendra-like virus – Malaysia and Singapore, 1998-1999*. MMWR 1999;48:265-69.
2. Yoo D, Giulivi A. *Xenotransplantation and the potential risk of xenogeneic transmission of porcine viruses*. Can J Vet Res 2000;64;193-203.
3. Hussaini SH, Skidmore SJ, Richardson P et al. *Severe hepatitis E infection during pregnancy*. J Viral Hepat 1997;4:51-4.
4. Meng XJ, Purcell RH, Halbur PG et al. *A novel virus in swine is closely related to the human hepatitis E virus*. Proc Natl Acad Sci USA 1997;94:9860-65.
5. Meng XJ, Halbur PG, Shapiro MS et al. *Genetic and experimental evidence for cross-species infection by the swine hepatitis E virus*. J Virol 1998;72:9714-21.
6. Meng XJ, Halbur PG, Haynes JS et al. *Experimental infection of pigs with the newly identified swine hepatitis E virus (swine HEV), but not with human strains of HEV*. Arch Virol 1998;143:1405-15.
7. Tischer I, Mields W, Wolff D et al. *Studies on epidemiology and pathogenicity of porcine circovirus*. Arch Virol 1986;91:271-76.
8. Harding JSC, Clark EG. *Recognizing and diagnosing post-weaning multisystemic wasting syndrome (PMWS)*. Swine Health Prod 1997:5:201-03.
9. Hamel AL, Lin L, Sachvie C et al. *PCR assay for detecting porcine cytomegalovirus*. J Clin Microbiol 1999;37:3767-78.
10. Ehlers B, Ulrich S, Goltz M. *Detection of two novel porcine herpesviruses with high similarity to gammaherpesviruses*. J Gen Virol 1999;80:971-78.
11. Ulrich S, Goltz M, Ehlers B. *Characterization of the DNA polymerase loci of the novel porcine lymphotrophic herpesviruses 1 and 2 in domestic and feral pigs*. J Gen Virol 1999; 80:3199-205.

Hospital Infection Control and Bloodborne Infective Agents

Francisco Diaz-Mitoma, Shirley Paton, Antonio Giulivi

Bloodborne infections are a worldwide health care burden. Many of these infections are acquired during a medical procedure and could be prevented by an appropriate preventive strategy in the health care setting. The purpose of this article is to review the current status of hospital infection control practices for well-recognized and emerging bloodborne viral infections. The prevention of bloodborne infections in the health care setting involves two main strategies: to decrease the risk of infection in patients who receive blood products and to avoid the transmission of potential pathogens between health care providers and patients. Significant evidence exists to suggest that not adhering to some form of consistently applied bloodborne pathogen protocol results in exposure to bloodborne pathogens from patient to health care worker (HCW), from HCW to patient, and from patient to patient[1,2].

Hospital infection control

The *Infection Control Guideline Series*[3], published by Health Canada, provides a comprehensive set of evidenced-based recommendations for hospitals and other health care facilities to adapt and implement in order to prevent and control infections that can be transmitted during the provision of health care. Infection control practices are continually evolving as new knowledge and new technology develop.

Historically, three forms of body fluid precautions have been practised in Canada. Before 1987, facilities used blood labeling precautions[4]; then, Universal Precautions (UP)[5] and Body Substance Isolation (BSI)[6] were developed. In 1997, new integrated bloodborne pathogen protocols were introduced with the publication of *Preventing the Transmission of Bloodborne Pathogens in Health Care and Public Service Settings*[7]. This was quickly followed in 1999 by the introduction of Routine Practices[8] (known as Standard Precautions in the United States[9]), a complete integration of bloodborne pathogen protocols with other critical infection prevention and control protocols. In the past 4 years most health care facilities in Canada have moved to adapt the new protocols.

UP and BSI address the problem of bloodborne pathogens from different perspectives. UP have an occupational health orientation focusing primarily on minimizing HCW exposure to bloodborne pathogens. BSI focuses on minimizing cross-infection risk from all pathogens for both patients and staff. The confusion between the two systems has led to frequent inconsistent, unsafe applications, often resulting in both underprotection of staff and overisolation of patients[10-12].

The principle of UP was that a single standard of blood and body fluid precaution be used with all patients at all times, i.e. it was assumed that all blood or visibly blood-contaminated body fluids were potentially infectious. UP were specifically intended to prevent transmission of bloodborne pathogens from patients to occupational groups that have the potential for exposure to blood in the line of duty. UP applied to blood and other body fluids containing visible blood, semen and

vaginal secretions, and cerebrospinal, synovial, pleural, peritoneal, pericardial, and amniotic fluids[13].

BSI, a strategy intended to prevent transmission of potential pathogens between patients, was introduced in 1987 as an alternative to UP[6]. Although BSI was implemented in a number of large Canadian and U.S. institutions, it was never embraced by government bodies in Canada or the U.S. BSI expanded the principles of UP to all body fluids. Unlike UP, BSI replaced all other traditional isolation strategies, with the exception of isolation for airborne infections and multiple drug-resistant organisms.

Routine Practices builds on the 1997 integration of the key elements of UP and BSI and then enables consistent application of key infection prevention and control protocols (including bloodborne pathogen protocols) to all patients at all times. Appropriately applied Routine Practices also enhance the safety of staff caring for patients.

The recent introduction of new needlestick prevention technology may offer additional protection from needlestick injuries when used in conjunction with Routine Practices.

Prevalence of bloodborne infections

Although little relevant information exists in Canada, the risk of transmission of bacterial infections via transfusion is now thought to be equal to or greater than the risk of viral infection. Bacterial infections account for > 10% of transfusion-related deaths reported to the Food and Drug Administration[14]. The risk of HCWs' exposure to bloodborne pathogens varies according to the prevalence of each potential infectious agent. The prevalence of bloodborne viral infections among people admitted to Canadian hospitals varies institutionally and provincially. The reported prevalence of hepatitis C seropositivity in the general population in the Yukon is 275 per 100,000[15]. In one Ontario community survey, 62 of 6,055 patients (1%) were seropositive for hepatitis C[16]. The prevalence rates of hepatitis B surface antigen, and antibodies to HIV and the hepatitis C virus (HCV) among people admitted to a Toronto hospital were 2.1%, 0.6%, and 0.5% respectively[17]. In a retrospective examination of donor records at the Eye Bank of Canada (Ontario), the prevalence of hepatitis B virus (HBV) was 0.25%, of HCV was 0.93%; and of HIV was 0.031%[18]. A seroprevalence survey of more than 6,000 individuals attending an Alberta STD clinic demonstrated HIV in 1.5% and HCV in 3.5% of the subjects[19]. In Vancouver, the prevalence rates of HIV-1 and HCV among intravenous drug users were 23% and 88% respectively[20]. The observed seroprevalence rates of these Canadian studies support the use of a proactive

prevention strategy to curtail the transmission of bloodborne pathogens in the health care setting.

Nosocomial sharp injuries

HCWs may be exposed to bloodborne pathogens during the course of their work, and percutaneous injuries are the main risk of exposure. Preliminary results from the new Canadian Needle Stick Surveillance Network (CNSSN) indicate that for the first 6 months of data collection, HCWs in 12 centres were exposed to 497 known sources. Forty-eight of the known sources tested positive for a bloodborne pathogen; more than half were from patients with hepatitis C, 15 % from patients with hepatitis B, and 20% from patients with HIV. Three exposures were from source patients positive for HIV and HCV (unpublished data).

Phlebotomy causes 13%-62% of the injuries reported to hospital occupational health services in North America[21,22]. CNSSN reports that phlebotomists have a rate of 14.5 exposures per full time employee equivalent (FTE), nurses have 2.21 exposures per FTE, and medical residents have 6.2 exposures per FTE (unpublished data) . There are more than 50 documented episodes of occupationally acquired HIV infection reported in the U.S., of which almost 40% occurred during phlebotomy[23,24]. In Canada, there has been only one documented case of HIV transmission to a health care worker, who had a needle stick injury[25]. The estimated risk of infection after sustaining a sharp injury for HIV, HBV, and HCV is 0.3%, 10%-35%, and 2.7% respectively[23,26,27].

Recognized bloodborne pathogens

Guidelines have been published on hepatitis B (as well as hepatitis C and HIV) postexposure prophylaxis for health care workers[28]. Hepatitis B immunization of health care workers at occupational risk reduces transmission in the health care setting. It is estimated that 5% to 8% of individuals are poor responders to HBV vaccination[29], but the rate of non-responders among Canadian HCWs is unknown. Individuals at high risk of exposure will benefit from confirmation of immunologic response to HBV vaccination by a test for anti-HB surface antigen. In addition, there is a small number of reported hepatitis B infections that have been contracted from health care providers who are chronic hepatitis B carriers[30]. It has been estimated that the risk of hepatitis B infection contracted from a physician or dentist is in the order of 240-2,400 per 1 million procedures. The *Proceedings of the Consensus Conference on Infected Health Care Workers* were published in July 1998[31]. More than 70 recommendations were accepted at the meeting, including mandatory hepatitis B immunization

and testing for health care workers (supported by 70% of participants). However, responses from the Canadian Medical Association and the Canadian Dental Association indicate that there is still strong controversy concerning maintenance of individuals' rights[31]. All hospitals in Canada have a voluntary immunization and testing policy for hepatitis B. To date, there are no Canadian data on the number of patients who have contracted infections from health care workers.

HCV is now rarely transmitted by blood transfusion. During 1985-1990, cases of transfusion-associated non-A, non-B hepatitis declined by greater than 50% because of screening policies that excluded donors with HIV infection and donors with surrogate markers for non-A, non-B hepatitis[32]. By 1990, the risk of transfusion-associated HCV infection was approximately 1.5% per recipient or approximately 0.02% per unit transfused[33]. In May 1990, routine testing of donors for evidence of HCV infection was initiated, and in July 1992 more sensitive multi-antigen testing was implemented, which further reduced the risk of infection to 0.001% per unit transfused[34]. Albumin or immune serum globulins have not been associated with viral transmission in Canada.

Approximately 30% of transfused patients are unaware that they have undergone transfusion of blood products. In one study, only 6.3% of patients transfused before 1990 had undergone testing for hepatitis C[35]. Notification programs have had success in convincing patients to undergo testing for HIV and HCV.

Several prevention strategies have been successful in decreasing the incidence of new hepatitis C infections. Blood screening and perhaps needle exchange programs have helped in reducing the rates of infection. Unfortunately, little improvement has been made in postexposure prophylaxis. The use of interferon alpha early during exposure is controversial, and there is no consensus recommendation. At present, the only licensed treatment for hepatitis C is interferon alpha and ribavirin, which are given as combination therapy[36]. Efforts are now directed to developing more effective antiviral agents for treatment. High affinity antibodies could be used in the future after liver transplantation of hepatitis C positive recipients. A vaccine is not likely to be available in the short term because of the inherent difficulty of developing a protective response to a virus with a rapid mutation rate and multiple genotypes.

Few HIV seroprevalence studies of HCWs have been published. These studies are important, because they may assist in estimating the extent of occupational risk of HIV infection. In one survey of HIV seroprevalence among 3,420 surgeons, 87.4% reported a blood-skin contact and 39.2% reported a percutaneous blood contact in the previous month, but none

was positive for HIV antibody[37]. Extensive reviews and postexposure guidelines have been published recently[31,38-44].

The combined administration of three antiviral drugs is recommended in cases of high risk exposure when the HCW has been exposed to a large volume of blood, a source patient with high HIV viral titre, or a patient suspected of having a multi-drug resistant HIV strain[42].

Nucleic acid testing (NAT) has been used to screen for blood or blood products potentially contaminated with HIV or HCV. The advantage of this method is that it can detect viral infections during the window period (from when a donor's blood is capable of transmitting HIV until detectable antibody appears). It is difficult, however, to assess the impact of NAT on the safety of the blood supply. The incidence of HIV and HCV associated with transfusion is already extremely low. The estimated risk of HIV infection per blood unit in Canada is 1 in 913,000[44]. In a recent review, Leparc found two donations in the U.S. that were reactive by HCV-NAT and one by HIV-NAT that were not detected by serologic tests. Since several blood components are prepared from each blood donation, the number of preventable transmissions may represent 2 to 3 times the number of rejected donations[45]. Therefore, the impact of NAT testing may be assessed from the rate of rejected donations, rather than through serology studies of blood recipients. In addition, it is difficult to determine the rate of infection transmission after a transfusion because of the short shelf life of some of the blood products, such as platelets, which could be transfused before results are available.

Since viremia precedes seroconversion by several days in the case of HIV and several weeks for HCV, tests that detect viral nucleic acids are considered a significant technologic advance and an additional step in our quest to achieve the goal of zero risk for blood transfusion recipients.

Currently, two test systems are being used by about 20 testing sites that test all blood collected in the U.S.: a combined HIV-1/HCV RNA in a single tube in a multiplex format (Genprobe/Chiron) and a single-probe system for HCV (Roche).

In Canada, HCV NAT was implemented first because it has a bigger impact on safety. Mathematical models indicate that NAT for HCV would detect an additional 4-6 cases of HCV a year in Canada, whereas NAT for HIV is predicted to detect 1 additional case of HIV every 18-24 months. (This is because the window period is significantly longer for HCV than HIV, and the reduction of this window period by NAT has a much greater impact on HCV detection). There are no data suggesting that human T-cell lymphotropic virus (HTLV) type

II or I is transmitted in the health care setting, and the seroprevalence rates in the population are extremely low. A recent survey of transfused patients found no cases of HTLV infection in 5,939 recipients[46].

Potential bloodborne infective agents

Herpesviruses

Transmission of human herpesvirus 6 (HHV-6), HHV-7, Epstein-Barr virus (EBV), cytmomegalovirus (CMV), and other herpesviruses, such as HHV-8, require close contact between mucous membranes and direct inoculation of mucous membranes with fresh secretions. The viruses are found in genital secretions and blood. Removal of lymphocytes may decrease the transmission of CMV through blood transfusion and likely also EBV and HHV-8, as these are also cell-associated viruses[47-49]. HHV-8 is associated with Kaposi's sarcoma in 80% of cases. Its prevalence (0%-20%) varies, depending on the country[50]. Kaposi's sarcoma has never been reported after blood transfusion. Viral DNA searches based on polymerase chain reaction (PCR) have yielded negative results for HHV-8 in 19 poly-transfused subjects. Continual monitoring is required for recipients at risk (e.g. those who are immunosuppressed). The practice of lymphocyte removal from blood products has decreased the risk of transmission of CMV, and it may likely also decrease the risk of transmission for other pathogens in susceptible populations[51,52].

Parvovirus

In Canada, the rate of parvovirus infection among adults is around 40%. Most infections occur in childhood between the ages of 4 and 12. The spectrum of parvovirus disease varies widely. The most distinctive presentation is that of fifth disease or erythema infectiosum, which is characterized by a rash mainly in the cheeks. Parvovirus can also cause arthritis, a frequent presentation when the infection occurs in adult women. Patients with an underlying hemoglobinopathy or immunodeficiency may have severe anemia during parvovirus infections. In addition, transplacental spread of infection may result in intrauterine infection and the onset of hydrops fetalis. Parvovirus is an infrequent cause of infection transmitted during blood transfusions[53-56].

Hepatitis G

Hepatitis G virus (HGV), also known as GB virus C (~9,392 nucleotides), is a newly discovered flavivirus that is transmissible by blood transfusion and other possible routes. It has been detected in 2%-4% of blood donors[57]. Hepatitis G virus is not an accurate name for this bloodborne agent, as it is not a cause of hepatitis[58]. Ten percent of patients with chronic non-A-E hepatitis are HGV RNA positive. The incidence of HGV infection is higher than expected from PCR studies, and HGV has a high prevalence in the world. Among 220 cases of needle-stick injuries, 21 employees were contaminated with HGV[59]. Initially, none of the 21 recipients was HGV positive. Fourteen of them were followed up and further tested for HGV RNA and serum anti-envelope (E2) specific antibody. None of the 21 recipients exposed to HGV developed liver function abnormalities, but one of the 14 recipients who were followed up became positive for HGV RNA after the injury[59].

TTV

Transfusion transmitted virus (TTV) is a novel family of parvo-like non-enveloped DNA viruses recently classified in the family *Circinovidae*[60]. TTV is an agent in search of a disease association. Its prevalence varies from 2% to 80%, and although infections are found in the general population they are more common in patients who have received multiple transfusions with blood products. TTV was found in approximately 10% of U.S. volunteer blood donors, 13% of commercial blood donors, and 17% of intravenous drug abusers. As well, the rate of TTV infection among non-A, non-E hepatitis patients in the U.S. was only 2%[61]. There are no published studies of TTV prevalence in Canadian populations.

SEN-V

Discovered in 1999, SEN-V is a single-stranded DNA virus without an envelope. As with TTV, it is highly variable in nucleic acid sequence and comprises at least eight viral subtypes or genotypes. It is approximately 3,340 base pairs in length and contains at least three open reading frames (ORFs) that code for one protein each[62]. None of the SEN-V ORF sequences hybridizes specifically to that of TTV.

Some strains of this virus are reportedly associated with acute and chronic hepatitis. Between 80% and 90% of viral hepatitis cases are caused by hepatitis viruses A, B, C, D, and E; up to 20% are caused by unknown agents, hence, the acronym non-A non-E hepatitis, or NANE. Because SEN-V is present in 80% of such cases, it is believed to play a role in these illnesses. Although the presence of the virus does not imply that it causes illness, some scientists are optimistic that they

have found a cause of hepatitis that had previously gone unnoticed. Before the discovery of SEN-V, TTV had been a promising candidate for NANE causation because it was present in a large proportion (55%) of NANE patients. It was later shown, however, that TTV is also present in a relatively large proportion (5%-7%) of healthy donors[63,64].

References

1. Ricketts M, Deschamps L. *Reported seroconversions to human immunodeficiency virus among workers worldwide — a review.* Can J Infect Control 1992;7:85-90.

2. Jagger J, Powers RD, Day JS et al. *Epidemiology and prevention of blood and body fluid exposures among emergency department staff.* J Emerg Med 1994;12;6:753-65.

3. URL: <www.hc-sc.gc.ca/hbp/lcdc/publica>

4. Health and Welfare Canada. *Infection control guidelines for isolation and precaution techniques.* Ottawa: Health and Welfare Canada, 1985.

5. Health Canada. *Recommendations for prevention of HIV transmission in health-care settings.* CDWR 1987;13S3:1-10.

6. Lynch P, Jackson MM, Cummings MJ et al. *Rethinking the role of isolation practices in the prevention of nosocomial infections.* Ann Intern Med 1987;107:243-46.

7. Health Canada. *Preventing the transmission of bloodborne pathogens in health care and public services settings.* CCDR 1997;23S3.

8. Health Canada. *Routine practices and additional precautions for preventing the transmission of infection in health care.* CCDR 1999;25S4.

9. Garner JS. *Guideline for isolation precautions in hospitals.* Infect Control Hosp Epidemiol 1996;17:54-80.

10. Jackson MM, Lynch P. *An attempt to make an issue less murky: a comparison of four systems for infection precautions.* Infect Control Hosp Epidemiol 1991;12:448-50.

11. Birnbaum D, Schulzer M, Mathias RG et al. *Adoption of guidelines for universal precautions and body substance isolation in Canadian acute-care hospitals.* Infect Control Hosp Epidemiol 1990;11:465-72.

12. Gruendemann BJ. *Are universal precautions (UPs) up for question?* Asepsis 1994;16:1.

13. Health Canada. *Update: universal precautions for prevention of transmission of human immunodeficiency virus, hepatitis B virus and other bloodborne pathogens in health-care settings.* CDWR 1988;14:117-24.

14. Carson JL, Altman DG, Duff A et al. *Risk of bacterial infection associated with allogeneic blood transfusion among patients undergoing hip fracture repair* [see comments]. Transfusion 1999;39(7):694-700.

15. Spurgeon D. *Canadians sue over hepatitis C infection* [news]. BMJ 1997;315(7104):330.

16. Manuel DG, Johnson I, Fearon M et al. *The prevalence of hepatitis C in a community-based population, Ontario, 1996.* CCDR 1999;25(23):193-9.

17. Louie M, Low DE, Feinman SV et al. *Prevalence of bloodborne infective agents among people admitted to a Canadian hospital* [see comments]. Can Med Assoc J 1992;146(8):1331-34.

18. Armstrong SA, Gangam N, Chipman ML et al. *The prevalence of positive hepatitis B, hepatitis C, and HIV serology in cornea donors prescreened by medical and social history in Ontario, Canada.* Cornea 1997;16(5):512-6.

19. Romanowski B, Campbell PJ, Preiksaitis JK et al. *Human immunodeficiency virus seroprevalence and risk behaviors in patients attending sexually transmitted disease clinics in Alberta.* Sex Transm Dis 1997;24(8):487-94.

20. Strathdee SA, Patrick DM, Currie SL et al. *Needle exchange is not enough: lessons from the Vancouver injecting drug use study.* AIDS 1997;11(8):F59-F65.

21. McCormick RD, Meisch MG, Ircink FG et al. *Epidemiology of hospital sharps injuries: a 14-year prospective study in the pre-AIDS and AIDS eras.* Am J Med 1991;91(suppl 3B):301S-307S.

22. McGeer A, Simor AE, Low DE. *Epidemiology of needlestick injuries in house officers.* J Infect Dis 1990;162:961-4.

23. Henry K, Campbell S. *Needlestick/sharps injuries and HIV exposure among health care workers. National estimates based on a survey of U.S. hospitals.* Minerva Med 1995;78(11):41-4.

24. Henderson DK, Fahey BJ, Willy M et al. *Risk for occupational transmission of human immunodeficiency virus type 1 (HIV-1) associated with clinical exposures. A prospective evaluation* [see comments]. Ann Intern Med 1990;113(10):740-6.

25. Deschamps L, Archibald C. *National surveillance of occupational exposure to the human immunodeficiency virus.* CCDR 1996;22(7):52-4.

26. Gerberding JL. *Transmission of HIV in health care workers.* J Thorac Imaging 1991;6(4):12-5.

27. Gerberding JL. *Incidence and prevalence of human immunodeficiency virus, hepatitis B virus, hepatitis C virus, and cytomegalovirus among health care personnel at risk for blood exposure: final report from a longitudinal study* [see comments]. J Infect Dis 1994;170(6):1410-17.

28. Health Canada. *An integrated protocol to manage health care workers exposed to blood-borne pathogens.* CCDR 1997;23(S2):1-14.

29. Franks AL, Berg CJ, Kane MA et al. *Hepatitis B virus infection among children born in the United States to Southeast Asian refugees.* N Engl J Med 1989;321:1301-5.

30. *Transmission of hepatitis B to patients from four infected surgeons without hepatitis B e antigen. The Incident Investigation Teams and others.* N Engl J Med 1997;336(3):178-84.

31. Health Canada. *Proceedings of the Consensus Conference on Infected Health Care Workers: risk for transmission of bloodborne pathogens.* CCDR 1998;24(S4)

32. Dufour MC. *Chronic liver disease and cirrhosis.* In: Everhart JE, ed. *Digestive diseases in the United States: epidemiology and impact.* Washington, DC: US Government Printing Office, 1994. NIH publication no. 94-1447, 614-45.

33. Chappel RJ, Dax EM. *Blood screening — the next generation in testing* [editorial]. Aust N Z J Med 1999;29(6):763-4.

34. Williams I. *Epidemiology of hepatitis C in the United States.* Am J Med 1999;107(6B):2S-9S.

35. Heddle N, Kelton JG, Smaill F et al. *A Canadian hospital-based HIV/hepatitis C look-back notification program* [see comments]. Can Med Assoc J 1997;157(2):149-54.

36. Gutfreund KS, Bain VG. *Chronic viral hepatitis C: management update.* Can Med Assoc J 2000;162(6):827-33.

37. Tokars JI, Chamberland ME, Schable CA et al. *A survey of occupational blood contact and HIV infection among orthopedic surgeons. American Academy of Orthopaedic Surgeons Serosurvey Study Committee.* JAMA 1992;268(4):489-94.

38. Babl FE, Cooper ER, Damon B et al. *HIV postexposure prophylaxis for children and adolescents.* Am J Emerg Med 2000;18(3):28.

39. Goldberg D, Johnston J, Cameron S et al. *Risk of HIV transmission from patients to surgeons in the era of post- exposure prophylaxis.* J Hosp Infect 2000;44(2):99-105.

40. Sidwell RU, Green JS, Novelli V. *Management of occupational exposure to HIV— what actually happens.* Commun Dis Public Health 1999;2(4):287-90.

41. Lurie P, Miller S, Hecht F et al. *Postexposure prophylaxis after nonoccupational HIV exposure: clinical, ethical, and policy considerations* [see comments]. JAMA 1998;280(20):1769-73.

42. *Public Health Service guidelines for the management of health-care worker exposures to HIV and recommendations for postexposure prophylaxis.* MMWR 1998;47(RR-7):1-33.

43. Centers for Disease Control and Prevention. *Case-control study of HIV seroconversion in health-care workers after percutaneous exposure to HIV-infected blood — France, United Kingdom, and United States, January 1988-August 1994.* MMWR 1995;44(50):929-33.

44. Remis RS, Delage G, Palmer RW. *Risk of HIV infection from blood transfusion in Montreal.* Can Med Assoc J 1997;157(4):375-82.

45. Leparc, G F *Nucleic acid testing for screening donor blood.* Infect Med 2000;17(5):310, 333.

46. Regan FA, Hewitt P, Barbara JA et al. *Prospective investigation of trans-fusion transmitted infection in recipients of over 20 000 units of blood. TTI Study Group.* BMJ 2000;320(7232):403-6.

47. Zwicky C, Tissot JD, Mazouni ZT et al. *Prevention of post-transfusion cytomegalovirus infection: recommendations for clinical practice.* Schweiz Med Wochenschr 1999;129(29-30):1061-6.

48. Pamphilon DH, Rider JR, Barbara JA et al. *Prevention of transfusion-transmitted cytomegalovirus infection.* Transfus Med 1999;9(2):115-23.

49. Wagner HJ, Kluter H, Kruse A et al. *Relevance of transmission of Epstein-Barr virus through blood transfusion.* Beitr Infusionsther Transfusionsmed 1994;32:138-41.

50. Whitby D, Smith NA, Matthews S et al. *Human herpesvirus8: seroepidemiology among women and detection in the genital tract of seropositive women.* J Infect Dis 1999;179(1):234-6.

51. Gilbert GL, Hayes K, Hudson IL et al. *Prevention of transfusion-acquired cytomegalovirus infection in infants by blood filtration to remove leucocytes.*

Neonatal Cytomegalovirus Infection Study Group [see comments]. Lancet 1989;1(8649):1228-31.

52. Pietersz RN, van der Meer PF, Seghatchian MJ. *Update on leucocyte depletion of blood components by filtration.* Transfus Sci 1998;19(4):321-8.

53. Wakamatsu C, Takakura F, Kojima E et al. *Screening of blood donors for human parvovirus B19 and characterization of the results.* Vox Sang 1999;76(1):14-21.

54. Vrielink H, Reesink HW. *Transfusion-transmissible infections.* Curr Opin Hematol 1998;5(6):396-405.

55. Jordan J, Tiangco B, Kiss J et al. *Human parvovirus B19: prevalence of viral DNA in volunteer blood donors and clinical outcomes of transfusion recipients.* Vox Sang 1998;75(2):97-102.

56. Simmonds P. *Transfusion virology: progress and challenges.* Blood Rev 1998;12(3):171-77.

57. Linnen J, Wages J Jr, Zhang-Keck ZY et al. *Molecular cloning and disease association of hepatitis G virus: a transfusion-transmissable agent.* Science 1996;271(5248):505-8.

58. Alter H. *Discovery of non-A, non-B hepatitis and identification of its etiology.* Am J Med 1999;107(6B):16S-20S.

59. Shibuya A, Takeuchi A, Sakurai K et al. *Hepatitis G virus infection from needle-stick injuries in hospital employees.* J Hosp Infect 1998;40(4):287-90.

60. Mushahwar IK, Erker JC, Muerhoff AS et al. *Molecular and biophysical characterization of TT virus: evidence for a new virus family infecting humans.* Proc Natl Acad Sci USA 1999;96(6):3177-82.

61. Desai SM, Muerhoff AS, Leary TP et al. *Prevalence of TT virus infection in US blood donors and populations at risk for acquiring parenterally transmitted viruses* [see comments]. J Infect Dis 1999;179(5):1242-4.

62. Fiordalisi G, Bonelli M, Olivero P et al. *Identification of SENV genotypes.* Requested Patent WO0028039. 18 May 2000.

63. Berg T, Schreier E, Heuft HG et al. *Occurrence of a novel DNA virus (TTV) infection in patients with liver diseases and its frequency in blood donors.* J Med Virol 1999;59(1):117-21.

64. Pisani G, Antigoni I, Bisso G et al. *Prevalence of TT viral DNA in Italian blood donors with and without elevated serum ALT levels: molecular charac-terization of viral DNA isolates.* Haematologica 2000;85(2):181-85.

Germicide Inactivation of Hepatitis B and C Viruses*

Syed A. Sattar, Jason Tetro, V. Susan Springthorpe, Antonio Giulivi

HBV and HCV are enveloped and relatively sensitive to many physical and chemical agents. Both viruses are difficult to culture in the laboratory, and this seriously limits our understanding of their environmental survival as well as the need and choice of chemical germicides in preventing/controlling their environmental transmission. The information often quoted on the environmental stability of HBV and HCV comes from experiments in which the integrity of viral particles, antigens, nucleic acid, or enzymes was used as an indicator of the presence or absence of infectious virus. Doubtless, such approaches were justified in the absence of readily available means of detecting and quantitating such particles, but their conclusions must be interpreted very carefully. For example, when medical devices disinfected with 2% alkaline glutaraldehyde were tested for the presence of duck HBV (DHBV), PCR showed many of them to be positive, whereas no infectious virus could be detected when the same samples were injected into susceptible ducklings.

Virtually nothing is known about the environmental survival of HCV except that its RNA in plasma or serum has been found to be stable at $4°$ C for 7 days[1]. However, the stability of viral RNA should not be equated with the preservation of virus infectivity.

Relatively little is known about the inactivation of HBV and HCV by chemical germicides, and the wide variations used in working with these viruses in particular make it quite difficult to properly compare the limited data available. The findings of representative studies on HBV inactivation by chemical germicides based on the chimpanzee model have been summarized before[2,3].

Until recently, there were no *in vitro* tests for the virucidal activity of chemical germicides against HCV. Bovine viral diarrhea virus (BVDV) has some properties similar to HCV and has been used in the blood product industry as a surrogate for it. HCV has been found to replicate in Vero cells without producing any cytopathic effects. Since molecular or immunologic methods can be used to detect the virus in infected cells, this opens the door for direct testing of germicides against it.

The following are specific details on the known or expected activities of major classes of chemical germicides against these two viruses and the application of such chemicals in health care. The same information is relevant to other settings where there is potential for hepatitis B and hepatitis C spread by means other than direct person-to-person contact and transfusion of tainted blood and product products.

Aldehydes

As can be seen from Table 1, formulations based on formaldehyde and glutaraldehyde can be highly effective in inactivating HBV and HCV. Recent and well-designed studies with DHBV have clearly reinforced the importance of precleaning in the chemical disinfection of heat-sensitive medical devices. As has been shown in a recent study by Chaufour et al[4], decontamination even with otherwise highly effective chemicals such as glutaraldehyde can fail in the absence of proper cleaning of the devices being disinfected.

It is interesting to note that, some two decades ago, glutaraldehyde-based products were being recommended as a substitute for bleach in the decontamination of environmental surfaces. Obviously, this view is no longer relevant in view of the current safety concerns with glutaraldehyde. However, such use continues in some places.

Chlorine and iodine

Sehulster et al[5] showed that exposure of Dane particles of HBV to sodium hypochlorite (5600 ppm) disrupted them and also inactivated their polymerase activity. Agolini et al[6] have shown that chlorine (2500 ppm) could reduce the binding of HCV to host cells and that a contact time of at least 10 minutes was required to achieve a 91.7% cell reduction and infection. This observation needs confirmation.

No differences were found in the susceptibility of HBV and DHBV to about 3000 ppm of available chlorine as bleach or as sodium dichloroisocyanurate (NaDCC), a compound that releases chlorine on demand[7].

A 1:10 dilution of domestic bleach, which contains about 5000 ppm of available chlorine, is commonly recommended for clean up of blood spills, and this level of chlorine should be considered more than adequate to deal with HBV and HCV in such blood[8]. However, the use of undiluted bleach (> 50,000 ppm of available chlorine) for the decontamination of shared needles and syringes[9] requires review (see Decontamination of shared needles).

Experimental data on the ability of iodine-based germicides to inactivate HBV and HCV are limited, but it is expected that such products would be effective in concentrations equivalent to those of available chlorine.

Phenolics and quaternary ammonium compounds

Prince et al[10] determined the activity of two quaternary ammonium-based products (500 and 700 ppm) as well as a phenolic (700 ppm) using a carrier test with either human HBV or DHBV. The contact time was 10 minutes at 20° C. All products proved effective against both viruses in the chimpanzee inoculation and the morphologic alteration and disintegration tests (MADT)[3].

Agolini et al[6] have also determined that subjecting HCV to a phenolic for 5 minutes effectively eliminated the ability of the virus to attach to Vero cells.

Alcohols

Ethanol and isopropanol, in the range of 70% to 80%, are effective against HBV[11,12] and most likely against HCV as well. Therefore, alcohol-based surface disinfectants, hand rubs and pre-operative skin preparations would be expected to interrupt virus spread effectively. However, it is important to ensure adequate contact between the disinfectant and the viruses on contaminated surfaces. This may not always occur by simple wiping with alcohol. Furthermore, the presence of gross amounts of blood may interfere with the germicidal action of alcohols, in that their fixative properties may hinder the ability of alcohols to penetrate through the dried organic debris.

Peroxygen systems and gas plasma

Vickery et al[13] have shown that the Sterrad system, which is based on a high concentration of vaporized hydrogen peroxide, was highly effective in inactivating DHBV even in the presence of blood as a soil load. Formulations based on stabilized hydrogen peroxide[14] have not been tested against HBV but, on the basis of their activity against tougher organisms, such as mycobacteria and non-enveloped viruses[14,15], would be expected to work against it.

Smith and Pepose[16] regard 3% hydrogen peroxide to be adequate for the inactivation of a variety of pathogens, including HCV, on tonometer prisms and trial contact lenses. It is important to note that a 3% solution of hydrogen peroxide, unless mixed with other chemicals to accelerate and potentiate its activity, is a relatively weak germicide[17] and may require several hours of contact to be effective against susceptible organisms such as vegetative bacteria and enveloped viruses.

We are not aware of any published data on the activity of the Steris system against HBV and HCV, but it is most likely to be effective against them because of the relatively high levels of peracetic acid and temperature employed.

Gasparini et al[18] showed that a 1% (weight per volume) solution of Virkon could destroy the surface antigen of HBV (HBsAg) with a contact time of 10 minutes. The virus

Table 1
Various means of hepatitis B and hepatitis C spread and the relevance of chemical germicides in infection control

Means of spread	Degree of relevance	Comments
Spread from infected mother to the fetus, during childbirth and/or possibly during breast-feeding	Very low	Germicides can play no role in preventing such spread.
Artificial insemination with semen from unscreened donors		
Transplantation of organs from unscreened donors		
Accidental exposure of healthcare personnel to needles and sharps		
Body contact with blood during sports such as wrestling and rugby		
Transfusion of inadequately screened blood or blood products	High	Germicides, alone or in combination with physical agents, can be used for virus inactivation in blood products.
Sharing of needles and syringes in illicit drug use	Very high	Germicides can play a crucial role in interrupting virus spread through such means. This is especially true in the decontamination of shared needles and syringes. Although bleach is commonly recommended and used for this purpose, there is an urgent need to find an equally cheap, effective yet safer substitute for it. Such objects may pose the greatest risk when freshly contaminated; items such as toothbrushes are not meant to be shared and are also generally unsuitable for chemical disinfection; but, if items such as disposable or non-disposable shaving razors are to be shared, they must be chemically disinfected between different users.
Sharing of paraphernalia in using non-injectable drugs		
Use of contaminated needles and syringes in administering injectables		
Use of improperly decontaminated medical, dental and surgical devices		
Use of blood-containing sharps and instruments in ritual scarification, circumcision, blood-letting, tattooing, ear- and body-piercing, acupuncture, hair removal by electrolysis and sharing of shaving razors		
Hemodialysis with shared equipment and in inadequately cleaned and monitored settings	Moderate	Chemical disinfection of shared hemodialysis equipment can reduce the risk of virus spread. Use of gloves and other standard precautions would be more useful than the use of chemical germicides alone for the decontamination of environmental surfaces.
Unprotected sexual contact with virus-infected individuals	Moderate	In addition to barrier protection, use of germicidal gels may reduce the risk of such spread; however, chemicals that can inactivate the viruses may not be safe for repeated long-term use.
Non-venereal contact in domestic and institutional settings with chronic carriers of HBV or HCV	Low	The vehicle(s) for such spread, which occurs predominantly in conditions of overcrowding and poor hygiene, remain(s) unidentified. Sharing of toys and items of personal use such as toothbrushes are most likely to play a role, in which case, use of germicides is unlikely to be useful in infection control.

Table 1
Various means of hepatitis B and hepatitis C spread and the relevance of chemical germicides in infection control

Means of spread	Degree of relevance	Comments
Nosocomial and iatrogenic spread other than through the use of contaminated medical, dental and surgical devices	Low to moderate	In most settings, hands probably play a minor role in the spread of the viruses; however, regular and proper handwashing with soap and water may be sufficient to virtually eliminate the risk. Use of alcohol-based hand gels between handwashings is also considered effective; residual germicidal activity is not likely to be protective if damaged skin of hands is exposed to blood containing HBV or HCV.
		Any HBV or HCV on the skin surface would be readily removed/inactivated during the scrubbing procedure; however, the viruses in any leaked blood during surgery from a chronically infected surgeon's hands would most likely remain infectious.
		Skin antisepsis may be helpful only in situations in which the surgical site is contaminated with blood other than that of the patient.
Contact with environmental surfaces	Low to moderate	Environmental surfaces rarely act as vehicles for the two viruses, with the possible exception of those in hemodialysis units.
		Germicide decontamination of spills of blood and other contaminated fluids before and after their clean up forms an essential part of infection control.
Non-intact or compromised skin, e.g. chapped hands	Moderate	Topicals may play a role but proper testing is needed to confirm product potency.

challenge was a 1:30 dilution of a pool of HBsAg-positive sera. The authors suggest that the low toxicity and non-irritating nature of this product also make it a better substitute for glutaraldehyde. Similar studies have been done with the no-foam version of Virkon, and a 3% solution of the product was found to be effective against HBV in a contact time of 10 minutes[19].

Sodium hydroxide

As would be expected, 0.1 N NaOH was found to be capable of inactivating pseudorabies virus and BVDV, used as surrogates for HBV and HCV respectively, in 30 seconds at 60° C[20]. Obviously, the highly corrosive nature of this procedure restricts its use to the treatment of biomedical wastes and process residues.

Acidic electrolyte water

A recent study using acidic electrolyte water has shown that a 5-minute exposure resulted in complete loss of HCV infectivity[21]. These observations, based on the detection of viral RNA as an indicator for the presence or absence of infectious virus, require corroboration. However, these electronically produced mixed oxidant systems may be effective at lower concentrations than single oxidant species such as chlorine.

Other types of germicidal chemicals, including topicals

The relatively low resistance of HBV and HCV to germicides tested so far indicates strongly that many properly formulated products based on a variety of chemicals may also inactivate the two viruses. These may include some novel formulations, and the advent of acceptable surrogate test systems promises to expand our understanding of HBV and HCV disinfection.

Special mention needs to be made of topical products. Widespread use of products such as chlorhexidine gluconate in infection control suggests that they should be examined for activity against HBV and HCV.

Table 1 summarizes the recognized means of HBV and HCV spread and the relative importance of chemical germicides in interrupting their transmission.

Decontamination of shared needles and syringes

There is no doubt that injecting drug users are at the greatest risk of acquiring a bloodborne infection as a result of the practice of sharing needles. At the moment, there is only one rapid and cost-effective method to interrupt the spread of bloodborne pathogens through shared needles, and that is the proper use of a germicide to disinfect them between uses. Domestic bleach is often recommended and used for this purpose[9].

Disinfection of critical and semi-critical heat-sensitive medical devices

Improperly decontaminated medical devices can play a role in the spread of bloodborne pathogens, and HBV and HCV are no exception in this regard. At the same time, it must be remembered that high-level disinfectants as a class should be considered strong enough to inactivate these two viruses on such instruments with proper precleaning[4].

The duck hepatitis model offers considerable promise in the evaluation of emerging products and technologies for the decontamination of HBV-contaminated medical devices. Parallel studies on HCV may not be necessary in view of the fact that it is not known to be any more resistant than HBV.

Spermicidal gels

Chemicals such as nonoxynol-9, commonly used in spermicidal gels or "invisible condoms", can produce micro-ulceration of the vaginal mucosa with prolonged use, thereby actually increasing the risk of exposure to pathogens such as HIV, HBV, and HCV. Renewed efforts are needed to find safer substitutes for such chemicals and properly test their activity against major types of sexually transmitted pathogens.

Although many of the studies cited here show successful inactivation of HBV and HCV, it must be emphasized that the test conditions often bear little resemblance to field use.

The proposed surrogates offer the opportunity to examine HBV and HCV disinfection under more realistic conditions. This is particularly true for HBV using the DHBV model, as already shown by Chaufour et al[4]. In our view, environmental surface disinfectants to be used in most settings require no demonstrated activity or label claims against such viruses.

Manufacturers of chemical germicides must be actively discouraged from having their products tested against HBV and HCV using animals such as the chimpanzee. Label claims against such viruses may be permitted for high-level disinfectants only when the testing has been conducted using (a) a proper carrier test, (b) a suitable surrogate virus, (c) a soil load high enough to reflect that found in blood and other body fluids, (d) a contact time and product:target virus ratios commensurate with the recommended field use(s) of the product and (e) use of sufficient replicates from at least three lots of the product. The importance of proper product neutralization and other controls to make the results scientifically and statistically valid also needs to be emphasized. In the case of cell culture, it is important to show that any product residual affects neither the virus nor the virus-cell interactions, which form the basis for the assay[22].

Glutaraldehyde and ethylene oxide, both commonly used for decontaminating heat-sensitive medical devices, are unsafe for humans. Accidental or deliberate exposure of eyes to domestic bleach, a germicide frequently employed in the decontamination of shared disposable needles and syringes, can be quite harmful and has recently caused concerns for the safety of penitentiary staff in particular.

Manufacturers of reusable and disposable medical devices must be encouraged to work with germicide makers as well as infection control practitioners and other health care workers so that such devices can be made safer and easier to clean and disinfect. Lack of such input increases the risk of spread of infections. For example, a spring-loaded fingerstick device for blood sample collection, designed to a hold sterile and disposable lancet, was incriminated in the spread of hepatitis B because the reusable holder itself would become contaminated with blood but did not require decontamination between uses[23].

The continuing reports of HBV and HCV spread in hemodialysis units, even those that apparently adhere strictly to established infection control guidelines[24], require further investigation to elucidate the exact means of virus spread. Such studies should also help in better defining the need for environmental decontamination in such settings.

References

1. Cardoso MS, Koerner K, Hinz W et al. *Hepatitis C virus stability: the issue!* Vox Sang 1999;76:124-27.

2. Sattar SA, Tetro J, Springthorpe VS et al. *Preventing the spread of hepatitis B and C viruses: Where are germicides relevant?* Am J Infect Control (in press).

3. Thraenhart O. *Measures for disinfection and control of viral hepatitis*. In: Block SS (ed): *Disinfection, sterilization and preservation.* Philadelphia: Lea and Febiger, 1991:445-71.

4. Chaufour X, Deva AK, Vickery K et al. YE. *Evaluation of disinfection and sterilization of reusable angioscopes with the duck hepatitis B model.* J Vasc Surg 1999;30:277-82.

5. Sehulster LM, Hollinger FB, Dreesman R et al. *Immunological and biophysical alteration of hepatitis B virus antigens by sodium hypochlorite disinfection*. Appl Environ Microbiol 1981;42:762-67.

6. Agolini G, Russo A, Clementi M. *Effect of phenolic and chlorine disinfectants on hepatitis C virus binding and infectivity*. Am J Infect Control 1999;27(3):236-39.

7. Tsiquaye KN, Barnard J. *Chemical disinfection of duck hepatitis B virus: a model for inactivation of infectivity of hepatitis B virus.* J Antimicrob Chemotherp 1993;32:313-23.

8. Health Canada. *Infection control guidelines: preventing the transmission of bloodborne pathogens in health care and public service settings*. CCDR 1997;23S3:1-43.

9. Shapshak P, McCoy CB, Shah SM et al. *Preliminary laboratory studies of inactivation of HIV-1 in needles and syringes containing infected blood using undiluted bleach*. J Acquired Immunodeficiency Syndrome 1994;7:754-59.

10. Prince DL, Prince HN, Thraenhart O et al. *Methodological approach to disinfection of human hepatitis B virus.* J Clin Microbiol 1993;31:3296-304.

11. Bond WW, Favero MS, Petersen NJ et al. *Inactivation of hepatitis B virus by intermediate-to-high level disinfectant chemicals*. J Clin Microbiol 1983;18:535-38.

12. Kobayashi H, Tsuzuki M, Koshimizu K et al. *Susceptibility of hepatitis B virus to disinfectants and heat.* J Clin Microbiol 1984;20:214-16.

13. Vickery K, Deva AK, Zou J et al. *Inactivation of duck hepatitis B virus by a hydrogen peroxide gas plasma sterilization system: laboratory and "in-use" testing*. J Hosp Infect 1999;41:317-22.

14. Sattar SA, Springthorpe VS, Rochon M. *A product based on accelerated and stabilized hydrogen peroxide: evidence for broad-spectrum germicidal activity*. Can J Infect Control 1998;13:123-30.

15. Sattar SA, Taylor YE, Paquette M et al. *In-hospital evaluation of 7.5% hydrogen peroxide as a disinfectant for flexible endoscopes.* Can J Infect Control 1996;11(2):51-4.

16. Smith CA, Pepose JS. *Disinfection of tonometers and contact lenses in the office setting: Are current techniques adequate?* Am J Ophthalmol 1999;127(1):77-84.

17. Best M, Springthorpe VS, Sattar SA. *Feasibility of a combined carrier test for disinfectants: studies with a mixture of five types of microorganisms*. Am J Infect Control 1994;22:152-62.

18. Gasparini R, Pozzi T, Magnelli R et al. *Evaluation of in vitro efficacy of the disinfectant Virkon*. Eur J Epidemiol 1995;11:193-97.

19. Scioli D, Pizzella T, Vollaro L et al. *The action of VIRKON No Foam on the hepatitis B virus.* Eur J Epidemiol 1997;13:879-83.

20. Borovec S, Broumis C, Adcock W et al. *Inactivation kinetics of model and relevant blood-borne viruses by treatment with sodium hydroxide and heat.* Biologicals 1998;26:237-44.

21. Tsuji S, Kawano S, Oshita M et al. *Endoscope disinfection using acidic electrolyte water.* Endoscopy 1999;31:528-35.

22. Sattar SA, Springthorpe VS. *Viricidal activity of biocides: activity against human viruses*. In: Russell AD, Hugo WB, Ayliffe GAJ (eds): *Principles and practice of disinfection, preservation and sterilization* 3rd edition. Oxford: Blackwell Science, 1999:168-86.

23. Centers for Disease Control and Prevention. *Nosocomial transmission of hepatitis B virus infection associated with reusable fingerstick blood sampling device. Ohio and New York 1996.* MMWR 1997; 47:217-21.

24. Grethe S, Gemsa F, Monazahian M et al. *Molecular epidemiology of an outbreak of HCV in a hemodialysis unit: direct sequencing of HCV-HVR1 as an appropriate tool for phylogenetic analysis.* J Med Virol 2000;60:152-58.

The Effectiveness of Harm Reduction Strategies in Modifying Hepatitis C Infection among Injection Drug Users in Canada

Lynne Leonard, Christine Navarro, Linda Pelude, Leslie Forrester

Populations with high levels of exposure to potentially infected blood are at the highest risk of being infected with HCV. Injection drug users (IDUs) are primarily at risk of HCV infection when they inject with previously used needles and syringes contaminated with the infected blood of another user. In addition, they are at increased risk when they share other contaminated injecting equipment, such as spoons, cookers, or cotton filters. It has been estimated that the average prevalence of HCV among IDUs in Canada is approximately 80%[1-7].

Injection drug use is currently the most important risk factor for HCV infection. In Canada, it accounted for 63.2% of acute hepatitis C cases with known risk factors identified through HC's Enhanced Surveillance System for Hepatitis B and Hepatitis C, for the period 1998-1999. Moreover, 77.8% of the IDUs who were interviewed under this system, reported having shared needles in the 6 months before diagnosis.

HCV may be a more serious threat to IDUs than either HBV or HIV. Persistent HCV infection develops in up to 85% of those acutely infected, whereas less than 10% of adults who become infected with HBV develop a chronic infection. Although persistence is even higher for HIV, the reservoir of HIV-infected IDUs is smaller[8], and HIV is less easily transmitted parenterally than HCV. Thus, the high prevalence, the high rate of persistent infection, and the high

transmissibility of HCV all contribute to its endemicity in this group. Combined with the high rates of long-term sequelae, HCV among IDUs is of major public health importance[9].

The harm reduction framework

In 1987, the Canadian government adopted harm reduction as the framework for Canada's National Drug Strategy[10]. The objective of the harm reduction approach is to reduce the harm associated with injection drug use to the individual, the community, and society as a whole. The economic, social and health-related consequences of injection drug use rather than its elimination are the focus of harm reduction strategies[10]. Numerous international examples of harm reduction programs and policies exist and include needle exchange programs (NEPs), methadone maintenance treatment (MMT) programs as well as educational and outreach programs. For many, NEPs exemplify the harm reduction approach. The rationale behind NEPs is that the provision of sterile needles and syringes to current injectors will help to reduce the risk of infection or transmission of HIV, HBV, HCV, and other bloodborne pathogens. In Canada, NEPs opened unofficially in Toronto in 1987, and officially in Vancouver in 1989. There are now more than 200 NEPs operating across Canada[11]. Although evidence exists that NEPs have been effective in modifying most HIV-related injection practices[12] it cannot

be assumed that HIV-harm reduction strategies have been equally effective in addressing HCV in IDUs[13].

The effectiveness of harm reduction

The present paper provides a summary of a systematic review, the principal objectives of which were to document and characterize the prevalence and incidence rates of HCV among IDUs in Canada, and to examine the effectiveness of harm reduction strategies in modifying these rates[14]. HCV-related outcomes of interest were end-point physical health status at either the population or individual level, including modification in the reported incidence and prevalence of HCV among IDUs.

On-line computer searches of six electronic databases, hand searches of relevant studies, examination of potentially relevant studies suggested by key informants at the federal and front line levels, and review of local and community publications resulted in the retrieval of 84 studies from 1990 to 2000 related to the effectiveness of harm reduction strategies. A review of the relevance and quality of the studies resulted in the inclusion of 15 relevant* but largely methodologically weak primary studies, none of which was Canadian. It is important to note that not one of the studies examined had the express objective of directly evaluating harm reduction strategies in terms of HCV.

Of the 15 studies, three were American, three were Australian, and nine were European. The studies varied in the number of IDUs participating (range from 46 to 673) and composition of the IDU population. Although all studies recruited IDUs as at least one component of the study population, one study was composed exclusively of the inmates of a small prison for women in Switzerland[15], and one study focused on heterosexual IDUs only[16]. In all studies, with the exception of the study of women inmates, the proportion of male IDUs to female IDUs was approximately two-thirds to one-third, a ratio frequently documented in studies of IDUs. In terms of the interventions described, little similarity was observed across studies. NEPs and MMT were the most prevalent types of intervention described. One Scottish[17] and two U.S. studies[16,18] described NEPs as their only intervention, whereas MMT was the only intervention described in one Swiss[19], one Australian[20], and one Italian study[21]. The remaining nine studies described multi-faceted harm reduction interventions, including any combination of NEPs, MMT and other forms of drug treatment, education, counselling, prevention, and community outreach.**

With regard to the effectiveness of harm reduction strategies in reducing the incidence and prevalence of HCV, the studies reviewed reported high rates of HCV prevalence and incidence despite apparent widespread implementation of prevention strategies. More specifically, it was observed that the earlier protective effect of NEP attendance against HCV seroconversion, as reported by Hagan and colleagues in 1995[16], has not been consistently sustained[18]. Similarly, although a marginally protective role of MMT in the control of HCV infection was reported by Rezza and colleagues[21], this was not supported in any of the other studies reviewed, suggesting that the simple provision of methadone to IDUs at risk of HIV infection or of HIV transmission is not necessarily effective against HCV transmission.

Absence of a decline in incidence, or even the presence of incident cases, among IDUs already attending a prevention setting, albeit primarily focused on prevention of HIV transmission, strongly suggests that current efforts aimed at the prevention of bloodborne viral transmission are inadequate to stem HCV infection. Results from the studies reviewed document incidence rates ranging from a low of 4.2 per 100 person-years in a private Swiss MMT Centre[22] to highs of 20.9 per 100 person-years among IDUs attending a well-established HIV prevention facility in Australia[23] and 28.6 per 100 person-years among IDUs attending one of three drug treatment centres in Naples, Italy[21].

In summary, evidence from these primary studies suggests that HIV prevention strategies have been relatively ineffective in preventing HCV infection in the IDU population. Although harm reduction measures have contributed to the maintenance of a low prevalence and incidence of HIV, transmission of HCV clearly continues at extremely high levels, and from the evidence from many of the studies reviewed, this is particularly true among younger IDUs.

These findings, however, need to be considered in the context of certain limitations. As observational studies, none of the studies examined had the express objective of directly evaluating harm reduction strategies in relation to HCV infection. To determine the effectiveness of such strategies in modifying levels of HCV infection, a longitudinal design with a large number of IDUs randomly assigned to receive the

---

* The precise methodology, including search strategy, relevance testing for study selection, and quality testing of relevant studies is documented in the full review article[14].

** A complete description of the interventions in terms of modes of program delivery, duration, consistency, and setting is documented in the full review article[14].

intervention and others to receive no intervention together with a significantly high seroconversion rate over time would be necessary. Ethical and legal considerations preclude implementation of such an experimental study design in the face of evidence of effectiveness in relation to the prevention of HIV transmission. In addition, the review considered effectiveness in terms of modifying end-point measures of HCV prevalence and incidence. Emphasis on these end-point outcomes may well have masked the effectiveness of the programs and strategies reviewed in terms of modifying intermediate measures towards declines in HCV incidence and prevalence. An example of this would be a lower level of engagement in HCV-related risk behaviours, such as the use of previously used needles and other injection equipment.

Elimination versus reduction of risk behaviours

High HCV prevalence and incidence rates have been reported in a number of studies despite apparent widespread implementation of risk reduction strategies that appear to have been adequate to maintain a low or lower prevalence of HIV. In particular, HCV seroconversion among attenders of harm reduction programs suggests that prevention directed

selectively against HIV transmission is only partly effective in preventing HCV infection among IDUs. Public health measures to reduce HIV risk-related injection behaviours have had an impact on HIV transmission. However, in view of the documented large reservoir of existing HCV infection in the IDU population and the high degree of infectivity and transmissibility of HCV per episode of blood contact compared with HIV, research should be conducted to examine the feasibility of modifying existing programs or developing new ones that target the elimination rather than reduction of HCV risk-related injection behaviours. For instance, research could be carried out to examine the utility of interventions aimed at encouraging transitions to relatively less risky non-parenteral forms of drug ingestion such as smoking, snorting and swallowing. Similarly, research could be conducted to examine the effectiveness and feasibility of implementing MMT programs that administer methadone at the highest levels of the dose-response gradient associated with completed cessation of injecting, rather than simply reducing HCV risk-related injection practices. Establishing that HCV infection among IDUs is an important and high priority public health issue is fundamental to further interventions to control the spread of HCV.

References

1. Anand CM, Fonseca KI, Walle RP et al. *Antibody to hepatitis C virus in selected groups of a Canadian urban population.* Int J Epidemiol 1992;21(1):142-45.

2. Chaudhary RK, Mo T. *Antibody to hepatitis C virus in risk groups in Canada*. Can J Infect Dis 1992;3(1):27-9.

3. Johns DG, Gill MJ. *Seroprevalence of cytomegalovirus, **Toxoplasma gondii**, syphilis, and hepatitis B and C virus infections in a regional population seropositive for HIV infection*. Can J Infect Dis 1998;9(4):209-14.

4. Lamothe F, Vincelette J, Bruneau J et al. *Prevalence, seroconversion rates and risk factors for hepatitis B core, hepatitis C and HIV antibodies among intravenous drug users (IDU) of the Saint-Luc cohort* [Abstract # 221]. Can J Infect Dis 1997;8(suppl A):28A.

5. Patrick DM, Cornelisse PG, Sherlock CH et al. *Hepatitis C prevalence and incidence in Vancouver IDUs during an outbreak of HIV infection* [Abstract #13296]. International Conference on AIDS 1998;12:145.

6. Strathdee SA, Patrick DM, Currie SL et al. *Needle exchange is not enough: lessons from the Vancouver injecting drug use study.* AIDS 1997;11(8):F59-F65.

7. Stratton E, Lior LY, Gully P et al. *HIV, HBV and HCV risk behaviours in a semi-rural community in Canada* [Abstract #23219]. International Conference on AIDS 1998;12:385.

8. Villano SA, Vlahov D, Nelson KE et al. *Incidence and risk factors for hepatitis C among injection drug users in Baltimore, Maryland.* J Clin Microbiol 1997;35(12):3274-77.

9. Crofts N, Hopper JL, Bowden DS et al. *Hepatitis C virus infection among a cohort of Victorian injecting drug users*. Med J Australia 1993;159(4):237-41.

10. Canadian AIDS Society. *Under the influence: making the connection between HIV/AIDS and substance abuse.* Ottawa, ON: Canadian AIDS Society, 1997.

11. Riley D. *Drug policy and HIV/AIDS*. Canadian HIV/AIDS Policy & Law Newsletter 1996;2(4).

12. Leonard L, Forrester L, Navarro C et al. *The effectiveness of needle exchange programmes in modifying HIV-related outcomes: a systematic review of the evidence, 1997-1999.* Prepared for the Effective Public Health Practice Project of the Public Health Branch, Ontario Ministry of Health, 1999.

13. Wodak A, Crofts N. *HIV revisited: preventing the spread of blood-borne viruses among injecting drug users*. Australian J Public Health 1994;18(3):239-40.

14. Leonard L, Navarro C, Pelude L. *Injection drug use and hepatitis C in Canada: the effectiveness of harm reduction strategies. A systematic review of the evidence 1990-2000.* Report prepared for Bloodborne Pathogens Division, Health Canada, Ottawa, 2000.

15. Nelles H, Bernasconi S, Dobler-Mikola A et al. *Provision of syringes and prescription of heroin in prison: the Swiss experience in the prisons of Hindelbank and Oberschongrun*. Int J Drug Policy 1997;8(1):40-52.

16. Hagan H, DesJarlais DC, Friedman SR et al. *Reduced risk of hepatitis B and hepatitis C among injection drug users in the Tacoma Syringe Exchange Program*. Am J Public Health 1995;85(11):1531-37.

17. Goldberg D, Cameron S, McMenamin H. *Hepatitis C virus antibody prevalence among injecting drug users in Glasgow has fallen but remains high.* Commun Dis Public Health 1998;1(2):95-7.

18. Hagan H, McGough JP, Thiede H. *Syringe exchange and risk of infection with hepatitis B and C viruses*. Am J Epidemiol 1999;149(3):203-13.

19. Chamot E, de Saussure PH, Hirschel B. *Incidenceof hepatitis C, hepatitis B, and HIV infections among drug users in a methadone maintenance programme.* AIDS 1992;6:431-32.

20. Crofts N, Nigro L, Oman K et al. *Methadone maintenance and hepatitis C infection among injecting drug users.* Addiction 1997;92(8):999-1005.

21. Rezza G, Sagliocca L, Zaccarelli M et al. *Incidence rate and risk factors for HCV seroconversion among injecting drug users in an area with low HIV seroprevalence.* Scandinavian J Infect Dis 1996;28:27-9.

22. Boers B, Junet C, Bourquin M et al. *Prevalence and incidence rates of HIV, hepatitis B and C among drug users on methadone maintenance treatment in Geneva between 1988 and 1995.* AIDS 1998;12(15):2059-66.

23. Van Beek I, Dwyer R, Dore GJ et al. *Infection with HIV and hepatitis C virus among injecting drug users in a prevention setting: retrospective cohort study.* BMJ 1998;317 (7156):433-7.

List of Contributors

Alphabetical Order

Francisco Diaz-Mitoma, MD, PhD, FRCPC
Division of Virology
Department of Laboratory Medicine and Pathology
University of Ottawa and Children's Hospital of
  Eastern Ontario
Ottawa, Ontario, K1H 8L1
Tel: (613) 737-2736
Fax: (613) 738-4825
E-mail: Diaz@cheo.on.ca

Leslie Forrester, BA(Hons), MA, MSc
Community Acquired Blood-Borne Infections
Blood-Borne Pathogens Division
Centre for Infectious Disease Prevention & Control
Population & Public Health Branch, Health Canada
Ottawa, Ontario, K1A 0L2
Tel: (613) 957-3041
Fax: (613) 952-6668
E-mail: Leslie_Forrester@hc-sc.gc.ca

Antonio Giulivi, MD, FRCPC
Associate Director, Bureau of Infectious Disease
Chief, Blood-Borne Pathogens Division
Centre for Infectious Disease Prevention & Control
Population & Public Health Branch, Health Canada
Ottawa, Ontario, K1A 0L2
Tel: (613) 957-1789
Fax: (613) 952-6668
E-mail: Antonio_Guilivi@hc-sc.gc.ca

Zhiyong Hong, MD, PhD
Community Acquired Blood-Borne Infections
Blood-Borne Pathogens Division
Centre for Infectious Disease Prevention & Control
Population & Public Health Branch, Health Canada
Ottawa, Ontario, K1A 0L2
Tel: (613) 952-4631
Fax: (613) 952-6668
E-mail: Zhiyong_Hong@hc-sc.gc.ca

Steven Kleinman, MD
Kleinman Biomedical Research , Inc.
1281 Rockcrest Avenue
Victoria, British Columbia V9A 4W4
Tel: (250) 995-3110
Fax: (250) 995-3202
E-mail: krskle@islandnet.com

Marian Laderoute, PhD
Community Acquired Blood-Borne Infections
Blood-Borne Pathogens Division
Centre for Infectious Disease Prevention & Control
Population & Public Health Branch, Health Canada
Ottawa, Ontario, K1A 0L2
Tel: (613) 941-6087
Fax: (613) 952-6668
E-mail: Marian_Laderoute@hc-sc.gc.ca

Lynne Leonard, MA, CQSW
Community Health Research Unit
Department of Epidemiology & Community Medicine
University of Ottawa
451 Smyth Road
Ottawa, Ontario, K1H 8M5
Tel: (613) 562-5800 ext. 8286
Fax: (613) 562-5465
E-mail: leonard@zeus.med.uottawa.ca

Gerald Y Minuk, MD, FRCPC
Liver Diseases Unit, Health Sciences Centre
John Buhler Research Centre
Winnipeg, Manitoba, R3E 3P4
Tel: (204) 787-4393
Fax: (204) 775-4255
E-mail: gminuk@cc.umanitoba.ca

Christine Navarro, BSc
Community Health Research Unit
Department of Epidemiology & Community Medicine
University of Ottawa
451 Smyth Road
Ottawa, Ontario, K1H 8M5
Tel: (613) 562-5800 ext. 8286
Fax: (613) 562-5465
E-mail: navarro@zeus.med.uottawa.ca

Linda Pelude, BScN
Department of Epidemiology & Community Medicine
University of Ottawa
451 Smyth Road
Ottawa, Ontario, K1H 8M5
Tel: (613) 562-5410
Fax: (613) 562-5465
E-mail: pelude@zeus.med.uottawa.ca

Shirley Paton, MN, RN
Chief, Division of Nosocomial and Occupational Infections
Bureau of Infectious Diseases
Centre for Infectious Disease Prevention and Control
Population & Public Health Branch, Health Canada
Ottawa, Ontario, K1A 0L2
Tel: (613) 957-0326
Fax: (613) 998-6413
E-mail: shirley_paton@hc-sc.gc.ca

Syed A. Sattar, PhD
Centre for Research on Environmental Microbiology
Faculty of Medicine, University of Ottawa
451 Smyth Road
Ottawa, Ontario, K1H 8M5
Tel: (613) 562-5800 ext 8313/4
Fax: (613) 562-5452
E-mail: ssattar@uottawa.ca

Susan Springthorpe, MSc
Centre for Research on Environmental Microbiology
Faculty of Medicine, University of Ottawa
451 Smyth Road
Ottawa, Ontario, K1H 8M5
Tel: (613) 562-5800 ext 8313/4
Fax: (613) 562-5452
E-mail: sspring@uottawa.ca

Martin Tepper, MD, MHSc, FRCPC
Head, Counter-Terrorism Coordination and Medical
  Intelligence Section
Office of Public Health Security
Centre for Emergency Preparedness and Response
Population and Public Health Branch, Health Canada
Ottawa, Ontario, K1A 0K9
Tel: 613-957-2948
Fax: 613-952-8286
E-mail: martin_tepper@hc-sc.gc.ca

Jason Tetro, BSc
Centre for Research on Environmental Microbiology
Faculty of Medicine, University of Ottawa
451 Smyth Road
Ottawa, Ontario, K1H 8M5
Tel: (613) 562-5800 ext 8313/4
Fax: (613) 562-5452
E-mail: jtetro@cyberus.ca

LianneVardy
Hepatitis C Prevention, Support & Research Program
Hepatitis C Division
Centre for Infectious Disease Prevention & Control
Population & Public Health Branch, Health Canada
400 Cooper Street, 2nd Floor, AL4602A
Ottawa, Ontario, K1A 1B4
Tel: (613) 946-3206
Fax: (613) 941-7563
E-mail: Lianne_Vardy@hc-sc.gc.ca

Jun Wu, MD, PhD
Community Acquired Bloodborne Infections
Blood-Borne Pathogens Division
Centre for Infectious Disease Prevention & Control
Population & Public Health Branch, Health Canada
Ottawa, Ontario, K1A 0L2
Tel: (613) 946-8819
Fax: (613) 952-6668
E-mail: Jun_Wu@hc-sc.gc.ca

Dongwan Yoo, PhD
Department of Pathobiology
Ontario Veterinary College
University of Guelph
Guelph, Ontario, N1G 2W1
Tel: (519) 824-4120, ext 4729
Fax: (519) 767-0809
E-mail: dyoo@uoguelph.ca

Jun Zhang, MD, MSc
Transfusion Transmitted Injures
Blood-Borne Pathogens Division
Centre for Infectious Disease Prevention & Control
Population & Public Health Branch, Health Canada
Ottawa, Ontario, K1A 0L2
Tel: (613) 954-6210
Fax: (613) 952-6668
E-mail: Jun_Zhang@hc-sc.gc.ca

Shimian Zou, MD, PhD
Chief, Community Acquired Blood-Borne Infections
Blood-Borne Pathogens Division
Centre for Infectious Disease Prevention & Control
Population & Public Health Branch, Health Canada
Ottawa, Ontario, K1A 0L2
Tel: (613) 946-8819
Fax: (613) 952-6668
E-mail: Shimian_Zou@hc-sc.gc.ca