IMPACT monitoring network: A better mousetrap

EVERY INFECTIOUS DISEASES OR PUBLIC HEALTH SPECIALIST knows that active disease surveillance is preferable to voluntary reporting because active systems offer more complete and uniform information. The challenge is to find a way to conduct active surveillance that combines a broad catchment with efficient case-finding to minimize labour costs. Such properties are embodied in an innovative new program of the Canadian Pediatric Society and Laboratory Centre for Disease Control (LCDC) called IMPACT (Immunization Monitoring Program, ACTive).

IMPACT is funded by the Childhood Immunization Division of LCDC and one corporate sponsor. Surveillance activities centre upon severe vaccine-associated adverse events, vaccination failures and infections soon to be vaccine-preventable.

The surveillance network is based upon 10 pediatric referral centres extending from St John's to Vancouver. These centres comprise over 2000 pediatric beds and admit over 85,000 children annually, encompassing about 80% of pediatric admissions to Canadian academic centres. Investigators are infectious diseases specialists, with one exception, and serve as unpaid volunteers. Each supervises a nurse monitor who is employed for 10 to 20 h per week depending upon the size of the hospital. Monitors have established a network of contacts within each hospital, including infection control nurses, admitting office staff, ward nurses, medical staff, health records personnel and others who help them to find cases of interest. They daily scan admission lists and review potential cases on the wards. Monitors adhere to predetermined case definitions and report their findings on thoroughly tested forms. A coordinating centre in Vancouver receives the reports and manages data entry and analysis. A project manager in Ottawa oversees financial matters and communications. The investigators meet annually to review progress and make key decisions. The project operates in liaison with LCDC. Operating policies and general organization were fine-tuned during an initial 18-month pilot project involving five of the centres and subsequent to an external review.

There are numerous surveillance tasks well-suited to such a network. The group has, for example, been enumerating cases of invasive *Haemophilus influenzae* type b (Hib) infection and was quickly able to demonstrate a sharp decline in the occurrence of cases following the establishment of Hib vaccination programs for young infants. Of all the existing surveillance systems reporting to LCDC, IMPACT was the only one that recognized a substantial number of vaccine failures (from older products) among recent cases. No failures have been identified in fully vaccinated infants but investigators are poised to recommend appropriate investigations if instances occur, illustrating the 'real time' nature of the system. Comparable surveillance is directed at cases of varicella, pertussis and congenital rubella syndrome.

The corporate sponsor is funding a study of pneumococcal disease in children in anticipation of a pneumococcal conjugate vaccine. Over a two-year period, 1000 isolates from invasive infections will be serotyped by collaborators and correlated with clinical and epidemiological data, providing sound information for the final decisions about vaccine composition and routine programs.

The surveillance of vaccine-associated adverse events has been reassuring: thousands of neurological cases have been screened and few were attributable to prior vaccination. Most cases resulted from already established mechanisms, such as febrile seizures after diphtheria-pertussis-tetanus or measles-mumps-rubella vaccines. No instance of paralysis from wild- or vaccine-type polio was detected even though all cases of acute flaccid paralysis are scrutinized by monitors. The system is well-positioned to detect any acute neurological syndromes associated with newly introduced programs such as those for Hib, hepatitis B and, in the near future, varicella and acellular pertussis vaccines. Cases involving serious adverse events are reported to LCDC and provincial epidemiologists within days of

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being recognized, providing a 'finger on the pulse' of childhood immunization unlike any other.

While IMPACT has specific purposes, a functional multicentre network is an asset in approaching other studies. The willingness of Canadian investigators to work together is a noteworthy fact that is being utilized for the betterment of child health.

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ADULT INFECTIOUS DISEASE NOTES

Hepatitis C: Recent advances

SINCE THE INITIAL PUBLICATION OF THE DISCOVERY OF HEPATITIS C virus (HCV) by Choo et al (1) from Chiron Corporation in April 1989, much has been learned about the biology, epidemiology and clinical features of HCV infection. In this edition of the notes, we highlight some of the more recent findings.

Better serological testing: Second generation serological tests are now in use. The second generation enzyme immunoassay (EIA) is more sensitive than the first generation assay (2). Furthermore, the second generation recombinant immunoblot assay (RIBA), used by many laboratories as a confirmatory test for HCV infection, is more specific than earlier assays (2,3). Although the second generation tests permit earlier detection of HCV antibody than first generation tests, the diagnosis of HCV infection can seldom be made serologically in the first six weeks following infection.

Finally, the previous speculation that the high rate of HCV seropositivity when tested by EIA seen in autoimmune chronic hepatitis (4) is spurious has been confirmed by the absence of HCV RNA in such patients (5).

Screening of blood donors: There is now conclusive evidence that excluding blood donated by individuals who test HCV-seropositive substantially reduces the incidence of post-transfusional non-A, non-B hepatitis to a greater extent than the use of serum alanine aminotransferase (ALT) and hepatitis B surface antigen antibody as surrogate markers (6).

Transmission: The most established route of transmission of HCV is parenteral, with high rates of infection in injection drug users and recipients of large quantities of blood products, such as hemophiliacs. Consistent with this route of transmission, occupational HCV infection of health care workers via needlestick injuries is well documented (7,8), and likely accounts for the higher rate of HCV-seropositivity reported in dentists, compared with controls (9). The risk of HCV infection with a single needlestick injury has been reported at 4% in one study (7) and 10% in another (8); thus the risk is intermediate between that of human immunodeficiency virus at approximately 0.3% and hepatitis B virus (HBV) at 20 to 40%.

Transmission via organ transplantation has also been documented with high rates of transmission reported in two studies (10,11), and a low rate of transmission reported in another (12). Given the limited supply of organs for transplantation, some programs permit the transplantation of organs other than the liver from HCV-seropositive donors into recipients who are already HCV-seropositive. Sexual (13) and vertical (14) transmission of HCV remain infrequent but both clearly occur. Of note, the route of transmission remains unknown in about 40% of cases (15), a proportion comparable to that for HBV.

HCV RNA: Since the report of the initial polymerase chain reaction (PCR) assay for HCV RNA by Weiner et al (16) from Chiron, many research laboratories now perform this assay. However, the significant interlaboratory variability of this assay suggests that standardization and proficiency testing will be required (17).

Several investigators have developed quantitative assays for HCV RNA. A particularly promising quantitative assay is the novel technique of branched DNA signal amplification (18), which has recently been assessed clinically (19).

HCV RNA assays offer the potential of earlier diagnosis and high specificity where serology is equivocal. Quantitative assays are now essential in clinical trials assessing antiviral therapy (20).

Essential mixed cryoglobulinemia (EMC): EMC is a relatively rare condition characterized by purpura, arthralgia and weakness, often together with glomerulo-

nephritis. The diagnosis of EMC requires the demonstration of serum cryoglobulins made up of polyclonal immunoglobulin (Ig) G and monoclonal IgM rheumatoid factors.

Several groups of investigators have demonstrated a high prevalence of HCV seropositivity in patients with EMC (21,22), with concentration of both HCV RNA and anti-HCV in the cryoprecipitate (22,23). Some of these patients also have membranoproliferative glomerulonephritis (23).

HCV in liver disease: Recent studies indicate that a majority of HCV-seropositive individuals have liver disease, despite the fact that most are asymptomatic (24). Normal serum aminotransferase levels do not exclude the presence of chronic hepatitis (25). Furthermore, whereas individuals with chronic hepatitis usually have detectable HCV RNA in serum, circulating HCV RNA may remain detectable for several years in the absence of liver disease (26). Thus, the assessment of asymptomatic HCV-infected individuals with persistently normal serum aminotransferases has become confusing, and arguments can be made for and against peforming a liver biopsy in such individuals, largely influenced by one's belief regarding the efficacy of treatment.

Treatment of HCV: Currently, the only approved treatment for chronic HCV infection is with interferon-alpha. However, interferon-alpha is expensive, toxic and has limited efficacy. No more than 50% of patients experience improvement with this therapy and relapses are very common (27,28). Unfortunately, as with recent antiretroviral drugs, interferon-alpha was licensed for the treatment of HCV on the basis of surrogate data, ie, improvement in ALT, rather than convincing data demonstrating either a sustained antiviral effect or long term clinical benefits. Thus, it remains to be determined whether interferon-alpha prevents the development of cirrhosis or hepatocellular carcinoma. Furthermore, a recent study indicates that individuals who are followed an average of 18 years after developing transfusion-associated non-A, non-B hepatitis have no increase in mortality from all causes, compared with two control groups (29). There was a small, statistically significant increase in deaths related to liver disease, but 71% of these occurred in chronic alcoholics (29). Therefore, the potential for an effective HCV therapy to reduce mortality is limited. Until placebo controlled trials demonstrate that inteferon-alpha results in a sustained clearance of HCV RNA from serum in a substantial proportion of patients and/or reduced progression to cirrhosis and/or hepatocellular carcinoma, its use in HCV must still be considered experimental (30).

Oral ribavirin has also been evaluated in the treatment of chronic HCV infection in two open-label pilot studies (31, 32). In both studies, nearly all patients experienced a significant fall in serum ALT, and the drug was well tolerated. Furthermore, a fall in quantitative HCV RNA was observed (32), although HCV RNA did not disappear completely. Unfortunately, virtually all patients relapsed following discontinuation of therapy (31,32). In contrast, some patients treated with interferon-alpha achieve sustained virological remissions with undetectable HCV RNA over a period of several years (33).

Prospect for vaccine: Although about 50% of HCV-infected individuals clear the virus spontaneously, the determinants of immunity in such individuals have not been defined. Furthermore, at least five HCV genotypes are now recognized (34), and it is unknown whether immunity to one type confers cross-immunity to one or more of the other genotypes.

Even more discouraging is the observation that chimpanzees inoculated with HCV who clear the virus do not develop protective immunity to repeat intravenous challenge with either homologous or heterologous HCV (35). Interestingly, chimpanzees who become chronically infected with HCV are resistant to superinfection with heterologous HCV (35). These data suggest that HCV vaccine development will be considerably more challenging than the development of vaccines for hepatitis A virus and hepatitis B virus.

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