Estimation of the secondary attack rate for delta hepatitis coinfection among injection drug users

CHRISTIANE POULIN, MD, MSc, THERESA GYORKOS, PhD, LAWRENCE JOSEPH, PhD

C POU LIN, T GYORKOS, L JOSEPH. Estimation of the secondary attack rate for delta hepatitis coinfection among injection drug users. Can J Infect Dis 1993;4(1):47-51. The secondary attack rate for delta hepatitis coinfection was estimated among a cluster of injection drug users (IDUs). The infections occurred during an epidemic of hepatitis B in a rural area of Nova Scotia in 1988 and 1989. Six IDUs formed a cluster of delta hepatitis coinfections, representing the first reported outbreak of delta hepatitis in Canada. Contact-tracing was used to identify a cluster of 41 IDUs potentially exposed to delta hepatitis. The index case of delta hepatitis coinfection was presumed to have led to five secondary cases. The secondary attack rate was estimated to be 13.2% (95% confidence interval 0.044 to 0.281). The estimated secondary attack rate may be a useful predictor of disease due to delta hepatitis coinfection in similar IDU populations.

Key Words: Delta hepatitis, Hepatitis D coinfection, Injection drug use, Secondary attack rate

Estimation du taux d’attaque secondaire de co-infection au virus de l’hépatite delta chez des utilisateurs de drogues par injection

RÉSUMÉ: Le taux d’attaque secondaire pour ce qui est de la co-infection au virus de l’hépatite delta a été étudié chez un groupe d’utilisateurs de drogue par voie intraveineuse. Les infections se sont produites durant une épidémie d’hépatite B dans une région rurale de la Nouvelle-Écosse en 1988 et 1989. Un groupe de six utilisateurs de drogues intraveineuses a présenté une co-infection au virus de l’hépatite delta, représentant ainsi la première épidémie déclarée d’hépatite delta au Canada. En retraçant les personnes avec qui ces 6 patients avaient été en contact, un groupe de 41 personnes utilisatrices de drogues intraveineuses, potentiellement exposées au virus de l’hépatite delta a pu être identifié. Cela a mené au diagnostic formel de cinq cas secondaires de co-infection au virus de l’hépatite delta. Le taux d’attaque secondaire a été estimé à 13.2% (intervalle de confiance de 95%; 0.044 à 0.281). L’établissement du taux d’attaque secondaire estimé peut être un facteur de prévisibilité utile de la maladie attributable à une co-infection au virus de l’hépatite delta dans des populations utilisatrices de drogues intraveineuses similaires.
The hepatitis B epidemic occurred on Cape Breton Island, in several communities with a total population of approximately 30,000 persons, predominantly caucasian of British descent. The epidemic resulted from the introduction of hepatitis B virus into a susceptible rural IDU population with complex needle-sharing patterns (11). Contact-tracing was aimed at the exhaustive identification of all IDUs in the epidemic area, resulting in the identification of 186 IDUs, of whom 153 (82%) were interviewed. Of 133 (72%) IDUs who underwent serological testing, 78 had serological evidence of hepatitis B infection. It was demonstrated that 57 IDUs formed a cluster of recent hepatitis B infections.

OVERVIEW OF THE HEPATITIS B EPIDEMIC

The hepatitis B epidemic occurred on Cape Breton Island, in several communities with a total population of approximately 30,000 persons, predominantly caucasian of British descent. The epidemic resulted from the introduction of hepatitis B virus into a susceptible rural IDU population with complex needle-sharing patterns (11). Contact-tracing was aimed at the exhaustive identification of all IDUs in the epidemic area, resulting in the identification of 186 IDUs, of whom 153 (82%) were interviewed. Of 133 (72%) IDUs who underwent serological testing, 78 had serological evidence of hepatitis B infection. It was demonstrated that 57 IDUs formed a cluster of recent hepatitis B infections.

METHODS

Methods for the investigation of the hepatitis B epidemic are described in full elsewhere (11). Serology: From November 1988 until the end of June 1989, all sera submitted for hepatitis B testing from the epidemic area were tested for hepatitis B surface antigen (HBsAg) (Abbott Ausyme), anti-HBs (Abbott Auszyme), and immunoglobulin (Ig) G anti-hepatitis C (HBe) (Abbott Corzyme). Selected sera, primarily of asymptomatic individuals found to be immune at first testing, were also tested for IgM anti-HBc (Abbott Corzyme-M rDNA).

A particularly severe and protracted course of acute hepatitis in one IDU prompted the initial testing for delta hepatitis. A cluster of IDUs potentially exposed to delta hepatitis was defined by reviewing drug-use histories and by repeatedly cross-referencing contacts with their serological status. Sera of this group of IDUs were tested for total anti-delta hepatitis antibody (Abbott anti-delta enzyme immunoassay). Case definitions: Hepatitis B infection or seropositivity was defined as serological positivity for HBsAg and/or anti-HBc, or positivity for both anti-HBs and anti-HBc. A cluster case of hepatitis B was defined as hepatitis B seropositivity with all of the following conditions: infection occurring between October 1, 1987 and June 30, 1989 (except for index cases and chronic carriers); permanent or temporary residence in the epidemic area; and definite evidence that exposure could have originated from contact with known infected IDUs (verified by cross-referencing contacts named with other cluster cases). The timing of hepatitis B infection was established by means of the onset of symptoms, serological progression, the presence of IgM anti-HBc antibody and drug-use history. A case of delta hepatitis coinfection was defined as anti-delta hepatitis positivity in a case of recent hepatitis B infection.

The diagnosis of hepatitis B disease in a hepatitis B-seropositive person was based on the group of symptoms reported on the questionnaire. Considered sufficient was: the presence of jaundice or, in the absence of jaundice, illness severe enough for hospital admission; presence of at least two of arthritis, dark urine, rash, pruritus, anorexia, weight loss; or 'flu-like illness only if coupled with serological progression in keeping with the onset of symptoms.

Data analysis: The secondary attack rate is the number of cases occurring within the incubation period following exposure to a primary case divided by the total susceptible persons (12). The numerator of the secondary attack rate for hepatitis B virus/delta hepatitis virus coinfection was all hepatitis B virus/delta hepatitis virus-seropositive (recently infected with hepatitis B) IDUs, symptomatic within six months of the index case. The denominator was the number of IDU contacts exposed to delta hepatitis virus. The index case was presumed to be the hepatitis B virus/delta hepatitis virus-seropositive IDU whose onset of illness was the earliest. Hepatitis B-seropositive IDU contacts were presumed to be susceptible to delta hepatitis virus for a six-month period.

The confidence interval was calculated by the exact binomial method. Owing to the uncertainty of the
denominator, the robustness of this confidence interval was checked using a mixture binomial model over the set of all possible denominators (13).

**RESULTS**

Forty-one IDUs were identified as forming a cluster potentially exposed to delta hepatitis (including the IDU first diagnosed with delta hepatitis). Of these, two asymptomatic IDUs were not tested, seven were hepatitis B-seronegative and 32 IDUs were hepatitis B-seropositive (Table 1).

Six hepatitis B-seropositive IDUs tested positive for anti-delta hepatitis antibody. The cases of delta hepatitis comprised five males (ranging from 24 to 34 years old) and one female (25 years old). All were symptomatic and two were severely ill and hospitalized; all recovered.

The apparent index case of delta hepatitis acquired his infection in another province, returning to the rural area at the onset of illness in June 1988. Only one serum sample was obtained from the apparent index case, six months after the onset of illness. The apparent index case was seropositive for IgG anti-HBc and seronegative for HBsAg, IgM anti-HBc and anti-HBs. It is likely this case was in the recovery phase of hepatitis B virus/delta hepatitis virus coinfection, although hepatitis B virus/delta hepatitis virus superinfection with depletion of serum HBsAg cannot be ruled out entirely.

The subsequent cases had onset of illness from three to six months after the apparent index case. All were HBsAg-positive on presentation. Two subsequently seroconverted to hepatitis B immunity, and were therefore likely hepatitis B virus/delta hepatitis virus coinfections. Repeat serology tests at six or more months were not available on the remaining three cases. However, these were considered hepatitis B virus/delta hepatitis virus coinfections on the basis of drug use and contact histories, and knowledge of the occurrence of hepatitis B in the region.

Sixteen hepatitis B-seropositive IDUs in the cluster were symptomatic. Of these, eight tested negative for anti-delta hepatitis and two were not tested for anti-delta hepatitis. The onset of illness of the latter preceded (by two or more months) that of the apparent delta hepatitis index case, and neither had a second episode of clinical hepatitis. These two were eliminated from the denominator. Sera of the anti-delta hepatitis-positive IDUs were obtained from one week to six months after the onset of illness. Sera of the anti-delta hepatitis-negative IDUs were obtained from six weeks to nine months after the onset of illness.

The secondary attack rate was estimated to be 13.2% (=5/[41-2-1]) (95% confidence interval 0.044 to 0.281). Since the denominator could actually have ranged from 31 to 38, the confidence interval was checked for robustness to errors in the denominator. The resulting 95% credible region was 0.045 to 0.275, indicating little effect resulted from uncertainty in the denominator.

**DISCUSSION**

Four sources of uncertainty render the estimation of a secondary attack rate for hepatitis B virus/delta hepatitis virus coinfection associated with IDUs problematic. These are: the concept of coinfection; assumptions concerning infectiousness, susceptibility and exposure; definition of a cluster of IDUs; and limitations of the serological tests.

Delta hepatitis occurs either as a coinfection simultaneously with acute hepatitis B or as a superinfection in which acute delta hepatitis is superimposed upon chronic hepatitis B. In coinfection, delta hepatitis virus may be transmitted concomitantly with hepatitis B virus or it may be transmitted to a person in the hepatitis B virus-replicative phase of a recent hepatitis B infection.

In the present study, there were complex needle-sharing links among the cluster of IDUs potentially exposed to delta hepatitis virus. The hepatitis B epidemic among IDUs started before the introduction of delta hepatitis virus but none of the delta hepatitis virus-exposed IDUs was a hepatitis B chronic carrier. There was opportunity for concomitant transmission of both delta hepatitis virus and hepatitis B virus by a single infected IDU, or transmission of hepatitis B virus soon followed by delta hepatitis virus infection, by different IDUs on different occasions. Infectiousness and susceptibility were therefore assumed to have existed for a six-month period.

Among IDUs, transmission of delta hepatitis virus depends on the frequency of needle-sharing and the timing of sharing relative to an IDU's infectiousness or susceptibility. Assessment of the level of exposure was limited by poor recall of precise needle-sharing activity by IDUs, especially during bingeing. Furthermore, in an IDU population, the difficulty of obtaining periodic serum samples limits serological assessment of infectiousness or susceptibility. In the present study, no differentiation - vis-à-vis exposure - was possible among IDUs.

**TABLE 1**

<table>
<thead>
<tr>
<th>HBV markers</th>
<th>Symptomatic IDUs</th>
<th>Asymptomatic IDUs</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbsAb+</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>Only anti-HBc+</td>
<td>1,3</td>
<td>0</td>
</tr>
<tr>
<td>Anti-HBs+ and anti-HBc+</td>
<td>0,2</td>
<td>0</td>
</tr>
<tr>
<td>HB-seronegative</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Untested for HBV</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>6,8</td>
<td>0,0</td>
</tr>
</tbody>
</table>

HbsAb Hepatitis B surface antigen; HBV Hepatitis B virus; HBc Hepatitis C; IDU Injection drug user
Injection drug use is a covert activity potentially associated with legal, socioeconomic and medical repercussions. The findings of the investigation of the hepatitis B epidemic suggested that contact tracing was, to a large extent, successful. However, the defined cluster may have been incomplete. This error would result in an underestimate of the denominator and possibly of the numerator.

The limitations of the serological testing done in this study are twofold. First anti-delta hepatitis testing was performed only on a single serum sample per IDU. Second, only total anti-delta hepatitis antibody testing was available. A strong serological response to delta hepatitis virus usually develops in IDUs (14). Total anti-delta hepatitis has been found to be a sensitive test for delta hepatitis virus infection. Lettau et al (15) reported that 95% of delta infections in their series were detected with this test, and that total anti-delta hepatitis antibody remained strongly positive for a mean of 7.8 months and up to 15 months after the resolution of disease. Among Dublin IDUs, total anti-delta hepatitis antibody was found 10 to 60 days (mean 29 days) after the onset of illness (16). Shattock and co-workers (17) found that delta antigenemia was the best marker of delta hepatitis virus coinfection in early serum samples, and that IgM anti-delta hepatitis was a sensitive test for acute delta hepatitis virus infection as well as a potential window marker. The mean duration of IgG anti-delta hepatitis in that study was 25 months.

In the present study, testing for anti-delta hepatitis antibody was probably a sensitive means of diagnosis among symptomatic IDUs, since sera were drawn one week to six months after the onset of symptoms. Testing for other delta hepatitis virus markers could have resulted in an increased detection of delta hepatitis virus infection. The IgM anti-delta hepatitis antibody test would have been especially useful to confirm delta hepatitis virus infection among asymptomatic hepatitis B-seropositive contacts. This would also have enabled the estimation of the delta hepatitis virus infection rate (the incidence of all infections, manifest or inapparent).

The World Health Organization uses a transmission coefficient of 90% for the parenteral transmission of hepatitis B in the evaluation of strategies related to the testing of transfusion blood supplies (18). The ratio of asymptomatic to symptomatic hepatitis B infection cited in the literature is 6:4 (19). The estimated secondary attack rate of hepatitis B virus for percutaneous transmission would therefore be 36%. Delta hepatitis virus has been found to be less efficiently transmitted than hepatitis B virus experimentally (2). The present study’s estimated secondary attack rate of 13% for delta hepatitis coinfection therefore is compatible with knowledge of hepatitis B virus transmission and the hepatitis B virus attack rate. The estimated secondary attack rate also is compatible with indirect information provided by seroprevalence studies among IDUs. For example, in Los Angeles, 8% of IDUs with acute hepatitis B infection had antibody to delta hepatitis virus, compared with 73% among those with chronic hepatitis B infection (3).

The estimated secondary attack rate may be useful in the mathematical modelling of delta hepatitis coinfection. For example, an indirect estimate of the infection rate for delta hepatitis virus coinfection in man may be calculated. Zanetti et al (20) described delta hepatitis virus infection as invariably pathogenic. However, Shattock et al (16) found evidence of simultaneously acquired hepatitis B virus/delta hepatitis virus infection in four IDUs among 29 who remained asymptomatic. The proportion of symptomatic infections based on the latter study would be 87%. Using the present authors’ estimated secondary attack rate and this proportion of symptomatic infections, an approximate infection rate in man of 15% for percutaneous transmission associated with IDU is suggested.

The secondary attack rate reflects host, agent and environmental factors. The circumstances of the hepatitis B and delta hepatitis epidemic in Nova Scotia are probably representative of rural IDUs. The estimated secondary attack rate may be a useful predictor of disease due to hepatitis B virus/delta hepatitis virus coinfection in similar IDU populations.

ACKNOWLEDGEMENTS: Thanks are extended to the study population and to the hospital staff for their cooperation and assistance. Special thanks are extended to: Dr Spencer Lee. Nova Scotia Provincial Pathology Laboratory; Dr Walter Schlech III. Faculty of Medicine. Dalhousie University; public health nurses Juanita MacPhee, Beverly Cann, Janet Bickerton and Heather MacSween; and Dr Leo MacCormick. Nova Scotia Department of Health. Information in this article was presented, in part, at: The 1990 International Symposium on Viral Hepatitis and Liver Disease, April 4 to 8, 1990, Houston, Texas. USA. Abstract 229; Addictions in the 90’s: Challenges and Responses, April 29 to May 3, 1990, St John’s, Newfoundland; The 58th Conjoint Meeting on Infectious Diseases, November 25 to 29, 1990, Halifax. Nova Scotia. Abstract E-3. Funding was provided, in part, by the Laboratory Centre of Disease Control. Nova Scotia Department of Health and Fitness, and Fonds de la Recherche en santé du Québec.

REFERENCES