Hepatitis B vaccination strategies

The Ontario Government recently announced that it will begin providing vaccination against hepatitis B for all children in grade 7. This follows the example of British Columbia, which has been providing hepatitis B vaccination to all grade 6 children for two years now. Furthermore, the National Advisory Committee on Immunization has approved this policy, namely of universal vaccination for all pre-adolescents, accompanied by targeted vaccination for specified high risk groups. The purpose of this article is to examine the evidence that this will be an effective form of vaccination.

The first points to consider relate to the patterns of transmission of disease. Many studies have clearly demonstrated that the epidemiology of hepatitis B infection is different in parts of the world where this condition is endemic, compared with areas of low prevalence. In endemic areas the major routes of transmission are perinatal, from an infected mother to her newborn infant, and horizontal transmission among young children. Neonatal infection is well recognized, and vaccination strategies to prevent this have been in place for several years. Horizontal infection is less well recognized, but may be equally important. Horizontal transmission has been demonstrated among children in Taiwan vaccinated against hepatitis B, where longitudinal follow-up of antibody titers showed that there was an anamnestic rise in titres at the time when children first went to school, indicating exposure. Similar findings from Africa and Alaska also suggest that transmission in childhood is frequent. In countries where hepatitis B is endemic, the preferred vaccination strategy is to vaccinate all newborns. Some countries have also instituted catch-up programs to vaccinate all children who did not get neonatal inoculation.

In contrast, in low prevalence areas infection occurs most commonly between ages 15 and 40, probably related to sexual transmission, intravenous drug use and, to a lesser extent, professional exposure to hepatitis B. This is certainly true in the United States, and possibly in Canada. However, the mechanism of transmission in immigrant families in the United States and Canada is likely to be different.

The rate at which subjects infected with hepatitis B virus develop the carrier state is highly dependent on the age at infection. More than 90% of infants who become infected with hepatitis B become carriers. In young children the carrier rate following infection is between 40 and 50%. In adults the carrier rate is classically given as 5 to 10%. Most of the studies on which this is based are old. However, a more recent study in Yupik Eskimos demonstrated a 7.7% carrier rate in adults newly infected with hepatitis B. Other data suggest that in young, otherwise healthy adults, the carrier rate may be as low as 1% or less. The evidence for this comes mainly from a long term follow-up of more than 42,000 American servicemen infected with hepatitis B during the Second World War. About 300 of these servicemen were traced in the late 1980s. Only one carrier was found. Selection bias might have been present because the hepatitis B carriers might have died before being contacted. There was a slight excess mortality from hepatocellular carcinoma in this cohort. Another study in Greece involving more than 500 subjects with acute symptomatic hepatitis B showed that the carrier rate following acute infection was 0.2%.

The majority of adults who become infected develop acute hepatitis B. Indeed, acute hepatitis B is well recognized as a disease of young adults, and in most instances is spread by sexual transmission, intravenous drug use and the usual recognized exposure to blood and blood products. In one study about 30% of cases had no identifiable risk factor. However, in that study the families of the index cases were not tested so the contribution of intrafamilial spread could not be estimated. Nor was it certain that the so-called acute hepatitis B represented new infections. A flare of chronic hepatitis B can mimic acute hepatitis B exactly.

The major morbidity and mortality from hepatitis B occur in chronic carriers, and not in patients with acute symptomatic disease. Chronic hepatitis B carries a mortality which, in endemic areas, may be up to 55% in males. There are no good data for females, and we do not know whether the mortality in North America is similar or lower. Available data, with respect to hepatocellular carcinoma at least, are conflicting. In a study of Caucasian hepatitis B carriers infected in childhood, no hepatomas were found approximately 40 years later. In contrast, in Toronto, which has a large immigrant population, hepatoma is as frequent as in Taiwan (600 per 100,000/year) (unpublished data). As an estimate, the mortality from chronic hepatitis B may be in the 20 to 30% range.

There are no good data as to the prevalence of chronic hepatitis B in Canada, nor any information as to which population groups are affected. However, I have derived data (Table 1) that indicate that at least 50% of chronic hepatitis B occurs in immigrants from endemic areas, namely southeast Asia, Africa, southern and eastern Europe. These data were derived using information from Statistics Canada from 1986. A conservative estimate of the prevalence of chronic hepatitis B was derived from each immigrant population by considering the known carrier rate in the native country and reducing the rate by 3 to 5% to allow for reduced prevalence in the second generation. As shown in Table 1, about half of all hepatitis B occurs in immigrant communities. Admittedly the table is a crude estimate, but it is likely to be an underestimate — first, because immigration from endemic areas since 1986 has added more than 100,000 additional at-risk subjects; and second, because it is likely that the rates chosen are underestimates.

The current universal vaccination strategies are aimed at pre-adolescents. There are several reasons why this age group has been chosen. These include that seroprevalence data clearly show that the prime age of infection in Canada, as in the United States, is in the young adult. However, the Canadian data are suspect because they come from Red Cross data (which exclude known hepatitis B carriers) and from screening of pregnant women, which is unlikely to include known hepatitis B carriers. It is believed that vaccination of pre-adolescents will be more acceptable to pre-adolescents than neonatal vaccination will be to the infants’ parents. Follow-up for the second and third doses of vaccine should be better in pre-adolescents and, finally, it is believed that by vaccinating pre-adolescents, protection against chronic hepatitis B will be advanced by 10 to 15 years, compared with introducing neonatal vaccination.

It is clear that the current vaccine strategies, including universal vaccination of pre-adolescents, and targeted vaccination of other groups are likely to miss providing protection to children who may acquire the disease by horizontal transmission from sources other than the mother. The big question therefore is: to what extent is horizontal infection in children a factor in disease transmission in Canada? This has only been addressed in one study, performed in the United States. In a Vietnamese refugee community in Atlanta, Georgia, among children of noncarrier mothers the carrier rate was 6.6%. In households where there were no other infected individuals, the carrier rate was 4%: these children must have acquired their infection from sources other than their parents.\n
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TABLE I
Hepatitis B carriers in Canada: An estimate derived from Statistics Canada databases

<table>
<thead>
<tr>
<th>Country of origin</th>
<th>Number of immigrants in Toronto</th>
<th>Number of immigrants in Canada</th>
<th>Prevalence</th>
<th>Number of hepatitis B carriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Italy</td>
<td>292,270</td>
<td>705,690</td>
<td>3%</td>
<td>21,288</td>
</tr>
<tr>
<td>Greece</td>
<td>62,255</td>
<td>143,780</td>
<td>3%</td>
<td>4313</td>
</tr>
<tr>
<td>Portugal</td>
<td>98,085</td>
<td>199,595</td>
<td>3%</td>
<td>5988</td>
</tr>
<tr>
<td>South Asia</td>
<td>105,045</td>
<td>266,800</td>
<td>7%</td>
<td>18,676</td>
</tr>
<tr>
<td>China</td>
<td>126,235</td>
<td>360,315</td>
<td>7%</td>
<td>25,222</td>
</tr>
<tr>
<td>Vietnam</td>
<td>10,275</td>
<td>53,018</td>
<td>7%</td>
<td>3711</td>
</tr>
<tr>
<td>Africa</td>
<td>90,945</td>
<td>174,790</td>
<td>3%</td>
<td>5,235</td>
</tr>
<tr>
<td>South America</td>
<td>33,325</td>
<td>101,665</td>
<td>3%</td>
<td>3,050</td>
</tr>
<tr>
<td>Aboriginals</td>
<td>11,561</td>
<td>746,410</td>
<td>2%</td>
<td>14,928</td>
</tr>
<tr>
<td>Middle East</td>
<td>17,210</td>
<td>101,665</td>
<td>3%</td>
<td>3,050</td>
</tr>
<tr>
<td>Philippines</td>
<td>37,145</td>
<td>93,280</td>
<td>5%</td>
<td>4,664</td>
</tr>
<tr>
<td>Korea</td>
<td>14,310</td>
<td>26,855</td>
<td>7%</td>
<td>1,880</td>
</tr>
<tr>
<td>Low risk</td>
<td>2,100,000</td>
<td>24,000,000</td>
<td>0.56%</td>
<td>120,000</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td>237,570</td>
</tr>
</tbody>
</table>

Such transmission is also likely to occur at a significant rate in Canada in communities in which hepatitis B is endemic because children in these communities play and go to school with, and are cared for by, other members of the community, thus allowing for transmission of disease. There are no Canadian data on this point because the issue has not been studied. However, there is no reason why the findings in endemic countries should not apply in Canada to immigrant communities coming from those countries.

It has been argued that these children will be covered by targeted vaccination. However, this is not so: first, as the above study shows, infection can occur even in children whose parents do not have hepatitis B; and second, in order to provide vaccination to family members of contacts, the index case first has to be identified. Previous experience has shown that recognition of at-risk groups is poor. When screening of pregnant women was first introduced it was recommended that only women in high risk categories be screened. This strategy, in the best of circumstances, missed 50% of carrier women. Chronic hepatitis B is an asymptomatic disease—infected patients do not present themselves to be identified, but rather the diagnosis is made because an alert family practitioner recognizes an at-risk individual or on a routine check-up elevated liver enzymes are found, and investigation turns up hepatitis B.

At present, targeted vaccination involves several groups, including newborn infants of carrier mothers and family members of an index case. Immigrants as a group are not targeted. Yet from Table 1 it is clear that immigrants contribute a significant number of new hepatitis B cases.

Screening of pregnant women is usually, but not always, appropriately performed. If a woman goes into labour over a weekend the hepatitis testing results are not always available to the hospital staff, and mother and baby may be discharged before the in-hospital test results are available. These kinds of oversights occur in hospitals that serve endemic communities, in which the staff is generally well educated about hepatitis B. They almost certainly also occur in hospitals in which the diagnosis of hepatitis B is less frequently made. Universal screening of pregnant women was introduced because screening of mothers identified to be at high risk found only 50% of pregnant hepatitis B carriers. Identification of high-risk children is likely to be even less effective because children are generally considered to be at low risk.

Vaccination of family members of an index case can only occur once the index case has been identified. In the absence of formal screening programs, many, if not most, hepatitis B carriers will remain undiagnosed. Most hepatitis B carriers are unaware of their disease, and therefore the family contacts cannot be traced and vaccinated. Even when adult carriers are identified, it is often too late to prevent transmission to family members who are young children. Very few carriers are diagnosed because they present with the clinical syndrome of acute hepatitis.

Thus, symptomatic illness cannot be used to identify index cases. The strategy of vaccinating family contacts of known carriers can only reach families where a carrier has been identified. This is the minority of hepatitis B carriers. In the absence of a strategy to identify existing hepatitis B carriers, the strategy of targeting family members of an index case is inadequate.

The choice of teenage vaccination may be appropriate for hepatitis B in nonimmigrant communities in which a significant number of infections that become chronic are acquired in adulthood, but it may not be appropriate for Canada, where approximately 50% of chronic hepatitis B occurs in immigrants (Table I) who acquire the disease in childhood. Indeed, even in nonimmigrant communities the strategy may not be appropriate, particularly if the rate of developing chronicity after a new infection in young adults is as low as recent data suggest.

The crux of the argument against teenage vaccination versus vaccination in infancy is: how prevalent is infection in early childhood in Canada? Unfortunately there are no data that I am aware of to answer this. However, among immigrant communities it is likely that transmission of disease is similar to that in their native countries, i.e., about a third occur perinatally and about a third occur in childhood. In those communities childhood transmission is likely a major factor.

Another concern with pre-adolescent vaccination programs is that many children who are already carriers will be given the vaccine. Particularly among the Chinese and Vietnamese communities, the carrier rate can be expected to be somewhere between 8 and 15%. That means that 8 to 15% of the Chinese or Vietnamese children who are vaccinated will not be immune (but will believe that they are), whereas they will in fact be carriers and will still be at risk of spreading the disease.

Thus, several major issues remain to be resolved before we can be sure that pre-adolescent vaccination will have the desired effect, namely of reducing the hepatitis B carrier rate. These are:

- Do young, otherwise healthy adults who are infected with hepatitis B become carriers with a 5 to 10% frequency, or with a frequency of less than 1%?
- What proportion of hepatitis B carriers are immigrants from high prevalence areas, and is transmission in these groups in Canada similar to that in their native countries?
- Put another way, the question is whether horizontal transmission is a major factor in the spread of hepatitis B in Canada.

On the positive side, new polyvalent vaccines are being developed that will incorporate the hepatitis B vaccination with other childhood vaccination, so that universal childhood vaccination will come, although it is still some years away.

REFERENCES