Surveillance of the Molecular Epidemiology of Hepatitis B Virus in Industrialized Countries: Necessary Despite Low Prevalence and an Available, Effective Vaccine?

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(See the article by Hallet et al. on pages 945–52)

Hepatitis B virus (HBV) infection is a major global health problem. The World Health Organization (WHO) estimates that ~2 billion persons are infected worldwide, including 350 million carriers of chronic HBV infection [1]. In industrialized countries, the prevalence of HBV infection is low. After a highly effective vaccine was implemented in these countries in the early 1990s, the incidence of acute HBV infection decreased significantly; for example, in the United States the incidence of infection decreased from 8.5 per 100,000 population to 2.8 per 100,000 population during a 12-year period [2]. However, outbreaks of HBV infection still occur, particularly in at-risk groups, such as injection drug users, persons with sexually promiscuous behaviour, and prison inmates, which reflects the poor vaccination coverage among these groups [2]. An outbreak of infection leads to an amplification of specific HBV strains. These viral strains may have increased pathogenic potential, thereby inducing, for instance, a high rate of fulminant hepatitis B [3]. Also, HBV variants with escape of vaccine-induced immunity may be selected during an outbreak [4]. Therefore, continuous surveillance of the spread of HBV strains is necessary.

For this purpose, molecular typing methods have been developed for HBV (reviewed in [5]). Methods that are widely used involve the sequencing of complete HBV genomes or the analysis of single genes or parts of genes. Alternatively, restriction fragment–length polymorphism analysis has been developed to overcome the need for HBV sequencing. Each method has been shown to have the potential to differentiate accurately between the 8 HBV genotypes A–H. By definition, these HBV genotypes have a nucleotide divergence of >18% across the complete genome [5]. Because HBV genotypes correlate strongly with geographic regions and ethnicity [5, 6], this fairly rough classification is not sufficient for the investigation of transmission routes or the spread of particular HBV variants (e.g., within defined subgroups of persons). For this purpose, a more detailed analysis of the viral genome is required. This need represents the main problem in the molecular investigation of HBV epidemiology. The unique structure of the HBV genome, which has overlapping reading frames, leads to a low mutation rate in vivo [5]. Because of this so-called constrained evolution [7], which region of the HBV genome is best suited for precise subgenomic typing is not clear at present. Therefore, in most studies, sequencing of full-length genomes or analysis of ≥2 independent HBV genes has been performed to achieve maximum sensitivity in the differentiation of particular HBV variants. Thus, molecular typing of HBV isolates is laborious and expensive.

Data on HBV epidemiology also are currently limited because epidemiological studies of HBV mainly focus on the cross-sectional investigation of HBV genotypes or subtypes that are prevalent in certain geographic regions or in particular subgroups of patients. Results of longitudinal surveys have been published rarely [8]. Therefore, conclusions about the kinetics of the spread of HBV strains are difficult to make.

In this issue of Clinical Infectious Diseases, Hallett et al. [9] describe the spread of a particular HBV variant (HBV\(^{\text{PV}}\)) in England. This study is remarkable for several reasons. It is a longitudinal investigation involving a large series of serum samples obtained from patients with acute cases of hepatitis B. A method was opti-
mized for genome analysis that appears to be a feasible means for large-scale investigation of HBV strains. Most importantly, outbreak cases were compared with representative sporadic cases, and the incidence of HBVPV infection was determined by year. Hallett et al. [9] found a trend for an increase in cases of acute hepatitis B caused by this particular viral strain in some but not all regions of England that occurred by year. Hallett et al. [9] found a trend for the investigation of transmission events, characterized in future studies. Second, in epidemiological dynamics should be further subtypes [10]. In HBV infection, these demonstrated recently for hepatitis C virus subtypes [10]. In HBV infection, these epidemiological dynamics should be further characterized in future studies. Second, in the investigation of transmission events, the analysis of HBV in outbreak cases of infection absolutely must be compared with results for unlinked, sporadic cases occurring in the same geographic region. Otherwise, conclusions about the source of an outbreak can be misleading. Third, the natural genomic variation of HBV in individual patients should be known longitudinally (i.e., intraintividual variation), to calculate the significance of nucleotide differences between viruses obtained from different patients (i.e., interindividual variation). Only this knowledge will facilitate valid investigation of the sources of outbreaks. Finally, the sequence data obtained by Hallet et al. [9] may serve as a basis for future studies of transmission events, at least for transmission events occurring in England.

The results reported by Hallet et al. [9] also suggest that industrialized countries that pursue a selective, rather than a universal, vaccination policy should aim to vaccinate at-risk groups consistently, such as injection drug users and prison inmates. The experience in Germany, however, has been that selective vaccination of at-risk groups does not lead to an eradication of HBV infection. This goal seems to be achievable only by mass vaccination of the entire population, as has been proposed already by the WHO. As long as high vaccination coverage does not exist in at-risk groups or in the general population, surveillance of the spread of particular HBV variants by sophisticated molecular methods is mandatory. Because of the difficulties described above, much work remains to be done with regard to the molecular epidemiology of HBV.

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References