A recent report of an outbreak investigation in this journal (1) explored the heterogeneity of variability across the hepatitis B virus (HBV) genome. As expected, genomic regions encoding a single gene product tended to be more variable than overlapping open reading frames (ORFs) with multiple translated products. The investigators recommend the use of the most rapidly evolving regions, such as nonoverlapping stretches of core and pol genes, for transmission investigations or studies of sequences deriving from a recent common source.

There have been many investigations of HBV transmission using sequencing of various genomic targets. In a recent study of occult HBV infection in household contacts of carriers (2), S-gene sequencing was undertaken for the purpose of transmission analysis. It was observed that the sequences from some (presumably epidemiologically unconnected) families clustered together, a phenomenon it was suggested may be due to gene flow through the extensive mixing of HBV strains as was hypothesized for precore/core sequence similarities in an investigation of HBV transmission in Gambia (3).

An alternative explanation is the high degree of conservatism in the S region, and in the Gambian study the authors reported that S-gene sequence analysis was unsuitable for demonstration of common source infections due to this conservatism, which is related to the overlapping S and reverse transcriptase domain of pol ORFs in this region (5, 9, 11). Indeed, multiple epidemiologically unrelated S-gene sequences were found to be identical.

Similar findings were reported from Australia 3 years earlier than the Gambian study (9). In this study of recently emigrated families, separate analyses of S-gene and distal-X-precore sequences were performed. The S genes allowed categorization of HBV strains into dominant strains related to country of origin, which were not recognized by distal-X-precore sequence analysis, but the latter was better able to discriminate between family groups. Both observations are presumably due to the differing variability in these regions, with the distal-X-precore being more variable and therefore preferred by the authors for tracing recent HBV transmission events.

Discussion of the optimal genetic targets for sequence analysis of transmission is neither new nor restricted to HBV (6, 8, 10). In response to the controversy surrounding single-gene sequence analysis of human immunodeficiency virus type 1 (HIV-1) transmission, Gonzalez-Candelas and Moya (4) state that given the heterogeneity of the evolutionary rate along the genome of this virus, analysis of phylogenetic relationships must be based on a domain with an appropriate level of evolution for the issue under investigation. Assessing recent transmission events requires the analysis of fast-evolving regions, whereas older events must be studied by sequencing more-stable regions. Thus, in the HBV context, conserved areas, such as the S gene, are useful for determining genotypes and strains associated with particular regions or communities (where common ancestor virus strains are more distant) but potentially less so for studying the chain of transmission between individuals, where a more mutable and therefore variable area of the genome is preferable. Bracho and colleagues reinforce this argument in their recent article (1).

Again drawing from the controversy surrounding HIV-1 transmission, it perhaps could also be said for HBV that “there is no such thing as an ultimate gene for evolutionary analyses . . . ideally, full-length sequences should be used for the investigation of potential linkages by phylogenetic means” (7) and that no single region is equal to them all.

I thank Heath Kelly for comments and suggestions to improve this letter.

This work was financially supported by the Centre for Clinical Research Excellence in Infectious Diseases and by a Public Health Postgraduate Scholarship from the National Health and Medical Research Council, Australia. I had no conflict of interest.

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Benjamin C. Cowie
Victorian Infectious Diseases Reference Laboratory
10 Wreckyn Street, North Melbourne
Victoria 3195, Australia
Phone: (61 3) 9342 2606
Fax: (61 3) 9342 2666
E-mail: Benjamin.Cowie@mh.org.au