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Hepatitis A Epidemiology Goes Global

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It may not be appreciated that a hepatitis A virus (HAV) outbreak investigation in several states in Australia, as described in this issue of *Clinical Infectious Diseases* [1], was viewed with intense interest on the other side of the world. In fact, it is considered a harbinger of hepatitis A investigations to come. This seemingly straightforward investigation—with molecular epidemiologic techniques now almost standard in any outbreak examination—may nonetheless be considered a landmark. The world is “flatter” and food and food products produced in one country (along with the pathogens they may carry) can be exported almost anywhere. We observed this in the United States when HAV infections in several states were acquired from green onions imported from northern Mexico [2, 3]. Although somewhat downplayed in the Donnan et al [1] article, molecular epidemiology from their investigation showed that samples from affected persons in both the Netherlands and Australia had sequence identity, and standard “shoe-leather” epidemiology showed large odds ratios for persons in both countries who had consumed semidried tomatoes from Turkey. These semidried tomatoes are different from the sun-dried tomatoes common in US supermarkets and are often used by restaurants and in commercial food production to make pizza, sauces, and similar items. The Australian investigation showed that, indeed, those who ate not only semidried tomatoes but also those who ate tomato-based foods in restaurants were at substantially greater risk of HAV infection.

In this country, there has been an abiding concern that imported food items potentially contaminated with hepatitis A can and do enter this country frequently. With funding from the Center for Disease Control and Prevention (CDC) Food Safety Initiative, several state and city health departments interview and collect serum from persons with acute hepatitis A. The specimens are then processed at CDC’s Division of Viral Hepatitis Laboratory, where recent marked improvements in sequencing of the HAV genome (and other types of viral hepatitis genomes) have made such work easier and faster than ever. CDC now holds a “library” of partial and complete gene sequences of the HAV genome, which include >3000 domestic specimens and >2000 specimens from other countries (although some are duplicate sequences from outbreak investigations). As new specimens are sent to CDC, they are sequenced and compared with extant sequences held in the library to gain insight into origins and transmission patterns.

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In the outbreak described here, the Netherlands shared their gene sequences with CDC, other domestic samples of HAV genotype IB were examined, and a seeming possibly related “cluster” was found in Brooklyn, New York. Subsequent investigation by the NY City Health Department and CDC showed that these were mainly among Koreans who lived distant from one another and did not share markets or restaurants. About half had apparently acquired HAV infection during travel to Korea. Subsequent investigations this year and last of potential international outbreaks with US cases that were linked to cases or clusters in Mexico and Canada have likewise not established linkage. Still, the principle has been established: advances in molecular laboratory diagnostics and computer-based analytic applications have revolutionized HAV epidemiology. The outbreak described by Donnan and colleagues uncovered cases on 2 continents, and we should expect some future ones to involve the Americas as well.

Where is US hepatitis A epidemiology currently? Only a little more than a decade ago, rates of infection were much higher as outbreaks in children, in whom the disease causes no or few symptoms, spread infections to susceptible older children and adults through fecal-oral means [4, 5]. Hepatitis A vaccination of infants and children in certain high-prevalence Western states starting in 1999 [6] and for all US-born infants after 2006 [7] has clearly had a large impact on herd immunity [8, 9] and resulted in a marked 10-fold decline in incidence and mortality from HAV infection over the past 15 years [10, 11]. Thus, about one-half of all HAV infections among US residents are now acquired from travel to endemic countries, typically Hispanic residents traveling to Mexico [12]. Only ~7% of infections can be definitively ascribed to a food or water source (usually in investigated outbreaks), although many “unknown” source cases (~36%) probably are acquired from food. Since large multistate outbreaks linked to oysters in 2005 [13] and green onions in 1998 through 2003 [2, 3], no large food-borne outbreaks have been detected in the United States. Rather, a common problem has been the public concern and the emergency recruitment of limited public health resources to identify restaurant patrons and get them vaccinated when an HAV-infected food handler is discovered. In the last 12 months CDC is aware of 6 instances of this. As these are often food handlers in popular restaurant chains, 3 situations involved thousands of potentially exposed persons and vaccination of hundreds of concerned restaurant patrons. These are cases where the reaction is usually much more costly in terms of limited health department personnel, resources, and funding than the actual infections, which are unlikely to—but still may—occur among the worried populace.

Nonetheless, ~20 000 acute hepatitis A infections and ~100 deaths per year are still estimated to be occurring in the United States [10], so complacency is not warranted. In some South American countries there is concern that unvaccinated adults in urban and suburban settings are now in contact with unvaccinated rural populations and that this could result in outbreaks in susceptible adults in urban settings. A similar concern exists in the United States in which we have seen seroprotection decline among adults as those who were exposed naturally to hepatitis A in the past are replaced by an adult population that is neither vaccinated nor previously exposed [8]. As the investigation described in these pages documents, vaccination of persons in developed countries is increasingly being counterbalanced by the importation of foods from highly endemic areas of the world [14]. We should expect to be investigating other international outbreaks of hepatitis A in the

United States in concert with overseas colleagues. To re-phrase John Donne, “no outbreak is an island” anymore.

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