with treatment success was a prominent theme of continuing education for staff. Combination fixed-dose, NNRTI-based regimens have been widely used in low- and middle-income countries, and switching to second-line regimens is now more frequently reported [7]. We emphasize the potential benefits of promoting high rates of adherence to antiretroviral medication regimens to optimize the long-term success of antiretroviral treatment, as well as minimizing treatment fatigue and the need to switch regimens because of treatment failure.

Acknowledgments

Financial support. Thammasat University Infectious Diseases and Infection Control Research Fund.

Potential conflicts of interest. L.M.M. is a consultant to WWF-Epidemiology at GlaxoSmithKline, Inc. A.A.: no conflicts.

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References


Household Data from the Ugandan Hepatitis E Virus Outbreak Indicate the Dominance of Community Infection

To the Editor—Teshale et al [1] assessed the potential for person-to-person transmission of the hepatitis E virus (HEV) during a large outbreak in Uganda. The following 2 findings were suggestive of person-to-person transmission: (1) the long-lasting outbreak despite the absence of a common source, and (2) no virus was isolated from environmental sources. However, I have serious concerns regarding the analysis of the household data.

There has been extensive discussion about serial intervals (the time interval between the onset of symptoms in 2 cases within a household) in infectious disease epidemiology [2–4]. Figure 1A shows the serial intervals within households resulting from 3 distinct epidemiological mechanisms: (1) independent infection (in which both case patients are infected independently within the community), (2) coprimary cases (in which 2 case patients are infected within the community at the same time), and (3) household transmission (in which one case patient is infected in the community and the other is infected by the primary case patient within the household). Ideally, this argument applies to households with only 2 case patients [2]. To prove person-to-person transmission from the household data, one must identify a second peak in the observed bimodal distribution of the serial interval attributable to household transmission (mechanism 3). The second peak should correspond to the sum of the mean incubation period and the mean time from the onset of symptoms in the primary case to secondary transmission [5], 3–9 weeks in the case of HEV.

Figure 2 in the article by Teshale et al [1] implicates the presence of a second peak in the observed serial intervals. How-

Figure 1. Time intervals between symptom onset in 2 cases within households. A, There are 3 underlying epidemiological mechanisms for the observed serial intervals. The bold line shows the situation when both case patients were infected independently within the community. The dashed line represents when both were infected at an identical time in the community. The unbroken line represents secondary transmission within households. The dominance of household transmission is indicated if a second peak (expected at ~10 weeks in this panel) of the bimodal mixture distribution is apparent. B, The serial intervals observed during the hepatitis E virus outbreak in Uganda in 2007–2008. In the paper by Teshale et al [1], Figure 2 shows the number of cases observed over different periods of time, whereas this Figure shows a modified version in which the vertical axis denotes the average number of cases per week. Because it is not technically feasible to identify coprimary cases manually, 1280 household cases in which the second case was observed within 2 weeks of the first were grouped in 1 category. For the interval denoted as >20 weeks, the length of the interval was assumed to be 20 weeks, because the outbreak continued for >40 weeks.
ever, as shown in Figure 1B in this letter, these data are better represented as the average number of cases observed per week, rather than the absolute number of cases over a particular time period. To avoid any ambiguity in correctly identifying coprimary cases, 1280 household cases in which the second case was observed within 2 weeks of the first were grouped in 1 category. Figure 1B clearly shows that a second peak in the serial interval distribution, which would suggest person-to-person transmission as explained by household transmission (mechanism 3), does not occur. Rather, the steady decrease in its frequency indicates the dominance of community infection, which is explained by independent infection and coprimary cases (mechanisms 1 and 2).

Given the dominance of community infection (perhaps caused mostly by environmental transmission, but also partly by person-to-person transmission), the epidemiological comparison of both personal and household characteristics should have had a different focus. Rather than comparing households having \(\geq 2\) cases with those having one or none, the long and short serial intervals among households with \(\geq 2\) cases should have been compared. If a risk factor is identified as more prevalent in households with long serial intervals than in those with short serial intervals, it implies the presence of person-to-person transmission in those households.

The household data from Uganda do not indicate substantial person-to-person transmission within households. Developing objective analytical methods for accurately assessing the level of person-to-person transmission with use of household data is crucial [6–8].

Acknowledgments

Financial support. Funded in part by the Japan Science and Technology Agency PRESTO program.

Potential conflicts of interest. H.N.: no conflicts.

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References


Reply to Nishiura

To the Editor—We appreciate the opportunity to address the comments of Dr Nishiura [1]. To briefly recapitulate, the findings that underlay our conclusion of person-to-person transmission of hepatitis E virus (HEV) during a very large outbreak (>10,000 symptomatic cases) in a susceptible population of northern Uganda [2] include the following: (1) the distribution of cases occurred over many months, now up to 2 years; (2) we could not recover HEV from dedicated drinking water sources; (3) we could not recover epidemic HEV genotype 1 from zoonotic sources (ie, local pigs); (4) cases occurred among very young children who would not otherwise have access to contaminated external sources; (5) extensive control efforts targeting unprotected (and distant) water sources did not apparently impede the epidemic; (6) epidemiologic studies indicated frequent communal hand washing and eating food by hand in the community; and (7) HEV was recovered from hand lavage of infected case patients.

Dr Nishiura questioned 1 of these findings—the distribution of symptomatic hepatitis (jaundice) in households, as shown in Figure 2 of our article [2]. We would argue that the modeling of person-to-person transmission as shown in Nishiura’s Figure 1A [1] is based on assumptions that may not apply to HEV infection in this setting. Hypothetical models for person-to-person transmission of HEV should consider the long incubation period, dose-dependent symptom onset, and frequent inapparent illness. The unique attributes of the population we investigated included crowded living conditions, traditional practices (communal feeding and hand washing), and an apparently immunologically naive population.

However, more to the point, we have examined the modeling effort by Dr Nishiura in Figure 1B [1] by changing the x-axis of our Figure 2 [2] to represent weeks of onset rather than time interval between the primary case and subsequent cases. Given the way questions were asked and the vagueness of recall some weeks or months after events, we could not provide a more detailed analysis of occurrence of cases by week. However, we have reanalyzed our data to look at families with \(\geq 1\) case and specific date of onset and have found that 68% of cases occurred in families with \(\geq 2\) cases. Table 1 shows the interval between primary and secondary (subsequent) symptomatic cases in families with only 2 cases and the interval between primary and secondary and tertiary cases.