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LETTERS

Reservoir Host Expansion of Hantavirus, China

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To the Editor: Hemorrhagic fever with renal syndrome (HFRS) is caused by hantavirus. During 1995–2005, China reported 20,000–50,000 cases of HFRS annually, which represents 90% of HFRS cases worldwide (1–3). In China, HFRS is caused mainly by 2 serotypes of hantavirus: Hantaan virus (HTNV) and Seoul virus (SEOV) (4). Pathogenic hantavirus serotypes are considered to be strictly associated with their serotype-specific reservoir hosts. HTNV is associated with the striped field mouse (Apodemus agrarius), and SEOV is associated with the brown rat (Rattus norvegicus) and the black rat (Rattus rattus) (4,5). HTNV causes a severe form of HFRS, characterized by renal failure that in some cases is followed by pulmonary edema and disseminated intravascular coagulation; the estimated death rate is 5%–15%. SEOV causes a moderate form of HFRS (6).

Jiaonan County in Shandong Province is one of the high-incidence HFRS areas in China. To detect the hantavirus infection in small mammals, we trapped rodents and shrews during December 2012–November 2013 using snap-traps in Jiaonan County (longitude 119°30′–120°°30′, latitude 35°35′–36°08′).

We captured 1,276 animals comprising 5 rodent species and 1 shrew species (Table) and analyzed serum antibody against hantavirus of each animal using an antigen sandwich ELISA Kit (Shanghai Jiahe Biotechnology, Shanghai, China). The serum was considered to contain antibodies against hantavirus when the optical density (OD)450nm of the sample was greater than the threshold. The threshold was calculated by using the equation: threshold = the average OD of the negative control + 0.15. ELISA results showed that 23.3% of animals were seropositive to hantavirus antigen (Table). The seropositive rate to hantavirus was 44.0% in Asian house shrews (Suncus murinus), 25.3% in house mice (Mus musculus), 15.4% in Chinese hamsters (Cricetus griseus), 10.3% in brown rats, 10.1% in striped field mice (Apodemus agrarius), and 3.0% in greater long-tailed hamsters (C. triton). The seropositivity rate for rodents was higher during summer (May–August) and lower during spring (March and April) and winter (October and November) but not significantly different among the months.

To determine what types of hantavirus infected the animals, we amplified viral RNA of HTNV and SEOV from animal lung samples using reverse transcription PCR with serotype-specific primers (7); 2.1% of animals had viral RNA of HTNV, and 2.1% had viral RNA of SEOV (Table). HTNV RNA was detected in striped field mice (6.3%), house mice (1.4%), and brown rats (0.6%). The hantavirus-positive animals were captured in February, April, and November for striped field mice; November for brown rats; and April and November for house mice. SEOV was detected in brown rats (8.2%) and Asian house shrews (1.7%). These SEOV-positive animals were captured in January, March, May, June, and July for brown rats and March and November for Asian house shrews. The phylogenetic analysis of sequences amplified by reverse transcription PCR is presented in the online Technical Appendix Figure (http://wwwnc.cdc.gov/EID/article/21/1/14-0960-Techapp1.pdf). The nucleotide sequences of the PCR products have been deposited in GenBank (accession nos. KM357423–KM357452).

Hantavirus had been considered to be strictly associated with specific reservoir hosts and to have the same geographic distribution pattern as these reservoir hosts. All hantaviruses that caused human diseases had been associated with rodents, including members of Murinae, Arvicolinae, and Sigmodontinae spp. Insectivore hantaviruses were not known to cause human disease. The rodent hantavirus and the insectivorous hantaviruses were thought to have co-evolved with their specific rodent and insectivorous hosts over millions of years (8). One observed geographic clustering of hantavirus strains, and the association of hantaviruses with their reservoirs, might have been caused by an isolation-by-distance mechanism (9,10) and mixture of both host switching and co-divergence (10). Our study demonstrated that HTNV not only infects its traditional host, the striped mouse, but also infects house mice and rats; SEOV infects not only rats but also shrews, suggesting host expansion for both HTNV.
and SEOV in China. Our hypothesis is that the hantavi- 
ruses co-evolved with their animal hosts, such as SEOV 
with rats and HTNV with striped mice, but when their ani-
mal hosts expanded their territory, hantavirus had more 
chance to infect other susceptible rodents and expanded 
their animal hosts.

Both Asian house shrews and house mice are closely 
associated with humans by living inside and outside of hu-
man houses in China. The Asian house shrew and house 
mouse have been underestimated as potential animal hosts 
of SEOV and HTNV. To our knowledge, only 1 previous 
study had associated Asian house shrews with SEOV; in 
that study, an SEOV strain was isolated from an Asian 
house shrew in China (2).

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Endophthalmitis Outbreak Associated with Repackaged Bevacizumab

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To the Editor: An outbreak of endophthalmitis asso-
ciated with repackaged bevacizumab occurred during Feb-
uary–March 2013 in Georgia and Indiana, USA. Bevaci-
zumab (Avastin; Genentech, Inc., South San Francisco, CA, 
USA) is a vascular endothelial growth factor inhibitor that 
is approved by the US Food and Drug Administration as 
an antineoplastic agent but is commonly used off-label to 
treat retinal disorders, including age-related macular degener-
ation (1,2). Bevacizumab is manufactured in single-use,

Table. Seroprevalence rate and RT-PCR-positive rate of hantaviruses in small mammals, Jiaonan County, China, December 2012–November 2013*.  

<table>
<thead>
<tr>
<th>Animal species</th>
<th>No. (%) animals</th>
<th>Seroprevalence of hantavirus</th>
<th>No. tested/no. RT-PCR positive (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>*HTNV</td>
<td>SEOV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apodemus agrarius</td>
<td>268 (21.0)</td>
<td>27 (10.1)</td>
<td>12/191 (6.3)</td>
</tr>
<tr>
<td>Cricetulus griseus</td>
<td>156 (12.2)</td>
<td>24 (15.4)</td>
<td>0/63</td>
</tr>
<tr>
<td>C. triton</td>
<td>135 (10.6)</td>
<td>4 (3.0)</td>
<td>0/48</td>
</tr>
<tr>
<td>Mus musculus</td>
<td>245 (19.2)</td>
<td>62 (25.3)</td>
<td>2/143 (1.4)</td>
</tr>
<tr>
<td>Rattus norvegicus</td>
<td>213 (16.7)</td>
<td>22 (10.3)</td>
<td>1/159 (0.6)</td>
</tr>
<tr>
<td>Suncus murinus</td>
<td>259 (20.3)</td>
<td>114 (44.0)</td>
<td>0/121</td>
</tr>
<tr>
<td>Total</td>
<td>1,276 (100)</td>
<td>253 (19.8)</td>
<td>15/725 (2.1)</td>
</tr>
</tbody>
</table>

*HTNV, Hantaan virus; RT-PCR, reverse transcription PCR; SEOV, Seoul virus.
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Technical Appendix

Technical Appendix Figure. Phylogenetic tree of hantaviruses from small mammals, Jiaonan County, China, December 2012–November 2013. A maximum-likelihood tree was constructed by using MEGA5 software (http://www.megasoftware.net) with 2,000 replicates for bootstrap testing. The tree was rooted with Rift Valley fever virus (GenBank accession no. DQ380147.1). Scale bar indicates nucleotide substitutions per site.