Is Vertical Transmission Sufficient to Maintain Junin Virus in Nature?

By ALFREDO D. VITULLO* AND MARIA SUSANA MERANI

Departamento de Microbiologia, Facultad de Medicina, Universidad de Buenos Aires, Paraguay 2155, piso 11, 1121-Buenos Aires, Argentina

(Accepted 12 February 1988)

SUMMARY

The quantitative contribution of vertical transmission to the prevalence rate of Junin virus infection in subsequent generations of its natural reservoir, Calomys musculinus, was analysed. Data on mortality and reproduction of C. musculinus infected at birth with a wild strain of Junin virus were used to estimate the infection-dependent relative survival rate ($\beta = 0.4849$) and relative fertility of the infected host ($\alpha = 0.2088$). Prevalence rates of infection, obtained by mathematical simulation in optimal conditions of vertical transfer, dropped steadily to zero in a few generations. Vertical transmission was found to be insufficient to overcome the effect of highly depressed survival and fertility of the infected host and maintain a stabilized prevalence of Junin virus infection in successive generations; this suggested that viral maintenance is mainly dependent upon horizontal transmission.

The term vertical transmission refers to the parent-to-progeny transfer of an infectious agent or parasite (Gross, 1951) occurring during gestation or soon after birth (postnatal vertical transmission) (Mims, 1981). Although such a mechanism could provide an efficient inter-generation transfer of the pathogen, it is necessary to take into account the effects of infection upon the host in order to assess the epidemiological significance of this mode of transmission (Fine, 1975).

The arenavirus Junin (JV), aetiological agent of Argentine haemorrhagic fever, gives rise to persistent infection in its natural host, Calomys musculinus (Sabattini et al., 1977). Both horizontal and vertical (postnatal) transmission have been found (Sabattini et al., 1977). Recently, it has been shown that persistent infection affects both the survival and fertility of the host (Vitullo et al., 1987), suggesting that vertical transmission could have some epidemiological significance (Vitullo & Merani, 1987). Nonetheless, the question of whether vertical transmission in itself might be insufficient for the continued maintenance of JV in nature remains unanswered.

We analysed the contribution of vertical transmission to the maintenance of JV in C. musculinus, if no horizontal transfer occurred, according to the quantitative model proposed by Fine (1975). For this purpose a colony of C. musculinus infected with JV was established. Animals were obtained from a JV-free colony maintained under standard conditions ($20 \pm 2 ^\circ C$; 12:12 h light:dark). A total of 85 C. musculinus were inoculated 24 to 48 h after birth by nasal instillation of 100 TCID$_{50}$ of the Cba An 9446 strain of JV. This strain was originally obtained from whole blood of one C. musculinus trapped in the endemic area of Argentine haemorrhagic fever. The virus stock employed in this study had been passaged six times in mouse brain. The course of infection was analysed over a period of 480 days by virus assay of blood, urine and/or saliva samples collected without killing the animals. It was found that intranasal infection at birth produced persistence of the virus during the lifetime of the animals. More detailed information on this matter has been published elsewhere (Vitullo et al., 1987).

Primary data were derived from the daily mortality and fertility records kept of infected and uninfected animals. Fertility was estimated from the reproductive success (number of mating
Table 1. Survival probability and fertility rate in C. musculinus infected at birth with Junin virus*

<table>
<thead>
<tr>
<th>$x$</th>
<th>$l_x$</th>
<th>$l_x$</th>
<th>$l_x/l_m$</th>
<th>$f_x$ §</th>
<th>$f_x$ ¶</th>
</tr>
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<tbody>
<tr>
<td>1</td>
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<td>13</td>
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<td>21</td>
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<td>0.8144</td>
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<tr>
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<td>0.6067</td>
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<td>1.0</td>
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<tr>
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</tr>
<tr>
<td>180</td>
<td>0.1765</td>
<td>0.4369</td>
<td>0.5999</td>
<td>0.7201</td>
<td>0.0</td>
</tr>
</tbody>
</table>

* Data collected from infected (n = 85) and uninfected (n = 53) animals, at the same time.
† $x$, Age in days.
‡ $l_x$, Probability of survival to day $x$. Superscripts (+) and (−) denote infected and uninfected animals respectively.
§ $f_x$, Fertility, i.e. number of mating pairs littering at least once/number of mating pairs.
¶ $m$, Age at which reproductive capacity is attained, estimated from Merani et al. (1988).

pairs delivering a litter at least once/number of mating pairs) of infected and uninfected animals mated at weaning (21 to 25 days) in monogamous pairs. Both mortality and fertility records for selected times are summarized in Table 1. The age at which reproductive capacity is attained ($m$) was taken as 50 days, from the data of previous studies on these animals (Merani et al., 1988); thus, $l_m$ refers to the probability of surviving until the reproductive age. Other symbols are explained in the footnotes.

The infection-dependent relative survival rate ($\beta$) was calculated according to Fine & Sylvester (1978): $\beta = l_m/l_m$, and relative fertility of infected animals ($\alpha$) was estimated as:

$$\alpha = \frac{\sum (l_x/l_m) f_x}{\sum (l_x/l_m) f_x}$$

where the term $l_x/l_m$ takes account of the mortality only after age $m$ (Fine & Sylvester, 1978).

By comparing the data from columns 1 and 2 (Table 1) it is clear that infection did not alter the probability of survival during lactation (until 21 days); however, from weaning to 50 days infected animals showed a large decrease in survival potential. From these data, the infection-dependent survival rate can be calculated as $\beta = l_50/l_50 = 0.2942/0.2942 = 0.4849$. This value indicates a 50% reduction in the probability of reaching the reproductive age when animals have received the infection at birth. Two of 33 monogamous mating pairs with infection, established at weaning and which were maintained for a 5 month period, delivered litters at least once. Fifty percent of the pairs were lost because the animals died before they reached the reproductive age. As this mortality is measured by $\beta$, these mating pairs were not taken into account to calculate the fertility of infected rodents. From columns 3 to 6 in Table 1, the relative fertility of infected animals was estimated as $\alpha = 0.2088$, where $m = 50$ in the equation above.

On the basis of these parameters ($\alpha$ and $\beta$), the quantitative contribution of vertical transmission to the rate of prevalence of infection in subsequent generations of C. musculinus was predicted by iteration of the fundamental vertical transmission equation [see Fine (1975) for the derivation of the equation]:

$B'_a = \frac{\beta [B_a \alpha d (1 - B_a + B_a \alpha) + B_a \alpha w (1 - B_a + B_a \alpha - B_a \alpha d)]}{\beta [B_a \alpha d (1 - B_a + B_a \alpha) + B_a \alpha w (1 - B_a + B_a \alpha - B_a \alpha d)] + (1 - B_a + B_a \alpha - B_a \alpha d) (1 - B_a + B_a \alpha - B_a \alpha w)}$
Fig. 1. Prevalence rates of Junin virus infection ($B_e'$) in successive generations of host rodent Calomys musculinus, predicted by iteration of the fundamental vertical transmission equation (see text), if no horizontal transmission occurred. In each case, the assumed prevalence rate in the parental generation ($B_a$) is as indicated by curves, $\alpha = 0.2088$ and $\beta = 0.4849$. (a) Biclinal vertical transmission to the whole progeny of both parents, $d = v = 1$; (b) Monoclinal vertical transmission to the whole progeny from either the males or females, $d = 1$ and $v = 0$ or $d = 0$ and $v = 1$.

in which $B_a$ and $B_e'$ are defined as the prevalence rates of infection of the parental and filial generations and $d$ and $v$ represent maternal and paternal vertical transmission rates, respectively. The mathematical simulation included two different assumptions: first, biclinal vertical transmission of JV to the whole progeny of infected animals thus $d = v = 1$ or, second, monoclinical vertical transmission to the whole progeny from either the males or females thus $d = 0$ and $v = 1$ or $d = 1$ and $v = 0$. In both cases, different initial prevalence rates of infection ($B_a = 0.95, 0.90, 0.50$ and $0.25$) were assumed. Results of such iterations are illustrated in Fig. 1. In all cases, the prevalence rates were seen to drop steadily to zero in a few generations even if high initial prevalence rates ($0.95$ and $0.90$) were considered. The vertical transmission of infection to the whole progeny ($d = v = 1$) was insufficient to stabilize the prevalence rate of infection and to overcome the effect of highly depressed fertility and survival of infected animals. It is of interest to note that vertical transmission failed to support the infection for more than one generation with initial prevalence rates close to known natural rates ($B_a = 0.25$) (Sabattini et al., 1967).

This analysis underlines the inefficiency of vertical transmission for the continued maintenance of JV in C. musculinus, thus suggesting that viral maintenance is mainly dependent upon horizontal transmission. It must be pointed out that the mathematical model used here represents a discrete-time model analogous to the genetic models predicting the prevalence rates of a given gene or allele in a species or population. However, similar results were obtained with a continuous-time model (Anderson & May, 1979) in which the population number is a dynamic variable rather than a specified constant (data not shown).

It is evident that vertical transmission is not qualitatively essential because of the option of inter-generation horizontal transfer of the infection. Nevertheless, we must consider the role of animals that are infected by intra-generation horizontal transmission. In contrast with the decrease in survival and reproductive ability of C. musculinus infected at birth, animals that receive the infection as adults do not show altered reproduction and survival (Vitullo et al., 1987); therefore, vertical transmission might contribute, to some extent, to the maintenance of infection in this case. In terms of a natural population of C. musculinus, it may be assumed that animals vertically infected (during lactation), if unable to transfer the infection satisfactorily to the next generation, contribute towards intra-generation infection by horizontal transmission. Adults which are horizontally infected may secure the inter-generation transmission by both
vertical and horizontal means. Under these circumstances, JV maintenance may arise from an equilibrium between both modes of transmission, with the horizontal representing the main route resulting in viral persistence in nature and vertical transmission being an added option for inter-generation transfer that may support the infection when population numbers are reduced and horizontal transmission is precluded.

Our analysis outlines the first step in understanding the maintenance of JV in its natural hosts. Similar studies performed in the two other cricetid rodents involved in the natural cycle of JV, C. laucha and Akodon azarae, may help to elucidate the significance of host interactions and the role of JV in determining the ecological structure of rodent communities.

The authors wish to thank Eduardo Roldán for his comments on an early version of the manuscript, and Cristina Videla for her active interest and suggestions during the preparation of the manuscript. This work was supported by grants from the Consejo Nacional de Investigaciones Científicas y Técnicas (PID-3907102/85) and Fundación Emilio Ocampo.

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(Received 9 November 1987)