Finally, we compared the change of prevalence which was derived from the model with the observed value based on a mass examination of villagers (Table 1). Following the executed plan in Sto. Thomas, the simulation used the actual value as coverage. In this area, a snail control program using molluscicides was operated from 1986. The effective rate of molluscicides was assumed to be 30%. Because we could not determine the exact change of the density of infected snails (Section 2.2), we showed the change of infection rate in snails instead of the density in Sto. Thomas (Fig. 5). It should be noted that the change of the density of infected snails is more useful than that of the infection rate in snails for making the assessment of transmission from snail hosts to definitive hosts due to abundance of cercariae in water. The χ^2-value for 5 points of time when the number of positive cases will be expected to be beyond 1 (1986–90) is estimated at 9.0 ($P>0.05$, $df=5$), and the differences of positive rates for the other points of time (1991–95) stay within 0.7%, while the correlation coefficient between simulated and observed positive cases of all 10 points is 0.99. On the other hand, though we could not make a precise comparison between the simulated and observed infection rates in snails because of the instability of observed data, their correlation coefficient was 0.92. From the above point of view, the transition curve of prevalence derived from the model is in accordance with the observed data. The transition curves of prevalence derived from the model for the remaining two villages were less accordant with the observed data than that for Sto. Thomas (figures not shown). The correlation coefficients are 0.90 and 0.93 for San Vicente (1986–94) and San Roque (1985–93), respectively, while the χ^2-values for the points of time except when positive cases are above 1 could not be confirmed for $P>0.05$.

4. Discussion

It is important to consider the relationship between the model and the reality. It is unavoidable for the model of transmission for *S. japonicum* to have a somewhat complicated structure, because *S. japonicum* has a complicated life cycle which involves human and animal reservoirs, and snail hosts, and is exposed to the environment. To avoid too much complexity, we have aimed at a simple model structure so that all the epidemiological parameters involved in the model except transmission rates are determined in field surveys and studies of experimental infections. Thus, we did not introduce mating mechanism, immune mechanism in the model, or the intensity of *S. japonicum* in humans or snail.

A distinct feature of the model is the division of the shedding stage in snails into two classes according to cercaria output. This is adequate to prevent overestimating or underestimating the abundance of cercariae because of a long shedding duration.

The range of theoretical reproduction potential of an adult worm pair may increase from 1 to 10^{11} [19]. The transmission rates cannot be measured directly by the field observation and are also influenced by various human and environmental factors. Therefore, we have used a set of equilibrium values which can describe an epidemic situation among hosts for a pre-control period in the model as transmission rates. Those values chosen for an endemic village are reflected on by regional differences (Table 2, Fig. 5). Social behavioral changes have an influence on the transmission rates, and therefore regarding the prevalence of *S. japonicum*, further research from the viewpoint of a model incorporating behavioral changes is desirable.

In a 10-year study, we found less accordance of the transition curves of prevalence derived from the model for San Vicente and San Roque with the observed data than for Sto. Thomas. This would be attributable to a small epidemic that was observed in 1991–92 in San Vicente and San Roque (see Table 1). The model works well provided that there is no immigration or emigration in the target region, but it was reported that there was actually some immigration and emigration.

In the model, we have to give careful consideration to animal reservoirs. When they play a part in the reproduction of *S. japonicum*, it is difficult to eliminate *S. japonicum* by means of chemotherapy for people only. Generally, it is difficult to manage control of animal reservoirs. Field surveys showed that rats might contribute to *S. japonicum* prevalence. The simulation suggested that rats had a small influence on the prevalence of *S. japonicum*. It is possible that *S. japonicum* would prevail in other animals if the prevalence rate rose by a large margin.

Using the model for *S. japonicum*, Williams et al. [8] evaluated the anti-fecundity bovine vaccine in Jiangxi Providence of China, where bovines are the major reservoirs and play an important part of *S. japonicum* transmission. This vaccine was not used in the endemic villages of Bohol island. Their result of simulation was similar to the variation in the prevalence of *S. japonicum* under human control only with selected mass treatment in Sto. Thomas (Fig. 3). The comparison predicted that the prevalence in the human population would recover swiftly after annual mass treatment of humans for 5 years, and that, after a program of 5 years mass treatment for both humans and bovines, the prevalence would decrease for up to 5 years but that the equilibrium prevalence would remain at the initial level [8]. In the World Bank Schistosomiasis control project in China, snail control was limited [20], while in the Schistosomiasis Control Project on Bohol island, control procedures were carried out twice a year. If the density of snails in a target region cannot be reduced, the prevalence in inhabitants will resurge swiftly after 4-year selective mass chemotherapy. On the other hand, selective mass treatment together with snail control has a conspicuous and continuous effect on decline (Fig. 3). Therefore, an effective plan for snail control is necessary to maintain the elimination of schistosomiasis for a long time. The simulation showed that there is little probability of resurgence of an epidemic in the northeastern villages of Bohol island for several years because the program in Bohol has attained a high coverage of selected mass treatment based on stool examination and has been accompanied by snail control operation since its commencement.

Acknowledgements

We would like to thank Prof. A. Ishii of the Jichi Medical School for his helpful comments. This work was supported in part by a Grant-in Aid for Scientific Research from Japan Society for the Promotion of Science (grant no. 16540105), Sasakawa Memorial Health Foundation and by Pfizer Health Research Foundation. We are indebted to Dr. E. Teleron and Ms. C. C. Auza, Schistosomiasis Coordinator, Regional Field Office No. 7 Department of Health. We also thank all of the village captains, land owners and villagers in the municipalities of Talibon and Trinidad for their cooperation.

References

[1] Blas BL, Rosales MI, Lipayon IL, Yasuraoka K, Matsuda H, Hayashi M. The schistosomiasis problem in the Philippines: a review. Parasitol Int 2004;53:127–34.
[2] Macdonald G. The dynamics of helminth infections with special reference to schistosomes. Trans R Soc Trop Med Hyg 1965;59:489–506.
[3] Woolhouse MEJ. On the application of mathematical models schistosome transmission dynamics: I. Natural transmission. Acta Tropica 1991;49: 241–70.
[4] Woolhouse MEJ. On the application of mathematical models schistosome transmission dynamics, II. Control. Acta Tropica 1992;50:189–204.
[5] Allen EJ, Victory Jr HD. Modelling and simulation of a schistosomiasis infection with biological control. Acta Tropica 2003;87:251–67.
[6] Anderson RM, May RM. Prevalence of schistosome infections within molluscan populations: observed patterns and theoretical predictions. Parasitology 1979;79:63–94.
[7] De Vlas SJ, Van Oortmarssen GJ, Gryseels B, Polderman AM, Plaisier AP, Habbema JDE. Schistosim. A microsimulation model for the epidemiology and control of schistosomiasis. Am J Trop Med Hyg 1996;55:170–5.
[8] Williams GM, Sleigh AC, Li Y, Feng Z, Davis GM, Chen H, et al. Mathematical modelling of schistosomiasis japonica: comparison of control strategies in the People's Republic of China. Acta Tropica 2002; 82:253–62.
[9] Liang S, Maszle D, Spear RC. A quantitative framework for a multi-group model of Schistosomiasis japonicum transmission dynamics and control in Sichuan, China. Acta Tropica 2002;82:263–77.
[10] Liang S, Spear RC, Seto E, Hubbard A, Qiu D. A multi-group model of *Schistosoma japonicum* transmission dynamics and control: model calibration and control prediction. Trop Med Int Health 2005;10:263–78.
[11] Yasuraoka K, Blas BL, Matsuda H, Irie Y, Nihei N, Ohmae H, et al. Approaches to the elimination of Schistosomiasis on Bohol Island, Philippines. Jpn J Parasitol 1996;45:391–9.
[12] Blas BL, Dazo BC. Schistosomiasis survey and preliminary control work in the Province of Bohol. J Philipp Med Assoc 1968;44:80–7.
[13] Pesigan TP, Hairston NG, Jauregui JJ, Garcia EG, Santos AT, Santos BC, et al. Studies on *Schistosoma japonicum* infection in the Philippines, 2. Bull WHO 1958;18:481–578.
[14] Pesigan TP, Farooq M, Hairston NG, Jauregui JJ, Garcia EG, Santos AT, et al. Studies on *Schistosoma japonicum* infection in the Philippines: 1. Bull WHO 1958;18:345–455.
[15] Moloney NA, Webbe G. The host-parasite relationship of *Schistosoma japonicum* in CBA mice. Parasitology 1983;87:327–42.
[16] Loker ES. A comparative study of the life histories of mammalian schistosomes. Parasitology 1983;87:343–69.
[17] Wilkins HA, Goll PH, Marshall TF, Moore PJ. Dynamics of Schistosoma haematobium infection in a Gambian community: III. Acquisition and loss of infection. Trans R Soc Trop Med Hyg 1984;78:227–32.
[18] Doumenge JP, Mott KE. Global distribution of schistosomiasis: CEGET/-WHO atlas. World Health Stat Q 1984;37:186–99.
[19] Gryseels B. Uncertainties in the epidemiology and control of Schistosomiasis. Am J Trop Med Hyg 1996;55:103–8.
[20] Zhang W, Wong CM. Evaluation of the 1992–1999 World Bank Schistosomiasis control project in China. Acta Tropica 2003;85:303–13.

Journal of the Faculty of Environmental Science and Technology,
Okayama University
Vol.11, No.1, pp.1-7, February 2006

Modeling of Re-emerging *Plasmodium vivax* in the Northern Area of the Republic of Korea Based on a Mathematical Model

Kazutoshi FUJITA[1], CHEN Tian Tian[2], Tomohiko NISHINA[2]
and Hirofumi ISHIKAWA[2]

(Received November 30, 2005)

Plasmodium vivax re-emerged in 1993 near the demilitarized zone (DMZ) in South Korea, although *P. vivax* malaria disappeared in South Korea in 1979. The re-emergence of malaria in South Korea is believed to have originated from infection by mosquitoes from North Korea across the DMZ. The principal vector of *P. vivax* in the Korean Peninsula is *Anopheles sinensis*. The density of *An. sinensis* has a peak during the second week of July. The North Korean strain of *P. vivax* has 2 characteristics: a wide distribution of the terms of relapse and a high rate of relapse. Therefore, we may well wonder why the incidence of malaria is concentrated in summer, especially in August. Mathematical models in North Korea and South Korea were constructed, in which the South Korean model was affected unidirectionally by the North Korean model. We carried out simulations of the model for the Paju-shi and Yonchon-gun situations near the DMZ region. The simulation results followed the time-course of the re-emergence of *P. vivax* there, and revealed the mechanism of the elevation of the incidence of *P. vivax* in summer.

Key words: *DMZ, Korea, model, Plasmodium vivax, re-emergence*

1. Introduction

Plasmodium vivax malaria was endemic in the Korean Peninsula for many centuries. Infection by *P. vivax* was common after the Korean War. Later, the National Malaria Eradication Service (NMES) was established in collaboration with the World Health Organization, and the WHO declared in 1979 that indigenous malaria had disappeared in South Korea (Paik *et al.*, 1987). In 1993, the first occurrence of the re-emergence of *P. vivax* was reported in Paju-shi of Kyonggi-do near the demilitarized zone (DMZ). Thereafter, the incidence of malaria increased exponentially, and in 2000, more than 4,000 cases of *P. vivax* infection were diagnosed. After 2000, the incidence of malaria decreased due to malaria control measures. It was suggested that the re-emerging malaria in South Korea originated from infection by mosquitoes from North Korea (Kho *et al.*, 1999). The North Korean strain of *P. vivax* has 2 characteristics: the terms of relapse after infection are widely distributed from several months to 1 or 2 years (Kim, 2001; Oh *et al.*, 2001; Bray *et al.*, 1982), and the rate of relapse is relatively high compared with that of other strains of *P. vivax* (Kim, 2001; Oh *et al.*, 2001; Bray *et al.*, 1982). Most cases of malaria in South Korea are observed in June-September, with especially high incidence in August.

There are 7 *Anopheles* species in Korea, and only 2 species, that is, *An. sinensis* and *An. yatsushiroensis*, are capable of acting as vectors for the transmission of *P. vivax* (Ree *et al.*, 1967). The principal vector of *P. vivax* is *An. sinensis*, and the density of *An. sinensis* has a peak during the second week of July (Lee *et al.*, 2002).

Mathematical models are useful for forecasting the prevalence of infections diseases and for evaluating control strategies. Such a model for *Plasmodium falciparum*, the DMT model, was constructed by Dietz *et al.* (1974). In the present study, a mathematical model of the re-emergence of malaria in South Korea was constructed based on the DMT model and using the characteristics of the North Korean strain of *P. vivax*, which include a wide distribution of the terms of relapse and a high rate of relapse. The model consisted of models in North Korea

Department of Environmental Synthesis and Analysis, Graduate School of Natural Science and Technology, Okayama University, 700-8530, Japan[1], Department of Human Ecology, Graduate School of Environmental Science, Okayama University, 700-8530, Japan[2]

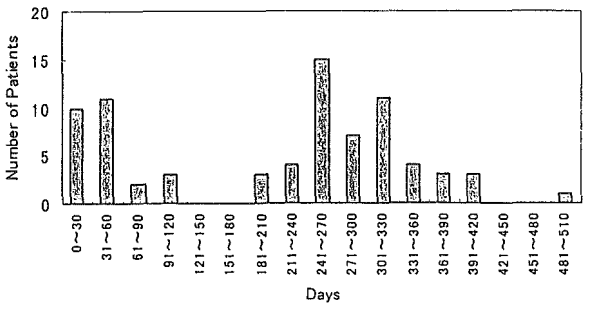

Fig. 1 The distribution of the latent period of the re-emergence of malaria in 77 patients in South Korea. Derived from Oh *et al.* (2001).

and South Korea. In the North Korean model, the population of individuals was divided into 5 epidemiological classes. On the other hand, in the South Korean model, the population of individuals was divided into 4 classes due to the different public health circumstances. The South Korean model was affected unidirectionally by the North Korean model.

The simulation was carried out for the situations of Paju-shi and Yonchon-gun in Kyonggi-do with the initial condition that there were no infected individuals. The results of simulations in Paju-shi and Yonchon-gun followed the time-course of the re-emergence of *P. vivax*. They also revealed the mechanism by which the incidence of *P. vivax* is highest in the summer considering the above 2 characteristics of the North Korean strain of *P. vivax*.

In the near future, *Anopheles* mosquito vectors capable of malaria transmission may invade countries that are free from malaria because of the effect of global warming, and malaria may re-emerge. Our method will be useful for the prediction of the prevalence of malaria in countries in which malaria re-emerges.

2. Materials and Methods

2-1 Relapses

The North Korean strain of *P. vivax* has the characteristics that the terms of relapse after infection are widely distributed from several months to 1 or 2 years (Kim, 2001; Oh *et al.*, 2001; Bray *et al.*, 1982). The surveillance of the incubation periods of relapse for 73 veterans receiving prophylaxis of chloroquine and 4 civilians who were diagnosed at 3 university hospitals, Seoul National University Hospital, Chungbuk National University Hospital and Chonnam National University Hospital (January 1, 1996 - December 31, 1999) is shown in Fig. 1 (Oh *et al.*, 2001). It was reported that

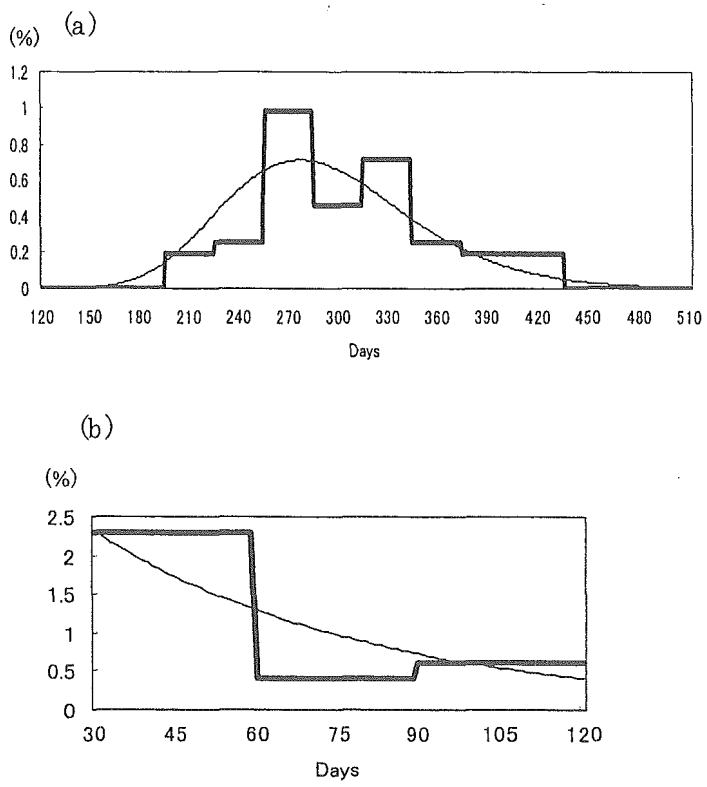

Fig. 2 The distribution of long incubation period (a) and short incubation period (b). The log-normal distribution (thin curve) (a) and the exponential distribution (thin curve) (b) compared with the surveillance data (thick line).

there were no cases of relapse 4-6 months after infection and that the outbreak of relapse cases had 2 peaks at 1-2 months and 8-9 months after infection. Therefore, the distribution of the terms leading to relapse is grouped into 2 parts: 1 - 4 months after infection and more than 6 months after infection, which are called "short incubation period" and "long incubation period", respectively, while the cases who develop parasitemia within 1 month after infection are regarded as "primary infection". In this study, it was assumed that prophylaxis of chloroquine would not prevent relapses, while it prevents primary infections. In order to establish modeling of the relapse-distribution, the distribution of short incubation period would be applied to the exponential distribution for the regression curve (mean = 0.019 1/days), (Fig. 2-(b)), and the distribution of long incubation period would be applied to the log-normal distribution (mean = 288 days, mean$\pm$S. D. =288-52, 288+64 days) (Fig. 2-(a)). A χ^2-value 13.37 (15.51, *d.f.* = 8) was accepted as statistically significant ($P < 0.05$) by the χ^2-fitness test.

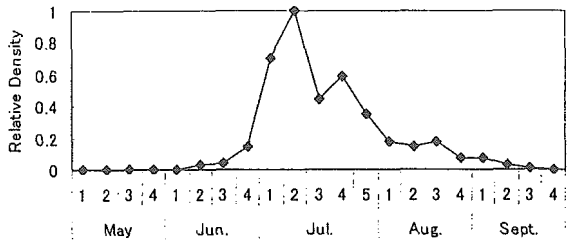

Fig. 3 The relative variation of the weekly density of female mosquitoes to the highest density in August. Derived from Lee *et al.* (2002).

2-2 The ratio of primary infection to relapse

The North Korean strain of *P. vivax* has the characteristics that the rate of relapse is relatively high compared with that of other strains of *P. vivax*. Kim (2001) observed that only 4 cases (8%) were primary infection while 52 cases (92%) were relapse. Moreover, Park *et al.* (2003) reported that the number of people infected with malaria in the military was 393 during 1993 - 2000 and that 56 cases had been in the non-endemic region of *P. vivax*. Therefore, it is speculated that the rate of primary infection is at least 14% of the total cases. Oh *et al.* (2001) also indicated that the numbers of primary infection and relapse were 10 (13%) and 67 (87%), respectively. We adopted 87% as the average rate of relapse based on the above 3 reports.

2-3 The seasonal fluctuation of *Anopheles sinensis*

It is known that there are 7 species of *Anopheles* in Korea, and that only 2 species, that is, *An. sinensis* and *An. yatsushiroensis*, are capable of acting as vectors for the transmission of *P. vivax*. (Ree *et al.*, 1967). *An. sinensis*, the principal malaria vector, comprises more than 80% of total malaria vectors (Cho *et al.*, 2002). Therefore, it is assumed that malaria in Korea would be transmitted only by *An. sinensis* species. The population of *An. sinensis* rises steeply from the second week of June, reaches a peak during the second week of July, and then gradually decreases through the fourth week of September (Lee *et al.*, 2002). The seasonal fluctuation of relative density compared with the peak week (the second week of July) is shown in Fig. 3.

2-4 The seasonal pattern of the incidence of *P. vivax*

The monthly time-course of malaria cases in 1993-1994 and 1998-2000 is shown in Fig. 4 (National

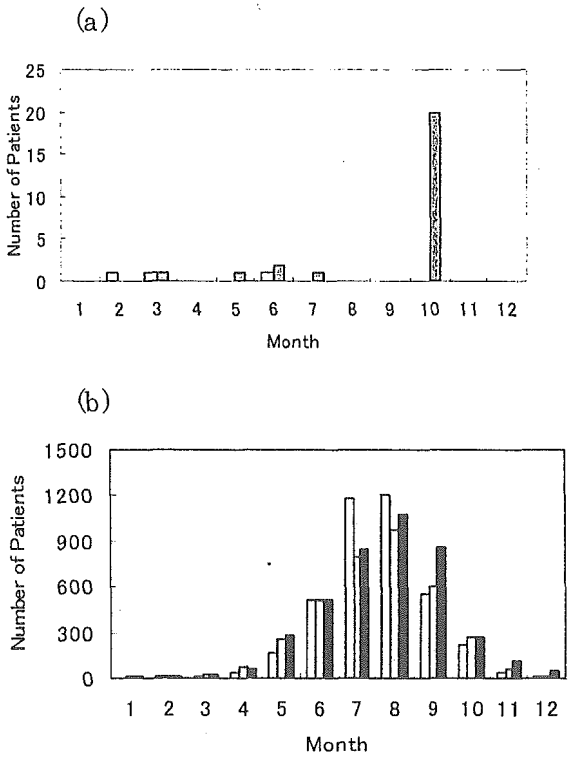

Fig. 4 The monthly incidence of *P. vivax* in South Korea (a) in 1993 (white bars) and 1994 (gray bars) and (b) in 1998 (white bars), 1999 (gray bars) and 2000 (black bars).

Institute of Health, Korea, 2003). Most cases of malaria were observed in June-September, with an especially high incidence in August from 1995 to 2003, whereas an elevated incidence of malaria cases was not observed in the summer in 1993-1994. The seasonal pattern of the incidence was also noted in an old report (Hasegawa, 1913) stating that the incidence of *P. vivax* was highest in June - October. Given these 2 characteristics, that is, the wide distribution of terms to relapse (1-16 months) and the high relapse rate (87%), why is the incidence of malaria concentrated in the summer, especially in August?

2-5 Malaria cases in the northern part of South Korea

In 2 regions near the DMZ, Paju-shi, where the first case of the re-emergence of malaria was discovered, and Yonchon-gun, where most of the cases of malaria were observed in the beginning of re-emergence of malaria, the incidence of *P. vivax* increased until 1999, but it subsequently decreased thereafter (CDMR, 2003). Fig. 5 shows the civilian cases of malaria in Paju-shi (1994-2002) and Yonchon-gun (1995-2002), where the surveillance data was derived from CDMR (2003); Moon (2001); Lee (1998); Park (2003).

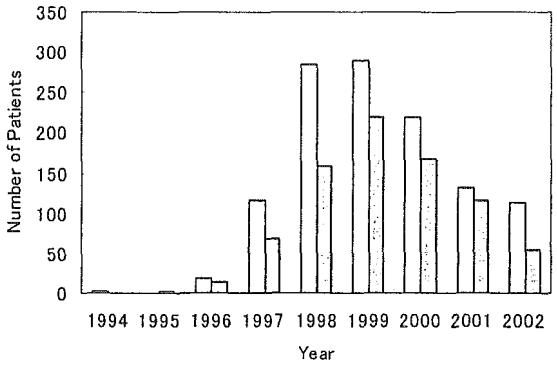

Fig. 5 Cases of malaria in civilians in Paju-shi (white bars) and Yonchon-gun (gray bars) in 1994 – 2002. The vertical axis represents the number of cases per 100,000.

2-6 Re-emergence of *P. vivax*

In 1993, *P. vivax* malaria re-emerged in South Korea, although WHO declared in 1979 that indigenous malaria had disappeared. The first possibility regarding this re-emergence was that in the beginning of the 1990's, immigrant workers from countries with endemic malaria provided a nidus for re-establishment of the epidemic of *P. vivax*. The second possibility was that mosquitoes infected with *P. vivax* came to South Korea across the DMZ. The facts that most of the cases in the beginning of the re-emergence occurred in military personnel who served near the DMZ, and that the cases of malaria spread from the DMZ toward the south supported the second possibility (Kho *et al.*, 1999). In this study, it was assumed that the infected mosquitoes will come across the DMZ at a constant rate based on the second possibility.

2-7 Mathematical model

The mathematical model in South Korea and North Korea was established on the basis of the DMT model (Dietz *et al.*, 1974). The South Korean model is affected unidirectionally by the North Korean model, because the infected mosquitoes will come to South Korea across the DMZ.

North Korean model

In the North Korean model, the population of individuals is divided into 5 epidemiological classes: susceptible (S), dormant hypnozoites without parasitemia (H), latent for primary infection (Pr), positive with gametocytes (In) and positive without gametocytes (Po). Moreover, H, Pr, In, Po classes are subdivided into 3 subclasses which are denoted by the suffix i (i=0, 1, 2) according to the number of hypnozoites in their livers. We

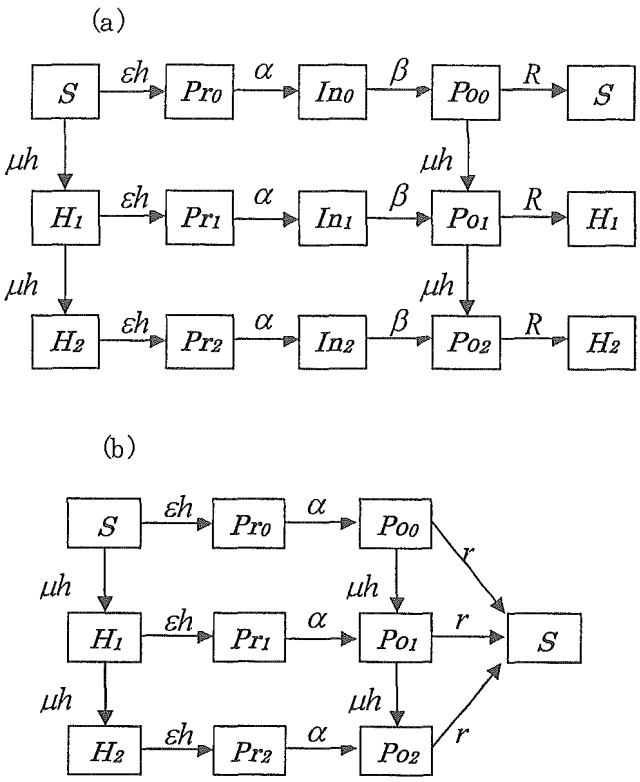

Fig. 6 The scheme of models in North Korea (a) and South Korea (b).

introduce the epidemiological parameters: inoculation rate (h), the onset rate of symptoms with infection (α), the rate of loss of infection (β) and the rate of recovery taking account of superinfection (R). Moreover, ε and μ are the ratio of primary infection and that of relapse, respectively ($\varepsilon+\mu=1$). The classes H_i, Pr_i and In_i, (i=1, 2) transfer into the class In_{i-1} when the individuals of these classes relapse into parasitemia. Moreover, the class Po_i (i=1, 2) transfers into the class Po_{i-1} when the individuals of this class relapse into parasitemia. The scheme of the model in North Korea is illustrated in Fig. 6-(a).

South Korean model

Although the North Korean strain of *P. vivax* prevails in both North Korea and South Korea, the model for transmission in South Korea is modified compared to that for North Korea due to the different public health circumstances. In South Korea, cases of malaria usually recover in about 1 week upon treatment with chloroquine, and therefore the positive with gametocytes class (In) is combined with the positive without gametocytes class (Po). Since the radical treatment results in the clearance of hypnozoites in the malaria patients, it is assumed that the class (Po) transfers to the class (S) on recovery.

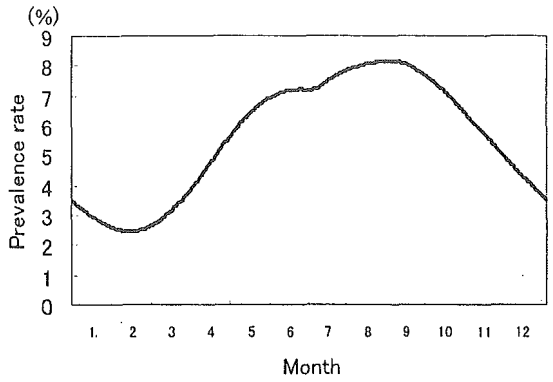

Fig. 7 The time-course of the prevalence in North Korea predicted by simulation by the model (the average rate of prevalence being 5.6%).

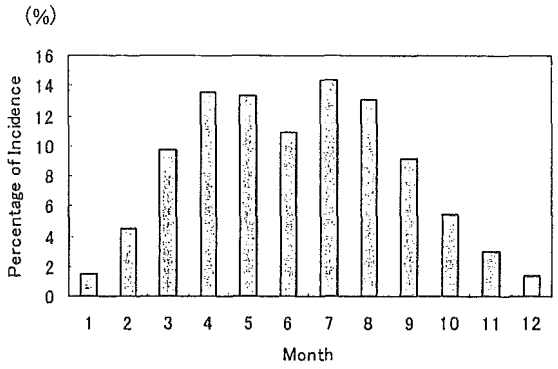

Fig. 8 The monthly incidence predicted by simulation using the model.

It is assumed that there are no infected individuals at the initial time in South Korea and that the infected mosquitoes come across the DMZ from North Korea, the number of which depends on the distance from the DMZ. The scheme of the model for South Korea is illustrated in Fig. 6-(b).

3. Results

North Korean model

The average prevalence rate is estimated as 5.6% by the simulation based on the transmission model of *P. vivax* in North Korea (Fig. 7).

Seasonal change of incidence

The seasonal change of incidence in South Korea is obtained through the simulation, where we take account of the distribution of relapse terms, the rate of relapse, the seasonal fluctuation of *An. sinensis* and the average prevalence rate in North Korea (Fig. 8). The simulation indicates that the prevalence is maintained at a high level from March to September, and has 2 peaks in April – May and July – August. In spite of the wide distribution of relapse terms and high rate of relapse, the simulation succeeded in modeling the peak incidence of malaria cases in the summer.

Re-emergence of malaria in Paju-shi and Yonchon-gun

A comparison of the surveillance data of cases of malaria in Paju-shi and Yonchon-gun in 1996 – 2002 and the prediction of the simulations is shown in Fig. 9-(a) and (b). The results of simulations followed the time-course of the re-emergence of *P. vivax* in 1996-1999 for both regions. On the other hand, the time-courses of the actual prevalence in Paju-shi and Yonchon-gun deviated from the predictions of the model simulation after 2000, because the model did not take into account any malaria control measures.

4. Discussion

In this study, we assumed that the southward movement of infected mosquitoes across the DMZ caused the re-emergence of *P. vivax* in South Korea. Mosquitoes that had been released 21 days before in Kyonggi-do were recaptured at rates of 37.1%, 29.4%, 21.1%, 10.3% and 2.1% at 1, 3, 6, 9 and 12 km from the release point, respectively, namely, about 90% of the mosquitoes were recaptured within 6 km from the release point (Cho *et al.*, 2002). Therefore, it is reasonable for mosquitoes to fly across the DMZ because the DMZ is about 2 km wide.

The 2 mathematical models in North Korea and South Korea could be constructed with 4 epidemiological parameters. It was difficult to decide the rate of prevalence in North Korea in the beginning of the 1990's, because there was little and uncertain information about the cases of malaria in North Korea. In the parasite survey implemented in South Korea in 1960, the year after the Korean War, 212 blood smears were positive among 18,697 collected blood smears (the average parasite rate being 1.1%), and the highest prevalence detected was 5% (Paik *et al.*, 1987). Therefore, we presume the prevalence in North Korea to be 5%. The transmission model for South Korea is modified from that for North Korea due to the different public health circumstances. We succeeded in evoking the re-emergence of *P. vivax* in Paju-shi and Yonchon-gun near the DMZ in South Korea, through 2 cooperative models in which the South Korean model was unidirectionally affected by the North Korean model.

In South Korea, *P. vivax* malaria has re-emerged since

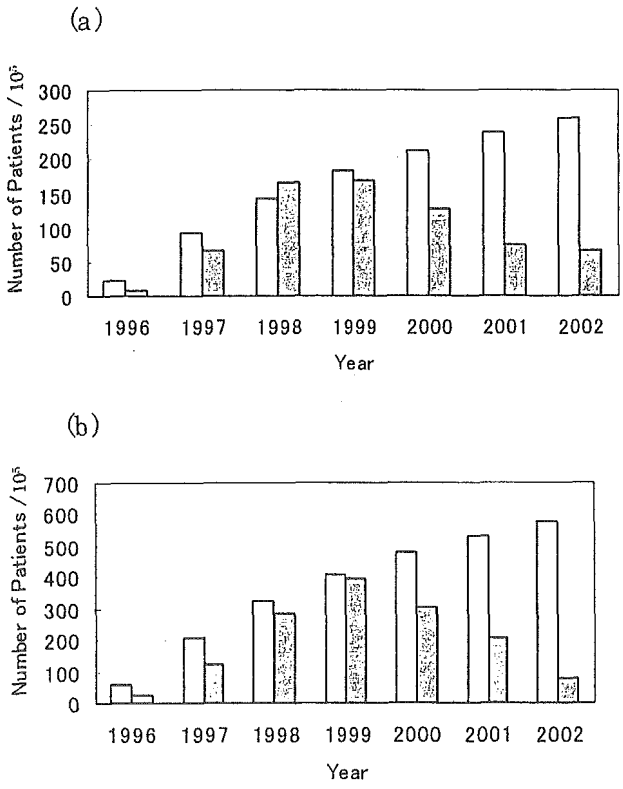

Fig. 9 The comparison of the prevalence between actual surveillance and the results of simulation in Paju-shi (a), Yonchon-gun (b). The time-courses of malaria cases per 100,000 obtained from surveillance and from the results of simulation are shown as gray bars and white bars, respectively.

1993 and the prevalence increased yearly until 2000. The incidence of *P. vivax* was highest in summer (June - September) in spite of the 2 characteristics of North Korean strain of *P. vivax* described in the text, that is, the high relapse rate and the wide distribution of relapse terms (Kim, 2001; Park *et al.*, 2003; Oh *et al.*, 2001; Bray *et al.*, 1982). The incidence in Korea had 2 peaks (April – May, July - August) in the simulation using our model. The simulation results revealed the mechanism by which the incidence of *P. vivax* was highest in summer, assuming the above 2 characteristics of *P. vivax*. The seasonal pattern of incidence would be affected by the incubation period. The first peak (April - May) and the second peak (July - August) would be related to the long incubation period and the short incubation period, respectively. If the average of the long incubation period would be prolonged from 288 days to 1 year, the incidence of *P. vivax* would be concentrated in summer and have a peak in August. However, the reason for the divergence of the peaks of the incidence of *P. vivax* in South Korea between the surveillance and the simulation is unknown.

The long incubation period (6 – 16 months) would be applied to the log-normal distribution, where the χ^2-value 13.37 was accepted as statistically significant (15.51, $d.f. = 8$, $P < 0.05$) by the χ^2-fitness test. The log-normal distribution was selected because of the long incubation period. The skewness (G) and the kurtosis (H) of the logarithmic transformation of 50 surveillance data are estimated as G=0.257 (0.533, P<0.05) and H=0.127 (0.99, P<0.05), respectively, which lead to fitting the distribution of the long incubation period to the log-normal distribution.

The number of civilian malaria cases increased until 1999 in Paju-shi and Yonchon-gun, where the malaria cases in these 2 regions accounted for 60-70% of the total malaria cases in Korea from 1993 to 1997. We succeeded in modeling the re-emergence of *P. vivax*. The time-courses of the true prevalence in Paju-shi and Yonchon-gun diverged from the time-course predicted by the model simulation after 2000, because the model took no account of any malaria control measures. The rate of contact with infected mosquitoes may be reduced by public health education and the use of window screens, while chemoprophylaxis prevents malaria infection. Early diagnosis and treatment may reduce the prevalence. In order to accurately predict the prevalence of *P. vivax* in South Korea, it would be necessary to incorporate the effect of malaria control measures in the South Korean model.

In the coming years, *Anopheles* mosquito vectors capable of malaria transmission may invade countries that are free from malaria because of the effect of global warming, and may cause the re-emergence of malaria. Our method will be useful for prediction of the prevalence in countries in which malaria re-emerges.

ACKNOWLEDGEMENTS: This work was supported in part by a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (Grant No. 16540105) and by grants from the Ministry of Health, Labour and Welfare, Japan for "Research for emerging and re-emerging infections" (Principal investigator: Dr H. Watanabe).

REFERENCES

Bray, R. S. & Garnham, P. C. C. The life-cycle of primate malaria parasites. *Br Med Bull.* 1982, **38**: 117-122.

CDMR. Communicable Disease Monthly Report, 2003, **14**: 367-372.

Cho, S. H., Lee, H. W., Shin, E. H., Lee, H. I., Lee, W. G., Kim, C. H., Kim, J. T., Lee, J. S., Lee, W. J., Jung, G. G. & Kim, T. S. A mark-release-recapture experiment with *Anopheles sinensis* in the northern part of Gyeonggi-do, Korea. *Korean J Parasitol.* 2002, **40**: 139-148.

Dietz, K. Molineaux, L. & Thomas, A. A malaria model tested in the Africa Savannah. *Bull. WHO.* 1974, **50**: 347-357.

Hasegawa. Malaria in Korea. *Chosen Igakkai Zasshi*, 1913, **4**: 53-69 (in Japanese).

Kho, W. G., Jang, J. Y., Hong, S. T., Lee, H. W., Lee, W. J. & Lee, J. S. Border malaria characters of reemerging vivax malaria in the Republic of Korea. *Korean J Parasitol.* 1999, **37**: 71-76.

Kim, M. B. Epidemiologic characteristics of malaria in non-malarious area, Jeollabuk-do, Korea in 2000. *Korean J Parasitol.* 2001, **39**: 223-226.

Lee, J. S., Lee, W. J., Gho, S. H. & Ree, H. I. Outbreak of vivax malaria in areas adjacent to the demilitarized zone, south korea, 1998. *Am J Trop Med Hyg.* 2002, **66**: 13-17.

Lee, J. S., Kho. W. G., Lee, H. W., Seo, M. & Lee, W. J. Current status of vivax malaria among civilians in Korea. *Korean J Parasitol.* 1998, **36**: 241-248.

Moon, J. J. & Cho, S. Y. Incidence patterns of vivax malaria in civilians residing in a high-risk country of Kyonggi-do (Province), Republic of Korea. *Korean J Parasitol.* 2001, **39**: 293-299.

National Institute of Health, Korea. *Communicable disease statistical year book.* 2003.

Oh, M. D., Shin, H., Shin, D., Kim, U., Lee, S., Kim, N., Choi, M. H., Chai, J. Y. & Choe, K. Clinical features of vivax malaria. *Am J Trop Med Hyg.* 2001, **65**: 143-146.

Paik, Y. H., Ree, H. I. & Shim, J. C. Malaria in Korea. *The Kyung Hee University Medical J.* 1987, **12**: 17-31.

Park, J. W., Klein, T. A., Lee, H. C., Pacha, L. A., Ryu, S. H., Yeon, J. S., Moon, S. H., Kim, T. S., Chai, J. Y., Oh, M. D. & Choe, K. W. Vivax malaria: a continuing health threat to the Republic of Korea. *Am J Trop Med Hyg.* 2003, **69**: 159-167.

Ree, H. I., Hong, H. K. & Paik, Y. H. Study on natural infection of *Plasmodium. vivax* in *Anopheles sinensis* in Korea. *Korean J Parasitol.* 1967, **5**: 3-4.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Parasitology International 55 (2006) S259 – S261
www.elsevier.com/locate/parint

Mathematical modeling of *Echinococcus multilocularis* transmission

Hirofumi Ishikawa *

Department of Human Ecology, Graduate School of Environmental Science, Okayama University, Tsushimanaka, Okayama 700-8530, Japan

Available online 15 December 2005

Abstract

A mathematical model for the transmission cycle of *Echinococcus multilocularis* would be useful for estimating its prevalence, and the model simulation can be instrumental in designing various control strategies. This review focuses on the epidemiological factors in the *E. multilocularis* transmission cycle and the recent advances of mathematical models for *E. multilocularis* transmission.

Keywords: *Echinococcus multilocularis*; Fox; Mathematical model; Vole

1. Introduction

Echinococcus multilocularis is distributed in central Europe, North America, and northern and central Eurasia [1]. In Japan, human alveolar *Echinococcus* (HAE) caused by *E. multilocularis* has spread throughout the mainland of Hokkaido [2], making it desirable to design effective control strategies against HAE. It is difficult to elucidate the source of infections due to the long incubation period [3]. A mathematical model for the transmission cycle of *E. multilocularis* would be useful for estimating its prevalence, and the model simulation can be instrumental in designing various control strategies. A few models about *E. multilocularis* transmission have been proposed since 1995 [4–6]. This review focuses on the epidemiological factors in the *E. multilocularis* transmission cycle and the recent advances of mathematical models for *E. multilocularis* transmission.

E. multilocularis carries out its transmission cycle in two hosts; the definitive hosts are canines, while the intermediate hosts are mainly rodents and ungulates [1,7–9]. Individuals are infected by the accidental ingestion of parasite eggs. The intermediate hosts are infected by ingesting parasite eggs voided in the feces of infected definitive hosts, while the definitive hosts are infected by preying on the intermediate hosts that have hydatid cysts. A mathematical model which quantitatively describes the transmission of *E. multilocularis* needs to include the following components [5,10]:

1. dynamics of definitive host population,
2. dynamics of intermediate host population,
3. predator–prey relationship between the definitive hosts (canines) and the intermediate hosts (rodents), and
4. longevity of parasite eggs in the environment.

2. Dynamics of definitive hosts

Foxes mainly maintain the transmission cycle of *E. multilocularis*. The major definitive host is the red fox (*Vulpes vulpes*) for most endemic regions, or the arctic fox (*Alopex lagopus*) for the tundra zone of Eurasia and North America [1,7,9,11]. The dynamics of the fox population show marked seasonal variations because foxes are wild animals. Therefore, a quantitative transmission model needs to include a host population dynamic component [5]. In Hokkaido, Japan, the breeding season of red foxes is generally in the early spring (the last third of March – the first third of April) and newborns after weaning, which might be exposed to *E. multilocularis* infection, emerge from their dens 1 month after birth [12]. Generally, for any wild animal, the death rate of juveniles is significantly higher than that of adults. The death rate of juvenile (under 1 year old) red foxes in Hokkaido was estimated to be 2.5 times higher than that of adults [5]. The seasonal population model of red fox density in Hokkaido is shown in Fig. 1. The arctic fox population is

* Tel.: +81 86 251 8826; fax: +81 86 251 8837.
E-mail address: ishikawa@ems.okayama-u.ac.jp.

1383-5769/$ - see front matter © 2005 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.parint.2005.11.038

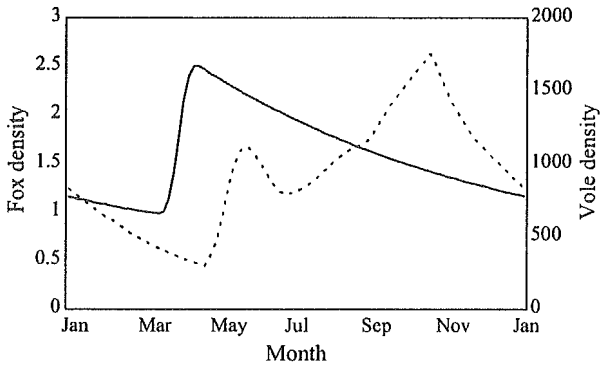

Fig. 1. The seasonal population dynamics models for foxes and voles in Hokkaido. The solid line and the dotted line shows the variations in fox and vole density/km^2, respectively [5].

also influenced by emigration and immigration due to long-distance traveling [11].

3. Dynamics of intermediate hosts

Rodents mainly maintain the transmission cycle of *E. multilocularis* as the intermediate hosts, and the species that are involved in the cycle vary in different endemic regions [1,9]. In Hokkaido, the major intermediate host is the gray-sided vole (*Clethrionomys rufocanus*) [7]. The gray-sided vole breeds in three seasons of the year (all seasons except winter) [13,14]. The survival rate of voles depends on the season and age, with that for the first month of life being lower than that of >1 month [13,14], while the survival rate in winter is higher than that in summer [15]. Besides the season variation, the dynamics of the vole population vary on a large scale annually and have certain geographical characteristics [16]. There is no necessity to consider emigration or immigration in the dynamics of the vole population because of the small size of home ranges [13].

4. Transmission processes of *E. multilocularis*

The definitive host is infected with *E. multilocularis* by preying on rodents which harbor multilocular *Echinococcus* with infectious protoscoleces. Therefore, the prevalence of *E.*

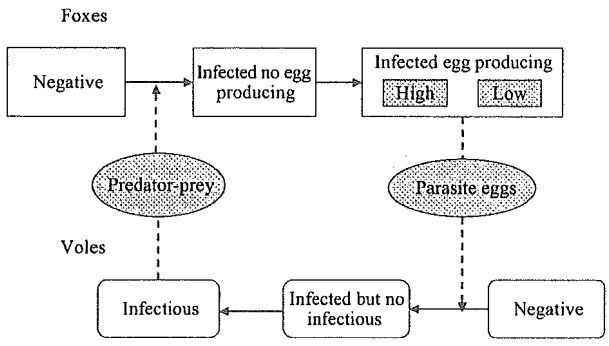

Fig. 2. The basic scheme for the model of the *Echinococcus multilocularis* transmission cycle between foxes (the major definitive host) and voles (the major intermediate host).

multilocularis is affected by the average number (NVF) of voles ingested by a fox each day, which depends on the density of the vole population and on the depth of the snow factors [17, 18], which were introduced into the transmission model [5].

The intermediate host is infected by ingesting *E. multilocularis* eggs voided in the feces of infected definitive hosts. The duration of the egg's infectious ability is mainly affected by temperature and humidity. The tenacity of eggs is sensitive to elevated temperature, to very low temperature and to desiccation [19]. The experimental formula for the longevity (d for days) of eggs at temperature (t at °C) was established as $d=\exp[-0.135(t-43.7)]$ [20].

5. Mathematical models of *E. multilocularis* transmission

A deterministic model for the transmission of a parasite essentially describes its transmission cycle as a set of differential equations. Roberts and Aubert [4] constructed a simple deterministic *E. multilocularis* transmission model to evaluate the effect of control by addition of praziquantel in France. Ishikawa et al. [5] proposed a model that took into account the influence of the dynamics of both the definitive and the intermediate host populations and the seasonal effects on the longevity of *E. multilocularis* eggs and NVF to describe the mechanism of seasonal transmission in Hokkaido quantitatively. Hansen et al. [6] tried to develop a stochastic transmission model from the Roberts and Aubert model to devise a hypothesis that would fit well with the prevalence data during the pre- and post-control periods in the northern Germany. In these models [4–6], each host population is broadly divided into three epidemiology classes. Moreover, in the quantitative model shown in Fig. 2 [5], the infected egg-producing class in foxes is subdivided into two subclasses according to whether egg production is abundant or not.

The basic reproductive rate (R_0) is the theoretically maximum number of secondary infections. R_0 was estimated from the Roberts and Aubert model [4] or the

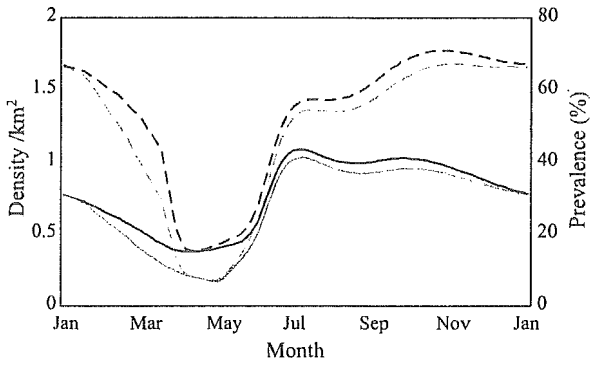

Fig. 3. Seasonal variations in the density/km^2 of foxes infected with *E. multilocularis* (solid line) and the prevalence of *E. multilocularis* in the fox population (broken line). The black and gray lines show the Nemuro and Abashiri situations, respectively [5].

model of Ishikawa et al. excluding seasonal factors [5] as follows:

$$R_0 = \frac{\lambda_f \lambda_v \overline{N_f}}{\delta_v(1+\delta_v\tau_v)(1+\delta_f\tau_f)(1+\delta_f\eta_t)}\eta_t$$

$$R_0 = \frac{s_f \overline{\mathrm{NVF}}\ \lambda_v \overline{N_f}}{\delta_v(1+\delta_v\tau_v)(1+\delta_f\tau_f)(1+\delta_f\eta_h)}\left(\rho\eta_h + \frac{\eta_l}{1+\delta_f\eta_l}\right)$$

The symbols λ_a, δ_a, τ_a, s_f, $\overline{\mathrm{NVF}}$, $\overline{N_f}$, η_t, η_h, η_l, and ρ represent the infectious contact rate ($a=f$, v), the death rate ($a=f$, v), the period of no egg production ($a=f$) or for acquiring infectious protoscoleces ($a=v$) expressed as days after infection, the conditional probability of maturity of worms (f), the average NVF, the average of density (f), the durations of total, high and low egg production, and the multiplicative factor caused by high egg production, with the suffixes f and v standing for fox and vole, respectively.

The seasonal variations of the prevalence and the density of infected foxes were simulated for the two endemic regions in Hokkaido, Japan: Nemuro and Abashiri, where the average prevalence rates (1995–2000) were 53% and 48%, respectively. There is a great difference between the two regions in terms of snowfall. Comparison of two regions using the model simulation shows that the winter density of the infected foxes is maintained at a certain level in Nemuro, while it falls to a low level in Abashiri, which leads to the difference of the winter prevalence between Nemuro and Abashiri (Fig. 3) [5].

6. Risk of HAE

The risk to the human population of being infected with HAE has a close relation to the amount of *E. multilocularis* eggs that maintain infectious ability in the environment. A comparative study on the risk of HAE between Sapporo, the capital of Hokkaido, and Nemuro was carried out by simulating the seasonal fluctuation in *E. multilocularis* egg dispersion in the environment based on the model [5].

7. Prospects

Recent advances in mathematical modeling of *E. multilocularis* transmission were summarized here. There has been steady progress in mathematical modeling of *E. multilocularis* transmission into consideration taking seasonal factors. Further follow-up studies based on field data will be needed to precisely estimate the effects of control strategies against *E. multilocularis* using model simulations.

Acknowledgements

This work was supported in part by a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (Grant No. 16540105) and by grants from the Ministry of Health, Labour and Welfare, Japan for "The control of emerging and reemerging diseases in Japan" (Principal investigator: Prof. M. Kamiya).

References

[1] Eckert J, Gemmell MA, Meslin FX, Pawlowski ZS. WHO/OIE Manual on Echinococcosis in Human and Animals: A Public Health Problem of Global Concern. Paris: World Organisation for Animal Health; 2001.
[2] Annual reports of the council for alveolar *Echinococcus* in Hokkaido 1984–1994. Department of Health and Welfare, Hokkaido Government, Sapporo, 1995.
[3] Doi R, Nakao M, Nihei N, Kutsumi H. Epidemiology of alveolar hydatid disease (AHD) and estimation of infected period of AHD in Rebun Island, Hokkaido. Jpn J Public Health 2000;47:145–52 [in Japanese with English abstract].
[4] Roberts MG, Aubert MFA. A model for the control of *Echinococcus multilocularis* in France. Vet Parasitol 1995;56:67–74.
[5] Ishikawa H, Ohga Y, Doi R. A model for the transmission of *Echinococcus multilocularis* in Hokkaido, Japan. Parasitol Res 2003;91: 444–51.
[6] Hansen F, Tackmann K, Jeltsch F, Wissel C, Thulke H-H. Controlling *Echinococcus multilocularis* – ecological implications of field trails. Prev Vet Med 2003;60:91–105.
[7] Ohbayashi M. Host animals of *Echinococcus multilocularis* in Hokkaido. In: Uchino J, Sato N, editors. Alveolar echinococcosis: strategy for erradication of alveolar echinococcosis of the liver. Sapporo: Fujishoin, 1996. p. 59–64.
[8] Petavy AF, Deblock S, Walbaum S. Life cycles of *Echinococcus multilocularis* in relation to human infection. J Parasitol 1991;77:133–7.
[9] Rausch RL. Life cycle patterns and geographic distribution of *Echinococcus* species. In: Thompson RCA, Lymbery AJ, editors. *Echinococcus* and hydatid diseases. Wallingford Oxon: CAB International, 1995. p. 88–134.
[10] Saitoh T, Takahashi K. The role of vole populations in prevalence of the parasite (*Echinococcus multilocularis*) in foxes. Res Popul Ecol 1998;40:97–105.
[11] Fay FH, Rausch RL. Dynamics of the arctic fox population on St. Lawrence Island, Bering Sea. Arctic 1992;45:393–7.
[12] Uraguchi K, Takahashi K. Ecology of the red fox in Hokkaido. In: Tsuduki T, editor. Alveolar *Echinococcus* in Hokkaido. Sapporo: Hokkaido Institute of Public Health, 1999. p. 39–48 (in Japanese).
[13] Ota K. Study on wild murid rodents in Hokkaido. Sapporo: Hokkaido University Press; 1984 (in Japanese).
[14] Yoccoz NG, Nakata K, Stenseth NC, Saitoh T. The demography of *Clethrionomys rufocanus*: from mathematical and statistical models to further field studies. Res Popul Ecol 1998;40:107–21.
[15] Dewa H. Seasonal variation of the daily activity rhythms in snow season. Res Bull College Exp Forests Hokkaido Univ 1975;22:105–20 (in Japanese with English summary).
[16] Saitoh T, Stenseth NC, Bjornstad ON. The population dynamics of the vole *Clethrionomys rufocanus* in Hokkaido, Japan. Res Popul Ecol 1998;40:61–76.
[17] Abe H. Winter Food of red fox, *Vulpes vulpes schrencki* Kishida, in Hokkaido, with special reference to vole populations. Appl Entomol Zool 1975;10:40–51.
[18] Yoneda M. Influence of red fox predation upon a local population of small rodents: III. Seasonal changes in predation pressure, prey preference and predation effect. Appl Entomol Zool 1983;18:1–10.
[19] Veit P, Bilger B, Schad V, Schafer J, Frank W, Lucius R. Influence of environmental factors on the infectivity of *Echinococcus multilocularis* eggs. Parasitology 1995;110:79–86.
[20] Ishige M, Itoh T, Yagi K. Biological characters of *Echinococcus multilocularis* on temperature effects on life span of eggs. Rep Hokkaido Inst Public Health 1993;43:49–51 [in Japanese with English summary].

Journal of the Faculty of Environmental Science and Technology,
Okayama University
Vol.11, No.1, pp.9-14, February 2006

A stochastic model of *Echinococcus multilocularis* focusing on protoscoleces

Tomohiko NISHINA [1], CHEN Tian Tian[1], Kazutoshi FUJITA [2] and Hirofumi ISHIKAWA[1]

(Received November 30, 2005).

The red fox (*Vulpes vulepes*) and the vole (*Clethrionomys refocanus*) are principal hosts of *Echinococcus multilocularis* in Hokkaido, Japan. How protoscoleces increases in voles and the level of immunity in foxes remain unknown because of the lack of survey data, so that it is important to clarify these mechanisms in order to develop control strategies against *E. multilocularis*. In this study, the growth of protoscoleces in the infected voles was approximated as the logistic curve, the level of immunity in the fox was assumed to depend on the experience of the infection with *E. multilocularis*, and the worm burden in the fox was assumed to be governed by the amount of protoscoleces in the vole. Our model showed that the population densities of the hosts and the level of immunity influenced the prevalence of the *E. multilocularis*.

Key words: *Echinococcus multilocularis, protoscoleces, immunity, worm burden, stochastic model*

1. INTRODUCTION

Echinococcus multilocularis, a type of zoonoses, is now prevalent in Hokkaido, Japan. The life-cycle of *E. multilocularis* takes place in the definitive hosts and the intermediate hosts. The principal definitive host and the principal intermediate host in Hokkaido are recognized as the red fox (*Vulpes vulepes*) and the grey-sided vole (*Clethrionomys refocanus*), respectively. The prevalence of *E. multilocularis* in the foxes was estimated as 45% in 1998, and has remained high until now (The Department of Health and Welfare, the Hokkaido Government). Moreover, domestic dogs may also be infected with *E. multilocularis* as the definitive hosts. In 1965, the first case of human alveolar echinococcusis was reported (Yamamoto et al., 1966). In the future, 1000 new patients are predicted to be infected over the next ten years, so that immediate control strategies against of *E. multilocularis* are needed (Doi, 1995).

Humans and voles become infected with *E. multilocularis* when they ingest free living parasite eggs discharged by the definitive hosts orally. The parasite eggs start to make protoscoleces in the vole about 40 days after infection (Yagi and Ito, 1998). When a fox preys upon an infected vole which has an adequate amount of protoscoleces, *E. multilocularis* will be transmitted from the vole to the fox. It is important to consider the population dynamics of both the definitive and the intermediate hosts because the variances of the population of the both hosts influence the transmission of *E. multilocularis* greatly. Both fox and vole populations have a seasonal fluctuation so that the time-course of *E. multilocularis* infections depend on the season.

Mathematical models have been developed to explain observations from field studies. Recently, Ohga et al. (2002) investigated the seasonal differences of the food habits of foxes, and Ishikawa et al. (2003) the seasonal fluctuations of both host populations, which had a large effect on the time-course of *E. multilocularis* population levels. Hansen et al. (2003, 2004) introduced a spatial model which included heterogeneity of the dispersing hosts.

Moreover, Kato et al. (2005) reported that foxes had an immune response, although the relation between the level of immunity and worm burden was not well known.

Department of Human Ecology, Graduate School of Environmental Science, Okayama University, 700-8530, Japan[1]
Department of Environmental Synthesis and Analysis, Graduate School of Natural Science and Technology, Okayama University, 700-8530, Japan[2]

In the model, we supposed that the level of immunity in the fox depends on the experience of the infection of *E. multilocularis*.

There have been few critical studies on the formation of protoscoleces in the infected voles. Yagi and Ito (1998) carried out experimental infections to investigate how protoscoleces increase in the infected vole. It was uncertain how to protoscoleces increase up to numbers in the millions in voles and how many protoscoleces are attached to the intestine of a fox when the fox preys on an infected vole. In the model, the growth of protoscoleces in the infected voles was approximated as a logistic curve.

The model simulates the infection from voles to foxes stochastically under the condition that the worm burden in the fox is governed by the amount of protoscoleces in the vole. Additionally, the model takes into consideration the seasonal fluctuation of the hosts through the population dynamics for the definitive and the intermediate hosts.

We carried out 1000 repeated trials of the model to study the seasonal fluctuation of the prevalence and also to consider mechanism of the immunity of foxes. We observed that the prevalence was influenced by the population densities of the hosts. Moreover, from the results of the simulations, it was plausible that a high level of immunity would be acquired in the several first exposures to infection.

2. Materials and Methods

2-1 Population dynamics of hosts

Regarding the life cycle of *E. multilocularis*, the population dynamics of definitive and intermediate hosts which have a seasonal fluctuation play an important role in the transmission of *E. multilocularis*. In Hokkaido, the major definitive hosts are foxes and the major intermediate hosts are voles.

The breeding season of foxes in Hokkaido begins in spring. The mortality of juvenile foxes (less than 1 year old) is considerably higher than that of adult foxes (more than 1 year old) (Uraguchi and Takahashi, 1991, 1998). Although foxes eat voles by preference, the deeper the snow falls, the less foxes feed on voles (Kondo et al., 1986).

The breeding season of voles is recognized as occurring in three seasons every year. The main breeding seasons are spring and autumn, since the breeding rate in summer is much less than that in the other breeding seasons (Kaneko et al., 1998). The females born in spring reach maturity and account for a large part of pregnant voles in autumn. On the other hand, only the females born in autumn breed in the spring. When the density of the vole population is fairly high, their pregnancy rate will tend to decrease because of the tendency of a slowdown in the rate of maturity. In contrast, they will mature faster and become active for breeding, resulting in their population becoming large, when the density of the vole population is low (Ota, 1984).

In this report, the fox population dynamics will be modeled stochastically with survival, infection and experimental status for every fox, which leads to various situations regarding the prevalence of *E. multilocularis* in every trial. On the other hand, the vole population dynamics will be modeled deterministically. The parameter values in both the host population models change according to the season and densities to take into account the seasonal fluctuation.

2-2 Transmission of *E. multilocularis* from foxes to voles

If a vole ingests a free living egg contained in the feces of a fox orally, it becomes infected with *E. multilocularis*. The environmental conditions such as temperature and humidity can influence the longevity of *E. multilocularis* eggs. Yagi and Ito (1991) gave the experimental formula on the relationship between the longevity (d days) and the temperature (t℃) for experimental infections:

$$d = \exp(-0.135(t - 45.37))$$

In Nemuro, Hokkaido, Japan, the longevity of eggs in summer at the average temperature 19.9℃ (observed by the Japan Meteorological Agency in August, 2005) is about 31 days according to the experimental formula. We assume that the longevity of eggs cannot exceed 100 days due to the experimental report that the infectivity was maintained only for 125 days after infection (Yagi and Ito, 1998), as the low temperature in winter will surpass the limits of the formula. It is very difficult to survey how many eggs exist in the environment, how often voles come into contact with and ingest infectious eggs, and additionally the number of eggs required to infect a vole.

Nevertheless, it is natural to think that the risk of infection for voles may depend on the number of free living parasite eggs. Then, the infection risk depends

on the number of active eggs and the number of contacts. Therefore, we use the infection risk as the transfer rate from the susceptible class to the infected class.

2-3 Growth of protoscoleces in voles

An ingested egg starts to develop protoscoleces of *E. multilocularis* in the vole about 40 days after infection. If a fox preys on a vole having an adequate amount of protoscoleces, it can be infected with *E. multilocularis*, so the amount of protoscoleces in voles plays a fundamental role in the transmission of *E. multilocularis*. However, there are few studies about the growth of protoscoleces in voles. Yagi and Ito (1991) reported in experimental infections that 11 voles produced 200 eggs, with one of the necrospied voles starting to make protoscoleces 44 days after infection, and another vole having 3.300.000 protoscoleces 142 days after infection. We assume that the number of protoscoleces in voles increases exponentially after the latent period, that the rate of increase declines slowly due to environmental factors, and that the number of protoscoleces is finally saturated. In the model, we approximate the growth of protoscoleces ($P(t)$, say, protoscoleces-day model) voles as the logistic curve (Fig.1):

$$\frac{dP}{dt} = r\left(1 - \frac{P(t)}{P\ \max}\right)P(t)$$

with P_{max}, r being the maximum number of protoscoleces and the growth rate, respectively.

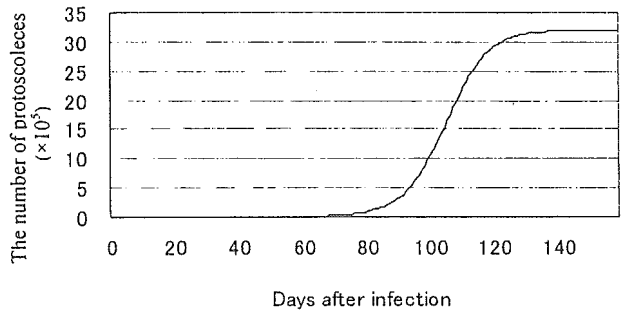

Fig.1 The time-course of prevalence of infection in voles. The curve was obtained using the logistic differential equation.

2-4 Transmission of *E. multilocularis* from voles to foxes

A fox becomes infected with *E. multilocularis* after ingestion of an infected vole which has a sufficient amount of protoscoleces. *E. multilocularis* in the fox starts to produce eggs about 30 days after infection, and egg production lasts for about 80 days after infection (Yagi and Ito, 1998). The more protoscoleces in the vole eaten by a fox, the larger worm burden the fox has. In addition, the total number of eggs discharged depends on the number of worms in the fox. We propose a model scheme from preying on voles to discharging eggs as below:

1. The number of voles preyed on by a fox per day follows the food habit function (Ohga et al., 2002)
2. If a fox preys on infected voles which have an adequate amount of protoscoleces, the fox will be infected. The probability that foxes will become infected follows from the vole prevalence. Precisely, the probability follows the binominal distribution function $f(k)$, where n, k and p stand for the number of voles ingested by a fox per day, the number of infected voles ingested and prevalence rate of voles:

$$f(k) = \binom{n}{k} p^k (1-p)^{n-k}$$

   Then, the sum of $f(k)$ over $k \geqq 1$ is the probability that a fox will become infected per day.
3. For an infected fox, we decide the age of infected voles preyed on by the fox following from the age distribution (the number of protoscoleces in the vole following the protoscoleces-day model).
4. The worm burden in the fox is determined by both the protoscoleces-day model and the immune response, which will be discussed in the next section. The infected fox discharges parasite eggs constantly, depending on its worm burden after the latent period (30 days) during a 50 days period (from the end of latent period).

2-5 Immune responses against *E. multilocularis* in foxes

Various studies concluded that foxes might have immunity (Kato et al., 2005a; 2005b), but it is not well known such immunity would affect the worm burden. Hofer et al. reported (2000) that there were remarkable differences of worm burden between

Table 1 Range and mean worm burden of foxes collected in the city of Zurich in winter [a]

	Number of examined infected foxes	Worm burden range	Mean worm burden
juvenile	68	1-56970	4995
adult	65	1-19344	907

[a] Derived from Hofer et al. (1999)

males and females, and also between juveniles and adults. Especially, the mean worm burden in juveniles was five-seven times higher than that in adults (Table 1). Then we assume that the immunity of *E. multilocularis* in foxes can be strengthened in proportion to the number of infection experiences, and adopt the following formula for the level of immunity:

$$I_{fox} = 1 - 0.8^{n}$$

with n being the number of infection experiences.

3. Results

Each fox structure consists of 8 characteristics, which we listed in Table 2.

Table 2 Structure of characteristics in fox in the model

litter size (only female)
alive or dead
sex
age (year)
number of infection experiences
day after infection
number of worms
pregnancy or not (only female)

We carried out simulations of the model 1000 times under the immune assumptions argued in the "immune response against *E. multilocularis* in foxes" subsection.

Prevalence of infection of host population

The mean prevalence of infection of the fox population in 1000 trials varied within the range of 12~48%, and the yearly mean prevalence ranged over 6.0~57%, and the average was estimated as 33%, which agreed with the recent reports of prevalence (30~50%) in Hokkaido. The prevalence falls remarkably after the breeding season (May), and quickly rises to the peak thereafter (Fig.2). The prevalence falls slightly from autumn to winter, but the prevalence in winter always fluctuates on a large scale. For the case of high prevalence in the breeding season, the prevalence in the next winter tends to remain at a low level, and diminishes 20~30% compared to the prevalence in summer, while for the case of low prevalence in the breeding season, the prevalence in the next winter tends to remain fairly high, and diminishes only 10% compared with the prevalence in summer.

The mean prevalence of the vole population in 1000 trials varied within the range of 1.8~6.2%, and the yearly mean prevalence ranged over 1.26~8.77%, and the average was estimated as 3.8%. The prevalence in spring has a tendency to fall with a small fluctuation (Fig.3), and the prevalence in voles in spring remained low in all the trials because the variance was fairly small. In contrast, the prevalence in voles increases

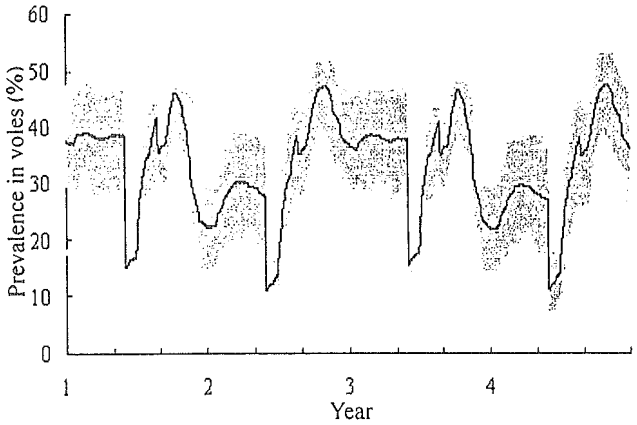

Fig. 2 Variation in the prevalence of infection in the fox population obtained by simulation. The black line shows the average prevalence in 1000 trials. The grey zone shows the prevalence in 100 trials.

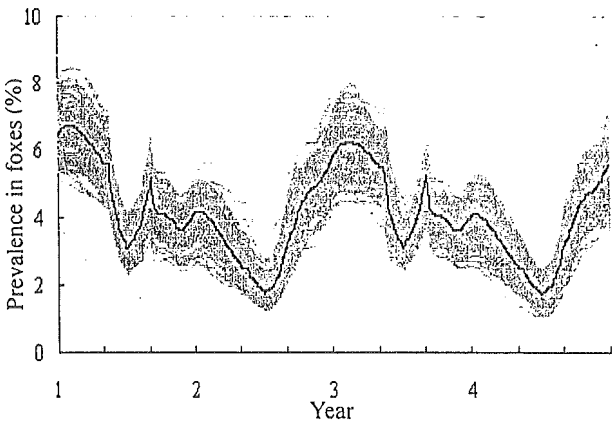

Fig. 3 Variation in the prevalence of infection in the vole population obtained by simulation. The black line shows the average prevalence in 1000 trials. The grey zone shows the prevalence for 100 trials.

Table 3 Range and mean worm burden of foxes in the results of simulations

	Number of examined infected foxes	Range of worm burden	Mean worm burden
juvenile	35	28-99300	22270
adult	65	1-25670	3300

together with a large scale of fluctuation in summer. The peak of prevalence occurs variably between autumn and winter depending on the year in repeated trials.

Worm burden in foxes

It followed from the simulations that the worm burden in juvenile and adult foxes infected with *E. multilocularis* ranged from 28~99,300 and from 1~25,670, and that it averaged 22,220 and 3,300, respectively (Table 3), which would lead to the overgrowth of the worm burden, especially in juveniles, because Hofer (2000) estimated the average worm burden as 4,995 and 907 based on actual surveys (Table 1). Fig.4 shows the graphs of the distributions of worm burden and logarithmic worm burden. Since the latter curve was almost a straight line, the worm burden would disperse exponentially. The stochastic system of foxes preying on voles taking into consideration the age structure and the growth of protoscoleces resulted in a reasonable distribution of worm burden.

4. Discussion

Although little is known about how protoscoleces increase in infected voles due to the lack of survey data, our approximate protoscoleces-day model could reproduce the distribution of the worm burden in foxes. Actually, stochastic simulation achieved a reasonable distribution of worm burden in foxes.

The average worm burden obtained from simulations went beyond the bounds of the field survey (Hofer, 2000), although the range of worm burden in foxes agreed with the field survey. We assume that the immunity is strengthened in proportion to the number of infections experienced by a fox. However, it is plausible that a high level of immunity would be acquired in the several first experiences. In the model, we take no account of the reduction of immunity or shortening of the period of discharging eggs, which must be addressed in

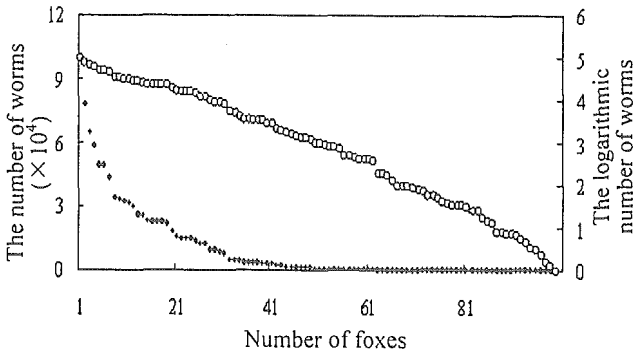

Fig. 4 Distribution of the worm burden in the infected foxes obtained by simulation. The number of worms (worm burden) and the log number of worm burden are shown by dots and circles, respectively.

further studies.

The prevalence of infection in the fox population varies according to the season. It decreases remarkably after the breeding season (May) because of newborns, afterwards, newborns become infected so that the prevalence quickly rises to a peak. Actually, most newborns experience infection with *E. multilocularis* by summer. It was shown that the prevalence of infection in foxes decreases slightly from the peak, and the prevalence in winter varies on a large scale from year to year. The dangerous term for the infection of individuals with *E. multilocularis* comes after the fox breeding season because that is the time with the highest density of foxes, which is supported by the fact that the prevalence of infection in the vole population increases from summer to winter. When the fox population is large in a certain trial, the prevalence tends to hold at a high level compared with the prevalence in a small fox population in other trials. A large fox population and a high prevalence lead to a large number of infected foxes and free living parasite eggs, and may increase the prevalence in voles, too. If the fox population increases by some chance, the prevalence of *E. multilocularis* becomes high in both the fox and vole populations.

The low prevalence in voles from June to July is due to the short longevity of the parasite eggs and the fact that most juvenile foxes stay in the latent period. In winter, the prevalence in vole population increases along with prevalence in the fox population, reaches a peak and varies widely, which means that the prevalence in voles strongly depends on the population dynamics of the fox.

In the model, the infection risk in the vole population depends only on active parasite eggs

because the contact rate is set at a constant value. The human risk of infection with *E. multilocularis* can be thought of as the same as the vole risk because both humans and voles are infected by ingesting parasite eggs orally.

In the model, the longevity of the parasite eggs is assumed to depend on only temperature, but actually it also depends on humidity. Moreover, it was reported that there were some hot spots because voles are distributed heterogeneously. It is conceivable that under natural circumstances the rate of contact of voles with parasite eggs is influenced by some environmental factors such as the densities of both the definitive and the intermediate hosts and the habits of the hosts. Further improvement of the model, including consideration of the effect of control measures against *E. multilocularis,* is needed to forecast future prevalence precisely.

ACKNOWLEDGEMENTS: This work was supported in part by a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (Grant No. 16540105) and by grants from the Ministry of Health, Labour and Welfare, Japan for "Research for emerging and re-emerging infections" (Principal investigator: Prof. M. Kamiya).

REFERENCES

Doi R (1995) A critical situation of the prevalence of echinococcos is (alveolar hydatid disease) – necessity immediate action for the prevention (in Japanese). Japanese Jounal of Public Health **42**:63–68

Hansen F, Tackmann K, Jeltsch F, Wissel C, Thulke HH. (2003). Controlling *Echinococcus multilocularis* ecological implications of field trials. Preventive Veterinary Medicine **60**:91–105

Hansen F, Jeltschb F, Tackmannc K, Staubachd C, Thulke HH (2004): Processes leading to a spatial aggregation of *Echinococcus multilocularis* in its natural intermediate host *Microtus arvalis*. International Journal for Parasitology **34**:37–44

Hofer S, Gloor S, Muller U, Mathis A, Hegglin D, Deplazes P (2000): High prevalence of *Echinococcus multilocularis* in urban red foxes (*Vulpes vulpes*) and voles (*Arvicola terrestris*) in the city of Zuerich, Switzerland. Parasitology **120**:135–142

Ishikawa H, Ohga Y, Doi R (2003): A model for transmission of *Echinococcus multilocularis* in Hokkaido, Japan. Parasitol Reserch **91**:444-451

Kaneko Y, Nakata K, Saito T, Stenseth NC, Bjornstad ON (1998): The biology of the vole *Clethrionomys rufocans*: a review. Researches on Population Ecologies **40**:21-37

Kato N, Nonaka N, Oku Y, Kamiya M (2005): Modified cellular immune responses in dogs infected with *Echinococcus multilocularis*. Parasitol Reserch **95**:339–345

Kato N, Nonaka N, Oku Y, Kamiya M (2005): Immune responses to oral infection with *Echinococcus multilocularis* protoscoleces in gerbils: modified lymphocyte responses due to the parasite antigen. Parasitol Reserch **96**:12-17

Kondo N, Takahashi K, Yagi K, (1986):Winter food of the red fox, *Vulpes vulpes schrenki* Kishida, in the endemic area of multilocular Echinococcosis. *Bulleten of Preparative Office of Nemuro Municipal Museum* **1**:23-31

Ohga Y, Ishikawa H, and Doi R (2002): Simulations of Prevalenceof *Echinococcus multilocularis* in Hokkaido on the Basis of Vole Population Dynamics. Jounal of Faculty of Enviromental science and technology, Okayama University **7**:1-5

Ota K(1984) Study on wild murid rodents in Hokkaido, Hokkaido Univercity press, Sapporo, (in Japanese)

Uraguchi K, Takahashi K (1991) Wildlife conservation. In: Maruyama N, Bobek B, Ono Y, Regelin W, Bartos L, Ratcliffe PR (eds) Proceedings of the International Symposium on Wildlife Conservation in Tsukuba and Yokohama, Japan 1990, p228

Uraguchi K, Takahashi K (1998) Ecology of the red fox in Hokkaido. In: Tsuduki T, Yano S, Furuya K, Takahashi K, Kawase S, Yagi K, Sudo S (eds) Alveolar echinococcus in Hokkaido (in Japanese). Hokkaido Institute of Public Health, Sapporo, pp 39–48

Yagi K, Itoh T (1998) Biological characteristics of *Echinococcus multilocularis* clarified in experimental infections (in Japanese).In: Tsuduki T, Yano S, Furuya K, Takahashi K, Kawase S, Yagi K, Sudo S (eds) Alveolar echinococcus in Hokkaido.Hokkaido Institute of Public Health, Sapporo, pp 51–63

Yagi K, Itoh T (1999) Influence of low temperature and desiccation on the infectivity of *Echinococcus multilocularis* eggs (in Japanese). Rep Hokkaido Institute Public Health **49**:167–168

Yamamoto K, Tanaka T, Yamada J, Sasaki H, Ohira S, Suzuki R, Iida H, Danjyo T (1966): A child case of alveolar hydatid disease in Nemuro, Hokkaido(in Japanese). Rinsho Shoni Igaku/J Clinical Pediatrics, Sapporo **14**:60-64

Special edition

6 海外旅行と輸入感染症

木村幹男　国立感染症研究所 感染症情報センター 第二室長

▶ Summary and Keywords

①世界中のあらゆる感染症が国内に入る可能性
②ウエブサイト，電子メールネットワーク，PCソフトの活用
③頻度の高い疾患を優先的に鑑別
④マラリア，腸チフス／パラチフスでは特異的治療が必須
⑤ウイルス性出血熱の可能性も考慮

輸入感染症　発熱性疾患　下痢性疾患　マラリア　ウイルス性出血熱

はじめに

2001年9月の米国同時多発テロ，2003年のイラク戦争および重症急性呼吸器症候群（SARS）の影響を受けて減少した日本人出国者数は，2004年には再び1,600万人を大幅に超えた．また，同年には外国人入国者数は600万人を大幅に超えた．このような状況では，日本人海外渡航者や外国人入国者を介して，世界各地にみられるあらゆる感染症が常時国内に入る可能性があり，したがって，それに対応できる国内での医療体制が必要となる．なかでも，発熱性あるいは下痢性疾患に対する適切な医療対応が重要であるが，本稿では診断を中心としてそれらの要点を述べる．

対処の基本

海外感染の発熱性疾患には重篤化あるいは死亡するものや，周囲に感染させる危険が高いものがあるので，診断および治療の開始を速やかに行うことが重要である．その際には，潜伏期，感染機会，発熱以外の随伴症状・徴候のみならず，それらの疾患の世界各地域での分布，その時々での疾患の流行状態について最新の知識が必要となる．これには通常の書籍のみならず，種々の無料のウエブサイト，電子メールネットワーク（国際旅行医学会など），あるいは民間で発売している有料のウエブサイトやコンピュータソフト（GIDEON，TROPIMED，TRAVAX，その他）など，IT時代に特徴的な情報源を活用することも求められる．

熱帯・亜熱帯地域からの有熱帰国者の診断に当たっては，初めからまれな疾患を考えるのでなく，頻度の高い疾患を優先的に鑑別する．

具体的にはマラリア，腸チフス／パラチフス，デング熱，A型肝炎，アメーバ性肝膿瘍，リケッチア症，レプトスピラ症などであるが，なかでも特異的治療を要する疾患を優先する．同時に，特にアフリカからの帰国者では，ラッサ熱，エボラ

出血熱，マールブルグ病，クリミア・コンゴ出血熱などのウイルス性出血熱（一類感染症）の可能性を念頭におき，必要に応じて二次感染防止策も講じておく．短期間で確定診断が得られない場合，検査技術の問題はもちろんであるが，診断へのアプローチに問題があることも多い．したがって，外部の専門機関への相談をためらってはならない．

状況により，エンピリック治療も考慮する必要がある．ただしマラリアの場合，熟練者であれば古典的な血液塗抹ギムザ染色標本で診断が可能である．エンピリック治療を行わざるを得ない場合として，菌の分離同定に時間がかかる（結核，ブルセラ症，レプトスピラ症），抗体上昇までしばらく待つ必要がある（リケッチア症，レプトスピラ症），本来的に病原体を検出しにくい（内臓リーシュマリア症，赤痢アメーバ症，まれに四日熱マラリア），抗菌薬の投与で培養が陽性になりにくい（腸チフス／パラチフス），などが挙げられる．

主要疾患

海外で感染する代表的な疾患のいくつかにつき，概説に続いて診断や治療の要点を述べる．

マラリア

メスのハマダラカの刺咬により生ずる発熱性疾患である．熱帯熱，三日熱，卵形，四日熱マラリアの4種類があるが，なかでも熱帯熱マラリアは急速に重症化・死亡の危険があるので，十分な注意が必要である．マラリアは100ヵ国以上で流行しているが，特にアフリカ，中東，南アジア，東南アジア，メラネシア，中南米などで問題となる．

発熱時に悪寒をともない，ときに戦慄も生じ，解熱時に大量の発汗を見る．「発熱，貧血，脾腫が3主徴」との記載があるが，初期には貧血，触知するほどの脾腫は多くはない．一般検査では白血球数は不定であるが，血小板数はほとんどの例で減少する．生化学検査でLDHの上昇，総タンパクやアルブミンの低下，総コレステロールやHDLコレステロールの低下が高頻度に生ずる．

診断の基本は，古典的なギムザ染色血液塗抹標本の光学顕微鏡検査であるが，非熟練者では見逃しが起きやすく，陰性の判定には慎重さが求められる．したがって，ただちに専門家に相談することも必要となる．補助手段として，海外で市販されているマラリア原虫抗原検出のためのNow® Malaria（Binax社），OptiMAL-IT（DiaMed社）などが有用であり，医師の個人輸入で入手できる．また，岡山大学薬学部綿矢らの開発になる原虫種特異的PCR法も，診断の確定に有用である．

熱帯熱マラリアでは薬剤耐性を考慮した薬剤の選択が重要である．しかも，国内で発売されている抗マラリア薬は少ないので，「熱帯病治療薬研究班（略称）」（http://www.ims.u-tokyo.ac.jp/didai/orphan/index.html）の保管薬剤が必要になることも多い．

国内でのハマダラカによるマラリアの伝播は無視できるので，通常，患者の個室管理は行わない．ただし，針刺しによる二次感染が国内外で発生しており，医療従事者は注意が必要である．