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REPORT OF THE WHO INFORMAL CONSULTATION ON ALVEOLAR ECHINOCOCCOSIS

Hohenheim, Federal Republic of Germany, 14-16 August 1989*

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1. Introduction

Professor W. Frank, University of Hohenheim, Federal Republic of Germany, host of the meeting, and Dr. D. Pittler, Federal Ministry of Food, Agriculture and Forestry, representing his government, each welcomed the group (Annex 1). Dr Pittler stated that there were many gaps in knowledge of transmission mechanisms of alveolar echinococcosis and that this meeting should fill some of these. Dr K. Bögel, Chief, Veterinary Public Health, opened the meeting on behalf of Dr H. Nakajima, Director-General of the World Health Organization. He emphasized the importance of acquiring a more in-depth knowledge of the dynamics of transmission of Echinococcus multilocularis in its natural host. Only through a greater understanding of this could we hope to break the cycle. He wished to take advantage of the extensive experience that has been gained in the ecology of rabies in foxes and apply this to the problem of E. multilocularis.

Professor W. Frank was elected Chairman, and Professor J. Eckert, Vice-Chairman. Dr. P. M. Schantz, served as Rapporteur.

Since a group of experts met to discuss research requirements in echinococcosis/hydatidosis in Montreal, August 1987[1], international cooperation in research in this area has been strengthened. In a meeting held in Geneva, September 1988[2], seven working groups were formed to develop global research activities on biology and strain variation, immunology, immunodiagnosis, medical aspects, epidemiology and control, and chemotherapy, headed by a coordinating team.

In line with these global research activities, but independent of the above working groups, another group of scientists working mainly in E. multilocularis infection in Europe, met in Zurich in 1987[3] to discuss international cooperation, taking into consideration the epidemiological situation in Central Europe. This group organized a second meeting in Geneva, in November 1987[4] to develop international cooperation on E. multilocularis infection, through the formation of: (1) a working group on epidemiology, including ecology of intermediate and final host; and (2) a group on immunodiagnosis, with special reference to Em2-ELISA and application to the human and animal population in endemic areas. An institutional network was also developed to facilitate cooperation and information exchange.

At the third meeting of the Working Group on E. multilocularis, which met in Zurich, June 1988[5], the group elaborated two guidelines to facilitate the development of common ground for research activities and to make their data comparable, namely: (1) guidelines on eco-epidemiological studies; and (2) on Em2-ELISA immunodiagnosis.

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[1]Report of the WHO Consultation on Research Requirements for Echinococcosis/Hydatidosis, Montreal, Canada, 13 August 1987 (WHO/CDS/VPH/87.72)

[2]Report of the WHO Informal Meeting of Working Groups on Echinococcosis Research, Geneva, 15-16 September 1988 (WHO/CDS/VPH/88.79)

[3]Report of Informal Discussions on the Ecology of Echinococcus multilocularis, Zurich, Switzerland, 30 April 1987 (WHO restricted document)

[4]Report of the WHO Informal Consultation on the Ecology of Echinococcus multilocularis Infection, Geneva, 26-27 November 1987 (WHO restricted document)

[5]Report of the WHO Informal Consultation on Echinococcus multilocularis Research, Zurich, 16-17 June 1988 (WHO/CDS/VPH/88.78)

Since then, the working groups have continued to develop their research activities and have exchanged views and results on these with participating scientists from North America, Asia and Central Europe. Dr T. Fujikura, WHO, recalled the aims of the present meeting, which were to:

(1) review the working group activities on E. multilocularis research which has been carried out since 1988;

(2) discuss the current epidemiological situation on alveolar echinococcosis (E. multilocularis infection) in Central Europe and in other regions, e.g., America (USA), Asia (China and Japan), and Eastern Europe (USSR), and to exchange views;

(3) advise local public health services of the health risks of alveolar echinococcosis, of methods of diagnosis and treatment in man, and of possible ways of preventing and controlling E. multilocularis based on the results of control programmes in endemic areas in Central Europe, some of which are now available:

(4) develop work plans for further international cooperation on global research, prevention and control of alveolar echinococcosis.

2. Report of the Working Groups

2.1 Epidemiology

2.1.1 Prevalence and geographical distribution

In North America, E. multilocularis is currently recognized in 2 distinct geographic regions: the northern tundra zone and central North America. The range of the cestode in the tundra zone is roughly equivalent to that of the arctic fox, Alopex lagopus, its principal natural host. It extends along the coast of Alaska from the mouth of the Kuskokwim River northward and eastward to Canada, and extends southward along the western shore of Hudson Bay. The principal intermediate host is the northern vole, Microtus oeconomus. The central North American enzootic focus is currently known to include 9 contiguous states and 3 Canadian provinces. Life cycles involve the red fox and the coyote as final hosts and the deer mouse and meadow vole as intermediate hosts. Domestic cats have also been infected and this implies the possibility of domestic cycles involving cats and house mice. To date, 52 human cases of alveolar echinococcosis have been diagnosed in 33 men and 19 women in Alaska, USA. All patients were Eskimos who had been born, or resided, in villages on the western coast of Alaska or St. Lawrence Island. The average annual incidence of diagnosed cases was 33 per 100 000 population but, on St. Lawrence Island, where the majority of cases have occurred, the rate was 67 per 100 000 population. Two cases have been diagnosed within the central North American focus. However, the potential for more widespread exposure is apparent.

Western Europe contains the oldest known foci of E. multilocularis infection. Human cases have been recognized there since the middle of the last century. In recent years autochthonous E. multilocularis infection in humans have been observed in Austria, Federal Republic of Germany, France, Switzerland, and Turkey. Within these countries, the occurrence of the infection is very focal, and some areas appear to be infection-free.. Life cycles of E. multilocularis in Europe primarily involve the red fox as definitive host and several species of rodents as intermediate hosts. There have also been reports of infected dogs and cats. Although human alveolar echinococcosis is under-diagnosed and under-reported, an average of 20-30 cases are reported each year from European countries. In Switzerland, the national morbidity rate calculated for 1980 was 0.18 cases for 100 000 inhabitants; the highest rate was in the Jura region (0.74 cases

per 100 000). Serological screening of blood donors from northern Switzerland with Em2-ELISA (1984/85) with clinical diagnostic follow-up of seropositives resulted in a confirmed prevalence rate of 0.01%.

In France, approximately one third of patients are employed in agriculture. However, specific risk factors for infection remain poorly defined.

Recent work in Austria indicates that the infection is more widely dispersed than previously known and that it exists in some of the lower regions of the country as well as the Alpine regions.

Alveolar echinococcosis is widespread in both European and Asian parts of the USSR. The disease is recognized as an important public health problem due to its severe morbidity, disability and mortality rates, and because it occurs in areas of the country which are under intensive industrial development. Within endemic areas, the annual morbidity rate has been calculated as 10 cases per 100 000 inhabitants. The most intense foci of alveolar echinococcosis are northern Siberia where the Yakut ASSR, the Chukotsk autonomous territory and Yamal Peninsula have morbidity rates as high as 1.7 cases per 1 000 people. A serological monitoring programme has been initiated in the USSR for the purpose of assessing the problem in quantitative terms, and identifying priority areas for intervention.

In Japan, E. multilocularis has spread to the north and west of the original endemic area in the east. Recent studies have shown infection in 14% of 1 277 red foxes and 3% of 98 domestic dogs. The major intermediate hosts are red-backed voles, but pigs are also commonly infected. Approximately 3-17 cases of human disease are diagnosed each year in Hokkaido. A serological screening programme to detect new cases has been in operation, based on screening with a sensitive ELISA procedure followed by serological confirmation by immunoblot.

Alveolar echinococcosis is known to be widespread in the People's Republic of China. However, very little has been reported on the distribution of the infection in the natural animal hosts, or the numbers and geographical distribution of human cases. In 1989, a national hydatid centre was created in Urumqi, Xinjiang Uyghur Autonomous Region, with responsibility for coordinating research and control activities in China.

Although the completeness of information on alveolar echinococcosis varies greatly from one endemic area to another, it is recognized that the lack of adequate reporting systems in most of the endemic areas makes it very difficult to obtain data on the current prevalence and geographical distribution of E. multilocularis in humans and animals. In Switzerland, echinococcosis has been made a notifiable disease, and experience there may prove the value of such administrative steps for better understanding of the epidemiology of the disease. The geographical distribution of E. multilocularis in the above countries is given in Annex 2.

2.1.2 Epidemiological key factors

It is recognized that the development of an effective strategy for interrupting transmission of E. multilocularis requires a thorough understanding of the population dynamics of the host species, the interactions between prey and predators, and the many other ecological factors that determine transmission of the parasite. Methods for such studies have been reported. However, they must be evaluated and adapted for each different ecological situation. Data from both the Federal Republic of Germany and Japan reveal very high infection rates in young foxes suggesting their importance in transmission. In Japan, recent studies have shown that fox breeding behaviour is closely related to the transmission of E. multilocularis. Infection rates were most common in young foxes and a clustered distribution of infected voles was identified in association with fox dens where litters had been raised that season. Such observations may permit development of effective strategies for intervention. There is a need to bring together

already-available data on fox and rodent population dynamics and to develop quantitative models to describe the basic reproductive rates and the epidemiological status of E. multilocularis in each biocenose. Such information will determine the feasibility of control as well as the optimum control strategies.

It was recognized that mathematical models describing the life cycle of taeniid cestodes in the dog-sheep life cycle contributed markedly to an understanding of the transmission dynamics of the family Taeniidae. Such models could also contribute to an understanding of the epidemiology and control of echinococcosis in wildlife. Immediate steps include: (1) identifying the biological and ecological research programmes that must be undertaken; and (2) estimating the force that must be applied if meaningful policies are to be developed for reducing transmission to human beings. In addition, modelling could be used to predict cost-effective control measures and their outcome.

Knowledge of the physical factors which affect survival of taeniid eggs in the environment and their mechanisms of dispersal is necessary for an adequate understanding of the mechanisms of transmission. Studies in the Federal Republic of Germany have recently confirmed the susceptibility of E. multilocularis to heat and desiccation. However, under most European conditions, eggs survive several months in summer and perhaps indefinitely in autumn and winter.

It has been previously shown that a major factor in dispersal of E. multilocularis eggs from the site of faecal deposition is flies which feed on faeces. In the Federal Republic of Germany, flies of the genera Lucilia and Musca were particularly efficient in transporting eggs in their intestinal tracts. Other insects, such as flesh-eating beetles (Dermestes), cockroaches and slugs, are also capable of taking up E. multilocularis eggs and dispersing them. Such studies demonstrate the theoretical possibility that egg contamination of berries, vegetables and other foodstuffs might occur. Due to the extensive dispersal of flies between the time of ingestion of eggs in faeces and ejection of eggs by vomition or defecation onto foodstuffs, human infection is most likely to occur at some distance from the original site of egg deposition.

2.2 Pathogenesis and diagnosis

Purified E. multilocularis antigen (Em2) used in a standardized ELISA system (EM2-ELISA) now serves as a reference standard for serological diagnosis of alveolar echinococcosis in humans. This system was developed in Switzerland and has been extensively evaluated in laboratories in other countries of Europe and North America. Diagnostic sensitivity is approximately 94%. With the exception of some other larval cestode infections which sometimes give low level reactivity, the test is highly specific. By comparing the reactivity of diagnostic sera to Em2 antigens and to other fraction-sharing components of both E. granulosus and E. multilocularis, it is possible to detect cases of alveolar and cystic echinococcosis with a reliability of 95%. The test is also sensitive for post-surgical monitoring and shows negative sero-conversion in most patients following successful resection of the lesion. The Em2-ELISA test results give high predictive values when used for sero-epidemiological studies, even in areas with extremely low prevalence of disease.

The importance of a similarly-comprehensive evaluation of the operating characteristics of other antigens proposed for diagnosis of E. multilocularis was emphasized. Recently, the group of Swiss scientists produced a recombinant antigen of E. multilocularis consisting of 2 polypeptides which, on evaluation, shows 98% sensitivity with sera of patients with alveolar echinococcosis. A second recombinant E. multilocularis antigen with high specificity for alveolar echinococcosis was reported from the United Kingdom. These developments represent a major advance in that highly specific antigens may be available in unlimited quantities in the near future.

In Japan, more than 150 000 serum specimens have been screened in ELISA followed by immunoblot analysis of ELISA positive sera. Clinical evaluation of seropositive persons

has detected 57 new cases of alveolar echinococcosis. Similar screening projects have taken place in Austria, the Federal Republic of Germany and the USSR, although the characteristics of the antigens and the sensitivity and specificity of the tests are not as well defined as the Em2-ELISA.

The successful in vitro cultivation of E. multilocularis protoscoleces or germinal cells were reported from Austria, the Federal Republic of Germany, and Japan. In Japan, germinal cells have been maintained in RPMI 1640[6] with 10% bovine foetal serum for 23 passages, to date. In the Federal Republic of Germany, efforts to obtain continuously-reproducing E. multilocularis cell line have included fusion with myeloma cells. It was recognized that stable cell culture lines have multiple applications in immunology and studies of growth-promoting and cell differentiation factors and drug screening.

Diagnostic examinations of foxes for intestinal stages of E. multilocularis using necropsy and parasitological techniques are time-consuming and are associated with potential infection risk for investigators, necessitating cumbersome and expensive facilities and equipment. These considerations have inhibited epidemiological surveys. There is a need for improved and simplified examination techniques. Two immunological approaches have been evaluated in this respect. The first approach was detection of serum antibody. This has been shown to be feasible in dogs infected with E. granulosus who develop antibodies against homologous protoscolex somatic antigens and oncospheres.

The Em2-ELISA was sensitive for detecting antibody in foxes infected with E. multilocularis. However, it did not distinguish between present and previous infections. Testing of foxes from areas where E. multilocularis infection is not known to occur, has shown very low or negative results, thus suggesting that this approach may be useful for screening and distinguishing infected, and infection-free fox populations. The second approach is the detection of copro-antigens. An ELISA was recently developed for detection of antigens in the stools of dogs experimentally infected with Taenia hydatigena. On preliminary evaluation, all infected animals had detectable copro-antigens well before the excretion of eggs and/or proglottids. Copro-antigens became non-detectable within 5 days of successful anthelminthic treatment. Faeces from dogs infected with helminths other than Taenia spp. did not give false-positive reactions. This test will be further evaluated for applicability for diagnosis of Taenia and Echinococcus infections in dogs under field conditions.

It is well documented that in the species E. granulosus, multiple strains exist with adaptation to life-cycles in different host species in different geographical areas. Little information exists on possible strain variation in E. multilocularis, therefore, more research is required. Criteria of practical importance for strain identification include the morphology of adult and metacestode stages, isoenzyme and total protein analysis, DNA hybridization, developmental studies of adult and/or larval stages in vivo or in vitro, and epidemiological characteristics. As a first step for strain identification, information and materials can be collected and sent to the WHO Collaborating Centre at the School of Veterinary Medicine, Murdoch University, Murdoch 6150, (Western Australia), or to another specialized laboratory.

2.3. Treatment

Mortality rates from alveolar echinococcosis have declined in the past 30 years. Although the various studies carried out have not been directly comparable, data exists

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[6]Roswell Park Memorial Institute medium

that suggest that the survival rate 10 years after treatment, which was as low as 20% in early case series, has increased to as high as 50% in more recent case series, probably as a result of improved diagnosis and treatment.

2.3.1 Surgery

Improvements in surgery have apparently contributed to increased survival of patients. Radical procedures including hepatectomy and reconstruction of the bile duct with an intestinal loop are employed in 30-40% of patients. In other patients, palliative procedures, such as biliary drainage and abscess drainage, are now more efficient and may be both life-prolonging and life-enhancing. For patients with advanced terminal stage disease, liver transplantation may be an alternative. In France, 12 patients of 16 treated in this manner since 1986 have survived. Transplantation experiences have raised the question whether immnuosuppression used for the liver transplantation procedure may permit the recurrence of primary or metastatic parasitic lesions.

2.3.2 Chemotherapy

Although information on chemotherapy of human alveolar echinococcosis is still limited, incomplete experiments in Europe and North America suggest that many patients treated with benzimidazole carbamates for extended periods undergo stabilization or regression of lesions with prolonged patient survival time. In Switzerland, 60 patients with non-resectable alveolar echinococcosis have been treated with mebendazole. The efficacy of treatment was associated with the plasma levels of mebendazole and the duration of chemotherapy. The majority (80%) of patients showed no change of lesions by imaging studies. Lesions in 9 patients showed a definite decrease in size after chemotherapy of 2 years or longer. Progression of lesions was noted in 14 patients. However, these patients experienced stabilization or improvement of their signs and symptoms. Reported trials comparing mebendazole and albendazole are still too limited to draw conclusions. The results of experimental animal chemotherapy and human clinical trials suggest that benzimidazole chemotherapy is parasitostatic in most patients rather than parasitocidal. In 19 patients treated with mebendazole for 3 years or longer, cessation of therapy was associated with apparent recurrence in 37%. Potentially-severe adverse reactions, mainly neutropenia and abnormalities of liver function, although reversible in all cases to date, required cessation of therapy in some patients.

It was agreed that, to date, the results with mebendazole and albendazole suggest that benzimidazole carbamates are not the ideal drugs for larval echinococcosis. New initiatives are needed for identification and development of new drugs.

Although many methods have been suggested for determining the viability of metacestodes tissue isolated from untreated patients and those under chemotherapy, it was agreed that viability can be examined best by transfer of material to susceptible rodents. This can be done through intraperitoneal inoculation of minced metacestode material or by intraperitoneal transplantation of blocks of tissue. It is important that investigators using these techniques to assess the results of chemotherapy should evaluate the efficiency of their techniques in comparison with those published by other groups.

2.4. Prevention and control

2.4.1 Potential methods of food decontamination

Recognizing that E. multilocularis eggs may be potentially ingested by people on contaminated berries, vegetables and other foodstuffs, some work has been carried out in the Federal Republic of Germany on methods to destroy the eggs whilst maintaining the taste and value of the foodstuffs. Heating for 3 hours to a critical temperature of about 45°C kills eggs indicating that boiling or cooking foodstuffs renders them safe. Eggs survive freezing at -18°C for 240 days indicating that home freezing is not adequate

for destroying eggs. However, E. multilocularis eggs lose their infectivity when frozen at -80°C, therefore, commercial freezing processes, when carried out adequately, render contaminated food safe.

Given the increased number of workers carrying out field and laboratory investigations of E. multilocularis in definitive hosts, and the potential risks associated with these studies, it is important that workers be advised of the risks and how to avoid them. Safety precautions need to be updated and made available to all workers in this field (Annex 3).

2.4.2 Control measures

Few attempts to apply control measures against E. multilocularis have been reported. It has generally been considered that the technology did not exist to interrupt transmission in life cycles involving wildlife. One exception is on Rebun Island, Japan, where, in 1968, eradication of E. multilocularis was achieved by eliminating all foxes from the island. One innovative approach to interrupting life cycles in the fox/wild rodent cycle is administering praziquantel in baits. Approximately 20 baits per km^2 were placed at approximately 6-monthly intervals beginning in July 1988 in a high endemic area of the Swabian Alb in the Federal Republic of Germany. The fox acceptance of the baits was 70-90%. Reduction of infection in voles was not conclusive. However, the preliminary results suggest a reduction in fox infection rates. Plans have been discussed for reducing the cost of such a programme by combining rabies vaccine with praziquantel in the same baits. A similar field trial of praziquantel baiting of foxes is scheduled to begin this year in Hokkaido, Japan.

In a village on St. Lawrence Island, Alaska, USA, monthly praziquantel treatments of dogs was used to interrupt transmission between dogs and commensal rodents. Dog treatments reduced contamination with E. multilocularis eggs within the village as measured by the significantly reduced rates of infection in voles trapped in the village. However, even after 5 years of monthly treatments some voles became infected. Continued monthly treatments of dogs combined with control of canine populations and their movement, and health education of the public may be required to reduce E. multilocularis infection in humans in this epidemiological setting.

It was suggested that a slow-release formula of praziquantel might be useful for control in foxes. However, the prospects for development of such a formula are very poor due to the pharmacokinetics of the drug and the fact that carnivores tend to vomit foreign bodies such as a bolus. Implants such as silicone foams impregnated with praziquantel cannot be readily administered to foxes.

3. Conclusions and recommendations

3.1. Epidemiology

The group recognized that there are very wide gaps in knowledge of the ecology of the various hosts involved in the life cycle of E. multilocularis and in the epidemiology of this parasitic zoonosis. An immediate priority would be the development of reporting and surveillance systems to identify high-risk areas and the exact ways in which people become infected (adequate efforts of governmental services are called for in this respect). This includes epidemiological studies on the pathways of transmission between foxes, rodents and human beings.

Specifically, the group recommends that:

3.1.1 International collaborative efforts should be organized to solve these research problems. In the long-term, this collaboration is aimed at identifying the various options available for control that can be expected to differ in the many ecological situations where this parasite exists.

3.1.2 The standardization of methods and approaches to eco-epidemiological research is essential. The objective of this research is to identify as yet unknown factors, such as weather, topography and the many other factors that may modify transmission.

3.1.3 Standardization and calibration should be made for all methods used for host censuses and diet surveys.

3.1.4 An atlas of the distribution of E. multilocularis together with known hosts, should be prepared by the collaborating groups with support from the WHO.

3.1.5 Research in the following areas should be given priority and are identified by the following questions:

What factors determine the geographical distribution or, alternatively, why is the parasite absent from what appear to be suitable niches?

Is the parasite hyperendemic or endemic and what biological and ecological factors determine the transmission dynamics?

Are there seasonal or annual variations; if so, what determines these?

3.1.6 Groups already studying special areas in different institutes should collaborate in order to ensure that field studies will provide comparable results.

3.1.7 Where possible, standardized computer software should be developed for use by collaborating groups.

3.1.8 Adequate reporting systems for human cases of alveolar echinococcosis should be introduced and the data should be used to describe the demographics and risk factors of infection.

3.1.9 Special care is necessary to standardize immunodiagnostic techniques that are used in studies on transmission dynamics in humans and animals, including copro-antigen studies in definitive hosts.

3.1.10 Examination and further development of tests for copro-antigens (possibly in comparison to sero-antibody) in fox and dog surveys is recommended. Plans for field investigation should be developed by the ecological groups of Drs Aubert and Müller.

3.2. Diagnosis

3.2.1 For serodiagnosis of alveolar echinococcosis the Em2-ELISA should be accepted as a current reference system.

3.2.2 Reference sera with defined antibody titres determined in the Em2-ELISA should be prepared. They should include a number of positive sera with different titres and also a negative standard.

3.2.3 Promising new test systems (including new antigen preparations) should be compared with the Em2-ELISA, in terms of sensitivity, specificity and other characteristics.

3.2.4 A standardized file should be prepared for collecting data on:

(a) patients; and
(b) persons included in serological surveys.

For this standardized file, basic diagnostic criteria should be provided.

3.2.5 Techniques for the diagnosis of infected definitive host populations should be improved, including immunological methods.

3.2.6 Ultrasound mass screening should be further evaluated for detection of alveolar echinococcosis in human populations.

3.3. Treatment

Unfortunately, at present, the treatment of human patients is only life-protecting but not yet life-saving.

3.3.1 New surgical procedures, such as liver transplantation and long-term, high-dose treatment with mebendazole or albendazole are very expensive. Since significant further progress cannot be expected from these drugs, available funds should be diverted to new approaches which have the potential for curative results after short-term administration. In fact, new drugs should be developed.

3.3.2 Technical conditions for successful drug development are now defined: methods for *in vitro* screening, *in vitro* evaluation, pharmacology and toxicology. Protocols for clinical phase I to III have now been developed.

3.3.3 A group of experts should be convened who might serve as a project development team. They should receive starting support, e.g., from WHO, in order to evaluate the actual cost of the disease, to draft a plan of action, and to develop protocols which can be submitted to granting agencies. It must be realized that this is a major project. Yet, unless new approaches are tried, a break-through is not to be expected. Analogously to other diseases, an effective short-term treatment for echinococcosis will be the most economical method to deal with the disease.

3.4. Prevention and control

The ultimate objective of research on alveolar echinococcosis is the elimination of the infection from its reservoirs in nature. The participants noted, with appreciation, that working teams are being set up by WHO to investigate potential approaches.

3.4.1 Since an effective echinococcidal drug is now available, strategies for its administration to definitive hosts of *E. multilocularis* should be developed and evaluated. Possible approaches include praziquantel baiting of foxes to interrupt fox/rodent cycles, and mass treatments of dogs to interrupt dog/commensal rodent cycles. Such trials should be developed based on an adequate understanding of the local patterns of transmission and should be adequately evaluated to understand the details of what happens and the cost/benefit of the intervention.

3.4.2 Water, berries, fruits, greens and other foodstuffs potentially contaminated by fox faeces should be sampled directly to confirm the possibility that they serve as fomites for transmission of *E. multilocularis* or other helminth eggs.

3.4.3 Further studies should be carried out to investigate physical and chemical agents for decontaminating foodstuffs potentially contaminated by *E. multilocularis* eggs.

3.5. Biosafety

3.5.1 The working group recommends that WHO safety guidelines should be developed for laboratory and field examinations on *E. multilocularis* incorporating new knowledge in this field. Personnel working with such materials should be monitored serologically at annual intervals. Guidelines should be based on the principles described in Annex 3.

3.6. International Cooperation

3.6.1 Working group activities on echinococcosis research (mentioned in WHO/CDS/VPH/88.78 and WHO/CDS/VPH/88.79[7]) should be developed in line with terms of references and work plans which are already agreed upon.

3.6.2 Each working group should be encouraged to extend its network of institutes and scientists at international level, in particular to groups in developing countries.

3.6.3 Reference material and guidelines of standardized procedures and methods for research and diagnosis of E.multilocularis infection should be elaborated in collaboration with WHO collaborating centres and other interested institutions. WHO should strengthen ecological studies on alveolar echinococcosis and entrust one WHO collaborating centre with the task of coordinating research. Emphasis may be placed on the fox/vole interactions and critical path analysis. Fox stomach content studies should be standardized and teams in infected areas should be trained in survey techniques.

3.6.4 Where required, international workshops, seminars and training courses on E. multilocularis diagnosis, prevention and control, and related research, should be organized, in collaboration with WHO.

3.7 Conclusions and recommendations for public information and education

The participants of the meeting strongly recommended that a specimen statement on alveolar echinococcosis, dealing with its occurrence, significance, and preventive measures, should be made available to health personnel and the general public. Based on the discussions, the WHO Secretariat, in collaboration with the Chairman of the meeting, has prepared such a specimen statement, which is given in Annex 4. National authorities are advised to use this material, modifying it according to local conditions and needs. Care should be taken that the information provided to the public is not in discordance with national or local policy on this subject area.

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[7]Report of the WHO Informal Consultation on Echinococcus multilocularis Research, Zurich, 16-17 June 1988 (WHO Limited document WHO/CDS/VPH/88.78).

Report of the WHO Informal Meeting of Working Groups on Echinococcosis Research, Geneva, 15-16 September 1988 (WHO Limited document WHO/CDS/VPH/88.79).

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ANNEX 1

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Annex 1

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ANNEX 2

Geographical distribution of alveolar echinococcosis in endemic countries

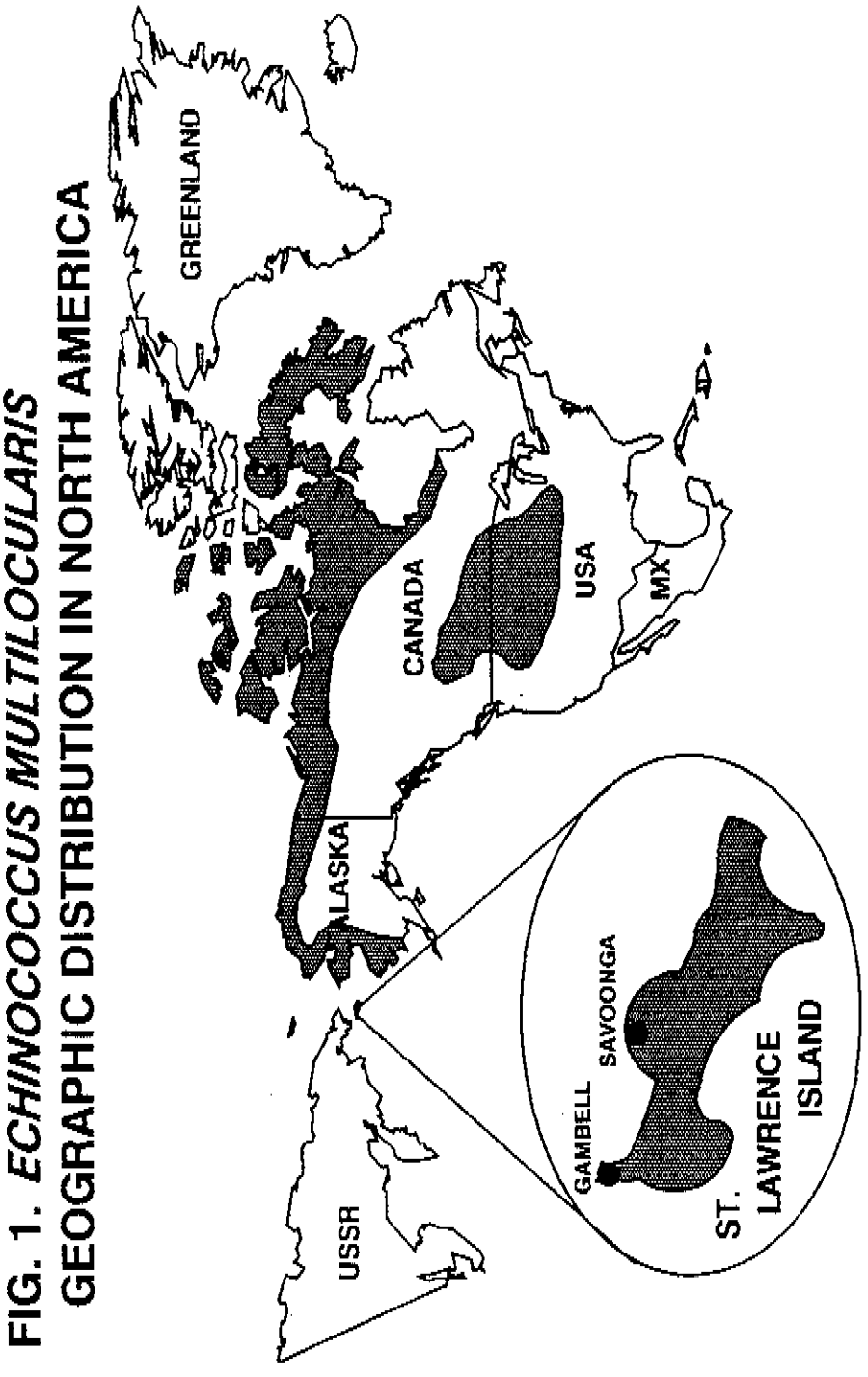
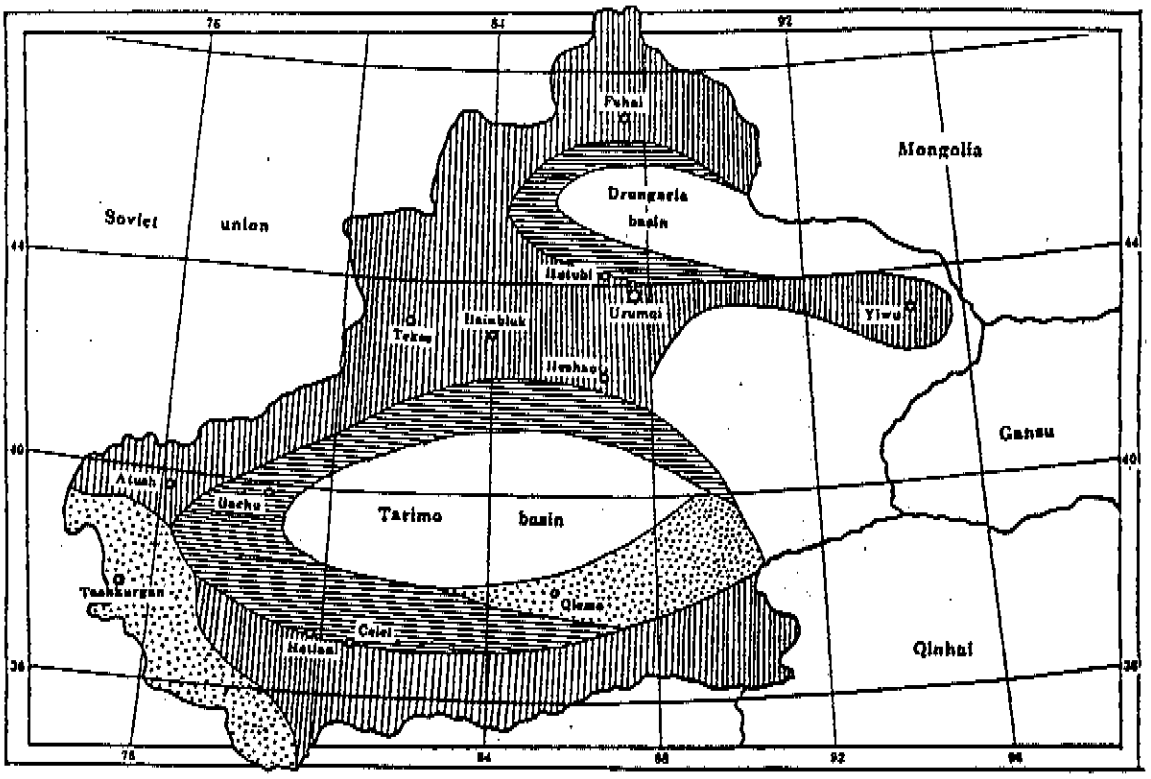


FIG. 1. *ECHINOCOCCUS MULTILOCULARIS* GEOGRAPHIC DISTRIBUTION IN NORTH AMERICA

Fig. 2 Distribution of echinococcosis in the human population in Xinjiang Province, People's Republic of China



○ Investigated area

Mild prevalent area

Moderate prevalent area

Severe prevalent area

(The three pilot areas are Heshao, Hutubi and Tekes)

Fig. 3 Prevalence of E. multilocularis in red foxes in the district of Hokkaido, Japan, 1986-1989

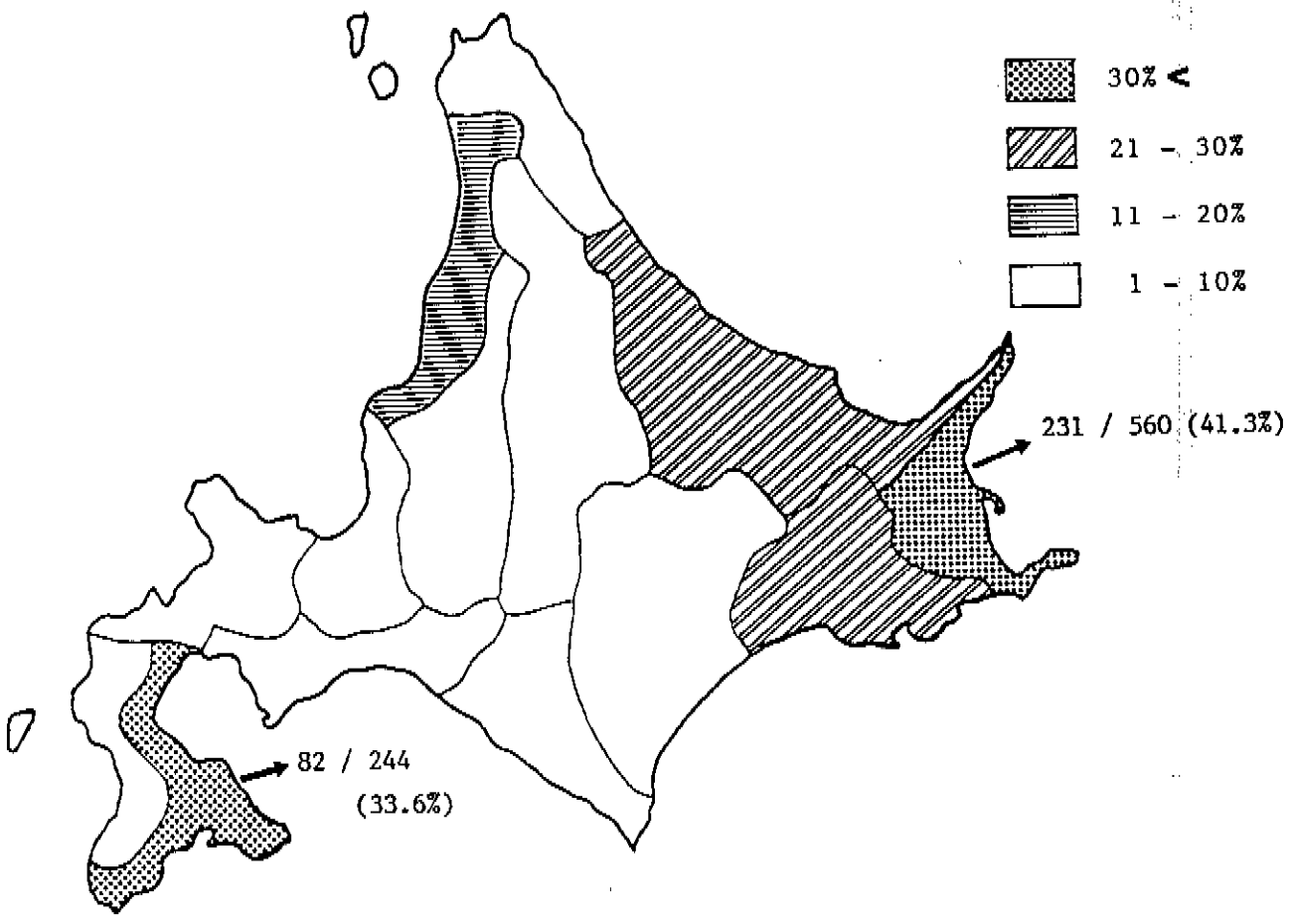
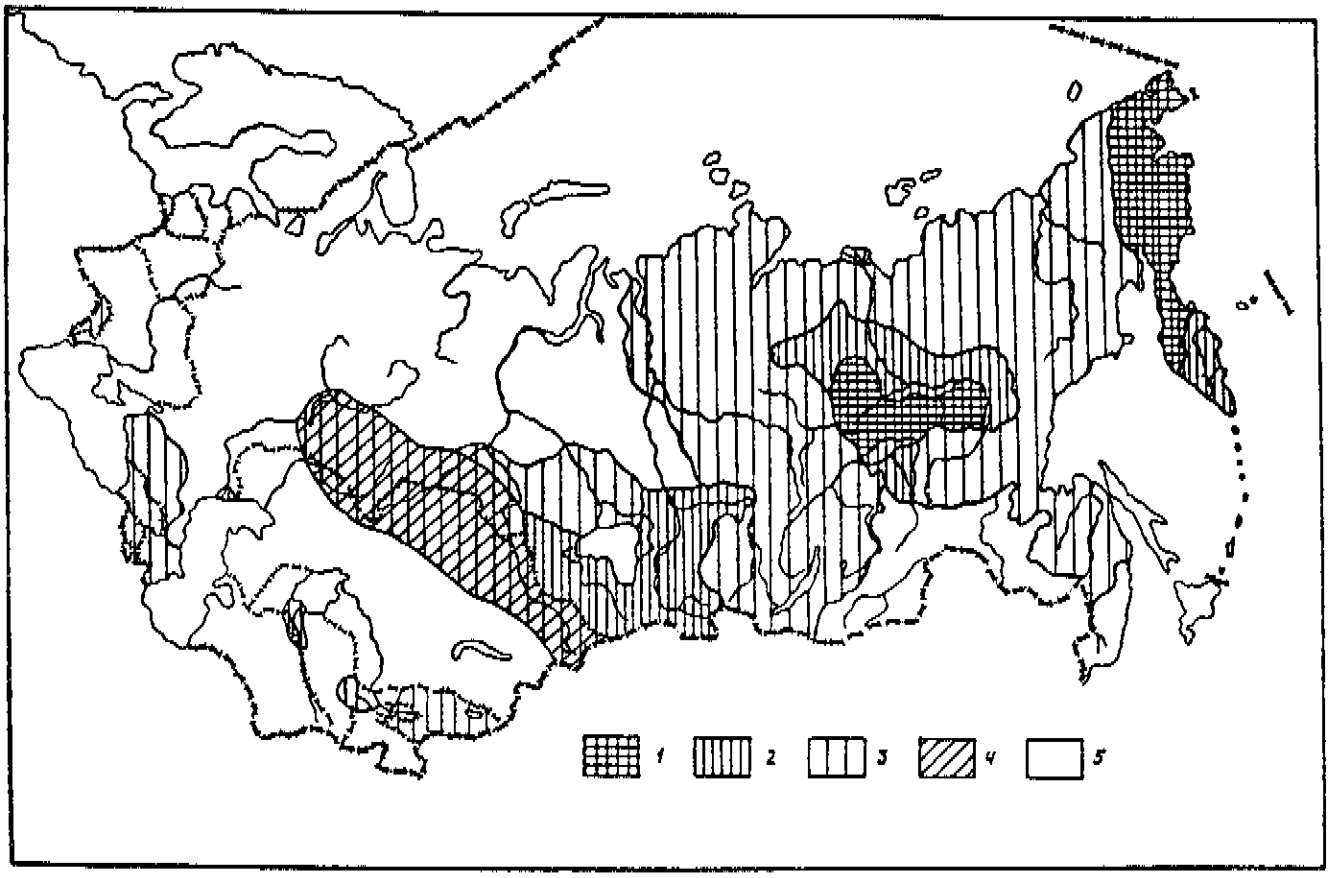
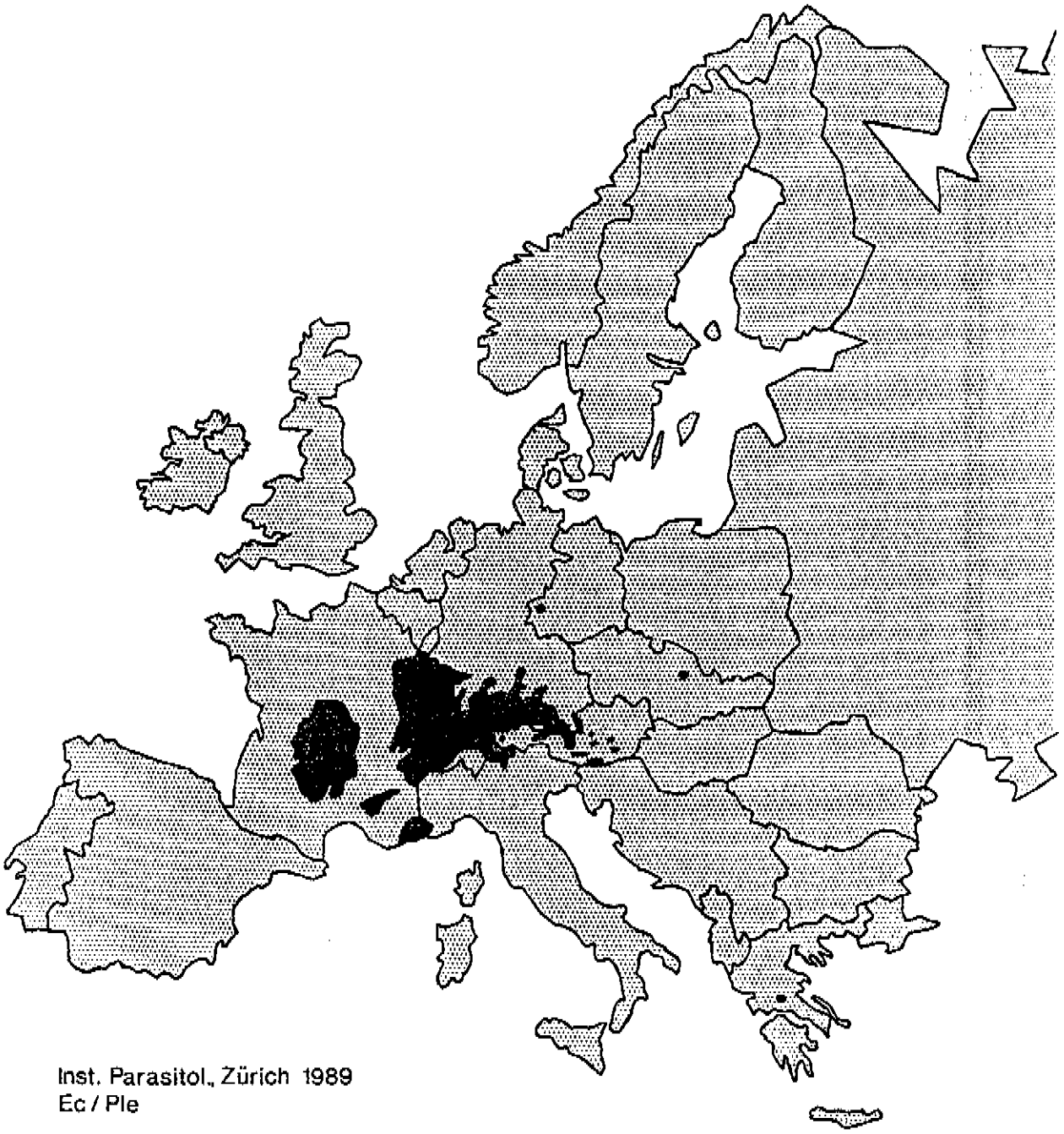


Fig. 4 Distribution of alveolar echinococcosis amongst the human population in the USSR



1. Territories and areas with very high incidence
2. High incidence
3. Low incidence
4. Higher incidence is anticipated
5. No data available

Fig. 5 **Geographical Distribution of Echinococcus multilocularis in Central Europe (1988)**



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ANNEX 3

Biosafety Guidelines for Laboratory and Field Examinations of Echinococcus multilocularis Infection

1. All studies should be carried out under the responsibility of an experienced scientist well trained in handling infectious material. This person should be fully informed of the national/regional biosafety regulations in force. All other persons involved in such examinations should be well trained.

2. Special necropsy rooms with floors and walls which can be easily cleaned and disinfected, equipped with an apparatus for heat disinfection, should be available. This room can also be used for necropsy of other carcasses, but other laboratory work should not be permitted. It should be kept free from flies.

Special protective clothing should be used in this room, including boots, gloves, coats - if necessary face masks and aprons. This material should be disposable or disinfectable.

3. Carcasses should be thoroughly lubricated before being dissected on special tables or trays, to prevent dust-borne transmission. At each stage of dissection, only material and instruments which can be easily decontaminated by heat should be used. Carcasses to be disposed of should be incinerated or heated to at least 75-80°C for an adequate period so that all parts of the carcass are exposed to this temperature.

Carcasses can be disposed of at an incineration plant. Special treatment of waste water is required if sewage sludge decontamination is not guaranteed.

4. Although to date there is no evidence of infection of persons involved in examining foxes with Echinococcus multilocularis, serological surveillance of such persons is recommended. The first examination should be carried out at the beginning of the work and, subsequently, twice a year. The specialized laboratories responsible for the regular surveillance service should be nominated on a national level by the health authorities.

ANNEX 4

Specimen statement on alveolar echinococcosis addressed to health personnel and the general public in endemic countries

Alveolar echinococcosis, caused by a small tapeworm (Echinococcosis multilocularis) that exists in the small intestine of foxes and sometimes of dogs and cats, is a very serious human illness with characteristics similar to cancer. Most patients ultimately die of the disease, although progress in surgical and medical treatment has increased chances of survival.

The tapeworm occurs in focal areas of many countries, notably, parts of the Federal Republic of Germany, France, Switzerland and Austria, in Europe; Alaska, some of the United States and Canadian provinces; Siberia, and other parts of the USSR, the People's Republic of China, and Japan. People become infected when they accidentally swallow eggs of the tapeworm passed by the faeces of infected foxes or dogs. The ways of egg transmission are not exactly known and current research is aimed at clarifying the mode of infection.

Fortunately, human disease is rare in Europe. According to recent data from Switzerland, the annual number of new cases is 0.18 per 100 000 inhabitants, but in some areas, morbidity rates may be higher. At present, there is no evidence to suggest that the disease is spreading in Europe or that the number of human cases is increasing. Most cases occur in farmers and their family members. Some people, mainly hunters, become infected by direct handling of foxes, or hunters of other fur-bearing animals like muskrats. Theoretically, other sources of infection could be water, berries, greens or vegetables accidentally contaminated with faeces of infected foxes or dogs. The source of infection for most patients has not been established. Until further information is available, it is recommended that people belonging to the high-risk groups mentioned above, or living in endemic areas, apply general measures of hygiene and that those living in areas identified as "high risk" avoid contact with foxes and their faeces; vegetable gardens should be fenced off to keep out foxes. Hunters should touch foxes only if hands are protected with plastic gloves. If fruits or vegetables are likely to have been contaminated with fox, dog or cat faeces, they should be carefully washed, cooked or frozen to -80°C (for at least 3 days) before eating.

Considerable progress has been achieved in the early diagnosis of the disease, using immunodiagnostic tests, computer-assisted tomography, ultrasound examination and other methods. Highly specific immunodiagnostic tests can now be applied for sero-epidemiological studies in endemic areas aimed at early detection of human cases.

Early-detected cases with small lesions in the liver are likely to be cured by surgical intervention. In advanced cases many patients ultimately die of the disease although progress in surgical techniques, medical care and chemotherapy has increased survival of patients. However, the presently available methods of treatment are very costly and still unsatisfactory. Therefore, there is an urgent need for developing more effective chemotherapy.

Several working teams are being set up to investigate the various aspects of alveolar echinococcosis in a new approach at international cooperation. An immediate priority must be the development of reporting and surveillance systems to identify risk areas and the exact ways in which people become infected.

ANNEX 5

List of Working Papers

VPH/ECHIN.RES./WP/89.1	List of participants
VPH/ECHIN.RES./WP/89.2	Draft agenda
VPH/ECHIN.RES./WP/89.2.1	Background, purpose and scope
VPH/ECHIN.RES./WP/89.3	Final and intermediate host population dynamics and methods for their study. M. Aubert
VPH/ECHIN.RES./WP/89.4	Prevalence and geographical distribution of E. multilocularis infection in humans and animals in Europe. J. Eckert
VPH/ECHIN.RES./WP/89.5	Modelling the transmission dynamics of wildlife echinococcosis. M. A. Gemmell, M. G. Roberts and J. R. Lawson
VPH/ECHIN.RES./WP/89.5.1	Transmission dynamics of taeniid eggs with reference to hydatid diseases caused by E. granulosus and E. multilocularis. M. A. Gemmell
VPH/ECHIN.RES./WP/89.6	Prevalence and geographical distribution of E. multilocularis infection in the USSR. T. I. Podoprigora and T. V. Starkova
VPH/ECHIN.RES./WP/89.7	Host species and geographical distribution of E. multilocularis in North America. P. M. Schantz
VPH/ECHIN.RES./WP/89.8.	Not submitted
VPH/ECHIN.RES./WP/89.9	Prevalence and geographical distribution of E. multilocularis infection in humans and animals in Japan. K. Takahashi and K. Furuya
VPH/ECHIN.RES./WP/89.10	Ecological factors influencing prevalence of E. multilocularis in final and intermediate host populations, including man. K. Takahashi and K. Furuya
VPH/ECHIN.RES./WP/89.10.1	Survival of E. multilocularis eggs in the environment and potential mode of transmission. W. Frank

VPH/ECHIN.RES./WP/89.11	Survival of E. multilocularis protoscoleces and antigen production in vitro. H. Auer and H. Aspöck
VPH/ECHIN.RES./WP/89.11.1	Cellular proliferation of E. multilocularis in vitro. A. Dieckmann-Schuppert and W. Frank
VPH/ECHIN.RES./WP/89.12	Serological and parasitological examinations of fox populations for E. multilocularis infections. B. Gottstein, J. Eckert, P. Deplazes, B. Müller and E. Schott
VPH/ECHIN.RES./WP/89.13	Criteria and techniques for Echinococcus strain identification. J. Eckert and R.C.A. Thompson
VPH/ECHIN.RES./WP/89.13.1	Isolation of germinal cells capable of sequentially subculturing from larvel E. multilocularis of man. K. Furuya
VPH/ECHIN.RES.WP/89.13.2	Immunodiagnosis of E. multilocularis infection in human populations. P. Jacquier, B. Gottstein, and J. Eckert
VPH/ECHIN.RES./WP/89.14	Viability testing of E. multilocularis metacestodes from untreated and treated patients. J. Eckert and P. Jacquier
VPH/ECHIN.RES./WP/89.14.1	Clinical efficacy in human alveolar echinococcosis and adverse event profile of albendazole. H. L. Bock and K. Meuser
VPH/ECHIN.RES./WP/89.15	Treatment of experimental E. multilocularis infection with a combination of interferons and mebendazole. V. Schad, T. Pfister, I. Rennet and W. Frank
VPH/ECHIN.RES./WP/89.16	Progress in surgery of human alveolar echinococcosis. D. A. Vuitton
VPH/ECHIN.RES./WP/89.17	Safety precautions for laboratory and field workers. M. Aubert
VPH/ECHIN.RES./WP/89.18	Should alveolar echinococcosis be a notifiable disease? J. Eckert
VPH/ECHIN.RES./WP/89.19	Potential ways of decontaminating food from E. multilocularis eggs and sensitivity of these eggs against physical and chemical methods of disinfection. W. Frank, J. Schäfer, T. Pfister and V. Schad

VPH/ECHIN.RES./WP/89.20	Not submitted
VPH/ECHIN.RES./WP/89.21	Mass praziquantel treatment of dogs for control of *E. multilocularis* on St. Lawrence Island, Alaska. J. F. Wilson, R. L. Rausch and P. M. Schantz
VPH/ECHIN.RES./WP/89.22	Control of alveolar echinococcosis by fox baiting with praziquantel. K. Takahashi
VPH/ECHIN.RES./WP/89.22.1	Control of alveolar echinococcosis by baiting with praziquantel. U. Scheling and W. Frank

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