REPORT OF THE WORKING GROUP ON THE PREVENTION AND CONTROL OF HANTAVIRUS INFECTIONS

Seoul, Republic of Korea
5-6 November 1997

Manila, Philippines
June 1998
REPORT

WORKING GROUP ON THE PREVENTION AND CONTROL
OF HANTAVIRUS INFECTIONS

Convened by:
WORLD HEALTH ORGANIZATION
REGIONAL OFFICE FOR THE WESTERN PACIFIC
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5-6 November 1997

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This report has been prepared by the World Health Regional Office for the Western Pacific for governments of Member States in the Region and for those who participated in the meeting of the Working Group on the Prevention and Control of Hantavirus Infections, which was held in Seoul, Republic of Korea from 5 to 6 November 1997.
SUMMARY

A meeting of the Working Group on the Prevention and Control of Hantavirus Infections was held in Seoul, Republic of Korea from 5 to 6 November 1997. The objectives of the working group meeting were to:

1. review the current epidemiological situation of hantavirus infections worldwide and assess the scope of impact of the disease;
2. review the latest developments in laboratory diagnosis of hantavirus infections;
3. assess the efficacy and safety of newly developed vaccines; and
4. discuss various operational issues regarding wider immunization and the usefulness and feasibility of hantavirus vaccines.

1) Epidemiology

Hantavirus infections are among the important emerging and re-emerging communicable diseases that are of increasing concern in international public health. In the Western Pacific Region, cases of human hantavirus infections were identified among dengue haemorrhagic fever (DHF)-suspected cases for the first time in Viet Nam in 1995.

Based on the current global epidemiological situation of the disease, the prevention and control of hantavirus infections should be a high priority for Member States and WHO. In the meeting, recommendations were made to strengthen preventive and control measures at the global, regional, and national levels in such areas as disease surveillance, rodent control, resources and training, research, laboratory diagnosis, information exchange, and vaccine development.

2) Surveillance and Control of HFRS and HPS

Epidemiological surveillance on hantavirus infections should be strengthened where there may be potential cases of HFRS, HPS or where HFRS/HPS are already known to exist. Serological differential diagnosis on undiagnosed respiratory distress syndrome (RDS) and/or haemorrhagic fever patients in Asia and Eurasia should be made, and unusual symptoms should be carefully monitored. WHO collaborating centres should collaborate with governments and their institutions for hantavirus surveillance if requested. In addition, WHO collaborating centres should be strengthened and expanded to enable them to provide well-documented strains and reagents to requesting laboratories. Where HFRS/HPS outbreaks occur, WHO should collaborate with Member States in the form of technical support to ensure effective control measures.

3) Surveillance and Control of Rodents

Prevention programmes should focus on controlling rodents in the environment, and on educating the community on how to prevent hantavirus infections. Epidemiological studies on reservoir animals (e.g. rodents, bats, wild birds) should be encouraged to increase understanding of the mechanism of the spread of the virus to humans. Surveys on house rats, rats in ports, and laboratory rodents should also be carefully monitored to prevent hantavirus infections from spreading to non-endemic areas.
(4) Resources and Training

In some countries where hantavirus infections have been newly identified, the shortage of resources and technology has been seen as an impediment to the effective control of the disease. Technology transfer for laboratory diagnosis and case management of the disease should be expedited in collaboration with WHO and other institutions worldwide, including WHO collaborating centres.

Training is important for laboratory-based diagnosis, surveillance and case management of hantavirus infections. Training should be provided for health-care workers at the national, provincial and community levels.

(5) Research

Research studies to clarify the pathogenesis of hantavirus infections should continue to be strengthened.

(6) Laboratory Diagnosis

New developments in laboratory diagnostics, as well as further advances in currently used diagnostic methods, were discussed (e.g. IFAT, HDPA, ELISA). Rapid, simple and cost-effective laboratory diagnosis should be of high priority for countries because the proper recognition of HFRS/HPS cases and rodent reservoirs is important in detecting potential HFRS/HPS endemic regions and in understanding rodent-human interactions. The cross-reaction and specific reaction should be clarified for differential diagnosis or serotype or genotype of identification among hantavirus infections. WHO should coordinate the exchange of reference reagents among various institutions to standardize worldwide diagnosis of hantavirus infections. To ensure timely action for outbreaks of hantavirus infections by governments and WHO, it is essential that all countries with epidemic potential possess technology for early diagnosis in advance. Furthermore, procedures for international collaboration on laboratory diagnosis in emergency situations should be coordinated by WHO.

(7) Information Exchange

Information exchange on occurrences of HFRS and HPS among countries should be strengthened to effectively prevent and control hantavirus infections at the global and regional levels. The most appropriate rapid forms of communication for each country should be used (e.g., e-mail, fax, telephone).

(8) Hantavirus Vaccines

The efficacy and safety of the vaccines developed in the Republic of Korea and China, as well as genetically engineered candidate vaccines that are currently under development, were reviewed. Recommendations were made for WHO to provide technical support for all candidate hantavirus vaccines to undergo safety and efficacy trials. It was also recommended that a meeting be held in the near future to discuss a set of international criteria for hantavirus vaccines to become available for widespread distribution. In the meantime, WHO minimum requirements/criteria used for Japanese Encephalitis vaccines should be followed.

(9) Nomenclature of Hantaviruses

As previously recommended in the last working group meeting in 1991, an international standard for nomenclature of hantaviruses based on the International Committee on Taxonomy of Viruses (ICTV) should be used in defining and reporting all hantaviruses.
1. INTRODUCTION

1.1 Objectives

The objectives of the working group meeting were to:

(1) review the current epidemiological situation of hantavirus infections worldwide and assess the scope of impact of the diseases;
(2) review the latest development in laboratory diagnosis of hantavirus infections;
(3) assess the efficacy and safety of newly developed vaccines; and
(4) discuss various operational issues regarding wider immunization and the usefulness and feasibility of hantavirus vaccines.

1.2 Participants

Sixteen temporary advisers from eight countries, one consultant, and four Secretariat members attended the meeting. Three observers were also present.

The group selected Dr Ho Wang Lee as Chairperson, Dr Ana Gligic as Vice-Chairperson, and Dr Connie Schmaljohn as Rapporteur.

The agenda and list of participants are attached as Annexes I and II.

1.3 Organization


1.4 Opening ceremony

The meeting was opened by Dr S.T. Han, Regional Director, WHO Regional Office for the Western Pacific. Dr Han stated that the control of emerging and re-emerging communicable diseases is one of seven priorities for WHO in the Western Pacific Region, and that the prevention and control of hantavirus infections was thus a concern for WHO. With the emergence of hantavirus pulmonary syndrome in 1993 and continual outbreaks of haemorrhagic fever with renal syndrome, he emphasized the global public health problem of hantavirus infections and the importance of the Working Group in strengthening global and regional surveillance and control of hantavirus infections.

2. PROCEEDINGS

2.1 Update on the epidemiological situation of hantavirus infections

2.1.1 Global overview of hantavirus infections

Worldwide, roughly 150 000 people are hospitalized with haemorrhagic fever with renal syndrome (HFRS) every year with a case-fatality rate of 3-15%. A severe form of HFRS
caused by the Hantaan and Belgrade viruses occurs in Asia and the Balkan countries, while a less-severe illness (nephropathia epidemica) caused by the Puumala virus is seen in most European countries, including Russia. The Seoul virus is found worldwide and leads to a moderate form of HFRS. In 1993, a new type of hantavirus infection, hantavirus pulmonary syndrome (HPS), was recognized in the southern part of the United States of America and has since been reported in other states as well as in Central and South America. In the United States, HPS is primarily caused by the Sin Nombre virus, and in Central and South America, the Andes, Juquitiba, and Leguna negra viruses have been identified as aetiologic agents of HPS. Roughly 100 people with HPS are hospitalized each year, with a case-fatality rate of 60-70%. With the availability of various diagnostic tools, there is an increasing recognition of hantaviruses and hantavirus infections worldwide. At present, inactivated hantavirus vaccines against HFRS have been developed in China and the Republic of Korea (further discussed in section 2.3)

2.1.2 Americas region

In 1993, HPS was first recognized in the four corners region of the United States (where New Mexico, Arizona, Colorado, and Utah intersect). Since then, approximately 173 confirmed HPS cases in 28 states of the United States and 20 confirmed HPS cases in 3 Canadian provinces have been reported. Most cases of HPS in North America have been caused by the Sin Nombre virus and the rodent host is the deer mouse, Peromyscus maniculatus. Two cases of HPS have been attributed to infection by the New York virus, the rodent host being the white-footed mouse, Peromyscus leucopus. A single case of HPS has been attributed to the Black Creek Canal virus, the rodent host being the cotton rat, Sigmodon hispidus. Also, the Bayou virus, carried by the rice rat, Oryzomys palustris has caused HPS in two states. In addition to these viruses, at least six other hantaviruses not known to be human pathogens exist in North America: Seoul, Prospect Hill, Isla vista, Mulseshoe, El Moro Canyon, and several distinct Prospect-Hill-like viruses.

In Central and South America, at least 179 confirmed cases of HPS have been reported in five countries: Argentina (108 cases), Paraguay (34 cases), Chile (29 cases), Brazil (6 cases), and Uruguay (2 cases). In Argentina and Chile, HPS was caused by the Andes virus (rice rat, Oligoryzomys longicaudatus). In Brazil, HPS was caused by the Juquitiba virus while in Paraguay, the Leguna negra virus (vesper mouse, Calomys laucha) was known to be the aetiologic agent of HPS. At least five other hantaviruses not yet associated with HPS have been identified in the region: El Moro Canyon virus in Mexico, Rio Segundo virus in Costa Rica, Panchana virus in Peru, Rio Mamore virus in Bolivia, and Cano Delgado virus in Venezuela. The first description of person-to-person transmission of HPS caused by the Andes virus was reported in Argentina.

2.1.3 China

HFRS is considered a major, expanding public health problem in China, where more than 90% of the total number of HFRS cases in the world occur. HFRS was first recognized in the country in 1931, and at present, 28 out of 31 provinces are considered endemic areas for HFRS. During 1950-1995, the total number of HFRS cases in the country was 1 169 570 with 43 458 deaths (CFR=3.72%). The highest incidence occurred in 1986 caused by the Seoul virus (11.08 per 100 000 population). In recent years, 40 000-65 000 cases have been reported annually. In 1995 and 1996, 62 754 cases and 630 deaths and 43 399 cases and 411 deaths were reported respectively. The Hantaan virus (Apodemus agrarius) and the Seoul virus (Rattus norvegicus) cause HFRS in the country. Besides the commonly recognized mode of transmission via contact with rodents, gamasid mites and chiggermites have also been reported by Chinese scientists as potential vectors and reservoir hosts of Hantaan and Seoul viruses. Vertical transmission has also been found in pregnant patients of HFRS and in reservoir hosts. Three kinds of inactivated
vaccines of HFRS have been developed in China—the golden hamster kidney cell (GHKC), the Mongolian gerbil kidney cell (MGKC), and the purified suckling mouse brain (PSMB) vaccine. These are further described in section 2.3. The current prevention and control strategy of HFRS in China is a combination of rodent control and vaccination in highly endemic areas.

Morbidity and Case-Fatality Rates of HFRS in China

<table>
<thead>
<tr>
<th>Period</th>
<th>Number of Cases</th>
<th>Morbidity (/100 000)</th>
<th>Number of Deaths</th>
<th>Case-Fatality Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1950-1959</td>
<td>3 568</td>
<td>0.02 - 0.03</td>
<td>297</td>
<td>8.3</td>
</tr>
<tr>
<td>1960-1969</td>
<td>23 764</td>
<td>0.1 - 0.5</td>
<td>3 597</td>
<td>15.1</td>
</tr>
<tr>
<td>1980-1989</td>
<td>696 074</td>
<td>3.12 - 11.08</td>
<td>22 876</td>
<td>3.3</td>
</tr>
<tr>
<td>1990-1995</td>
<td>302 215</td>
<td>3.55 - 5.16</td>
<td>5 286</td>
<td>1.7</td>
</tr>
</tbody>
</table>

2.1.4 Finland and surrounding countries

In Finland and Sweden, approximately 200 to 1000 HFRS cases are reported annually, while in Russia, several thousand HFRS cases are diagnosed each year. The Puumala and Belgrade (Dobrava) viruses are known to cause HFRS in Europe. The Puumala virus occurs widely in Europe and its reservoir host is the bank vole, *Clethrionomys glareolus*. *Nephropathia epidemica*, a mild form of HFRS caused by the Puumala virus, is endemic in Scandinavia, European Russia, and in the Balkans. The Belgrade/Dobrava virus causes severe HFRS, and is found mainly in the Balkans (including Bosnia and Herzegovina), Estonia, and Russia, and the reservoir hosts are the yellow-necked mouse, *Apodemus flavicollis* and the striped field mouse, *Apodemus agrarius*. Other hantaviruses, such as the Tula and Topografov viruses have not been associated with human hantavirus infections in Europe. The Department of Virology, Haartman Institute, University of Helsinki; and the Swedish Institute of Infectious Disease Control, Stockholm are qualified to act as European reference centres to which samples from problem cases can be sent.

2.1.5 Japan

Since 1960, Japan has experienced two epidemics of Seoul-type hantavirus infections. The first epidemic was reported during 1960-1970 in Osaka city, and 119 cases and 2 deaths were reported. The reservoir host was the urban rat. The second epidemic was reported from 1970 to 1984, and a total of 126 cases and 1 death were reported from 21 institutions throughout the country. Laboratory rats were associated with this infection. Since 1985, no HFRS cases have been reported in Japan. However, urban rat colonies contaminated with the Seoul virus have been identified in international port areas. In addition, antigenically and genetically related Puumala virus infections were found among indigenous rodents (mainly *Clethrionomys refocanus*) in Hokkaido in 1993.

2.1.6 Republic of Korea

In 1951, the first case of HFRS was reported in the Republic of Korea among United Nations troops during the Korean War. In 1976, the Hantaan virus was isolated and identified and since then, the disease has been sporadically occurring not only among military troops along the Demilitarised Zone (DMZ) region, but also among civilians living elsewhere in the country. Among military troops, there had been over 100 HFRS patients until the 1980s; since then, cases
have decreased with 30 HFRS patients in 1995. As for HFRS occurrence in the entire country, the incidence rate was highest in 1977 (4.8/1,000,000) and had decreased to a rate lower than 2.0/1,000,000 by 1979. The incidence rate was roughly 1.0-2.0/1,000,000 in the 1980s. However, the actual number of HFRS cases appears to be much higher than the number of reported cases. In the Republic of Korea, wild rodents carrying the hantavirus consist of Apodemus agrarius (70-80%), Microtus fortis (10%), Crocidura lasiura (7-8%), and others (3%). Wild birds, bats, cats, squirrels, and domestic ducks have also been found to carry the hantavirus. An inactivated vaccine against the Hantaan virus has been developed and used since 1990. Further research is required concerning mode of transmission and effective and safe vaccine production.

2.1.7 Russia

Among zoonotic virus infections, HFRS is a leading cause of morbidity in Russia. In 1930, HFRS was recognized in Russia, and since 1978, the disease has been considered a notifiable disease. Between 1978 and 1996, a total of 91,603 cases were registered from 61 of the 89 administrative regions in the country. Of these, 88,322 cases (96.4%) were from the European part (46 of the 60 administrative regions) and 3,281 cases (3.6%) were from the Asian part of the country (15 of the 29 administrative regions). Annual average morbidity rates were 4.0 and 0.6 per 100,000 population respectively. As of October 1997, HFRS morbidity rates increased 3.5 times in the country and more than 5 times in certain administrative regions of European Russia since 1996. Although distribution of HFRS occurrence is scattered throughout the country, the highest morbidity rates are found in the Ural, Volga, and Viatka territories. Among these territories, the Bashkiria region has the highest HFRS morbidity rate in Europe. As of September 1997, 4377 cases of HFRS (CFR = 0.6%) caused by the Puumala virus have been reported from this region this year. Also, Orenburg has reported 122 serologically confirmed cases of HFRS this year. The hantavirus antigen has been found in 47 species of mammals and 13 species of birds in the country, and at least six types of hantavirus are known to exist in Russia: Hantaan, Puumala, Seoul, Tula, Khabarovsk, and Taimyr (or Topografov). In the European and Siberian parts, the Puumala virus (Clethrionomys glareolus) is the primary aetiological agent of HFRS while in Far-Eastern Russia, the Hantaan virus (Apodemus agrarius and Apodemus peninsulae) is common. HFRS human infection caused by the Seoul virus has been confirmed by virus isolation and serology from a HFRS outbreak of 50 cases in the European part and serologically among patients from the Far-Eastern part of the country.

2.1.8 Viet Nam

Until 1995, no human cases of HFRS had been reported in Viet Nam. In 1995, a preliminary serological investigation was carried out in some areas in southern Viet Nam. Seventy-eight human serum samples with haemorrhagic fever syndrome were found negative for dengue antibodies and tested positive for hantavirus antigens. 26.9% of the human serum samples were found positive for IPH (Seoul, Puumala and Hantaan) antigens and 35.9% were positive for the HTN (Hantaan) antigen based on the IgG-capture ELISA test. The positive sera were sent to Pasteur Institute Paris for the IgM-capture ELISA and IFA tests. Such preliminary results have shown that hantavirus associated with HFRS have been in circulation in southern Viet Nam.

2.1.9 Yugoslavia

Since 1952, when the first HFRS cases were reported in former Yugoslavia, sporadic cases and epidemics of clinically mild and severe forms of the disease have been recorded annually throughout the country (Annex 4). More than 6000 HFRS cases have been reported in the country, with mortality rates of 1%-16% during epidemics and 33% out with epidemics. In 1961, the first recognized HFRS epidemic occurred west of Belgrade among military soldiers.
In 1967, the second HFRS epidemic occurred in Bosnia and Herzegovina, Croatia, and Montenegro, with 200 cases and a case-fatality rate of 2.5%. In 1986, an HFRS outbreak occurred in all six republics and two provinces of former Yugoslavia. There were 161 serologically confirmed cases and 11 deaths (CFR=6.8%). In 1989, a major outbreak was reported in Bosnia and Herzegovina and in Serbia and Croatia. HFRS was serologically confirmed in 226 individuals out of 609 suspected cases. The last epidemic occurred in 1995 in Bosnia and Herzegovina and Serbia and Montenegro. Roughly 3000 people were estimated to be infected with the hantavirus during this epidemic. HFRS in the Balkan countries is caused by the Hantaan, Belgrade, Puumala, Tula, and Seoul viruses and common reservoirs in the country include the Norway rat (Rattus norvegicus, 66.6%), the bank vole (Clethrionomys glareolus, 57%), Microtus arvalis (50%), the yellow-necked mouse (Apodemus flavicollis, 46.5%) as well as other rodents.

During 1996-1997, an epidemiological study of the Hantavax vaccine (Green Cross Co. Korea) against the Hantaan virus was carried out among adults living in several HFRS-endemic areas in the country. Two thousand adults were given two doses of vaccine in these areas. Clinical responses were observed and antibodies against the Hantaan virus were examined at different levels. No remarkable adverse reactions to the vaccinees were reported. Antibodies against the Hantaan virus were examined by the immunofluorescence (IF) test a month after the first dose and a month after the second dose of vaccination; results have shown that the seroconversion rates were 46.8% and 77.8%, respectively. Antibody responses of vaccinees after the third dose of vaccination after one year is currently being studied. Preliminary results have shown that no confirmed cases of HFRS were observed among the vaccinees.

2.2 Update of laboratory diagnosis

Serological diagnosis of hantavirus infections is of importance as two-thirds of patients with hantavirus do not show hemorrhagic manifestations. Such diagnoses can be made by demonstrating a rise of antibody titre to hantaviruses. Five serological tests against hantavirus infections are currently available, such as the hemagglutination inhibition (HI), IgG/IgM enzyme-linked immunosorbent assay (ELISA), and indirect immunofluorescence antibody (IFA) tests. Recently, a simple rapid diagnostic test was developed for Hantaan, Seoul, and Puumala virus infections using high-density particle agglutination (HDPA) coated with purified Hantaan virus antigen that can be used in the field (Lee et al.). These kits have been found to be specific with higher sensitivity than the IFA test. Similar kits have been developed for Hantaan, Sin Nombre, and Puumala virus infections. ELISA tests are also simple, rapid, and sensitive tests. Also, the polymerase chain reaction (PCR) can be used for laboratory diagnosis but is not effective for large-scale epidemiological surveillance. Although PCR identifies hantaviruses before virus isolation, live virus isolation and storage is still essential for virus reference and characterization. Commercial laboratory diagnostic kits are available in China, the Republic of Korea and Russia.

2.3 Update of vaccines

At present, vaccines against HFRS have been developed and used in China and the Republic of Korea. In the Republic of Korea, a formalin inactivated suckling mouse brain-derived Hantaan virus vaccine has been developed which is commercially available in the country (Lee et al.). As of 1996, more than seven million doses of this vaccine have been given to people in the country, including soldiers. A month after vaccination, 79% of subjects developed hantavirus antibody titre by IFA and 62% by ELISA. A month after booster vaccination, seroconversion rates increased to 97%. Likewise, 13% of vaccinees produced neutralizing antibody a month after the first vaccination with an increase to 80% after the booster dose. Re-vaccination a year later produced antibody titres in 94%-100% of vaccinees while only 50% of the vaccinees produced neutralizing antibodies. The persistence of
antibodies after immunization suggest that a booster vaccination after one year is necessary for the maintenance of protective antibodies against the Hantaan and Seoul virus. Field-efficacy trials of this vaccine are currently in progress. An inactivated Hantaan and Puumala virus combination vaccine derived from inactivated suckling mouse and suckling hamster brain extracts with formalin has also been developed in the country. Field-efficacy trials of this vaccine in HFRS-endemic areas are needed for evaluation. An inactivated experimental Sin Nombre vaccine has also been developed recently.

In China, three kinds of inactivated vaccines have been developed and licensed for mass production: the Golden hamster kidney cell (GHKC), the Mongolian gerbil kidney cell (MGKC), and the Purified suckling mouse brain (PSMB) vaccine. Since the last working group meeting, the Phase III clinical trials of these vaccines have been conducted. Trials for the GHKC Seoul-type vaccine show that among the 40 757 people who were vaccinated, the overall protection rate was 97.63% after one year and 88.73% after two years. For the MGKC Hantaan-type vaccine, 61 231 people were vaccinated and the overall protection rate was 93.2% after one year and 92.17% after two years. Among the 26 492 people vaccinated with the PSMB vaccine, overall protection rate was 96.21%. Results of the trial are shown in the following table:

<table>
<thead>
<tr>
<th>Type of Vaccine</th>
<th>Vaccines</th>
<th>Number of Cases</th>
<th>Infectivity Rate (%)</th>
<th>Control Group</th>
<th>Number of Cases</th>
<th>Infectivity Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MGKC</td>
<td>61 231</td>
<td>3</td>
<td>6.80</td>
<td>204 779</td>
<td>214</td>
<td>114.7</td>
</tr>
<tr>
<td>PMB</td>
<td>26 492</td>
<td>1</td>
<td>3.79</td>
<td>35 007</td>
<td>33</td>
<td>101.3</td>
</tr>
<tr>
<td>GHKC</td>
<td>40 757</td>
<td>1</td>
<td>2.37</td>
<td>47 313</td>
<td>52</td>
<td>109.9</td>
</tr>
</tbody>
</table>

In the United States of America, a recombinant vaccinia Hantaan virus vaccine has been developed. The Phase I clinical trials conducted at the Army Research Institute of Infectious Diseases (USAMRIID) showed that neutralizing antibodies could be elicited in vaccinia-naive individuals, but only in some of the vaccinia-immune individuals. In the Phase II clinical trials conducted among United States soldiers stationed in the Republic of Korea, results showed that neutralizing antibodies could be elicited in the majority of vaccinia-naive individuals, but only 20% of vaccinia-immune individuals. Multivalent nucleic acid-based vaccines for hantaviruses are currently being studied.

3. CONCLUSIONS AND RECOMMENDATIONS

The Working Group made the following conclusions and recommendations:

(1) Epidemiology

Hantavirus infections are among the important emerging and re-emerging communicable diseases that are of increasing concern in international public health. Hantavirus infections are distributed all over the world, and the emergence of hantavirus pulmonary syndrome (HPS) in the Americas in 1993 poses an international threat via international travel and trade, including the trade of experimental animals. In the Western Pacific Region, cases of human hantavirus
infections were identified among dengue haemorrhagic fever (DHF)-suspected cases for the first time in Viet Nam in 1995.

Based on the current global epidemiological situation of the disease, the prevention and control of hantavirus infections should be a high priority for Member States and WHO. In the meeting, recommendations were made to strengthen preventive and control measures at the global, regional, and national levels in such areas as disease surveillance, rodent control, resources and training, research, laboratory diagnosis, information exchange, and vaccine development.

(2) Surveillance and control of HFRS and HPS

Epidemiological surveillance on hantavirus infections should be strengthened where there may be potential cases of HFRS/HPS or where HFRS/HPS are already known to exist. Serological differential diagnosis on undiagnosed respiratory distress syndrome (RDS) and/or haemorrhagic fever patients in Asia and Eurasia should be made, and unusual symptoms should be carefully monitored. WHO collaborating centres should collaborate with governments and their institutions for hantavirus surveillance if requested. In addition, WHO collaborating centres should be strengthened and expanded to enable them to provide well-documented strains and reagents to requesting laboratories. Where HFRS/HPS outbreaks occur, WHO should collaborate with Member States in the form of technical support to ensure effective control measures.

(3) Surveillance and control of rodents

Prevention programmes should focus on controlling rodents in the environment, and in educating the community on how to prevent hantavirus infections. Epidemiological studies on reservoir animals (e.g. rodents, bats, wild birds) should be encouraged to increase understanding of the mechanism of the spread of the virus to humans. Surveys on house rats, rats in ports, and laboratory rodents should also be carefully monitored to prevent hantavirus infections from spreading to non-endemic areas.

(4) Resources and training

In some countries where hantavirus infections have been newly identified, the shortage of resources and technology has been seen as an impediment to the effective control of the disease. Technology transfer for laboratory diagnosis and case management of the disease should be expedited in collaboration with WHO and other institutions worldwide, including WHO collaborating centres.

Training is important for laboratory-based diagnosis, surveillance and case management of hantavirus infections. Training should be provided for health-care workers at the national, provincial and community levels. Training can be provided in the form of lectures and workshops with audio-visuals and printed materials on laboratory and clinical diagnosis and the prevention and control of hantavirus infections.

(5) Research

Research studies to clarify the pathogenesis of hantavirus infections should continue to be strengthened.

As there is a possibility of person-to-person transmission of the hantavirus pulmonary syndrome (HPS), follow-up surveys and monitoring should be carefully conducted in this area.
(6) Laboratory diagnosis

New developments in laboratory diagnostics, as well as further advances in currently used diagnostic methods, were discussed (e.g. IFAT, HDSA, ELISA). Rapid, simple and cost-effective laboratory diagnosis should be of high priority for countries because the proper recognition of HFRS/HPS cases and rodent reservoirs is important in detecting potential HFRS/HPS endemic regions and in understanding rodent-human interactions. The cross-reaction and specific reaction should be clarified for differential diagnosis or serotype or genotype of identification among hantavirus infections. WHO should coordinate the exchange of reference reagents among various institutions to standardize worldwide diagnosis of hantavirus infections. To ensure timely action for outbreaks of hantavirus infections by governments and WHO, it is essential that all countries with epidemic potential possess technology for early diagnosis in advance. Furthermore, procedures for international collaboration on laboratory diagnosis in emergency situations should be coordinated by WHO.

(7) Information exchange

Information exchange on occurrences of HFRS and HPS among countries should be strengthened to effectively prevent and control hantavirus infections at the global and regional levels. The most appropriate rapid forms of communication for each country should be used (e.g. e-mail, fax, phone).

(8) Hantavirus vaccines

Since the previous working group meeting on HFRS in 1991, further advances have been made in the area of inactivated vaccines developed in China and the Republic of Korea. Large scale vaccine field trials for these vaccines have been conducted and are currently still in progress. As of 1996, more than seven million doses of hantavirus vaccine have been given to people in the Republic of Korea, including soldiers. In addition, an attempt has been made to develop experimental multivalent vaccines for hantavirus infections in China and the Republic of Korea. Further research is needed in the development of multivalent vaccines for use in regions where multiple hantaviruses circulate. In China, three kinds of inactivated vaccines against HFRS have been developed. The GHKC (Golden hamster kidney cell), MGKC (Mongolian gerbil kidney cell), and PSMB (Purified suckling mouse brain) vaccines have proved to be safe and highly effective, but immunogenicity of these vaccines must be increased. Large-scale field trials have been conducted and the efficacy of these vaccines has been demonstrated.

The efficacy and safety of the vaccines developed in China and the Republic of Korea, as well as genetically engineered candidate vaccines that are currently under development, were reviewed. Recommendations were made for WHO to provide technical support for all candidate hantavirus vaccines to undergo safety and efficacy trials. It was also recommended that WHO/WPRO organize a meeting in the near future to discuss a set of international criteria for hantavirus vaccines to become available for widespread distribution. In the meantime, WHO minimum requirements/criteria used for Japanese Encephalitis vaccines should be followed.

(9) Nomenclature of hantaviruses

As previously recommended in the last working group meeting in 1991, an international standard for nomenclature of hantaviruses based on the International Committee on Taxonomy of Viruses (ICTV) should be used in defining and reporting all hantaviruses.
INFORMATION BULLETIN NO. 2

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WORKING GROUP ON PREVENTION AND CONTROL OF HANTAVIRUS INFECTIONS

WPR/OCD/CDS(2)/97.1
25 October 1997
ENGLISH ONLY

Seoul, Republic of Korea
5-6 November 1997

AGENDA

1. Opening ceremony
2. Adoption of agenda
3. Overview of hantavirus infections: A growing problem
4. Update on current worldwide epidemic situation of hantavirus infections (HFRS and HPS)
5. Update on recent development of laboratory diagnosis on hantavirus infections
6. Update on hantavirus vaccines
7. General discussion
8. Preparation of conclusion
9. Conclusion
10. Closing ceremony
PROGRAMME OF ACTIVITIES

Wednesday, 5 November 1997

1330 - 1400 - Registration

1400 - 1430 - Opening Ceremony
- Dr S. T. Han, Regional Director, WHO/WPR

Election of Chairperson, Co-chairperson and Rapporteurs

Group Photograph

1430 - 1600 - Update on Current Worldwide Epidemic Situation of Hantavirus Infections (HFRS and HPS)
- Dr C. Schmaljohn - Americas Region
- Dr Song Gan - China
- Dr A. Vaheri - Finland

1600 - 1615 - Coffee Break

1615 - 1715 - Update on Current Worldwide Epidemic Situation of Hantavirus Infections (HFRS and HPS) (con’t)
- Dr J. Arikawa - Japan
- Dr J.S. Kim - Korea
Thursday, 6 November 1997

0830 - 1000 - Update on Current Worldwide Epidemic Situation of Hantavirus Infections (HFRS and HPS) (con't)
  - Dr E. Tkachenko - Russia
  - Dr Do Quang Ha - Viet Nam
  - Dr A. Gligic - Yugoslavia

1000 - 1015 - Coffee Break

1015 - 1145 - Update on Recent Development of Laboratory Diagnosis on Hantavirus Infections
  - Dr J. Arikawa - Japan
  - Dr T. Tomiyama - Japan
  - Dr H.W. Lee - Korea

1145 - 1300 - Lunch

1300 - 1500 - Update on Hantavirus Vaccines
  - Dr C.N. Ahn - Korea
  - Dr H.W. Cho - Korea
  - Dr C. Schmaljohn - Americas Region
  - Dr Hung Tao - China

1500 - 1515 - Coffee Break

1515 - 1615 - Preparation of Conclusion

1615 - 1645 - Adoption of the Conclusion

1645 - 1700 - Closing Ceremony
- Distribution of hemorrhagic fever with renal syndrome cases in the six republics and two provinces of Yugoslavia during a nationwide epidemic in 1978. Each serologically confirmed case was serotyped A, Hanan serum type; *, fatal case with Hanan serotype; O, Puumala serum type; #, fatal case with Puumala serotype and displayed according to the month of occurrence.