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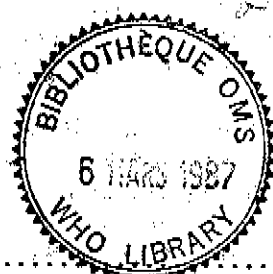
Q fever

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REPORT OF WHO WORKSHOP ON Q FEVER

Giessen, 2 - 5 September 1986

Germany, Fed. Rep. of



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I. Introduction

Q fever is one of the zoonoses which attracts relatively little attention because of the assumed low disease incidence in both man and animals. Q fever infection is generally believed to be mainly asymptomatic. However, new findings about the epidemiology of infection in animals and Q fever-associated clinical syndromes in man, including serious chronic diseases, call for a review of the situation.

With the support of the Government of the Federal Republic of Germany and the Faculty of Veterinary Medicine of the University of Giessen, the World Health Organization convened a Workshop on Q Fever in Giessen from 2-5 September 1986. Dr K. Bögel welcomed the participants (see Annex 1) on behalf of Dr H. Mahler, Director-General of the World Health Organization. He pointed out that the workshop should serve two major purposes: firstly, to give guidance to public health workers at government and district levels on the diagnosis, surveillance, prevention and treatment of Q fever, and secondly, to formulate proposals for further collaborative research between national laboratories.

Recommendations made in 1967 by the Joint FAO/WHO Expert Committee on Zoonoses¹ require updating in respect of Q fever. The WHO Expert Committee on Bacterial and Viral Zoonoses² which met in 1982 concentrated on the planning and management of intersectoral collaboration in disease prevention and control, and this should be seen in conjunction with the following report.

Professor H. Krauss was elected Chairman, with Professor I.V. Tarasevich as Vice-Chairman of the meeting. Dr I.D. Aitken was appointed Rapporteur.

II. National Reports

The contributions in this session assessed the past and present position regarding Q fever in four countries of Eastern Europe and six in Western Europe. Although some points of difference emerged there was a common view that Coxiella (C.) burnettii infections of man and animals merit continued surveillance and research, both as a zoonosis and as a potential threat to livestock production.

In the four countries of Eastern Europe, Q fever was first reported in the late 1940's and early 1950's. All the early cases occurred in people having occupational links with animals or animal products. In consequence of its wide distribution in the USSR, Q fever became a notifiable disease in 1957. Medical records and epidemiological investigations over the last

¹ WHO Technical Report Series, No. 378, 1967

² WHO Technical Report Series, No. 682, 1982

30 years reveal that geographic distribution of Q fever has remained stable with sheep, goats and grazing cattle being important sources of infection. Whilst those working with animals or their products are particularly at risk, cases also occur amongst non agricultural workers moving into endemic areas.

During the 1950's to 1970's several outbreaks and small epidemics of Q fever occurred in Rumania. Most affected individuals had an occupational link with animals but those handling excreta were more frequently involved than dairy workers. Within the last few years the disease has become sporadic, the number of reported cases has declined and only a minority are linked to an animal source.

In Hungary, most of the 87 documented cases of human disease caused by C. burnetii have been traced to an animal source. Whereas atypical pneumonia was a common feature in the past, more recent sporadic cases have involved granulomatous hepatitis. Amongst livestock, C. burnetii has been incriminated as the cause of sporadic bovine abortion and of more serious outbreaks of abortion in sheep.

Over the last 35 years most parts of Czechoslovakia have experienced Q fever. Of particular note were outbreaks in factories processing imported cotton, wool and hides that had been contaminated in their countries of origin. Currently, C. burnetii appears to be dormant in areas where ticks are not present as only sporadic cases are encountered. Cattle vaccination practised since 1980 may have contributed to the decreasing incidence of human Q fever.

Variable epidemiological patterns have been observed in Western European countries. In Italy, epidemics of Q fever occurred in the late 1950's but now the disease occurs sporadically. Only 17 cases were reported in 1984, the majority without any evident animal contact. However, serological evidence of infection in some 3 % of humans and 5 - 20 % of sheep suggests that the reported incidence of human Q fever is under estimated. Similar underreporting is suspected in France as serological surveys revealed a seropositive rate of 1 - 4 % in the general population of one rural area rising to 26 % among livestock breeders and 36 % among veterinary personnel without any record of clinical illness. Despite the evidence of common infection with C. burnetii 133 cases of Q fever were confirmed between 1982 and 1985, amongst which were 38 cases with chronic disease.

Over the last 20 years in the Federal Republic of Germany small outbreaks and sporadic cases of Q fever have involved 27 - 100 people per year with a strong bias to the southern states. There is also an increased seroprevalence of C. burnetii antibodies in the human population. On the basis of serological evidence, infections in livestock have increased, especially in cattle. C. burnetii has been incriminated in bovine infertility problems.

In the Netherlands, recent serological surveys have yielded evidence of infection in the general population and particularly amongst high risk

groups. Cattle are infected, dairy cows twice as commonly as non dairy cattle while the infection rate in sheep is 3.5 % and that in goats is negligible. Since Q fever was made notifiable in 1976 the number of cases has risen from 3 in 1977 to an average of 26 in each of the last 3 years.

Q fever was first reported in Britain in 1949 and in Ireland almost 20 years later. In each country, cattle and sheep are known to be infected but no significant role has been ascribed to C. burnetii as a cause of disease in these species. Each year in Britain some 100 cases of human Q fever are encountered. Most of these are sporadic and without clear animal associations.

III. Epidemiology and Nonspecific Methods of Control

Q fever is a disease of world wide distribution. The infection caused by C. burnetii constitutes a public health hazard and sometimes a problem in livestock.

C. burnetii is an obligate intracellular bacterium which infects man, other vertebrates and ticks and other arthropods. It resides and multiplies within phagolysosomes or vesicles of various cell types including the trophoblasts of the epithelial cell lining of the ruminant placenta. In the tissues and cells of ticks C. burnetii grows to very high titres. Up to 10^{10} organisms per g have been recovered from faeces of experimentally infected ticks. The organism exhibits a phenomenon of phase variation occurring as two antigenically distinct forms known as phase I and phase II. This is comparable to the smooth-rough variation in bacteria. In nature and in laboratory animals C. burnetii exists exclusively in phase I, but prolonged passage through embryonated eggs results in conversion to phase II.

The epidemiology of C. burnetii infection is influenced by the agent's high degree of resistance to physical and chemical agents, comparable to that of sporogenic bacteria. This resistance might be attributable to endospore-like forms which may be generated during reproduction and account in part for the high risk of infection. At 4°C viability is retained for one or more years in dried fomites such as tick faeces or wool, as well as in sterile skimmed milk or unchlorinated water. Meats remain infected for at least one month.

Following its initial description in Australia in 1937 and subsequently in the USA, Q fever remained an exotic disease but during the second World War severe epidemics of Q fever occurred amongst military personnel of various armies in the Mediterranean area. Later C. burnetii was found to be prevalent throughout Europe with the exception of the Scandinavian countries.

In nature C. burnetii has been found primarily in a cycle involving ticks and free-living vertebrates. From this cycle it is transmitted to

domestic animals either by ticks (many species of ticks may carry the organism) or indirectly through contact with their infected excreta. Different species of ticks are the vectors in different geographical areas of Europe. Tick-independent cycles of infection can develop within populations of domestic animals, especially cattle. In some states of Europe, for instance in the Federal Republic of Germany, a steep rise in the prevalence of infection in cattle has been found in recent years. Up to 30 % of all herds investigated and 80 % of those with infertility problems have been found to contain shedders of the agent. In tick-infested areas sheep and goats constitute a particular risk. Tick faeces, heavily infected with C. burnetii, can contaminate the fleece and infect man or animals.

In the infected ruminant the organism is shed in vast numbers at parturition and can be found throughout the body and in the excreta, both faeces and urine. Abortion is seldom a consequence of infection but may occur. Due to multiplication of the agent in the trophoblasts of the placental villi, placenta and birth fluids contain large amounts of coxiellae which, during parturition, contaminate the ground and the surroundings. Coxiellae are also present in the milk. Shedding through milk may be continuous or intermittent for one or more periods of lactation. Seropositive cows must be considered potential shedders, but animals seronegative by some tests may also be infected and shed the agent. In some areas, up to 50 % of dairy cows have been found to excrete the agent in milk. Individual milk samples may contain up to 10^5 or more guinea pig infectious doses per ml. By proper pasteurization (see later) C. burnetii is inactivated. Dairy products prepared from unpasteurized milk may harbour viable C. burnetii for one to two months.

Where lambing management is intensive, large numbers of coxiellae may contaminate the environment, increasing the risk of infection. Since the organism is highly resistant and little affected by extreme environmental conditions (drought, humidity, low or high temperature) it can form a highly infectious dust. A clear relationship between dry weather, strong wind, and the spreading of infection in dust from a variety of animal sources has been reported many times.

Dogs or cats, especially strays, can become infected by ticks and by eating contaminated placental membranes or prey. In such cases, coxiellae can pass intact through the gut and be spread over a large area by the faeces of these carnivores. However, these animals are themselves infected by the agent and their role in the epidemiology of Q fever is not yet fully elucidated. However, there are some confirmed cases of human infection acquired from dogs and cats. In seroepidemiological investigations, for instance in two areas of Switzerland, 29 and 45 % of dogs, respectively, have been found to carry antibodies against C. burnetii; in another survey in the Federal Republic of Germany 13 % of dogs and 22 % of cats were seropositive.

Infection of both wild and domestic birds has been demonstrated especially in pigeons and sparrows. Compared to mammals birds probably play a minor role in the natural history of Q fever but the matter needs further

investigation.

In some countries where Q fever is endemic and cases are continuously encountered the disease in man does not show any considerable yearly fluctuation. In contrast, the antibody prevalence rate has increased significantly in cattle in Central Europe and in sheep and goats in Eastern Europe. Infection acquired from these small ruminants has been associated particularly with chronic Q fever in humans. This association should be studied in more detail. In some countries, after an epidemic the incidence of human disease has diminished. These phenomena indicate differences in ecologic conditions that need further clarification.

Ticks seem to play a central role in maintaining the viability of C. burnetii in nature. Outbreaks of human Q fever in areas where ticks are not present tend to be of limited duration without recurrence although sporadic cases may arise. In contrast, outbreaks in tick infested areas may involve repeated episodes of Q fever, sporadic in the local population but tending to outbreaks involving susceptible individuals including newcomers to the area.

Movement of livestock from localities where C. burnetii infection is present to previously unaffected areas can result in the appearance of Q fever in these areas. This is a factor to be considered in the control of infection. In non-tick areas occurrence of C. burnetii in mammalian hosts, e.g. cattle, may still be associated with high prevalence of infection in these animals but usually without outbreaks in humans. However problems of herd infertility have been encountered in these circumstances.

By far the commonest route of infection leading to clinical disease is by inhalation of infected dust or aerosols. Ingestion of contaminated food such as milk can result in infection and seroconversion and in some circumstances may trigger disease. These special circumstances require to be defined. Those in contact with animals or their products are most likely to become infected (farmers, veterinarians, abattoir workers, etc). Infections are detected in 30 to 70 % of exposed persons; thus, many infections remain undiagnosed. The discrepancy between the number of persons found serologically positive and the relatively low incidence rate of the disease implies that the infection is often of mild or inapparent nature. On the other hand, the data also suggest that Q fever is probably underreported. Common source and large scale outbreaks which may signify exposure to particularly high concentrations of the agent provide evidence of rates above 50 % for infection accompanied by relatively severe clinical symptoms.

Human to human transmission cannot be excluded. Large numbers of coxiellae may be found in the placentae and milk of women who experienced infection prior to parturition. The risk of lactogenic transmission of infection needs to be evaluated.

In some areas Q fever continues to be a significant problem that needs attention, particularly in relation to occupationally exposed indivi-

duals. Not only people exposed to infected ruminants but also those in close contact with infected dogs and cats should be considered. However, the definitive role of these small animals and other pets as reservoirs for human Q fever still needs to be determined. Repeated seroepidemiological investigations of defined groups of the human population are required.

Some control methods that have proved effective are as follows:

1. Adoption of general hygienic precautions including the provision of separate facilities for animal parturition.
2. Placental membranes suspected of harbouring *C. burnetii* must be destroyed and not left in the open air.
3. To protect abattoir workers special precautions are recommended during slaughtering of known infected animals. Mammary glands and inner organs should be carefully removed and destroyed. Skins must be kept wet until salting.
4. Heat treatment of milk is a measure that can be applied easily and should be mandatory. Pasteurization using the high-temperature short-time (HTST) method with a temperature of 74°C for 15 seconds inactivates the agent.
5. Where feasible, the tick population should be reduced by non chemical habitat control (e.g. removal of shrubbery) and livestock protected against infestation by dipping or spraying with approved acaricidal preparations.

The group participants noted that in the USSR and Czechoslovakia considerable importance is attached to epidemiological surveillance of zoonotic infections in human and animal populations. With respect to *C. burnetii* these measures involve control of morbidity, early diagnosis, studies of the immunostucture of human and livestock populations, monitoring habitats in foci of infection including the detection of the agent in ticks. The extent to which these procedures can be adopted by other countries will depend upon individual circumstances.

IV. Human Infection and Treatment

Human infection may be subclinical, acute or chronic.

Acute Q Fever

Clinically apparent cases usually present as influenza-like syndromes sometimes accompanied by signs of pneumonia and/or hepatitis. The incubation period usually ranges from 2 - 4 weeks. The onset is often quite sudden, with fever, shivering, malaise, myalgias, severe frontal headache, and photophobia. The headache may become generalized and continue

throughout the disease. Fever usually lasts for 1 - 2 weeks. A weight loss may occur and persist. Auscultation is usually normal but chest radiographs reveal that 30 - 50 % of Q fever patients have interstitial pneumonia. The typical lesion consists of a "ground-glass" change. A major proportion of patients have abnormal liver function tests. Jaundice may occur. As the infection is systemic, several other organs may be affected and give clinical signs and pathological changes accordingly. Recovery to good health can take several months.

C. burnetii is sensitive to the tetracyclines and their derivatives. There have been reports of the successful treatment of Q fever with cotrimoxazole and erythromycin. Doxycycline is possibly the most active tetracycline against C. burnetii. Treatment should continue for at least three days after remission of fever.

Chronic Q fever

Experiments with animals have shown that C. burnetii persists for long periods in tissues such as mammary gland, liver, spleen, lymph nodes, kidney, bone marrow and brain. Isolation of C. burnetii from cardiac valves and liver from human patients with chronic Q fever indicates that the agent can also persist in man. The mechanism of escape from the host defence is still unclear. The role of sporogenic differentiation remains to be determined. Recent experiments have indicated that T-cell unresponsiveness may also be involved. Autoimmune phenomena may participate in the pathological process since IgM rheumatoid factor is frequently present in sera from patients with chronic Q fever but usually not in sera from patients with acute disease.

Chronic infection with C. burnetii may present as a specific endocarditis and/or a chronic granulomatous hepatitis. In the USSR pneumonic fibrosis is also associated with chronic Q fever. Q fever endocarditis has been recognized for over 25 years. It may follow a clinically apparent or inapparent infection and mainly affects the mitral or aortic valves. Previous rheumatic heart disease or aortic stenosis or calcification are predisposing factors. The interval between the primary coxiella infection and the clinical onset of endocarditis varies from six months up to even ten years and more. There may be a low grade fever, night sweats, anaemia, joint pains, liver dysfunction and heart murmur. Microcolonies of C. burnetii are found in the vegetations on the valves or endocardium. Upon histopathological investigation, the microcolonies in heart valve vegetations rarely appear to be inside the cells.

C. burnetii was isolated from aortic valve vegetations of patients with endocarditis, and from biopsy specimens of liver and bone marrow of patients with chronic granulomatous hepatitis. Liver biopsy shows characteristic small granulomas and epithelioid cells in annular (doughnut) arrangement.

Patients in whom persistent or recrudescent coxiella infection leads to chronic Q fever have persistently high levels of anti-phase II antibodies and greatly increased anti-phase I antibody titers. Anti-phase I IgA

titers are considered diagnostic for coxiella endocarditis.

Treatment of chronic Q fever is less successful than that of acute Q fever. Patients need to be treated with tetracyclines for at least 12 months, or may even require life-long therapy. In addition, these patients have to be serologically monitored every three months.

In vitro, rifampicin is more active against C. burnetii than tetracyclines; its role in therapy of endocarditis remains to be determined. Replacement of a diseased heart valve by prosthesis does not ensure cure since re-infection by C. burnetii, presumably originating from the liver, may occur. Alternatively, valve prosthesis may yield a predisposition for C. burnetii endocarditis.

V. Diagnosis

The clinical signs associated with coxiella-induced diseases are not specific enough for an accurate diagnosis. Detection of C. burnetii in clinical specimens is indicative for an aetiological involvement. The direct visualization of the agent in infected tissues by Giménez in conjunction with immuno-detection methods such as immunofluorescence represents a relatively simple, rapid and specific procedure. Eventually, monoclonal antibodies may further facilitate this procedure. The isolation of the pathogen from clinical specimens using embryonated hen's eggs, or the inoculation of samples into guinea pigs or mice and subsequent detection of seroconversion, is time-consuming and cumbersome and should be restricted to specialized laboratories. It should be noted, however, that appropriate clinical specimens are sometimes hard to obtain, especially from man. Detection of bovine C. burnetii infections by inoculation of milk samples into guinea pigs is of limited value because the agent is shed intermittently in milk. In future, cell culture isolation techniques may also prove useful.

Consequently, a tentative diagnosis of human and bovine Q fever in most cases has to be confirmed by serological procedures. The standard diagnostic procedures are the complement fixation test (CF) and the micro-immunofluorescence test (IFT). CF has a relatively low sensitivity, it is not useful with anti-complementary and haemolytic sera and fails if predominantly non-complement-fixing (non-CF) immunoglobulins are present. Naturally infected cattle produce mainly complement-fixing IgG1 and thus CF is still a suitable technique for diagnosis on a herd basis. In contrast, there is evidence that early coxiella-specific IgM may not be detected by standard CF. Furthermore, presence of high levels of non-CF antibodies may inhibit complement fixation and thus produce false negative results. Good results have been reported with a microagglutination test (MA) and although it appears to detect different immunoglobulins than CF, it shares some of the disadvantages.

Remarkable progress has been made by applying indirect serological procedures, i.e. the immunofluorescence test (IFT) and enzyme-linked

immunosorbent assay (ELISA) in which commercially available CF-antigens can be used. In contrast to CF, these techniques have a higher sensitivity, are applicable with haemolytic and anti-complementary serum samples, and using L-chain specific conjugates they are able to detect all isotypes of immunoglobulins including non-complement-binding antibodies. Moreover, the use of immunoglobulin isotype-specific conjugates permits distinction of immunoglobulin classes and subclasses without tedious separation procedures. Early stages of C. burnetii infections can be diagnosed with a single serum sample by demonstration of specific IgM before appearance of antibodies detectable by CF and consequently must be considered the best technique for diagnosis of acute Q fever. However, simultaneous presence of IgM and IgG indicates recent infection but can occur also in persistent (chronic) infections. Employing conjugates specific for bovine IgG1 and IgG2, cattle which were vaccinated with a commercial phase II vaccine could be distinguished from naturally infected animals.

High titers of specific IgA and IgG against the phase I antigen of C. burnetii appear to be diagnostic for chronic Q fever endocarditis. On the other hand, in clinically severe chronic Q fever cases high CF titers against phase II as well as phase I antigens are always present and thus diagnostic for these infections. Thus, CF may offer a suitable technique for detection of chronic Q fever.

IFT is a relatively simple technique which can be performed in most laboratories provided with an ultraviolet microscope. ELISA reaction can be visualized by colour changes without special equipment but photometric reading is more precise. If such special ELISA equipment is not available, IFT should be considered the standard test for serodiagnosis of Q fever on an individual basis.

For seroepidemiological studies, however, the ELISA supersedes CF and IFT because the ELISA is more sensitive, and using a single serum dilution, large numbers of sera can be objectively screened with an ELISA-reader within a short time. Unfortunately, this test is not yet standardized nor is a test kit commercially available. Recent developments have shown that the dot-blot technique for diagnostic serology combines some of the advantages of IFT and ELISA without the necessity of specific equipment. The dot-blot technique deserves further evaluation.

VI. Immunity and Immunization

C. burnetii infections usually induce an immune response, which provides long lasting protection against further disease. To what extent the agent persists in recovered individuals is still unclear. In both man and animals persistent infections have been observed in the presence of high antibody titres. Persistent infection may lead to recurrent or chronic disease. For the prevention of disease efficient and safe vaccines are needed. Experimental investigations have revealed that protection against C. burnetii is based mainly on antibody-dependent cellular immunity.

Experiments with guinea pigs have shown that phase I antigens have a protection potency many times greater than phase II antigens. Recent studies with restriction endonucleases as well as serological investigations with different antigens of C. burnetii have demonstrated an antigenic heterogeneity independent of phase variation suggesting that vaccine strains should be analysed and carefully selected.

Vaccines for man

Vaccination of human beings against Q fever is indicated for people at high risk such as laboratory workers, abattoir workers, veterinarians, individuals in contact with coxiella-infected animals and their products, persons with cardiac valve prosthesis and immuno-compromised individuals. Development of vaccines for man is still in an experimental stage. Potential vaccine candidates include killed whole cells of C. burnetii in phase I, chloroform/methanol-extracted residues of phase I particles and a soluble fraction extracted by trichloroacetic acid. Unfortunately, these vaccines sometimes induce local and even generalized reactions, particularly in individuals who have been exposed to the agent prior to vaccination. In order to avoid these reactions, individuals with positive skin tests should be excluded from these vaccinations. Experimentally, the best results have been achieved by vaccination with chloroform/methanol-extracted phase I antigens. However, before mass application further studies are required. Promising but preliminary results in producing large amounts of C. burnetii in cell cultures may help to improve vaccines.

Vaccines for animals

Vaccination of cattle and other ruminants is indicated to reduce the risk of human infections and if C. burnetii causes infertility in livestock. Experimental vaccines of whole cells in phase I prevent coxiella infections of cows exposed to naturally infected environments, provided they are vaccinated as non-infected calves. To monitor calves for this purpose the ELISA test, not CF, is recommended. It may be noted that encouraging results have been obtained in field trials of a bivalent vaccine (C. burnetii phase II and Chlamydia psittaci) with a significant improvement of fertility in vaccinated herds. Cattle given this bivalent vaccine can be distinguished from naturally infected animals because the former produce predominantly non-complement-fixing IgG2. Sometimes this vaccination causes undesirable local reactions. A potential vaccine candidate without such side effects is represented by chloroform/methanol-extracted cells of C. burnetii.

VII. Conclusions

1. In recent years Q fever has been brought to the forefront of interest due to
 - (a) records of common source outbreaks of great health and economic significance

- (b) serological data indicating increasing prevalence rates in livestock and
 - (c) evidence of the significance of C. burnetii in cases of chronic endocarditis and chronic granulomatous hepatitis.
2. Progress has been made in the development of diagnostic procedures but simple, rapid techniques for the detection of the agent still have to be developed. Investigations of the best possible treatment of patients are still needed.
 3. There is a great discrepancy between the clinical and serological evidence of the incidence and significance of the infection on the one hand and on the other of our knowledge of the patterns, modes of transmission and occurrence of human and animal diseases associated with C. burnetii.
 4. Molecular biological characteristics of C. burnetii need to be elucidated to facilitate studies on the epidemiology and pathogenesis of the agent.
 5. The highest health hazard due to C. burnetii is associated with environmental contamination by birth fluids and placental membranes of domestic animals. In addition, fleeces and hides contaminated with infected tick faeces or animal excreta are an important source of infection.
 6. Although people consuming contaminated raw milk seroconvert the rare reports of clinical illness resulting from ingestion of food of animal origin require confirmation. Heat treatment of milk to at least 74°C and storage periods applied to fresh cheese in food hygiene destroy the agent. However, more research is needed to define the pathogenicity of C. burnetii by the oral route of infection.

VIII. Recommendations

1. That, at national level, further epidemiological information concerning acute and chronic human Q fever and C. burnetii infection in livestock and other animals be gathered. For this purpose, a central reference laboratory should be nominated in each country.
2. That a panel of reference antisera to facilitate the evaluation of diagnostic procedures be established.
3. That a centralized collection of C. burnetii isolates of defined origin and history be established.
4. That existing laboratory diagnostic procedures be standardized.
5. That simple, economic tests to facilitate rapid and early diagnosis be developed.

6. That monoclonal antibodies for immunological and molecular characterization of C. burnetii be developed.
7. That the general awareness of medical practitioners regarding the diagnosis and treatment of Q fever be improved and that medical and veterinary institutions be encouraged to give more attention to this zoonosis.
8. That improved vaccines for protection of high risk groups be developed.

IX. Continuing Cooperation

The participants of the workshop decided to continue their collaboration beyond the period of the workshop as an international working group in order to promote the implementation of their recommendations. Regional and global cooperation will be sought. Dr. H. Krauss was asked to coordinate the group's activities and to convene the next meeting, possibly in conjunction with the International Rickettsiology Conference in Palermo in June 1987. The international working group invites WHO to lend its assistance in its secretariat functions.

Primary responsibility:

- for points 2 and 3: Krauss, Schmeer, Giessen;
- for point 4: Houwers, Lelystad; Krauss, Schmeer, Giessen;
- for point 5: Edlinger, Paris; Houwers, Lelystad; Rady, Budapest;
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ANNEX 1

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