

Anthrax: Memorandum from a WHO meeting*

The risk of anthrax can be reduced through international collaboration in health education and training, promotion of research, and provision of scientific and technical advice. These issues were discussed by a WHO Working Group on Anthrax in September 1995, and this Memorandum presents their priority concerns and recommendations in several areas: surveillance, epidemiology, diagnosis in humans and in animals, prevention and control, and international cooperation.

Introduction

Anthrax is enzootic in many countries in Africa and Asia, and in a number of industrialized countries, and is sporadic in many others (1). The main source of human infection is direct or indirect contact with infected or contaminated animal products. The occurrence of human infection correlates with the presence of disease in the animal population. Considering its public health significance, WHO has prepared guidelines on the surveillance and control of anthrax in humans and animals,^a and contributed to the worldwide surveillance of anthrax jointly with the Food and Agriculture Organization of the United Nations (FAO) and the International Office of Epizootics (OIE) (1). At a meeting in Mongu, Zambia, in 1992, the WHO Working Group discussed and made proposals for a comprehensive national programme on anthrax control in Africa (2).

This Memorandum is based on the report of a WHO meeting held in Winchester, England, on 22–23 September 1995. The participants were R. Bohm, Stuttgart, Germany; B. L. Cherkasskiy, Moscow, Russian Federation; V. de Vos, Skukuza, South Africa; M. Doğanay, Kayseri, Turkey; M. Hugh-Jones, Baton Rouge, Louisiana, USA (*Chairman*); S. F. H. Jiwa, Morogoro, United Republic of Tanzania; D. D. Joshi, Kathmandu, Nepal; A. F. Kaufmann, Atlanta, GA, USA (*Rapporteur*); M. K. Lalitha, Vellore, Tamilnadu, India; J. Melling, Porton Down, Salisbury, England; and P. C. B. Turnbull, Porton Down, Salisbury, England. *WHO Secretariat*: F.-X. Meslin and O. Cosivi (*Secretary*). This meeting was preceded by a workshop; all 81 papers have been published in *Proceedings of the International Workshop on Anthrax*, 19–21 September 1995, *Salisbury medical bulletin*, 1996, No. 87 (special supplement). Enquiries and orders should be sent to Dr P. C. B. Turnbull, CAMR, Porton Down, Salisbury, Wiltshire, England.

Requests for reprints of this Memorandum should be sent to Disease Surveillance and Control, Division of Emerging and Other Communicable Diseases Surveillance and Control, World Health Organization, 1211 Geneva 27, Switzerland. A summary in French of this Memorandum appears on page 469.

^a **World Health Organization. Guidelines for the surveillance and control of anthrax in humans and animals.** Unpublished document WHO/Zoon./93.170, 1993, available on request from Division of Emerging and Other Communicable Diseases Surveillance and Control, World Health Organization, 1211 Geneva 27, Switzerland. Reprint No. 5727.

Objectives

In view of the need to integrate anthrax control and research activities with broader human and animal health concerns, the Working Group endorsed the following statement as its mandate: "to promote human health and well-being, enhance livestock production, and preserve the wildlife populations by reducing the risk of anthrax through strengthening of education and training, promotion of research, provision of scientific and technical advice, and international collaboration."

The objectives of the Working Group included identification of priority issues and promotion of anthrax-related research in the framework of international collaboration. The following activities were identified as priority concerns:

- identifying areas, countries and regions of major risk;
- improving the quality and expertise of national medical and veterinary personnel for the treatment, prevention, diagnosis and surveillance of anthrax;
- promoting public awareness and information through education on anthrax in infected areas;
- promoting the exchange of information on anthrax between WHO Member States;
- promoting problem-oriented research;
- providing advice on how to prevent the introduction of anthrax in countries or areas where it is not present or not reported, or where the incidence is very low;
- promoting and updating WHO's guidelines on anthrax;^a
- promoting training and educational activities on anthrax through WHO Regional Offices, WHO Collaborating Centres, and other specialized centres or institutions; and

- promoting intersectoral collaboration on research, education, control and prevention of anthrax.

Summary of discussions

- The success of most anthrax *control programmes* tends to be undermined by the lack of precise case mapping and accurate single-case finding and reporting. Fully structured surveillance programmes are rare and most national anthrax programmes are given low priority. The lack of precise information on the source of infection (whether contaminated feed, "latent" infections, etc.) in individual outbreaks is seen as a major limiting factor for effective control at national and international levels. This reflects the traditional but false view that "because the ground is permanently contaminated, nothing can be done or is worth doing". In addition, livestock owners should be convinced that control programmes are useful; efficient marketing is therefore required. A regional approach to control programmes is needed because anthrax-infected areas may cross national borders and because trade in hides, goat hair, and bone-meal may spread infection between as well as within countries. As there may be barriers to international trade, international standards for certifying a country or area as free of anthrax are necessary.
- There is a great need for *training and education* in the clinical aspects of anthrax in humans in areas where the disease is sporadic and often unrecognized, whether in developing or in industrialized countries. Laboratory diagnosis of patients who are culture-negative because of previous antimicrobial therapy may be facilitated by newer rapid antigen detection assays and other approaches such as Anthraxm[®] skin testing (3–5). New tests must be validated in the field before extensive application, preferably in collaborative studies that include WHO.
- There is concern for *biosafety in clinical laboratories*, the requirements varying in different countries. Biosafety level 2 is considered appropriate for clinical laboratory evaluations, while biosafety level 3 is more appropriate for research studies involving spore suspensions in liquids or large-scale cultures.
- Although *diagnostic methods* for animal anthrax are dictated by circumstances, all outbreaks must be confirmed by examination of blood, tissue fluids or exudates (smears stained with polychrome methylene blue or McFadyean stain), or by culture of at least a proportion of the cases. Clinical presentation, necropsy findings, and exposure history are of value

in preliminary diagnosis prior to laboratory results. Tests developed recently, such as the polymerase chain reaction (PCR) or enzyme-linked immunosorbent assay (ELISA), will help but must be suitable for field application and be affordable. The ideal laboratory test should be sensitive, specific and inexpensive. The hand-held immunochromatographic assay, developed recently at the U.S. Naval Medical Research Institute, Bethesda, MD, USA, and made suitable for field use, was considered by the group to be a major step forward (6). It is hoped that this will supersede the very old Ascoli test which is still used in certain countries, but for which there remain the problems of standardizing the reagents and poor specificity.

- Anthrax *prevention, control and surveillance* methods must take into account the normal incidence of anthrax and the risk factors present in a given area; surveillance must be effective. Research is needed to improve decontamination, by chemical or physical means or both, of complex environments. Specific needs include decontamination methods for soil at burial sites and for other areas with large volumes of tannery waste (deposited sewage sludge from tanneries and hide processing plants). The application of chemicals is limited because of environmental and occupational health risks posed by the disinfectant (e.g., formaldehyde) or the disinfection procedures.
- It cannot be overemphasized that if *livestock vaccination* programmes are effective, there is rarely any need to vaccinate occupationally exposed people. Development of oral animal vaccines imparting long-lasting immunity is desirable. Oral vaccines offer several potential advantages, including ease of administration in remote areas (where adequate help and equipment to restrain animals are not available) and a reduced risk of disease transmission between vaccinated animals due to contaminated needles. Oral vaccines would be particularly useful for wild animals. Before live oral vaccines are used, concerns about potential environmental contamination must be resolved. Similar concerns were raised about the use of antimicrobial-resistant vaccine strains. The feasibility of using non-living oral vaccines, such as microencapsulated or liposome-entrapped protective antigen(s), needs serious evaluation.
- Research to improve the duration of *immunity* in various species must continue. More research is also needed on the number of years an effective herd vaccination programme must be sustained to reduce local environmental contamination to a level where animal vaccination can safely be dis-

continued. Three years was suggested as adequate, but scientific evidence to support this recommendation is weak. The duration of vaccination programmes also varies according to circumstances, for instance whether the disease is enzootic, or when an isolated outbreak occurs in a non-enzootic area.

- No major breakthroughs have occurred in *treatment for humans*. Penicillin is the drug of choice, doxycycline and other tetracyclines being alternatives for patients who are allergic to penicillin. Bacteriological cure of cutaneous lesions often occurs after a single dose of the antimicrobial agent. Prolonged treatment, however, is a prudent safety measure, especially in view of the risk of meningitic infections. Quinolones (such as ciprofloxacin) and first generation cephalosporins (such as cefazolin, cefradine and cefalotin) have good *in-vitro* activity, but second and third generation cephalosporins (such as cefuroxime, cefotaxime and ceftizoxime) show no good activity against *B. anthracis in vitro*. Only cefoperazone has good activity among third generation cephalosporins. There is no clinical experience with cephalosporins in the treatment of human anthrax. Specific anthrax antiserum seems to be of value in toxic patients but is not commercially available in most countries. Further research on the therapeutic application of specific antiserum in critically ill patients is needed. More research is also needed on the "latent" infections in humans and in animals — how they occur, how they can be prevented, and how the risks can be minimized

- Penicillin is also the drug of choice for *treatment in animals* with clinical signs that suggest anthrax. Immediate intravenous administration followed by intramuscular injection of long-acting preparations may be used. Other antimicrobials such as oxy-tetracycline, streptomycin (often commercialized in combination with penicillin) or sulfathiazole may also be used. In the carcasses of treated animals that go on to die (from the effect of toxin), the infecting *Bacillus anthracis* will have been greatly reduced, if not entirely eliminated, thereby significantly reducing environmental contamination and, therefore, transmission to other animals and humans. It should be noted that in several countries treatment of animals infected with anthrax is forbidden; they must be killed and safely disposed of

- Concerning the potential use of *B. anthracis* as a *biological warfare agent*, the Working Group is willing to provide technical advice to organizations and/or Member States on the development of prepared-

ness and response plans in case anthrax is used against civilian populations

Recommendations

Surveillance

The need to develop and evaluate effective and economic disease surveillance programmes, particularly in countries with limited resources, was stressed. These programmes must coordinate with those in neighbouring countries on the use of agreed standards for diagnosis and laboratory confirmation, the production and use of vaccines, and appropriate reporting. Collaboration with international organizations such as the FAO and the OIE should be requested in this activity

Epidemiology

Research should be initiated or strengthened on the ecology of anthrax, especially in relation to the apparent persistence, spread, and "disappearance" of the disease. Further research is also needed to:

- elucidate the social factors relevant to the prevention of individual cases (human or animal);
- elucidate the persistence of spores in soil;
- investigate the risk of introduction of anthrax through the recycling of carcasses and contaminated animal products into areas which traditionally have not been associated with the disease;
- develop methods for typing anthrax strains for epidemiological purposes; and
- monitor potentially contaminated animal feeds, using PCR or other rapid, cheaper but effective techniques.

Diagnosis in humans

The following areas are in urgent need of attention and research.

- A methodology for the diagnosis, at a sufficiently early stage, of pulmonary, intestinal, systemic and meningitic forms of anthrax in order to ensure effective treatment.
- A methodology for the reliable early diagnosis of culture-negative patients, mainly those who were treated by general practitioners before diagnosis was attempted or before referral to a hospital.

In addition, continuing education of physicians and clinical microbiologists in non-endemic areas is needed to ensure prompt recognition of anthrax when it does occur. In this connection, the

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Anthraxin® skin test (including possible side-effects) should be further evaluated, refined and standardized (3-5).

Diagnosis in animals

Further research should be undertaken in the following areas:

- evaluation of the simple, rapid and specific field diagnostic tests for anthrax developed at the U.S. Naval Medical Research Institute, Bethesda, MD, USA (6);
- antemortem diagnosis of latent/chronic anthrax states in animals; and
- standardization of serological tests and evaluation of Anthraxin® as a diagnostic or confirmatory procedure.

Prevention and control

The four major components in prevention and control continue to be education, outbreak-site management, detection, and immunization. All historically successful programmes have implemented these with discipline and thoroughness.

Education. It is strongly recommended that socio-anthropological studies be carried out on the attitudes of people, especially those living in poor social and economic conditions, to the recognition of anthrax. These groups, while aware of the real risks they incur in handling and consuming animals infected with anthrax, may often disregard advice and laws against slaughtering and consumption of such carcasses because of their need for meat, leather and other animal products. Traditional requirements, such as the need to prove — by submitting the animal's skin — that the animal was not stolen or sold, but in fact died, may have similar consequences. Identifying such cultural and societal imperatives will help the communities to see that the control programmes are working for their benefit and not against them. Efforts to control anthrax should be translated into education programmes at farm and village level, along the lines previously described (2).^b In this connection, the group endorsed the activities on anthrax prevention being carried out in Zambia (7).

Outbreak-site management. More research is required regarding safe disposal and destruction of

carcasses, including the evaluation of the safety of residual materials. This is especially important in areas where wood or other fuel is scarce. In many countries the skills and equipment needed for burning carcasses safely and economically are not available. Practical manuals are needed to provide guidance.

The safe disposal of cadavers of infected anthrax victims should be achieved in all cases within the frame of social and religious customs of the community. Cremation rather than burial should be chosen, where possible.

Further research is required on the decontamination, by chemical or physical means, of soil and soil-related materials in contaminated areas; this applies especially to technical equipment designed for other purposes, such as rotating drum-ovens for burning limestones or technical equipment used for washing soil in order to remove organic and non-organic pollutants. Anthrax is rarely so common that public health authorities can maintain specific heavy equipment simply for anthrax control. Chemicals and cleaning methods should be assessed for their environmental impact in the short and long terms. Further information should be collected and reviewed on the application of modern chemical and thermal sporocidal techniques for the treatment of animal products potentially infected with anthrax. Similarly, techniques and standards should be developed for examining and releasing potentially contaminated materials for subsequent use.

Proper epidemiological investigations to assess the cause and source of animal outbreaks and of human cases should be the rule and not the exception, as is too often the case at present. The information gained should always be fed back into the surveillance programme.

Detection. There is a strong need for research to improve the methods of identification of animal products, soil and other materials contaminated with anthrax spores, so that they are rapid, sensitive, specific and reliable. The most likely lines of approach would be based on the use of monoclonal antibody and PCR, but improvements in conventional detection procedures are still worth pursuing.

Immunization. Vaccines for veterinary purposes must be improved, especially with respect to easy application and duration of immunity. Possible examples are microencapsulated or genetically engendered oral vaccines based on bacteria, viruses or plants, which stimulate T-cell-mediated immunity. Further research is required on the oral approaches to immunization. However, where engineered live vector organisms are proposed, the potential un-

^b See footnote a, p 465

fact of the release of biological organisms into the environment should be evaluated before larger field trials are carried out. In this connection, studies should take into consideration internationally agreed recommendations.^c Non-living vaccine alternatives for oral administration, such as micro-encapsulated or liposome encapsulated protective antigens with adjuvants should be looked at carefully.

In the case of wildlife, where anthrax is increasingly regarded as part of the ecological balance, research needs to be concentrated in three areas: (i) factors upsetting this balance in the environment, which in the case of wildlife is often nowadays managed in artificially enclosed areas; (ii) socioeconomic relationships, which include the attitudes and relationship between conservators within park boundaries and farmers on the outside of these boundaries, and the true extent to which anthrax is spread from wildlife to livestock; and (iii) suitable vaccine and vaccination contingency plans if anthrax should get out of control in any one species.

Laboratory-derived multidrug-resistant vaccine strains would make possible the simultaneous treatment and immunization of persons known to have been exposed to *B. anthracis* (9). In this connection, it was recommended that laboratory workers deriving multidrug-resistant strains should, at all stages of their development, monitor and record the antibiotics to which the strains remain susceptible. Failure to do this would, according to the Working Group constitute irresponsible behaviour.

International cooperation and plan of work

Training courses for veterinary and medical technical personnel and education campaigns for the public in endemic areas should be organized at regional and/or subregional levels. The Working Group represents a core of expertise for the technical and scientific support of these activities. The need for training on the clinical and diagnostic aspects of anthrax also exists in those countries where the disease occurs rarely, because the loss of experience in clinical diagnosis of anthrax leads to delayed diagnosis. WHO, in close collaboration with the Working Group, should facilitate training on the clinical and post-mortem aspects of anthrax, site control management, vaccination programmes, and surveillance.

^c *Voluntary code of conduct for the release of organisms into the environment*. Prepared by the UNIDO Secretariat for the Informal UNIDO/UNEP/WHO/FAO Working Group on Biosafety, July 1991. Vienna, United Nations Industrial Development Organization, 1991 (unpublished).

The National Zoonoses and Food Health Research Centre in Nepal is designing, in collaboration with WHO, a questionnaire on human and animal anthrax which will be sent to Member States of WHO's South-East Asia and Western Pacific Regions. The questionnaire would be used for a pilot regional survey.

Suggestions for updating and improving the anthrax guidelines^c are being incorporated into the next edition of the guidelines. These guidelines aim to provide concise but comprehensive and practical information on anthrax for public health, veterinary, agricultural, laboratory and extension personnel in the field. The revised edition will include additional sections on emergency preparedness in the face of anticipated, suspected or confirmed instances of use of *B. anthracis* as a biological warfare or terrorist weapon, biosafety issues including the principles on which to base risk assessment and a summary of the most recent work on anthrax control problems in Africa (7).

Résumé

Charbon: Mémoire d'un réunion de l'OMS

Le risque de charbon peut être considérablement réduit par l'élaboration et la mise en œuvre de programmes durables de lutte au niveau régional, national ou subnational. La collaboration internationale en matière d'éducation et de formation, de promotion de la recherche, et de fourniture d'avis scientifiques et techniques reste indispensable à la réussite de ces programmes.

Ces questions ont été examinées par un Groupe de travail de l'OMS sur le charbon en septembre 1995; le présent Mémoire présente les priorités et les recommandations formulées par le Groupe dans des domaines tels que surveillance, épidémiologie, diagnostic chez l'homme et l'animal, prévention et lutte, et coopération internationale.

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