REPORT OF THE 6TH WHO ADVISORY GROUP MEETING ON BURULI ULCER

10-13 MARCH 2003

WHO HEADQUARTERS, GENEVA, SWITZERLAND

World Health Organization
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Contents

ABBREVIATIONS AND ACRONYMS

AFB	acid-fast bacilli
AFRF	Association Française Raoul Follereau
AIFO	Associazione Italiana Amici di Raoul Follereau (Bologna, Italy)
ALM	American Leprosy Missions
ALES	Aide aux Lépreux Emmaüs-Suisse
ANESVAD	Acción Sanitaria y Desarrollo Social (Madrid, Spain)
AS	Aires de santé
BAC	bacterial artificial chromosome
BCG	bacille Calmette-Guérin
BNITM	Bernhard Nocht Institute for Tropical Medicine (Hamburg, Germany)
BU	Buruli ulcer
BURF	Buruli Ulcer Research Fund
CDC	Centers for Disease Control and Prevention (Atlanta, USA)
CDTUB	Buruli ulcer detection and treatment centre (Allada, Benin)
DNDi	Drugs for Neglected Diseases Initiative
DFID	Department for International Development
DHMT	District health management team
EWARN	Early Warning and Response Network
GBUI	Global Buruli Ulcer Initiative
HART	Humanitarian Aid Relief Team
HFG	Health Foundation of Ghana
HIV	human immunodeficiency virus
HR	Human resources
IDP	internally displaced persons
IEC	information, education, communication
IFN	inteferon
IICD	International institute for communication and development
IL	interleukin
IRB	institutional review board
ITM	Institute of Tropical Medicine (Antwerp, Belgium)
KAP	knowledge, attitudes and practices
KCCR	Kumasi Center for Collaborative Research in Tropical Medicine (Kumasi, Ghana)
KEMRI	Kenya Medical Research Institute (Nairobi)
MAP	Medical Assistance Programme
MBBS	Bachelor of Medicine and Bachelor of Surgery
MSF	Médecins Sans Frontières
MUCF	*Mycobacterium ulcerans* culture filtrate
NGO	nongovernmental organization
NP	national programme
PBMC	peripheral blood mononuclear cell
PBS	phosphate-buffered saline
PCR	polymerase chain reaction
PHANS	Projet Humanitaire Afrique Nord Sud
PKS	polyketide synthase
PNLUB	national Buruli ulcer control plan
PNUM	Programme National de lutte contre les Ulcères à Mycobactéries (Côte d'Ivoire)
POID	prevention of impairment and disability
R&D	research and development
RT-PCR	reverse transcriptase polymerase chain reaction
SD	standard deviation

TDR	UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases
UCL	University College London
UNHCR	United Nations High Commissioner for Refugees
WFP	World Food Programme
WHO	World Health Organization

INTRODUCTION

Background

Buruli ulcer, caused by *Mycobacterium ulcerans,* is largely a neglected problem of the poor in remote rural areas. Since 1980, it has emerged as an important cause of human suffering. There is limited awareness of the disease both within the medical community and among the general public, resulting in under-recognition and under-reporting. Buruli ulcer has been reported or suspected in more than 30 countries worldwide. Currently, West Africa appears to be the most affected region. About 70% of those affected are children aged under 15 years.

In 1998, the World Health Organization (WHO) established the Global Buruli Ulcer Initiative (GBUI) with financial support from the Nippon Foundation in response to the growing spread and impact of the disease. That same year, WHO established an 18-member Advisory Group to guide its activities on Buruli ulcer. Members meet every March in Geneva and represent some of the world's experts on the disease in the areas of control, management and research.

During the past few years, the scope of this meeting has broadened to allow some field health workers from endemic countries, researchers and nongovernmental organizations (NGOs) currently involved in Buruli ulcer control activities to attend and present their work. The meeting is an important part of global advocacy and a necessary component of efforts to raise awareness and interest about this poorly known disease, to share and disseminate new information and to coordinate efforts among endemic countries, researchers and NGOs.

Thanks to continued support from the Nippon Foundation, Acción Sanitaria y Desarrollo Social (ANESVAD) and other NGOs, from dedicated researchers and field health workers and commitment from an increasing number of countries dealing with Buruli ulcer, much progress has been made during the past five years in advocacy, control and research. However, much work remains to be done and many challenges await in finding better ways of diagnosing, treating and preventing this debilitating disease.

The 2003 meeting was aimed at assembling experiences and evidence to date with a view to intensifying control activities at country level and accelerating priority research.

Objectives

1. To agree on a common strategy for intensifying control activities in selected priority countries and to develop synergies with other disease control activities to enhance Buruli ulcer control.
2. To review national action plans for intensifying control activities.
3. To examine ways to strengthen the delivery of health services through the implementation of Buruli ulcer control activities.
4. To implement the activities in research priorities on Buruli ulcer.
5. To strengthen collaboration and coordination among NGOs and to reach out to new ones.
6. To explore mechanisms for better fundraising to meet the above objectives.

Welcoming remarks

Dr David Heymann, Executive Director, Communicable Diseases, opened the meeting. He outlined a new WHO approach for dealing with neglected diseases, of which Buruli ulcer is but one. Dr Kingsley Asiedu then presented the objectives and expected outcomes of the meeting together with a progress report on GBUI since 1998. Although progress has been made in a short time for a disease that was virtually unknown, much remains to be done in the areas of early detection, treatment and research.

Organization of the meeting

The meeting was conducted in English and French, with interpretation facilities. Professor Jacques Grosset chaired the meeting. Presentations and discussions of country-level control activities, activities of NGOs and of research were held during the first two days. The third day was devoted to group work on control, research, antibiotic treatment and NGOs. The reports and recommendations of the groups were presented at a plenary on the fourth day followed by discussions. The meeting was closed by Dr Kingsley Asiedu and Dr Nevio Zagaria.

WORKING GROUP
REPORTS AND RECOMMENDATIONS

WORKING GROUP
ON CONTROL ACTIVITIES

Early detection of cases

There is a need for countries to introduce an early detection system. Strategies to enhance early detection could be adapted to countries, although there seemed to be unanimity over some approaches.

1. Use of community relays/volunteers with focus on community awareness campaigns: education of schoolchildren and teachers; screening of schoolchildren; training of village volunteers; finding mechanisms to sustain and motivate these volunteers (organizing periodical meetings, trainings including per diem, distribution of T-shirts, etc.).
2. Explore the involvement of opinion leaders and other social groups.
3. Where feasible, Buruli ulcer programmes should explore potential collaboration with other diseases control activities (e.g. leprosy, Guinea worm).

Case management

1. Health facilities:

– Needs assessment of health facilities in endemic areas that could manage cases.
– Facilities to confirm cases need to be set up to provide reliable information on the disease. Although case management does not require confirmation, samples have to be taken and case confirmation subsequently organized. Programmes were encouraged to implement this.

2. Provision of equipment to these facilities (e.g. dermatomes and meshgrafts):

– The equipment available in facilities would need improvement on the basis of the standards adopted.
– A small working group could be set up with Dr Priuli to produce a preliminary document on standards. The kits proposed in the book published by WHO could also serve as a model.
– Physicians and nurses from different levels of the health system would need to be trained in case management of Buruli ulcer.

3. Provision of medical supplies for patient care; NGOs may assist in this direction.

Rehabilitation

Need to incorporate basic physiotherapy in the management of patients. This is an important component of case management.

1. Initiatives along the lines of those under way in Benin may serve as a lesson for other countries. Benin has trained nursing staff in facilities providing case management to perform simple movement exercises. This can achieve significant results at little cost.
2. Possibility of setting up equipped rehabilitation units in the countries should also be considered.
3. Collaboration with existing rehabilitation facilities at country/local level.
4. Some NGOs, such as the American Leprosy Missions (USA) and AIFO (Italy) may be interested in this area.
5. Endemic countries were also encouraged to contact other NGOs, e.g. Handicap International.

Surveillance

1. The need to put in place an effective mechanism to ensure a better recording and reporting of data using the WHO BU 01 and 02 forms. Benin has developed a register with detachable stubs that provides quality data. It could be used in other countries. WHO is also developing mapping software to help with work at the country level. A mission could be organized to train programme officials in the use of this software. However, for this to be possible, countries need quality data first. Countries were asked to make registers out of the BU 02, as Benin and Ghana have done.
2. WHO will organize a training for programme managers on surveillance and HealthMapper.

Capacity development

1. The Group referred to the recommendations of the October 2002 Cotonou workshop.
2. The draft document to accelerate capacity development was adopted. A section on laboratory confirmation of cases is to be added. Endemic countries should use this draft plan to guide their capacity development activities.
3. Countries are to select 1–2 health institutions that can serve as training centres for health workers, as indicated in the draft document to accelerate capacity development. Names of selected institutions should be submitted to WHO by the end of March 2003.
4. The group recommended that WHO organizes a regional/subregional workshop on the laboratory diagnosis for laboratory scientists (microbiologists and pathologists).

National programme management

1. All endemic countries that had not produced a medium-term strategic plan were encouraged to do so by end of June 2003; without this plan, advocacy and resource mobilization will be problematic.
2. WHO will continue to provide basic equipment and logistics to strengthen national control programmes.
3. NGOs working in countries were encouraged to support some of the coordination activities of the national programmes.
4. Human resources are an important element. National programmes should involve experts in other disciplines (anaesthetists, physiotherapists, etc) in programme activities.
5. It is also necessary to organize programme reviews to assess the performance of national programmes.

Advocacy, social and resource mobilization

1. The need for reliable data to support advocacy efforts was discussed at length.
2. The need to improve awareness at country level was stressed. National programmes were encouraged to work closely with the media to bring the social and economic problems caused by Buruli ulcer to the attention of the population and policy-makers. For example, countries could negotiate airtime on radio and television once every six months to draw the attention of the general public and decision-makers to Buruli ulcer disease, whose severity and socioeconomic impact should be emphasized.

3. A periodic national and regional meeting of actors and NGOs involved in Buruli ulcer control could also prove an effective tool for advocacy and lobbying to persuade other partners to join the effort.
4. This will ensure a better understanding of each partners' activities and to share information.
5. WHO will support a national partners meeting in 2003 to improve awareness (see point 2 above) in selected endemic countries.
6. Initiatives should originate from countries. WHO will, as far as possible, encourage and support them.

Research

1. The Group encouraged national programmes to take the necessary steps to support mechanisms for collecting quality data and carefully to document cases. Such information will be very valuable for a clear understanding of the disease and for improving control.
2. Medical students should be encouraged to devote their final year studies to this disease, for their thesis at a reduced cost. WHO could encourage and support such initiatives.

WORKING GROUP ON NONGOVERNMENTAL ORGANIZATIONS AND *MYCOBACTERIUM ULCERANS* DISEASE – ESTABLISHMENT OF AN INFORMATION COORDINATION SYSTEM

The presentations made at the Sixth WHO Advisory Group Meeting on Buruli Ulcer in Geneva revealed that several NGOs are working in endemic countries. WHO therefore asked those NGOs present at the meeting to discuss the possibility of establishing an information coordination system. The ad hoc working group discussed the following questions:

1. Is there a need for an information coordination system?

The answer to this question is clearly YES. In Ghana, for example, many NGOs, both national and international, are active in various *M. ulcerans* disease-related activities. Some local NGOs knew of other NGOs only through the newspapers. Had this information been available to them earlier, NGOs could have combined their efforts to make a greater impact on the activities undertaken. This, of course, assumes that NGOs make themselves known to the national programme (NP) and that the NP knows which NGOs are active in its country. It is therefore extremely important to know who is working in the country and where.

2. Why should there be this system?

There are several reasons for there being such a system. The most relevant are:

- to avoid duplicate financing,
- to prevent overlapping activities,
- to use funds in the most efficient way.

The aim of the system is to ensure complementarity between the different actors (NP, NGOs, research institutions, etc.).

3. What information should be shared?

It is clear that a lot of information is available, but too much information may mean that the relevant information gets lost. A minimum amount of information must therefore be shared. This minimum could be an NGO questionnaire prepared by WHO. There could also be added a brief description of the NGO, its overall goals and the goals directly related to the disease, a schedule (plan) of activities, the needs and/or opportunities for assistance and a contact person. Experiences could be exchanged among NGOs.

4. Where and how should the information be shared?

There are several levels at which the information must be shared.

National level

In the short term, NGOs should gather to agree the creation of a network, forum or other structure, to meet each other and to appoint one NGO as the referral to the NP. This referral NGO should have the mandate to discuss with and to share all the relevant information. The communication must be bi-directional (NGOs ? NP and NP ? NGOs). In Benin, for example, all the actors meet once a year (actual status) in the Follow-up Committee (*Comité de suivi*) which was set up soon after the NP was established.

Regional level

In Africa, WHO invites the NP and NGOs to a regional meeting, at which NGOs from one country could be represented by their referral NGO.

International level

At a higher level, a first system could be an e-mail list, managed by one person (or NGO), in close contact with WHO. This person acts as a focal point to collect and dispatch all the available information. In the long term, a web site could be created.

5. Next steps and recommendations

From the statements above, four next steps are proposed:

1. In Cameroon, Côte d'Ivoire, Ghana and other endemic countries, one NGO should take the first step and organize a meeting between all NGOs involved in *M. ulcerans* disease.
2. An e-mail list should be set up immediately. Robert Kohll is in charge of this and all information can be sent to him at robert.kohll@ffl.lu.
3. A web site should be designed, presenting NGOs activities in the disease. Robert Kohll is also in charge of this area, but all are welcome to give ideas.
4. It is recommended that the WHO server hosts the NGO web site because the Global Buruli Ulcer Initiative Web site already exists. WHO also wishes to see what is published. Dr Kingsley Asiedu will be the contact person.

6. Overall recommendations to WHO

The NGO Working Group has three overall recommendations to WHO:

1. Ensure timely follow-up of the recommendations formulated at the annual March meeting in Geneva and provide an update to all concerned.
2. The update should be given to Working Group spokesmen during formal meetings or by e-mail. The frequency of the update has still to be determined.
3. WHO (Dr Asiedu) should carry out some in-house lobbying. It has been noted that at WHO only a few persons know of *M. ulcerans* disease.

WORKING GROUP ON ANTIBIOTIC TREATMENT

The group considered the current state of knowledge on antibiotic treatment of *M. ulcerans* disease in the light of presentations made at the meeting. Preliminary analysis of results from the WHO sponsored trial (Study I) had shown that treatment with rifampicin and streptomycin was successful in causing excised lesions to be culture negative after 4 to 12 weeks but not after 2 weeks. During the period of observation before excision, most lesions had become smaller, so there were grounds for believing that clinical cure might be achievable using antibiotics alone, but the trial did not demonstrate this. Further encouragement came from the results reported by Professor Kanga concerning his open study in Côte d'Ivoire comparing treatment with rifampicin, amikacin and heparin with no treatment. Some patients improved considerably on antibiotic treatment, although it was unclear whether heparin influenced the outcome. Finally, Dr Asiedu and Dr Etuaful had treated a small group of patients with oedematous disease with rifampicin and streptomycin and shown reduction in oedema so that a smaller excision was needed. All these results had been achieved without any antibiotic toxicity.

The group agreed unanimously that the next objective should be to establish whether antibiotics are able to cure lesions without the need for surgery and to compare different durations of treatment. An outline protocol was drawn up for a trial of rifampicin and streptomycin in patients with early lesions (nodules, plaques and small ulcers = 5 cm in diameter). After calculating the number of subjects needed to distinguish between treatment groups with 85% power and within 95% confidence limits, it was decided to compare two treatment periods of 4 weeks (determined by Study I) and 8 weeks (arbitrary). If 25% of patients treated for 4 weeks and 75% of those treated for 8 weeks showed complete resolution of their lesion within 6 months, 30 patients would be needed in each group. The same number would be needed for 50% and 95% of the two groups showing resolution. It was recognized that complete resolution could mean disappearance or stabilization of the lesion leaving, for example, a scar or a palpable nodule. Another outcome measure would be recurrence, but since the rate is likely to be less than 20% it should not be used to calculate the number of subjects per group.

STUDY II

Aim: To establish the minimum duration of treatment with antibiotics alo ne required to cure early lesions of *M. ulcerans* disease.

Design: Open comparative study of two groups of 40 subjects with early lesions (nodules, plaques or small ulcers = 5 cm in diameter). Treatment with rifampicin 10 mg/kg and streptomycin 15 mg/kg for 4 or 8 weeks.

- Diagnosis to be attempted using punch biopsies of lesions before treatment. Histology, culture and PCR of biopsies.
- Follow-up for 6 months to assess cure and for 12 months to observe recurrences.
- Recurrent lesions to be excised for histology and culture. AFB and PCR may not be helpful in recurrences.

Logistics: It will be necessary to involve at least two centres in recruitment; both Benin and Ghana expressed an interest in participating in this study. After discussion between all the groups at the meeting, Dr Asiedu agreed to convene a separate meeting to design a protocol for this study.

Further studies in the future

It was agreed that it may not be possible to extrapolate the results of Studies I and II to the treatment of patients with established ulcers, and there was considerable debate about the ethics of conducting studies in such patients if a group that does not receive antibiotics is included. By the time these studies are planned, more will be known from Study II and a fresh judgement will have to be made at that time. However, with the current state of knowledge, it was agreed that it is legitimate to conduct a trial with three treatment arms:

Arm 1. Wide excision of lesions followed by grafting with no antibiotics (current standard of treatment).

Arm 2. Debridement (not wide excision) with antibiotic cover, e.g. rifampicin and streptomycin for 4 weeks with grafting at an appropriate time.

Arm 3. Rifampicin and streptomycin for 4 weeks followed by assessment to decide whether further antibiotics alone or immediate surgery/debridement and grafting are needed.

Several other areas of treatment research were discussed. The interesting results of topical treatment with nitrogen oxide generating creams were noted and further study was encouraged. Preliminary results from a small controlled trial of topical phenytoin powder treatment had been reported by Dr Klutse and the healing effect of this therapy was encouraging. Interest was expressed in further studies combining such therapy with surgery or with antibiotic treatment. The use of an antibiotic combination that can be taken orally was considered and it was suggested that it may be possible to substitute a macrolide for the aminoglycoside after an initial period of microbicidal therapy. This could be another fruitful area of research once study II is complete.

Guidelines for the use of antibiotics in management of *M. ulcerans* disease

It was acknowledged that many clinicians managing patients with *M. ulcerans* disease will be encouraged by the results of tudy I and will feel that antibiotics should be used until more results are available. The advice of the working group was that it is reasonable to use the combination of rifampicin and an aminoglycoside (streptomycin/amikacin) for 4 weeks to treat any patient with strongly suspected *M. ulcerans* disease when the circumstances allow suitable supervision of such therapy. After the first 4 weeks, an assessment should be made before deciding on further antibiotics or surgery. If the lesion has stabilized or is getting smaller during this time, further antibiotics may be justified rather than immediate surgery, but the possibility of an alternative diagnosis must always be borne in mind. A lesion that enlarges during antibiotic therapy should probably be excised and sent for histological diagnosis if possible.

It was felt strongly that patients with **disseminated disease** or **osteomyelitis**, including those **associated with HIV infection**, should always receive antibiotics for at least 2 weeks before continuing through the day of surgery and 2 weeks after surgery. Antibiotic treatment is also strongly advocated in patients with **oedematous and plaque** disease since it is thought that it may reduce the extent of surgical excision and possibly the need for surgery.

All clinicians who decide to use antibiotics for the treatment of *M. ulcerans* disease are asked to document carefully the response to treatment and to report the results to a future meeting of this group.

WORKING GROUP ON RESEARCH

The group discussed a draft document on research priorities for *M. ulcerans* disease (Annex 3) in view of new research information presented at the meeting. The summary of discussions of each section and recommendations are presented below.

Transmission

Status

- Conducting long-term environmental surveys correlating environmental incidence with patient data (Portaels et al., King et al., Ofori-Adjei et al.).
- Modeling biofilms, aquatic plants, passive hosts and biting insects to determine whether they play a role in the natural ecology of *M. ulcerans* (Johnson PDR et al., Carbonnelle et al.).

Recommendations for future studies

- Study the prevalence of *M. ulcerans* in the environment and correlate the presence of *M. ulcerans* in the environment with the incidence of disease in endemic areas:
  - multidisciplinary: microbiologists, entomologists, epidemiologists,
  - use of best available technology (e.g. quantitative PCR).

Early diagnostics

Status

- Serodiagnosis using IgG and IgM in progress (King et al.).
- Identification of additional unique *M. ulcerans* antigens (Demangel & Johnson PDR et al., King et al., Pluschke et al.).
- Mycolactone antibodies and antitoxin (Small, Pluschke et al.).

Recommendations for future studies

- Develop a rapid diagnostic field test for early clinical disease e.g.:
  - identify *M. ulcerans* specific proteins in lesions and urine,
  - identify *M. ulcerans* toxin (mycolactone) in lesions,
  - identify *M. ulcerans* specific antibodies in blood,
  - presence of carbohydrates (e.g., PGL-1) in body fluids.

Vaccine

Status

- BCG vaccination protocol has been developed (Johnson PDR et al.).
- Protective efficacy studies of two doses of BCG in mice (Demangel & Johnson PDR et al.).
- Antigen 85 study (Huygen et al.).
- Investigation of the potential of defined *M. ulcerans* mutants as vaccine candidates (Small et al.).

Recommendations for future studies

- Evaluate the potential role of a single or second dose of BCG in the prevention of BU in an endemic population. Consider adding an immunology component to the BCG study, before and after (markers for "vaccine failure" or "correlates of protection").
- Develop a conjugate toxoid vaccine.
- Search and evaluate protein-based/subunit vaccine candidates.
- Investigate the potential of defined *M. ulcerans* mutants as vaccine candidates.

Socioeconomic studies

Status

- Household economic study (Mumma et al.).
- Facility-based and outpatient treatment costs (Dadzie et al.).

Recommendations for future studies *(Refer to pages 11–12 of draft proposal)*

- Priority: Measuring true attributable cost of Buruli ulcer:
  - prevalence studies.
- Other recommended studies remain important.

Epidemiology

Status

- Case-control studies to identify risk factors, BCG, other tropical diseases related to potential susceptibility (Portaels et al., Stienstra et al., Raghunathan et al., Johnson PDR, Hayman et al., Tonglet et al.).

Cultural studies

Status

- Beliefs and attitudes (Aujoulat et al., Stienstra et al., Johnson C et al.).

Recommended studies remain important.

Treatment recommendations (other than antibiotics)

- Develop antitoxin therapeutics.
- Studies to validate the encouraging results from topical treatments:
  - phenytoin,
  - nitrogen oxides,
  - clay.

Missing categories

- Animal models for pathogenesis of *M. ulcerans* (Ofori-Adjei et al.).
- Epidemiology.
- Immunology.

PRESENTATIONS:

COUNTRY-LEVEL ACTIVITIES

ACTIVITIES OF NONGOVERNMENTAL ORGANIZATIONS

RESEARCH ACTIVITIES

SUMMARY PLAN OF ACTION, BENIN, 2003

Dr Christian Johnson

Early case detection

- Continue rounds to provide early case detection in villages where the disease is endemic.
- Train community relays to identify and refer suspect cases.
- Train teachers for information campaigns in schools through distribution of WHO cartoon strips.

Improved case management

- Construct and launch the Pobé Buruli ulcer treatment centre.
- Strengthen the capacity of the Allada and Lalo centres to perform operations.

Generalized means of surveillance

- Introduce registers with detachable stubs in the different communes in which Buruli ulcer is endemic.
- Regularly supervise case registration and notification.

Capacity building and training

- Train surgeons and physicians in surgical case management in regions where the disease is endemic.
- Organize a half-yearly meeting to enable the different actors in surgical case management to exchange experiences.
- Supervise training for health workers involved in patients' functional rehabilitation.

Information and social mobilization

- Produce a documentary on Buruli ulcer.

UPDATE ON BURULI ULCER CONTROL IN BENIN

Dr Christian Johnson

Activities carried out in 2002

Case detection and treatment

A total of 565 patients were screened and treated at treatment facilities in Benin : Allada (31 cases), Lalo (98 cases), Zagnanado (394 cases) and Zinvié (42 cases). Of these cases, 25 (4.4%) were recurrent; non-ulcerative forms accounted for 35.5%. Of the 565 patients who received treatment, 437 (77.3%) were cured without any sequelae and were treated at various treatment facilities, including Allada, which was built and began operating in 2002.

Training

A number of training activities were organized in 2002. The principal activity was training in case diagnosis and referral for 9 physicians and 180 nurses. Nurses from facilities in areas where the disease is endemic also received 11 days' training in functional rehabilitation.

An international workshop on surgical case management was held on 7–11 October 2002 in Cotonou.

Research

The case confirmation capability of the mycobacterium reference laboratory has been enhanced using Ziehl-Neelsen stain and culture. Case studies are under way with University College London (UCL) and the Institute of Tropical Medicine (IMT) on BCG vaccine and on coinfection with human immunodeficiency virus (HIV) and sickle-cell anaemia.

Outlook for 2003

The programme intends to build on its achievements in 2003 by providing training in early case detection for community relays and schoolteachers, training surgeons to improve case management and in implementing research projects.

UPDATE ON THE BURULI ULCER SITUATION IN CAMEROON

Dr Charles Nsom Mba

Introduction

Background information on Cameroon
- Population: 15 million
- Area: 475 000 square kilometres
- 10 administrative provinces
- Three-tier health system: Central (Ministry of Public Health, whose role is to define the country's health policy and its directions), Intermediate (Provincial Health Directorate, whose role is to provide operational support for the implementation of health policy) and peripheral (Health Districts and Areas, responsible for implementing health policy)
- Since 1995, there have been approximately 150 health districts in Cameroon
- Geographically, Cameroon represents Africa in miniature
- Its boundaries, in a clockwise direction starting at 10 o'clock, are with Nigeria, Chad, the Central African Republic, Congo, Gabon and Equatorial Guinea

The disease itself

- The disease is certainly present in Cameroon, in Centre province and in two health districts: Ayos and Akonoliga. Buruli ulcer control activities began there almost three years ago after a focus survey by ALES.
- The disease situation in the rest of the country has yet to be determined, and this will be done in the next few days.
- Since cases were detected in these two districts, there has been a clear commitment and deep involvement by our partners, ALES and MSF-CH, with whom it has been possible to initiate activities.

Activities carried out since the most recent meeting of the WHO Ad-hoc Advisory Group

Case management
- Case detection: case detection is passive and is carried out during routine activities.
- Case management: medical and surgical care in hospital and adapted to the form of the disease.
- Statistics: the number of cases has increased significantly: since the last meeting, 132 new cases have been detected; 66 in Ayos and 66 in Akolinga.
- Data collection: data collection aids have been introduced.
- The infrastructure has been adapted on site with the help of partners (*see* presentation of partners involved in Buruli ulcer control in Cameroon, p78).
- Staff are trained on the job at the two sites providing case management.

Prospects
- Depending on the results of the survey, activities will be continued at new sites.
- Development and implementation of a strategic plan for elimination of the disease with the objective of integrating activities into the operational minimum package of activities.

Conclusion

Buruli ulcer has not spared Cameroon. Although the data currently available do not give a clear picture of the scale of the problem, there is every indication that the disease is present beyond the known foci and that it is a real and serious threat to the health of the populations, calling for particular attention from senior authorities and partners.

BURULI ULCER SITUATION IN THE REPUBLIC OF THE CONGO, BRAZZAVILLE, 2002

Dr Hilaire Bassakouaou

Introduction

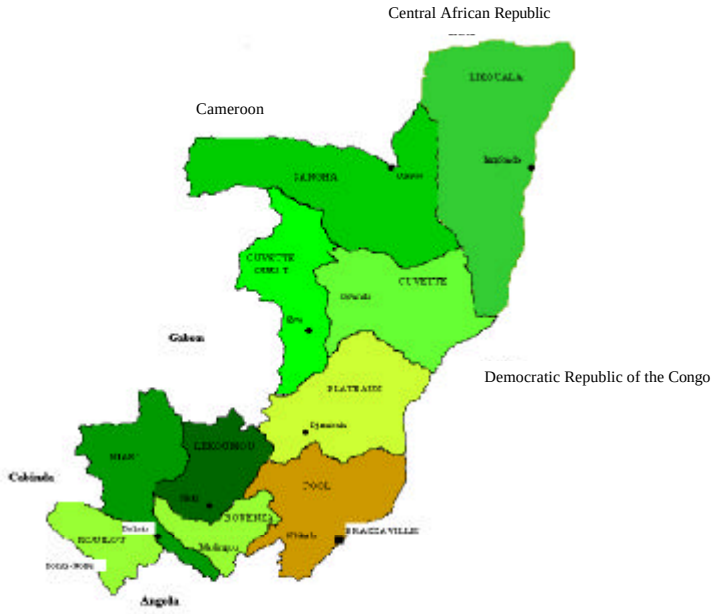
The National Buruli Ulcer Control Programme in the Congo is a "baby that is just starting to crawl", since it really came to life only nine months ago. Even so, a number of activities were carried out in 2002, thanks to financial support from WHO in Geneva, including:

- awareness-raising in the 10 villages in Kouilou province affected by Buruli ulcer,
- diagnosis and treatment of those suffering from the disease,
- monitoring,
- training.

Overview

The Congo is located in Central Africa, straddling the equator. It is a territory of 342 000 km^2 with a population of about 3 000 000, of whom 51% are women and 50% are young people. Three-fourths of its land area is covered by water and forest. The primary health problems are malaria, HIV, tuberculosis and Buruli ulcer.

Map of the Congo



Land area: 342 000 km^2
Population: 2 813 205 (2000)
Target population: 20% of the total population, 562 641 children aged under 5 years.

Boundaries:
- northern: Central African Republic and Cameroon
- eastern:Democratic Republic of the Congo
- southern: Angola
- western: Gabon

Buruli ulcer situation in 2002

Departments						Total
Kouilou		Niari		Bouenza		
Sites	**Cases**	**Sites**	**Cases**	**Sites**	**Cases**	**cases**
Loaka	27	Ntsimba	3	Madingou	3	**33**
Magne	15	Makabana	6	Mouyonzi	1	**22**
Sexo	3	Kimongo	2	N'kayi	3	**8**
Boungolo	1	–	–	Loudima	4	**5**
N'Kamba	3	–	–	Mouindi	6	**9**
Kakamoeka	3	–	–	Diessé	8	**11**
Wollo	3	–	–	–		**3**
Mbouyou	2	–	–	–	–	**2**
Tchisseka	1	–	–	–	–	**1**
Mboukoumassi	4	–	–	–	–	**4**
N'dinga	3	–	–	–	–	**3**
Yembo	1	–		–	–	**1**
Total	**66**	–	**11**	–	**25**	**102**

Activities

Community awareness efforts

Communities in the 10 villages affected by Buruli ulcer (Boungolo, Kamba, Loaka, Magne, M'boukoumassi, M'bouyou, N'dinga, Sexo, Tchisseka and Wollo) have been informed about the disease.

Case detection and treatment

Although passive case detection is carried out, active case detection is not currently being undertaken because the necessary structures are not yet operational. Those suffering from the disease in the three affected departments are generally treated by traditional medic ine practitioners and in existing health centres.

Monitoring

A total of four monitoring campaigns have been carried out in the districts of Kakamoeka and Madingo-Kayes (Kouilou department) with the help of vehicles from the AFP Project. Monitoring has consisted of observing patients undergoing treatment in the health centres and with traditional

medicine practitioners, possible infection sites, the disease's evolution in time and space and technical support to health care staff in the field.

Training

The coordinator of Buruli ulcer control activities was afforded a 14-day study trip to Benin. The terms of reference were the structural and functional organization of a Buruli ulcer control programme, with technical support from Dr Augustin Guédénon, National Buruli Ulcer Control Plan (PNLUB) coordinator (National Buruli Ulcer Control Programme) in Benin.

Research activities: case studies

CASE STUDY I

Buruli ulcer occurred in five members of a single family (a grandmother and her four grandchildren) in the village of Loaka in Kakamoeka district, where the disease is endemic. Through this study, we have sought to understand the possibility of transmission between humans.

Sometime in the 1990s, the grandmother contracted Buruli ulcer, and remissions of the disease have continued to this day. In 1998, the eldest of her grandchildren, then aged 15, contracted the disease, followed in 1999 by the second eldest grandchild, aged 13. The two youngest, aged 11 and 9 respectively, contracted the disease in 2000 and 2001.

The epidemiological study carried out on these five cases yielded the following results:

- Following separation from their mother, each grandchild in turn shared the same bed as the sick grandmother (notion of promiscuity).
- Upon questioning, the family complained of chronic pruritus and the presence of insects in their beds.
- The health team accordingly examined the domestic environment (bedrooms and bedding) and found a great quantity of bedbugs (small blood-sucking insects) in the beds.
- Question: could the bugs found in the bedding be the source of transmission of Buruli ulcer in this family?

CASE STUDY II

Buruli ulcer in two patients (a schoolboy aged 9 years and a housewife aged 32 years) following insect bites in Magne, a lumber company housing development in which Buruli ulcer is endemic, in Kakamoeka district.

The objectives of the study were:

1. To determine the probability of Buruli ulcer transmission by insect bite.
2. To prevent the haematogenous spread of *M. ulcerans* (see sites of lesions) through antituberculosis tritherapy (rifampicin–dexamethasone–isoniazid).
3. To avoid the disease's debilitating sequelae in these two young patients (blindness, shoulder dislocation).

Both patients were bitten in the upper right eyelid and the left deltoid by a variety of fly familiar among the population a few days before the monitoring team arrived. Redness emerged at the site of the bite several hours later, followed by a nodule. Given the anatomical location of the lesions and the lack of training in surgical intervention for Buruli ulcer, administration was proposed of a triple antituberculosis treatment (rifampicin–dexamethasone–isoniazid) in 10 mg/kg doses of rifampicin and 25 mg/kg of dexamethasone–isoniazid daily for an initial treatment phase of two months (rifampicin–dexamethasone–isoniazid), followed by a continuation phase of six months' treatment with dexamethasone–isoniazid.

Results

Two months after the administration of antituberculosis tritherapy to the two sufferers, the disease evolved in the usual stages (oedema, fistula, then ulceration) but with sudden onset and moderate extension compared with sufferers not treated with topical antituberculosis medications. After ulceration, bandages moistened with Dakin's solution were applied. Six months later, the wounds had completely healed with no unpleasant sequelae.

Discussion

The populations had been telling us of the insect-borne spread of the disease since the 1980s, but we had never encountered the phenomenon. The mode of transmission, which until recently had remained a mystery to us, began to be elucidated slowly but surely. The hypothesis could be further reinforced through tests such as polymerase chain reaction (PCR), which would reveal *M. ulcerans* antigens in the salivary glands of the insect. The test cannot be performed in our laboratories, but only abroad, for lack of appropriate resources. The questions arising are how the insect could host the mycobacteria in its salivary glands and how the mycobacteria could reproduce; both questions remain unanswered to this day.

The combination of rifampicin–dexamethasone–isoniazid slowed the spread of the infection, proving that healing could be achieved in a very short time and without sequelae, contrary to what is seen in patients who are not given antituberculosis treatment. Since our sample group is not representative, we will refrain from any comments. A study with a representative sample group would be desirable, especially if sufferers could be identified very early (nodular stage). Much patience and perseverance is required.

Suggestions and prospects

In order to improve the treatment of patients in the three departments affected by Buruli ulcer, we would like to achieve the following:

- As with Benin, to gain the support of associations and NGOs to assist the Congo in establishing its national programme to combat Buruli ulcer.
- To have the assistance of 2 consultants (a surgeon and a Buruli ulcer programme coordinator) to supervise 6 general practitioners and 12 nurses in the hospitals of the three departments affected by the disease.
- To train physicians and health care personnel in the three departments to carry out public awareness campaigns, diagnosis and early treatment of patients.
- To rehabilitate the health care centres in Kakamoeka (Kouilou department), Makabana (Niari department) and Mouindi (Bouenza department) with a view to their conversion into Buruli ulcer diagnosis and treatment centres.
- To equip these future centres with medical and technical supplies and consumables.
- To provide coordinators of Buruli ulcer control activities with communication and mobilization equipment (megaphone, camcorder, camera, film projector).
- To provide Buruli ulcer control coordinators with vehicles for carrying out monitoring and operational research.
- To identify one or two laboratories for diagnosis confirmation.
- In the context of research, we request that inter-state exchanges be encouraged.

Conclusion

Activities to control Buruli ulcer in the Congo are still at an embryonic stage. Technicians in the field have the necessary will but face logistic problems in carrying out their activities. What we have found particularly significant in 2002 is the probable implication of insects in the spread of the disease, based on the two modest studies that we were able to carry out. Treatment of patients is still relatively unstructured, and we think that with the involvement of all our partners and the commitment of our political decision-makers, it can be improved.

Acknowledgements

Participants involved in drafting this report: Dr Louis Ngoma, Departmental Director of Health, Kouilou; Dr Hilaire Bassakouahou, Coordinator of Buruli ulcer (BU) control activities, Congo; Dr Eugenio Malfati, Chief Physician, CMSO, Agip Congo; Ms Alice-Evelyne Backouma, Head of Epidemiological Surveillance; Mr René Mbouangui-Ndouma, BU Regional Supervisor, Kouilou department; Ms Antoinette Ognongo-Ibiaho, Accountant-secretary, Kouilou; Mr Gaston Mampinga, WHO driver, Kouilou.

COMMUNITY-BASED EARLY DETECTION IN CÔTE D'IVOIRE

Professor J-M Kanga, Dr D.E. Kacou, Dr K.J. Yao, Dr K. Kouamé and Dr L. Avoaka

In Africa, the frequency of ulcerative forms and disabilities associated with Buruli ulcer poses a problem for case management of the disease. For this reason, early case detection is one strategic area of Buruli ulcer control for which priority has been given. In Côte d'Ivoire, early detection has been pursued since 1998, following the international conference on Buruli ulcer that was held there.

The overall aim is to reduce the proportion of ulcerative forms and cases of residual disability. The targets are:

- primarily, cases involving papules, nodules and ulcers 2 cm or less in diameter, which may be treated by excision-grafting on the spot;
- all other cases requiring transfer to a health centre for plastic surgery.

The strategy involves an initial mass detection campaign, which is carried out by a mixed team of physicians from the central level and district health workers (community health workers, nurses and physicians). This mass campaign is then relayed by district health workers, through small-scale detection activities (systematic passive case detection in health centres, active case detection in the communities).

Case detection activities began in Zoukougbeu prefecture, the pilot zone. All villages in the prefecture were covered. Starting in 2001, five other zones were covered (Danané, Douékoué, Sakassou, Tanda and Yamoussoukro). After four years' activity, the results achieved in Zoukougbeu are positive: case detection of nodular forms has increased and there has been a concomitant reduction in the number of cases with ulcerative forms.

These measures have also resulted in an increase in the number of patients who consult when the disease is at an early stage and in improved technical capacity.

Mass detection campaigns, supported by small-scale case detection activities, are an effective strategy for Buruli ulcer control; their more widespread use could help better to control prevalence of complicated forms and disabilities.

BURULI ULCER CONTROL IN TIME OF CONFLICT: THE CASE OF CÔTE D'IVOIRE

Professor Henri Assé

Introduction

Since 19 September 2003, Côte d'Ivoire has been torn by an armed conflict, with deep repercussions on the Buruli ulcer control programme. The consequences of this six-month old conflict are felt at every level of the health-care pyramid. Today, the primary objective of all those involved in Buruli ulcer control in Côte d'Ivoire is the search for a global strategy with which rapidly to rebuild the health care system.

I. The state of Buruli ulcer control prior to the conflict

Côte d'Ivoire has made an undeniable effort to implement Buruli ulcer control. For over a decade now, we have participated in all the major meetings that have made it possible to develop and implement control measures in the field. The National Mycobacterial Ulcer Control Programme has succeeded in marshalling numerous resources in order to improve the operational capacities of peripheral treatment centres. Many clinics have been equipped with operating facilities and mobile surgical teams have made it possible to treat the majority of patients in peripheral centres.

The Raoul Follereau Institute of Côte d'Ivoire is resolutely committed to providing surgical treatment for active forms and sequelae of Buruli ulcer. Thanks to their considerable admission capacity and expertise in the field of rehabilitative surgery, its two facilities at Adzopé and Manikro have become essential referral centres for the case management system. At the same time, basic and operational research programmes have been undertaken both by the Institute and the National Programme.

Over the past five years, training programmes have made it possible to train many nurses and physicians in the skills needed to provide early diagnosis and treatment for patients. Although things could certainly have been better, year by year we were improving our programme's performance thanks to our partners:

– the French Raoul Follereau Association,
– ANESVAD,
– WHO,

as well as many other anonymous partners working unstintingly in the shadows to help us to develop a treatment system that may be described as almost up to scratch.

II. The present consequences of the armed conflict

On 19 September 2002, an armed conflict burst upon us like a thunder clap in a clear sky. In a single night, rebels occupied a part of the country including all the areas in which Buruli ulcer is endemic. Since that date, the country has been divided into several zones:

1) The free zone

This zone is located in the south, and includes:

– two referral centres:
  - the Raoul Follereau Institute (Adzopé),

- the dermatology department at Treichville Teaching Hospital (Abidjan),

– one specialized peripheral centre at Kongouanou, to which surgical missions are no longer possible.

2) The occupied zone

This zone is separated from the free zone by a buffer zone which lies south of Bouaké; the zone comprises:

a) the major Buruli ulcer foci in the Bandama valley and the Great Lakes region;
b) a huge western focus which stretches into Guinea and Liberia. It includes:
   - in the centre
     One referral centre: the Manikro Raoul Follereau Institute, which is surrounded by a host of peripheral clinics that are deeply involved in providing treatment for Buruli ulcer (such as the Sakassou clinic);
   - in the west
     One specialized centre (the Zouan-Hounien Buruli ulcer clinic) which is well equipped for surgery.

At present, the Manikro institute is closed and there are no surgical missions to the Zouan-Hounien clinic.

3) The buffer zone

This is a 50-kilometre-wide strip between Bouaké and Yamoussoukro in which the international forces are stationed. However, it is a combat area. It includes many villages in which the disease is endemic and which are at present isolated.

4) The liberated zone

This is an area which was liberated after a bitter struggle. It is located around Daloa, the site of the earliest Buruli ulcer focus in Côte d'Ivoire. It includes one centre specialized in Buruli ulcer treatment, located at Zoukougbeu. This situation means that most patients and frontline facilities are now located in sensitive areas. Consequently, the conflict has had an immediate impact on Buruli ulcer control. This involves:

– large-scale and sudden movements of population and health workers;
– patients abandoned in certain facilities and the interruption of their treatment;
– the breakdown of the patient referral system;
– the emergence of new health priorities, overshadowing Buruli ulcer;
– the overburdening of those health facilities still operational;
– the plundering and destruction of equipment.

Large-scale movements of population

People fleeing from the centre, north and west have been concentrated in the south of the country (the free zone). At present, 80% of the population lives on 40% of the country's territory. These population movements affect both patients and health workers, some of whom are still living in refugee camps in Guinea or Mali.

Patients abandoned in health facilities

The most telling example is the Manikro centre. Together with Adzopé, Manikro forms the Raoul Follereau Institute of Côte d'Ivoire. It is located in the heart of the endemic region and has a capacity of 156 beds. It is the referral centre for the whole of the lakes region, which is known to be an area of high prevalence. Because it is located near Bouaké (the second city in Côte d'Ivoire and now the rebel capital), the centre ceased its activity on 19 September 2002. The staff were compelled to abandon the centre overnight, leaving more than 100 patients, most of whom had undergone operations or were immobilized in plaster. Dr Sica, who alone had stayed at the centre, was forced to leave five days later after a systematic evacuation order was issued for the war zone.

Since then, rather than curative treatment, the need has been to provide humanitarian assistance, which only the Red Cross, Médecins Sans Frontières and WFP (the World Food Programme) are capable of handling.

As is the case of any bitter armed conflict, it has been difficult and dangerous to secure a humanitarian corridor.

As the Government was not able to take into account the special situation at Manikro, it was necessary to use the missionary network to enable patients to survive and to provide primary care, pending the organization of their medical evacuation.

Finally, all the patients at Manikro were evacuated to Adzopé. There are no longer any patients at Manikro, and the centre, much of which has been transformed into a bunker, has become a rear base for the rebels.

Breakdown of the patient referral system

In fact, it is as if we live in two different countries divided by the horizontal strip running close to Bouaké. In the occupied area, personal travel is restricted or prohibited. In addition, means of transport are in short supply or totally lacking. No rural roads or tracks are really safe and the referral system is completely paralysed. Moreover, all surgical missions have been put on hold because of the danger, and because of the disruption of the teams and the breakdown of much of the logistics.

The emergence of new health priorities

The humanitarian situation caused by the large-scale population movements has overshadowed Buruli ulcer, even in those centres in which activity has been maintained.

For example, the Zouan-Hounien Buruli ulcer centre, which is now located in occupied territory, is the only operational health centre in an area in which there has been heavy fighting and numerous massacres of civilians. Clearly, Buruli ulcer cannot be a priority.

Overburdening of those health facilities still operational

Significantly, in the occupied territory, only those facilities run by missionaries are still operating. However, they suffer from isolation and lack of communications with the referral centres located in the free zone. As a result, they are permanently overburdened. Nowadays, they are no longer visited by surgical missions or able to transfer serious cases. The closure of Manikro is also responsible for a high occupancy rate in the referral centres. Besides this, once cured, patients are unwilling to leave the hospital for security and humanitarian reasons. This overloading inevitably affects the quality of care in the system as a whole.

Plundering and destruction of equipment

We had become accustomed to vehicles being hijacked. All the teams involved in Buruli ulcer control had experienced it. However, nowadays, things have got worse. Raiding parties run wild and most of the rebels' vehicles in the occupied zone have been taken from the health services. The fighters have also turned their attention to stocks of drugs and the violence that has accompanied these acts of vandalism during the conflict means that a huge budget will be needed to rehabilitate some of the centres.

Conclusion

In spite of these deep upheavals which have affected Buruli ulcer control, we look forward to rapidly rebuilding our treatment system because our human resources, while scattered, are fortunately still alive.

For the time being, the upsets are mostly of an operational nature. Nevertheless, there will probably be a sharp increase in morbidity and a surge in infirmities caused by Buruli ulcer on account of the poor quality of treatment because of the conflict.

We are also convinced that with the end of the crisis, many humanitarian priorities will overshadow Buruli ulcer and that, perhaps for many years, our leaders will find it hard to listen to our concerns.

For this reason, while repeating my thanks to our partners, I assure them that we have not given up our efforts and appeal to them for continued support so that our efforts to control Buruli ulcer may ultimately end in victory.

UPDATE ON THE BURULI ULCER SITUATION IN THE PROVINCE OF BAS-CONGO

Dr Eric Bafende

This report describes the Buruli ulcer situation in the Bas-Congo region of the Democratic Republic of the Congo from 1989 to 2002. A total of 121 consecutive cases were treated at the Evangelical Medical Institute, Kimpese. The admission rate increased from an average of 4.5 cases to 31 cases per year. In 2002, only 14 cases were treated.

The number of reported cases is underestimated. Firstly, the average cost of treatment in our hospital is US$ 466 per patient. This is extremely high for the populations affected in a country where the average annual income per year of the rural population in Bas-Congo is less than US$ 200. Secondly, in August 2002, we visited one of the villages near Songololo, where we found 20 cases in a day. Thirdly, both health workers and the population are poorly informed about the disease. For several reasons including the high cost of treatment, many patients prefer to use local traditional medicine. In the past, 80% of the BU patients came from Songololo. These days, the number of patients coming from Songololo has decreased four times, which could mean that people are not seeking medical treatment. Based on our findings, the Songololo area needs to be investigated further.

The proportion of patients coming from Kimpese has also decreased from 11% to 0%, probably due to the good politics of water supply at Kimpese which results in lesser risks for children to play and swim in the river. The proportion of patients coming from Angola, living in the two refugee camps near Kimpese, has increased from 9% to 42%. Because of the good water supply in these refugee camps, we speculate that the patients were infected in Angola or on the road from Angola to the refugee camps. The proportion of patients coming from Lukala, a small city located 11 km away from Kimpese, has also increased from 0% to 16%. This situation needs to be further investigated.

The average age of Buruli ulcer patients is 24±5 years. More than 60% are under 15 years old and none under 4 years old. The 4 to 15 year old range corresponds to the age at which children play and swim in rivers and stagnant waters. Most patients report late and this observation is similar to the 96.4% of cases reported in Benin.

From 1989 to 2002, the duration of the hospitalization of the patients has decreased from 6 to 3 months due to improved management practices at the hospital. However, the duration of the hospitalization of one-and-half months reported from Zagnanado in Benin is impressive. These days all patients admitted to our hospital stay until their wounds have fully healed. In the past, about 11% absconded before they were fully cured. Mortality rate has also reduced from 7% to 0%.

In conclusion, there may be many cases of Buruli ulcer in the Bas-Congo and possibly the whole of DRC. Because of difficulties in accessing health care, the number reported may represent only the tip of the iceberg.

BURULI ULCER ACTIVITIES IN GHANA, 2002

Dr Edwin Ampadu

Introduction

A national case search was conducted in 1999. The overall prevalence rate of active Buruli ulcer lesions was 20.7/100 000 but was as high as 150.8/100 000 for the population in the Amansie West and Upper Denkyira districts. The first recorded case was in 1972. During that time, the probable presence of additional cases was postulated along the tributaries of the river Densu. Since 1972, Buruli ulcer has been identified along the tributaries of the Densu river and in other rivers including the Offin and Tano rivers in the middle belt of the country.

Case detection and surveillance

In 2002, a total of 853 new cases were recorded from 20 endemic districts.

Clinical form	New cases	% covered
Nodule	92	10.8
Plaque	11	1.2
Oedema	80	9.4
Ulcers	**652**	**76.4**
Osteomyelitis	18	2.2
Total	**853**	**100**

With the introduction of the new WHO surveillance format, 20 of the 60 targeted districts are currently reporting regularly, representing one-third of the national strategic plan for the next five years. Some 20 officers countrywide have been trained in the use of the forms and there are plans to scale up to cover the other districts in the coming years.

Two major training activities in early case detection were carried out for 200 village volunteers in four endemic districts.

Capacity building

Training

Five separate regional trainings were organized in the Ashanti and Central regions of Ghana, with support from American Leprosy Missions (ALM) and the Health Foundation of Ghana (HFG). The training targeted doctors, nurses and other paramedical staff. A total of 10 doctors and 37 other health care staff, including nurses, were trained. HFG, a local NGO, also supported two district hospitals to train 200 community volunteers in case detection and referral.

Case management

ALM provided surgical dressing materials to support management of Buruli ulcer to benefit 12 health institutions. Acción Sanitaria y Desarrollo Social (ANESVAD), a Spanish nongovernmental organization, provided a surgical theatre to improve patient care at St Martin's Catholic Hospital in Agroyesum, Ashanti.

Research/research collaborations

A clinical trial study to assess the efficacy of streptomycin and rifampicin for early Buruli ulcer lesions took place at St. Martin's Catholic Hospital, one of the endemic district hospitals. WHO supported the initiative together with the Association Française Raoul Follereau (France) and the Nippon Foundation (Japan). The Centers for Disease Control and Prevention in Atlanta (United States) are also researching the economic costs to household due to Buruli ulcer disease, a joint activity being carried out with the national Buruli Ulcer Control Programme. The Kumasi Centre for Collaborative Research (KCCR) is working with the Bernhard Nocht Institute for Tropical Medicine (BNITM) in Hamburg (Germany) to establish the dry reagent-based "field PCR" as a novel tool for the rapid detection of *M. ulcerans* in Ghana. Research on functional limitations due to Buruli ulcer is currently under way with external medical student researchers from Groningen University (Netherlands).

National programme level

The programme has enjoyed considerable support from WHO and the Ministry of Health of Ghana. A new national office for Buruli ulcer control has been established .The programme has a vehicle to facilitate work at both national and district levels. The staff strength is two.

Constraints

- High costs of treatment.
- National exemption policy on Buruli patients is poorly applied at facility levels.
- Huge backlog of patients needing surgical treatment.
- Late reporting.
- Management of the disease is seen as unattractive in medical circles and health workers are not interested in the management of the disease.

The way forward in 2003

Surveillance

- Strengthening of surveillance activities in endemic districts and training of 20 district disease control officers in the use the new forms.
- Job training offer for field officers in the proper use of the surveillance forms.
- Introduction of local health education materials to the medical community and the general public.

Advocacy

- Intensify advocacy work using media houses and the television network.
- Collaborate in research activities on the disease epidemiology and case management.
- Search, explore and collaborate with local healers in treatment of the disease.

Capacity building

Train doctors, nurses and community volunteers in case management and early case detection.

Case management

Use the remaining tissue culture stored at the Noguchi Institute to treat as many Buruli ulcer patients as possible.

Acknowledgements

International level

The national programme is grateful to WHO for materials and financial support to establish the country office. The programme received support from the Sasakawa Memorial Health Foundation for the tissue culture trial and for putting the remaining tissue material at the disposal of the national programme. Makuaka (Japan) provided support to rehabilitate Buruli ulcer patients. ALM and Medical Assistant Programme provided dressing material totalling US$ 500 000 to 10 endemic districts and supported three surgical training programmes in the Ashanti region. ANESVAD supported the construction of a modern theatre for St. Martin's Catholic Hospital in Agroyesum. The Humanitarian Aid Relief Team (HART) visited the programme and carried out surgical outreach services with local health staff.

Local level

The national programme thanks the Noguchi Memorial Medical Research Institute for its support and the research series on Buruli ulcer disease. The Ministry of Health has also been helpful in running the programme office. HFG has supported two endemic districts with the application of phenytoin for treatment of the disease. AIFO assisted the national programme by providing funds for the Ga District Health Management Team to carry out district control activities.

MINISTRY OF PUBLIC HEALTH, NATIONAL PUBLIC HEALTH AUTHORITY, REPUBLIC OF GUINEA

Dr Adama Marie Bangoura

Overview

The Republic of Guinea is in west Africa. It shares borders with Côte d'Ivoire and Mali to the east, Liberia and Sierra Leone to the south, Guinea-Bissau and Senegal to the north and has 300 km of coastline on the Atlantic Ocean to the west. Buruli ulcer is endemic in most countries bordering Guinea (Côte d'Ivoire, Liberia and Sierra Leone). Guinea has a total area of 245 857 km^2 and an estimated population nearing 8 million inhabitants. It is subdivided into four natural regions (Lower Guinea, Central Guinea, Upper Guinea and Forest Region (the Guinea Ridge), and various administrative units (Conakry, the capital city, and 7 administrative regions, 33 prefectures and 5 communes).

Despite its rich subsoil and progress in development, Guinea remains among the least developed countries of the world. Its principal activities are agriculture, livestock farming, trade, the craft industry and fishing.

The environment has suffered severe deterioration during the past few years as a result of development efforts (construction of dams, agricultural development projects, fishing) and the massive inflow of refugees from Côte d'Ivoire, Liberia and Sierra Leone.

- The health system is pyramidal, with three levels: national, intermediate and peripheral. It offers opportunities for rapid integration of disease management activities.
- The predominant diseases are malaria, acute respiratory infection, diarrhoeal diseases, intestinal parasitic disease and sexually transmitted infections, including AIDS.

Mycobacterial diseases such as Buruli ulcer, leprosy and tuberculosis are also endemic.

Buruli ulcer situation

While the exact extent of the disease in the country is not known, data from a situational survey on Buruli ulcer in the Forest Region and from passive case detection in health facilities has revealed the following:

A yearly increase in the number of cases

Despite underreporting, cases have increased from 4 in 1995 to 324 in 2001 and 332 to date, 228 of which are active; 48% of cases are women and 43% children. At the time of the survey, the active case detection ratio was 9.8 to 155 per 100 000 inhabitants in the surveyed zone. There is also a high rate of late-stage cases: 87% compared with 5.42% of early-stage cases.

Geographical spread of the disease

Some 95% of Buruli ulcer cases are in the Forest Region (the only region surveyed), affecting all six of its prefectures, including its refugee camps. However, some cases have been reported in the prefectures of Forecaria and Kindia (Lower Guinea), Kankan and Siguiri (Upper Guinea), Dalaba and Mamou (Central Guinea), revealing a geographical distribution of cases across the country's natural regions.

Case management

The serious problem faced in controlling this disease lies in case management of patients, which sometimes requires specialized treatment (plastic surgery) at a very high cost in relation to the income of patients, who are usually poor. Some of the difficulties encountered include lack of information and training for health workers to recognize the disease and treat patients; lack of adequate management facilities (limited hospital capacity, lack of surgical equipment); and sociocultural factors and the cost of modern treatment methods that seriously limit access to treatment.

Underreporting of cases

This is a result, inter alia, of the disease situation not being evaluated throughout the country. Buruli ulcer is not integrated in the Minimum Package of Activities of treatment facilities or in the National Health Information and Management System, hindering the establishment of a database with reliable data that can be updated.

Update on Buruli ulcer control

Buruli ulcer is a major public health problem for which the Government of Guinea has shown the political will to control by creating PNLUB in 2001. This programme is a response by the Ministry of Public Health to assist these neglected populations.

The year 2002 marked the first year of implementation of the five-year 2002–2006 PNLUB Plan of Action.

Activities

1. Improvement of working conditions of the programme coordinating body

Procurement of a computer, audiovisual and communications equipment and purchase of a vehicle.

2. Validation by the cabinet council of the Ministry of Public Health of the five-year Plan of Action and the national Buruli ulcer control policy

The plan has four strategic areas: advocacy and resource mobilization, promotion of early detection, global case management and promotion of research.

3. Advocacy for resource mobilization

- State involvement in financing PNLUB through the 2003 National Development Budget.
- Ongoing discussions for cooperation with NGOs in the endemic zone: Plan Guinée, Mission Philafricaine in Macenta (UNCHR);
- Requests for cooperation have been addressed to foreign NGOs (MAP International, Association Française Raoul Follereau, Nippon Foundation).

4. Strengthening the knowledge and skills of health workers:

Twenty-four laboratory technicians, 50 health professionals, most of whom work in surgery, and 24 district heads, through 3 training workshops, including a national workshop on surgical case management, held in November 2002.

5. Health promotion activities

Health promotion activities have focused on:

- Awareness-raising for administrative, political and health officials; the distribution of promotional material (1000 brochures, 500 posters and 2000 comic books on Buruli ulcer) in

rural schools of the Forest Region, the community health worker training school in N'Zérékoré and to health professionals.
– University of Conakry involvement, by organizing a lecture discussion on Buruli ulcer and introducing a module on the disease in the School of Medicine's curriculum.

6. Case management activities

These take place mainly in the medical centre of the Macenta Mission Philafricaine, where 40 patients have received free treatment. A study on the cost-evaluation of Buruli ulcer treatment is being carried out; five patients have been treated at the N'Zérékoré regional hospital and one patient has been treated at the Donka teaching hospital.

The implementation of the "July–December" Plan of Action financed by WHO will rapidly make it possible to provide case management for a significant number of cases detected during the survey.

7. Mission and Monitoring

Monitoring of control activities by the national coordinating body and a joint WHO-PNLUB mission headed by the WHO Representative in Guinea has been carried out in the Forest Region and in the Kolla, Kouankan and Nona camps for Liberian and Sierra Leonean refugees.

8. VIP visits

The following have visited coordinating body headquarters:
– WHO Representative in Guinea and her chief staff members;
– Director of International Affairs of the Nippon Foundation;
– Assistant Coordinator of Côte d'Ivoire's PNUM (in connection with the development of a five-year plan and the national policy document).

The following persons have met with the coordinating body in N'Zérékoré:
– Coordinator of Côte d'Ivoire's PNUM;
– Director of the Raoul Follereau treatment centre in Adzopé, Côte d'Ivoire, in connection with the national workshop on surgical management, where a south–south cooperation agreement for managing complex cases and training for surgeons in the endemic zone was mentioned and should be implemented as soon as hostilities in the country cease.

Constraints

– Insufficient resources: PNLUB receives technical, material and financial help from WHO only.
– Lack of information on national prevalence rates.
– Under-equipment of treatment facilities' surgical and laboratory services.
– Low level of community involvement in controlling Buruli ulcer. The disease is considered to be the result of ill fate and responsive only to traditional methods.

Prospects

– Continue advocacy and resource mobilization.
– Evaluate the disease situation in the Forest Region and at least one natural region.
– Continue health worker training activities and treatment of patients.
– Raise awareness in communities with a view to changing behaviour in endemic zones.
– Strengthen the monitoring of control activities.
– Build and equip PNLUB headquarters.
– Further equip treatment facilities with surgical and laboratory material.
– Further equip the national coordinating body with computer, logistic and communications equipment.
– Supply selected management facilities with drugs, consumables and laboratory reagents.
– Organize a study abroad trip to share experiences.

Conclusion

Buruli ulcer has been the subject of increasing interest and commitment from the State of Guinea through the creation of PNLUB and its contribution to funding control activities and health workers. Despite these efforts to control the epidemic, much remains to be done. Control of Buruli ulcer presents a challenge to Guinea in terms of resources and thus requires assistance from the international community. In controlling this disease, the following points should be emphasized:

- multidisciplinary training of health workers in all fields and the need to strengthen health facilities' equipment to help put lessons learned into practice;
- the involvement of traditional healers and intercountry cooperation in sharing experience and the promotion of research to curb the disease and its consequences.

Acknowledgements

Ministry of Health officials and the PNLUB coordinating team would like to thank Côte d'Ivoire's PNUM team for its quality technical support in developing policy documents and the five-year plan as well as in organizing the national training workshop on surgical case management of Buruli ulcer; and WHO for its continuous technical, material and financial support to our new programme.

We would welcome support from other partners to help us carry out our activities and help with other control programmes and research institutes for experience-sharing.

PROGRESS REPORT ON THE PREVALENCE OF BURULI ULCER IN THE NAKASONGOLA DISTRICT, UGANDA

Investigative team: *Dr H. Wabinga, Principal investigato (PI)r; Dr R. Najjemba, Co-Principal investigator (CO-PI)*

Purpose of the study: to determine the current trend of Buruli ulcer in Nakasongola (formerly Buruli county), a disease first described in the region. Buruli ulcer is currently reported in epidemic proportion in west Africa.

Study procedure

The principal investigator made three trips (from 18 to 22 January) to Nakasongola district to explain the purpose of the study to the district health authorities, which was basically the concern of international health workers about Buruli ulcer in Nakasongola district. Specifically, the concern was whether the disease was still present in the community and whether health workers were missing the diagnosis. Another concern was whether the disease had disappeared and what factors might have led to its disappearance. The principal investigator met with the District Director of Health Services to outline the activities of study, to seek permission to undertake the study and to request that the information be communicated to district government officials. The Office of the District Director of Health Service was also asked to mobilize health workers to carry out the study.

A programme was drawn up for training the health workers who would be involved in the study. The date of training was Thursday, 23 January, and invitation letters were sent out to all the 18 health centres in district to select one health worker who would be willing to participate in the study.

Health worker training, 23 January 2003

The training took place at Zion Guest House in Nakasongola. A total of 25 participants attended. The Assistant Secretary for Health, who represented the District LC 5 chairman, officially opened the workshop. The District Director of Health welcomed participants and officially invited the Assistant Secretary for Health to officially represent CAO and open the meeting. The training programme included an outline of the epidemiology of the disease, of the methods to be used in the study, a review of the study tools, the role played by participants and the way forward.

A total of 17 health workers accepted to participate in the study, which included administration of questionnaires to patients suspected of having Buruli ulcer and key informant interviews with elders in their community. The health workers would also advise patients with ulcers to attend the health centre for further management.

It was agreed that in one month (February 2003), health workers would follow up suspected cases in the community, administer the questionnaires and advise patients on the next steps of management. To ensure close supervision of the data collectors, a district focal person was identified and specific dates for the visit by the PI and a CO-PI plus a surgeon from Mulago hospital were set for patients with suspected Buruli Ulcer to attend health centres III and IV. The surgeon from Mulago Hospital would manage these patients and also train the health workers in the health centres on how to manage these ulcers. Tissue samples would be taken for analysis to confirm the diagnosis of Buruli ulcer.

A questionnaire was also administered to health workers to assess their level of knowledge about Buruli ulcer and whether they had observed similar lesions before.

FIRST CONFIRMATION OF BURULI ULCER (*MYCOBACTERIUM ULCERANS*) OUTBREAK IN SOUTH SUDAN, JULY 2002

Dr Abdourahmane Sow, Dr Ayana Yeneabat

In July 2002, WHO South Sudan sent an investigative team to Mabia Camp fro for internally displaced persons (IDP) in Tambura County, Western Equatoria, South Sudan, where many cases of tropical ulcer had been reported. The team included WHO, the Kenya Medical Research Institute (KEMRI) and CARE International, Sudan. The objectives of the investigation were to verify the extent of the outbreak, to collect specimen for confirmation of *M. ulcerans* infection, to assess the response needs and to advise authorities on public health measures.

Mabia Camp is located 15 miles south of Tambura, which is 154 miles north of Yambio, the capital city of Western Equatoria Region. People displaced by war came from Raga County in the Bahr el Ghazal Region of southern Sudan and from Central African Republic. Many were in a poor condition after trekking for more than one month through the jungles to escape war. United Nations agencies, international NGOs, local churches and the county authorities provided assistance to resettle these newcomers.

The IDP camp is in an equatorial tropical climate area with thick equatorial rainforest. The rainfall starts in March/April and continues until November. Newcomers are given plots of land to cultivate and, since their arrival, have been working in these fields. Camp registration shows a total of 4074 households and a population of 20 794 (49.3% female and 50.7% male).

Since the settlement on December 2001, there have been no reports of any significant disease apart from eye infections and a few cases of diarrhoea.

Materials and methods

Using a working case definition of "any child or adult who presented with skin ulcer that started as a painless nodule or papule on the limb or any other part of the body and resident of Mabia IDP Camp", data were gathered from case histories and observations made during investigations and from medical records from the clinics.

The health unit established a separate record book in the clinic for all suspected cases of Buruli ulcer and deployed a mobile team to the camp to register new cases and treat those who were too sick to come to the health unit. Data on sex, age and date of first visit were extracted from both the clinic and the mobile team registration books.

The investigation team also visited and interviewed local authorities and some families where those affected live. Data on demography, history of the camp, source of drinking-water and history of the outbreak were gathered from these interviews. The team also visited a stream and a shallow hand-dug well where some of the affected families collected water for domestic use. Soil from the well, the stream's bed and the compound of at least one family were collected for laboratory investigation in KEMRI.

Summary findings

The outbreak started in mid-May 2002, and almost all affected were from the IDP camp. The disease presents with painless nodule, which later ulcerates. Most lesions are on the lower legs, although people had some abdominal and upper limb lesions. There were no reported deaths associated with the disease. A total of 939 cases were recorded and more than 70% were children under 15 years of age. The proportion of males affected is much higher than females (60% were male). It is interesting to note that even when the clinic and mobile data are treated separately the ratio remained the same. Recent follow-ups show that there are new cases from the host community and the disease tends to spread to neighbouring villages of the indigenous community. Moreover, some ulcers that had healed have opened, showing the need for improving wound care and surgical excision.

Laboratory investigations were carried out in collaboration with WHO, KEMRI, and Tropical Institute of Medicine, Belgium. All the samples were processed at KEMRI Centre for Virus Research in a BSL 2+ facility. Specimens in transport media were centrifuged at 1500 rpm for 10 minutes and the supernatant was discarded. Fresh transport medium was added immediately and aliquots made for shipment to Mycobacteriology Centre in Antwerp. Swab specimens were sent for PCR analysis. The smears were exposed to auramine staining. General PCR was designed using *Mycobacterium ulcerans* (Pam small's Malaysian strain) with the gene of interest being 16S ribosomal DNA gene.

The samples were all subjected to the PCR using oligonucleotide primers synthesised by Bioserve Biotechnologies. All *Mycobacterium* species exhibit the 16S rDNA gene, which is highly conserved within this population. *M. ulcerans* DNA from Pasteur Institute-France served as a positive control for the diagnosis. A second species-specific PCR was run with oligo-primers coding for the Insertion Sequence (IS*2404*) gene that targets a gene found only in *M. ulcerans* (Portaels et al.). Primers for the PCR were synthesised by Bioserve Biotechnologies-US.

Auramine staining showed acid-fast bacilli in one of the samples tested. PCR results for the presence of ribosomal DNA were positive for some of the samples. The expected size of the target fragment is 1430 base pairs (bp) on 1% agarose gel. See Figure 1.

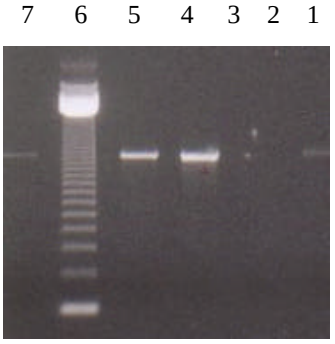


Figure 1: Lanes 1 & 7 test samples, lanes 2& 3 are negative controls, lane 4 *M. tuberculosis* (control), lane 5 *M. ulcerans* (control), lane 6 123 bp marker

PCR results for the IS*2404* gene picked on only one sample as positive for *M.ulcerans*. This produced a weak product. See Figure 2.

Figure 2: Lane 1 positive control (*M. ulcerans*), Lane 2 sample on lane 3 spiked with positive control DNA, lane 3 test sample, lane 4 test sample, lane 5 negative control

From the results obtained it is evident that *Mycobacterium ulcerans* was the etiological agent of the skin ulcer outbreak in Mabia, South Sudan.

Conclusions

Before July 2002 there were no confirmed cases of Buruli ulcer in Sudan although the disease has been reported in neighbouring Uganda and in many other sub-Saharan countries. Thus, this is the first confirmed Buruli ulcer in Sudan, showing that the disease is spreading to non-endemic countries. The high number of recorded new cases shows the potential outbreaks in remote and crowded areas.

Buruli ulcer poses a challenge not only in early recognition, but also in case management. This is particularly so in areas like Southern Sector of Sudan where existing health services are fragile and trained health workers are scarce. To narrow this gap, WHO South Sudan, with support from the GBUI and its EWARN partners, will continue to retrain health workers, orient communities and scale up community surveillance for early recognition and case management. Request for supporting such efforts is submitted to the GBUI and is expected to get continued support.

MYCOBACTERIUM ULCERANS INFECTION IN FRENCH GUYANA

Dr Roger Pradinaud

Improvements in diagnosis, including the installation of the Pasteur Institute in Cayenne (Dr Pascal Launois and Ghislaine Prévot-Linguet), were already described last year. In addition, epidemiological research can now be carried out through the Institute's Entomology Department, with the possible participation of the Research and Development Institute for soil sciences, hydrology and malacology.

- The work of Laurent Marsollier and the teams working with Bernard Carbonnelle (Angers) may benefit from our geographical position as a French province in the Americas as a research site.
- The same is true for the Tropical Medicine Institute in Antwerp (Professor Françoise Portaels), since French Guyana is "part of Europe" and the Guyanese Institute for Tropical Dermatology is increasingly turned towards that continent.

The convening of a WHO meeting in Cayenne, initially restricted to French-speaking participants, may be envisaged for next year and even extended to international participants.

Regarding treatment, we are continuing with the surgical excision of necrotic tissue, physiotherapy by heating with "super Vapozone" and, in the event of uncertainty about intracellular diffusion of the mycobacteria (particularly where multiple lesions are present), supplementation with 1–2 months' treatment with clarithromycin in daily doses of 1 g. Since 2002, we have stopped using the rifampicin–clofazimine combination.

Our patients have generally been cured within two months. Some cases of recurrence have been observed but none of reinfection.

An extensive manifestation, resembling erythema nodosum, was observed on both legs of an HIV-infected patient. PCR was negative but the culture, which was positive, confirmed the presence of *M. ulcerans.*

In all the other patients, we have seen single and isolated sites, with multiple lesions being found on only one limb.

One case, in which HIV infection developed into AIDS, did not respond to our therapeutic protocol and the patient died, with the single knee lesion in a chronic state. An extremely unusual case of coexistence of *M. ulcerans* and cryptoccosis was found in a diabetic whose immune system had been weakened by corticosteroid therapy (J. Versapuech, D. Sainte Marie, F. Bissuel, Sarrouy, C. Aznar, P. Launois, R. Pradinaud. Cryptococcose cutanée et mycobactériose à *Mycobacterium ulcerans* chez un malade VIH négatif. Ann Dermatol Venereol 2001;128:3S184)..

The Dermatology Department has recorded 2903 cases of leishmaniasis and this parasitic disease was associated with *M. ulcerans* in 7 cases (out of 197 cases of *M. ulcerans* recorded in the same department).

MYCOBACTERIUM ULCERANS IN PAPUA NEW GUINEA, 2002

Sister Joseph

Table 1. **Average annual incidence of *M. ulcerans* in 2002 compared with 2000**

	Average annual incidence of *M. ulcerans* in PNG, 2002	Incidence in 2000
Sepik river	20	13
Aitape	3–4	0
Vanimo	8–10	3
Kavieng	1–2	0
Port Moresby	6	0
Oro Province	4	7
Fly River	2	1

East Sepik Province, 2002

In 2002, all the cases were children. This year, the pattern has reverted to 2.25:1 children to adults. The excess of girls is seen again, as last year, 5:3. Adults almost equal (M 3; F 2).

The commonest site, as usual, is the leg (8 cases), the others being elbow and hand (2 cases), sacrum (2 cases) and shoulder (1 case).

As usual, we have seen no papules, nodules or small plaques. There were five large plaques and **eight oedematous types**, which is far more than in previous years when oedema was a rarity.

The standard work-up is:
1. slides for acid-fast bacilli (AFB) in Wewak
2. specimen for PCR and culture in Antwerp
3. histopathology in Port Moresby.

Table 2 shows the tabulated results.

Table 2. ***M. ulcerans*** **in East Sepik Province, 2002**

No.	Analyses in PNG		Analyses at ITM, Antwerp, Belgium		
	AFB Wewak	Histo	PCR	AFB	Culture
1	–ve	+ve		–ve	
2	+ve	NS		+ve	
3	–ve	+ve		–ve	
4	+ve	NS	+ve	+ve	+ve
5	+ve	NS			
6	+ve	+ve			
7	+ve		+ve	-ve	–ve
8	+ve	+ve			
9	+ve	+ve		+ve	
10	–ve	+ve	+ve	+ve	+ve

- 3 patients had no specimens taken; the other 10 all had specimens taken
- 10 AFB slides were taken; 7 were positive
- 10 histopathology: 6 positive, 3 nonspecific, 1 lost
- Specimens to Portaels: 7 reported
- Results show good correlation with the Belgian laboratory and all cases were positive on at least one test

Oro Province, 2002

Seven cases were seen. All were confirmed histologically. All cases had plaques and ulcers; none had oedema, nodules or papules.

Table 3. **Standard adult : child ratio and site (mainly legs), Oro Province, 2002**

No.	Age (years)	Sex	Location of lesion
1	36	Male	Leg
2	40	Female	Leg
3	Child	Female	Leg
4	Child	Female	Arm
5	Child	Male	Leg
6	Child	Male	Leg
7	Child	Male	Hip

Sandaun Province, 2002

3 cases (1 adult, 2 children)

- Abdomen = 1
- Axilla = 1
- Knee = 1

Table 4. **Seasonal incidence of *M. ulcerans*, 1971–2002**

Year	Jan.	Feb.	Mar.	April	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Total
1971	–	–	–	–	–	–	7	2	1	2	4	3	19
1972	5	3	8	2	2	3	2	3	2	2	0	2	34
1973	2	0	2	1	3	1	2	3	0	1	3	2	20
1974	0	1	4	2	1	2	1	2	1	2	1	1	18
1975	1	4	1	–	–	–	–	–	–	–	–	–	6
1977	–	–	–	2	2	1	1	1	2	3	1	4	17
1978	1	2	1	2	5	0	2	2	7	4	1	0	27
1979	3	7	7	4	4	–	–	–	–	–	–	–	–
1987	–	–	–	3	5	2	1	1	1	0	0	0	13
1988	0	0	2	2	1	0	0	2	2	3	8	5	25
1989	3	2	2	4	2	2	1	0	0	1	2	1	20
1990	0	1	1	0	0	2	2	4	1	3	1	2	17
1991	2	0	0	0	0	4	1	2	0	1	1	1	12
1992	1	0	2	0	0	1	1	0	1	0	0	2	8
1993	5	4	1	4	0	0	1	3	1	1	3	1	24
1994	2	6	3	2	1	1	3	0	3	1	3	1	26
1995	1	2	2	1	3	6	0	1	0	0	0	0	16
1996	0	1	0	3	0	0	2	1	1	3	0	4	15
1997	3	5	4	3	4	0	2	3	2	4	0	0	30
1998	1	1	0	0	0	0	0	0	0	0	0	2	4
1999	0	0	1	1	2	0	0	0	0	0	0	1	5
2000	0	0	1	1	1	2	1	0	1	0	0	1	8
2001	2	1	1	1	1	0	1	1	1	2	2	0	13
2002	**1**	**1**	**0**	**0**	**0**	**1**	**0**	**2**	**1**	**2**	**2**	**3**	**13**
Total	**33**	**41**	**43**	**38**	**37**	**28**	**31**	**33**	**28**	**35**	**32**	**36**	**415**

Activities in 2002

- March: Report presented at annual conference in Geneva.
- April: Survey of Fly River area (Kiunga, Matkumnae, Rumginae, Tabubil)
- August: Repeat survey of Fly River
- October: International conference in Benin
- October: Teach-in of 2 registrars and 1 resident and 1 medical student on latest in *M. ulcerans* surgery management and investigation
- 10–11 November: Visit by Mr Sasakawa and presentation of report on all past work
- December: Editors meeting; *Mycobacterium ulcerans* updated in the Health Extension Officer's Surgical Handbook
- December: Presentation at national surgeons meeting on MBU. First cultures achieved from PNG

Planned activities for 2003

- March: Annual conference Geneva
- April: Teaching visit to Oro Province MBU seminar
- April: Training session with national surgeons
- May: Visit to Angoram Health centre to set up local surveillance programme
- Monthly (from April to December): Visit to Angoram, Kaminabit, and Middle Sepik schools and clinics. Arrangements and funding already in hand
- September: Presentation at the National Surgical Symposium
- September: Presentation at the Annual Medical Symposium

Boat with multimedia facilities, laboratory for AFB smears, set up to tour upper and middle Sepik river villages. Funds partly raised, volunteer teams secured, building has started. Networking with AIDS, TB and leprosy programmes, and vaccination campaigns.

Projected national activities

- Compile and advocate a national *Mycobacterium ulcerans* surveillance and training plan.
- Compile study module for the MBBS. Problem-based learning course.
- Compile a module for secondary schools textbook.

Regional activities

- Start Tok Pisin translation of Buruli ulcer comic for the Sepik region.
- Prepare schools handout for Sepik region.
- Local school visits.

BURULI ULCER CASES IN AUSTRALIA

Dr John Hayman

In the 12 months to March 2003, there have been 26 new human cases in Victoria, the south-east state in Australia. These cases have occurred in all of the known endemic areas in the state – Frankston/Langwarrin (on the south-eastern edge of Melbourne), Gippsland, Phillip Island and in the relatively recently developed focus on the Bellarine Peninsula, south-west of Melbourne. Four cases have occurred in the Mossman/Daintree district of north Queensland. In addition, a case has occurred at Port Hedland in Western Australia. This latter case is of particular interest as it is the first known case to have occurred in Western Australia and it may represent the development of a new focus. Recycled sewerage water is used in Port Hedland for spray irrigation of the golf course, which may be a factor in the appearance of the disease, as it was for the cases that appeared on Phillip Island in Victoria.

As well as human cases, two cases have been diagnosed in possums, both from Phillip Island, and one case in a long-footed potoroo (*Potorous longipes*), a long-tailed small marsupial that lives above ground but digs for fungi (truffles), which form its principal food source. The animal is confined to a small area in east Gippsland and is classified as an endangered species. Another animal in the same area almost certainly had the infection 10 years ago but the diagnosis then was never confirmed. The clinical infection was on the tail but at postmortem there was evidence of the mycobacteria in the liver and spleen. The case is again of epidemiological interest as there is no major lake or river system anywhere near where the animal lived, only a small shallow water soak some 2 m in diameter. Human cases have occurred near the coast some 30 km apart but there have been none in the immediate vicinity, unlike the areas where infection has occurred in the koala, possum and alpaca. A different infective mechanism seems likely in this one case and here the role of a biting insect may be important.

ACCION SANITARIA Y DESARROLLO SOCIAL (ANESVAD)

Ms Verónica Malda, Mr Andrés Ginés

At the end of its statement made last year in this forum, ANESVAD reiterated its commitment to efforts to control Buruli ulcer and to continued use of every available means for that purpose in the fields of patient care, research, training of personnel and information and awareness-raising campaigns. It was also our intention to extend our activities to other countries where the disease is endemic.

One year later, we are able to confirm that ANESVAD has achieved its objective and, in the fields mentioned above, implemented more than 20 projects to control Buruli ulcer in Benin, Côte d'Ivoire and Ghana. In Côte d'Ivoire, despite the events of the past few months, ANESVAD has continued to support the projects concerned and hopes that there will soon be a return to peace in the country. Since last year, ANESVAD has invested about four million euros in field projects, awareness-raising and development education.

Furthermore, since one of ANESVAD's objectives is to ascertain the scale and prevalence of Buruli ulcer in other countries such as Benin, where it is endemic, an ANESVAD team visited the country for that purpose in June 2002. Accompanied by Dr Guédénon, Coordinator of Benin's National Buruli Ulcer Control Plan (PNLUB), we visited treatment centres and were able to pinpoint shortcomings and needs.

After assessing the Buruli ulcer situation in Benin and noting the absolute need to take action there, ANESVAD has implemented some health projects in the centres of Davougon and Zagnanado aimed at the provision of surgical equipment, improvement of facilities and assistance with feeding patients.

Among its 2003 activities to control Buruli ulcer, ANESVAD is seeking to support and encourage the work of the centres and programmes with which it is already involved in Benin, Côte d'Ivoire and Ghana. With regard to collaboration with WHO, ANESVAD is supporting, as it has done over the past year, training programmes for health personnel, currently in seven priority countries.

As its final contribution to this forum, and in response to the explicit request of the WHO Global Buruli Ulcer Initiative, ANESVAD will conclude its statement with a presentation of its experience with early detection and treatment campaigns in rural areas of Côte d'Ivoire where the disease is endemic. For ANESVAD and the Côte d'Ivoire national programme, these detection and treatment campaigns constitute a major activity in the country's efforts to control Buruli ulcer.

The main objectives of the campaigns are to persuade local populations to seek medical advice at an early stage and thus prevent advanced forms of the disease and sequelae. The results obtained exceeded all our expectations and the campaigns enjoyed a real success among both the health personnel and the local community.

In consequence, one of the main activities in ANESVAD's Buruli ulcer strategy for 2003 is to continue with this programme of early detection and treatment campaigns in Côte d'Ivoire and to extend it to Ghana and, shortly, to Benin. In the case of Ghana, ANESVAD is currently examining the final details before implementing the programme.

Last year, under the early detection and treatment programme in Côte d'Ivoire, 34 villages were visited and a total of 29 430 persons examined, among whom 347 displayed forms of Buruli ulcer (most of them – 72% – were ulcerative forms). Some 2198 cases of other diseases were treated.

These campaigns were carried out by local staff of the health district supported by a PNUM (National Buruli Ulcer Control Programme) team. Before a campaign is launched, the team arranges a preparatory mission in order to meet and sensitize village authorities, fix a date for the campaign and identify the local agents (doctors, nurses, community health workers) who will back up the PNUM team.

Some 10 days later, the campaign is launched. This period allows a district health worker to visit all the villages to inform them of the date of the detection team's visit and the objectives and progress of the campaign.

To illustrate the practical operation of a screening campaign, we shall now show you a summary video recorded by an ANESVAD team during a visit to monitor ANESVAD projects in Côte d'Ivoire in May 2002. The full version of the video will be shown during the breaks and a copy of it may be obtained by anyone interested.

[VIDEO]

CONTRIBUTION BY MAP INTERNATIONAL TO BURULI ULCER CONTROL

Mr Edouard Yao[1], *Dr Julien Aké*[2]

[1] Regional Director, West and Central Africa
[2] Director of Health Programmes, Western and Central African Bureau

Introduction

Buruli ulcer is an emerging disease that is responsible for major disabilities. It affects the populations of rural areas and, first and foremost, children aged under 15 years and women. Cases at an advanced stage require major and costly surgery that is beyond the means of victims and which involves prolonged immobilization.

The population at large – and most health professionals – know little about the disease, hence its name "the mysterious Daloa disease" in Côte d'Ivoire. Buruli ulcer is also present in many countries in west and central Africa.

The scale of the disease's social and economic consequences and the fact that its main victims are women and children have led MAP International to throw its efforts into controlling the disease.

1. Presentation of MAP West and Central Africa

1.1 *Background*

MAP is a religious NGO, founded in 1954 in the state of Illinois in the United States. It operates five offices throughout the world. MAP International's contribution to control is implemented by the West and Central Africa office based in Abidjan, Côte d'Ivoire.

1.2 *Vision*

A world in which individuals, families and communities have the hope and capacity to build conditions that promote Total Health. (Total Health: the capacity of individuals, families and communities to work together to transform the conditions that promote, in a sustainable way, their physical, emotional, social, economical, environmental and spiritual well-being.)

1.3 *Mission*

MAP International promotes the total health of people living in the world's poorest communities by partnering other actors who share our objectives in the provision of essential medicines, the prevention and eradication of disease and the promotion of health development.

1.4 *Areas of intervention*

- promotion of the development of community health,
- provision of and promotion of the rational use of essential medicines,
- prevention and eradication of disease,
- Buruli ulcer control programme.

Programme in support of Buruli ulcer control

MAP International and ALM (an American religious NGO involved in leprosy control.) have decided to combine their efforts in a partnership to support the BU control programmes of Côte d'Ivoire, Ghana and Guinea. The joint actions undertaken are implemented by MAP International West Africa.

2.1 Objectives

2.1.1 *Overall objective*

To provide support for the efforts of national programmes to reduce both morbidity and mortality from Buruli ulcer and the consequences of the disease.

2.1.2 *Specific objectives*

1. To provide assistance for the development of the comprehensive strategic plans of national programmes.
2. To build the capacity of national programmes to provide case management.

2.2 Strategies

- Assistance with the institution of an integrated and multidisciplinary operational framework
- Capacity building
- Operational research (KAP, socio economic impact and response)
- Partnership
- Provision of material and financial resources

2.3 Activities in 2002

- Finalization of Côte d'Ivoire's strategic national plan: funding, organization and steering.
- Completion of a mission to evaluate the laboratories and operating theatres of 25 district referral hospitals in the area where Buruli ulcer is endemic: inventory of existing/required infrastructure for surgical case management.
- Construction project for a hospital ward to accommodate Buruli ulcer patients at Treichville University teaching hospital's dermatology unit: plan adopted, timetable established and funding available.
- Purchase of 20 nodulectomy kits and of 10 poupinel sterilizers for the regional health centres (CSR) in the Daloa, Sakassou, Yamoussoukro and Zouan Hounien endemic areas.
- Design and production of image boxes to be used by community health workers for community-based health education.
- Provision of medicaments and consumables worth US$ 430 816.91 for the Ghanaian National Plan, for distribution to 12 facilities providing case management.
- Provision of medicaments and consumables worth US$ 27 445.11 for the Ivorian National Programme.
- Financial assistance for surgical treatment of 17 patients transferred from Sakoussou to the Treichville university teaching hospital's dermatology unit.

2.4 Prospects

- Help the national programmes to institute an integrated, multidisciplinary operational framework.
- Continue to provide support for national programmes through this integrated framework.

– Enhance the capacity of communities in endemic zones to control the physical, socio economic, spiritual and psychological consequences of Buruli ulcer.

Conclusion

Buruli ulcer is a disabling disease that can prove costly if treatment is delayed. It is absolutely necessary to develop early case detection and treatment. The community is the key to disease control; its participation is an efficient means of reducing incidence, ensuring early case detection and providing epidemiological surveillance. The efficacy of actions will be greater if they achieve synergy within a multidisciplinary framework that includes NGOs, national control programmes and communities living in endemic areas.

PREVENTING IMPAIRMENT AND DISABILITY

Dr Paul Saunderson, American Leprosy Missions

Introduction

American Leprosy Missions supports early detection and treatment of Buruli ulcer disease in certain endemic areas of Côte d'Ivoire and Ghana. In addition in Ghana, ALM supplied a container of dressing materials and supports the training of doctors in the surgical treatment of Buruli ulcer in Ashanti Region.

We note that measures to limit the disability associated with Buruli ulcer and to rehabilitate people affected by the disease have not been given much attention up to now. Our experience with leprosy may allow us to contribute in this area, and one of our consultants, Linda Lehman, an occupational therapist based in Brazil, spent one week in Ghana in October 2002 to review the situation. This report is based on her findings.

Prevention of impairment and disability

The main finding was that surgery and wound-dressing are generally the only specific interventions offered in the early stages of the disease. It is essential to introduce other activities, which will complement surgery, to prevent and minimize impairments and disability , tha. Such activities need to be done **early** in the course of the disease and **aggressively.** Preventive measures are needed, both **before and after surgical interventions**, at the hospital and within the community.

Key activities for the prevention of impairment and disability (POID) need to be clearly identified. More practical "hands on" POID/rehabilitation training should be developed and included in the Buruli ulcer programmes at the local, regional and national levels, focusing on these key activities. Specific skills need to be developed in the areas of evaluation and monitoring of patients.

Daily and frequent practice of self-care, exercise, activity, correct use of splints and use of pressure garments within the hospital and at home are fundamental to acquiring the best results in rehabilitation and preventing more severe secondary impairments and disabilities.

Other problems that need to be addressed are the burden of prolonged hospitalization on the patient and family, difficulty in accessing specialized services, financial reimbursement or provision of materials used in treatment.

Basic activities

The following is a preliminary list of basic POID/rehabilitation activities that are needed within the early stages of treatment:

- **Wound care** techniques that promote healing, minimize infection, reduce adhesions, reduce scarring and facilitate movement.
- **Functional positioning/splinting** of affected limbs and other parts to reduce contractures, and promote mobility and participation in activities of daily living.
- **Oedema control**: positioning, frequent movement and activity; compression if needed.
- **Scar management**: massage, use of pressure garments, splinting, movement and activity.

- **Early mobilization** to minimize adhesions, oedema and contractures.
- **Self-care education** for patient and family.
- Use of **adaptations and modifications** that promote independence and participation (i.e. handles on spoons, toys, games, etc).

After the acute phase, activities dealing with long-term rehabilitation will be needed:
- Use a problem solving approach to **minimize restrictions in activities and promote participation** in daily activities within the hospital setting and at home.
- Identify the need for prostheses and for more complex rehabilitation interventions.
- Examine issues of schooling and socio economic rehabilitation.
- Systematic follow-up.

Recommendations

1. Define the specific activities (appropriate knowledge and skills) needed for POID/rehabilitation in Buruli ulcer. Those doing POID/rehabilitation in the field or in the hospital will need to have specific skills developed from a combination of professional backgrounds.
2. Develop a team of facilitators with these skills in POID/rehabilitation, who can train and supervise others in the future. Training must concentrate on practical skills.
3. Early inclusion and integration of Basic POID/rehabilitation activities in the Buruli ulcer programme at every level: hospital, community, family and self-care by the patient.
4. Inclusion of POID/rehabilitation adviser within the national and regional Buruli ulcer technical teams.
5. Develop a POID/rehabilitation register that documents and monitors impairments, activity limitations and participation restrictions and the interventions that are used.
6. Use of WHO International Classification of Functioning, Disability and Health.
7. Inclusion of POID/rehabilitation activities in training materials and other publications on Buruli ulcer.
8. Further research.

HEALTH FOUNDATION OF GHANA

Lynda Arthur, Country Director

Buruli ulcer interventions in Ghana

Who are we?
- a locally registered NGO based in Ghana (office location Accra);
- governed by a seven-member board;
- supported by Dreyfus Health Foundation, IICD, DFID and other local and international organizations;
- core group of professionals (volunteers) assist to achieve foundation's objectives;
- works at both district and national level.

Objectives
1. To advocate for better health delivery in the country.
2. To assist the national Buruli ulcer control programme and DHMTs of endemic communities in control to eradicate the disease.
3. To assist communities to design and implement innovative cost-effective solutions to self-identified health problems using available resources – target communities at district level.
4. To disseminate and improve access to relevant health information – target health workers.

HFG's programme
- Buruli Ulcer Control Programme – Target: DHMTs, National Buruli Ulcer Control Programme
- Problem Solving for Better Health Programme – Target: health workers, communities, government agencies, NGOs HIV/AIDS, malaria
- Communication for Better Health Programme
- "Ghana Health Digest" publication: Target: health workers
- Health lectures in reproductive health: Target: youth

Buruli Ulcer Control Programme
- *Research:* topical phenytoin in healing of Buruli ulcers supported by Dreyfus Health Foundation
- *Training:* nurses, medical assistants, wound dressers, community surveillance volunteers and doctors
- *Education:* teachers, schoolchildren, traditional healers, opinion and traditional leaders

The way forward
- Enhance training of health workers and community surveillance volunteers at district level.
- Intensify education activities with community health nurses, teachers, students and traditional healers in endemic communities.
- Foster collaborations with NGOs to assist in the fight against Buruli ulcer in Ghana.

HUMANITARIAN AID RELIEF TEAM (HART)

Kimball Maurice Crofts, Plastic Surgery Institute of Utah

The 10-minute presentation first reviewed the status of HART and is present direction. The last surgical mission to Ghana was also summarized. The remainder of the presentation highlighted the direction that HART wants to take in collaborating with local in-country physicians and health care workers. The problems that arise in the collaboration of international surgical teams working to treat various medical conditions are:

- poor coordination between teams
- short stays by NGO teams
- too many patients to realistically treat in 6–7 days regardless of the team size
- poor follow-up
- overburdening the system
- inadequate educational exchange

Consequently, HART devised the concept of a mini-residency project with an educational core curriculum to address these challenges. By doing so we believe that 1) education, 2) collaboration, 3) exchange of ideas, 4) treatment of disease and 5) data procurement can all be better carried out. The following outlines the concept:

An approach for future humanitarian surgical projects

"Mini-Residency:" The concept here is to develop an environment that maximizes education by coinciding it with the concurrent surgical mission. In particular, it would not focus so much on the immediate debulking of the extensive number of Buruli ulcer disease cases that are present, but rather on developing improved capacity in the local medical personnel to treat the large bulk of Buruli ulcer disease patients. Such an educational exchange could be done within the context of a scaled down residency or mini-residency. The purpose for this is that in evaluation of the previous surgical missions, it is believed the most effective way to address this pervasive disease is to further develop the capacity of the local health care system so it can address the problems over the long term rather than just debulking a number of cases within one-weeks period. Evolution of ideas and skills through education and communication is the key!

a. Develop a one-week residency concept.

i. During the period of the "residency", various instructional modalities will be employed. Most importantly, the local doctors would be expected to be present for that period of time just as the NGO doctors are present. In other words, just as the humanitarian NGO team physicians and medical personnel have set aside at least two weeks of their time from their busy schedules back in their homelands to come out and spend time addressing this problem, so would it be appropriate for the local physicians to put their practice on hold for the one week that the medical team is present. This would ensure that there is maximal collaboration and exchange of information at the time of the project.

ii. It has been very apparent during the previous missions that the amount of teaching that goes on is not adequate. This is partly the fault of the busy schedule of the local physicians. Therefore, it is proposed that, just as the project team of foreign physicians and medical personnel take off two weeks of their time, the local doctors also take off about one week of their time so as to coordinate efforts. It could be looked upon as a hands-on conference.

iii. Develop a curriculum (a definite set of problems could be addressed through a curriculum for one week). This would involve distribution of material and handouts as well as sitting in on core curriculum classes and lectures. The local medical personnel would also teach some of the courses.
iv. Video conferencing. It would be appropriate to set up some type of video medium for large group education. Use of laptops, PowerPoint and a digital projector would ensure greater and more effective education both in the medical personnel and the people in general . Outreach teams would oversee the education of patients, families of patients and those not yet afflicted with an ailment.
v. Interactive exchange of ideas daily, either before and/or postoperatively.
vi. Develop local teaching techniques with the physicians, nurses, and to the local healthcare workers.
vii. Provide a nursing training camp also so as to address nursing issues.

b. Curriculum ideas:

i. Buruli ulcer disease: define and update the latest information on the disease. Review various treatment modalities, whether it be antibiotic delivery, wound-care protocol, or surgery
ii. Review treatment options and discuss these with the group of medical personnel
iii. Instruments and supplies
iv. Develop sterile technique. handouts, and education
v. Review triage protocols – When to operate and not
vi. Wound care protocols – What's new and what works

c. Approach:

i. Learn local doctors' objectives
ii. Collaborate with local physicians. Work within their system
iii. Triage
iv. Periodic educational meetings using digital projectors and computers for that purpose
v. Operate together
vi. Aggressive and accurate follow-up

Core curriculum for Buruli ulcer disease surgical management

Establish two separate surgical teams – Team A and Team B. Each team would consist of a volunteer surgeon and local surgeon from Ghana and possibly more. There would be two foreign volunteer anesthesiologists.

The week would be set up one through seven days. Day one would be Team A triage day with Team B setting up in the OR. In the afternoon, educational rounds would start with both teams, both sets of surgeons, and the nursing staff. Residents and MA's would also participate. This would be a review of Buruli ulcer disease as well as an effort to cover other topics such as sterile technique in the OR, instrument and supply management, OR staffing, triage principles, and treatment options. Additionally, case reviews and case presentations could be offered. Selected triage cases would be reviewed by both teams and management options discussed. The cases selected would then be the cases taken to the OR on the following days.

Operating Theatre

Day two would be OR Team A. Day three would be OR Team B. Day four would be OR Team A. Day five OR Team B. Day six OR Team A. Day seven OR Team B.

Triage clinic and follow-up

On day two, it would be Team B triage. Day three, team A triage. Day four, team B triage. Day five, Team A triage. Day six, Team B triage. Day seven, Team A triage.

Patient rounds would be done each day (see graft below). In the afternoon, educational rounds will be undertaken as well as case presentations and case review. Presentations would be given by both volunteer staff and local staff physicians and nurses. Topics could be assigned prior to arrival to permit preparation. In fact, the local doctors should take that week off in conjunction with the foreign physicians so that there can be a true exchange of ideas and educational opportunity.

Ideally, at week's end, local physicians will be doing virtually all of the surgery based upon the discussion and the case presentation. In conclusion, an oral examination could possibly be given so as to assess understanding. In fact, it could be an oral board-type examination in which cases were presented, questions were asked, and management was discussed. They could then be evaluated, and upon completion of the week-long core curriculum, a certificate could be given to certify completion of the course and recognized skill for the management of Buruli ulcer disease.

Other course topics that could be covered are medications, anesthetics, coordination of anesthesia and surgery. Monitors, computers, digital projectors would be used, as well as handouts and brochures, and so forth.

	Day 1	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
AM	Team **A** Triage Team **B** OR Setup	Team **A** OR Team **B** Triage	Team **B** OR Team **A** Triage	Team **A** OR Team **B** Triage	Team **B** OR Team **A** Triage	Team **A** OR Team **B** Triage	Team **B** OR Team **A** Triage
PM	Teaching Rounds	Teaching Rounds	Teaching Rounds	Teaching Rounds	Teaching Rounds	Cleanup	Cleanup

The hope is that such an approach will ultimately lead to better and through long-term treatment at the hands of the local medical personnel.

BURULI ULCER CONTROL ACTIVITIES SUPPORTED BY AIFO IN GHANA (Area of intervention: Ga Rural District)

Dr George Abram, AIFO Representative in Ghana, Dr Giovanni Gazzoli

Introduction

For many years, even though the disease has had wide incidence, very little could be done by health authorities in the country, especially because of the reluctance of patients to come forward. One of the reasons for this is the belief that spells or evil supernatural forces cause the wounds, and this has led those affected to turn to shamans and healers rather than to doctors. Another factor is that the few who did turn to official medicine did not gain any noticeable advantages and there was no healing. Added to this is the fact that the disease is practically painless because of the precocious destruction of the nerves, so there has never been a great urge to turn to a doctor. Now we know that prevention of the ulceration is possible by intervening surgically and in time. Even the wounds can be cured by surgical cleaning and in the most severe cases with skin grafts and through daily disinfecting and dressing. However, the ulcer heals slowly and leaves a visible scar. It would seem that the agent that causes this disease, *Mycobacterium ulcerans*, prefers to live along slow-flowing rivers, in stagnant waters, and wherever the area has been degraded (as in the case of the Ga Rural District). Most of those affected by the disease are children, equally proportioned between male and female. From this, we can deduce that the mycobacterium usually affects weak or debilitated immune systems. The disease is contagious, though how it is transmitted is as yet not fully known.

Area of intervention

Deeply moved by the painful situation of many children suffering festering sores, Associazione Italiana Amici di Raoul Follereau (AIFO) decided in 2000 to become involved in Ghana to alleviate the pain of some of the young patients. The involvement is limited due to the limited availability of funds. The area of intervention was chosen on the basis of the mutual understanding between the Government of Ghana and the AIFO Resident Representative.

The project is located in a rural area on the outskirts of the capital city of Ghana, Accra. The District, called "Ga Rural" or more currently "Amasaman", from the name of its main town, has only been recently created and therefore lacks many of the structures present in other districts. It was decided that Ga Rural District was the one that needed the most immediate attention because of its total lack of public structures as well as the high number of patients: 1110 active cases of Buruli ulcer in a population of 250 000. The urgency for the intervention was also demonstrated by the need to block transmission of the disease to overcome and eliminate it.

Buruli ulcer is not a new disease in Ghana. From visits to ex-patients, it is evident that some cases already existed about 40 years ago. However, it seems to have exploded with unexpected virulence during the past few years. Of a total of 110 districts in Ghana, 20 districts have cases of Buruli ulcer. Excluding Ga Rural District, the number of cases varies from 500 to 70 in the other 19 districts. Two of the districts with the same characteristics as Ga, in particular the lack of health structures and the degradation of the area, are in the Brong-Ahafo region and in the Western region, both registering about 200 cases.

Above all, the ecological equilibrium in the Ga Rural District area has been upset by the unexpected and uncontrolled extraction of sand for building purposes in the nearby capital, when it was forbidden to take sand from the coastline. The forest is being destroyed as an uninterrupted flow

of trucks carries away thousands of cubic metres of sand every day, leaving holes and depressions in the devastated terrain, which fill with water and create marshes and swamps. The district is one of the most neglected areas of the country because of its geographical location: while close to the outskirts of the capital, it is a rural area and has been excluded from the possible benefits deriving from its closeness to Accra because of the construction of a dam in the Denso River, which closed the main avenues of access to the district. The water basin formed is used to supply the aqueduct for Accra, without any benefit for the Ga Rural District, where there is no pipe-borne water. Only during the past few years has the district been connected to the national electricity grid.

Activities

The objective of the intervention is the elimination of *M. ulcerans* in the district through timely prevention and care of affected patients; through health education of all the inhabitants of the area to avoid the spread of the disease by using appropriate measures of hygiene; and through the social and psychological integration of those who are healed but bear the devastating signs and debilitating effects of the disease for the rest of their lives.

In many districts where there is a functional hospital, it is possible to intervene at the beginning as well as during the disease. Unfortunately, in the Ga District there was only one so-called health centre, a clinic where patients went to be seen and treated but had no chance of being admitted because of the lack of a hospital structure with operating theatres and wards or even with just a few beds. This is where the children should be after the operation or excision of the nodule as well as those in precarious conditions needing special care to avoid the complete destruction of the limbs. Until now, the most severe cases were sent to the Teaching Hospital of Accra, but very few would go there because of the costs involved in doing so: travel, housing, food (here the family must provide for the patient's meals), the doctor's fees, etc. Therefore, AIFO proposed building a small hospital, including an operating room with the necessary services, and two wards with all the required furniture. The project has been developed in four stages:

Stage 1. Build a hospital with 20 beds, an operating room and medication room for the day hospital.

Stage 2. Provide medical and paramedical personnel with residential courses and non-residential seminars in the various peripheral locations.

Stage 3. Buy two vehicles, one to be used mainly for research of cases, the second containing the materials and instruments necessary for minor surgery for the care of patients no longer in the hospital or for those not requiring hospitalization.

Stage 4. (This stage should be the starting point if not for the high costs involved.) Create boreholes in the most endemic areas to supply fresh and clean water, thus avoiding the use of polluted water for drinking.

Conclusion

Buruli ulcer shares many similarities with leprosy at both the medical and social levels. Home care therefore plays a fundamental psychological and educational role to fight the rooted mentality of those believing that the disease comes from supernatural powers and is therefore incurable. Seeing that a patient gets better with the passing days, and finally heals, helps convince people that Buruli ulcer is a disease like many others and therefore curable. I often get this question put to me, "Is it because of dirtiness, poverty or ignorance that this happens?" Always with an emphasis on the third reason. An easy answer could always be, "All three together", but it would be false, or at least misleading.

It is too easy to name ignorance for any behaviour that is far from one's culture and cannot be justified according to one's usual parameters. For example, when I talk about Trokosi, people openly show their disapproval. Trokosi is the most evident form of belief that any illness is linked to a sin and becomes divine punishment and atonement. For this belief – though now forbidden by the law of the country – there are in Ghana some shrines where young girls are confined, slaves of the fetish priest for the rest of their lives. They are sent there by their families to atone for some appalling sin committed in the clan. Without reaching this extreme point, some diseases, and leprosy is among the first ones together with Buruli ulcer, are believed to be caused directly by the gods as punishment for personal or communal sins. Therefore, any treatment is considered to be useless. It is too easy to dismiss all this as ignorance. I believe that this argument – if I may use a western terminology that is worlds away – could be considered a scientific explanation of the cause of illnesses and death, studied by people, unaware of the existence of bacteria and contagion, and yet looking for a reason to explain life and death, both linked to the supernatural world.

I chose to underline these particular aspects, leaving it to others in this eminent assembly to expose the scientific, medical and pharmacological findings. I would like to stress the need for a global effort that may take into consideration the social and cultural motivations, the holistic person and not only the medical and hygienic necessities.

In harmony with all the above, AIFO has started a new venture in a different district, which is furnished with the necessary health structures. The first stage has been concerned with the training of groups of volunteers. These will then visit the remotest corners of the forest district and will hopefully be the force behind the disappearance of the fatalistic belief that still hinders the cure of Buruli ulcer in Ghana.

HYPERBARIC OXYGEN THERAPY

Dr Franco Poggio, Rotary Club Milano, Italy

In the presentation I made at the fourth meeting in 2001, I informed you that my Rotary Club, the Milan Aquileia, intended to offer a chamber for hyperbaric oxygen therapy in order to test a method for integration into the treatment of Buruli ulcer to accelerate healing.

In the past, hyperbaric oxygen therapy has been used in experiments on animals and has produced good results. I have discussed the matter with Professor Mayer, the author of the research, and have presented to him my Rotary Club's project, which he has encouraged me to carry out.

I am here with you again this year to let you know that the hyperbaric oxygen chamber is now ready and will be offered by my Rotary Club in order that research and experimental protocols may be drawn up under the aegis of WHO.

I also bring with me a proposal from the Italian Navy that, through Admiral Martines, has promised to send physicians specialized in hyperbaric oxygen therapy to the places where the experiments will be conducted. This was officially announced at the Leghorn Naval Academy, on the occasion of the centenary of the discovery, in Uganda in 1902, of the origin of sleeping sickness by military physician, General Aldo Castellani.

I had considered, with Professor Assé, the possibility of sending this hyperbaric chamber to Adzopé hospital in Côte d'Ivoire, to allow the experiments to begin.

We had also agreed on this with the Abidjan Rotary Club. Unfortunately, the civil war that has broken out in Côte d'Ivoire has brought all our projects to a standstill. I now personally, on behalf of my Rotary Club, offer the hyperbaric chamber to you, so that it may be sent wherever you choose.

The ideal location would be a hospital with the following facilities:
- a surgical department,
- a medical laboratory,
- a team of surgeons and physicians with extensive experience of treating Buruli ulcer.

The hyperbaric chamber for oxygen therapy may also be of value in treating osteitis, osteomyelitis, gaseous gangrene and other illnesses.

I am pleased to confirm to you that my Rotary Club is fully willing to follow the progress of this project, whose purpose is to alleviate the terrible suffering of people with Buruli ulcer.

PRESENTATION BY THE DELEGATION OF THE LUXEMBOURG RAOUL FOLLEREAU FOUNDATION

Professor Henry-Valère T. Kiniffo, Mr Robert Kohl

The new Buruli ulcer detection and treatment centre at Allada, Benin

A documentary film

Following the presentation two years ago of the plans and a cost evaluation of more than one thousand million CFA francs (i.e. € 1 524 490) and of the buildings completed last year, this film presents the new Buruli ulcer detection and treatment centre (CDTUB) at Allada, Benin, which has been entirely built and equipped by the Luxembourg Raoul Follereau Foundation and which is now operating after its official inauguration on 8 July 2002.

Following an introduction showing a child seriously affected by Buruli ulcer, then press cuttings and scenes from the inauguration, the film takes us on a visit to the CDTUB, following the path of a patient from admission to discharge. The visit gives us an opportunity to meet staff and patients who describe their experience. The accent is on the reception given, the quality of care, the service offered to patients and life at the centre.

The closing sequence shows a child back in his village, cured and happy. Thanks to CDTUB, he rediscovered the desire to live like other children. The child and his parents express their satisfaction.

THE ROLE OF HUMANITARIAN ASSOCIATIONS IN THE RESPONSE TO BURULI ULCER

Dr Rémy Zilliox, Interplast – France, a humanitarian organization for plastic and reconstructive surgery in the developing countries.

Humanitarian associations, especially those providing plastic and reconstructive surgery, have their place in the action undertaken by WHO to control Buruli ulcer.

The skills of "humanitarian" plastic surgeons, who are fully acquainted with the techniques for treating loss of tissue by graft or flap, are perfectly suited to the treatment of the disease, which is essentially by surgery.

The surgical teams, made up of surgeons, anaesthetists and specialized surgical nurses, are accustomed to working outside their usual professional environment and are capable of adjusting to locations where there are fewer facilities. Consequently, humanitarian associations providing plastic and reconstructive surgery have a useful role to play in the WHO response to Buruli ulcer and especially in partnership with the health systems of countries affected by the disease.

Besides providing treatment through multiple surgical operations, humanitarian specialists in plastic and reconstructive surgery also fulfil an educational function by teaching their local colleagues the simplest methods of dealing with the major damage caused by *M. ulcerans*.

However, voluntary associations with limited financial resources need to be supported by WHO, international agencies and the host countries. While the surgical teams are capable of putting together the equipment, consumables and anaesthetics, it is the responsibility of the local authorities to provide the simple daily needs of those involved in providing the treatment.

A fine illustration of this type of action is the forthcoming mission of Interplast to Benin in March 2003, where all the favourable factors have come together. The mission has been organized under the auspices of WHO and in agreement with the Beninese Ministry of Health and will involve surgical treatment and teaching of the basic principles of plastic and reconstructive surgery at Allada hospital in Benin.

The underlying philosophy must be to combine all the requisite actions in a unified effort bringing together all the logistic and human resources to achieve a common goal.

ESSAY ON ECOPATHOLOGY: ON THE TRACKS OF A TROPICAL ULCER

Dr Vincent Stoffel, North–South Humanitarian Project for Africa

Since 1998, the Projet Humanitaire Afrique Nord Sud (PHANS), a French medical NGO, has been training local health workers through a form of "buddy system". Since 1998, PHANS has detected numerous cases of Buruli ulcer in the rural sub-prefecture of Bonou, located in the Oueme river valley (altitude 50 m). Since 2001, PHANS has been active on a second site (the plateau of Ketou rural sub-prefecture, culminating at 273 m and located to the east of the Oueme, along the Nigerian border), where it has detected low prevalence of Buruli ulcer.

The purpose of this study was to compare the distribution of skin ulcers in the two sub-prefectures. Subsequently, the ulcers were grouped by type, for both sub-prefectures as a whole, and a correlation established with sex, age and site on the body.

A "here and there" study was initiated by identifying in plain language all the results of consultations registered, then coding them in accordance with ICD-10 and with the dictionary of the *Société Française de Médecine Générale*. It was decided to carry out two medical missions: five weeks in Bonou sub-prefecture in November and December 2000 (dry season) and three weeks in Ketou sub-prefecture in January and February 2002 (dry season).

A total of 41 (6.8%) and 35 consultations (10.4%) at Bonou and Ketou, respectively, were for treatment for ulcers. The patients fell into the following categories:
- 14 Buruli ulcers, 1 phagedenic ulcer, 1 varicose ulcer and 1 pressure ulcer at Bonou;
- 1 Buruli ulcer, 8 phagedenic ulcers and 1 ainhum at Ketou.
- Buruli ulcers were significantly more frequent at Bonou (82%) tham at Ketou (10%) with $P < 0.01$.

Comparison of Buruli ulcers with other ulcers revealed the following:
- the absence of any correlation with sex;
- overrepresentation of Buruli ulcer among children aged under 15 years ($P < 0.001$); and
- overrepresentation of lower limb sites where other ulcers were concerned ($P < 0.02$).

This study confirms the recognized link between Buruli ulcer and the environment. A swampy (flooded) ecosystem favours the emergence of Buruli ulcer, whereas there seems to be a correlation between phagedenic ulcer and a dry ecosystem. Buruli ulcer is overrepresented among the under 15s, while phagedenic ulcer affects mainly the lower limbs. Consequently, physicians should not overlook the importance of ecological factors, especially in poor areas. In September 2002, a French team (Marsollier, Carbonnelle et al.) described the biological substratum accounting for the relationship between Buruli ulcer and a swampy ecosystem in a leading article, "Aquatic insects as a vector of *Mycobacterium ulcerans*", which was published in *Applied and Environmental Microbiology*. This publication holds out hope of new prospects for treatment.

ASSOCIATION FRANCAISE RAOUL FOLLEREAU (AFRF)

Jehan-Michel Rondot

AFRF: partner in the campaign against Buruli ulcer

A new challenge has faced AFRF since 1995: how to respond to the re-emergence of Buruli ulcer? We ultimately opted for a pragmatic and clear-sighted strategy in line with the recommendations of the WHO Advisory Group on Buruli ulcer.

A new challenge taken up by the AFRF

AFRF is an organization dedicated to leprosy control which still devotes the lion's share of its efforts to programmes of this type. Although well represented in the field, it remains responsive to the needs voiced by the health authorities in those countries where it is active.

In 1995, AFRF was asked to provide assistance to Benin and Côte d'Ivoire. After receiving the go-ahead from its Medical Committee, AFRF decided to get involved in this new programme. Several working groups were rapidly formed and over the months drew up what would eventually lead to the Yamoussoukro Conference in 1998. AFRF acted as the cosponsor, and was one of the signatories of the final declaration, the founding act to the subsequent Global Buruli Ulcer Initiative.

The nature of the problem

The following facts rapidly emerged:
- the incidence of Buruli ulcer (BU) is growing in known endemic areas
- *M. ulcerans* remains poorly understood and expert opinion about the disease is scanty
- surgery is the sole treatment
- few health units are equipped to look after patients
- affected populations are very poor and treatment is almost unaffordable

A three-part strategy

1. Supporting patient management

We decided to pool our efforts and provide our support to private and public health units that looked after patients in Benin and Côte d'Ivoire.

1.1 Benin Gbémontin centre

- **Gbémontin centre** at Zagnanado in Zou

Material assistance was provided in the form of medications and medical supplies (€ 61 000), i.e. 40% of running costs. We also provide fee-for-service costs for a surgeon who works alongside Sister Julia, the Centre's director.

Roughly 50% of the Centre's activities are taken up with *M. ulcerans.* In 2002, the Centre treated 394 patients affected by *M. ulcerans* of which 230 were referred from a centre in Davougnan.

1.2 Benin CTUB Pobè
Following an epidemiological study carried out in 1998/99 by the National Coordinator of the Buruli ulcer campaign which found high endemicity at Ouémé in the east of Benin, the national programme recommended that a BU treatment centre should be developed at Pobè in order to meet demand, and made an application to AFRF.

The AFRF medical committee approved this project in 2001: it involved constructing a unit with wards for hospitalizing patients, an outpatients' room, an operation suite and a laboratory. Construction work is scheduled for completion at the end of 2003. Aside from the construction work, the AFRF has undertaken to equip the Centre for a total amount of € 600 000 and will also meet its running costs.

The project is being supervised by Dr Annick Chauty who has already been working in the region for several months and is an dedicated and willing contributor to the activities of the National Programme.
The latest information we have received from her confirms that a large number of cases have been detected in the surrounding villages.

1.3 Côte d'Ivoire: Raoul Follereau Institute of Adzopé-Manikro
It may be recalled that this institute is a public hospital under the aegis of the Department of Health, and that its director and chief surgeon is Professor Henri Assé. In 1999, AFRF signed an agreement required by the Ministry of Health on the management of BU patients. Since this date, AFRF has provided an annual contribution of € 100 000 to 115 000 in the form of medications, reagents and medical supplies.

2. Research funding

Since 1995, AFRF has supported research programmes for the prevention and treatment of the disease that are based on a better understanding of *M. ulcerans.* In 2002, the following actions were initiated for an annual cost of € 157 000:
- an *M. ulcerans* ecology study and a therapeutic trial of clinical lesions of *M. ulcerans* infections using combined aminoglycoside–rifampicin by Professor Carbonnelle and Mr Laurent Marsollier of the Angers Medical Faculty;
- a research programme on the treatment of leprosy and Buruli ulcer by Professor Jarlier of the Pitié-Salpétrière Medical Faculty;
- an analysis of bacterial genomes by Professor Stewart Cole.

3. Knowledge distribution and awareness raising

AFRF allocated sums of € 17 000 and € 40 000 to defray the costs of publishing different editions of various recent publications dealing with Buruli ulcer. Moreover, since 1995, AFRF has been informing the French public and raising awareness of this new disease. Its publications and annual congresses are a good occasion for distributing information from reputable sources.

There is no doubt that our efforts have been effective, even if there is no denying that the often horrifying visual impact of photos is often instrumental in achieving it.

Conclusion

- A still poorly understood mycobacterium
- A true challenge for scientists
- A disorder which affects the poorest and concerns economically indigent regions
- The need for early detection to prevent disabilities
- Severely handicapping sequelae which already raise the issue of SER
- *Mycobacterium leprae*? No: *Mycobacterium ulcerans*

We would appear to be taking the right approach:

Clear objectives:

- to improve patient management
- to upgrade research
- to publicize and coordinate knowledge
- to raise awareness of the disease and mobilize people

Cooperative partners:

- national programme directors
- WHO and the Global Buruli Ulcer Initiative
- humanitarian and welfare organizations
- continual advances in research.

This annual meeting is the proper time to share our experience, acquire the habit of exchanging information, to make contacts, in short to develop team spirit. That will require pragmatism, modesty and mettle, because the battle will be a long and hard one.

Lastly, we cannot conceal our very great concern about the crisis in Côte d'Ivoire the impact of which is already becoming apparent in the entire subregion.

An additional reason, if one were required, to remain vigilant. The Association Française Raoul Follereau assures you that it will remain a receptive partner.

It has been a reliable partner since 1995 and is better prepared than ever to uphold all its undertakings.

The delegation of the AFRF would like to thank you for listening so attentively.

MEDECINS SANS FRONTIERES (BENIN) – LALO SUBPREFECTURE HEALTH CENTRE

Christophe Dupont

Background

The Buruli ulcer treatment centre was set up on the express request of a national programme within a health centre infrastructure in Lalo subprefecture. Médecins Sans Frontières (Luxembourg) has been dealing with this treatment centre (CDT) since the outset, at both the human resources (HR) and financial level.

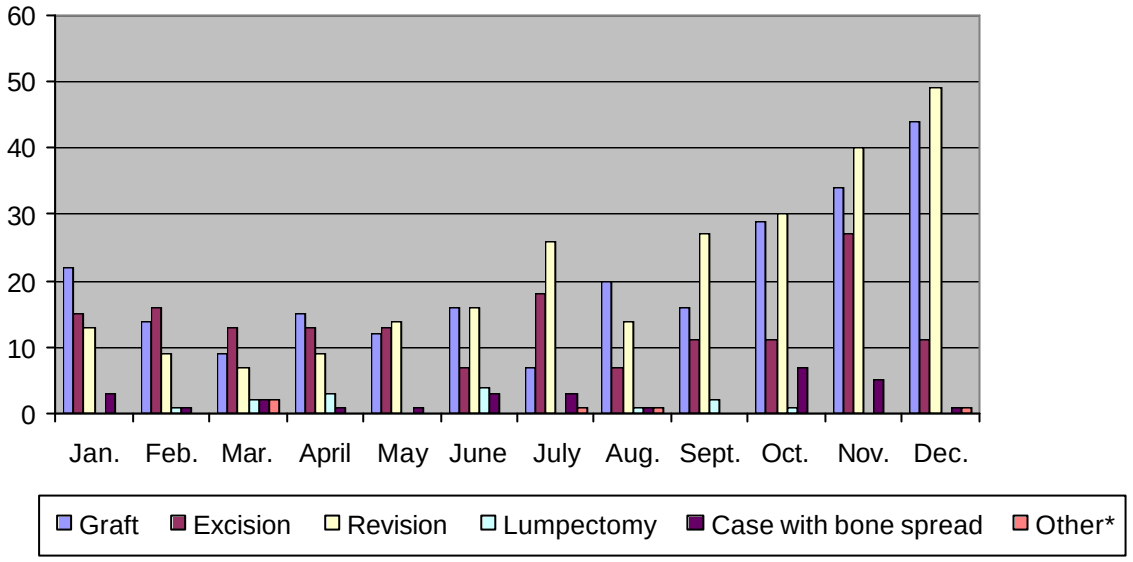
Médecins Sans Frontières (MSF) support breaks down as follows:

1. Human resources (expatriate and national)
2. Logistics (transport and construction)
3. Medicosurgical:
   - upgrading of operating capacities
   - setting up of physiotherapy facilities (equipment, organization, follow-up, pain management, psychological support, etc.)
   - upgrading of nutritional management
4. Socio-educative (library, schooling, games room)
5. Eyewitness reports (making of a film on the human impact of BU)
6. Financial: the estimated cost of local expenditure is € 195 000, which includes about € 78 000 for medicosurgical equipment and medications and about € 37 000 for local staff. More than € 27 000 have been set aside for construction.
   - The MSF contribution for each operation amounts to € 163 based solely on medical costs and HR set against € 276 for each act based on the total budget
   - The MSF contribution per patient amounts to € 835 based solely on medical costs and HR as set against € 1400 per patient based on the total budget

Some key data in 2002

- 154% rise in the number of operations
- Fall in median age from 18 in 2001 to 12 in 2002
- Length of hospitalization “reduced” to 85 days
- Disability quotient on admission approximately 30%
- Recovery rate with sequelae approximately 30%
- Doubling of the number of operating days
- Rise in the number of operations to over 100 per month

Operating statistics



Controversial points

- Recurrence rate is too high (20%)
- Case-fatality rate
- Anorexia, psychological support
- Late detection (traditional healers, fear, socioeconomic consequences, disability, pain, etc.): how can this situation be addressed?
- Are there any innovative solutions that might reduce the length of hospitalization?
- Improvement of surgical management
- Implementation of standardized protocols
- Development of healer–patient empathy

KNOWLEDGE, ATTITUDES AND PRACTICES OF POPULATIONS OF THE AYOS AND AKONOLINGA HEALTH DISTRICTS REGARDING BURULI ULCER

Dr Um Boock

Context

Buruli ulcer is without doubt one of the major health problems in the Centre province of Cameroon.

A survey covering about 75% of the population of the Ayos and Akonolinga health districts was conducted in 2001 to better understand the extent of the disease. In the Ayos health district, the survey was conducted in five of the seven health areas referred to as *Aires de Santé* (AS), covering about 35 villages and communities with an estimated population of 40 000 inhabitants (81% of the total population of the district). In the Akonolinga health district, the survey was conducted in seven of the eleven AS, covering about 50 villages and communities with an estimated population of 56 000 inhabitants (70% of the total population of the district). The survey was not conducted in the Akak, Edjim, Ekoudou or Endom AS in the south-west of the Akonolinga health district because the local development centre considers this zone to be only weakly affected, if at all, by the endemic.

A total of 438 cases of Buruli ulcer (active and inactive) were recorded, bringing the rate of prevalence of Buruli ulcer in all its forms to 4.4 cases per 1000 inhabitants. Of these 438 cases, 97 were recorded in the Ayos district and 331 in the Akonolinga district. The 10 remaining cases, recorded by the Ayos district surveyors, were in the Atok AS in the Abong Mbang health district, East province.

Table 1. **Prevalence of Buruli ulcer by health district**

District	AS covered by the survey	Total population	Population surveyed	Cases with active BU	Cases with BU sequelae	Reported cases (all)
Ayos	Mboke, Nganga	49 296	40 000	79	18	97
Akonolinga	Akak, Edjim, Ekoudou, Endom	79 787	56 000	125	206	331
Abong Mbang	Atok (one part)	95 000	2 500	5	5	10

Table 2 shows the distribution of 199 recorded cases by age and sex. Of the 199 patients, 107 (53.8%) are children aged under 15 years: 113 (56.8%) are male and 86 (43.2%) are female, with a ratio of 1 female to 3 males. Males are more affected by the disease in the 11–15 years age group, while females are most affected from ages 20 and older.

Table 2. **Distribution of 199 active cases of Buruli ulcer by age and sex**

Age group	Male (%)	Female (%)	Total (%)
0–5	4 (3.5)	9 (10.5)	13 (6.5)
6–10	27 (23.9)	19 (22.1)	46 (23.1)
11–15	34 (30.1)	14 (16.2)	48 (24.2)
16–20	17 (15.1)	10 (11.7)	27 (13.5)
20+	31 (27.4)	34 (39.5)	65 (32.7)
TOTAL	**113 (100)**	**86 (100)**	**199 (100)**

Reason for the study

Of the 199 patients with active lesions, 88.4% were treated using traditional methods at least once compared with 31.7% having received modern medical treatment; 63.3% of patients received care only from a traditional healer.

According to field data collected, the disease is considered to be a curse that cannot be cured at a hospital. Furthermore, medical personnel have poor knowledge about the disease.

Apart from the 2001 survey results, there is a serious lack of data to enable an understanding of the context in which Buruli ulcer control activities are planned in the Ayos and Akonolinga districts; this survey will serve as a basis for developing a structured intervention. The various subjects addressed in the questionnaire will make it possible to identify strategies for information, education, communication (IEC) and to raise awareness about the disease.

Review of existing literature

M. ulcerans is the causative agent of the deep, necrotizing, relatively painless cutaneous lesions with characteristic undermined edges, commonly referred to as Buruli ulcer. First described by MacCallum et al. in Australia in 1948, endemic foci of Buruli ulcer were subsequently reported in many countries in Africa, north America (Mexico), south America, south-east Asia and in Australia. According to van der Werf et al. (*1*), Buruli ulcer is the third most common mycobacterial infection in human beings, after tuberculosis and leprosy, in the rural intertropical zone. Since 1980, a dramatic increase in the incidence of the disease has been reported in several regions of the world, especially western Africa. In 1998, recognizing Buruli ulcer as a major emerging disease, WHO established the Global Buruli Ulcer Initiative.

Cases of Buruli ulcer typically occur in intertropical zones and geographically well-contained endemic foci around an aquatic ecosystem: slow-flowing rivers, natural or artificial lakes and wetlands. The disease affects mainly children under 15. The risk factors and mode of transmission are not well known and the best treatment – by wide excision of the lesion and skin graft – is unsatisfactory.

In Cameroon, the disease, with its often ghastly cutaneous lesions and disabling sequelae, was first described by Ravisse et al. (*2*) and Boisvert (*3*). The 47 cases they studied all stemmed from very local foci in the Nyong valley, between the towns of Ayos and Akonolinga. In the past several years, health personnel have been sporadically reporting suspected cases of Buruli ulcer without diagnostic confirmation. These cases have been recorded in various regions of the country, but principally in the extreme north, and in the South-West and Centre provinces. In the Centre

province, the reported cases were in the Ayos–Akonolinga area. Unfortunately, the serious epidemiological nature of this disease does not appear to have drawn the attention of health officials since it is completely overlooked in routine health statistics and is often even poorly recognized by health personnel.

We carried out a document search to assess the knowledge, attitudes and practices (KAP) of populations regarding Buruli ulcer; in doing so, we found only 552 publications in French (using Google), only one of which is relevant to our study: *Poids des croyances et des représentations*, a survey conducted by Aujoulat and colleagues in Benin in 2000.

Objectives of the survey conducted in Benin

The Benin survey was conducted in connection with a programme to provide information to populations in the endemic zone, by means of a relevant awareness campaign, on Buruli ulcer and case management facilities, in order to incite them to seek care as early as possible.

Effects assessed by the survey

The Benin survey assessed the factors facilitating or hindering early management of Buruli ulcer cases.

Benin survey results

1. Buruli ulcer is well known and recognized, even at the early stage.
2. Buruli ulcer is seen as a serious and frightening disease.
3. Buruli ulcer is often attributed to witchcraft, even by health care personnel.
4. Those surveyed do not believe that hospital treatment is effective

Hypothesis

Data from the assessment of the knowledge, attitudes and practices of the populations of the Ayos and Akonolinga districts regarding Buruli ulcer will serve as a basis for developing an awareness-raising programme to promote early case management. This data will also serve as a basis for identifying needs in health-care personnel training.

Overall objective

To enhance the knowledge of Buruli ulcer in order to organize its case management.

Specific objectives

1. To disseminate a questionnaire for assessing the knowledge, attitudes and practices of populations of the Ayos and Akonolinga health districts regarding Buruli ulcer.
2. To develop recommendations for the establishment of an awareness-raising programme.

Research methodology

What the study will involve

KAP will be assessed by means of a descriptive, quantitative study.

KAP surveys always aim to develop and capitalize on the knowledge, attitudes and practices of populations when faced with a given phenomenon, thus enabling them to become more involved in policies and steps towards a solution to the problem.

The chosen methodology, without any doubt, aims to encourage interaction among those affected by Buruli ulcer, namely through the transfer of knowledge between health care workers and the population. KAP surveys also attempt to quantify social, health and behavioural phenomena that can vary from person to person.

However, KAP surveys have been sharply criticized by anthropologists, who favour ethnographical studies (such as those by Jenking and Howard, 1992; Hermann and Bentley, 1992). The ethnological approach is inductive: individuals are considered to be producers of knowledge of interest to researchers, ready to take action. Answers provided in KAP surveys are unavoidably unverifiable, and results are sometimes difficult to interpret.

Despite its weaknesses, the KAP survey remains relevant for our purposes since our concern is to determine the relationship between our subject and demographic, geographical and sociofamilial variables. The results will give an idea of the general situation throughout the country, thus providing a solid basis for planning certain interventions to control Buruli ulcer.

Internal validity

This survey rests on a questionnaire assessing the effects of KAP on a population.

External validity

The validity of the study will be guaranteed through precautions in methodology, particularly in terms of the villages selected, pre-testing, and optimal mastery of cross-sectional survey techniques.

Biases

The pretest will be carried out in a neighbouring district having the same characteristics as Ayos and Akonolinga, in order to avoid regression biases towards the mean.

The survey will be conducted by the same surveyors from beginning to end, using the starting methodology throughout.

Observational bias will also be prevented through various measures:
- guaranteeing absolute anonymity and confidentiality to participants,
- simplifying language as much as possible and adapting it to the various groups by using popular jargon.

Duration of the study

The study will be carried out over a one-week period in February 2003.

Place

The study will be carried out in the department of Nyong and Foumou in the Ayos and Akonolinga districts. The department of Nyong and Foumou is located in Centre province and consists of three arrondissements (Akonolinga, Ayos and Endom) and two districts (Mengang and Kobdombo). It

covers an area of 6167 km^2 with a population of 136 000. In terms of health care, the department comprises the two health districts of Ayos and Akonolinga.

The terrain alternates between low hills and plains that flood in the rainy season. The department is watered by the relatively slow-flowing river Nyong that runs through an alluvial basin bordered by marshland. It is rich in fish, in particular "kanga", which are greatly prized by the local population.

It has a tropical climate with four seasons. The vegetation consists of areas of tropical forest interspersed with shrub-covered plains in the north.

The autochthonous population is Bantu, belonging to the large "Fan-Beti" group, comprising the following ethnic groups: Maka, Mbida Mbani, Mvog Niengue, Omvang, Sso, Yebekolo, Yelinda, Yembama and Yengono. The percentage of children in full-time education is low and French is not spoken everywhere.

The main activities are fishing and farming. The principal towns in order of size are Akonolinga, Ayos and Endom. Of the department's population, 59% lives within the area served by the Akonolinga health district, which is divided into 11 health areas covering 390 villages. The Ayos health district serves approximately 50 000 people in six health areas covering 102 villages.

Recruitment criteria

Anyone living within the department of Nyong and Mfoumou will be able to take part in the survey. Respondents should be heads of families (fathers or mothers) aged 17 years or more.

Sampling

Sample villages, known as clusters, will be chosen and a questionnaire sent to a specified number of individuals within the cluster who have been randomly selected. Stratified cluster sampling will then be carried out as follows:

Stratum 1. Villages will be selected at random and with weighted probability proportional to the number of inhabitants.

Stratum 2. One household in each village will be randomly selected as a launch pad for the survey.

A complete list of villages will be compiled for the purpose of singling out certain villages on the basis of the size of their population. As a preliminary step to identifying 30 respondents in each village, the first household will be drawn by lot.

The department in which the survey will be carried out will be divided into two statistical entities comprising the health districts of Ayos and Akonolinga.

Sample size

The formula devised by Bennet et al. (1991) gives the requisite number of clusters: $C = P \times (1 - P) \times D / s^2 \times b$, in which P is the estimated proportion, D is the design effect ($D = 1 + (b - 1)$ rho), s is the standard error and b is the number of respondents per cluster. Given that the prevalence of Buruli ulcer in the population is estimated at 2.5%, and allowing for a standard error of 0.2 and a slippage or possibly an inter-class correlation (rho) of 0.5, the total number of subjects in each district is calculated to be 1440 (48 clusters each containing 30 people).

Implementing the survey

The survey will be validated in the Abong Mbang or Mfou health districts and will involve seven clusters. The purpose of the pilot study will be to evaluate the survey method, for example, by identifying respondents, the length of the interviews, the nature, acceptability and clarity of the questions and the reliability of the answers.

A survey team trained in survey techniques (confidentiality, approach, etc.) will be chosen by the heads of district health services. A supervisory team comprising heads of district health services, health departments and health centres will also be established. The heads of health centres will also act as interviewers during the survey.

Data analysis

Data will be analysed using EpiInfo version 6 software.

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ACTIVITIES CARRIED OUT IN 2002 TO DEAL WITH BURULI ULCER IN CAMEROON

Sarah Eyango, Alphonse Um Boock, Patrick Biason

Background

After a prevalence survey in 2001 showed that Buruli ulcer is a public health problem in the health districts of Ayos and Akonolinga, an intervention programme was set up in partnership with the Cameroonian Ministry of Health, Aide aux Lépreux Emmaüs-Suisse, and Médecins Sans Frontières, Switzerland. The Centre Pasteur in Cameroon has participated in this effort by carrying out bacteriological diagnosis of Buruli ulcer in the cases registered.

Strategies

The sites for intervention are two districts in the Centre province of Cameroon, each with about 50 000 inhabitants. The host institutions are the hospitals of these districts.

The two hospitals in Ayos and Akonolinga are participating with their regular staff. In particular, physicians and nurses are responsible for reporting cases that arrive at the institutions and for giving local, pre- and post-operative treatment, performing debridement and assisting in skin grafts. Operating theatre staff are responsible for carrying out general anaesthesia using ketamine.

The following facilities were refurbished at Akonolinga Hospital in late 2002: two wards, one wound dressing room, one laundry, one shower block and two latrines for patients, a septic tank and a waste management facility. The water supply system was renovated and its capacity increased. A new operating theatre and a kitchen for patients are under construction. Equipment in the operating theatre and wound dressing room has been adapted to the new requirements.

At Ayos Hospital, the following additions were made in late 2002: equipment of the wound dressing unit and provision of the necessary medical supplies for proper wound dressing, provision of stock forms and patient records as well as a system for gathering statistical data and creation of a nutrition programme for patients.

Cases registered and epidemiological data

Akonolinga. The number of patients in which the emergence or recurrence of Buruli ulcer was reported was 66 in 2002. These cases were identified through passive detection and all are from the village of Akonolinga or nearby areas. They break down as follows:

- 33 men, 33 women,
- 37 children aged under 15, 29 adults,
- 38 persons who have received BCG vaccination at least once, 22 who have never had BCG vaccination and 6 whose BCG status is unknown,
- 22 lesion sites on upper limbs, 46 on lower limbs, 5 on the head or trunk (the number of sites is greater than the number of patients since each patient may have several sites).
- On the limbs, 42 right and 26 left sites.

The first appearance of signs dates back to anywhere from two weeks to 25 years earlier, with a median of two months.

Seven cases are recurrences on the same site after local treatment, 12 are appearances on other sites after signs of active disease disappeared on the first site.

Ayos. The number of patients in which Buruli ulcer was reported to have emerged or recurred in the same year, 2002, was likewise 66. The patients are also from areas near Ayos. They break down as follows:

- 34 men, 32 women,
- 30 children aged under 15 years, 30 adults,
- 42 persons who have received BCG vaccination at least once, 23 who have never had BCG vaccination and 1 whose BCG status is unknown,
- 18 lesion sites on upper limbs, 35 on lower limbs, 6 on the head or trunk and 7 on unspecified sites.
- On the limbs, 25 right and 28 left sites.

The first appearance of signs dates back to anywhere from two weeks to two years earlier, with a median of eight months. The programme of operations began on 17 October 2002 in Akonolinga and expanded to Ayos in late 2002. By late 2002, eight patients had received grafts.

Bacteriological diagnosis

Two swabs per ulcer were taken for each patient in Akonolinga identified since the start of the programme of operations, and in cases of surgical debridement, a biopsy was taken and sent to the mycobacterial laboratory at Cameroon's Centre Pasteur for microscopic examination of the smears, culture and PCR. The same procedure has been adopted for patients in Ayos since January 2003.

Microscopic examination was carried out using Ziehl-Neelson staining, the culture was incubated at 30 °C in Löwenstein-Jensen medium, PCR was carried out on the basis of the published primers of the IS*2404* sequence (MU5 and MU6) following DNA elution from a Qiagen column.

In late 2002, the Mycobacterial Laboratory received 66 specimens: 36 swabs and 30 biopsies. Seventeen smears from swabs and 23 smears from biopsies were found positive by direct microscopic observation. These 40 smears, which were found positive by direct microscopic observation, were confirmed positive by PCR. The first cultures were obtained after 10 weeks of incubation, with the majority still under incubation. Ten cultures were found positive, eight of them specimens already found positive under microscopic examination and PCR and two of them specimens found negative.

Communication

Video spots to raise awareness among the population of the two districts are being made.

BURULI ULCER RESEARCH FUND

Dr Paul Johnson

Buruli ulcer is a widespread disease with terrible disfiguring complications. It is caused by *Mycobacterium ulcerans* which produces a destructive toxin. The main burden of disease falls on children living in sub-Saharan Africa. Buruli ulcer is the third major mycobacterial disease of man after tuberculosis and leprosy, and is endemic in at least 30 countries. In contrast to leprosy, it is increasing in incidence and geographic distribution. The main burden of disease falls on children living in sub-Saharan Africa. In response to the growing spread and impact of Buruli ulcer, WHO established the Global Buruli Ulcer Initiative (GBUI) in 1998 to coordinate control and research efforts into Buruli ulcer. The small but dedicated group brought together through this initiative has made significant progress since 1998, but there is much still to be done. Members of the GBUI have identified priority areas that urgently require further research, but there is no budget with which to support these projects. Furthermore, as Buruli ulcer is an orphan disease largely restricted to developing countries, it is difficult to attract the necessary funds from wealthy nations. To overcome this problem, a new research fund is proposed—the **Buruli Ulcer Research Fund** (BURF). The goal of the fund is to accelerate and coordinate research to develop better tools for the control of Buruli ulcer. Among the many potentially important areas of research on Buruli ulcer, **five priority areas** were selected by the research subgroup at the 5th WHO Advisory Group Meeting on Buruli Ulcer, held in March 2002 in Geneva.

Priority areas for new research:

1. **The mode of transmission of *M. ulcerans* to humans**
2. **Development of better methods for early diagnosis**
3. **Drug treatment and new treatment modalities**
4. **BCG trials and development of novel vaccines**
5. **Cultural and socioeconomic aspects of Buruli ulcer**

An ambitious and focused research agenda is envisaged, which will require US$ 4 million over five years. Applications to BURF will be open to existing and new Buruli ulcer researchers and will be awarded according to the merit of the proposal, the track record of the applicants and the relevance of the project to our stated goal. Progress in these keys areas is most likely to provide direct benefit to Buruli ulcer patients. Once established, researchers will be able to apply to the Buruli ulcer Research Fund throughout the year, and application processes will be streamlined to ensure that quality projects are funded immediately. We extend a warm invitation to all donor agencies to help us to build the Buruli Ulcer Research Fund, so that we can deliver better lives to those who live where Buruli ulcer is endemic.

A PROTOCOL TO STUDY THE PROTECTIVE EFFECT OF A SECOND DOSE OF BCG ON THE INCIDENCE AND SEVERITY OF BURULI ULCER – EXECUTIVE SUMMARY

Dr Paul Johnson

Buruli ulcer is a widespread disease with terrible, disfiguring complications. It is caused by *Mycobacterium ulcerans*, which produces a destructive toxin. The main burden of disease falls on children living in sub-Saharan Africa. The mode of transmission is unknown. A recent study estimated an incidence of 280/100 000 per year in a highly endemic district in Ghana. Treatment of advanced disease is complex because surgery, skin grafting and prolonged physical rehabilitation are required. Buruli ulcer may cause months or even years of suffering and leave patients psychologically, socially and physically scarred. The disease places a huge burden on strained health budgets.

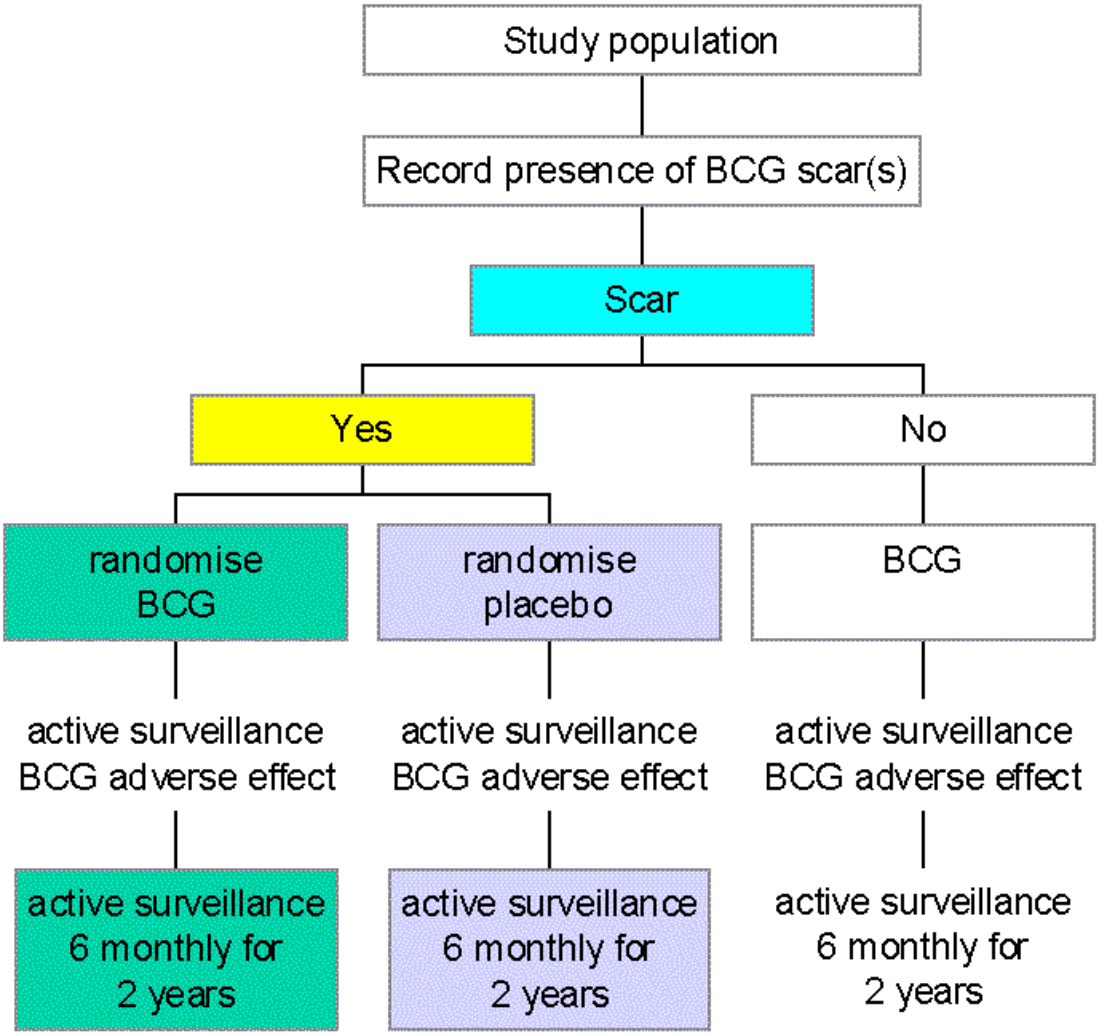
Primary prevention will require a vaccine, but no *M. ulcerans*-specific vaccine will be available in the near future. There is evidence that a single dose of BCG is effective against Buruli ulcer, but protection wanes quickly. A study in Malawi has shown that a second dose of BCG provides additional protection against leprosy and was safe in a large African population.

We hypothesize that a second dose of BCG may also enhance protection against Buruli ulcer. A placebo-controlled study is proposed to investigate this possibility. Subjects will be children aged 3 months to 15 years as this is the group at highest risk. End-points will be the incidence of new cases of Buruli ulcer and severity of disease at diagnosis. We will need to recruit 30 000 children to ensure that 8500 randomized subjects in each arm can be followed. The study will be performed in duplicate in one francophone and one anglophone African country (30 000 recruited per country) to ensure that access to data will be immediate in highly endemic countries.

A preparatory phase of 6–12 months will precede the main study to accurately establish the pre-study incidence, train staff, establish referral pathways and help refine the study design. Subjects without a history of Buruli ulcer who have evidence of past BCG will be randomized to receive an additional dose of BCG or placebo. Children without evidence of previous BCG will be vaccinated and followed but not randomized. Newly detected cases of Buruli ulcer will be referred for appropriate treatment according to national guidelines. Figure 1 shows an outline of the study design.

The study will be a collaboration between national governments, NGOs and academic institutions and will be coordinated by WHO. The estimated budget is US$ 2.2 million. If successful, this trial will lead to an effective public health intervention for Buruli ulcer within two years.

Figure 1. **Diagram showing outline of study design**



BONE INVOLVEMENT IN BURULI ULCER: A STUDY OF 73 CASES IN BENIN

F. Portaels,[1] C. Zinsou,[1,2] J. Aguiar,[2] M. Debacker,[1] E. de Biurrun,[1,2] A. Guédénon,[3] R. Josse,[4] V. Lagarrigue,[5] M.T. Silva,[6] C. Steunou,[2] W.M. Meyers[7]

[1] Mycobacteriology Unit, Department of Microbiology, Institute of Tropical Medicine, B-2000 Antwerp, Belgium
[2] Centre Sanitaire et Nutrionnel, Gbemoten, Zagnanado, Bénin
[3] Programme National de Lutte contre l'Ulcère de Buruli, Ministère de la Santé, Cotonou, Benin
[4] Hôpital d'Instruction des Armées 'Robert Picque', Bordeaux, France
[5] Religieuses de l'Assomption, Abomey, Benin
[6] ICVS, Universidade do Minho, Braga and IBMC, Universidade do Porto, Porto, Portugal
[7] Armed Forces Institute of Pathology, Washington, DC, USA

Summary

Buruli ulcer (BU), an infection caused by *Mycobacterium ulcerans*, is best known for its characteristic cutaneous lesions. *M. ulcerans*, however, often also causes lesions of the bone. Bone involvement has received little attention, although as many as 14% of all BU cases have osteomyelitis.

In Benin, during the period 1996–2002, we collected 73 cases of *M. ulcerans* osteomyelitis that were confirmed bacteriologically and/or histologically. All patients were treated by surgery (excision, curettage and skin grafting) at the Centre Sanitaire et Nutrionnel Gbemoten at Zagnanado. In 22 patients (30.1%), bone lesions were immediately beneath a lesion of BU in the skin (contiguous osteitis). The remaining 51 patients had osteomyelitis at a site distant from lesions in the skin (metastatic osteomyelitis).

Of the 73 patients, 20 presented at the hospital without bone lesions. Of these 20 patients, 6 developed bone lesions during hospitalization and 14 patients developed bone lesions after the skin lesions had healed.

A total of 23 patients presented with only a single bone lesion: 17 of these patients were cured following surgery and 6 developed bone lesions after the initial lesion had healed.

Some 30 patients presented at the hospital with metastatic osteomyelitis: 9 of these patients with multifocal bone lesions were cured by surgery, 16 patients developed additional lesions during hospitalization and 5 patients healed initially but developed new bone lesions later. Metastatic bone lesions may develop by haematogenous or lymphatic spread of the aetiological agent from earlier *M. ulcerans* disease of the skin.

The median hospital stay was 49 days for patients with bone lesions, compared with 35 days for those with skin lesions only seen during the same study period; 10 patients required amputation of an extremity or portion thereof and 2 patients died of causes unrelated to BU.

Delay in presentation to the hospital following onset of disease was an important risk factor for the development bone lesions: 152 days for those with osteomyelitis and 46 days for those with skin lesions only.

During follow-up by visits to the village or at a check-up at the hospital, we found that 56 patients were in good health without significant physical disability, except for those who had amputations. The remaining 15 patients have yet to be followed-up.

Four significant risk factors for bone involvement were identified:

– presence of a typical scar of BU that had not been treated surgically,
– a markedly prolonged median delay in presentation to the hospital,
– absence of BCG vaccination,
– HIV infection.

Other risk factors that must be taken into account are virulence of the strain of *M. ulcerans*, coexistence of other tropical diseases (for example, schistosomiasis and sickle-cell anaemia), host heredity and immune system status. Identification of these factors would contribute to the development of plans of action to reduce the frequency of *M. ulcerans* osteomyelitis and the severe physical disability that it causes.

ECOLOGY AND TRANSMISSION OF *MYCOBACTERIUM ULCERANS*

Laurent Marsollier,[1] Jacques Aubry,[2] Jean-Paul Saint André,[3] Timothy Stinear,[4] Raymond Robert,[5] Pierre Legras,[5] Anne-Lise Manceau,[1] Bernard Carbonnelle,[1] Steward T. Cole[4]

[1] Laboratoire de Bactériologie-Virologie-Hygiène, CHU, 49033 Angers, France
[2] Laboratoire d'Anatomie Pathologique, CHU, 49033 Angers, France
[3] Unité 463 INSERM, Institut de Biologie, Faculté de Pharmacie, 44035 Nantes, France
[4] Unité de Génétique bactérienne, Institut Pasteur, 75015 Paris, France
[5] Groupe d'Interaction Hôte-Parasite, Faculté de Pharmacie, 49000 Angers, France

Mycobacterium ulcerans is an emerging environmental pathogen concerning mainly tropical countries; it is the causative agent of Buruli ulcer, which has become the third most important mycobacterial disease in humans after tuberculosis and leprosy. *M. ulcerans* is the only mycobacterium known to produce a dermonecrotic toxin, which induces an important and extensive skin ulceration. Despite water-linked epidemiological and PCR data to identify the sources of *M. ulcerans*, the reservoir and the mode of transmission of this organism remain elusive. To determine the ecology and the mode or transmission of *M. ulcerans*, we have set up an experimental model with aquariums that mimic aquatic microenvironments.

To demonstrate the role of water bugs as a vector of *M. ulcerans*, *Naucoris* (*Naucoris cimicoides*) were infected by feeding with grubs contaminated by *M. ulcerans*; 45 days later, 10 BALB/c mice were bitten by these infected insects. Three months after being bitten, 7 mice exhibited cutaneous and biological signs of *M. ulcerans* infection confirmed by culture and by PCR. This experimental model demonstrated that water bugs were able to transmit *M. ulcerans* by bites.

The localization of bacilli in insect tissues was established by Ziehl-Neelsen staining and by immunostaining. Four mycobacteria species (*M. marinum, M. chelonae, M. fortuitum, M. kansasii*) were studied as negative controls under the same conditions. *M. ulcerans* was shown to be localized exclusively within the salivary glands of insects, where it could both survive and multiply, contrary to other mycobacteria species.

In another experimental study, we report that the crude extracts from aquatic plants stimulate in vitro the growth of *M. ulcerans* as much as the biofilm formation by *M. ulcerans* has been observed on aquatic plants. These results suggest that in the environment, *M. ulcerans* may be attached to aquatic plants that provide the nutriments necessary for its survival and replication despite competition with other microorganisms. Given that the water bugs are essentially carnivorous, it is difficult to suppose a direct contact with the contamination of aquatic bugs and plants. It seems highly probable that an intermediate host can be infected by eating some aquatic plants.

Thirdly, the role of aquatic snails was examined. The snails belonging to the families of Ampullariidae and Planorbidae could be contaminated by *M. ulcerans* after being fed with aquatic plants covered by a biofilm of *M. ulcerans.* They can be considered passive hosts because, under our experimental conditions, no expansion of bacilli was demonstrated but the bacilli detected in the digestive tract survived within 60 days after an initial contamination.

In the endemic area of Daloa in Côte d'Ivoire, contamination of aquatic plants and snails by *M. ulcerans* was established by PCR only. Among 80 *Naucoris* captured, 5 infected insects were identified by PCR from the salivary glands of these specimens; in two of them, *M. ulcerans* was isolated for the first time from the environment. These insects are good flyers, so they could

colonize new swampy areas and create new foci of Buruli ulcer, providing an effective means to study the epidemiology and the identification of *M. ulcerans* strains.

In conclusion, we have provided the first strong evidence of the implication of water bugs in the transmission of *M. ulcerans* (see article in *Applied Environment Microbiology*, 2002, 4623–4628) as well as original data concerning the role of aquatic snails and plants in the ecology of *M. ulcerans* [manuscripts in progress].

APPROACHES FOR THE DEVELOPMENT OF NEW TOOLS FOR THE DETECTION AND CHARACTERIZATION OF *MYCOBACTERIUM ULCERANS*

Gerd Pluschke,[1] *Diana Diaz,*[1] *Simona Rondini,*[1] *Thomas Bodmer,*[2] *Ernestina Mensah-Quainoo,*[3]

[1] Swiss Tropical Institute, Basel, Switzerland
[2] University of Bern, Switzerland
[3] Ga District Health Directorate, Amasaman, Ghana

For early diagnosis of Buruli ulcer, no tools are currently available that can be easily implemented in the rural environment of developing countries. Development of methods for early diagnosis is therefore one of the priority areas of research selected by the research subgroup at the Fifth WHO Advisory Group Meeting on Buruli Ulcer. Accordingly, we are trying to improve detection, quantification and subtyping methods for *M. ulcerans* with the help of immunological and molecular genetic techniques.

Broad antigenic overlap between mycobacterial species complicates the analysis of adaptive immune responses to *M. ulcerans* and hampers the development of test systems suitable for areas where TB is also endemic and BCG vaccination is commonly done. We have started to dissect the humoral immune response against *M. ulcerans* with a panel of monoclonal antibodies. Both broadly cross-reactive and highly specific antibodies were obtained. Their potential for the detection of *M. ulcerans* in clinical specimens and for the identification of antigens suitable for the development of a serological test is now being investigated. We expect that in future the description of the complete *M. ulcerans* genome will considerably facilitate the development of new tests and sub-typing methods required for the diagnosis of Buruli ulcer and for the investigation of the micro-epidemiology and transmission of the disease.

UPDATE ON SEROLOGY AS A POTENTIAL DIAGNOSTIC METHOD FOR BURULI ULCER DISEASE

D.M.N. Okenu,[1] L.O. Ofielu1, K.M. Dobos,[1] J. Guarner,[2] E.A. Spotts Whitney,[2] P.L. Raghunathan,[2] Y. Stienstra,[3] K. Asamoa,[4] T.S. van der Werf,[3] W.T.A. van der Graaf,[3] D.A. Ashford,[2] J.W. Tappero,[2] C.H. King[1]

[1] Emory School of Medicine, Atlanta, Ga, USA
[2] Centers for Disease Control and Prevention, Atlanta, Ga, USA
[3] Department of Internal Medicine, Groningen Hospital, Groningen, Netherlands
[4] Ministries of Health, Accra, Ghana

Correspondence to: Dr C. Harold King, Division of Infectious Diseases, Department of Medicine, Emory University School of Medicine, 69 Butler St. SE, Atlanta, GA 30303, USA.
Phone: +(1) 404 616 1447; Fax: +(1) 404 880 9305 (E-mail: cking01@emory.edu).

Buruli ulcer disease caused, by *Mycobacterium ulcerans*, is the most common mycobacterial disease after tuberculosis and leprosy among immunocompetent people in the tropical world (*1*). The disease is characterized by indolent, necrotizing skin ulcerations. Skin lesions progress over weeks to months from typically painless, subcutaneous nodules or plaques to large undermined ulcers, usually with an absence of systemic signs of illness. Adverse sequelae are common and include extensive scarring, flexion contractures, osteomyelitis, loss of limbs and blindness (*2*). Over the past decade, there has been a considerable increase in BU disease cases in the west African sub-region (*3–4*). In endemic areas, BU disease has replaced tuberculosis and leprosy as the most prevalent mycobacterial disease, affecting up to 22% of the population in some communities (*5*). Currently, the standard treatment strategy is limited to surgical excision at the pre-ulcerative stage, followed by skin grafting. The economic burden on the healthcare systems is therefore large (*6*).

At present, BU disease diagnosis is carried out using conventional techniques, namely acid-fast bacilli (AFB) Ziehl-Neelsen staining, bacterial culture, histopathology, polymerase chain reaction (PCR) (5) and, sometimes, skin testing using burulin, a purified protein derivative of *M. ulcerans* (*7*). The sensitivities and specificities of these assays are undefined because of the absence of a reference standard diagnostic (gold standard.) As part of a case-control study that was conducted in Ghana in 2000, we collected specimens from all case-patients for evaluation of the standard laboratory confirmation test for BU disease (*5*). We found that AFB, culture, histopathology and PCR (*15*) had sensitivities of 27%, 82%, 89% and 100% respectively (Whitney Spotts et al. [manuscript in preparation]). Using certain combinations of two tests increased the sensitivity consistently to 100%, supporting the recommendations for laboratory confirmation of BU disease (*5*).

However, apart from not being suitable for early disease detection, these individual techniques can be cumbersome, highly technical, capital intensive and/or time consuming, thus making them inadequate for broad use in developing countries where the disease is endemic. Currently, there is no rapid, clinically useful detection technique for early confirmation of disease at the pre-ulcerative stage. Consequently, the WHO Global Buruli Ulcer Initiative challenged the research community to develop a simple and rapid diagnostic test to identify patients at an early stage during the course of infection, so that early treatment options, including antimicrobial chemotherapy, may be fully exploited (*6*, *8*).

BU infection is thought to mediate a selective suppression of human T-cell responses (9–10). Humoral immunity however, may be of vital importance, since sera of infected individuals from endemic regions show high antibody titres to several *M. ulcerans* antigens (*11, 14*). Similarly, strong antibody responses have been observed with other known mycobacterial infections such as tuberculosis and leprosy (*12–13*). Such distinct serological differences among BU disease patients, healed and healthy individuals may be pertinent for developing a rapid, sensitive and highly specific diagnostic test for early disease detection. To assess the potential of such a serodiagnostic assay for BU disease, our laboratory previously evaluated the antibody responses against *M. ulcerans* antigens among clinically diagnosed (5) patients from endemic regions (*3, 14*). Human IgG antibody responses were measured against *M. ulcerans* culture filtrate (MUCF) proteins using patient sera from Côte d'Ivoire. More than 70% (43 out of 61) of the patients showed strong antibody reactivity against MUCF antigens (*14*), suggesting that MUCF serological response may be useful in early disease diagnosis. In a follow-up study in our laboratory (Whitney et al. [manuscript in preparation]), a promiscuous IgG response among confirmed BU-infected and healthy volunteers was found. This cross-reactivity is indicative that the immune system may have been primed by exposure to *M. ulcerans*, *M. tuberculosis* and other related pathogenic and non-pathogenic mycobacteria in this region. Reactivity to a 70 kDa antigen was again more specific to BU disease cases compared with non-endemic tuberculosis controls. Consequently, these human IgG responses could not distinguish between diseased, healed or healthy individuals in endemic regions. We have now compared the primary (IgM) antibody responses to *M. ulcerans* proteins released into culture filtrate (MUCF) by Western blot using confirmed cases (by any two laboratory methods) and matched family control sera from three disease endemic regions of Ghana.

As previously shown, MUCF antigens were recognized on immunoblots by serum IgG from both BU disease patients and their immediate healthy family controls living in the same household (Whitney Spotts et al. [manuscript in preparation]; Figure 1 shows representative responses).

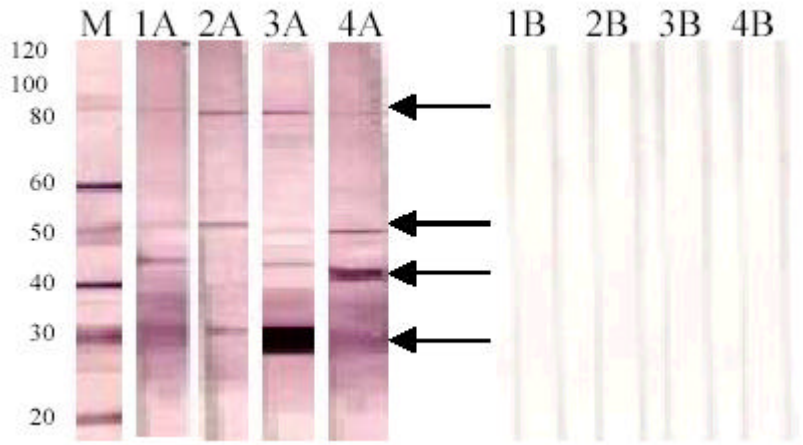


Figure 1. **Secondary (IgG) antibody reactivity against *M. ulcerans* culture filtrate proteins (MUCF) on Western blots. M, magic mark molecular weight marker (Invitrogen, Carlsbad, CA); lanes 1A–4A, representative BUD patient sera with IgG antibody reactivity to different MUCF antigens; lanes 1B–4B, representative sera from corresponding patients' apparent healthy relative living in the same household**

The primary antibody (IgM) responses were, however, restricted to confirmed BU disease patients only and not to their healthy family controls (Fig. *2*). A total of 84.8% (56 out of 66) confirmed BU disease patients showed positive IgM antibody reactivity against any MUCF protein, in comparison to only 4.5% (3 out of 66) of their healthy family controls. Interestingly, none of the tuberculosis

or onchocerciasis patients' sera from non-endemic BU disease regions in Ghana were positive for IgM antibody response against MUCF proteins (data not shown), although all were reactive to MUCF via IgG responses confirming immune competence. Primary antibody reactivity was therefore discriminatory for patients with clinical disease, their corresponding healthy family relatives living in the same household and patients with other diseases.

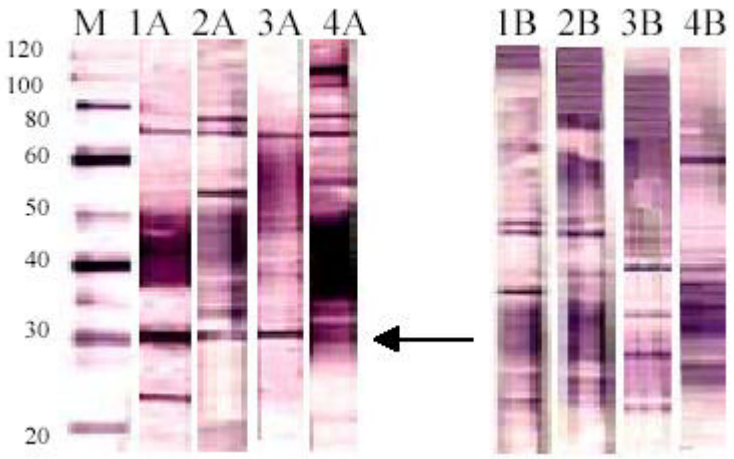


Figure 2. **Primary (IgM) antibody reactivity against M. ulcerans culture filtrate proteins (MUCF) on Western blots. M, magic mark molecular weight marker (Invitrogen, Carlsbad, CA); lanes 1A–4A, representative BU patient sera with IgM antibody reactivity to different MUCF antigens; lanes 1B–4B, representative sera from corresponding patients' apparent healthy relative living in the same household.**

Positive IgM antibody reactive sera recognized four distinct MUCF proteins, namely 30, 43, 50 and 80 kDa. When the number of positive IgM antibody relativities was scored against specific MUCF antigens, 85.7% (48 out of 56) recognized a 43 kDa protein, 69.6% (39 out of 56) reacted with a 30 kDa antigen, while 41% (23 out of 56) showed reactivity to a 50 kDa antigen. Only 14.3% (8 out of 56) IgM positive individuals recognized a high molecular weight antigen of 80 kDa. Generally, most patients recognized more than one MUCF antigen. The most frequent antigen recognized by both IgG and IgM serum antibodies was the 30 kDa, which was reactive against 79% (52 out of 66) of the total patient population, while the 80 kDa at 10% (7 out of 66) was the least commonality antigen. In effect, the 43 kDa antigen was the most frequent among IgM positive patients, whereas the 30 kDa protein was the commonality antigen for both IgG and IgM positive individuals. This may be indicative that a combination of both antigens (30 and 43 kDa) will increase both specificity and sensitivity in serodiagnosis.

To determine whether the present discriminatory IgM antibody reactivity will be suitable for early disease detection, antibody positivity was analysed under different disease stages. From a total of 56 patients who were IgM antibody-positive to MUCF antigens, 21 patients were at the early stage of disease progression (the non-ulcerative phase), as defined by the presence of nodule, oedema, plaque and nodule/scar (*5*), while 35 were at the later disease stage (an active ulcerative phase) characterized by ulceration of the dermis (*5*). A significant 85.7% (18 out of 21) of the early disease patients were reactive to the 43 kDa antigen, while 66.7% (14 out of 21) recognized the 30 kDa protein. Comparatively, 71.4% (25 out of 35) and 85.7% (30 out of 35) active disease patients recognized the 30 and 43 kDa, respectively. In the present study, the total number of patients at the early disease stage analysed was only 21 out of the 56 IgM antibody-positive individuals, and the result suggests that a combination of the 30 and 43 kDa antigens may have great potential in early disease detection. However, a larger patient population at the early disease phase may be required to confirm this important observation.

Preliminary screening of a genomic DNA expression library of *M. ulcerans* to identify the gene fragments encoding these antigens is in progress. The development of a rapid serological diagnostic test for early detection of *M. ulcerans* infection will be an important step to enable prompt treatment analysis of the disease.

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IMPLEMENTATION OF A DRY REAGENT-BASED PCR AS A NOVEL TOOL FOR THE LABORATORY CONFIRMATION OF CLINICALLY DIAGNOSED *M. ULCERANS* DISEASE IN GHANA

Gisela Bretzel,[1] Petra Plähn,[1] Julia Polansky,[1] Christian Drosten,[1] Paul Racz,[1] Ohene Adjei,[2] Christof Berberich,[2] Erasmus Klutse,[3] Thomas Kruppa,[2] Serwaa Akosua,[2]

[1]Bernhard Nocht Institute for Tropical Medicine, Hamburg, Germany
[2] Kumasi Center for Collaborative Research in Tropical Medicine, Kumasi, Ghana
[3] Dunkwa Government Hospital, Dunkwa, Ghana

Since 2001, the Kumasi Center for Collaborative Research in Tropical Medicine (KCCR) and the Bernard Nocht Institute for Tropical Medicine (BNITM) have been active in developing a diagnostic network for the laboratory confirmation of clinically diagnosed *M. ulcerans* cases in Ghana. The main objectives of the project are (i) to establish a dry reagent-based "field-PCR" as a novel tool for the rapid detection of *M. ulcerans* infection in Ghana and to field-test its applicability for the diagnosis of early *M. ulcerans* disease; (ii) to assess the diagnostic sensitivity of different laboratory methods (AFB smear microscopy, culture, PCR, histopathology) for the detection of early cases; (iii) to introduce a quality management system within the diagnostic laboratory network; (iv) to obtain laboratory-confirmed incidence data and to determine the burden of the disease in selected endemic areas in Ghana by means of active case-finding; (v) to establish the percentage of misclassified cases clinically diagnosed as Buruli ulcer and to determine the differential diagnosis by means of histopathology; (vi) to study the socioeconomic impact of delayed diagnosis and misclassification of *M. ulcerans* disease in terms of additional total treatment costs versus the potential savings in case of early case detection; (vii) to study the cost-effectiveness of implementing PCR as a sensitive and rapid diagnostic tool in endemic countries in terms of potential savings in total treatment costs; and (viii) to collaborate with the local health services and to provide the laboratory results obtained within the laboratory network to the collaborating diagnostic centres and the Ghanaian Buruli Programme.

Results from a preliminary study, including swabs and biopsies from 25 clinically diagnosed ulcerative cases from Ghana, indicated the following diagnostic sensitivities: Ziehl-Neelsen smear microscopy 16%; culture (swabs and biopsies) 40%; PCR (IS2404 standard reference method) 88% (swabs) and 92% (biopsies) respectively, histopathology 96%. These results are consistent with data reported by other research groups. The clinical diagnosis could be confirmed on the basis of at least two positive laboratory tests (in all cases including a positive PCR) in 44% (swabs), 92% (biopsies) or 96% (combination of swabs and biopsies) respectively.

In order to overcome technical difficulties accompanying the implementation of diagnostic PCR procedures in tropical countries (especially for use in the field), a dry-reagent-based IS*2404* PCR formulation for the detection of *M. ulcerans* has been developed at BNITM. A comparison with the standard IS2404 PCR as a reference method (serial dilutions of quantified plasmid suspensions) showed an equal sensitivity of both methods. The diagnostic sensitivity of both methods was compared by parallel testing of swab and tissue specimens of 19 clinically diagnosed Buruli ulcer patients (ulcerative lesions) from Ghana. Accordance (78.9%) and discordance rates (21.1%) between field PCR and standard reference method for swabs and tissue samples are shown in Table 1. Of 13/19 patients, (68.4%) had identical results for both methods and both specimens. In 15/19 cases (79%), both swab and tissue specimens showed identical results in the field PCR. These preliminary data suggest a high diagnostic sensitivity of PCR analysis of swab samples. Further studies will show if the PCR analysis of one swab specimen per ulcer (instead of swab and/or tissue

sample) is sufficient for diagnostic purposes. Among the discordant cases, 1/19 (5.2%) tested positive in the standard method only.

Table 1. **Percentage accordance and discordance rates between field PCR and standard reference method for swabs and tissue samples**

Specimen	Field PCR	Standard method	%	**% accordance**	Field PCR	Standard method	%	**% discordance**
Swab	+	+	36.8 (7/19)		+	–	0.0	
	–	–	42.1 (8/19)		– [a]	+	21.1 (4/19)	
				78.9 (15/19)				**21.1** (4/19)
Tissue	+	+	26.3 (5/19)		+	–	15.8 (3/19)	
	-	–	52.6 (10/19)		–	+	5.2 (1/19)	
				78.9 (15/19)				**21.1** (4/19)

[a] The extraction procedure for swabs has since been changed, yielding a higher diagnostic sensitivity.

The field PCR system has now been installed at KCCR laboratory. Testing of diagnostic samples from Agogo Presbyterian Hospital, Dunkwa Government Hospital and Goaso District (provided by HART) by AFB smear microscopy, culture, PCR and histopathology is under way.

(The first batch of PCR results are pending and will be submitted at the end of February.)

For purposes of quality assurance, each PCR run includes positive and negative controls, as well as extraction and inhibition controls for each sample. Furthermore, each sample is also subjected to the standard reference method at BNITM. Based on initial experiences, the interpretation as well as the reporting of PCR results follows standardized criteria. PCR specimens are considered positive if two independent results (obtained by field and/or standard method at KCCR and BNITM) are available. In case of isolated positive results or contradicting results from both laboratories, confirmation of the PCR result by another diagnostic method is required before the result is reported.

As a next step, it is planned to establish the diagnostic field PCR at KCCR laboratory facilities in Agogo and Dunkwa in order to carry out on-the-spot diagnosis of *M. ulcerans* disease.

IN THE ABSENCE OF AFB (*MYCOBACTERIUM ULCERANS*), IMMUNOREACTIVITY OF PHENOLIC GLYCOLIPID-1(PGL-1)-LIKE MATERIAL IN TYPICAL BURULI ULCER HISTOPATHOLOGICAL SPECIMENS

Keiji Suzuki,[1] Mikihisa Yajima,[1] Samuel Etuaful,[2] Milanga Mwanatambwe,[3] Kingsley Asiedu,[4] Nobutaka Yamada,[5] Norihisa Ishii,[3] Goro Asano[5]

[1] National Tamazensyouen Sanatorium, Tokyo, Japan
[2] St Martin's Catholic Hospital, Agroyesum, Ashanti region, Ghana
[3] National Institute of Infectious Diseases, Leprosy Research Center, Tama, Japan
[4] Global Buruli Ulcer Initiative, WHO, Geneva, Switzerland
[5] Nippon Medical School, Tokyo, Japan

Among the mycobacterial wall's carbohydrate-based antigens, phenolic glicolipids are now considered essential parts of mycobacterial clinical and research work (*1*). Studies on their efficient use in the field of immunosurveillance and the early diagnosis of leprosy have been of particular interest for the past two decades (*2*), not only because mycobacterial researchers consider these compounds among the first line of contact between mycobacteria and their host immune responses, but also because of their commercial availability.

For the past three years, the histopathological laboratory of the National Tamazensyouen Sanatorium in Tokyo, Japan, has been reporting observations on the presence of the immunoreactivity of phenolic glicolipid-1 (PGL-1) in tissue infected with *M. ulcerans*, the causal agent of Buruli ulcer (*3*). Until proven otherwise, well defined domains of this antigen are described as specific of *M. leprae*. Among the limitations to understanding the significance of the presence of this product in different clinical forms of histopathological lesions of Buruli ulcer is the lack of adequate serum specimen from the same patients. Now, highly defined monoclonal antibodies, raised against similar synthetic antigens as described in our previous work (*3*), have allowed the immunoreactivity of PGL-1 to be observed for the first time in the tissue specimen of one clinical case of Buruli ulcer in the absence of AFB. This case of Buruli ulcer, from the Agroyesum St Martin's Catholic Hospital in Ghana, presented all the major criteria of the histopathological diagnosis defining the disease. However, AFB stains failed to demonstrate the presence of *M. ulcerans*. This observation is quite common in the post-treatment monitoring of some cases of leprosy. As far as Buruli ulcer is concerned, this is the first such observation. From an immuno-histochemical point of view, this finding suggests that the PGL-1-like product being observed in tissue specimen of lesions infected with *M. ulcerans* can be found in the tissues after the disappearance of mycobacteria. Clinically, this may serve to prove a past infection with *M. ulcerans*. This observation greatly enhances the need to further investigate several other aspects of the presence of this antigen in Buruli ulcer lesions.

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EXPLORING RESEARCH AND DEVELOPMENT NEEDS AND OPPORTUNITIES FOR NEW DRUGS TO TREAT BURULI ULCER

Els Torreele,[1,2] *Laurence Ahoua,*[3] *Piero Olliaro*[1,4]

[1] DNDi portfolio building team
[2] Médecins Sans Frontières (MSF), Access to Essential Medicines Campaign
[3] Epicentre, Paris, France
[4] UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR), Geneva, Switzerland

The Drugs for Neglected Diseases Initiative (DNDi) is the brainchild of Médecins Sans Frontières (MSF) and the Drugs for Neglected Diseases Working Group, an independent body of international health experts. DNDi will be a not-for-profit research and development organization, which will create and manage global research and development (R&D) networks with the goal of producing new, effective, affordable and field-relevant drugs for patients suffering from neglected diseases that are currently being sidelined by the R&D-based pharmaceutical industry. A more detailed description of DNDi can be found in "DNDi: an innovative solution", available from www.accessmed-msf.org.

With the view to launching DNDi, we have started to identify suitable R&D opportunities, with results in the short, medium or long term, towards new drugs for neglected diseases such as Chagas disease, leishmaniasis and trypanosomiasis (sleeping sickness). Although the initial focus is on those three diseases, we are also open to consider other opportunities for other neglected diseases, for example **Buruli ulcer**. Two categories of projects are being explored:

Short- and medium-term projects are meant to fill an immediate drug development or registration need, with good chances of bringing a new therapeutic answer to patients within a few years. These can include an extension of indication for an existing drug in the field of the most neglected diseases, the extension of registration to additional geographical areas, new formulations of existing drugs for specific patient populations or indications (paediatric, long-acting, new route of administration) and/or that are better adapted to the conditions of use, fixed-dose combinations of existing drugs, etc. Depending on the amount of additional R&D work required, these projects will deliver new treatments in the short term (estimated at 3–4 years) and in the medium term (an estimated 5–6 years).

Long-term projects will start from newly identified lead compounds in basic research, from where promising candidates will be taken through the usual steps in drug innovation, including target identification, lead development, lead optimization, etc., before entering into the pre-development and development phase. This whole R&D process may take up to 10 years.

Considering the well-known and urgent need for new treatment options for **Buruli ulcer**, we are especially interested in exploring various opportunities **making use of existing drugs and compounds** (short/medium-term projects). One promising example may be the use of Dermacerium®, a cheap antiseptic and wound-healing cream currently used to treat burns and various types of ulcers. Although aspecific, it may be valuable for delaying or minimizing the extent of surgery and/or in the post-surgery healing process. Other options to explore could be a topical application of paromomycin (an aminoglycoside), new combinations of existing antibiotics, etc.

The DNDi portfolio building team is currently open to considering all exciting new and old ideas in this area, with the view of supporting the validation of one or several most promising R&D projects (following a competitive selection procedure by the Scientific Advisory Committee of the DNDi).

IN VITRO ANTIMICROBIAL ACTIVITY OF ACIDIFIED NITRITE ON *MYCOBACTERIUM ULCERANS*

R. Phillips,[1,2,3] *S. Kuijper,*[3] *N. Benjamin,*[4] *M. Wansbrough-Jones,*[2] *M. Wilks,*[5] *A.H.J. Kolk*[3]

[1] Komfo Anokye Teaching Hospital and School of Medical Sciences, Kumasi, Ghana
[2] St George's Hospital Medical School, London, England
[3] KIT Biomedical Research, Royal Tropical Institute, Amsterdam, Netherlands
[4] Department of Clinical Pharmacology, William Harvey Research Institute, London, England
[5] Department of Medical Microbiology, St Bartholomews Hospital, London, England

Background

Acidification of nitrite produces nitrous acid that rapidly decomposes to form oxides of nitrogen, one of which is nitric oxide. Nitric oxide, a lipophilic molecule, diffuses across membranes and inhibits respiratory chain enzymes through inactivation of iron–sulfur complexes (*1*) and it disrupts DNA replication by inhibiting ribonucleotide reductase (*2*). Nitrogen oxides have broad antimicrobial activity in vitro and mouse experiments suggest that they are active against *M. tuberculosis* (*3*). Application of topical nitrogen–oxide-generating creams has been shown to promote healing of ulcers caused by *M. ulcerans* (*4*). The aim of the present experiments was to investigate the ability of nitrogen oxides to kill *M. ulcerans* in vitro.

Methods

An African isolate of *M. ulcerans* in early log phase was exposed to sodium nitrite and citric acid monohydrate or acid alone for 10 min, 20 min, 1 h and 9 h in concentrations based on those used in a recent clinical trial in which 6% w/w nitrite and 9% w/w citric acid monohydrate were applied to lesions daily. Two fold higher and lower concentrations were also tested. After exposure, 10-fold serial dilutions of the bacteria were made and 0.1 ml of each was plated on Middlebrook 7H11 with oleic acid, albumin, dextrose and catalase supplements and incubated at 30 °C for 42 days, after which colonies were enumerated. *M. ulcerans* was also exposed to the test solutions in the presence of a high protein concentration to mimic an exudate.

Results

Exposure of an early log phase *M. ulcerans* culture to acidified nitrite for 1 h reduced the viable count by more than 6 $\log_{10}$ units, while exposure to acid alone reduced it by 0.6 $\log_{10}$. Similar results were found with a 35-day culture of *M. ulcerans* but here the effects of acid alone were more marked, causing a reduction of about 1.4 $\log_{10}$ units. The pH of the acid-alone mixture was lower than that of the test solution, so the experiments were repeated using an acid-alone control in which the pH matched that of the equivalent test solution. The times of exposure were also reduced as killing was complete by 1 h. Killing was again rapid, and viable counts were reduced below detectable limits after a 10-min exposure to acidified nitrite. Using the pH-matched acid controls, there was little reduction in viable count, suggesting that the killing was solely due to the action of acidified nitrite. Increasing the protein content of the medium during exposure did not influence killing by acidified nitrite.

Conclusions

We have shown that acidified nitrite, in concentrations which can be used clinically, reduced the viable counts of a clinical isolate of *M. ulcerans* by more than 6 $\log_{10}$ units within 10 minutes. This forms a strong basis for further clinical trials.

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TREATMENT OF *MYCOBACTERIUM ULCERANS* DISEASE (BURULI ULCER) WITH TOPICAL NITROGEN OXIDES – RAMDOMIZED DOUBLE-BLINDED TRIAL

R. Phillips,[1 & 2] O. Adjei,[1] S. Lucas,[3], N. Benjamin,[4] M. Wansbrough-Jones[2]

[1]Komfo Anokye Teaching Hospital & School of Medical Sciences, Kumasi, Ghana
[2]St George's Hospital Medical School, London, England
[3]Department of Histopathology, St Thomas's Hospital, London, England
[4]Department of Clinical Pharmacology, William Harvey Research Institute, Charterhouse Square, London, England

Background

An open-label pilot study on 12 patients with Buruli ulcer from the Atwima district of the Ashanti region in Ghana suggested that topical treatment of *M. ulcerans* disease with creams that generate nitrogen oxides when mixed in situ can heal most established Buruli ulcers of less than 15 cm diameter after administration on 6 days per week for 7 to 9 weeks. This study is a randomized, double-blind, controlled trial of nitrogen oxide-releasing acidified nitrite creams to assess the efficacy and safety of this form of treatment for Buruli ulcer.

Methods

A total of 37 patients with a clinical diagnosis of *M. ulcerans* disease were randomly assigned to receive in the first 6 weeks a topical combination of sodium nitrite (6% w/w) and citric acid monohydrate (9% w/w) or placebo, followed by a second 6-week period when they all received the combination of sodium nitrite (6% w/w) and citric acid monohydrate (9% w/w). Treatment was continued for a further 4 weeks for patients whose ulcers were not healed after 12 weeks. Ulcer surface area was monitored by weekly tracings made by assessors blinded to the treatment.

Results

In the first 6 weeks patients on sodium nitrite and citric acid monohydrate (group I, active treatment) showed a rapid decrease in ulcer size from 28.6±5.6 cm^2 to 12.6±3.2 cm^2 which was significantly greater than that in group II (15.3±3.1 cm^2 to 11.7±3.7 cm^2 ; $P = 0.03$). Five ulcers in the placebo group enlarged during this period compared with one in the active group. In the second 6 weeks (both groups on active treatment) the rate of healing was similar for both groups and there was a significant reduction in ulcer size in group II (previously on placebo). Yellowish pigmentation of the skin which disappeared 3 days after stopping treatment was the only side effect.

Conclusion

Creams releasing nitrogen oxides increase the healing rate of ulcers caused by *M. ulcerans* infection with minimal adverse events.

Support from Strakan Pharmaceutical Ltd is gratefully acknowledged.

MEDICAL TREATMENT OF BURULI ULCER IN CÔTE D'IVOIRE

Professor JM Kanga, Doctor DE Kacou, Doctor M Dion-Laine et al.

Introduction

Surgery is at present the treatment of choice for control of Buruli ulcer. However, it is not free from risk of relapse. One form of medical treatment, tried out in Côte d'Ivoire since 1998, combines use of a heparin product with antimycobacterial agents. The first cases given the treatment responded well. This led to a comparative clinical trial being initiated in 2001, to verify these first positive results.

Treatment hypothesis

The research hypothesis stemmed from the physiopathology of the disease, which is based on the toxin secreted by *M. ulcerans* as it proliferates and spreads. The toxin causes endarteritis, followed by thromboses of cutaneous blood vessels. Major ischaemic phenomena then set in and subsequently spark off an oedema, followed by tissue necrosis and ulceration. The ischaemia probably prevents antibacterials from reaching the site of the infection. That could explain their relative ineffectiveness in earlier trials, despite the sensitivity of *M. ulcerans* in vitro.

The treatment adopted was the simultaneous use of a heparinated agent to deal with the ischaemic phenomena, as with emergency treatment of poisonings from viper bites, and two antibacterials active against *M. ulcerans* in vitro.

Objective

The trial is designed to evaluate the effect of multidrug therapy on the evolution of Buruli ulcer in its ulcerative forms,

Materials

The study concerned 50 Buruli ulcer cases at the ulcerative stage, recruited using the following criteria:

- ulceration with an oedematous surround, showing the evolutive nature of the lesion,
- informed consent given in writing,
- laboratory confirmation of Buruli ulcer (PCR or anatomic pathology),
- no contraindication (clinical or biological) for the products used.

All the subjects were hospitalized and followed up in the dermatology department of Treichville Teaching Hospital, Abidjan. The antibacterials used were rifampicin and amikacin. The heparin product was enoxaparine, which is a heparin of low molecular weight. Dressings were made by Dakin Cooper®.

Methods

The subjects included in the trial were divided randomly into two equal groups of 25 patients. The subjects in Group A were treated with local dressings, while those in Group B underwent multidrug therapy according to the following protocol:

- rifampicin: 600 mg a day, i.e. 2 capsules taken simultaneously
- amikacin: 1 a day by intramuscular injection
- enoxaparin: 40 mg twice daily via subcutaneous injection

The duration of treatment and observation was 90 days for both groups. Once a week, potential side-effects of the products used were clinically and biologically monitored. The effects of the multidrug therapy were assessed on the basis of the evolution of the lesion: evolution of the perilesional oedema and of the ulceration itself.

Results

A complete cure rate of 48% was noted in Group B while no scarring occurred in Group A. Generally speaking, in 80% of Group B cases, evolution was favourable with no need for surgical intervention, whereas all the patients in Group A required surgery.

Conclusion

The medical treatment of Buruli ulcer is possible, by utilizing rifampicin and amikacin, two antibacterials active in vitro against *M. ulcerans*, in association with a heparin product, enoxaparin.

The combination of such multidrug therapy with surgery or even case detection and treatment in its early forms (papules, nodules, ulcerations of 2 cm in diameter at most) could constitute the integrated treatment therapy for Buruli ulcer.

Outlook

A project for “the implementation of medical treatment for Buruli ulcer” covering 150 patients at 3 treatment centres has been under way since the third quarter of 2002. The results should make it possible to fine-tune treatment indications.

Acknowledgements

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BACTERICIDAL ACTIVITY OF RIFAMPICIN AND STREPTOMYCIN TREATMENT FOR EARLY HUMAN *M. ULCERANS* LESIONS

S. Etuaful,[1] B. Carbonnelle,[2] J. Grosset,[3] S. Lucas,[4] C. Horsefield,[4] R. Phillips,[5] M. Evans,[5] D. Ofori-Adjei,[6] E. Klustse,[7] J. Owusu-Boateng,[8] G.K. Amedofu,[9] P. Awuah,[9] E. Ampadu,[10] G. Amofah,[10] K. Asiedu,[11] M. Wansbrough-Jones[5]

[1] St. Martin's Catholic Hospital, Agroyesum, Ghana
[2] Laboratoire de Bactériologie, CHU Angers, France
[3] Center for Tuberculosis Research, Johns Hopkins University School of Medicine, Baltimore, MD, USA
[4] St. Thomas's Hospital Campus, UMDS, London, England
[5] St George's Hospital Medical School, London, England
[6] Noguchi Memorial Institute for Medical Research, Accra, Ghana
[7] Dunkwa Government Hospital, Dunkwa-on-Offin, Ghana
[8] Public Health Reference Laboratory, Kumasi, Ghana
[9] Department of Ear, Nose and Throat, Speech and Hearing Assessment Center, Komfo Anokye Teaching Hospital, Kumasi, Ghana
[10] Ministry of Health, Public Health Division, Accra, Ghana
[11] World Health Organization, Geneva, Switzerland

Rationale

M. ulcerans is susceptible to several antibiotics in vitro, but the combination of rifampicin with streptomycin demonstrated potent bactericidal activity in the mouse footpad model.

Aim

The aim of the WHO sponsored study was to assess in humans with early *M. ulcerans* disease the bactericidal activity of daily rifampicin and streptomycin treatment for 2, 4, 8 and 12 weeks before surgical excision of lesions.

Patients and methods

The WHO Ethical Committee and the Ministry of Health, Ghana, approved the study. Informed consent was obtained from every participating patient or parent/guardian for those aged under 18 years. The study site was the St Martin's Catholic Hospital, Agroyesum in Ghana. The Noguchi Memorial Institute for Medical Research, Accra, University Hospital, Anger, France, and St. George's Hospital Medical School, London, England provided laboratory support.

Some 28 clinically diagnosed patients were recruited and randomized to 4 groups to receive rifampicin 10 mg/kg orally and streptomycin 15 mg/kg intramuscularly daily for 0, 4, 8 or 12 weeks followed by excision of the lesion. Excised tissue was analysed by AFB count, culture PCR for *M. ulcerans* and histology. During therapy, lesions were observed, traced onto acetate sheets and photographed weekly. Tracings were measured and a crude surface area was calculated by approximation to a circle. Side-effects of treatment were monitored by weekly laboratory assessment at the Public Health Reference Laboratory, Kumasi, and two-weekly hearing tests at the Hearing and Speech Assessment Center, Komfo Anokye Teaching Hospital, Kumasi. Patients were

followed up for 6 months after discharge from hospital. After preliminary analysis of results in October 2002, 5 further patients were recruited into a 2-week treatment group.

Results

Of the 33 patients recruited whose biopsy specimen was PCR positive for *M. ulcerans*, 21 are included in the analysis. Two patients withdrew from the study and one patient's lesion disappeared after 4 weeks of treatment. Of the 10 patients who were AFB, culture and PCR negative, histopathology showed lipoma (1), phycomycosis (1) and nonspecific chronic inflammation in 8. Positive cultures were obtained from all lesions excised from patients who did not receive antibiotic therapy (Group 1) whereas all lesions from patients who received antibiotics for 4 weeks or more were culture negative. Positive cultures were obtained from at least two of the five lesions excised after 2 weeks (final results pending). Preliminary analysis suggests the size of most lesions reduced during antibiotic therapy. The mean reduction in surface area after 4, 8 and 12 weeks was 52%, 21% and 42%. Histology of the untreated lesions showed classical changes of *M. ulcerans* disease, whereas those excised after antibiotics for 12 weeks showed nonspecific inflammation. No side-effects were observed and none of the lesions deteriorated during antibiotic therapy. One case of recurrence has been documented, a patient in Group 1 who did not receive antibiotic treatment.

Conclusion

M. ulcerans was not detectable by culture in early lesions after treatment with rifampicin and streptomycin for 4–12 weeks and there was evidence of clinical improvement during this time. Treatment for 2 weeks appears insufficient to achieve culture conversion but further work is needed to determine if clinical cure of early lesions is possible using this combination of antibiotics for 4 or more weeks and what role antibiotics may play in combination with surgery.

Acknowledgements

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MANAGEMENT OF BURULI ULCER CASES WITH TOPICAL APPLICATION OF PHENYTOIN POWDER

E.Y. Klutse,[1] *O. Adjei,*[2] *E. Ampadu,*[3] *L. Arthur*[4]

[1] Dunkwa Government Hospital, Dunkwa – Offin, Ghana.
[2] Kwame Nkrumah University of Science and Technology Kumasi Centre for Collaborative Research in Tropical Medicine, Kumasi, Ghana
[3] National Buruli Ulcer Control Programme, Accra, Ghana
[4] Health Foundation of Ghana, Accra, Ghana

Correspondence: Dr Erasmus Yao Klutse, Dunkwa Government Hospital, P.O. Box 49, Dunkwa – Offin, Ghana; E-mail eyklutse@yahoo.com.

Introduction

Buruli ulcers, which are caused by *Mycobacterium ulcerans,* are an increasing problem in tropical countries today. They present a difficult clinical and public health problem because they result in major morbidity that can be accompanied by disfigurement and disability. At present, surgical excision, applied early when the disease is nodular in form, is the only effective treatment. Unfortunately, this method, quite apart from its expense, requires the presence of, and action by, a qualified physician or surgeon. Since individuals with Buruli ulcers often live in rural areas without easy or regular access to a physician, the problem presented by these lesions is all the more difficult, especially since advanced ulcers are much more expensive and hard to treat than the early nodules. It is therefore necessary to find better, less expensive or more readily available methods for the treatment of these devastating lesions.

Experience with topical phenytoin powder has shown that it is effective against various types of ulcers. A recent pilot investigation of the use of phenytoin in the treatment of Buruli ulcers involving 10 patients showed remarkable promise in promoting their healing (Adjei et al., 1998). Based on these pilot findings, we undertook a further, more formal trial to determine the true efficacy of phenytoin powder in the treatment of Buruli ulcers.

Method

Ethical approval was obtained from the Local Research Ethics Committee at Dunkwa government Hospital and from the National Ethics Committee at the Ministry of Health, Accra, Ghana. Permission was also sought from the Food and Drug Board, the Regional Health Directorate and the District Assembly.

Informed written consent was obtained from adults or parent/guardians of patients aged below18 years before enrolment. Services offered to the patients free of charge included hospitalization, feeding, surgery, drugs, documentation and dressing materials.

A total of 58 patients with a clinical diagnosis of *M. ulcerans* disease were randomly assigned to two groups, Group A and Group B, with 29 in each group. Table 1 shows the age range and sex distribution.

Table 1. **Age range and sex distribution**

Sex		Age range	
Male	Female	0–30 years	Above 30 years
34	24	47	11

Group A (trial group) received a daily application of phenytoin powder for 8 weeks.
Group B (control group) received normal saline solution for daily dressing for 8 weeks.

Before the study began, baseline pictures of the ulcers were taken and the ulcer dimensions and areas were measured and recorded. Swabs were taken for Ziehl-Neelsen staining for AFB and culture. Biopsies were taken for histopathology and PCR to confirm that the ulcers were indeed due to *M. ulcerans.*

For Group A, each day before the application of phenytoin powder, the ulcers were cleansed with normal saline and phenytoin powder was then sparingly or thinly applied (i.e. approximately 7.8 mg/cm^2 of phenytoin powder). For the control (Group B), only normal saline was used to clean the ulcers. In both groups, the ulcers were bandaged and treated daily within the study period. The ulcer surface area was monitored weekly by taking pictures and by measuring the size of the ulcers.

Results

Of the 58 patients, 7 dropped out of the study. The reasons for the drop-outs are listed below:
- 2 abandoned treatment (control group)
- 1 died (control group) (cause of death not related to Buruli ulcer)
- 1 had difficulty in taking measurements because the ulcer was on the hand and fingers (trial group)
- 2 had inconsistent data (trial group)
- 1 had a confirmed squamous cell carcinoma (from trial group)

A total of 51 patients completed the 8 weeks of treatment. Of these, 25 received phenytoin powder (trial group) and 26 received normal saline (control group).

Table 2a. **Number of ulcers healed and percentage reduction in ulcer size within 8 weeks of treatment (trial group)**

Total	Healed	< 50% reduction	> 50% reduction
25	10 (40%)	7 (28%)	8 (32%)

Table 2b. **Number of ulcers healed and percentage reduction in ulcer size within 8 weeks of treatment (control group)**

Total	Healed	< 50% reduction	> 50% reduction
26	2 (8%)	17 (65%)	7 (27%)

Table 3a. **Age of ulcer and percentage reduction in ulcer size (trial group; *n* = 25)**

	Age of ulcer	
% reduction in ulcer size	**0–52 weeks**	**52 weeks and above**
Below 0	0	1
0–50%	2	3
51–100%	18	1

Table 3b. **Age of ulcer and percentage reduction in ulcer size (control group; *n* = 26)**

	Age of ulcer	
% reduction in ulcer size	**0–52 weeks**	**52 weeks and above**
Below 0	1	3
0–50%	7	6
51–100%	6	3

Table4a. **Age of patient and percentage reduction in ulcer size (trial group; *n* = 25)**

	Age of patient	
% reduction in ulcer size	**0–30 years**	**30 years and above**
Below 0	0	33%
0–50%	23%	0
51–100%	77%	67%
	n = 22	n = 3

Table 4b. **Age of patient and percentage reduction in ulcer size (control group; *n* = 26)**

	Age of patient	
% reduction in ulcer size	**0–30 years**	**30 years and above**
Below 0	24%	0
0–50%	24%	100%
51–100%	52%	0
	n = 17	*n* = 9

Table 5a. **Ulcer size and percentage reduction in ulcer size (trial group; *n* = 25)**

	Ulcer size (cm)	
% reduction in ulcer size	**0–30 cm**	**30.1 cm and above**
Below 0	1	0
0–50%	0	6
51–100%	17	1

Table 5b. **Ulcer size and percentage reduction in ulcer size (control group; *n* = 26)**

	Ulcer size (cm)	
% reduction in ulcer size	**0–30 cm**	**30.1 cm and above**
Below 0	2	2
0–50%	9	4
51–100%	7	2

From the results, it is interesting to note that 10 (40%) of a total of 25 on trial were completely healed within 8 weeks of treatment, 8 (32%) had > 50% reduction in ulcer size and 7 (28%) had < 50% reduction in ulcer size (Table 2a).

In the control group, only 2 (8%) of 26 were completely healed within 8 weeks of treatment; 7 (27%) had > 50% reduction in ulcer size and as many as 17 (65%) had < 50% reduction in ulcer size within the period (Table 2b).

In analysing the relationship between the age of the ulcer and the percentage reduction in ulcer size, 18 (72%) of a total of 25 on trial that had > 50% reduction in ulcer size had ulcers less than one year old; 2 (8%) that had < 50% reduction in ulcer size were also less than one year. None of the ulcers less than one year had negative reduction in ulcer size (Table 3a).

While in the control group of 26, only 6 (23%) that had > 50 % reduction in ulcer size were less than one year old, 7 (26.9%) had < 50% reduction in ulcer size that were less than one year old (Table 3b).

Table 3 shows the age of the patients and the percentage reduction in ulcer size.

In the trial group 77% of the ulcers that had > 50% reduction in ulcer size were patients aged below 30 years compared with 52% in the control group. This shows that the phenytoin powder gives better results in patients aged below 30 years (Tables 4a and 4b).

Table 4 shows the relationship between ulcer size and the percentage reduction in ulcer size.

In the trial group of 25 ulcers, 17 (68%) that had > 50% reduction in ulcer size had an average ulcer circumference of less than 30 cm compared with 7 (27%) in the control group. This shows that the phenytoin powder helps in the healing of the Buruli ulcers and that best results are obtained for ulcers with ulcer size less than 30 cm in average circumference (Tables 5a and 5b).

Discussion

The results to date indicate that topically applied phenytoin powder is effective in the treatment of Buruli ulcers. Our data confirm those obtained in an earlier pilot study. Specific points regarding our observations on topical phenytoin in Buruli ulcers include:

- The rate of healing is significantly faster with phenytoin powder than with controls. Phenytoin helps to prepare for surgical intervention and grafting to achieve even quicker healing.
- Phenytoin is easy and cheap to apply and so is appropriate for use in rural communities.
- The phenytoin has been found to be more effective on ulcers that are less than one year old (Tables 3a and 3b).
- Patients aged below 30 years with ulcers respond better to phenytoin powder than those aged above 30 years. See Tables 4a and 4b .
- No side-effects were detected. Patients tolerated the use of phenytoin well. In addition, they experienced significant pain relief compared with the controls.
- Scar formation was better with phenytoin than with the controls.
- Best results are obtained with phenytoin in ulcers with an average circumference of less than 30 cm.

Specific recommendations

- Ulcers respond best to treatment using phenytoin when slough has been debrided.
- Ulcers should not be disturbed during the dressing process. Bleeding during dressing should be minimized i.e. the dressing has to be soaked very well with normal saline before removal.
- Phenytoin powder is most effective on ulcers less than one year old.
- For optimum benefit, it is recommended that the phenytoin be used for patients aged below 30 years.
- To prevent the formation of crusts and poor healing, the ulcer must be cleaned thoroughly before fresh phenytoin is applied.
- Phenytoin powder works best on ulcers less than 30 cm in average circumference.

Fig. 1a. **Percentage reduction in ulcer size after 8 weeks of treatment with phenytoin powder**

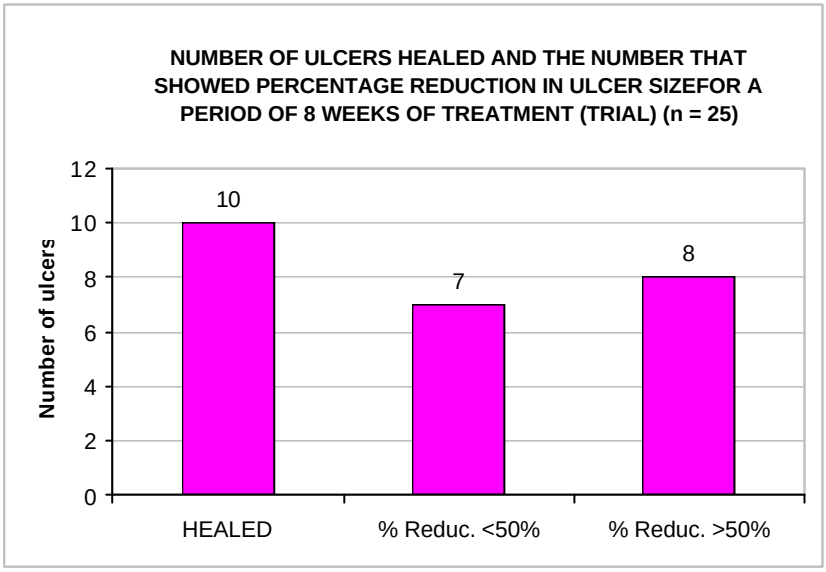


Fig. 1b. **Percentage reduction in ulcer size after 8 weeks of treatment with normal saline (control group)**

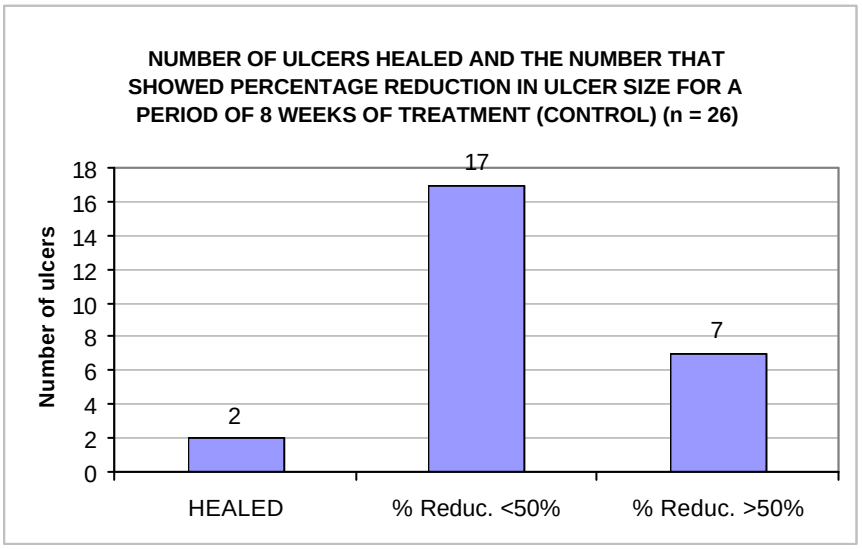


Fig. 2a. **Age of ulcer and percentage reduction in ulcer size with phenytoin powder (trial group)**

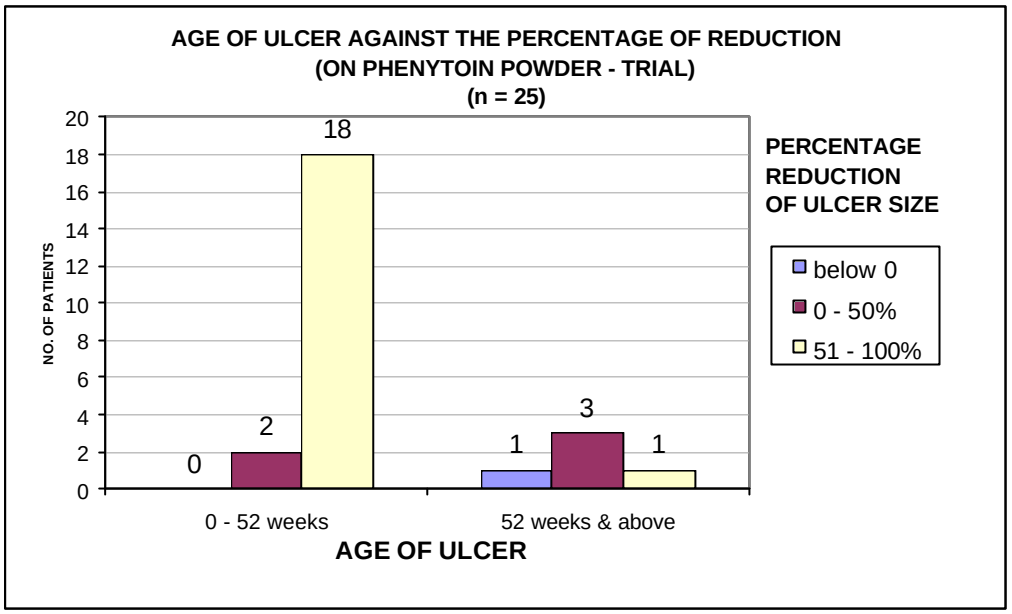


Fig. 2b. **Age of ulcer and percentage reduction in ulcer size with normal saline (control group)**

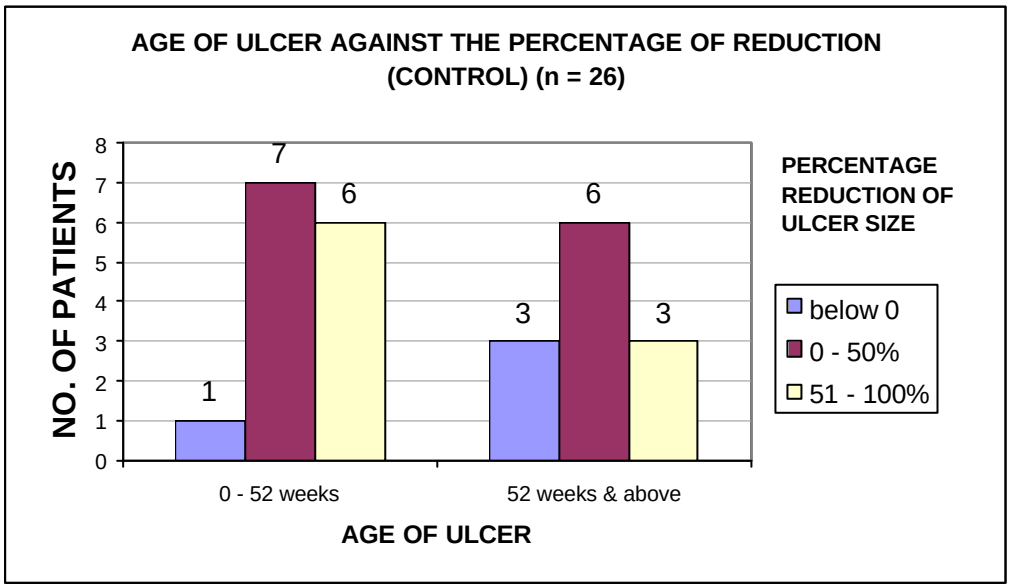


Fig. 3a. **Age of patient and percentage reduction in ulcer size (trial group)**

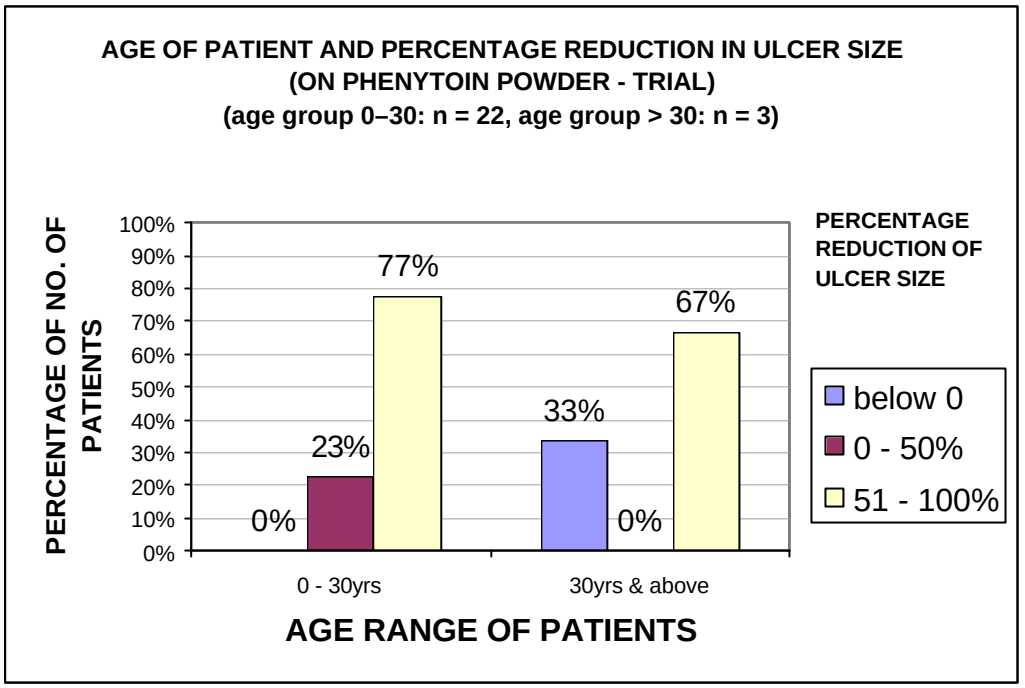


Fig. 3b. **Age of patient and percentage reduction in ulcer size (control group)**

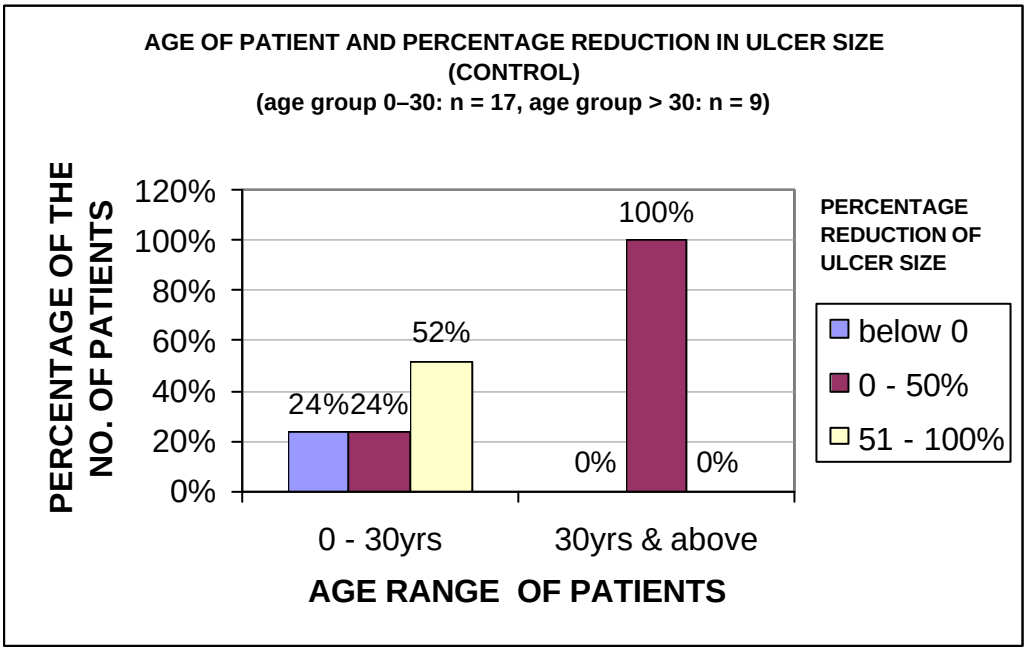


Fig. 4a. **Ulcer size before treatment and percentage reduction in ulcer size (trial group)**

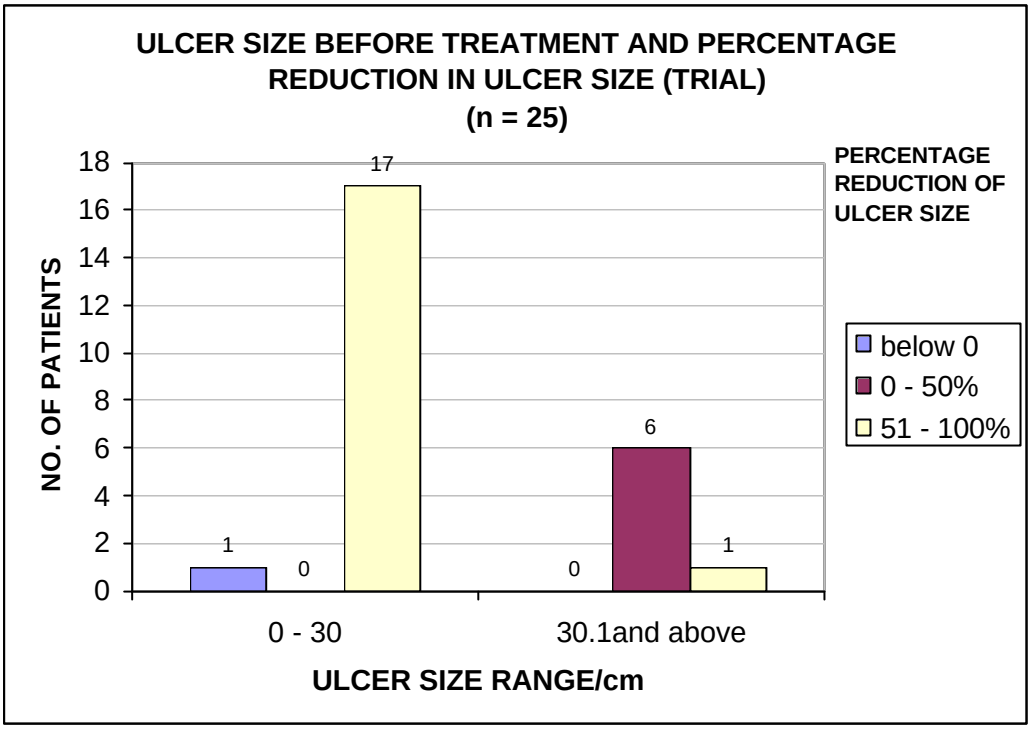
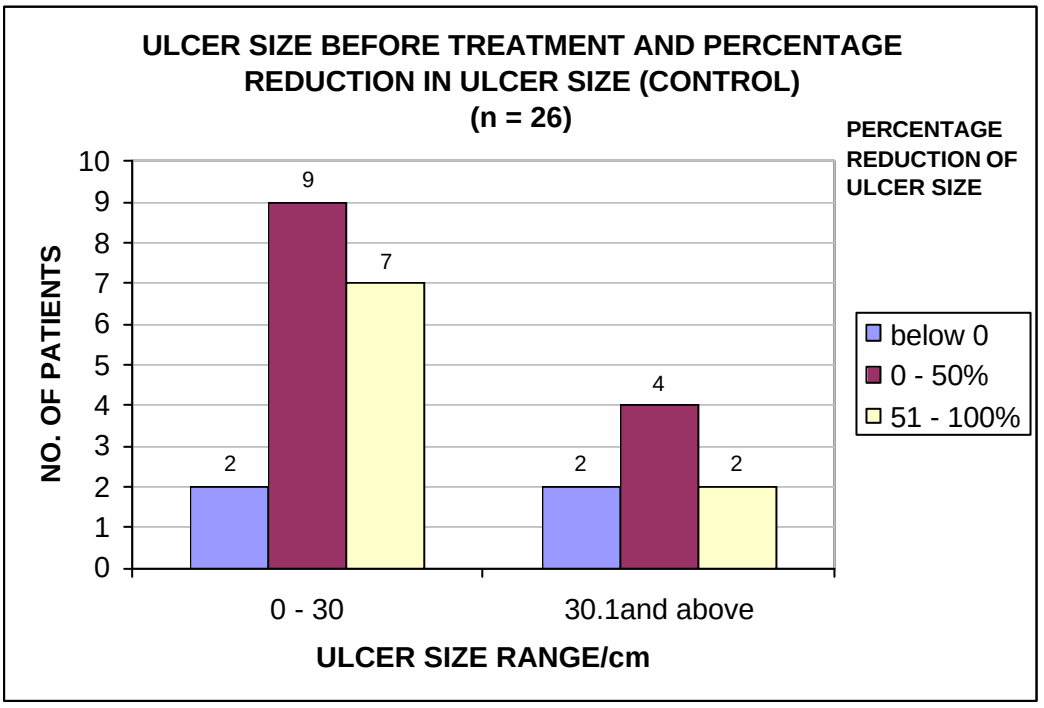


Fig. 4b. **Ulcer size before treatment and percentage reduction in ulcer size (control group)**



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DIFFERENTIAL PRODUCTION OF SYSTEMIC AND INTRALESIONAL IFN-g AND IL-10 IN NODULAR AND ULCERATIVE FORMS OF BURULI ULCER DISEASE

Ghislaine Prévot,[1] Eliane Bourreau,[1] Hervé Pascalis,[1] Roger Pradinaud,[2] Audrey Tanghe,[3] Kris Huygen[3] and Pascal Launois

[1] Institut Pasteur de la Guyane Française et Université des Antilles et de la Guyane – IESG, French Guiana
[2] Centre Hospitalier A. Rosemon, Cayenne, French Guiana
[3] Pasteur Institute of Brussels, Belgium

In this study, we compared systemic and intralesional cytokine production in patients presenting with a nodular and a necrotizing, ulcerative form of Buruli disease. IFN-γ levels in response to whole *M. ulcerans* and *M. bovis* BCG bacilli and in response to purified Ag85 protein from BCG were lower in peripheral blood mononuclear cell (PBMC) cultures from Buruli disease patients than in PBMC from healthy PPD-positive contacts. Neither IL-4 nor IL-13 could be detected in the PBMC culture supernatants. IFN-γ production after stimulation with *M. ulcerans* was significantly lower ($P < 0.05$) in PBMC cultures from patients with ulcers than in PBMC cultures from patients with nodules. In contrast to this T-cell anergy, PBMC from Buruli disease patients produced significant levels of IL-10 in response to *M. ulcerans* (but not to *M. bovis* BCG) and production was highest in PBMC from those with the ulcerative form. Thirdly, semi-quantitative RT-PCR analysis demonstrated a similar difference in the local, intralesional cytokine profile for the two forms of the disease: high IFN-γ but low IL-10 mRNA levels in nodular lesions and high IL-10 but low IFN-γ mRNA levels in ulcerative lesions.

Our results indicate that production of IL-10, rather than of IL-4 or IL-13, is involved in the low *M. ulcerans*-specific IFN-γ response in patients suffering from Buruli disease.

UNEXPECTED FINDINGS FOLLOWING MOUSE FOOTPAD INOCULATION WITH *MYCOBACTERIUM ULCERANS* – GANGRENE, AMPUTATION AND METASTASIS

Phyllis Addo, Enid Owusu, Benjamin Adu-Addai, Alfred Dodoo, David Ofori-Adjei
Noguchi Memorial Institute for Medical Research, University of Ghana, Legon

As part of preparatory experiments to use inocula of *M. ulcerans* in experiments to identify novel laboratory animal models and to determine antimicrobial sensitivity of isolates, a series of experiments were conducted using BALB/c mice. The experiments were preceded by the production of an infective *M. ulcerans* inoculum and its subsequent quantification for consistent and reproducible experimental infection of laboratory animals. The first experiment assessed the effectiveness of the *M. ulcerans* inoculum prepared in-house, while the second evaluated the effects of various dosages of the inoculum to facilitate an informed selection of the dosage to be used in future animal experiments.

The *M. ulcerans* inoculum was prepared from subcultures of primary isolates from a patient. The isolate was confirmed by PCR. Suspensions of the *M. ulcerans* subcultures were made in PBS and quantified by comparing their turbidity to that of the McFarland nephelometric standards.

Experiment 1

The *M. ulcerans* suspensions were also serially diluted and their colony-forming units correlated with that of the corresponding McFarland standard. Eighteen BALB/c mice were grouped into three equal batches and each inoculated in the left hind footpad with 0.05 ml of *M. ulcerans* with a dose equivalent to McFarland 1(10^6), McFarland 1(10^5) and McFarland 1(10^4) respectively. The animals were observed for post-inoculation changes until they died or were euthanized periodically at the appearance of lesions. The inoculation resulted in the presentation by all three groups of mice of localized erythema, foot and thigh oedema, necrosis, fluid exudation, scab formation and ulcers. The clinical picture in one mouse inoculated with a dose equivalent to McFarland 1(10^5) progressed from ulcerative lesions to gangrene, limb amputation, healing, recrudescence, generalized ill-health and death. The marrow of the amputated stump was positive for AFB, as was the spleen and liver. All the mice euthanized at the appearance of obvious lesions were either positive for AFB in the oedematous foot and negative for AFB in the oedematous thigh or positive for AFB in the oedematous foot and adjoining oedematous thigh. On the other hand, those that died after chronic necrosis and fluid exudation were positive for AFB in both the oedematous foot and oedematous thigh. Some of these were also sparsely positive for AFB in some of the visceral organs such as the spleen and the liver. The onset of lesions varied significantly with the inoculum dose – the higher the dose, the earlier the onset of the lesions. None of the controls presented any lesion and are still alive. The results suggest that the in-house inoculum was effective and the variation in response by dose suggest that the quantification of the inoculum was successful. Furthermore, the findings suggest haematogenous spread from the inoculation site to visceral organs such as the spleen and liver.

Experiment 2

Thirty BALB/c mice were used for the second experiment. Ten bacterial suspensions equivalent to the 10 McFarland standards were used for the inoculation. Each standard was inoculated into three mice. Each mouse was inoculated in the right hind footpad instead of the left hind footpad with 0.05 ml of the inoculum. The animals were observed daily for post-inoculation changes until they died or were euthanized periodically at the appearance of lesions. The limbs of the animals were measured weekly to assess the severity of the oedema. The results showed great similarities in the clinical (localized erythema, foot/thigh oedema, necrosis, fluid exudation, scab formation, ulcers, gangrene, autolimb amputation, healing, recrudescence, generalized ill-health and death) gross pathological (congestion of organs, pus in marrow of amputated stumps) and microbiological (positive AFB in lesions) findings of the first and second experiments. However, one mouse inoculated with a dose equivalent to McFarland 8 presented metastasis on the tail and testicles, which were copiously positive for AFB. The bone marrows of all the amputees were copiously positive for AFB. The uninfected limbs were also positive for AFB in addition to some of the internal organs, namely the liver, spleen and lungs. The sizes of foot and thigh oedema were significantly positively correlated to dose of the inoculum – the higher the dose the larger the oedema. Gross pathological examination of the healthy looking experimental mice did not reveal any apparent abnormality except congestion and hypertrophy of the foot and thigh muscles. Those that died after general ill-health showed generalized congestion of the subcutaneous tissue and muscles, congestion and hypertrophy of the foot and thigh muscles and slight darkening of the internal organs. The onset of the various lesions was significantly related to the inoculum dose. Dose of the inoculum was also significantly negatively correlated with the onset of the lesions.

Controls

Six mice were used as controls and were similarly inoculated (sterile PBS; sterile PBS on Lowenstein-Jensen medium) as for those in the first experiment, but in the right hind footpad instead of the left hind footpad. The mice were observed in a similar fashion to the experimental animals.

All the mice in the control group remained healthy with normal shiny coats during the period of observation and beyond. They remained active and behaved normally in all respects. None of the controls in either experiment developed any lesion and were alive beyond the period of observation.

Conclusions

The findings suggest that BALB/c mice elicit a wide spectrum of clinical manifestations when infected with *M. ulcerans.* In view of this finding, they could become a good template for investigating both the prevention and treatment possibilities of *M. ulcerans* infections. Lastly, the findings of the experiments support the conclusion that (i) the in-house inoculum is effective; and (ii) that the McFarland nephelometric standards are also applicable to the quantification of the *M. ulcerans* inoculum.

STUDIES ON THE DISTRIBUTION OF WATER BUGS, ESPECIALLY *NAUCORIS* SPECIES (*HEMIPTERA: NAUCORIDAE*) IMPLICATED IN THE TRANSMISSION OF *MYCOBATERIUM ULCERAN*S AND ESTABLISHMENT OF THEIR MODE OF INFECTION

D. Boakye, D. de Zouza, U.N. Gadzama, N.K.O. Amanhyia, L. Mosi and M.D. Wilson,
Noguchi Memorial Institute for Medical Research, University of Ghana

Summary

Recent observations on transmission have shown that adult water bugs of the family Naucoridae are naturally infected with *Mycobacterium ulcerans*. More importantly, it has been shown that the bacteria multiply in the salivary glands of the water bugs and that experimental animals can be infected through the bites of infective insects. Notwithstanding these findings, much remains to be done before a clear picture of the transmission process can be fully explained for use in prevention and control strategies. The WHO Advisory group meeting in March 2002 recognized this and recommended a continuous search for *M. ulcerans* in water bugs (Naucoridae, Belostomidae and Nepidae) in endemic areas to assess how the bugs are involved in the transmission process.

During the present period, studies were undertaken to map the distribution of members of Naucoridae, Belostomidae and Nepidae in endemic areas, the prevalence rate of infection among the bugs and to determine which of the life stages of the water bug are infected to obtain further information and improve the understanding of transmission of *M. ulcerans.*

A collection was made with a pond net and the insects dislodged, placed in polypropylene tubes and stored frozen until used for PCR analysis. Before processing for PCR, the bugs were grouped into the various families, genera and, where possible, species. Collections have been taken from various sites in the Ga district (*Table 1*). DNA was extracted and PCR undertaken to diagnose infection with *M. ulcerans.*

A total of 15 sites in Accra East have been sampled. Initial results indicate the presence of members of the three families of bugs in most of the areas sampled. A distribution map is being prepared. PCR diagnosis has indicated one bug to be naturally infected at one of the sites (Amasaman Dam). It is too early to give any prevalence of infection since most of the samples have yet to be examined.

Future work on transmission will involve:

1. Collection of samples from non-endemic and other endemic areas
2. Culture bacteria from any bug found positive by PCR
3. Analysis of data to determine whether bugs are infected through the food chain or by active adult bites or trans-ovarially.

Collection sites in Ga District (Accra East) :
Akramanian, Ayikai Doblo, Okushiebiade, Obeyie, Amasaman, Amasaman Dam, Achiaman, Adjin Kotoku, River Doblo, Opa (Pond), Nsakyi (Accra-Kumasi crossing), Nsakyi (Pokuasi Town), Sapeman, Afiaman, Domefase

DEVELOPMENT OF A GENETIC SYSTEM FOR USE IN *MYCOBACTERIUM ULCERANS*: IDENTIFICATION OF GENES REQUIRED FOR BIOSYNTHESIS OF MYCOLACTONE

Pamela L.C. Small, Terri Alford, Armand Mve-Obiang, University of Tennessee, Knoxville

Background

Mycolactone is a polyketide-derived macrolide toxin that is responsible for much of the immunosuppression and tissue damage found in Buruli ulcer. Although the toxin was purified and characterized in 1999, the genes for mycolactone have eluded identification for two reasons: the biosynthetic pathway for mycolactone requires an estimated 100 kb of genetic material, making cloning very difficult; and there were no genetic tools available for identifying mycolactone genes by mutagenesis that had proven successful in *M. ulcerans*. In our laboratory, we have recently been successful in identifying mycolactone genes by making mycolactone-negative mutants. The development of mycolactone-negative strains was listed as a high priority for research because of the potential such strains might have in development of an effective vaccine for *M. ulcerans*. In addition, understanding the regulation of mycolactone production through identification of regulatory genes could play an important role in understanding the requirements for virulence in *M. ulcerans*.

Methods

The first method used for making insertional mutants was based on the EZ:TN Kan transposase kit produced by Epicentre. This method has proven very successful in creating transposon libraries in enteric bacteria and had been used with modest success in *M. smegmatis*. For this method, DNA carrying the transposon:kanamycin resistance gene was introduced into *M. ulcerans* by electroporation. In these studies, we optimized *M. ulcerans* electroporation by doing electroporation on bacteria at 37 °C, using a BioRad electroporator and a resistance of 800 ohms. The second method used was a bacteriophage-based method using a TM4 bacteriophage derivative, phA87::MycoMarT7, developed by Eric Rubin at Harvard University Medical School. This bacteriophage has a temperature sensitive replication phenotype, meaning that the bacteriophage will replicate at 30 °C but not at 39 °C. This system would appear to be unsuitable for *M. ulcerans*, which cannot replicate at 39 °C; however by making minor changes in the protocol and infecting at 37 °C, we were able to use the system to obtain mutants in *M. ulcerans*. For both mutational methods, mycolactone-negative mutants were selected on the basis of kanamycin resistance and lack of pigmentation. Mycolactone-negative mutants were confirmed by mass spectroscopy and cytopathic assays.

Results

Using the EZ Transposase system produced by Epicentre, we obtained eight insertional mutations. Of these, one mutant lacked pigment. DNA sequence flanking the insertional site suggested that this mutation occurred in a regulatory gene and not in a polyketide synthesis. The poor yield of mutants obtained by this method was felt to be due to difficulties in electroporating DNA into *M. ulcerans*. The use of a phage delivery system was a much more effective method for making mutants in *M. ulcerans*. As Table 1 shows, we were able to obtain a library of more than 100 000 mutants using this method.

Table 1. **Efficiency of MycoMarT7 transposition under the delivery of mycobacteriophage phA87 into *M. ulcerans* 1615**

Experiment no.	Kanamycin resistant colonies	Transduction frequency	Transposition frequency
1	5.6×10^{4}	5.6×10^{-7}	5.6×10^{-6}
2	5.5×10^{4}	5.5×10^{-7}	5.5×10^{-6}

Of the mutations obtained, 44 non-pigmented colonies were grown up and tested for cytopathicity using L929 fibroblasts. Culture filtrate from all non-pigmented strains was non-cytopathic. Mass spectroscopic analysis of lipids extracted from these 44 mutants showed that mycolactone biosynthesis had been interrupted at several different places in the biosynthetic pathway. Using nested PCR and DNA sequencing methodology, we have identified the transposon insertion site for eight insertion mutants. In five mutants, polyketide synthase genes have been interrupted. A sixth mutation occurred in a lipid-modifying gene of unknown function, and two insertions occurred in regulatory loci. Although we have not identified all of the genes interrupted by mutation, we have evidence that six mutants are totally lacking the ability to make mycolactone production completely. Previous work has shown that such strains will be avirulent and thus might be good vaccine candidates for an *M. ulcerans*-based vaccine strain. The remaining classes of mutants produce truncated mycolactones. Whereas some of these truncated mycolactone are inactive, others have cytopathic activity at very high concentrations.

It is clear that the biosynthetic pathway for mycolactone production is extremely complex. We are currently collaborating with Dr Tim Stinear and Dr Stewart Cole in the assembly and analysis of the complete mycolactone biosynthetic pathway.

GENOME SEQUENCE ANALYSIS OF *MYCOBACTERIUM ULCERANS*

Timothy Stinear,[1] *Thierry Garnier,*[1] *Roland Brosch,*[1] *Laurence Ma,*[2] *Stéphane Ferris,*[2] *Stéphanie Duthoy,*[2] *Christiane Bouchier,*[2] *Paul Johnson,*[1] *Peter Leadley1and Stewart T. Cole*[1]

[1] Unité de Génétique Moléculaire Bactérienne, Institut Pasteur, Paris, France
[2] Génopole, Institut Pasteur, Paris, France

The *Mycobacterium ulcerans* genome sequencing project began in February 2001. The first phase (library preparation and end-sequencing) was completed in December 2001. The second phase, assembly of the end sequences (or reads), commenced in December 2001.The initial assembly process is performed by computer and has allowed us to reduce approximately 43 000 reads to 1500 continuous sequences (contigs). In July 2002, this information was made available to the international research community via a web-based server called Buruli List (http://genopole.pasteur.fr/Mulc/BuruList.html).

Preliminary analysis of our results has identified a discrete cluster of genes that encode a polyketide synthase (PKS). From work performed by collaborators in Australia, we know that these genes are not present in *M. marinum* (a close relative of *M. ulcerans*) and hence are likely to encode for synthesis of mycolactone.

Mycolactone is predicted to be the product of a unique PKS cluster and the principal virulence factor for *M. ulcerans.* This discovery immediately opens new avenues for research into how these genes are controlled and could provide targets for novel pharmaceutical agents.

We have also found that the previously identified insertion sequences (IS*2404* and IS*2606*) are present in much higher copy number than expected. This has slowed the assembly process because 30% of the contigs end in identical copies of either IS*2404* or IS*2606.* Our approach to overcome this problem has been twofold. We have commenced primer-walking along IS-containing clones, positioned at the ends of contigs. This strategy is permitting contigs to be joined by identifying unique flanking sequences. Secondly, we are creating physical and contig maps of the genome using bacterial artificial chromosomes (BACs). The BAC mapping project is now well advanced, and we have ordered and mapped 4 MB of the genome. This approach will identify an ordered set of BACs, which will be used as a backbone on which to place the remaining contigs.

The current assembly predicts a genome of 6.0 MB, greater than the initial prediction of 4.6 MB. To ensure adequate coverage of the larger genome, and as an additional step to overcome problems with repetitive DNA, we will need to make and sequence an additional 40 000 reads from a whole genome shotgun library. The Genopole at the Institut Pasteur has agreed to finance the cost of this additional sequencing.

Additional expert scientists have also recently joined the team of people involved with this project. Associate Professor Paul Johnson commenced in August 2002 and constructed the BAC map of the genome. Professor Peter Leadley, a polyketide expert, began in October 2002 and is assisting with the assembly and annotation of the PKS loci described above. Associate Professor Pam Small joined the team in November and will assist with genome annotation.

DEVELOPMENT OF A QUESTIONNAIRE ASSESSING BURULI ULCER-INDUCED FUNCTIONAL LIMITATION

Ymkje Stienstra, Pieter U. Dijkstra, Augustin Guédénon, R. Christian Johnson, Edwin O. Ampadu, Thomas Mensah, Erasmus Y. Klutse, Samual Etuaful, Sunil Deepak, Winette T.A. van der Graaf, and Tjip S. van der Werf

Abstract

Buruli ulcer is emerging mainly in west Africa. A limitation scoring system is needed to assess the nature and severity of its long-term consequences. A list of daily activities was developed and adjusted. Some 47 people in Benin and 41 people in Ghana, who had finished treatment for Buruli ulcer, were questioned on their ability to perform daily activities. Based on applicability and frequency endorsement, this resulted in a scale with 19 items with good internal consistency. The median age of the participants was 14 years. Participants on average could not perform 23% of the daily activities. Only 29 participants did not have any functional limitation. The average limitation score in Benin was 31% and in Ghana 15 % ($P = 0.006$). Participants without visible contractures (n = 65) had an average limitation score of 13%; patients with visible contracture ($n = 20$), an average score of 50%; and patients with an amputation ($n = 3$), a score of 64 %. The disease and its consequence are of long-term importance, with children who stop going to school and farmers with lowered productivity as a result of Buruli ulcer. This functional limitation score should be further evaluated with larger number of patients so that validity and reliability can be established. After development, the scale can be used for individual evaluation, as an end-point in intervention trials and, hopefully, as a guide in the planning of resources needed for the care of patients with functional limitations.

PILOT STUDY TO ESTIMATE THE COSTS TO HOUSEHOLDS PER CASE OF BURULI ULCER DISEASE IN THE CENTRAL AND ASHANTI REGIONS OF GHANA

G. Mumma,[1] E.A.S. Whitney,[2] F. Dadzie,[1] Y. Stienstra,[3] A. Kwame,[4] P. Raghunathan,[2] P. Enchill,[5] J. Adomako,[5] S. Etuaful,[6] D. Agyeman,[5] E. Klutse,[7] B. Appah,[5] E. Ampadu,[5] D.A. Ashford[2]

[1] Epidemiology Program Office, Centers for Disease Control and Prevention, Atlanta, GA, USA
[2] National Center for Infectious Diseases, Centers for Disease Control (CDC), Atlanta, GA, USA
[3] Groningen University Hospital, Groningen, Netherlands
[4] National Center for Chronic Disease Prevention and Health Promotion, CDC, Atlanta, GA, USA
[5] Ministry of Health (MOH), Republic of Ghana, Accra, Ghana
[6] St. Martin's Catholic Hospital, Agroyesum, Ghana
[7] Dunkwa Government Hospital, Upper Denkyira District, Ghana

Introduction

Buruli ulcer disease leads to massive destruction of the skin, debilitating disability and attendant deformities for affected individuals (*1*), with potentially devastating health and economic implications for individuals, households and communities in rural poor settings (*2–3*). Its potentially prolonged management and disruption of productive potential poses difficult resource allocation choices, challenges and demands on its victims (*2*). Based on estimates for hospitalized cases in Ghana, the disease imposes substantial costs to society (*1–2*). Currently, there are no generalizable population-based data on estimates of economic cost to affected individuals, households and communities (*1*). Accurate estimates of the costs of the disease that are related not only to its treatment but also to its management from a societal perspective are needed. We proposed to estimate the costs associated with Buruli ulcer disease to households in the central and Ashanti regions of Ghana. In November 2002, a pilot study was conducted in the regions to refine our protocol and questionnaire before initiating a larger study.

Methods

A study protocol and questionnaire was developed to collect data to estimate the costs to individuals and households as a result of Buruli ulcer disease, processed IRB exemption at CDC and Ghana, travelled to Ghana in November 2002 to pretest the questionnaire for reliability, validity and collected proxy data to identify the correct sample size for the subsequent larger study. Data were collected from households affected by the disease in three highly endemic districts in the central and Ashanti regions of Ghana: Amansie West, Atwima and Upper Denkyira during November 2002. A household was defined as a basic social and economic unit into which people were grouped and in which at least one person met the WHO clinical case definition for Buruli ulcer disease. One interviewer was trained in each district and the survey was implemented in at least one village in each district. Data collection relied on three strata, which were based on the stage of the disease: nodular, ulcerative or scar; 12 more specific function-related disease stages formed the substrata. Data were collected on the type of treatment sought, if any, time taken from other activities, resources used, opportunities foregone in the process, attempts at compensation, patient and caregiver related productivity loss and the socioeconomic status of the household. Questions about institution-catered treatment activities were excluded. Completed household cost questionnaires were coded and data entered using Excel spreadsheet software and analysed.

Results

As expected, results from the preliminary data analysis based on limited sample size reveal that there is a large difference in costs between pre-ulcerative, ulcerative and post-ulcerative stages of the disease. The results are not statistically binding and do not include inpatient costs. The preliminary median cost to the pilot households per case of Buruli ulcer disease ranged from US$ 6.1 (SD$ 68.6) for the pre-ulcerative case, US$ 114.7 (SD$ 410) for the ulcerative case, US$ 133.8 (SD$ 552), to US$ 908.9 (SD$ 3245) for the ulcerative case who already had a scar due to the disease. A breakdown of the costs to households based on the 12 more specific function-related disease stages increased with severity.

Conclusions

Costs of Buruli ulcer disease per case to the household, combined with institution-related costs and estimates of region-specific disease prevalence, will allow us to estimate the economic burden of the Buruli ulcer disease to the individual, households, communities and Ghanaian society. Knowledge of societal costs of the disease is important for future studies that will assess the magnitude of justifiable expenses per individual or household to provide and improve programmes for preventing and controlling Buruli ulcer disease.

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ASSESSING THE DIRECT COSTS OF FACILITY-BASED TREATMENT AND OUTREACH MANAGEMENT OF BURULI ULCER IN GHANA

F.N.F. Dadzie,[1] *K. Asamoah,*[2] *G. Amofah,*[3] *E.O. Ampadu,*[3] *F. Mork,*[3] *S, Paintsil,*[3] *E. Laing,*[3] *E. Klutse,*[3] *S.K.N. Etuaful,*[3] *W. Thompson,*[3] *P. Enchill*[3]

[1] Principal Investigator, Department of Economics, Clark Atlanta University, Atlanta, GA, USA
[2] Coinvestigator, NCCIDD, Centers for Disease Control and Prevention, Atlanta, GA, USA
[3] Coinvestigators, Ghana Health Service, Ministry of Health, Accra, Ghana

Introduction

It is generally acknowledged that Buruli ulcer confers considerable economic burden on its victims (*1–3*, *5*), but the burden that it imposes on health care systems has not been adequately studied. An attempt was made to capture the magnitude of the latter burden in the seminal paper on the disease in Ghana (*1*), although the authors indicated that their effort was meant to incite future research interests in fully assessing this aspect of the costs associated with the disease. In a recent study (*3*), the various manifestations of the burden on health care systems in Ghana were recounted, which pointed to the fact that the treatment of Buruli ulcer causes resource allocations to be altered routinely in most treatment facilities and that the changes often occur at the expense of other diseases, in the context of limited health care resources.

The objectives of this study were:
1. To capture the impact of Buruli ulcer on the health care systems in three endemic communities in Ghana.
2. To conduct a comparative analysis of the direct costs of facility-based treatment relative to the management of the disease in outreach efforts.

Both lines of investigation fall within the research priorities of the Global Buruli Ulcer Initiative and their results are important aspects of any attempt to capture the overall burden of the disease.

Methods

While this study was originally designed to administer a questionnaire to elicit information that includes indirect cost estimates, it became apparent that considerable time and resources would need to be invested in following-up past patients who are scattered over vast geographical areas in each endemic community. These communities cover a wide area around a given treatment facility. However, an ongoing extension to this study (*6*) is designed to capture the burden to households and has taken up this task of eliciting information relative to indirect costs of treatment. Consequently, this study was devoted to capturing the direct costs of treatment from secondary data obtained from each facility's records.

The study covers the period from January 1998 to June 2002, during which information was examined on the direct costs of treatment for all stages of the disease. However, in order to permit cross-sectional comparison of costs, the treatment costs of nodules in treatment facilities and in outreach efforts were examined. A nodule is the basic form of the disease development and there is an equal chance for effective treatment in an outreach effort as in a facility-based treatment.

Results

The total average direct cost of treatment for the period, adjusted for local currency depreciation, amounted to US$ 270. This result was derived from a total of 489 patients treated over the study period, whose records fell within the analytical requirements. The adjusted annual average (direct) costs were US$ 122 (SD$ 82) in 1998, US$ 149 (SD$ 100) in 1999, US$ 196 (SD$ 142) in 2000, US$ 277 (SD$ 203) in 2001 and US$ 488 (SD$ 352) by June 2002. These costs correspond to annual average hospitalizations of 77.0 days in 1998, 78.3 days in 1999, 68.6 days in 2000, 79.6 days in 2001 and 89.6 days in 2002.

Four major components of treatment costs are highlighted in this study in order of importance: cost of surgery, costs of drugs, cost of hospitalization and costs of dressings. While the share of surgery costs increased from 17% in 1998 to 44% in 2002, that of drugs remained stable at 32%; the shares of hospitalization costs and costs of dressings declined from 26% and 25% in 1998 to 14% and 10%, respectively, in 2002. In terms of 1998 prices, these four components increased by 817%, 255%, 121 % and 36% respectively.

The significance of these results can be appreciated in the context of the burden the disease imposes on treatment facilities. The costs are evaluated against the background of facilities that operate under various conditions of resource scarcity, with the attendant sacrifices in terms of other health outcomes foregone. The decision that treatment of Buruli ulcer must be free to all patients has different implications for government hospitals on the one hand and for church-based hospitals that depend on resources provided by the parent churches on the other. Government hospitals generally receive annual allocations into their district resource pools known as “Paupers Fund”. It is from this source that all ailments that befall the poor compete for funds to provide treatment and other control services, including outreach activities. The church-based hospital must first treat the disease and submit a request for reimbursement of treatment expenses incurred. Thus, irrespective of the resource situation of a given treatment facility, the latter must attend to patients by whatever means possible before seeking reimbursement or some other increase in allocations towards management of the disease.

The average annual direct treatment costs, based on the number of patients records examined for the four facilities, was approximately US$ 27 015. This amount constitutes a tremendous burden on health facilities and, faced with increased demand for curative services, facilities are compelled to change resource allocations among various diseases to accommodate treatment demands for Buruli ulcer. The direct treatment costs must be borne by these facilities upfront,[1] and the latter may need to divert resources away from other diseases to meet increased demand for curative services. This is in addition to other indirect costs borne by the facilities, for which the treatment facilities receive no reimbursements. Studies (*1–2*) have shown that the disease has relatively large indirect treatment costs. As a percentage of the total cost of treatment, Asiedu et al. *(1)* calculated that indirect costs accounted for an average of 72% of total costs of treatment. The extended study will have some conclusive result on this aspect of the study. Meanwhile, based on the study results, one can conclude that the direct costs reported represent an average of only 28% of the total costs of treatment. This suggests that the annual average total cost of treatment ranges from US$ 436 in 1998 to US$ 1742 in 2002.

Early detection of the disease, which translates into fewer extensive surgeries and fewer days of hospitalization, may ultimately lead to decreased costs of treatment. In 2000, some 70% of cases were hospitalized for fewer than 70 days, leading to a lower average cost of stay relative to hospitalizations in 1999.

[1] Nongovernmental health facilities are ultimately reimbursed on expenditures incurred in treating the disease.

Outreach costs were based on a total of 26 trips per year and a maximum of 10 patients treated on each trip. Assuming that a total of 260 nodules are detected and treated annually, the results show an overall average cost of US$ 84.86 per nodule in a static (facility-based) treatment. The costs ranged from US$ 74.38 in 1998 to US$ 103.75 in 2002. Again, the average age for nodule patients was 13.2 years, and the duration of hospitalization was 38.78 days.

However, when nodules were treated in an outreach effort, the average cost per nodule treated was US$ 67 in 2002. This result included costs relating to transportation, personnel and logistics, surgical expenses, including consumables, and drugs. The costs of outreach treatment compared with the median treatment cost for nodules in 2002 (US$ 179) show considerable savings when the disease is assessed from an outreach perspective. The prospects for savings are greater for other clinical stages of the disease, since most of the costs that may be incurred in the treatment facility could be saved if the disease could be detected and treated at the nodular stage.

Conclusions and recommendations

The direct costs of treatment of Buruli ulcer continue to consume an increasing share of health systems' limited health care resources. This part of treatment costs is driven by surgical costs, drugs costs, hospitalization costs and costs of dressings. Facility-based treatment of the basic form of the disease (nodules) significantly exceeds the cost of treating nodules in an outreach effort. These trends point to a rethinking of interventions, with heavy emphasis on outreach treatment and control of Buruli ulcer.

Evidence of the extent of the economic burden on health systems lies in their inability to respond quickly to increased resource needs for treating Buruli ulcer (*3*) at both outreach and facility treatment levels. At the facility treatment level, the economic burden of Buruli ulcer reveals itself in the frequent practice of having to change the allocation of scarce resources just to meet increasing treatment needs for Buruli ulcer patients.

The solution lies in investing in cost-saving strategies that require a complete reevaluation of the nation's policy with respect to Buruli ulcer control. Greater emphasis may need to be placed on control strategies that limit the development of advanced forms of the disease requiring extensive surgical treatment and longer hospitalization.

From the point of view of minimizing the burden on health care systems, control of the disease may require aggressive investment of resources and persistence in outreach efforts throughout the year. The cost savings documented in this study warrant such investments.

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6. Mumma GA et al. *Estimation of costs to households due to the burden of Buruli ulcer in the central and Ashanti regions of Ghana* [study in progress].

ANNEXES

ANNEX 1 – Agenda – 6th WHO Advisory Group Meeting on Buruli ulcer, 10–13 March 2003, WHO Headquarters, Geneva

Monday 10/03/03		
08:30 – 09:00	Registration	
09:00 – 09:20	Welcoming remarks	Dr David Heymann
09:20 – 09:30	Rationale and objectives of 2003 meeting Activities of the WHO Regional Office for Africa, AFRO	Dr Kingsley Asiedu Dr Eugene Nyarko
09:30 – 09:45	Benin	Dr Christian Johnson
09:45 – 10:00	Cameroon	Dr Charles Nsom Mba
10:00 – 10:15	Congo-Brazzaville	Dr Hilaire Bassakouaou
10:15 – 10:30	Côte d'Ivoire	Prof. Jean-Marie Kanga
10:30 – 11:00	***Coffee break***	
11:00 – 11:15	Buruli ulcer control in conflict situations: the case of Côte d'Ivoire/Overview of the osteo-articular lesions in Buruli ulcer	Prof. Henri Assé
11:15 – 11:30	Democratic Republic of the Congo	Dr Jacquie Singa Nyota/ Dr Eric Bafende
11:30 – 11:45	Ghana	Dr Edwin Ampadu
11:45 – 12:00	Guinea	Dr Adama Marie Bangoura
12:00 – 12:15	Uganda	Dr Henry Wabinga
12:15 – 12:30	Sudan	Dr Abdou Sow/ Dr Ayana Yeneabat
12:30 – 14:00	***Lunch***	
14:00 – 14:15	French Guiana	Dr Roger Pradinaud
14:15 – 14:30	Papua New Guinea	Sister Joseph
14:30 – 14:45	Australia	Dr John Hayman
14:45 – 15:30	**Discussions of country presentations**	**All**

15:30 – 16:00	***Coffee break***	
16:00 – 16:15	The Sasakawa/Nippon Foundations	Prof. Kenzo Kiikuni
16:15 – 16:30	ANESVAD	Ms Verónica Malda/ Mr Andrés Ginés
16:30 – 16:45	MAP International	Mr Edouard Yao
16:45 – 17:00	American Leprosy Missions (ALM)	Dr Paul Saunderson
17:00 – 17:15	Health Foundation of Ghana (HFG)	Mrs Lynda Arthur
17:15 – 17:30	Humanitarian Aid Relief Team, USA (HART)	Dr Kimball Crofts

Tuesday 11/03/03		
09:15 – 09:30	Associazione Italiana Amici di Raoul Follereau AIFO, Italy	Dr Giovanni Gazzoli/ Dr George Abram
09:30 – 09:45	Rotary Club of Milan, Italy	Dr Franco Poggio
09:45 – 10:00	Fondation luxembourgeoise Raoul Follereau (FFL)	Prof. Henry Kiniffo/ Mr Robert Kohll
10:00 – 10:15	Interplast, France	Dr Remy Zilliox
10:15 – 10:30	PHANS	Dr Vincent Stoffel
10:30 – 11:00	***Coffee break***	
11:00 – 11:15	Association Française Raoul Follereau (AFRF)	Mr Jehan-Michel Rondot
11:15 – 11:30	Médecins Sans Frontières (MSF) - Luxembourg	Dr Peter Firmenich
11:30 – 11:45	Aide Aux Lepreux EMMAUS-SUISSE (ALES)	Mrs Patricia Beauverd
11:45 – 12:00	Médecins Sans Frontières (MSF) - Switzerland	Dr Elisabeth Le Saout
12:00 – 12:30	**Discussions of NGOs presentations**	**All**
12:30 – 14:00	***Lunch***	
14:00 – 14:15	Buruli ulcer priority research proposal	Dr Paul Johnson
14:15 – 14:30	BCG vaccination protocol - draft	Dr Paul Johnson
14:30 – 14:45	Buruli ulcer and osteomyelitis	Prof. Françoise Portaels
14:45 – 15:00	Update on the mode of transmission	Prof. Bernard Carbonnelle/ Mr Laurent Marsollier
15:00 – 15:15	Development of new tools for the detection of *M. ulcerans*	Prof. Gerd Pluschke
15:15 – 15:30	Update on the potential for the serodiagnosis of Buruli ulcer disease	Dr Harold King

15:30 – 16:00	***Coffee break***	
16:00 – 16:15	Implementation of a dry reagent based PCR for the laboratory confirmation of *M. ulcerans* disease in Ghana	Dr Gisela Bretzel
16:15 – 16:30	Immuno-reactivity of PGL-1-like material in BU typical histopathological specimens	Dr Milanga Mwanatambwe
16:30 – 16:45	Drugs for Neglected Diseases Initiative	Dr Els Torreele
16:45 – 17:00	Treatment of Buruli ulcer with topical nitrogen oxide	Dr Richard Phillips
17:00 – 17:15	Results of drug treatment trial in Côte d'Ivoire	Prof. Jean-Marie Kanga
17:15 – 17:30	Preliminary results of drug treatment trial in Ghana	Dr Mark Wansbrough-Jones

Wednesday 12/03/03		
09:00 – 09:15	Immune response during *M. ulcerans* infection in French Guiana	Dr Ghislaine.Prévot-Linguet/ Dr Kris Huygen
09:15 – 09:30	Research activities at Noguchi Institute, Ghana	Prof. David Ofori-Adjei
09:30 – 09:45	Identification of mycolactone genes and potential for vaccine construction	Dr Pamela Small
09:45 – 10:00	*M. ulcerans* genome sequencing analysis - progress	Dr Tim Stinear
10:00 – 10:15	Development of a questionnaire for assessing Buruli ulcer induced functional limitation	Dr Ymkje Stienstra
10:15 – 10:30	Estimation of costs to households due to the burden of Buruli ulcer disease	Ms Ellen Whitney/ Mr Frank Dadzie
10:30 – 11:00	***Coffee break***	
11:00 – 12:30	**Discussions of research presentations**	
12:30 – 14:00	***Lunch***	
14:00 – 15:40	Group work	
15:40 – 16:00	***Coffee break***	
16:00 – 17:30	Group work	

Thursday 13/03/03		
09:00 – 10:30	Finalization of group work	
10:30 – 11:00	***Coffee break***	
11:00 – 11:20	Presentation of conclusions and recommendations of Group 1	
11:20 – 11:40	Presentation of conclusions and recommendations of Group 2	
11:40 – 12:00	Presentation of conclusions and recommendations of Group 3	
12:00 – 12:20	Presentation of conclusions and recommendations of Group 4	
12:20 – 14:00	***Lunch***	
14:00 – 14:20	Presentation of conclusions and recommendations of Group 5	
14:20 – 15:30	Discussions of presentations on group conclusions and recommendations	
15:30 – 16:00	***Coffee break***	
16:00 – 16:30	Concluding remarks	Chairperson

Working Groups

Group	**Discussion area**
Group 1	Control activities
Group 2	Control activities
Group 3	Drug treatment
Group 4	Research
Group 5	NGOs

ANNEX 2 – List of participants – 6th WHO Advisory Group Meeting on Buruli ulcer, 10–13 March 2003, WHO Headquarters, Geneva

Dr George Abram, International Anti-Leprosy Organization, Takoradi, Ghana

Mrs Laurence Ahoua, Epicentre, Paris, France

Dr Julien Aké Aké, MAP International, West Africa, Côte d'Ivoire

Dr Edwin Ampadu, Manager, National Buruli Ulcer Programme, Accra, Ghana

Mr Bill Ancell, IGI, London, England

Mrs Lynda Arthur, Health Foundation of Ghana, Accra, Ghana

Dr Sica Asso, Institut Raoul Follereau, Manikro, Côte d'Ivoire

Professor Henri Assé, Institut Raoul Follereau, Adzopé, Côte d'Ivoire

Dr Eric Bafende, Hôpital de Kimpese, Democratic Republic of the Congo

Dr Patrick Biason, Médecins Sans Frontières, Yaounde, Cameroon

Dr Adama Marie Bangoura, Programme National de lutte contre l'ulcère de Buruli, Guinea

Dr Hilaire Bassakouaou, Ministry of Health/Ministère de la Santé, Congo

Mrs Patricia Beauverd, Aide aux Lépreux Emmaüs-Suisse, Berne, Switzerland

Dr Gisela Bretzel, Bernhard Nocht Institute for Tropical Medicine, Hamburg, Germany

Professor Bernard Carbonnelle, Laboratoire de Bactériologie, CHU Angers**,** France

Dr Frédérick Chague, Projet Humanitaire Afrique Nord Sud, Pfastatt, France

Mrs Bénédicte de Charette, Association Française Raoul Follereau, Paris, France

Dr Kimball Crofts, Humanitarian Aid Relief Team (HART), Provo, UT, United States of America

Mr Frank Dadzie, Clark Atlanta University, Atlanta, GA, United States of America

Dr Pieter U. Dijkstra, Groningen University Hospital. Groningen, Netherlands

Mr Christophe Dupont, Médecins Sans Frontières-Luxembourg, Cotonou, Benin

Dr Samuel Etuaful, St Martin's Catholic Hospital, Agroyesum, Ghana

Dr Peter Firmenich, Médecins Sans Frontières, Luxembourg

Mr Kazuyuki Fukunishi, Aberystwyth, Wales

Mr Andrés Ginés, ANESVAD, Bilbao, Spain

Professor Jacques Grosset, Center for Tuberculosis Research, Johns Hopkins University School of Medicine, Baltimore, MD, United States of America

Dr. Giovanni Gazzoli, Associazione Italiana Amici di Raoul Follereau, Bologna, Italy

Dr John Hayman, Department of Anatomy and Cell Biology, Monash University, Clayton, Melbourne, Australia

Dr Richard Helh, c/o Aide aux Lépreux Emmaüs-Suisse, Berne, Switzerland

Dr Kris Huygen, Mycobacterial Immunology, Pasteur Institute of Brussels, Brussels, Belgium

Professor Komlanvi Denis James, Faculté de médecine et de pharmacie, Lomé, Togo

Dr Baohong Ji, Faculté de Médecine, Pitié-Salpetrière, Paris, France

Dr Christian Johnson, Programme National de Lutte contre l'Ulcère de Buruli, Cotonou, Benin

Dr Paul Johnson, Department of Infectious Diseases, Austin & Repatriation Medical Centre, Heidelberg, Melbourne, Australia

Sister Joseph, Wewak General Hospital, Wewak, East Sepin Province, Papua New Guinea

Dr Jacques Kaltenback, Projet Humanitaire Afrique Nord Sud, Pfastatt, France

Professor Jean-Marie Kanga, Programme National de Lutte contre l'Ulcère de Buruli, Abidjan, Côte d'Ivoire

Prof. Kenzo Kiikuni, Sasakawa Memorial Health Foundation, Tokyo, Japan

Dr Harold King, Department of Medicine, Division of Infectious Diseases, Emory University, Atlanta, GA, United States of America

Professor Henry-Valère T. Kiniffo, Fondation luxembourgeoise Raoul Follereau, Luxembourg

Dr Erasmus Klutse, Government Hospital, Dunkwa-on-Offin, Ghana

Mr Robert Kohll, Fondation luxembourgeoise Raoul Follereau, Luxembourg

Dr Kanga Kouamé, Programme National de Lutte contre l'Ulcère de Buruli, Abidjan, Côte d'Ivoire

Mr Samuel Kouassi Kouakou, Groupes Bibliques des Hôpitaux de Côte d'Ivoire, Abidjan, Côte d'Ivoire

Ms Verónica Malda, ANESVAD, Teófilo Guiard, Bilbao, Spain

Mr Laurent Marsollier, Laboratoire de Bactériologie, CHU Angers**,** France

Mr Johan Mouton, IGI, Victoria, South Africa

Dr Charles Nsom Mba, Ministry of Public Health, Cameroon

Dr Wayne M. Meyers, Division of Microbiology, Armed Forces Institute of Pathology, Washington, DC, United States of America

Dr Mwanatambwe Milanga, Department of Pathology**,** Nippon Medical School, Tokyo, Japan

Dr Sara Ngo Niobe-Eyangoh, Laboratoire Des Mycobactéries, Centre Pasteur, Yaoundé, Cameroon

Professor David Ofori-Adjei, Noguchi Memorial Institute for Medical Research, Accra, Ghana

Ms Makiko Ogihara, The Nippon Foundation, Japan

Dr Richard Phillips, Division of Infectious Disease, St. George's Hospital Medical School, London, United Kingdom

Dr Gerd Pluschke, Dept. of Molecular Immunology, Swiss Tropical Institute, Basel, Switzerland

Dr Franco Poggio, Rotary International, Rotary Club Milano, Italy

Prof. Françoise Portaels, Department of Microbiology, Institute of Tropical Medicine, Antwerp, Belgium

Dr Roger Pradinaud, Service de Dermatologie, Centre hospitalier général de Cayenne, Cayenne, French Guiana

Dr G. Battista Priuli, Hôpital St Jean de Dieu, Tanguieta, Benin

Mr Jehan-Michel Rondot, Association Française Raoul Follereau, Paris, France

Dr Jacquie Singa Nyota, Programme National de Lutte contre l'Ulcère de Buruli**,** Democratic Republic of the Congo

Dr Pamela L. Small, Department of Microbiology, University of Tennessee, Knoxville, TN, United States of America

Ms Agnès Sommet, Paris, France

Mr René Stäheli, Aide aux Lépreux Emmaüs-Suisse, Berne, Switzerland

Dr Vincent Stoffel, Projet Humanitaire Afrique Nord Sud, Pfastatt, France

Dr Ymkje Stienstra, Department of Internal Medicine, University Hospital, Groningen, Netherlands

Dr Tim Stinear, Unité de Génétique Moléculaire Bactérienne, Institut Pasteur, Paris, France

Dr Issaka Tiembre, Groupes Bibliques des Hôpitaux de Côte d'Ivoire, Abidjan, Côte d'Ivoire

Dr Napo Tignokpa, Programme contre la Lèpre et la Tuberculose, Ministère de la Santé, Lomé, Togo

Dr Els Torreele, Médecins Sans Frontières, Brussel, Belgium

Dr Alphonse Um Boock, Aide aux Lépreux Emmaüs, Yaoundé, Cameroon

Dr T. S. van der Werf, Department of Internal Medicine, University Hospital, Groningen, Netherlands

Dr Henry Wabinga, Department of Pathology, Faculty of Medicine, Makerere University, Kampala, Uganda

Dr Mark Wansbrough-Jones, Division of Infectious Disease, St. George's Hospital Medical School, London, England

Ms Ellen Whitney, Meningitis and Special Pathogens Branch, Centers for Disease Control and Prevention, Atlanta, GA, United States of America

Mr Atsushi Yagi, Aberystwyth, Wales

Mr Edouard Yao, Regional Office for West Africa, MAP International, Abidjan, Côte d'Ivoire

Dr Remy Zilliox, Interplast, France

WHO/OMS

Dr Ayana Yeneabat, WHO South Sudan Office

Dr Kingsley Asiedu, Global Buruli Ulcer Initiative, CEE, Communicable Diseases Control, Prevention & Eradication

Dr Denis Daumerie, Leprosy, CEE, Communicable Diseases Control, Prevention & Eradication

Dr Ulrich Josef Fruth, Research on Bacterial Vaccines, Initiative for Vaccine Research, Department of Vaccines & Biologicals, Health Technology and Pharmaceuticals

Dr David L. Heymann, Executive Director, Communicable Diseases

Dr Amedée Molamou, WHO Office in Congo

Dr Will Parks, Social Mobilization & Training (SMT), Communicable Diseases Control, Prevention & Eradication

Dr Piero Luigi Olliaro, Special Programme for Research and Training in Tropical Diseases, Communicable Diseases

Dr Elil Renganathan, Coordinator, Social Mobilization & Training (SMT), Communicable Diseases Control, Prevention & Eradication

Dr Abdourahmane Sow, Coordinator, WHO South Sudan Office

Dr Nevio Zagaria, Coordinator, Strategy Development & Monitoring for Eradication & Elimination (CEE), Communicable Diseases Control, Prevention & Eradication

ANNEX 3 – Buruli ulcer : Research Proposal – Draft

Background and current situation

Buruli ulcer (BU), a disease caused by *Mycobacterium ulcerans*, is largely a **neglected** problem of the poor in remote rural areas and has since 1980 **emerged** as an important cause of human suffering. There is limited awareness of the disease both within the medical community and the general public, which results in under-recognition and under-reporting. After tuberculosis and leprosy, Buruli ulcer is the third most common mycobacterial disease. It has been reported or suspected in over 30 countries worldwide (Angola, Australia, Benin, Bolivia, Burkina Faso, Cameroon, China, Congo, Côte d'Ivoire, Democratic Republic of the Congo, Equatorial Guinea, French Guiana, Gabon, Ghana, Guinea, India, Indonesia, Japan, Kiribati, Liberia, Malaysia, Malawi, Mexico, Nigeria, Papua New Guinea, Peru, Sierra Leone, Sri Lanka, Sudan, Suriname, Togo and Uganda). Current information indicates that west Africa is the most affected region.

More than 50% of those affected are children under the age of 15 years. Buruli ulcer often occurs in localized areas close to stagnant or slow moving waters. The mode of transmission is unclear; recent evidence shows that some aquatic insects may transmit the disease. It is not transmitted from person to person. A few cases have been reported in non-endemic areas in North America and Europe linked to international travel.

Buruli ulcer often starts as a painless nodule and if left untreated, leads to massive destruction of skin and sometimes bone (see Appendix 3). A corrosive toxin released by the bacteria called mycolactone causes tissue damage. The only treatment currently available is surgery. If patients seek treatment early, the surgery is simpler and less expensive. Unfortunately, most patients in Africa seek treatment too late partly due to factors such as sociocultural beliefs and practices, and geographical and financial access to medical care. Antibiotic therapy has so far been disappointing but new evidence suggests that some antibiotic combination given in early stages of the disease may cure Buruli ulcer. Though mortality from Buruli ulcer is low, morbidity and subsequent disability are very high. In some places, as much as 25% of those with healed lesions are left with disabilities that have long-term social and economic impact. Complications of Buruli ulcer include contracture deformities, amputation of limbs, and infection of eyes, breasts and genitalia.

In response to the growing spread and impact of the disease, the World Health Organization (WHO) established the Global Buruli Ulcer Initiative (GBUI) in 1998 to coordinate control and research efforts. The first international conference on Buruli ulcer was held in July 1998 in Yamoussoukro, Côte d'Ivoire. The Yamoussoukro Declaration on Buruli ulcer (see Annex 4) was adopted by the participants and co-signed by the presidents of three endemic countries and the Director-General of WHO. This conference marked a significant step in the fight against Buruli ulcer. Since then considerable progress has been made to control the disease. Several partners have joined the global efforts and more are showing interest. Some endemic countries have established control programmes and others are in the process of doing so.

Progress made on the research front for the past four years has been encouraging. However, definitive answers are needed for some of the critical questions surrounding Buruli ulcer so that effective control and preventive measures can be instituted. No one is sure where the bacterium lives in the environment and how it enters the body, although clearly the bacterium is unable to do so by itself. No one knows why this tropical disease can spontaneously erupt in temperate climates like Australia. It is also unclear whether everyone infected with Buruli develops the disease and, if not, why some are immune. There is no diagnostic tool, other than direct visual observation. Incubation periods are a matter of guesswork, and for unknown reasons, drug therapy frequently fails.

Justification

Much has been discovered by the work of a small band of dedicated Buruli experts over the past 30 years. The need for new control methods is **urgent** given the growing spread and impact of the disease. Inadequate health surgical facilities and expertise in affected areas, and the expense and complexity of surgical intervention limit the current treatment. WHO believes that finding answers to some of the mysteries surrounding the disease is very close. Information from the *M. ulcerans* genome sequencing project should greatly facilitate the ability to develop better diagnosis and treatment methods for Buruli ulcer (see Annex 2). **However, because of poor funding and low visibility of Buruli ulcer, progress has been slow. WHO is convinced that at this stage, a central dedicated funding body that is able to commission, direct and coordinate research efforts has the potential to significantly enhance the rate of progress**.

Among the many potentially important areas of research on Buruli ulcer, **five priority areas** were selected by the research subgroup at the 5th WHO Advisory Group Meeting on Buruli Ulcer, held on 11–14 March 2002 in Geneva, Switzerland, as most likely to provide immediate direct benefit to Buruli ulcer patients in the medium term (see Annex 1).

These are:

1. **The mode of transmission**
2. **Development of methods for early diagnosis**
3. **Drug treatment and new treatment modalities**
4. **BCG trials and development of new vaccines**
5. **Cultural and socioeconomic studies**

Purpose

The purpose of this proposal therefore is to establish a Buruli Ulcer Research Proposal at WHO, to promote, foster and accelerate research on the above-mentioned priority areas. An amount of at least US$ 4 000 000–5 000 000 for five years could meet the critical research needs and bring hope to potential victims of this debilitating disease.

Goal

The medium-term goal of this proposal is to help generate the missing scientific knowledge as quickly as possible so that better tools for controlling and preventing Buruli ulcer can be developed.

BURF – Strategy

WHO/GBUI strategy to date has been to gather the expertise of the world's scientific community, and form partnerships with other organizations, such as research institutions, ministries of health, academia and nongovernmental organizations. In this way, WHO has acted as a "lobal facilitator" of research. Because of competition for funding and the relatively poor knowledge of Buruli ulcer compared with diseases such as TB, malaria and HIV, research progress has been considerably constrained. WHO now plans to take its current approach one step further by creating a fund that will specifically focus on Buruli ulcer, so that it can directly fund priority research.

Funds will be awarded competitively according to the quality of the proposal and the track record of the applicants. WHO will model the application system for these competitive grants on the existing proven research systems such as the World Bank/UNDP/WHO Special Programme for Research and Training in Tropical Diseases (TDR) and the Special Programme for Research,

Development and Research Training in Human Reproduction (HRP).
It will actively seek to encourage researchers to work cooperatively, to avoid unnecessary duplication, and to focus on **the five priority areas**. WHO will also encourage researchers to continue to seek their own funding from other sources—the aim is to add capacity but not to replace existing support.

Who can contribute

All organizations, foundations, governmental and nongovernmental organizations and individuals working on or interested in Buruli ulcer are welcome to contribute to this fund.

Who can apply

It will be open to all researchers/scientists. Applications will be judged on merit. Calls for proposals will be advertised on the WHO web site for Buruli ulcer (www.who.int/gtb-buruli).

Essential requirements with applications

Ethical clearance: if the proposed research involves human subjects, Council for International Organization of Medical Sciences (CIOMS), Guidelines for Ethical Clearance should be consulted and the necessary ethical approval(s) obtained.

Standard Operating Procedures (SOPS)

All clinical studies supported by WHO/GBUI must be carried out aaccording to International Conference on Harmonization (ICH)/WHO Good Clinical Practice standards, regulatory authorities' requirements, and the appropriate Standard Operating Procedure (SOPs).

Implementation

WHO will be responsible for overall management and coordination. The subgroup on research from the current membership of the WHO Advisory Group on Buruli Ulcer will assist WHO to review proposals for funding. Other experts will be invited if needed.

Review process and evaluation

The subgroup on research will meet once a year in Geneva to review and approve proposals for funding as well as to evaluate the progress of work. Members may also review applications by mail/e-mail.

Reporting

Annual and meeting reports will be sent to all contributing and relevant partners.

Publication and dissemination of research results

Results of research activities will be published in peer review journals, and presented at meetings and conferences. Key findings will be provided to the ministries of health of the affected countries for integration into policy to control the disease.

Appendix 1 – Priority areas for research

1. Mode of rationale

Experience over the last 50 years has established the fact that transmission of Buruli ulcer is acquired through exposure to the environment, particularly through exposure to slow moving or stagnant bodies of water. The importance of understanding the mechanism of transmission from water to infected patients is obvious: if one can determine where the bacteria replicate, and how they are introduced into the patient, it may be possible to prevent exposure to infection. Isolation of *M. ulcerans* by cultures from samples taken from the environment has not been successful in the past. However, knowledge about transmission has recently increased thanks to the use of new molecular techniques such as polymerase chain reaction (PCR). The recent findings that *M. ulcerans* can be isolated from water bugs in endemic areas and can replicate in the salivary glands of these bugs heralds a major breakthrough in our understanding of the ecology of *M. ulcerans*. The bugs so far associated with *M. ulcerans* are large, easily identified and generally confined to specific aquatic niches. This information if confirmed by further studies could have an enormous impact on the control of Buruli ulcer leading to the development of strategies to prevent human contact with infected insects in endemic areas. The implementation of preventive strategies may be relatively simple and inexpensive. In addition, if people are informed of the risk of exposure to such insects, they may be more likely to pay attention to bites received while near the water and this could lead to earlier diagnosis of some infections. Diagnosis of early lesions is extremely important since treatment of small lesions can be done locally.

It should be emphasized that all of the scientific tools and knowledge necessary to conduct such studies successfully are available.

Recommended studies

1. To confirm the prevalence of *M. ulcerans* in water bugs (Naucoridae, Belostomatidae and Nepidae) in areas endemic for Buruli ulcer and the role these bugs may play in infection
2. To identify other species which may play a role in maintaining *M. ulcerans* in the environment. These studies are important because there is much evidence suggesting that *M. ulcerans* is
2. present in many reservoir species

2. Development of methods

Rationale: Although Buruli ulcer can be confirmed in tertiary hospitals or research laboratories equipped with modern techniques including histopathology, culture and PCR, there are no good tools available for early diagnosis that can be implemented in the rural environment of developing countries where the burden of disease exists. This is especially unfortunate since treatment of Buruli ulcer in its early nodular stage can be carried out locally with little trauma to the patient, whereas treatment of late-stage disease requires extensive surgery at major hospitals, prolonged hospitalization, and is very expensive. Furthermore, early forms of the disease may respond to antibiotic therapy, thus avoiding the need for surgery. The most desirable method of diagnosis would be a simple blood test to determine if a person has *M. ulcerans* infection or a test based on examination of a small amount of tissue from a suspected lesion. The assay should preferably be carried out by simple colorimetry or agglutination that can be done in a rural hospital. Such assays

are available for many infectious diseases. Thus high priority needs to be given to development of a good early diagnostic test.

Recommended studies

1. To identify *M. ulcerans*-specific proteins in lesions
2. To identify *M. ulcerans* toxin, mycolactone in lesions
3. To identify *M. ulcerans*-specific antibodies in blood

3. Drug treatment and new treatment modalities

Rationale: Current accepted therapy for Buruli ulcer consists of surgery with or without skin grafting. Such treatment may not be available in some rural areas where the disease occurs; it is extremely invasive and expensive, requires hospitalization and is feared by many patients. However, given the nature of the disease, surgery may continue to play a role in the management of some cases even after other interventions are found. Very promising preliminary results from ongoing studies in Ghana suggest that antibiotics (rifampicin + streptomycin or amikacin) may be effective in curing Buruli ulcer in the early stages. Drugs could serve as an adjunct to surgery to reduce extent of surgical excision or in preventing recurrence.

Antibiotic therapy has numerous advantages over surgical intervention. It is less expensive, less debilitating to the patient, can be given locally and is likely to be well accepted. It is important that results from recent antibiotic trials be confirmed as quickly as possible. Protocols are already in place for many of these studies; all that is required for implementation is funding.

Recommended studies

1. To determine which combinations of antibiotics are most effective and how long drugs must be given
2. To determine whether a regimen using oral antibiotics alone is efficacious
3. To determine the role of antibiotics as adjunct to surgery to reduce the extent of surgical excision (once drug efficacy has been established)
4. To investigate the role of novel topical therapies such as clay or nitric oxide in the management of the disease

4. BCG trials and development of new vaccines

Rationale: Data suggest the BCG may have some role in prevention of Buruli ulcer. In addition since Buruli ulcer appears to be a largely toxin-mediated disease, the development of an anti-toxin may be one of the approaches towards vaccine development and could also be therapeutically useful. Another factor that supports the feasibility of developing a subunit vaccine against *M. ulcerans* is that infection is largely extracellular. Therefore antibodies against mycobacterial cell surface structures may have protective activity.

Recommended studies

1. To evaluate the potential role of a single or a second dose BCG in the prevention of Buruli ulcer in an endemic population
2. To develop an antitoxin for use as a vaccine
3. To search and evaluate protein-based vaccine candidates

5. Cultural and socioeconomic studies

Rationale: In general, the aim of studies in this area is twofold:
a) to assist in the design and evaluation of specific, culturally appropriate and behaviourally feasible prevention and treatment interventions;
b) to inform policy-makers to incorporate findings of such studies in designing and changing policies aimed at managing the disease.

Patients' perceptions about a disease, its effective treatment, and the socioeconomic dislocation caused by the illness and related symptoms generally have a significant impact on when and where to go for diagnosis and treatment. Although these beliefs can vary considerably from culture to culture, there are some general traits that permeate several cultures. If a disease does not follow its expected course, (e.g. "wounds that do not heal") a supernatural cause such as a curse or witchcraft is often suspected. In such cases, patients seek supernatural cure. A second rational and universal behaviour is that people with limited resources (particularly those in rural areas) seek medical help first from the least expensive and the closest sources. Multiple, simultaneous or sequential sources of treatment may also be sought (e.g. home treatment, followed by faith healer, followed by pharmacy, followed by local clinic, etc.). A third determinant of response to illness is local understandings of what constitutes a "severe" disorder (or in the case of Buruli ulcer, a severe skin disorder). Perceptions of severity, intensity and persistence of symptoms may vary between age groups (e.g., what is considered "severe" for an infant may not be considered "severe" for a young adult), the sexes, and educational levels. Some skin disorders may be highly stigmatized (e.g. skins patches associated with leprosy). Buruli ulcer is complicated by the fact that very little pain is felt in cases of severe degradation of skin.

A fourth determinant of response to illness is the perceived (or lack of) threat to the individual. If there is little perceived threat of contracting the disease, people are generally very unwilling to do anything about prevention. There is a need to understand the rational calculations individuals make in weighing the perceived threat (of the disease and symptoms) and the cost of taking preventive action and/or seeking early treatment against the benefits or value of pursuing these recommended behaviours. An understanding of such behavioural factors can be very important in designing and implementing behavioural interventions. Cultural beliefs may prevent people from coming forward to be counted as a Buruli ulcer case, and may make patients unwilling to seek outside medical care. Local healers may have information about who is infected, and may even have knowledge of local remedies that are efficacious.

Finally, the "cost" of a disease can only be fully assessed by taking into account the effects of cultural and socioeconomic factors. Several questions still require conclusive answers. Does Buruli ulcer make it difficult for children to go to school or get work? What impact does Buruli ulcer have on agricultural activities in affected areas? What impact does a Buruli ulcer patient have on other family members? What impact does Buruli ulcer have on a person's ability to marry? Also, cultural factors will have an important impact on accurately determining the epidemiology of Buruli ulcer, its diagnosis, and the willingness of patients to seek and accept treatment or other medical interventions.

The economic factors may relate to the economic burden imposed on the lives of other members the family. [For example, does the cost of treatment of a Buruli ulcer patient compel a child of school age to quit schooling in order to work to support the family?] They may also relate to an assessment of the relative (direct and indirect) costs of treating the disease at different stages of development. Prospects for cost-saving are currently known to exist in identifying the disease at very early stages through outreach activities to endemic villages, and a study to assess the costs of outreach treatment activities is expedient. Such a study may need to begin at the treatment

centers where considerable data can be found in establishing the framework for assessing the costs of treatment at different stages of the disease. As a result of a specific country study, it can be possible to design an instrument for collecting such cost data in other endemic countries. Given an assessment of the public health burden of the disease, cost estimates will permit cost-effectiveness analysis of existing and future treatment strategies.

The economic studies must include the impact of the disease on the health services of the community and the country at large. The studies may include an assessment of the pressure on the system's limited resources and infrastructure for treating the disease, as well as the administrative and financial burden on the health system.

Recommended studies:

1. To determine local explanatory models of skin disorders and Buruli ulcer in particular (signs, causes, relative severities, treatments, perceived threat), local terminology associated with Buruli ulcer, patterns of resort (use of home remedies, traditional healers, local clinics, pharmacies, and other therapeutic resources), and factors influencing these patterns of resort
2. To determine community opinions of any proposed interventions such as health education, skin surgery, and community rehabilitation
3. To determine the potential role of traditional healers in the early recognition and treatment of Buruli ulcer and the possible use of home and traditional remedies
4. To determine the socioeconomic dislocations of social and cultural norms caused by Buruli ulcer and the coping strategies already employed by sufferers
5. To determine the impact of Buruli ulcer (including disabilities) on the lives of the patients and family members
6. To determine the costs of both static (or facility-based) and outreach management of Buruli ulcer. This will include both direct and indirect costs of such management strategies. Such costs studies must include the assessment of the costs of treatment at various stages of the disease
7. To determine the economic impact of the disease treatment on the health services system of the community and the country. It must typically include an assessment of the impact on the system's infrastructure and its variable resources, as well as its administrative and financial burdens on these systems

It should be noted that the financial cost of such studies could be very modest with quite high yield. It should also be noted that manuals on rapid anthropological procedures, rapid rural appraisal methods, disease-focused ethnographic techniques and social marketing research have been designed for research on other infectious diseases and could be readily adapted to some of the above recommended studies. Simple protocols to examine socioeconomic issues could be designed during the conduct of studies 4–6.

Appendix 2. The M. ulcerans genome project – Contribution to research

A two-year project to determine the complete genome sequence of *M. ulcerans* began at the Pasteur Institute, Paris, France, in February 2001 and is expected to finish by the end of 2002. A public server, called **BuruList**, will be made available around July 2002 so that researchers worldwide can have access to preliminary genome data.

A genome is the complete collection of genes in an organism. Genes are made of DNA and every gene contains a separate piece of information required by an organism to live, to replicate, and (for pathogenic microorganisms) cause disease. Genomics is the systematic analysis of the genome of an organism. It allows researchers to determine the biochemistry, physiology and genetics of an organism. Genomics has revolutionized biology and medicine and in particular, has made a major impact on the study of mycobacterial diseases. The complete genome sequences of *M. tuberculosis* and *M. leprae* have been recently completed and these have enabled researchers to identify new strategies for diagnosis, vaccination and drug therapy for fighting tuberculosis and leprosy.

The detailed knowledge of *M. ulcerans* that this work is providing will give researchers worldwide the fundamental resources to address the key research priorities for fighting this disease. In particular, this project is critical for the development of techniques for early diagnosis and disease prevention by identifying antigenic proteins specific for *M. ulcerans* that can be used for both serodiagnosis and vaccine strategies. The genome project is also central to identifying new treatment strategies by identifying key mechanisms that the organism uses to cause disease. For example by determining the pathways that *M. ulcerans* uses to produce the toxin, mycolactone it may be possible to design drugs that block these pathways.

The progress of the project to date has been very good and several key features about *M. ulcerans* have come to light. One of the most significant early findings is that the *M. ulcerans* genome contains a very large block of unique genes that are predicted to produce the enzymes involved in mycolactone synthesis. The genome has also been found to contain very large amounts of repetitive DNA and it thus seems likely that *M. ulcerans* has acquired the ability to readily mutate.

The determination of a complete genome sequence is not an end in itself. With respect to disease-causing microorganisms, it is the first step towards gaining a comprehensive understanding of the pathways of pathogenesis. A genome sequence is a resource upon which many other scientific disciplines draw. Several examples have been given above of how the genome of *M. ulcerans* could be used to directly affect the control of Buruli ulcer.

ANNEX 4 – Accelerated capacity development plan for the management of Buruli ulcer (2003–2007) – Draft

Executive summary

This document sets out a five-year draft plan for rapidly developing the capacity of endemic countries to detect and manage cases of Buruli ulcer. Although the full range of problems caused by this disease is addressed, emphasis is placed on the immediate need for prompt reporting and correct surgical management of cases at a stage when severe complications and permanent disabilities can be prevented. The plan also responds to the unique needs posed by a disease that affects impoverished populations in remote rural areas and is poorly understood by both the medical profession and general population.

With these needs in mind, the document sets out a series of clear objectives, actions, responsibilities, and indicators aimed at helping countries acquire the core surgical skills, equipment, and facilities needed for standard case management. The need to improve detection and reporting is also addressed. The strategy for improving skills stresses training in proper surgical excision and skin grafts and use of dermatomes, meshers, and nodulectomy kits. Several technical guides have recently been produced to assist these tasks. Training, as recommended in the plan, also extends to schoolteachers and community volunteers who can influence community attitudes and thus contribute to early case detection and referral.

The plan further covers provision of physiotherapy and the organization of short-term plastic surgical missions to assist countries in the management of severe and complicated cases and provide first-hand training in more sophisticated techniques. The roles of WHO, including assistance in acquiring essential surgical equipment and supplies, are also clearly identified in this comprehensive, forward-looking plan. As an additional benefit, implementation of the plan is expected to contribute to better documentation of the magnitude and relative importance of Buruli ulcer – a poorly understood, neglected, and rapidly emerging disease.

I. INTRODUCTION

Buruli ulcer, caused by *Mycobacterium ulcerans*, is largely a neglected problem of the poor in remote rural areas and has since 1980 emerged as an important cause of human suffering. The disease has been reported or suspected in over 30 countries worldwide. Africa is the most affected region. There is limited awareness of Buruli ulcer both within the medical community and the general public, which results in under-recognition and under-reporting, thus masking its relative importance. **Treatment requires surgical excision with or without skin grafting and physiotherapy. However, the skills to carry out skin grafting among health workers is very limited in most endemic areas and physiotherapy services are virtually absent in most rural hospitals.** There is ongoing research to evaluate the potential role of antibiotics. Mortality from Buruli ulcer is relatively low but the prolonged suffering and subsequent disability are very high. In some places, as many as 25% of those with healed lesions are left with disabilities and hence a long-term social and economic impact.

Since 1998, many guidelines and technical documents have been developed by WHO and its partners to address the information gaps needed to improve the knowledge and control of Buruli ulcer. With the existing tools and necessary financial support, it is possible to quickly develop the capacity and skills of health workers to manage Buruli ulcer patients effectively.

As part of efforts to improve knowledge about the disease among health workers, WHO with the financial support from a Spanish nongovernmental organization, ANESVAD, organized an International Workshop on the Surgical Management of Buruli ulcer in Cotonou, Benin, from 7 to 11 October 2002. This was the first technical meeting bringing participants together from the following endemic countries: Australia, Benin, Burkina Faso, Cameroon, Congo, Côte d'Ivoire, Democratic Republic of the Congo, Gabon, Ghana, Guinea, Kenya, Malawi, Nigeria, Papua New Guinea, Togo, Uganda and Zambia. There were other participants and facilitators from Belgium, France, Japan, the United Kingdom and the USA.

The objectives of the Cotonou workshop were two-fold: 1) to train selected surgeons from endemic countries on standard management of Buruli ulcer patients and thereby pass on their skills to fellow surgeons and general doctors, and 2) to develop national plans for training other health workers in their respective countries.

This draft accelerated capacity development plan takes into consideration the critical issues discussed and recommendations made at the Cotonou workshop, and seek to implement these recommendations. This will intensify training activities in a number of endemic countries [1] in an effort to develop national capacities in diagnosis and treatment of patients using the participants trained in the Cotonou workshop and other national experts. In addition, the plan seeks to develop the practical skills of health workers and equip selected health facilities with the essential surgical equipment to enable trained health workers to apply their practical skills and provide better service.

II. GOAL

To reduce the morbidity and disability caused by Buruli ulcer through improved capacity development of health workers to better manage cases.

III. OBJECTIVES

1. To improve the knowledge and skills of surgeons, doctors and other health workers to enhance early diagnosis and management of Buruli ulcer.
2. To strengthen health facilities in endemic countries to serve as Buruli ulcer training and research centres.
3. To provide essential equipment to health facilities to enhance the management of Buruli ulcer cases.

1V. ACTIVITIES

Objective 1. To improve the knowledge and skills of surgeons, doctors and other health workers to enhance early diagnosis and management of Buruli ulcer

[1] Priority countries (7): Benin, Cameroon, Congo, Côte d'Ivoire, Ghana, Guinea and Togo
Other countries (9): Burkina Faso, Democratic Republic of the Congo, Gabon, Malawi, Nigeria, Papua New Guinea, Sudan, Uganda and Zambia.

Activity 1. National- and regional-levels workshops

Training workshops will be conducted at national and regional levels targeting surgeons and doctors from endemic or at-risk areas of the country with the required level of expertise and responsibilities. The aim is to train a wide range of doctors and surgeons to improve the diagnosis and management of Buruli ulcer. Through these workshops, national and regional resource persons will be identified to help train other health workers. National-level workshops will target selected surgeons and doctors from endemic regions of the country while regional-level workshops will target the district surgeons and doctors.

Activity 2. District-level workshops

District-level workshops will target several groups of providers/people at health, school and community levels.

- **Group 1**: To train or retrain other health workers (medical assistants, nurses, laboratory technicians and disease control officers, etc.) on early case detection, recording and reporting using WHO surveillance forms; basic physiotherapy and referral of cases.
- **Group 2**: To train teachers to teach the disease so as to enhance early detection, and referral of suspected cases to the nearest health facilities;
- **Group 3**: To train community providers, e.g. village volunteers, traditional birth attendants, traditional healers, to enhance awareness and early detection of cases, and to strengthen the community-based surveillance system.

Activity 3. Practical training attachment for surgeons, doctors and other health workers

The aims are:

1. To train interested surgeons and general doctors in **skin grafting** techniques through on-the-job practical attachments.
2. To train other interested health workers (medical assistants, nurses, etc.) on **excision** techniques.

National control programmes in consultation with national experts will develop the criteria for selecting interested and motivated participants to ensure the maximum benefit to the programme and the patients. Participants selected should be in a position to provide sustained service to patients and train others health workers.

Activity 4. Exchange of plastic surgical expertise within and across countries

There are countable numbers of plastic surgeons in endemic countries who are almost all located in tertiary referral hospitals in the cities far from places where the Buruli ulcer occurs. As a result, patients' access to this specialist service is very limited.

Taking this problem into consideration, the Cotonou workshop recommended WHO's assistance in facilitating plastic surgical missions within and across endemic countries in order to extend this service to patients in need closer to their communities. As a result of the Cotonou workshop, a good network of experts has been established which can support endemic countries in creating the necessary capacity.

At the country level, the national control programmes will work out a mechanism to extend specialist services to endemic district hospitals. Such effort has been tried in some countries with success.

At the international level, WHO will seek the collaboration of the network of experts identified through the Cotonou workshop to assist some of the affected countries through short-term surgical missions. Prior arrangements will be made with the national control programmes of the recipient countries including time schedule, selection of hospitals (preferably one of the training centers), selection and preparation of patients, arrangements for consumables, etc. At the same

time, WHO will seek collaboration with plastic surgery associations and nongovernmental organizations that carry out surgical missions to developing countries, such as the International Association of Plastic Surgeons; Interplast; Humanitarian Aid Relief Team (HART) in providing technical assistance through short-term missions to complement national capacities.

Sustainability of such capacity depends on the transfer of technology skills to the local health facilities. With this approach, in addition to providing better care to needy patients, the visiting surgical team (plastic surgeons, anaesthetists, nurses, physiotherapists) could transfer their expertise in the medical/surgical and nursing management to their local counterparts by direct on-site demonstration and lectures. Furthermore, through these missions, promising candidates can be identified for further training. Such capacity can be strengthened with continued support and collaboration of partners.

Objective 2. To strengthen selected health facilities to serve as training centres

National control programmes will identify/select two or three hospitals that regularly treat reasonably large numbers of Buruli ulcer patients and can serve as training centres. The strengths and weaknesses of the proposed centers in surgical management of Buruli ulcer and facilities available to serve as training centres should then be assessed. Where necessary, WHO and its partners will assist these centres to bring them up to the standards expected of training centres. Surgeons, doctors and other health workers needing on-the-job practical training will be posted to these centres for an attachment of 2–4 weeks' duration. For economic reasons, trainees may be sent in sets of teams (e.g. 2–4 trainees per centre depending on facilities available including accommodation). In addition, these centres could also serve as Buruli ulcer training sites for the medical, nursing and allied schools as well as research centres.

Objective 3: To provide essential equipment to health facilities in endemic areas to facilitate the surgical management of Buruli ulcer[1]

Some health facilities have operating theatres but lack the necessary equipment to do skin grafting. The basic equipment required for skin grafting is a **dermatome** and a **skin graft mesher**. The participants at the International Workshop on the Surgical Management of Buruli ulcer, 7 November 2002 Cotonou recommended that WHO facilitates the availability of this set of equipment to countries.

To ensure that the skin grafting skills acquired by trainees during practical on-the-job training are put to immediate use, WHO will seek the collaboration of governments and partners to equip health facilities where the trainees come from once they have completed the practical training. In addition, equipment will be provided to health facilities with skilled staff who are hampered by lack of equipment. Nodulectomy kits will be provided to trainees' health centres once they have completed training in excision of nodules.

[1] To ensure sustainability, WHO advises countries to include the purchase of dermatomes and skin graft meshers in their national Ministries of Health budget. This set of equipment can be used for other patients both within and outside endemic areas.

V. MONITORING AND EVALUATION

Every training activity will be routinely evaluated by participants and facilitators to ensure continuous improvement in the quality of training. WHO experts and other identified experts will monitor and evaluate the quality of these training activities according to the standards set by WHO.

After the practical training, the trainers will visit those trained at least twice in a year to monitor and evaluate their progress. Criteria for such an evaluation will be developed later during the first phase of implementation. The second level of evaluation will focus on assessment of the impact of training programmes in improving management of Buruli ulcer cases and reducing suffering and disabilities.

V. Key indicators

Process indicators

These may include:

- Number of health workers and others trained through national, regional and district workshops
- Number of training centres identified and strengthened
- Number of surgeons/doctors trained through practical attachments
- Number of other health workers trained through practical attachments
- Number of dermatomes, skin graft meshers, and nodulectomy kits provided to countries
- Number of monitoring missions carried out by trainers at country level
- Number of surgical missions conducted/promoted within and between countries, number of doctors trained, and number and types of patients treated during these missions

Impact indicators

These may include:

- Number of early cases detected
- Proportion of nodules compared to ulcerative and other forms of the disease
- Proportion of Buruli ulcer cases managed properly and promptly
- Duration of hospitalization
- Number/proportion of case presenting with disabilities

VI. MANAGEMENT AND COORDINATION

WHO will be responsible for the overall management and coordination of this plan and the respective national control programmes/ministries of health will carry out the actual implementation. WHO country offices will oversee the technical and administrative implementation and report to WHO/Geneva and the regional offices. All partners will be kept informed of the progress of implementation of activities on regular basis.

VII. EXPECTED OUTCOMES

- With this strategy, the knowledge and skills of a large number of health workers to manage Buruli ulcer in a variety of places will be developed. This will enhance early treatment of cases thus reducing the current burden on a few health facilities. Furthermore, this strategy will provide services closer to patients and thus minimize the inconvenience to patients through reduced travelling distances to specialized health facilities.
- The health services will benefit through capacity development and provision of necessary equipment.
- Exchange of plastic surgical expertise within and across countries will be established to further strengthen capacities in affected countries.
- The skin grafting skills acquired will primarily benefit Buruli ulcer patients but will also be useful for treating other skin defects such as loss of skin due to burns and trauma.
- Finally, the increased knowledge gained by health workers would lead to a better recognition, documentation and reporting of Buruli ulcer. The true magnitude and relative importance of Buruli ulcer would eventually be established to attract the necessary attention and support.

VIII. AVAILABLE TRAINING MATERIALS

1. Diagnosis of *Mycobacterium ulcerans* disease (English and French) (2001)
2. Management of *Mycobacterium ulcerans* disease (English and French) (2001)
3. Buruli ulcer comic (English and French) (2001)
4. Ulcère de Buruli - Infection à *Mycobacterium ulcerans* (2000)
5. Buruli ulcer - *Mycobacterium ulcerans* infection(English, French and Spanish)
6. Diagnostic Guide (Published by Institute of Tropical Medicine, Antwerp, Belgium)
7. Posters
8. Leaflets
9. WHO Surveillance forms - BU 01 and 02

Appendix 1. Potential partners

Partners of this proposal would include but not limited to:

1. National control programmes/ministries of health of countries above

2. Nongovernmental organizations involved in Buruli ulcer control activities:
- Aide aux Lépreux Emmaüs-Suisse (ALES), Case postale 5252, 3001 Berne, Switzerland
- American Leprosy Missions (ALM), 1 ALM Way, Greenville SC 29601, USA
- ANESVAD, Teófilo Guiard, 2, 48001 Bilbao Spain;
- Association Française Raoul Follereau (AFRF), Association Française Raoul Follereau 31 rue de Dantzig BP 79, F-75722 Paris Cedex 15, France
- Associazione Italiana Amici di Raoul Follereau (AIFO), 4 via Borseli, 40135 Bologna, Italy
- Catriona Hargreaves Charitiable Trust (CHCT), Park Cottage, Teston, Maidstone, Kent ME18 5AY, England
- Fondation Luxembourgeoise Raoul Follereau (FFL), 151, avenue du 10 Septembre 2551, Luxembourg
- Humanitarian Aid Relief Team (HART), 3650 N. University Ave., Suite 200, Provo, UT 84604, USA
- Interplast, Centre des Brûlés 1 rue Laborde 69500 Lyon/Bron, France
- Médecins sans Frontières (MSF) - Suisse, 12, rue du Lac, Case postale 6090, 1211 Geneva 6, Switzerland
- Médecins Sans Frontières (MSF), 70, route de Luxembourg L7240 Bereldange, Luxembourg
- MAP International, West Africa Office, Immueble de la Ligue 23 Ave. Jean Mermoz, Cocody, 01 B.P. 1658, Abidjan 01, Côte d'Ivoire
- Sasakawa Memorial Health Foundation (SMHF), Nippon Zaidan Building, 1-2-2 Akasaka, Minatoku, Tokyo 107-0052, Japan
- The Nippon Foundation (TNF), Nippon Zaidan Building, 1-2-2 Akasaka, Minatoku, Tokyo 107-0052, Japan

3. Medical, academic and research institutions

4. Volunteer plastic surgeons, physiotherapists and other health workers

5. World Health Organization