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REPORT

**3rd WHO Advisory Group Meeting
on Buruli ulcer**

**1–3 March 2000
WHO Headquarters, Geneva**

CONTENT

<u>INTRODUCTION</u>	4
<u>RECOMMENDATIONS</u>	
Group 1: Research priority areas	7
Group 2: Surveillance, surveys and estimation of disease burden	8
Group 3: Drug treatment	12
Group 4: Training	14
<u>ABSTRACTS</u>	
GBUI : History of an initiative <i>Dr Mario Raviglione</i>	16
GBUI : Plan of work for 2000 <i>Dr Kingsley Asiedu</i>	18
Buruli ulcer control efforts in the African Region <i>Dr Eugene Nyarko</i>	19
Discussion paper, clinical manifestations of <i>Mycobacterium ulcerans</i> infection <i>Dr John Hayman</i>	22
Summary activities carried out in 1999 for Buruli ulcer control in Benin <i>Dr Augustin Guédénon</i>	24
Monitoring report from Benin <i>Dr Augustin Guédénon</i>	28
Situation of Buruli ulcer control in Côte d'Ivoire <i>Prof. Jean-Marie Kanga, Dr Djatch Edgard Kacou</i>	31
Early detection and treatment of Buruli ulcer <i>Prof. Jean-Marie Kanga</i>	33
<i>Mycobacterium ulcerans</i> infection in French Guyana, the situation at 19 february 2000 <i>Dr Roger Pradinaud</i>	37
Update on Buruli ulcer situation in Ghana <i>Dr George K. Amofah</i>	39

<i>Mycobacterium ulcerans</i> in Papua New Guinea <i>Sister Joseph</i>	47
Report from Togo <i>Drs Napo Tignokpa and Battista G. Priuli</i>	50
Update on research report from Australia <i>Dr Paul Johnson , Dr Tim Stinear, Dr Travis Gooding, Mrs May Smith, Dr John Hayman, Dr John Davies, Dr Andrew Kemp, Dr Roy Robins- Browne, Ms Frances Oppedisano, Dr Diane Campbell et al.</i>	52
Progress report on experimental chemotherapy of <i>Mycobacterium ulcerans</i> infection in the mouse model <i>Prof. Jacques Grosset, Hervé Dega, Nacer Lounis and Abdelhalim Bentoucha</i>	55
Update on research work form the Rocky Mountain Laboratory, Hamilton, Montana, USA <i>Dr Pamela Small</i>	59
Role of Centers for Disease Control and Prevention, Atlanta, USA <i>Dr Jordan Tappero</i>	61
Serodiagnosis of Buruli ulcer disease <i>Dr C. Harold King</i>	62
Buruli ulcer (<i>Mycobacterium ulcerans</i> infection) <i>Dr Wayne Meyers, Sister Julia Aguiar, Prof. Françoise Portaels</i>	64
Gamma interferon response to stimulation with <i>M. ulcerans</i> antigen preparations of peripheral blood T cells from patients with <i>M. ulcerans</i> disease <i>Drs Harry Thangaraj, Mark Evans, Richard Phillips, Mr Joseph Adomako, Mr Nasas Ofosu-Kwabi, Prof. Ohene Adjei and Dr Mark Wansbrough-Jones</i>	74
Conceptual problems in estimating the burden of Buruli ulcer <i>Mr Frank Dadzie</i>	75
Message from Professor Asano, Chancellor, Nippon Medical School, Tokyo, Japan, to the 3rd annual meeting of the WHO advisory group on Buruli ulcer <i>Dr Mwanatambwe Milanga</i>	85
Role of Noguchi Memorial Institute for Medical Research, Accra, Ghana <i>Prof. David Ofori-Adjei</i>	87
Sasakawa Memorial Health Foundation, Tokyo, Japan <i>Mrs Kay Yamaguchi</i>	89

Case management of patients at the specialized center in Lalo, Mono department, Benin, Médecins sans Frontières Luxembourg’s activities in Benin	
<i>Drs Antoinette Kapinga, Pierre Humblet, and Christian Johnson</i>	92
Contribution of the Kobe International University, Making of a new option to the Worldwide Movement for the Children of Buruli Ulcer: a case of Kobe International University	
<i>Prof. Yuki Shimomura</i>	98
Social mobilisation for Buruli ulcer	
<i>Dr Elil Renganathan</i>	101
<u>ANNEXES</u>	
Annex 1: Agenda	105
Annex 2: List of participants	108

INTRODUCTION

Background

Mycobacterium ulcerans infection (Buruli ulcer) has rapidly emerged as an important cause of human morbidity around the world. The following countries have reported or suspected cases to date: **Africa:** Angola, Benin, Burkina Faso, Cameroon, Congo, Côte d'Ivoire, Democratic Republic of Congo, Equatorial Guinea, Gabon, Ghana, Guinea, Liberia, Nigeria, Sierra Leone, Togo, Uganda, Sudan; **Americas:** Bolivia, French Guiana, Mexico, Peru, Suriname **Asia:** China, India, Indonesia, Malaysia, Sumatra and **Western Pacific:** Australia, Kiribati, Papua New Guinea.

Buruli ulcer is the third most common mycobacterial disease of non-immuno-compromised persons after tuberculosis and leprosy. The mode of transmission is not known. The disease generally affects impoverished inhabitants of remote rural areas with limited access to modern medical care. Most patients present late to the health services. About 70% of those affected are children under the age of 15 years. Buruli ulcer often starts as a painless nodule, which if left untreated, frequently leads to massive skin ulceration followed by debilitating complications. Currently, surgery is the treatment of choice but there are several limiting factors including: 1) inadequate surgical facilities in rural areas in the developing world; 2) high treatment costs; 3) recurrences after surgical treatment; and 4) the risk of transmission of infections such as HIV during surgery. Unfortunately, treatment with antibiotics has thus far been disappointing. The current social and economic burden imposed by Buruli ulcer on patients, their families and the health services is considerable.

In response to the growing spread and impact of Buruli ulcer, the World Health Organization (WHO) in 1998 established the Global Buruli Ulcer Initiative (GBUI) with the aims of raising awareness about this disease, mobilizing support to assist affected countries to deal with the disease, promoting and coordinating research, and coordinating the work of nongovernmental organizations (NGOs) and other partners. In February 1998, the first meeting of the Task Force (now called Advisory Group) consisting of some selected members was held in Geneva. A full membership of the Advisory Group has now been established consisting of 16 people whose expertise covers clinical and surgical intervention, epidemiology and research. The second meeting of this group was held in March 1999 in Geneva.

Objectives of the meeting

1. To define the research agenda for Buruli ulcer;
2. To define modalities for surveillance, surveys and estimation of the burden of the disease;
3. To define modalities for the use of drugs for the prevention of recurrences; and
4. To define training needs for Buruli ulcer.

Expected outcome

Recommendations to guide WHO's work on Buruli ulcer in the areas outlined in the objectives.

Welcome remarks

Dr David Heymann, Executive Director, Communicable Diseases welcomed and thanked all participants for attending the meeting. He presented an update on the reorganization at the WHO. The Buruli ulcer activity is now under the Department of communicable Disease Prevention and Control. He reiterated WHO's commitment to the Buruli Ulcer Initiative. He thanked The Nippon Foundation for providing financial support to the Initiative since its establishment in 1998 and also for the recent commitment to provide funds to cover Buruli ulcer activities up to 2002. He also thanked other partners who have joined the efforts to deal with the Buruli ulcer as a public health problem.

Dr Heymann emphasized the importance of obtaining the epidemiological and economic data needed to justify the efforts we are all putting into the disease. He stressed the need to find drug treatment for the disease given the problems associated with surgical treatment. In his concluding remarks, he was optimistic that the meeting will yield the recommendations needed to accelerate global efforts to fight the disease and wished the participants a successful meeting.

Dr Maria Neira, Director of the Department of Communicable Diseases Prevention and Control presented an overview of the Department's activities. She stressed the need to integrate some of the activities of various disease control activities. Through such collaborations, more can be achieved with the same resources. Dr Neira officially launched the WHO monograph on Buruli ulcer.

RECOMMENDATIONS

Group 1 – Research priority areas

1. **Establish a Web Page:** Global Buruli ulcer site (moderator: *Kingsley Asiedu*)

Purpose:

- encourage collaboration
- names
- list of current projects
- link with: 1. the Institute of Tropical Medicine, Antwerp
2. list of publications (Medline)
Newsletter (*John Hayman*)

2. **Genome sequencing**

Sanger center/St George's Hospital,
Welcome Trust/WHO (*Jacques Grosset & Mark Wansbrough-Jones*)

3. **Reference culture collection**

All cultures to be sent to Institute of Tropical Medicine, Antwerp, Belgium
(*Françoise Portaels*)

4. **Tissue repository** at AFIP, Washington DC, USA (*Wayne Meyers*)

5. **Establishment of collaborating centres to support research and training** (*WHO*)

6. **Artificial ecosystems** (*different centres*)

7. **Human response to infection**

Serological response—serum bank (*Harold King*)
Cell mediated response
Vaccine development: avirulent live vaccine

8. **Gene expression library**

9. **Development of finger-printing system** (based on PCR, as in TB) HLA susceptibility

10. **Identification of new foci**

Laboratory diagnostic facilities
Publicity

11. **Field work**

Behaviour modification
Anthropology studies
Serial BCG therapy/prophylaxis

12. **Historical collection:** Original papers, photographs, correspondence, X-rays, etc. (*WHO*)

Group 2 – Surveillance, surveys and estimation of disease burden

Objectives of surveillance

The working group discussed several valid objectives for surveillance of Buruli ulcer (BU) disease.

1. Monitor the number of cases of BU seen at health centers and hospitals that can diagnose and/or treat the disease.
2. Monitor improvement in the delay between disease onset and appropriate treatment.
3. Monitor changes in the prevalence (and in highly prevalent areas, the incidence) of BU disease.

Case definitions

Descriptive case definitions reflecting various presentations of the disease: papule, nodule, plaque, oedema or ulcer are outlined in the WHO monograph on BU disease (WHO/CDS/CPE/GBUI/2000.1). It has been shown that these definitions are useful for health care providers working in geographic areas of moderate to high prevalence for BU disease.

Types of surveillance and data collection

1. **Passive surveillance** (See Table 1 below).

1. Health Center and Referral Hospital Surveillance

The working group supported use of up to two forms at the Health Center (BU 02) and Hospital (BU 01 and BU 02). Forms BU 03 and BU 06 on pages 102 –103 of the monograph (not discussed) should be used at the national level for reporting aggregated data.

- A. BU 02 form (**Annex 1**) is a line of list of patients, with name, age, sex, address, and clinical form of disease. It would be completed by the most logical hospital personnel (e.g., records or disease control officer). Patients would be added to this list upon admission. At the end of the month, the records or disease control officer would report to the district health administration, either by sending the BU 02 directly, or by making a copy of the cases identified that month and forwarding it to the district health administration. The later method would allow the original BU 02 form to remain at the facility as a formal BU registry.

The group therefore recommended the use of BU 02 as a district register. It should be adapted to serve the needs of health center and community levels (see attached revised BU 02 for these levels).

B. *The working group also recommended the following alterations to form BU 02 for use in the hospital:*

- *Disability data field be dropped or if retained, clarify significantly*
- *Diagnostic confirmation data field be dropped¹*
- *Remarks: be dropped, or if retained, clarify as referral or specify therapy received locally.*

C. Selected hospital surveillance (sentinel surveillance): Admittedly, it captures only a selection of patients, those who require care at a referral center AND who follow-through with the referral. For this subset of patients, detailed outcome data can be provided for specialty studies, e.g., economic analyses. Unfortunately, sentinel surveillance does not provide outcome data for patients who are treated with basic wound management, and those who are referred but, for whatever reason, do not make it to the referral center.

The BU 01 form, completed by all selected hospital personnel, provides additional information beyond that collected on form BU 02, including for example, potential risk factors for infection, treatment and outcome. BU 01 would be completed at only selected referral hospitals for BU disease. The BU 01 form is to be retained in the patients folders and out of which the information needed for BU 02 and BU 06 would be derived on a monthly and quarterly basis respectively. The district records or communicable diseases officer could make use the BU 02 forms received monthly as a line list, to ensure that follow-up outcome information for these patients is obtained upon discharge.

The BU 01 form should also have some corrections/modifications.

- *First, some of the potential epidemiological risk factor variables (source of drinking water, cases among family members)² could be dropped. These factors would better be addressed through special studies, such as case-control studies to identify modifiable risk factors.*
- *The disability present upon presentation variable should be properly defined.³*
- *Confirmation of diagnosis section be revised to reflect the following: test done and if so, the results (positive or negative) or not done.*

¹ Experience from a visit the field (Ghana) from 5–12 March 2000 showed that the confirmation of diagnosis column on BU 02 was useful and has therefore been retained (see the attached revised form). Remarks column on the original BU 02 form has been deleted accordingly.

² Source of drinking water and cases in families are intended to allow observations to be made by health workers so that a more detailed studies/follow-up could be done if these observations point to such a need.

³ Disability is defined as any restriction or lack (resulting from impairment) of ability to perform an activity in the manner or within the range considered normal for a human being (*Disability prevention and rehabilitation in primary health care. WHO/RHB/95.1*). Disability present upon presentation therefore refers to any functional impairment/deformities (limited range of motion due to contractures or destruction of organs such as the eye, ear etc) when the patient presents with an active disease. This indicator reflects how late patients are presenting to the health facilities. In literal sense, disability present upon presentation may be a precursor for a sequel outcome depending on factors such as technical competence at the treatment center and available resources.

2. Active surveillance

Active, ongoing surveillance should not be initiated without first establishing areas of highly prevalence disease. In these areas, health care workers who know their populations best, could be used to complete form BU 01 and BU 02 on a timely basis. As for passive surveillance systems, good population census data will be required to provide accurate rates. This activity should not be initiated without a minimum time commitment (e.g., 5 years).

Global Information Systems (GIS)

Twenty-four orbiting satellites provide information for detailed mapping of planet earth. These maps, have been shown to be useful for evaluating environmental factors influencing several infectious diseases (climate, rain, vegetation, etc.). Because it has been hypothesized that the emergence of BU disease in West Africa is a direct consequence of human manipulation of the environment, tracking Geographical Information System mapping simultaneously with active surveillance efforts could provide great insight in to the factors affecting the emergence of this disease.

Laboratory back-up

An international network of laboratories for *M .ulcerans* infection was provided. These laboratories, one each per continent will need to have financial support to provide diagnostic services (e.g., histopathology, culture, PCR) for additional cases identified through expanded passive or active surveillance activities. Four of the six laboratories are already doing some work or planned to do some work on the disease and it is recommended that two centers are identified serve Asia and South American regions. The four are the Armed Forces Institute of Pathology (AFIP), Washington DC, USA (North America); Institute of Tropical Medicine (ITM), Antwerp, Belgium (Europe); Noguchi Memorial Institute for Medical Research (NMIMR), Accra, Ghana (Africa) and the Victorian Infectious Diseases Reference Laboratory (VIDRL), Melbourne, Australia (Western Pacific region).

WHO should officially contact these centers on this issue and assist them to secure the necessary funding to carry out these activities.

Surveys

In the absence of surveillance data, or to enhance surveillance data, two types of surveys were discussed, 1) rapid assessments in areas where BU is likely to be present but has not been, or has been only sporadically reported, and 2) well planned cross-sectional surveys at the district or national level. The former would be inexpensive, but would not provide prevalence data. The later survey would provide prevalence data, but would be costly. The Ministry of Health at the national level, should be responsible for conducting these surveys.

To assist endemic countries, WHO should provide a document, detailing the methods to be used for conducting both types of surveys.

Economic aspects of Buruli ulcer

More work on the economic aspects of Buruli ulcer is needed in order provide a better understanding of the economic dimensions of the disease.

WHO should identify interested individuals and institutions to carry out this work.

Table 1. WHO Surveillance strategies and forms for surveillance

Where	Who	Action	Form
Community/ village	Community/village health worker	Referral	Local Register (adapted form of BU 02) Monthly submission to health center
Health center	Health officer or nurse	Local wound care or referral	BU 02 Monthly submission to the district health administration
Selected referral hospitals	Physician/Surgeon or Nurse	Surgical treatment	Collection, collation of BU 01 and BU 02 forms Monthly submission of BU 02 and quarterly submission of BU 03 and BU 06 to the district health administration
District health administration	MOH	Reporting to regional level	BU 02 Monthly submission BU 03 and BU 06 quarterly submission.
Regional health administration	MOH	Reporting to national level	BU 02 Monthly submission
National programme	MOH	Reporting to international level e.g. WHO	Annually using BU 03 and BU 06 quarterly submission

Group 3 – Drug Treatment

Rationale

There are three different potential ways that drugs could be used in managing *Mycobacterium ulcerans* disease:

- Preventive therapy (unlikely??)*
- In the management of small early lesions
- Adjuvant therapy to prevent recurrences after surgical treatment after surgical intervention with the aim of shortening hospital stay, lowering morbidity and preventing recurrent disease.

**Use of antibiotics for prevention would depend on mode of transmission and time of exposure. Very little information, if any is available to assess this at this time.*

If antibiotics can be shown to be effective in humans as in the animal models, there is a potential role for their use as primary therapy.

Review of evidence

A number of antibiotics have been shown to have activity against *M. ulcerans* in vitro: these include rifampicin, aminoglycosides, fluoroquinolones, macrolides, minocycline.

In the mouse foot pad model of infection, rifampicin and aminoglycosides appear to have bactericidal activity with sustained reduction of viable organisms. In contrast, other antibiotics which are active *in vitro* have bacteriostatic effect.

During treatment with rifampicin and amikacin there was also a reduction of swelling associated with infection.

Further laboratory evidence needed

- Further work is needed to establish the role of combination or monotherapy in the emergence of mycobacterial resistance.
- At present it is not known what is the optimal duration of drug therapy to prevent recurrences; further work is therefore needed to gain a better understanding of duration of therapy.

Given the current preclinical evidence, work is needed to resolve the following questions in humans:

1. Do drugs penetrate into affected tissues?
2. Do drugs kill mycobacteria in these lesions?
3. Is there a clinical response?

Proposed design for clinical trial

In order to answer these questions it is proposed that patients with early lesions will be treated with a combination of rifamycins and aminoglycosides for different periods of time (**Fig. 2**). One group of patients will have nodules excised at baseline without antibiotic therapy. Other groups will start treatment with antibiotics and lesions will be excised after increasing periods of treatment, up to 12 weeks. The excised tissue will be examined for viable organisms. Possible assessments would include mycobacterial counts, cultures and surrogate markers such as mRNA. The completeness of excision will be checked by histopathology. The clinical response at the time of excision will be noted. The timing of excision with relation to the last dose of antibiotic administration prior to surgery will be standardized.

If drug treatment is found to be effective, the essential role of surgery in *Mycobacterium ulcerans* infections will need to be reconsidered. It will be imperative to initiate a search for long acting and non injectable antibiotics to facilitate disease control in the field.

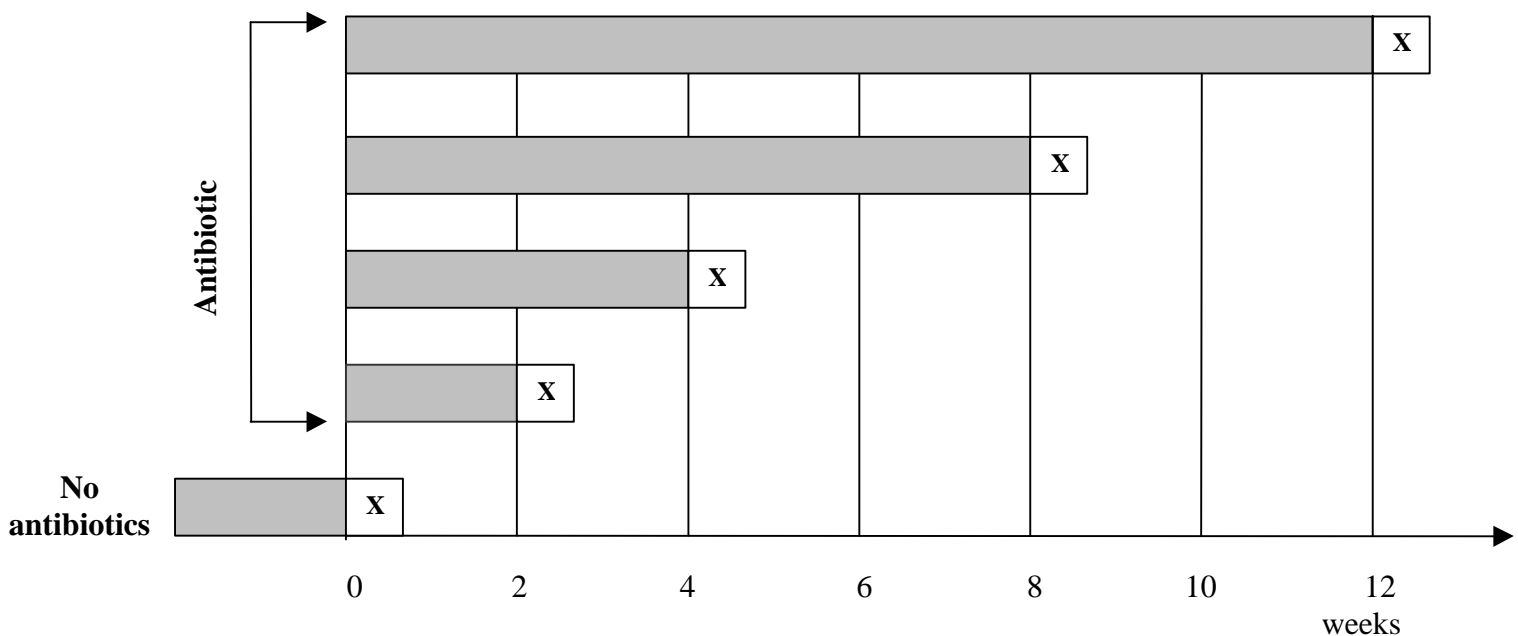
A detailed protocol will need to be designed (*action: Professor Jacques Grosset and Dr Mark Wansbrough-Jones are to develop a draft protocol by end of April 2000*).

The following points should be considered in the design:

- need for establishing initial diagnosis;
- number of patients in each group;
- time interval from last dose of antibiotic to excision;
- duration of antibiotic therapy prior to excision for each group;
- inclusion criteria, i.e. types of lesions, age of patients, etc.;
- define method of evaluation of lesions, e.g. photographs, measurement, etc.

The protocol will provide guidance for management of patients in the event of clinical deterioration or side effects.

Figure 2. Proposed design of a clinical trial.



X = Excision of lesion

Group 4 – Training

1. All documents relating to training and dissemination of information in connection with Buruli ulcer control be continually channel to WHO Headquarters so that an inventory of such documents could be created/maintained (*all partners*).
2. Prepare the following training modules (*action WHO*):
 - Community module (adapted to each situation)
 - Paramedical module
 - Basic medical module
 - University module
 - Global information module
 - Surgeons: describe and standardize surgical treatment and techniques and the minimum equipment required for effective case management at the different levels
3. Draw up the different flow charts for BU case management to establish a proper referral system (in each country, taking into account its health structure).
WHO should develop a generic chart to be adapted by endemic countries.
4. Disseminate these documents as widely as possible in the countries and centres concerned, through the local WHO Offices and also to make them available on the Internet and introduce them into an outreach network. (*action WHO*)
5. Involve all public and private agencies capable of participating in Buruli ulcer control in the national programmes and foster dialogue at the country and regional levels.
6. Integrate the Buruli ulcer control programmes into existing similar programmes, provided their suitability and efficacy have been recognized.
7. Develop a comprehensive strategy for training, social mobilization and advocacy (*action WHO*).

**ABSTRACTS PRESENTED
AT THE MEETING**

GBUI: History of an Initiative

Dr Mario Raviglione, Strategy Development and Monitoring for Endemic Bacterial and Viral Diseases, Communicable Diseases Control, Prevention and Eradication, WHO Headquarters, Geneva, Switzerland

January 1998	Establishment of the Global Buruli Ulcer Initiative (GBUI)
1998	Establishment of a 16-member Advisory Group Establishment of a scientific working group called IMuST
February 1998	First meeting of the Advisory Group in Geneva
March to June 1998	Situational analysis in selected countries in West Africa (Benin, Côte d'Ivoire, Ghana and Togo)
July 1998	First International Conference on Buruli ulcer in Yamoussoukro Côte d'Ivoire resulting in the adoption of the <i>Yamoussoukro Declaration on Buruli Ulcer</i>
March 1999	Second Advisory Group meeting in Geneva
June 1999	Workshop to develop a strategic framework for control of Buruli ulcer
October 1999	A meeting to develop a subregional action plan for control in West Africa in Abidjan, Côte d'Ivoire
Mid/late 1999	Implementation of pilot projects in Côte d'Ivoire and Ghana
February 1999	The first monograph on Buruli ulcer, which outlines the current knowledge on the disease
March 2000	Third Advisory Group meeting on Buruli ulcer

WHO Strategy of the GBUI

1. Coordinate development of a technical strategy to control BU; at the moment, early detection through community-based surveillance and immediate referral for surgery
2. Coordinate and prioritize research efforts
3. Advocacy to obtain financial resources from donors
4. Facilitate NGOs' work in countries

Rationale and objectives of the meeting

1. To define the research agenda for Buruli ulcer
2. To define strategies for effective control, modalities for surveillance, surveys and estimation of the burden of the disease
3. To define modalities for the use of drugs for the prevention of recurrences
4. To define social mobilization, advocacy and training needs for Buruli ulcer

Expected outcome

A WHO strategic framework document and a 5-year plan of work on Buruli ulcer in the following areas:

1. Research priorities
2. Control strategies, modalities for surveillance, surveys and estimation of disease burden
3. Drug treatment
4. Social mobilization, advocacy and training

GBUI plan of work for 2000

Dr Kingsley Asiedu, Global Buruli Ulcer Initiative, Communicable Diseases Control, Prevention and Eradication, WHO Headquarters, Geneva, Switzerland

WHO core activities

- Annual meeting of the Advisory Group, March 2000
- Monitoring visits to 5 selected countries (Benin, Côte d'Ivoire, Ghana, Togo and Guinea)
- Reprinting and distribution of existing IEC materials
- Global Advocacy

Support to WHO Regional Office for Africa

Monitoring visits to 5 selected endemic countries (Benin, Côte d'Ivoire, Ghana, Togo and Guinea)

General assistance to selected endemic countries

- Development of generic training materials (English & French)
- Field testing of generic training materials in Benin, Côte d'Ivoire and Ghana
- Printing of generic copies of training materials (to be adapted in the countries)

Benin

- Adaptation and printing of generic training materials
- Training of selected health workers on the management of Buruli ulcer
- Support to two ongoing pilot projects

Côte d'Ivoire

- Adaptation and printing of generic training materials
- Training of selected health workers on the management of Buruli ulcer
- Support to two ongoing pilot projects
- One cross-country vehicle for Kongouanou Health Centre
- Training of selected health workers on the management of Buruli ulcer

Guinea

Review results of recent surveys

Togo

Support surveys to determine the extent of Buruli ulcer

Research

- Collaborative research on the toxin between the Institute of Tropical Medicine, Antwerp, Belgium and Rocky Mountain Laboratory, Hamilton, Montana.
- Support laboratory studies on drug treatment of Buruli ulcer disease.

Buruli ulcer control efforts in the African Region

Dr Eugene Nyarko, Regional Office for Africa, WHO, Harare, Zimbabwe

Chronology of events:

- Late 1997**
- Recognition of magnitude of problem by senior management
- Early 1998**
- Appointment of Regional Focal point
 - Collaboration with HQ in development of surveillance tools
 - International conference & Yamoussoukro Declaration
- 1998**
- Sensitization of Member States about disease to mount up surveillance
 - Development of policy guidelines
 - Development of 5-year Strategic Plan; focus:
 - national program development
 - surveillance
 - operational research (epidemiology & case management - clinical trials)
- 1999**
- Financial support: regular budget allocation for activities (approx. US\$60,000)
 - Identification of a collaborating centre
 - Development of framework for designing a public health intervention strategy
 - Support to assessment of disease burden in one country
 - Field-testing of surveillance tools
- 2000**
- Development of training modules for national programs; focus on district level (in progress)
 - Capacity building at country level: e.g.
 - training of trainers
 - National Program support
 - program development & implementation
 - program monitoring
 - Advocacy & resource mobilization
 - Support operational research (priorities identified)

Highlights of the Framework for control strategy development:

Goal: reduce morbidity & disability

Objectives:

- early detection & early treatment
- standardized guidelines for appropriate care
- provision of appropriate rehabilitation services
- promotion of relevant research (epidemiology, case management & prevention)

Components of Control Strategy:

- Case finding methods: (using standardized case definitions)
- Case management methods (active & inactive disease), algorithms for district level
- Monitoring & evaluation methods
- Training program
- Research priorities & agenda
- Advocacy & resource mobilization strategy (appropriate tool development, etc.)

Training Modules – components

- Disease background:
 - epidemiology, pathogenesis
- Assessment of disease burden:
 - methodological principles
 - surveys data analysis & interpretation
 - application of survey results
- Case Finding
 - methods & practical application
 - resource requirements at different levels of care
 - integration into existing health services
- Case management
 - diagnostic methods & application
 - management of active & inactive disease
 - resource requirement at different levels of care
 - practical ways to incorporate into existing health services
- Monitoring & evaluation
 - treatment monitoring
 - recording & reporting (case-based, summary data etc.)
 - indicators
 - practical ways to incorporate into existing system
 - program evaluation

- Advocacy & resource mobilization
 - principles & practical application
 - essentials of project proposals
- Facilitator Guides - for each module
- Next steps:
 - finalization of framework & training modules
 - field-testing of training modules
 - submission of regional strategy to Regional Committee for approval (RC51)

Discussion paper, clinical manifestations of *Mycobacterium ulcerans* infection

Dr John Hayman, Department of Pathology, Box Hill Hospital, Melbourne, Australia

Clinical manifestations of *Mycobacterium ulcerans* infection have already been considered by the Advisory Group but these may need review, correlation with pathology findings and further publicity and publication so that clinicians may be aware of the diverse presentations of this disease. It is apparent that the common initial manifestations of the disease may be different in different regions. The following classification and staging is proposed:

Initial clinical manifestation	Pathology
Papule	disease confined to skin and deep dermis
Nodule	localized disease in subcutaneous fat
Papulo-nodular lesion	nodule in subcutaneous fat with overlying skin involvement
Plaque	disease in subcutaneous fat with skin edema, fatty septa preserved
Edematous acute	diffuse necrotic disease in subcutaneous fat, with pain and systemic symptoms (fever).
Edematous chronic	diffuse necrotic disease in subcutaneous fat, without pain or systemic symptoms.
Post-traumatic Infection	open wound closed wound (subcutaneous bruising)
Mixed forms	
Atypical presentations	

Staging of the disease		Pathology
Stage 0		latent infection, no clinical manifestations
Stage 1		preulcerative infection (as per initial clinical manifestations)
Stage 2		necrotic, ulcerative infection
	Stage 2A	small, discrete ulcer, easily excised with skin closure
	Stage 2B	large ulcer required staged excision, grafting
	Stage 2C	disseminated, metastatic infection infection of other tissues (joint, eye)
Stage 3		granulomatous, healing infection
Stage 4		fibrosis, scarring, calcification

Summary of activities carried out in 1999 for Buruli ulcer control in Benin

By Dr Augustin Guédénou, National Buruli Ulcer Control Programme, Ministry of Health, Cotonou, Benin

Introduction

The Republic of Benin is situated in the south-eastern part of West Africa, bordered by Nigeria to the east, Togo to the west, Burkina Faso and Niger to the north and the Atlantic Ocean to the south.

It has a land area of 112 622 km² and in 1999 the population was six million. It is subdivided into 12 regions, 77 districts, 517 towns and 3 400 villages. The pattern of disease is varied, and dominated by endemic and epidemic conditions including Buruli ulcer.

Buruli ulcer is considered a worrying health problem in Benin. It is endemic in six of the 12 regions.

There is a political commitment at the highest level. This was reflected in 1997 by the preparation and implementation of a national control programme to control the disease. The programme provides for the creation in each endemic region of a specialist structure for the management of Buruli ulcer. The activities carried out are as follows:

Case detection

This has been entirely passive and was conducted by the three centres listed in Table 1.

Table 1: Case detection

Centre	New cases	Recurrences	Total cases
CSNG ⁴	385	9	394
CS/SP Lalo ⁵	86	3	89
Hôpital de Zinvié*	96	5	101
Total	567	17	584

The recurrence rate based on passive detection at the health facility is 2% at Zagnanado CSNG, 3% at the Lalo CS/SP, and 5% at Zinvié. The true recurrence rate may be higher because in the event of recurrence, patients change their treatment

⁴ Gbémontin Health and Nutrition Centre, Zagnanado

⁵ Lalo Sub-prefecture Health Centre

* The cases at Zinvié were seen from 1995 to 1999 but notified for the first time in 1999.

centre or type of treatment. In order to determine the true recurrence rate it would be helpful to follow up the patients who have been cured.

The cumulative total of cases recorded from 1988 to 1999 is 3,159 cases, well below the true figure because there has been no nationwide prevalence survey. Our surveys have been confined to a few districts.

Confirmation of the diagnosis

The diagnosis was made by ZN staining technique, by culture, by histopathology or by PCR. The diagnosis was confirmed in only 171 of the 288 patients from whom samples were taken. It is at present impossible to take samples from all patients, so it is important to have a criterion of clinical diagnosis.

Case management

This primarily concerns cases in the course of development; there is very little case management of the disabling sequelae. Table 2 shows how case management is organized in Benin.

Table 2: Organization of case management of Buruli ulcer in Benin

	Institution	General structure	BU structure	Activities
Village	Health Area	Village health unit	Town	Case finding
Towns		Town health complex	Team	
Districts		District health centre Area hospital	Detection and Treatment Center/UB	Case finding and treatment
Region	Regional Public Health Directorate	Regional Hospital	Health Protection and Promotion Unit	Supervision
National	Ministry of Public Health	National Teaching Hospital	Coord/BU	Management, supervision, evaluation

The management of Buruli ulcer in Benin is carried out at all levels of the health pyramid. Case-finding and the follow up of cured patients are the task of the nurses of the town health complexes, district health centres and of the community health workers. Treatment is provided by a health team corresponding in level to the area hospital within the health pyramid. The regional level is responsible for supervision, while the national coordinating body is responsible for programme management and staff supervision.

These activities are not yet well organized, as the organizational arrangements are not yet fully in place. The information systems currently available cannot address all the questions arising.

Evaluation (assessment)

A rapid evaluation of the programme was made by Dr Kingsley Asiedu in June 1999. The evaluation showed the need for training of health and welfare personnel.

Staff training

In 1999, the NGO “Médecins Sans Frontières (MSF) – Luxembourg” trained 36 community agents. This training enabled it to set up town teams for the detection and follow-up of Buruli ulcer cases. The teams are highly effective.

Moreover, the programme collaborated in the preparation of an educational handbook and a strip cartoon and in a survey on the representation of the population.

Operational research

The programme collaborated in the research programmes developed by the Antwerp Institute of Tropical Medicine (ITM) and by the National University of Benin. It has done work on the environment, the HLA system and the search for other risk factors.

Mobilization of resources

The programme is continuing negotiations with its partners, the Association Française Raoul Follereau (AFRF) and the Foundation Follereau Luxembourg (FFL). A proposal for funding has been submitted to the European Union.

Difficulties encountered

1. Confirmation of the diagnosis of Buruli ulcer is now performed free of charge by research institutes. However, the samples need to be transported to those institutes. Consequently, it is not possible at present to take samples routinely from all patients. It is therefore important to have available a criterion of confirmation of clinical diagnosis. Work on this task has started at ITM.
2. The true recurrence rate for BU cases is not known. The rate varies from 2% to 5% at the health units and may be higher in reality. There is a need for each specialist centre to set up arrangements for the follow-up of cured patients.
3. The nutritional management of hospitalized patients remains a matter of concern for the programme. The Government recently instructed the Finance Ministry to find a definitive solution to this problem.
4. Increasingly severe forms of BU that do not respond to surgery are being encountered. It is therefore important to find drugs that are effective against *M. ulcerans*.

Prospects for the year 2000

The major concern of the programme is to continue the efforts to set up structures for BU case management. The framework document drafted in 1997 expired in 1999. It is necessary to conduct an evaluation of the programme and to undertake reprogramming for the next five years.

The “La Croix” Hospital in Zinvié deserves encouragement and support in its efforts for the case management of Buruli ulcer.

Monitoring report from Benin

Dr Augustin Guédénon, National Buruli ulcer Control Programme, Ministry of Health, Cotonou, Benin

Context

- December 1998 – Launch of the National Buruli Ulcer Control Plan (PNLUB)
- Case detection and management provided by 3 health facilities
- No active case detection in 1999
- Monitoring provided by Drs:
 - Augustin Guédénon
 - Roch-Christian Johnson
 - Franck Gandji and
 - Honoré Emapí

Objectives

- To test the WHO forms
- To make an assessment of 1999 activities

Results

Notification of new cases and recurrences

Table 1: New cases and recurrences at CSNG

	< 15 years		15–49 years		> 49 years		Total	
	H	F	H	F	H	F	H	F
New cases	96	72	66	84	45	31	207	187
Recurrence	0	4	1	2	1	1	2	7
Total	96	76	67	86	46	32	209	194

Table 2: New cases and recurrences at Lalo

	< 15 years		15 – 49 years		> 49 years		Total	
	H	F	H	F	H	F	H	F
New cases	20	17	22	14	7	6	49	37
Recurrence	1	0	0	2	0	0	1	2
Total	21	17	22	16	7	6	50	39

Table 3: New cases and recurrences at Zinvié Hospital*

	< 15 years		15 – 49 years		>49 years		Total	
	H	F	H	F	H	F	H	F
New cases	40	41	1	8	2	4	43	53
Recurrence	1	3	1	0	0	0	2	3
Total	41	44	2	8	2	4	45	56

* Aggregate cases from 1995 to 1999

Clinical forms of new cases and recurrences

Table 4 : Clinical forms (CSNG-Lalo-Zinvié)

Forms	Nodule	Papule	Plaque	Oedema	Ulcer	Osteomyelitis	Mixed	Disseminated	Scar	Total
Centres										
CSNG	19	0	178	5	137	36	2	23	3	403
LALO	1	0	3	3	68	9	0	5	0	89
ZINVIE	3	0	0	1	97	0	0	0	0	101
TOTAL	23	0	181	9	302	45	2	28	3	593

Evolution of cases managed at Lalo and Zinvié

Centre	Transferred	Cured without sequelae	Cured with sequelae	Left against medical advice	Deceased	Still under treatment	Total
Lalo	3	34	5	18	3	26	89
Zinvié	1	70	25	3	2	0	101
Total	4	104	30	21	5	26	190

Analyses and observations

- The BU5 form is difficult to fill out;
- Confirmation of diagnosis: 268 cases out of 593 and is provided by research institutes;
- Criteria to confirm diagnosis in the field are required;
- Rate of “left against medical advice” = 20% in Lalo: this is attributable to a number of operational problems which have now been resolved

Recommendations

- Six-monthly monitoring is desirable;
- There is a need for data sheets that are easy to fill out and accepted by all the centres; and
- WHO should produce different operational definitions

Situation of Buruli ulcer control in Côte d'Ivoire

Prof. Jean-Marie KANGA, National Buruli Ulcer Control Programme, Ministry of Health, Abidjan, Côte d'Ivoire

Dr Djatch Edgard KACOU, Projects and Epidemiology Department, National Buruli Ulcer Control Programme, Ministry of Health, Abidjan, Côte d'Ivoire

Epidemiological situation

Five endemic health districts (EU project) = 1351 cases in 1999

1. BONDOUKOU = 94
2. BOUAKÉ = 225
3. DALOA = 398
4. DANANÉ = 172
5. YAMOOUSSOUKRO = 432

Activities and projects

Workshop to organize case management (July 1999)
(Partner: WHO)

- *Main outcome* = case management network in the 5 endemic zones

Workshop to prepare a five-year control plan (October 1999)
(Partner: WHO)

- *Main outcome* = A national, followed by a subregional plan involving Benin and Ghana

Construction and rehabilitation of infrastructure:

- Operating theater and laboratory in Zoukougbeu (completed)
Partners: Japanese and Canadian Embassies, PSF
- Rehabilitation of the dermatology operating theater (in progress)
Partner: ANESVAD (a Spanish NGO)
- Construction of an operating theater in Kongouanou (in progress)
Partner: ANESVAD
- Strengthening a centre at Yamoussoukro (in progress)
Partner: ANESVAD
- Construction of an operating theater in Zouan-Hounien (in progress)
Partners: Capuchin Friars of Coseuze, Italy and PSF

Case management

- Surgical case management of 200 patients (ulcerative forms) per year (in progress)
Partner: Raoul Follereau Association, France
- Early case management at Zoukougbeu: results

Constraints and prospects

Constraints are essentially structural in nature

⌘ No effective political decision has yet been taken to approve the recommendations adopted to organize case management

Prospects = components of the subregional control plan

- Case management at all levels of health care in the 5 zones identified
- Early case detection at the community level
- A reliable referral system

Early detection and treatment of Buruli ulcer

J. M. Kanga, National Buruli Ulcer Control Programme, Ministry of Health, Abidjan, Côte d'Ivoire, and collaborators

Detection strategies in an endemic zone

Introduction

- Prevention of the late ulcerative forms and of disabilities caused by Buruli ulcer = early detection and treatment (Yamoussoukro Declaration)
- Treatment of the nodular form
 - simple surgical excision + suture
 - minor surgical material
 - can be performed in the field

Objectives

- To propose strategies to detect the nodular form of Buruli ulcer
- To evaluate the efficacy of excision of the nodule followed by suture

Methods

- Field study in the Zoukougbeu endemic zone
- Inclusion of carriers of non-inflammatory nodules
- Data collection on a card, with in particular, a clinical description of the nodules
- Excision of the nodules + suture and monitoring until six months after healing
- Diagnosis by histopathological examination (HES)

Results

Frequency of BU nodule

- 96 non-inflammatory nodules excised in 76 patients
- Proportion of BU nodules = 58.1% (54 BU /96)
- Prevalence rate of BU nodule = 1 per thousand (49 cases/47 742 inhabitants) (on 31 August 1999)

Distinctive clinical features of BU nodule

<i>Features</i>	<i>Nodule (%)</i>		<i>OR</i>	<i>p</i>
	<i>BU</i>	<i>non BU</i>		
located on a limb	83.3	71.8	1.96	0.181
\$ 5 years old	94.4	64.1	9.52	0.0001
<i>pruritic lesion</i>	37.0	15.4	3.24	0.021
<i>oedematous edges</i>	14.8	0.0	1.85	0.010
size \$ 3 cm	88.9	79.5	2.06	0.210
raised	88.9	84.6	1.45	0.544
firm or hard consistency	79.6	79.5	1.01	0.986
attached to the surface structure	42.6	23.1	2.47	0.051
mobile in the deeper structure	92.6	94.9	1.48	0.503

Clinical sensitivity features of the BU nodule

Reasons for choosing the sensitivity test:

- A sensitivity test is more likely to detect the disease
- A sensitivity test is advised when:
 - the disease is serious, a cause for concern
 - the disease is curable
 - and when false positive results have few psychological and physical consequences and entail little expenditure

This is the case of Buruli ulcer:

- BU is serious and a cause for concern, but curable, especially in its nodular form
- false positive results have few psychological and physical consequences and entail little expenditure

Minimum level of sensitivity chosen = 85%

Individual features

<i>Features</i>	Sensitivity	Specificity	PPV	FP	FN
located on a limb	83.3	28.2	61.6	30.1	9.7
<i>\$ 5 years old</i>	94.4	35.9	67.1	26.9	3.2
pruritic lesion	37.0	84.6	76.9	6.4	36.6
oedematous edges	14.8	100.0	100.0	0.0	49.5
<i>size \$ 3 cm</i>	88.9	20.5	60.8	33.3	6.4
<i>raised</i>	88.9	15.4	59.3	35.5	6.4
firm or hard consistency	79.6	20.5	58.1	33.3	11.8
attached to the surface structure	42.6	76.9	71.9	9.7	33.3
<i>mobile in the deeper structure</i>	92.6	5.1	57.5	39.8	4.3

Parallel combination 2 by 2 of sensitivity features >85%

<i>Criteria</i>	Sensitivity	Specificity	PPV	FP	FN
Located on a limb + firm or hard consistency	92.6	10.3	58.8	37.6	4.3
Located on a limb + attached to the surface structure	90.7	25.6	62.8	31.2	5.4
Firm or hard consistency + attached to the surface structure	90.7	20.5	61.3	33.3	5.4

Evaluation of the efficacy of excision + suture

<i>Parameters</i>	BU	Non BU	p
Healing rate after 6 months	100.0%	100.0%	1
Time taken to heal <i>in days</i>			
• minimum	10	12	-
• maximum	180	35	-
• average	21	20	0.156
Superinfection	9.3%	2.8%	0.412
Haemorrhage	3.7%	2.6%	0.621
Ulceration before healing	3.7%	2.6%	0.621
Recurrence before end Nov. 99	0.0%	0.0%	1

Conclusion

It is possible to recognize a BU nodule in an endemic zone

- For clinical diagnosis, the association of 3 distinctive features:
 - *recent appearance, (# 5years) + pruritic nature + oedematous edge*
- For community detection, at least one distinctive feature or at least one sensitive feature or criterion:
 - *size # 3cm*
 - *raised*
 - *mobile in the deeper structure*
 - *located on a limb + firm or hard consistency*
 - *located on a limb + attached to the surface structure*
 - *firm/hard consistency + attached to the surface structure*

Treat BU nodules by excision + suture

- It is efficacious
- It presents few risks
- It is not followed by recurrence

***Mycobacterium ulcerans* infection in French Guyana, the situation as at 19 February 2000.**

Dr Roger Pradinaud, Dermatology Department, Guyana Institute of Tropical Dermatology, Cayenne, French Guiana

The disease was identified for the first time in the Dermatology Department in 1969, under the name of “para-tubercular ulcer” (Pradinaud, Basset, Grosshans). The first positive culture confirming *M. ulcerans* was made in 1974 by Professor TACQUET in Lille (France) while I was presenting my first results to the Congresso de Dermatologia Tropicale in Sao Paulo in the presence of Wayne MEYERS.

The first thesis for a doctorate of medicine on the subject was that of Michel GABAUDAN (1975, Bordeaux II) “Cutaneous mycobacterioses in French Guyana”. The second was by Anne MOREL, married name LABOUCHE (1991, Brest): “Atypical mycobacterioses in French Guyana: a study of 113 cases”.

In 1980 R. PRADINAUD wrote “Atypical cutaneous mycobacterioses” for the Encyclopédie Médico-Chirurgicale, Paris, 12510, B10, 2.

For 16 years I have been teaching a course on what has become “Mycobacterioses environnementales” (environmental mycobacterioses) at the National Tropical Dermatopathology Course in Brazil, which keeps my colleagues in all the major universities of Brazil fully informed about such diseases. They have yet to identify a focus, although one case has been diagnosed in Suriname and five in Peru (no article has been written on the Bolivian case, and Professor Luis VALDA RODRIQUEZ is certain that it is a mistaken reference to one of the Peruvian cases, since only *M. fortuitum* has been found in cutaneous ulcers in Bolivia). In French Guyana, 132 cases had been notified by July 1997, and reported to the WHO Conference in Yamoussoukro. No case was observed in 1998. There were four cases in 1999, which brings the total to 136: 69 in men and 67 in women, 73 in under 20s, 63 in people between 20 and 80 years of age. The clinical aspects, the distribution among ethnic groups, the foci and the treatment remain the same, in percentage terms, as in our report at Yamoussoukro. The only thing to report in our epidemiological approach is a clear fall in the number of cases among under 20s: of the last 23 cases (Nos. 114 to 136, occurring between 1993 and 1999), only four patients were under 20: they were 14, 5, 5 and 12 years of age respectively, accounting for 17.39% of cases, as opposed to 63.30% in cases until then.

Improved administration of the BCG vaccine in the Guyanese coastal communities of Mana, Organabo, Iracoubo and Sinnamary, where children accounted for most cases, could be one element that has improved the situation. A study is under way with the department responsible for vaccine policy, to evaluate this possible improvement in immunization against mycobacteria, but it remains to be proven at global level that a “comfortable primo-infection” with BCG affords relative protection against mycobacterial infection in general.

The second point to note is the excellent contribution from the department of Professor Bernard CARBONNELLE (Angers) to bacteriology, with Bactec and Lowenstein cultures, inoculations in mice, and PCR using the technique set out in B.C. de ROSS, L. MARINO, F. OPPENDISANO, R.M. ROBINS-BROWNE and P.D.R. JOHNSON, "Development of a PCR assay for rapid diagnostics of *Mycobacterium ulcerans* infection", *J. Clin. Microbiol.*, 1997, 35: 1696-17000.

In terms of treatment, I wish to stress the beneficial effect of heating, which reduces the activity of the thermolabile toxin of *M. ulcerans*.

As to the name "Buruli ulcer", it could lead people to believe that Buruli was a famous doctor who described the disease, leaving them wondering about his first name and nationality, probably Italian (Antonio BURULI? Marcello BURULI? ...!).

All geographical denominations of diseases lead to great confusion; the list is unfortunately very long: BISKRA button, MADURA foot, MELEDA disease and MOZAMBIQUE ulcer – the last of which was observed in the early 1900s in Guyana, where, of course, it was called CAYENNE ulcer! Since, furthermore, the disease that will bring us together in Geneva because we cannot meet in Harare, Zimbabwe, includes oedematous, rubbery and ulcerating phases, and sometimes bone involvement, it should be entitled "*Mycobacterium ulcerans* infection", and classified along with the "Environmental mycobacterioses", which are increasingly "typical" clinically, bacteriologically and in terms of their specific therapeutic sensitivity; furthermore, they are part of increasingly well-defined ecosystems, well covered by the word "environment".

Finally, without minimizing or criticizing the tremendous work of religious institutions and charitable associations, our WHO group should bring these diseases into the medical curricula, especially dermatology, surgery and study of infectious diseases, rather than let the media dream up its own terminology, as recently happened on the French television channel TF1, which described it as "Buruli ulcer, a new leprosy"!

Update on Buruli ulcer situation in Ghana

Dr George K. Amofah, Public Health Division, Ministry of Health, Accra, Ghana

Background

The first recorded case of Buruli ulcer in Ghana was in 1972 when one case from Amasaman, a village in Greater Accra region, was admitted to Korle Bu Teaching Hospital in Accra. In 1989 van der Werf published a series of 96 cases from an endemic focus in the Asante Akim North district of Ashanti region. A few unpublished cases had by then been picked up in the Amansie West district of the same region in 1988, which led to a district case search in 1991. It was however in 1993 that heightened media coverage on the disease in the Amansie West district brought it to the attention of the ordinary man and the political authorities.

By the time of the Yamoussoukro conference on Buruli ulcer in Côte d'Ivoire in 1998, a number of endemic communities had been identified from 4 of the 10 regions in the country. A total of about 1100 cases had then been reported.

A number of intervention activities had been initiated and were going on especially in Ashanti region (one of the most endemic regions), some of which were reported during the conference. These activities included the following:

- Special outreach services from the regions and districts to endemic communities for health education, wound dressing and excision of pre-ulcerative lesions;
- Establishment of dressing stations in some communities and the construction of a health centre at one of the most endemic community (Tontokrom);
- Training of medical officers and some medical assistants in excision procedures;
- Production and use of a documentary on Buruli ulcer for community health education;

Collaborative research work on the disease including:

1. Efficacy of phenytoin powder on healing of Buruli ulcers,
2. Effectiveness of excision of pre-ulcerative Buruli lesions in field situations,
3. Design of a special outreach project and testing its cost-effectiveness in the field,
4. Epidemiology of the disease in some endemic districts;

Advocacy to improve the living environment of some endemic communities such as improving water supply, sanitation and access to health services.

Current situation

A number of activities has been undertaken since our last meeting in 1999. The disease continued to attract much media and political attention with TV coverage of major events.

Some specific activities undertaken are:

1. Advocacy/Political Commitment. Efforts have continued to be made towards eliciting political commitment for Buruli ulcer control and management. District Chief Executives (DCEs) of endemic districts have been lobbied to fund certain activities in their districts with some success in certain districts. Unfortunately not all DCEs have backed their support with release of funds.
2. Ghana hosted an International workshop on Buruli Ulcer in 1999 organized by WHO AFRO. The workshop was for the West Africa sub-region and it afforded the participants to share experience about the disease in their respective countries. A framework for control and management of the disease was also drafted.
3. Capacity building effort has continued throughout the year. Doctors from endemic districts in Brong Ahafo region were trained in surgical excision of Buruli nodules by a team from nearby Ashanti region.
4. The collaborative research with St George's Hospital, London, on immunological and other aspects of Buruli ulcer is continuing. Similarly, the special outreach project in Amansie West district is on going.
5. A team comprising a plastic surgeon, a medical officer and nurses from Komfo Anokye Teaching Hospital in Ashanti region provide weekly surgical services to patients at the district hospital of Amansie West district.
6. A team of plastic surgeons from an NGO (HART of USA) was once again in Upper Denkyira district to operate on Buruli ulcer patients. The team has made three of such visits to Ghana since 1997 and has so far operated (mainly skin grafting) on 250 patients from two regions. The team also donated surgical equipment and other logistic items to the hospitals and provided on-the-job training to local doctors on skin grafting procedures.
7. Two persons from Buruli ulcer programme management participated in a workshop on the disease in Côte d'Ivoire in 1999 and also assisted with the development of a funding proposal to European Union for support of Buruli ulcer activities.

National case search exercise

The main activity that was embarked upon since our last meeting was a national case search for Buruli ulcer in 1999. The main reason for undertaking this exercise was the fact that some people still think that we are dealing with a minor issue in terms of the magnitude and extent of the problem compared with the many other priority health problems like malaria and measles. It has been difficult to convince those who think so due to the absence of reliable national data on the disease. This has been so as a result of the fact that only the few cases that reported at our health facilities were captured through our routine data reporting system, while the majority of cases were known to be in relatively deprived, inaccessible areas.

Furthermore, we had just developed a national strategic document to guide the control and management of Buruli ulcer in the country and it was considered important to have baseline data against which intervention measures could be assessed.

Objectives

The main objective of the national case search was to establish the extent and burden of the disease in Ghana to facilitate the implementation of a national programme for the control of Buruli ulcer.

The specific objectives were to:

1. determine the geographical distribution of Buruli ulcer in the country;
2. assess the burden of the disease; and
3. determine physical accessibility of endemic communities to health care services.

Definition of variables

Geographical distribution was defined in terms of regional, district, sub-district and community/village distribution of cases of the disease.

The burden of disease was considered in terms of number of cases affected, age and sex distribution, clinical presentation (pre-ulcerative, ulcer, deformity) and site of lesion.

Pre-ulcerative lesions cover nodular, plaque, papular and non-ulcerative oedematous forms.

Deformities may be scars, constriction of limbs, ankylosis of joints, amputations etc.

Methodology

The case search covered every district and every known community in the country . A team of 20 national facilitators initially underwent a day's orientation to familiarize themselves with the survey instruments and the clinical presentation of the disease in an endemic focus. Two facilitators each were then sent to the regions to train regional teams (3 from regional level, 2 from each district). The two people trained from each district then trained the actual persons (7 teams of 2 persons each) from the sub-district and communities who undertook the case search.

For the search itself, the data collectors used the pictorial document designed by the Global Buruli Ulcer Initiative of WHO. At each community/village visited, they showed the pictures of Buruli ulcer at different stages of development to as many people as possible and inquired from them whether any person had a similar condition in the village. They then traced all such persons and if positive (using standard case definitions) made a line listing of all such cases on a simple designed form. They then moved to the next village and repeated the process till the whole district was covered.

Summary of provisional findings

A total of 6330 suspected cases of Buruli ulcer were identified from all 10 regions and from 90 (82%) of the 110 districts. It was however possible to analyze 5440 in detail. Of those districts with identified cases, about 14.4% had less than 5 cases while 85.6% had more than 5 cases.

Table 1: No. of districts reporting cases per region

<i>Region</i>	<i>No. of districts</i>	<i>No. reporting cases</i>	<i>No. reporting 0 case</i>	<i>No. reporting less than 5 cases</i>	<i>No. reporting 5 or more cases</i>
Ashanti	18	15	3	0	15
Brong Ahafo	13	9	4	4	5
Central	12	12	0	0	12
Eastern	15	14	1	0	14
Greater Accra	5	4	1	1	3
Northern	13	10	3	2	8
Upper east	6	5	1	0	5
Upper west	5	3	2	1	2
Volta	12	9	3	4	5
Western	11	9	2	1	8
TOTAL	110	90 (81.8%)	20 (18.2%)	13 (14.4%)	77 (85.6%)

Age distribution

The age distribution of the cases when they were identified is shown in Table 2. It can be seen that about 35.1% were under 15 years while 64.5% were over 15 years which indicates that a number of the patients had been affected for a long time. Unfortunately, information was not available for age of onset of the disease.

Table 2: Age distribution of cases when seen, by region

Region	0–4	5–9	10–14	15+	Not stated	TOTAL
Ashanti	56	186	306	853	2	1403
Brong Ahafo	6	72	74	188	0	340
Central	20	125	247	818	4	1214
Eastern	4	33	64	304	5	410
Greater Accra	40	217	283	617	7	1164
Northern	3	15	24	110	3	155
Upper east	0	2	15	80	0	97
Upper west	2	0	6	86	0	94
Volta	5	22	23	153	0	203
Western	17	15	27	299	2	360
TOTAL	153 (2.8%)	687 (12.6%)	1069 (19.7%)	3508 (64.5%)	23 (0.4%)	5440 (100%)

Table 3: Sex distribution of cases, by region

Region	Male	Female	Total
Ashanti	705	698	1403
Brong Ahafo	159	181	340
Central	658	556	1214
Eastern	238	172	410
Greater Accra	567	597	1164
Northern	81	74	155
Upper east	36	61	97
Upper west	42	52	94
Volta	97	106	203
Western	207	153	360
TOTAL	2790 (51.3%)	2650 (48.7%)	5440

Site of lesions

This is shown in Table 4. About 3.5% were on the neck/head, 5.1% on the trunk, 25.4% on the upper limbs and 66% on the lower limbs.

Table 4: Site of Lesions, by region

<i>Region</i>	Head/Neck	Trunk	Upper Limb	Lower Limb
Ashanti	52	70	398	940
Brong Ahafo	19	16	114	215
Central	23	31	267	988
Eastern	8	16	82	305
Greater Accra	67	117	506	614
Northern	3	4	20	131
Upper east	4	10	14	98
Upper west	4	8	24	74
Volta	5	12	26	171
Western	21	14	33	318
TOTAL	206 (3.5%)	298 (5.1%)	1484 (25.4%)	3854 (66.0%)

Physical access to health facilities

About 57.8% of all the communities visited were more than 5 miles from the nearest health facility which could provide the most basic wound dressing services to patients.

Table 5: Estimated distance of communities from nearest health facility

<i>Region</i>	< 1 mile	1–5 miles	> 5 miles
Ashanti	680	1049	1349
Brong Ahafo	593	1223	1808
Central	342	909	785
Eastern	349	931	772
Greater Accra	514	573	397
Northern	292	626	1131
Upper east	367	620	371
Upper west	426	864	982
Volta	415	577	458
Western	362	715	1056
TOTAL	4340 (20.2%)	8087 (37.6%)	9109 (42.2%)

Stage at detection

During the case search, 12.8% of the cases were detected at the pre-ulcerative stage, 48.8% at the ulcerative stage, 35.8% had healed lesions with scarring, and 2.6% had other forms of deformities apart from scars.

Table 6: Stage at detection of cases, by region

Region	Pre-ulcerative	Ulcer	Scar	Other Deformity
Ashanti	225	626	673	57
Brong Ahafo	45	189	141	40
Central	152	819	343	14
Eastern	57	303	91	10
Greater Accra	130	421	790	14
Northern	27	108	20	0
Upper east	12	78	11	1
Upper west	28	68	14	2
Volta	47	137	46	10
Western	64	257	73	15
TOTAL	787 (12.8%)	3006 (48.8%)	2202 (35.8%)	163 (2.6%)

BCG SCAR

Nine hundred (35.4%) of 2541 cases had BCG scar.

Conclusion

From this preliminary findings it can be seen that Buruli ulcer is a major problem in Ghana and appears to be spreading to other regions that were hitherto not considered candidates for the disease on account of the environmental condition. Unfortunately, accessibility to even the basic services is still poor and not until there is a massive infusion of resources, both internal and external, into control of the disease we are in for serious trouble in the foreseeable future.

Constraints

A number of factors militate against effective control and management of Buruli ulcer in Ghana, some of which are generic.

1. A major constraint is the lack of an effective treatment for Buruli ulcer; in addition, control effort is hampered by the lack of definitive knowledge about the mode of transmission of *M. ulcerans*.
2. Competing priorities for the limited funds available for the provision of other equally important health services is a major challenge.
3. The cost of providing services to Buruli ulcer patients is very high and a major burden to the scanty resources available to the health sector. The result of this is that many health administrations are unable to sustain control and management efforts especially in the communities for any length of time.
4. Most of the cases come from relatively inaccessible and poorly developed parts of the country. Unfortunately, the ministry of health does not have at its disposal enough vehicles to provide outreach services to these communities.
5. Due to a combination of factors, most of the Buruli ulcer patients only report to health facilities after massive ulceration has developed, often with extensive deformities.

Future plans

Plans for the future for the control and management of Buruli ulcer in Ghana include the following:

1. Training of medical officers and District Health Management Teams in control and management procedures.
2. Strengthening the surveillance system especially at the community level.
3. Strengthening the Noguchi Memorial Research Centre to provide PCR services and GIS mapping.
4. Collaborative research with interested partners.
5. Supporting districts to provide services to Buruli ulcer patients both at health facilities and in communities.
6. Advocacy for more funding of Buruli ulcer programme.

***Mycobacterium ulcerans* in Papua New Guinea**

Sister Joseph, Boram Hospital, Wewak, Papua New Guinea

Papua New Guinea lies just South of the equator above the Australian Cape York peninsula, separated from Australia by the Torres Strait. It is divided into eighteen provinces.

Mycobacterium ulcerans is found in those areas which have swamp vegetation, the Sepik area, Fly river area, the Cape Rodney area, Kavieng, Kimbe. The more dense the population in those areas, the higher the annual number of cases, by far the greatest being from the Sepik.

From the seasonal incidence table of the years 1971-79, and 87-99 it can be seen that the number of cases per year is very small compared to the African scene, and follows no discernible seasonal pattern.

Baseline figures were noted for these years. There were 377 cases registered in Wewak General Hospital registers having 1086 operations. There were 104 adults (58 men and 46 women), and 273 children, (160 boys, and 113 girls).

The sites are shown below.

Leg	41	(Mainly children)
Knee	36	
Foot	26	
Buttock	12	(Mainly males)
Thigh	11	(10 boys)
Arm	10	
Elbow	12	(9 boys)
Back	9	(8 boys)
Shoulder	6	(5 girls)
Finger	4	(all women)
Chest	3	
Breast	2	

Head, neck, clavicle, hand and trunk 1 each.

Action taken following the Yamoussoukro conference.

- The work was presented at the annual medical symposium which is attended by most of the doctors in Papua New Guinea.
- The posters were distributed in areas of known incidence.
- Cooperation of CEO's from all the major hospitals was requested in compiling a register of new cases henceforth.
- Tok Save's were given in Wewak itself, Aitape and Vanimo Hospitals, where registers were checked to verify validity of reportage, this was felt to be accurate.

Case hunting

- *1998*: a trip up the Sepik river was taken as far as the water would allow. One active case was seen in Ambunti, and one old healed case at Kaminabit.
- *1999*: an expedition was mounted to Bewani. Villages of previously reported cases were visited, but no new cases found. Water samples were taken but were negative on PCR.
- *1999*: a further up river trip on the Sepik this time to the Irian Jayan border revealed two old healed cases, and no new disease.
- *2000*: since the disease has moved west in Africa, a trip was made to Irian Jaya to see if they had MBU. West of the border as far as Jaya Pura, the local doctors said they had never seen the disease. Posters were left with them, and they will notify any cases which turn up.
- *May 2000*: since all the previous areas checked were on the fast flowing Sepik river, side trips were made into the lagoon areas to check the villages there, the areas covered were Chambri lakes and Blackwater lagoons. One old case was seen, and one small child with active disease of the elbow who was hospitalized for treatment. No other cases were seen, nor did direct questioning elicit word of other cases, though it was obvious the people were familiar with the disease, they all said they had seen very little recently.

For the future

There are now two service registrars at Wewak, who will proceed on to the University Surgical Masters course in two years time. They are doing their thesis work on MBU.

One is checking the records to pinpoint exactly from where the recorded cases have come, and go out to these villages to check the population and the water supply.

The other is doing a project to map the best place for taking specimens from the lesion to get the best true positivity rate for AAFB smears. This will be correlated with recurrence rate, to see if on the spot smears can help in mapping successfully the area of ablation of the disease at the time of operation, and whether washing the wound with a cytotoxic detergent such as savlon to kill free lying cells will reduce recurrence rates.

The local rehabilitation project of Callan Services is training nationals in splinting and joint mobilization in the peri-operative period, and it is hoped that a physiotherapy school can be started at the Divine Word campus of the University of Papua New Guinea. It will be the only such unit in the country.

There is a new TB control Medical officer now stationed at Timbunke who will monitor the area for MBU too.

With the help of the World Wild life Fund, an expedition will go up into the Hunstein range to check out the population there.

It is hoped that an MBU module can be included in the University of Papua New Guinea medical school curriculum.

It is noticeable that in the time of increased activity in looking for MBU, there has in fact been a notable decline in cases reported, last year we only had four cases in Wewak Hospital, and several other centres such as Port Moresby, Kavieng and Bewani had none at all. It is to be hoped this represents a true decline in the incidence of this devastating disease, and not just a temporary dip.

***Mycobacterium ulcerans* in the Sepik – Seasonal incidence**

Year	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Total
71							7	2	1	2	4	3	19
72	5	3	8	2	2	3	2	3	2	2	0	2	34
73	2	0	2	1	3	1	2	3	0	1	3	2	20
74	0	1	4	2	1	2	1	2	1	2	1	1	18
75	1	4	1										6
77				2	2	1	1	1	2	3	1	4	17
78	1	2	1	2	5	0	2	2	7	4	1	0	27
79	3	7	7	4	4								25
87				3	5	2	1	1	1	0	0	0	13
88	0	0	2	2	1	0	0	2	2	3	8	5	25
89	3	2	2	4	2	2	1	0	0	1	2	1	20
90	0	1	1	0	0	2	2	4	1	3	1	2	17
91	2	0	0	0	0	4	1	2	0	1	1	1	12
92	1	0	2	0	0	1	1	0	1	0	0	2	8
93	5	4	1	4	0	0	1	3	1	1	3	1	24
94	2	6	3	2	1	1	3	0	3	1	3	1	26
95	1	2	2	1	3	6	0	1	0	0	0	0	16
96	0	1	0	3	0	0	2	1	1	3	0	4	15
97	3	5	4	3	4	0	2	3	2	4	0	0	30
98	1	1	0	0	0	0	0	0	0	0	0	2	4
99	0	0	1	1	2	0	0	0	0	0	0	1	5
Total	30	39	41	36	35	25	29	30	25	31	28	32	381

Report from Togo

Dr Napo Tignokpa, Center of Dermatology, Lomé, Togo

Dr G. Battista Priuli, Hôpital Saint Jean de Dieu, Afagnan, Lomé, Togo

Case management

Survey of BU prevalence in the Mono, Kara and Oti river valleys

Summary

- Before 1995, it was thought that Buruli ulcer did not exist in Togo.
- In 1995, Dr Wayne Meyers and Prof. Françoise Portaels, assisted by Drs G. Battista Priuli and NapoTignokpa, found *Mycobacterium ulcerans* infection in two children hospitalized for BU.
- In January 1999, Prof. Portaels, Drs Meyers and Priuli carried out a survey in Yoto prefecture, leading to the discovery of 17 suspect cases, 4 of which were confirmed as BU.

Togo: general information

- Population: 4,405,500
- Population density: 72 persons per km².
- Administrative organization:
 - 5 regions
 - 30 prefectures
 - 4 districts
- Health Structure
 - 6 health regions
 - 30 health districts

Plan of Action 2000

Essential components:

- BU prevalence survey in the Mono, Kara and Oti river valleys;
- Training, supervision and IEC activities at the national, intermediate and peripheral levels to detect and treat BU cases.

Project objective

- The project's objective is to carry out a prevalence survey in order to assess the scale of the problem posed by BU in Togo.

Activities

Activities will focus essentially on:

- Training leprosy/TB monitors (CT/TB and nurses in charge of posts (ICP);
- Creation of detection circuits;
- Regular supervision of health staff;
- IEC; and
- Evaluation and publication of results.

Project zones

	Plateaux region	Kara region	Savanes region
No. large villages	178	90	60
No. CL/TB to be trained for the survey	7	7	4
No. nurses to be trained	20	20	12
No. village health workers	40	30	16

Situation analysis

- **The problems**

So far, all BU cases have been from a single prefecture. The prevalence rate in the prefecture is 3.47 per 10 000 inhabitants

Surveys need to be carried out in the other prefectures, and in particular in the Mono, Kara and Oti river valleys, which are risk zones

BUDGET

- Staff training: CFAF 1,600,000
- Equipment: CFAF 1,800,000
- Supervision: CFAF 1,600,000
- IEC activities: CFAF 1,000,000
(radio, television, puppet show)

TOTAL CFAF 6,400,000

Update on research report from Australia

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Incidence and geographic distribution of cases; environmental sampling
(M. Smith, PDR Johnson. Stinear TP et al)

During 1999, *M. ulcerans* infections were diagnosed in 8 patients from far north Queensland north of the town of Mossman. This region has a small population suggesting that there is significant ongoing transmission of *M. ulcerans* here. We conducted extensive environmental sampling (water, vegetation and water insects), but despite the continuing epidemic, all samples have tested negative by IS2404 PCR. This includes a sample of *Nacauridae* and *Belostomatidae* (water insects which have tested positive in Benin) that were captured from the dam of a fruit farm associated with 3 recent cases of *M. ulcerans* infection. There have also been isolated single cases from two other Queensland towns several hundred kilometres to the south.

In the southern temperate state of Victoria, we continue to observe occasional isolated cases of *M. ulcerans* infection from near Melbourne and from east Gippsland, but there have been no new cases from either Phillip island or Frankston-Langwarrin for 18 months. Sequential environmental samples from these regions which tested positive between 1995 and 1998 have tested negative recently. However, in January 2000, two cases of *M. ulcerans* infection were diagnosed in ring-tail possums (*Pseudocheirus peregrinus*) from east Cowes, Phillip Island (the scene of the previous human outbreak, 1993-5). One nearby environmental site has once again tested positive after returning repeated negative tests for over 3 years. These data suggest that *M. ulcerans* disease in humans or animals correlates with the results of environmental sampling in endemic areas in Victoria, and that numbers of *M. ulcerans* may wax and wane according to unknown environmental factors. At present, we are not able to explain why we cannot obtain positive environmental samples in north Queensland when we are able to in Victoria. However, it is possible that different subtypes of *M. ulcerans* occupy different environmental niches (see typing data below).

Subtypes of M. ulcerans
(TP Stinear et al)

We have studied the relationships between isolates of *M. marinum* and *M. ulcerans* obtained from Australia and around the world. Approximately 18 isolates were tested, 6 of which were sourced from Africa. The 6 African isolates came from Congo (1976), Benin (1994, 1997), Angola (1996), Ghana (1997) and Togo (1997). We used multilocus sequence typing (MLST) and inter-IS PCR to type these isolates. We have confirmed and extended previous work by others and shown that:

1. *M. marinum* is the progenitor, and that *M. ulcerans* branched off as a separate species relatively recently.
2. There are at least 9 major subtypes of *M. ulcerans*. All 6 African isolates fell into a single subtype.
3. There are at least 2 subtypes present in New Guinea (PNG) and a further subtype in Malaysia.
4. There are at least 2 subtypes present in Australia which correlate with the widely separated endemic regions in far north Queensland and south eastern Victoria.
5. The African, Australian, New Guinea and Malaysia isolates are closely related.
6. Isolates from Surinam, Japan, China and Mexico are not as closely related to the African subtype or to each other.

Susceptibility to M. ulcerans infection is associated with a Th-2 cytokine response.
(TM Gooding et al.)

We have examined the immune responses to mycobacteria in patients infected with *M. ulcerans* and uninfected control subjects from far north Queensland and southern Victoria. Peripheral blood mononuclear cells (PBMC's) from 39 patients with current or past *M. ulcerans* disease and 44 exposed control subjects who had lived with proven cases were harvested following stimulation with heat killed *M. ulcerans* or BCG bacteria. Th1- type responses were assessed by the production of IFN γ and IL-12 and Th2-type responses by the production of IL-4, IL-5, IL-6 and IL-10. Production of IFN γ was measured by ELISA and RT-PCR with remaining cytokines measured by RT-PCR only. Subjects with *M. ulcerans* infection showed significantly lower production of IFN γ and IL-12 ($P < 0.01$) and significantly higher production of IL-4, IL-5 IL-6 and IL-10 ($P < 0.001$) in response to both *M. ulcerans* and BCG compared with exposed control subjects. PBMC's from all subjects responded normally to stimulation with phytohaemagglutinin. These findings indicate that PBMC's from patients infected with *M. ulcerans* can recognise *M. ulcerans* antigens, while demonstrating specific Th1 cell anergy to these antigens. These findings may explain aspects of the pathogenesis of *M. ulcerans* induced disease and its failure to respond to conventional anti-mycobacterial chemotherapy.

Susceptibility of M. ulcerans to azithromycin.
(Oppedisano F, Johnson PDR.)

Azithromycin is a safe and effective drug with a long half-life, allowing infrequent dosing. These attributes are important when treating infections where patient adherence and duration of therapy are important clinical issues. As no previous data were available, we tested a single Victorian isolate of *M. ulcerans* for susceptibility to azithromycin. Bactec radiometric bottles containing Middlebrook 7H9 broth were

inoculated with 0.1 ml of a 1 in 10 dilution of bacterial suspensions of 1 mg dry weight /ml *M. ulcerans* cells in PBS. Azithromycin was added to replicate bottles at concentrations of 0.1, 1, 10 and 100 mg/l. Bottles were sampled weekly and compared with results from antibiotic-free controls.

All concentrations of azithromycin inhibited growth completely over 8 weeks. We conclude that the isolate of *M. ulcerans* we tested is susceptible in vitro to azithromycin with an MIC of less than 0.1 mg/l. We are now planning to extend this work to a range of other isolates from Australia and Africa.

Progress report on experimental chemotherapy of *Mycobacterium ulcerans* infection in the mouse model

Prof. Jacques Grosset, Hervé Dega, Nacer Lounis and Abdelhalim Bentoucha, Faculté de Médecine Pitié-Salpêtrière, Paris, France

What has been done.

1. The growth of *M. ulcerans* in the footpad of the mouse

The first step was to establish the model of *M. ulcerans* growth in the mouse footpad. The method used was adapted from that reported by Fenner in 1956 for the study of *M. ulcerans* in the mouse and that reported by Shepard in 1960 for the assessment of *M. leprae* growth in the footpad of mice. The kinetic of *M. ulcerans* growth was determined after infection of both hind footpads of mice with 0.03 ml of a suspension containing 6×10^3 CFU of a strain (Cu 001) isolated from a patient from Ivory Coast. The growth in the footpads was assessed in terms of mortality of the mice, footpad swelling, and AFB and CFU counts. Mortality of infected mice and footpad swelling were recorded on a weekly basis. AFB and CFU counts were performed every two weeks from 6 to 10 foot pads.

All mice had swollen footpads on week 10 after infection; the swelling reached the whole foot on week 11, and the trunk on week 12, and all mice were dead by week 15. The AFB and CFU counts are given in Figure 1. Four main conclusions can be drawn from this figure: (i) the growth curves of AFB and CFU are parallel and suggest a division time of 6 to 7 days; (ii) the AFB counts are 10 times (or $1 \log_{10}$) higher than the CFU counts, suggesting that the viability of *M. ulcerans* was limited; (iii) when the footpads began to swell, the AFB counts were above 10^5 , therefore indicating that an active multiplication of the inoculated organisms had occurred; this finding is of crucial interest because swelling may be used as a surrogate marker of *M. ulcerans* multiplication in the footpad of the mouse; (iv) all cultures from the infected footpads took at least 3 months to become positive on Löwenstein-Jensen medium incubated at 30 °C and were lost because of superinfection with *S. aureus* from week 10 onwards after infection.

2. Bacteriostatic activity of clarithromycin against *M. ulcerans* in the mouse model.

As clarithromycin had been demonstrated by Portaels and others to have in vitro activity against *M. ulcerans*, the second step was to assess its activity in mice infected with the Cu001 strain of *M. ulcerans*. In a first experiment, mice were treated the day after footpad infection with 5×10^3 for 10 weeks to determine whether or not the treatment could prevent the swelling of foot pad and the increase of AFB and CFU counts; in a second experiment, mice were started on treatment only when the swelling of footpad had occurred (on week 10) in untreated mice to determine whether or not the treatment could cure the swollen footpads and reduce the AFB and CFU counts. In both experiments, the drug was given orally through an esophageal cannula, five days a week at a daily dose of 100 mg/kg, a dose equipotent in mice to 15 mg/kg (1g/day) in humans.

The results of the first experiment (Fig. 2) can be summarized as follows: (i) no mouse died and no footpad swelling occurred during clarithromycin treatment, indicating that clarithromycin had a clear-cut activity against *M. ulcerans* in the mouse model; (ii) the AFB counts remained under the detection level ($4.5 \log_{10}$) from day 1 (D1) to week 8 (W8); on W10, only one of the footpad was AFB positive with $4.9 \log_{10}$; (iii) the CFU counts did not increase during the first 4 weeks of treatment but thereafter slowly increased to reach 2.1, 2.3, and $3.5 \log_{10}$ CFU per footpad at W6, W8 and W10, respectively. In conclusion, the growth of *M. ulcerans* was not suppressed in clarithromycin treated mice but only slowed down compared to control mice, indicating that the drug had a bacteriostatic activity against *M. ulcerans* in the mouse.

The results of the second experiment (Fig. 3) can be summarized as follows: (i) mice started on clarithromycin when the footpad was swollen (on W10) did not die as the controls by W15 but survived up to W18, i.e. three additional weeks; (ii) despite clarithromycin treatment, there was no improvement of the swollen footpads; (iii) the increase-in the AFB counts was more limited than in the control mice but the difference was not statistically significant ($p = 0.15$); two weeks (W12) after the beginning of treatment, the median CFU count was $4.3 \log_{10}$, compared to $4.9 \log_{10}$ on W10; thereafter all culture were superinfected with *S.aureus*. In conclusion, in curative therapy as well as in preventive therapy, clarithromycin had a bacteriostatic activity against *M. ulcerans* in the mouse model.

3. Comparative activity of minocycline, sparfloxacin, rifabutin, rifampicin, amikacin, and clarithromycin against *M. ulcerans* in the mouse model.

As clarithromycin exhibited only a limited bacteriostatic activity, the activities of several other drugs, including two rifamycin derivatives, rifampicin (RIF) and rifabutin (RBT), minocycline (MIN), the most active fluoroquinolone against mycobacteria, sparfloxacin (SPX), and amikacin (AMK) were tested in comparison of that of clarithromycin (CLR) against *M. ulcerans* in the mouse model. The kinetic method used by Shepard to assess the activity of antileprosy drug was used. In brief, both hind footpads of mice were infected with 5×10^5 AFB of *M. ulcerans*. A week later, on W1, daily (5 days a week) therapy with each of the drugs given alone was started for 8 weeks. On completion of the 8 weeks, the treatment was stopped and the mice were kept under observation for 17 additional weeks. The activity of each drug was assessed in terms of growth delay, determined by comparing the length of time needed for the footpads to swell in treated mice and in untreated control mice. Longer the delay induced by the treatment, more active the drug.

As shown in Figure 4, swelling of 50% of the footpads was recorded by 15 weeks in control mice, 18 weeks in MIN treated mice ($p = 0.18$), 21 weeks in SPX treated mice ($p = 0.008$), and 22 weeks in CLR treated mice ($p = 0.002$). As the growth delay induced by MIN, SPX, and CLR was inferior to the 8 weeks length of treatment, it suggests that the former drug had no significant activity and the latter two drugs, only a bacteriostatic activity against *M. ulcerans*. In complete opposition to the preceding findings, no footpad swelling occurred during the 17 weeks period of follow-up after completion of treatment in mice that had received RIF, RBT, or AMK. The difference between these mice and control mice was highly significant ($p < 0.001$) and suggested a bactericidal activity of all three drugs against *M. ulcerans*.

It is important to notice that, in all swollen footpads, the AFB counts were always above 5×10^6 indicating that the inoculated organisms had multiplied. Out of the 12 footpads from mice treated AMK, the AFB counts performed after the period of follow-up were all negative. Out of the 14 footpads from mice treated with RIF, 2 were AFB positive with 4.9 and 5.07 \log_{10} , respectively; out of the of 14 footpads from mice treated with RBT, also 2 were AFB positive with 5.07 and 5.3 \log_{10} , respectively. All cultures remained negative. In conclusion, minocycline was inactive, sparfloxacin and clarithromycin exhibited a bacteriostatic activity against *M. ulcerans* in the mouse model; rifampicin, rifabutin, and amikacin exhibited a bactericidal activity.

What is presently done

Because rifampicin alone (RIF) and amikacin alone (AMK) exhibited a bactericidal type of activity against *M. ulcerans* in the mouse model, the activity of the combination RIF + AMK was tested in the mouse. The first experiment aims to assess the preventive activity of the combination, and the second, its curative activity.

1. Preventive activity of the combination rifampicin-amikacin given daily or intermittently.

The activity of the combination RIF + AMK given once a week, twice a week and 5 days a week (daily) was tested in Balb C mice by using the proportional bactericidal test. Groups of mice were infected in the left hind footpad with serial suspensions containing 10^5 , 10^4 , 10^3 , 10^2 , 10^1 , 10^0 , 10^{-1} AFB of *M. ulcerans* harvested from a swollen footpad (strain Cu001). Except control mice, series of mice were given the combination RIF + AMK for 4 weeks. After completion of treatment, the mice were kept without treatment to determine the proportion of mice that would develop footpad swelling and AFB count $> 5 \times 10^5$ within the following 6 months (26 weeks); in other words, the proportion of mice in which multiplication of *M. ulcerans* would occur. Compared with the control mice, that proportion gives the most probable number of AFB giving rise to multiplication, thus the proportion of *M. ulcerans* killed by the 4 weeks treatments.

The experiment is not yet completed but the results after 15 weeks follow-up (table 1) are clear: 4-week therapy with once a week RIF + AMK that killed more than 2 \log_{10} organisms was active against *M. ulcerans*, but less active than twice a week therapy and much less active than daily therapy. Therefore daily administration of the combination RIF + AMK appeared as the most active. Because the period of follow-up was not yet completed, it is not possible to decide if 4 weeks of therapy are sufficient to killed all 10^5 *M. ulcerans*.

2. Curative therapy of *M. ulcerans* infection in the mouse

Except clarithromycin that was also tested against *M. ulcerans* in Balb C mice with swollen footpads, all other drugs and drug combination were tested as preventive therapy in their ability to prevent the swelling of infected footpads. Because the more likely clinical use of drug therapy against *M. ulcerans* is the curative therapy of patients with clinical lesions, mice were infected, let without treatment up to the development of swollen footpads, and finally treated to determine if the drug therapy was able to cure the swollen footpads. In practice, mice were infected with 10^5 *M. ulcerans* AFB harvested from a swollen footpad and let without treatment for several weeks. The treatments were started when footpad swelling had occurred and

given 5 days a week for 12 weeks. Three drug regimens were tested: (i) 10 mg/kg rifampicin (RIF) alone; (ii) RIF + 100 mg/kg amikacin (AMK); (iii) RIF + 100 mg/kg clarithromycin (CLR) + 50 mg/kg sparfloracin (SPX), an fully oral three-drug combination. The activity of each drug regimen was assessed in term of reduction of the mortality rate, the lesion index, and the AFB and CFU counts. The lesion index was defined as follows: index 0 = normal footpad; index 1 = non inflammatory footpad swelling; index 2 = inflammatory footpad swelling; index 3 = inflammatory hind foot swelling; index 4 = inflammatory trunk swelling; index 5 = death of the mouse. Each week, the footpads were examined and the average lesion index was calculated by drug regimen. On day 0 of therapy, AFB and CFU counts were done to establish the baseline values. They were done again after one week (W1), two weeks (W2), four weeks (W4), eight (W8) and twelve (W12) weeks of therapy.

The evolution of the average lesion index is given in Figure 5. The average lesion index steadily increased in untreated control mice that died by W8. In RIF-treated mice, it remained stable after a 2-week initial phase of increase from index 2 to 3; in addition none of RIF-treated mice died. In RIF + CLR + SPX-treated mice, there was an initial increase during the first 3 weeks of therapy, followed by a slow but constant decline of the lesion index to 1. In mice RIF + AMK-treated mice, the lesion index decreased during the first 4 weeks of therapy from 2 to 1. Thereafter, it remained stable or decreased slowly to reach 0.5 by week 12th. Likely the 0.5 index corresponds to the scar of the initial *M. ulcerans* lesion.

The corresponding mean AFB counts are given in table 2. In control mice, the AFB counts steadily increased from 6.22 to 7.27 log₁₀ between D0 and W4. As all mice were dead by W8, no more AFB count was possible. Curiously in treated mice, the AFB counts did not increase in the footpads of RIF- and RIF + SPX + CLX-treated mice during the initial 2 to 3 weeks of therapy despite the apparent worsening of lesions. Thereafter, it did not decline despite the apparent improvement of the lesions. Even in mice that steadily improved during therapy with the most active combination, RIF + AMK, the AFB counts remained stable, at least during the 12 weeks of treatment. One is tempted to relate that finding to the immuno-suppressive role of *M. ulcerans* toxin.

Though the CFU counts are not yet available, the results of the experiment are confirming the bactericidal activity of the combination RIF + AMK not only as preventive therapy but also as curative therapy against *M. ulcerans* infection. The recurrence rate remains to be evaluated as well as the optimal duration and rhythm of administration of treatment. As AMK is an injectable drug with a potential toxicity, other drug(s) active by the oral route are needed. Finally, the time has come to assess the potential of the RIF + AMK combination in humans.

Update on research work from the Rocky Mountain Laboratory, Hamilton, Montana, USA

Dr Pamela Small, Microscopy Branch, Rocky Mountain Laboratory, Hamilton, Montana, USA

1. Development of a cutaneous mouse model for Buruli ulcer.

We have begun to try developing a cutaneous mouse model for *M. ulcerans* infection, which reproduces the histopathology and immune response, found in the human infection. In this model bacteria are injected into the shaved neck of Swiss RML outbred mice. When *M. ulcerans* is injected subcutaneously in this site, there is an intense inflammatory response consisting of both neutrophils and macrophages. Most of the organisms remain extracellularly within a developing granuloma. In some cases a very small ulcer forms. Histopathology of these lesions shows few features associated with *M. ulcerans* infection in humans or in guinea pigs. Specifically there is little edema, tissue damage, vascular pathology, or immune suppression. We reasoned that perhaps the failure to get an ulcer was due to the superior innate immune response of the mouse. If this were the case, we thought it might be possible to overwhelm this response using purified mycolactone. For these experiments 100 ug of mycolactone were injected subcutaneously into mice. Although this amount of mycolactone produces an ulcer several centimeters wide in a guinea pig, no lesion resulted from introduction of purified mycolactone into the mouse.

2. The use of a mycolactone negative (ML-) *M. ulcerans* mutant as a vaccine for Buruli ulcer

In this experiment guinea pigs were injected subcutaneously in the inguinal area with 1) mycobacterial media (control); 2) wild type *M. ulcerans* 1615; 3) *M. ulcerans* 1615E, an isogenic mutant that does not produce mycolactone. The dose used was 1×10^5 bacteria. After 6 weeks, guinea pigs were challenged on the back with intradermal injection of 10^5 , 10^6 , and 10^7 *M. ulcerans* 1615. In control animals a typical Buruli ulcer developed within two weeks. Ulcers failed to develop in animals vaccinated with either wild type or mycolactone negative *M. ulcerans*. However, animals vaccinated with wild type *M. ulcerans* developed a large erythematous pus-filled lesion when challenged with virulent *M. ulcerans*. In contrast, animals vaccinated with the mycolactone mutant 1615E, showed little evidence of gross pathology when challenged with wild type *M. ulcerans*. Histopathology showed that vaccination with either wild type or mutant *M. ulcerans* led to a significant inflammatory response at the site of challenge characterized by the presence of neutrophils and mononuclear cells. By 21 days the site of infection appeared to be walled off. These results suggest immunization with a mycolactone-mutant of *M. ulcerans* results in protection against Buruli ulcer in a guinea pig model of infection. Although viable counts of bacteria have not yet been recovered from later time points, it appears that vaccination results in recovery of decreasing amounts of challenge inoculum over time.

3. Mycolactone variants from Australian isolates of *M. ulcerans*.

We have isolated mycolactone from 10 isolates of *M. ulcerans*. Four isolates from Africa as well as an isolate from Malaysia produce an identical mycolactone molecule as described. We recently isolated mycolactone from 5 Australian isolates; 3 from Queensland and two from elsewhere in Australia. These isolates all produce a mycolactone variant, Mycolactone C. Mycolactone C is slightly smaller and less polar than Mycolactones A&B made by our African and Malaysian isolates. Preliminary structural data suggests a modification in the ester side chain of these molecules. What the implications of this for virulence is being explored.

4. Plasmids in *M. ulcerans*.

We have begun making a BAC library of *M. ulcerans*. Examination of *M. ulcerans* 1615 by pulsed field gel suggests that this isolate may have a 175 kb plasmid. Completion of the physical map will reveal whether this is really a plasmid. We and others working in Australia (Tim Stinear) have found preliminary evidence of large plasmids from other *M. ulcerans* isolates.

5. We have tentatively identified PKS genes for mycolactone.

Role of Centers for Disease Control and Prevention, Atlanta, USA

Dr Jordan W. Tappero, Meningitis & Special Pathogens Branch, Centers for Disease Control & Prevention, Atlanta, Georgia, USA

Consultation

Dr Jordan Tappero, will continue to serve as a member of the WHO Ad Hoc Advisory Group on Buruli Ulcer, where has played an important role in helping the WHO launch the Buruli Ulcer Initiative since February 1998.

Research & Training

Setting up ongoing surveillance for Buruli ulcer disease in West Africa will begin first in Ghana, in collaboration with the Ghana Ministry of Health (MOH). To initiate Buruli ulcer surveillance, three pilot districts (Amansie West, Ga and Upper Denkyira) have been selected. The surveillance will be modeled after the Guinea Worm Eradication Program (GWEP). The GWEP in Ghana (orchestrated by the MOH in collaboration with The Carter Center, Global 2000) has offered enthusiastic support for the proposed training of GWEP village-based health care workers to conduct surveillance for Buruli ulcer disease.

Once the surveillance system is operational (August 2000), a case-control study will be performed at the village level to identify modifiable risk factors for infection. Identification of risk factors will be used to develop prevention strategies, and these strategies will be monitored for their effectiveness with ongoing surveillance. Environmental samples (vegetation, soil, water, and potential insect vectors) will be collected to check for sources of *M. ulcerans*; water samples will be tested for nitrogen levels, presence of indicator bacteria, and other variables associated with pollution. Finally, serum samples and clinical isolates of *M. ulcerans* will be obtained from consenting patients for the development of a serologic diagnostic test for infection (with or without active disease), and for the development of an anti-toxin or vaccine (see below). When and if an anti-toxin or vaccine becomes available, these well-characterized, highly seroprevalent populations at risk of developing Buruli ulcer disease will be ideal sites for a vaccine efficacy field trial.

Dr Harold King, Director, Mycobacterial Clinical Center, Emory University School of Medicine will develop an ELISA-based assay using native proteins for the serodiagnosis of Buruli ulcer disease. In addition, his laboratory will develop a proteomic database inclusive of all the proteins of different clinical isolates of *M. ulcerans* from different geographical regions of the world to identify other antigens that may increase specificity and sensitivity of second generation ELISA's as needed.

The analysis of the humoral response to *M. ulcerans* toxin(s) outlined above, and the panel of *M. ulcerans* isolates obtained from Ghana case-patients will also be used to characterize promising protein toxin candidates produced by these organisms for future development of an efficacious anti-toxin or vaccine. CDC recently awarded Dr King a grant to pursue the laboratory activities outlined above. Dr Tappero serves as the CDC project officer for Dr King's grant.

Serodiagnosis of Buruli ulcer disease

Dr C. Harold King, Mycobacterial Clinical Center, Emory University School of Medicine, Atlanta, Georgia, USA

The humoral immune response to *Mycobacterium ulcerans* may be a reliable mechanism for the generation of a diagnostic test for Buruli ulcer disease, but this has not been well characterized despite the fact that a strong humoral immune response is observed with all other known mycobacterial infections. We measured the humoral immune response of BU patients from a well defined case control study in Côte d'Ivoire to the culture filtrate of *M. ulcerans* (MUCF). This response was compared to the delayed type hypersensitivity (DTH) responses of these same patients tested with both Burulin and PPD to assess the potential of a serodiagnostic test for BU.

Evaluation of the patient DTH response generally supported BU diagnosis with overall reactivity to Burulin in 28 (71.8%) of 39 BU patients tested, versus 3 (14%) of 21 healthy case controls. However, among the 28 skin test positive BU patients, a positive response was observed predominantly in patients with healed disease (93.8%), less frequently in patients with ulcerative disease (64.7%), and rarely in patients with early ulcerative disease (33.4%), demonstrating a significant difference in the DTH response at disease stage ($p = 0.009$).

When BU patients were tested for a serologic response to MUCF, 43 (70.5%) of 61 BU patients tested had antibodies to these antigens versus 10 (37.0%) of 27 case controls and 4 of 13 (30.8%) tuberculosis patient sera ($p = 0.003$ and $p = 0.007$, respectively). There was no correlation between disease stage and the serum antibody response to MUCF antigens in BU patients ($p = 0.999$), indicating that this serologic response may be useful in the diagnosis and surveillance of BU.

Among the sero-reactive patients, significant antibody reactivity was observed against two specific *M. ulcerans* proteins of 70 and 38/36 kDa. The 70 kDa protein showed an association with BU disease (60.7% of the BU patients versus case controls, $p = 0.00002$), and was specific for *M. ulcerans* infection (88.8%). None of the tuberculosis patient sera and only three (11%) of the case control sera reacted to this antigen.

The presence of antibody to 38/36 kDa protein was also strongly associated with BU disease ($p = 0.0016$), with some cross reactivity observed in three of the tuberculosis patient and four case control sera. We then obtained serum specimens from 46 healed BU and 30 control persons (first degree relatives to these cases) from a village in Ghana. Healed BU persons were identified by the presence of old stellate scars with and without associated contractures by Dr Mark Evans (The Hospital for Tropical Diseases, London). Preliminary analysis of these sera indicated that the majority of the persons identified with healed BU retained reactivity to either the 38/36 kDa and/or the 70 kDa proteins, and some of the endemic control persons without evidence of scars were also reactive to the 38/36 kDa protein.

Interestingly, many of the healed BU and endemic control persons from this village had reactivity to a common 25–35 kDa doublet. Several of the patient and endemic

control sera from the Côte d'Ivoire study described above also had reactivity to this protein doublet suggesting that these endemic persons from different regions of West Africa were exposed to a common antigen. We have identified several of the putative diagnostic antigens from the MUCF, and we are now purifying these antigens for development of a first generation test to be analyzed in a pending case control study in the Republic of Ghana. Well characterized specimens from BU patients and endemic controls including tuberculosis and leprosy patients will be collected to determine if sero-reactivity to these MUCF proteins can be used to diagnose BU disease in these endemic areas.

Buruli ulcer (*Mycobacterium ulcerans* infection)

Dr Wayne M. Meyers, Armed Forces Institute of Pathology, Washington, D.C., USA, Sr. Julia Aguiar, Catholic Mission of Zangnanado, Zou, Benin, and Prof. Françoise Portaels, Institute of Tropical Medicine, Antwerp, Belgium

Definition and Etiology

M. ulcerans is a slow-growing mycobacterium that classically infects the skin and subcutaneous tissues, giving rise to indolent ulcers. After tuberculosis and leprosy, Buruli ulcer is the third most common mycobacteriosis. *M. ulcerans* grows optimally on routine mycobacteriologic media at 32 °C and elaborates a necrotizing immunosuppressive cytotoxin. Large ulcers almost certainly caused by *M. ulcerans* were first described by Cook in Uganda in 1897; however, the etiologic agent was not isolated and characterized until 1948 in Australia by MacCallum and associates.

Lesions of *M. ulcerans* infection have several synonyms (e.g. Bairnsdale ulcer or Searle's ulcer). The name Buruli ulcer has priority by precedence of publication, and reflects the name of the geographic site in Uganda of the first large number of reported patients; however, *M. ulcerans* infection is more appropriate because patients may present without ulcers.

Epidemiology and transmission

The source(s) of *M. ulcerans* in nature is becoming clearer from epidemiological data and from molecular biologic findings. *M. ulcerans* has been identified in water bugs collected from deep in the mud of permanent wetlands. One factor promoting the growth of *M. ulcerans* in this setting is its preference for microaerophilic ambience. The water bugs frequently take flight and often bite humans. This putative insect transmission of *M. ulcerans* does not obviate the possibility of other modes of transmission (e.g. aerosols). Because all major endemic foci are in wetlands of tropical or subtropical countries, environmental factors must play an essential role in the survival of the etiologic agent. Koalas and opossum are naturally infected in the wild in Australia. Many other species of animals have been infected experimentally. The disease is rarely transmitted from patient to patient; however, travelers in endemic areas have contracted Buruli ulcer.

Trauma is probably the most frequent means by which *M. ulcerans* is introduced into the skin from surface contamination. The inciting trauma reported has been as slight as a hypodermic needle puncture or as severe as gunshot or exploding land mine wounds. Individuals of all ages are affected, but the highest frequencies of infection are in children under 15 years of age. Children in rural areas of the tropics may contract the disease more often because of their scanty attire and increased activity in or near swamps.

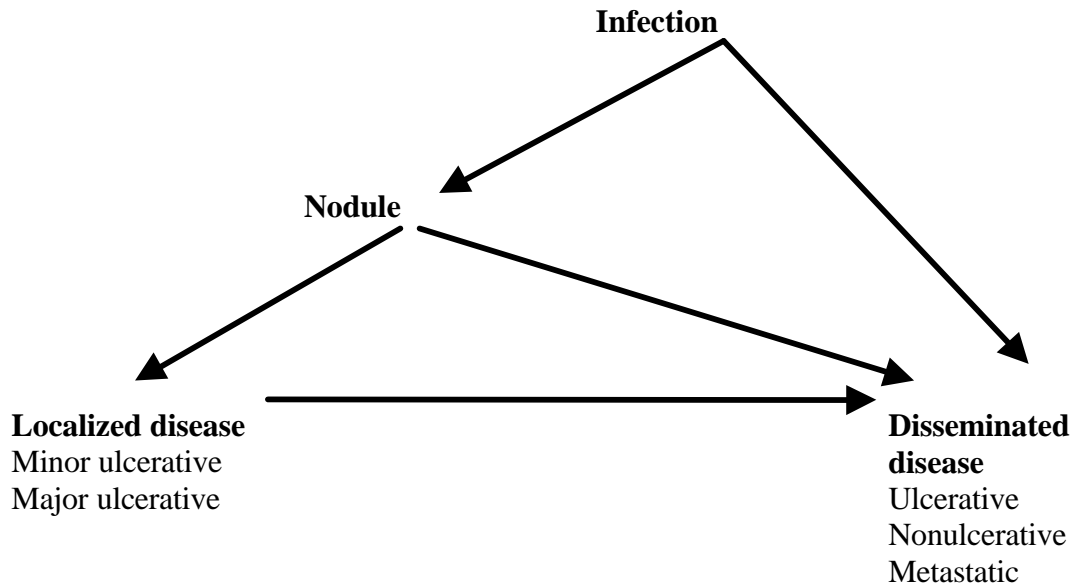
The largest known concentrations of patients have been in Uganda and Congo (Kinshasa) in Central Africa, and Côte d'Ivoire, Ghana and Benin in West Africa.

Other established endemic countries in Africa include Sierra Leone, Liberia, Guinea, Burkina Faso, Togo, Nigeria, Cameroon, Equatorial Guinea, Gabon, Republic of Congo (Brazzaville) and Angola. There are personal communications suggesting that foci exist in Chad, Malawi and Sudan. We expect to obtain confirmation of the situation in these countries in the near future. Some southeast Asian countries and Australia have significant foci, and there have been a few patients reported from South America (French Guiana, Surinam, Bolivia, Peru) and Mexico. Focal outbreaks have followed flooding, human migrations, and man made topographic modifications such as dams and resorts. Deforestation and increased basic agricultural activities may significantly contribute to the marked increases in incidences of *M. ulcerans* infections since about 1980, especially in West Africa where the disease is rapidly emerging. An explanation for the apparent recent striking decrease in incidence of *M. ulcerans* infection in Uganda would be of special interest.

Clinical manifestations

Classically, lesions are single and often begin as firm, painless, non-tender, movable, subcutaneous nodules 1 to 2 cm in diameter. Some geographic areas report a papule as the earliest manifestation. Most often the disease begins on the extremity, especially around articulations. Many patients complain of itching in the lesion. In 1 or 2 months, the nodule may become fluctuant and ulcerate, with a widely undermined edge. The skin adjacent to the ulcer, and often that of the entire corresponding limb, may be indurated. Clinical observations on large numbers of patients suggest that, in some patients, following inoculation the disease disseminates rapidly and widely, bypassing the initial nodule. Ordinarily, no clinical regional lymphadenopathy or systemic manifestations are noted. There is, however, speculation that massive disseminated lesions may cause specific systemic toxic effects. In depth laboratory studies on this topic are planned, but autopsy findings in patients dying with massive lesions is an important priority. Ulcers may remain small and heal without treatment, or may spread rapidly, undermining the skin over large areas, even an entire leg, thigh, or arm. Important structures such as the eye, breast, or genitalia are sometimes lost or severely damaged. Osteomyelitis may lead to amputation and other crippling disabilities. Most lesions heal spontaneously but without appropriate therapy frequently leave extensive scarring in their wake. Contraction deformities often follow mismanaged disease.

We propose a provisional clinical classification of active *M. ulcerans* lesions as outlined in the following diagram:



We believe that minor ulcerative lesion self-heal rather early, and major ulcerative lesions tend to self-heal, but may disseminate.

Pathogenesis and Pathology

After inoculation into the skin, *M. ulcerans* proliferates and elaborates a toxin(s) that causes necrosis of the dermis, panniculus, and deep fascia. One well-defined toxin of *M. ulcerans* is a polyketide-derived macrolide (named, mycolactone) and is a virulence factor for Buruli ulcer. Early lesions are closed, but as the necrosis spreads, the overlying dermis and epidermis eventually ulcerate, leaving undermined margins and a necrotic slough in the base of the ulcer. Histopathologic sections reveal contiguous coagulation necrosis of the deep dermis and panniculus, with destruction of local nerves, appendages, and blood vessels. Clumps of extra-cellular acid-fast bacilli (AFB) are plentiful and are frequently limited to the base of the ulcer and adjacent necrotic subcutaneous tissue. The etiologic agent may spread, probably hematogenously, to distant foci, usually to skin and bone. Specific, severe osteomyelitis is well known. Histologically there may be local and regional necrotizing lymphadenitis with invasion by *M. ulcerans*. In active lesions, inflammatory cells are conspicuously few, presumably as a result of the immunosuppressive activity of the toxin. With healing, there is a granulomatous response, and the ulcerated area is eventually replaced by a depressed scar.

While information on the topic remains limited, HIV infection does not seem to predispose to Buruli ulcer nor render infection with *M. ulcerans* more aggressive.

We have proposed the following histopathologic classification of stages of *M. ulcerans* infection: I, Necrosis, II, Organizing, and III, Healing.

In a histopathologic study of biopsy specimens of skin from more than 1000 patients, using the above classification, we have obtained the following results in confirmed lesions (AFB in the biopsy specimen, and/or PCR and culture positive for *M. ulcerans*):

Stage in Skin	Percent of Patients
Necrosis	70%
Organizing	2%
Combined (necrosis organizing, healing)	20%
Healing	8%
Total	100%
Osteomyelitis	10%

The following conditions were diagnosed in specimens submitted as *M. ulcerans* infection: squamous cell carcinoma; osteoma cutis; *Basidiobolus ranarum* infection; nonspecific panniculitis; staphylococcal panniculitis, and mycobacteriosis other than *M. ulcerans* infection.

In addition to their usual distribution in the skin, AFB were seen in bone marrow, osteocytes and in muscle.

Diagnosis

Smears from the necrotic base of ulcers stained by the Ziehl-Neelsen method usually reveal clumps of acid-fast bacilli. Appropriate selected biopsy specimens that include the necrotic base, the undermined edge of lesions, and subcutaneous tissue are nearly always diagnostic. Biopsy specimens from nonulcerated disease are probably best obtained from the presumed center of the lesion. *M. ulcerans* can be cultured from many lesions, either from exudates or biopsy specimens, but visible growth often requires 6 to 8 weeks or longer of incubation at 32°C. Inoculated media are usually retained for 1 year before discarding. Molecular biologic techniques are often useful in establishing the diagnosis, especially where culture and histopathologic analyses are negative for *M. ulcerans*.

Treatment

Preulcerative lesions are excised en bloc, and the skin is closed primarily. Ulcers, and disseminated nonulcerative lesions, are widely excised and skin grafts applied. Consideration should be given to appropriate studies to define the optimal extent of surgery in life-threatening disseminated lesions. Continuous local heating to a temperature of 40 °C (e.g. by circulating water jackets) promotes healing, even without excision. Amputation of limbs is sometimes necessary. Rifampin promotes healing of preulcerative lesions or early ulcers but is often not effective for extensive lesions. To limit the spread of *M. ulcerans* organisms, patients should receive antibiotics (e.g. rifampin and clarithromycin) prior to surgery and continued for several weeks after surgery. Appropriate physiotherapy is important when contraction deformities are likely to develop.

Prevention

No effective prophylactic measures have been demonstrated, but a single Bacille Calmette-Guérin (BCG) vaccination may provide protection or delay onset of lesions for approximately 6 months. BCG vaccination in series would seem to offer the only currently acceptable strategy for field studies in the immunoprophylaxis of Buruli ulcer.

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Gamma interferon response to stimulation with *M. ulcerans* antigen preparations of peripheral blood T cells from patients with *M. ulcerans* disease

Drs Harry Thangaraj, Mark Evans, Richard Phillips, Mr Joseph Adomako, Mr Nasas Ofosu-Kwabi, Prof. Ohene Adjei and Dr Mark Wansbrough-Jones.

It is known that (a proportion of) patients with *M. ulcerans* (MU) disease have a delayed hypersensitivity skin test response to burulin, a crude preparation of antigen from MU grown in protein free medium. Patients with a positive response are usually in a late stage of the disease when the tissue shows signs of healing. It is assumed that earlier development of this type of reaction is inhibited by mycolactone production in the tissues. We aimed to investigate further the cell mediated immune by measuring the production of gamma interferon when whole blood samples are stimulated by MU antigens.

Heparinized blood was drawn from patients with MU disease at different stages and from controls living in the same endemic areas. Further controls were patients with proven tuberculosis. A standard concentration of MU antigen was added in multi-well plates and other antigens were used for comparison including PPD, *M. avium* and lipid extracted MU. After overnight incubation, the supernatant was separated and frozen for subsequent assay. Gamma interferon was measured by ELISA assay.

In the first study, the MU antigen was prepared from mycobacteria cultured in a protein containing medium. 5 out of 10 subjects with healed ulcers but only 5 out of 28 with active ulcers had a positive response to MU antigens. These responses appeared to be specific in that they were significantly higher than those to PPD or *M. avium* antigens. A second study is under way using MU cultured in protein free medium and, so far, a smaller proportion of subjects have positive responses; 5 out of 46 with healed ulcers and 0 out of 11 with active disease. No responses to MU antigen have been detected in normal children from endemic areas or from patients with active tuberculosis. Chloroform extracted MU antigen was also tested in case small amounts of mycolactone were inhibiting gamma interferon production but the results were similar to those using unextracted antigen.

These results suggest that a small proportion of patients with MU disease develop a specific T cell mediated response to MU antigen. Further work is required to elucidate the time at which this develops.

Conceptual problems in estimating the burden of Buruli ulcer

Mr Frank Dadzie, Department of Economics, Clark Atlanta University, Atlanta, GA, USA

Introduction

Prior to the collaborative efforts of the World Bank and the World Health Organization in estimating the global burden of some 100 diseases, there had been attempts to quantify the state of health of a population by some index of health status. An index of health status is a specific measure of selected characteristics which purports to be useful in monitoring fluctuations in health status over time, and which can be compared to that of other populations. Society valued positive improvements in these indices as an accepted goal, and public health programs utilized the notion to compete with each other and with other government activities for budget allocations. Crude and age-adjusted death rates became popular indices, and the assumption had been made that a decline in mortality rates reflects changes in other aspects of health as well (Sullivan 1966).

However, as mortality rates declined and the scope of public and private health services increased, the health of the living became a very important aspect of health status. Although useful as a component of health status, changes in age-cause specific mortality were found to produce little change in the health status of the population in the United States (Moriyama, 1956). These considerations suggested that a more sensitive and informative measure of levels of health could be obtained with an index based on health characteristics of the living as well as mortality. The recent effort by the Global Disease Burden team arrived at such an index known as *disease-adjusted life years lost* (or DALYs). Construction of such an index requires selection of the concepts to be measured, specifications of operational definitions for these concepts, the determination of the measures to be used, and the method of combining them into a single index.

This paper does not propose a method for constructing an index for Buruli ulcer. That is expected to be the subject of a subsequent study. Instead, it attempts to discuss the conceptual problems, and to explore the aspects of Buruli ulcer that may be measured in an attempt to estimate its burden. It begins with an outline of some of the reasons why such an estimate is currently inevitable even for attracting the requisite funding for interventions. While earlier efforts were aimed at constructing an index for the overall health status, recent techniques have made it possible to estimate the effects of individual diseases on the overall health status. This way, scarce health resources could be allocated to those programs with the potential to produce greater reduction in the burden of the disease, or resources are reallocated away from those programs with the potential to produce the least increase in the disease burden.

The rationale for estimating the burden of Buruli ulcer

The general scarcity of resources in a given health sector is one compelling reason for the estimation of the burden of various diseases with the view to setting health service (both curative and preventive) and health research priorities. Besides priority setting, measures of the burden of disease can, among other things, help to identify disadvantaged and vulnerable groups within a country, and consequently permit the targeting of health interventions. An index of the burden would also provide a comparable measure of output of different interventions (or packages of interventions), permit comparison of cost-effectiveness of various interventions, and allow for program and sector evaluation and planning purposes (Morrow and Bryant, 1995). While these end uses of measures of the burden are of varying importance from country to country, it is their role in setting health priorities that is frequently the focus of attention in most developing countries where acute scarcity of resources is common.

The scarcity-based intent to measure the burden of disease is to promote a better (more efficient) use of scarce resources in reducing the effects of the disease on a given population, a group of individuals, or single individuals. However, one cannot examine issues of efficiency without looking at both inputs and outputs, i.e. costs and benefits, where benefits are measured in terms of reduction in the disease achieved by a particular intervention. The burden of disease, however it is measured, is not a particularly useful concept if it is assessed separately from the policies and resources associated with addressing the burden. Thus, conceptually, it is necessary to give some consideration to the relationship between the burden of disease and the effect that different treatment, care, or prevention interventions may have upon the disease. Therefore, the prime objective for estimating the burden of disease is best seen in the context of attempting to estimate the reduction in its burden through application of some treatment or preventive regime which inevitably involves the use of scarce resources. Such efforts are a means towards allowing the quantification of the effectiveness of a particular intervention on the disease. The relevant techniques for addressing such issues are cost-effectiveness and/or cost utility analyses.

By the foregoing arguments, the need to estimate the burden of Buruli ulcer is even more important when it comes to allocation of resources towards the control of the disease. Although prevalence of the disease had been reported in many tropical and sub-tropical areas (in Sub-Saharan Africa, Australia, Papua New Guinea, Malaysia, and other countries in the Pacific Islands) for many years, it has not captured the resource commitment of health authorities, especially in Sub-Saharan Africa, until recently when reports of high incidence and vivid images of its clinical burden became newsworthy in some countries. In both Ghana and Côte d'Ivoire, the supposedly alarming incidence of the disease has only recently raised serious concerns, and efforts to contain the disease have only begun to attract long overdue attention from government circles. Even so, in Ghana, as recently as the financial year 1995, no government budgetary appropriations had been made towards its control, prevention or studies pertaining to the disease. Thus, in terms of priorities setting in health resource allocations, Buruli ulcer has never successfully attracted the requisite resources for activities relating to its control. Knowledge of the burden of the disease could perhaps kindle and sustain interest in the disease's control and thereby attract both private and public budgetary allocations.

Buruli ulcer

Buruli ulcer, (hereafter referred to as BU) is the third most common mycobacterial disease of the immuno-compromised humans in the world after tuberculosis and leprosy in that order. This disease is caused by *mycobacterium ulcerans*, and leads to massive destruction of the skin layer, often resulting in debilitating deformities and severe prolonged morbidity (Meyers et al., 1996). Current evidence suggests that the infection is transmitted through abraded skin or mild traumatic injuries after contact with contaminated water, soil, or vegetation. The clinical picture ranges from a painless nodule to large, undermined ulcerative lesions that heal spontaneously but slowly. The disease is accompanied by remarkably few systemic symptoms, but occasionally secondary infections resulting in sepsis or tetanus cause severe systemic disease and death. Extensive scarring can lead to contractures of the limbs, blindness, and other adverse sequelae that impose a substantial health and economic burden. In Sub-Saharan Africa, the affected populations are typically underprivileged and poor, and the economic burden imposed by BU is daunting (van der Werf et al., 1999).

The disease affects individuals of all ages, but the highest frequencies of infection are in children under 15 years of age. The largest known concentrations of patients are in Uganda and Congo in Central Africa, and Côte d'Ivoire, Ghana, and Benin in West Africa. Some Southeastern Asian countries and Australia have major foci, and there have been a few patients reported from South America and Mexico (van der Werf et al., 1999).

Because Buruli ulcer has no specific clinical manifestations and indolent course, those who are afflicted usually delay in seeking medical care until there is extensive subcutaneous necrosis, which can only be controlled through extensive surgical excision. Early detection and diagnosis, however, could simplify surgical management and reduce the chance and extent of deformities or the need for amputation. Thus, this disease confers prolonged morbidity on its victims, mostly children of ages between 2 and 14, as has been reported in studies in some Sub-Saharan African countries (van der Werf, Graaf, Groothuis, and Knell, 1989).

The lack of attention may be traced to the absence of estimates of the burden of the disease, which may provide a basis for comparison with other diseases, competing for the already dwindling health resources. The absence of disease burden estimates can in turn be blamed on the paucity of formal epidemiological studies of the disease in specific communities. Where some studies exist, the information on incidence, prevalence, and other characteristics of the disease is rather scanty, and thus makes it difficult to initiate any serious estimation effort on its burden on the target populations. By its nature and effects, the disease may well be on its way to becoming one of the dominant sources of disability in some of the endemic countries. In a recent study in Côte d'Ivoire (Marston et al., 1995), an observation was made that "Buruli ulcer is associated with severe morbidity and a high proportion of ulcers lead to scarring, retraction, and long term disability." In the referenced study, it was observed that more than 63% of the patients surveyed were found to have stopped working or attending school, and in more that 25% of those affected, there was permanent handicap such as inability to use the limb. Thus, by the author's conclusion buruli ulcer "is a debilitating disease that is rapidly spreading in West Africa; and that "further research is urgently needed to identify environmental reservoirs of *M.*

ulcerans and to define specific activities that lead to acquisition of BU. In addition, better therapeutic options for affected individuals are needed to reduce the devastating sequelae of the disease.”

State of the art of intervention

Treatment is still primarily surgical, and includes excision, skin grafting, or both. Medical treatment of these ulcers is in general disappointing, leaving wide surgical excision as the only alternative (Portaels, 1995). Preulcerative lesions are excised en bloc, and the skin is closed primarily. Ulcers are widely excised, and skin grafts are applied. Continuous local heating to 40 degrees Celsius promotes healing even without excision. Amputation of limbs is sometimes necessary. Early diagnosis and treatment, especially in children, will have a positive economic impact by significantly reducing the disabilities that often result from delayed diagnosis. *Rifampin* promotes healing of pre-ulcerative lesions or early ulcers, but is often not effective for extensive lesions. Appropriate physiotherapy is important when contracture deformities are likely to develop. No effective prophylactic measures have been demonstrated, but *bacilli Calmette-Guerin* (BCG) vaccination may produce protection or delay onset of lesions for approximately six months. Although BCG has a mild but significant protective effect, new vaccine developments directed at the toxins produced by *M. ulcerans* are warranted.

Choosing a measurement approach

Perhaps the most important reason for the measure relates to the evaluation of the relative efficiencies of different types of interventions. Such evaluation is needed to guide optimal use of scarce resources to deal with the effects of disease. Discussions regarding the three known approaches for measuring the burden of diseases have occupied considerable space in the public health literature. They have included: (a) the Healthy Life Years approach (HLYs) developed by the Planning Unit of Ghana's Ministry of Health, also referred to as the Ghana Health Assessment Project Team; (b) the disability-adjusted life years approach⁶, also typically referred to as the DALYs approach.⁷ and (c) the quality-adjusted life years (QALYs) approach. The conceptual, methodological, and ethical issues underlying these approaches are far too engaging to be recounted in this paper. Rather, the paper highlights the conceptual underpinnings of the DALYs approach, and argues that for most developing countries DALYs approach may be the obvious choice, although QALYs may also be relevant for estimating the burden of BU for a country like Australia. Furthermore, the paper goes on to identify the critical epidemiological data gaps that need to be filled by preliminary studies to permit the application of the DALYs technique to estimate the burden of *BU*.

The conceptual bases for DALYs approach are summarized in terms of the following arguments (see Murray 1994):

- The set of value choices made in calculating DALYs differ from those of other indicators. These choices include the definition of the duration of life lost, the

⁶ Concept made popular by World Bank's World Development Report (1993)

⁷ . Foege (1994) defined the acronym DALYs as *disease-adjusted life years*, perhaps to emphasize its focus on common diseases facing developing countries.

assessment of the value of life lived at different ages, comparability of time lived with disability and time lost due to premature mortality, and the way to treat time preference. These choices are typically selected in such a way that the derived indicator is comparable across a wide range of environments.

- The difference between DALYs (and QALYs) approach on one hand and HLYs approach on the other is that DALYs (and QALYs) includes time lived with disability. This is especially important for BU, given its main legacy of prolonged and often permanent disability. However, QALYs approach requires refined measures of disability that may only be available in advanced industrialized countries. In developing countries, refined measures of disability are much less important because of the overwhelming importance of preventable premature death, inadequacy of data, and the relatively high cost of studies on quality adjusted life years gained⁸. Thus DALYs approach, with its basic linear measurement of disability is especially conducive for developing countries.
- Estimates of the burden of disease denominated in DALYs can easily be used in conjunction with the literature on cost-effectiveness of health intervention for purposes of priority setting in health services and research.
- The more original aspect of DALYs is not their design but the successful application of the indicator to measure the burden of disease for other diseases in different regions for different age groups among males and females. Also, while details such as the distribution of disabling sequelae by class are bound to change as more information becomes available, DALYs is already established as a feasible alternative for assessing the burden of disability and premature mortality.

A detailed discussion of the foregoing attributes of DALYs approach, along with a fuller exposition of the appropriate value choices and the methodology for estimating the burden of BU, is anticipated to be a logical development in a separate paper. Nonetheless, it suffices to say that both DALYs and QALYs approaches have a common advantage over the HLYs approach for the purpose of estimating the burden of BU because both approaches incorporate the effects of mortality and disability into the estimation of the composite index. However, because of the absence of elaborate data on BU, along with the lack of refined measures of disability in most developing countries, DALYs approach is particularly conducive for most of these countries, while QALYs approach may be relevant for countries with sophisticated data collection capabilities and with much refined measures of disability such as Australia. Moreover, for most developing countries, the uses of the index include its comparison with existing indicators of other diseases (such as those derived from the Global Disease Burden study). Thus, for the sake of consistency and comparability DALYs approach would be the warranted.

Epidemiological data gaps

⁸ QALY focuses on assessing individual preferences for different nonfatal health outcomes that might result from a specific intervention. In that approach, severity of illness is judged on the basis of two criteria namely, observed disability (loss of function or mobility), and subjective distress (pain or anguish) This systems identifies eight (8) levels of disability and four (4) distress levels, yielding a total of 29 disability/distress states, each with an assigned value for each patient. These values are averaged to give overall measure of disability for each possible outcome of alternative treatment for the patient in question. (Gudec and Kind 1988).

DALYs require for their computation extensive age and sex-specific information on the incidence of disease, the proportion of disease incidence leading to a disabling outcome, the average age of disability onset, the duration of disability, and the distribution of disability across the six classes of disability, adopted in the global burden of disease study. In addition to the foregoing requirements, information on prevalence, remission, and case fatality are needed in checking for internal consistency and calculating the duration of disability and mortality.

M. ulcerans, the source of BU, is a class of nontuberculous mycobacterial (NTM) diseases, which are generally undiagnosed or not reported in developing countries because of a lack of laboratory facilities or simply because of a lack of interest by public health services. The latter underestimates the importance of the disease partly on the assumption that it is not contagious. Portaels (1995) suggests that BU may be considered an “orphan” disease, as few medical programs pay attention to this affection. It is generally under diagnosed and in general not properly treated. In the absence of appropriate therapy, the disabilities caused by this disease may be devastating. The same study also observes that Buruli ulcers afflict many impoverished inhabitants, primarily children in remote areas where the facilities for modern medical science are unavailable or too expensive. The epidemiology of *M. ulcerans* disease seems to be closely associated with the natural environment and climatic changes (e.g. floods). However, the presence of this mycobacterium in the environment has not been conclusively established. Portaels (1995) asserts that because of the close association between the natural environment and *M. ulcerans*, control of the disease may be difficult. Like other NTM diseases, the Epidemiology of *M. ulcerans* is far from being fully understood. Sources of infection, the mode of transmission, and the relationship between host behavior and risk factors involved in disease contraction is yet to be confirmed.

The foregoing epidemiological characteristics of BU pose considerable problems in eliciting the requisite information for the estimation of disease burden. Since BU is generally unreported and undiagnosed, it is unlikely for actual disease incidence to be ascertained accurately. At best, the prevalence is the most likely statistic that may be readily obtainable. Estimates of the incidence consistent with the observed prevalence will need to be developed by some methodology. The age and sex-specific prevalence of the disease may be obtained but not without considerable investment of time and effort in surveying the target population.

A major obstacle to linking public health studies on particular diseases with research on disability is the absence of a probability mapping of diseases from its incidence to impairments to disabilities. For the Global Burden of Disease, this mapping was developed in iterative manner. For some conditions, the percentage becoming disabled is better interpreted as the proportion of time the individuals with this condition are disabled. The proportion going on to develop a disability is also a function of how one defines incidence; a restricted definition means a higher proportion will go on to develop disability and vice versa. Because Buruli ulcer is accompanied by remarkably few systematic symptoms, it is difficult to monitor its incidence through its disabling sequelae. An important improvement in the assessment of disability is to include short-term consequences of the disease. To be able to monitor adequately the disease from incidence will require advanced clinical capabilities to detect the disease from onset.

The other type of information required by DALY is the distribution of disability across the six classes of disability, in accordance with the GBD study approach. This classification could be accomplished by drawing from the experience of the GBD study. The six classes used in the study are provided in the appendix to this paper, with the appropriate weighting system provided.

Measuring the duration of disability involves estimates of the incidence of disability. There are at least two ways of measuring the aggregate time lived with disability. One method is to take point prevalence measures of disability and estimate the total time lived with disability as prevalence (P) x one year. The alternative method is to measure the incidence of disability and the average duration of each disability. The incidence perspective is more relevant to BU because it is more sensitive to current epidemiological trends, and will reflect the impact of treatment or rehabilitation more rapidly. Since the objective of DALYs is to quantify the current burden of the disease, it must take into account current activities including preventive and curative health care. Medical intervention can affect disability in four ways: changing the disease incidence, the probability of developing a disabling sequelae, the duration of disability, and the severity of disability. The accuracy of incidence estimates for disability would influence the estimates of its duration.

Conclusion

The problem of finding a more satisfactory index for the burden of Buruli ulcer arises from the nature of the disease's outcome. It has been confirmed by several researchers that Buruli ulcer is associated with prolonged severe morbidity, and that better therapeutic options are needed to reduce the devastating sequelae of the disease. Thus, a method of estimation of the disease's burden is required that incorporates both mortality and morbidity into its estimation process. While an index reflecting both morbidity and mortality is worth pursuing, its components need measurable definitions and conceptual clarification. This paper has only attempted to explore the conceptual problems that would be expected arise in the development of a suitable indicator for the burden of BU. The paper began by identifying the most relevant approach for estimating the disease burden, taking into consideration the characteristics of individuals that are typically affected by the disease, and drawing upon the experience of the global disease burden study. The author asserts that the conceptual framework of the disability-adjusted life years (DALYs) approach, coupled with its linear definition of disability and basic data requirements makes it conducive for its application in most developing countries. Nevertheless, QALYs approach would be applicable in industrialized countries, given its requirements of refined measures of disability and sophisticated data collection capacity. The paper goes on to identify the structural components of DALYs approach and emphasizes its expectation that a methodology that incorporates both disability and mortality would be brought to bear on the burden index for Buruli ulcer, since its outcome is generally non-fatal.

Methodological issues are considered to be outside the focus of this paper, and could be the logical corollary of this conceptual paper. Nonetheless, the paper reviews what is known about Buruli ulcer, the state of the art of its treatment, and an identification of the gaps in data with respect to each of the pieces of the DALYs formulation. Given this information, one can begin to prioritize the research agenda and the studies

that need to be done to collect the appropriate data. The section on epidemiological data requirements concludes that considerable information gap exists for such data, and that any estimation effort must begin with preliminary epidemiological studies to generate the basic required data such as disease incidence, prevalence, remission, case fatality, distribution of disability across the various classes, the duration of disability, and the average age of disability onset.

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World Health Organization Global Buruli Ulcer Initiative Website [www.who.int/gtb-buruli.]

Message from Professor Asano, Chancellor, Nippon Medical School, Tokyo, Japan to the 3rd annual meeting of the WHO advisory group on Buruli ulcer.

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

«Dear Colleagues, Ladies and Gentlemen,

In April 1999, Dr Wayne Meyers, the chief of Mycobacteriology at the AFIP, Washington DC, USA presented a special lecture on Buruli ulcer at the 72nd meeting of the Japanese Leprosy Society, in Tokyo. He made a request, being a member of the WHO Advisory Committee on Buruli ulcer, for any kind of contribution, from Japanese researchers, to the Buruli ulcer issue.

I have been a member of the Japanese Leprosy Society for about 30 years, President of the 66th and 68th annual meeting in 1993 and 1995 and I am now Chief Editor of its journal. I attended the meeting in April and promised to respond to Dr Meyers' request.

Our interest grew even bigger when for our second gathering related to Buruli ulcer in Japan, we joined Kobe International University, which organized a fund raising event, International Symposium on Buruli ulcer, on November 26th, 1999.

The symposium was a success, in terms of raising the awareness of the disease in a country almost ignorant on the subject. Professor Shimomura and Dr Fukunishi were present and were very instrumental in organizing this symposium. Lastly, on behalf of the Medical Association of Nippon Medical School, we invited Dr Kingsley Asiedu, Coordinator of the Buruli Ulcer Initiative at WHO, to give a special lecture on Buruli ulcer at our school in Tokyo, on November 29, 1999. An urgent need for assistance to Africa, on Buruli ulcer was officially expressed by Dr Asiedu to our School. The first line of answers to those needs was from our department of pathologists.

It has been established that the histopathology of lesions caused by *Mycobacterium ulcerans* is unique. As such, we may be able to provide training for pathologists to serve not only Buruli ulcer but the general of pathology in tropical diseases.

Hence, we believe that we can do the following:

1. Establish a Collaborating Reference Center for Tropical Diseases to serve Africa and Asia.
2. Train medical doctors from those geographic areas first, as general pathologists.
3. Provide the frame for research in histopathology and immunopathology of specific diseases, including *Mycobacterium ulcerans* infection and leprosy.

4. Establish a strong research link with centers (e.g. AFIP, Washington DC, USA; CDC, Atlanta, USA; Institute of Tropical Medicine in Antwerp, Belgium and Noguchi Memorial Institute for Medical Research, Accra, Ghana) already involved in research on specific tropical diseases such as Buruli ulcer, Haemorrhagic fevers and Malaria;
5. Provide diagnostic support in histopathology for these diseases;
6. Provide logistic support to strengthen laboratories in endemic countries.

Dear colleagues, I would like to end my speech, by praising the efforts being made by WHO in the fight against Buruli ulcer as well as other diseases. We have come to know Buruli ulcer only recently, but it is an honour for the Nippon Medical School, the Department of Pathology and myself, to have been invited on two occasions to participate in workshops in the fight against this skin disfiguring disease, with devastating socioeconomic consequences, especially in children. We have already informed WHO of what we can do along with other Japanese institutions as our contribution to the fight against this disease. I renew the pledge of our objectives and I am looking forward to having a fruitful collaboration with WHO in the field of tropical diseases.

Thank you.»

Role of Noguchi Memorial Institute for Medical Research, Accra, Ghana

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

Objectives and mandate of the Institute

- To conduct research into infections and communicable diseases prevalent in Ghana and into nutritional problems;
- To provide training opportunities for post graduate students in medical research; and
- To provide specialized laboratory diagnostic and monitoring services in support of public health programmes.

The Noguchi equation

Facilities

Science

Application of science

Local

National

International

Facilities

- Existing building contains nine research units;
- Bio-safety level 3 laboratory facilities (HIV and TB);
- Laboratory animals facility;
- Conference facilities and
- Field stations.

Staff

- 23 research fellows
- 47 senior staff
- 21 junior staff

Science

Research focus on:

- communicable diseases
- nutrition
- phytomedicines
- non-communicable diseases of public health importance
- emerging diseases of public health importance.

Major disciplines

Epidemiology	Clinical trials
Bacteriology	Parasitology
Immunology	Virology
Clinical pathology	Nutrition
Electron microscopy and histopathology	Biostatistics
Laboratory animals	Medical sociology

Research partners

Japanese International Cooperation Agency (JICA) experts;
Local universities and institutes
Ministry of Health, Ghana
External universities and institutes in Africa, Europe and USA

Funding partners

JICA, Government of Ghana/Ministry of Health, UN agencies (WHO, IAEA, UNICEF, UNAIDS), DANIDA, CIDA, European Union, Wellcome Trust.

Role in Buruli ulcer control and research

- Topical public health problem in Ghana;
- Rising incidence of Buruli ulcer;
- National commitment to control the disease;
- Regional Director, WHO Regional Office for Africa has contacted the Institute to collaborate on work on Buruli ulcer and
- New facilities for mycobacterial research.

Science relevant to Buruli ulcer

Epidemiological tools, GIS facilities, access to remote sensing equipment, clinical trials (GCP standards), genetic polymorphism, electron microscopy (2), immuno-histochemistry, immuno-fluorescence facilities, animal laboratories, FACScan (2), PCR, ELISA, maintenance of cell lines, culture media preparations, culturing of mycobacteria, antibiotic sensitivity testing, bacterial toxin studies and established field stations.

Application of science

- Training (undergraduate, postgraduate and in-service);
- Laboratory diagnostic support;
- Dissemination of findings;
- National health policies and
- Disease surveillance and quality control.

Enabling environment

Bridging gap – science and policy

Information technology (cataloguing and inventory, local area network, internet access – VSAT [MIMCOM], library, improved administrative procedures and sharing of resources.

Sasakawa Memorial Health Foundation, Tokyo Japan

Mrs Kay Yamaguchi, International Programs, Sasakawa Memorial Health Foundation, Japan

First of all let me thank WHO, in particular Buruli ulcer unit for organizing this meeting and have given us an opportunity to introduce our involvement in BUI. Let me briefly go back to how Sasakawa Memorial Health Foundation (SMHF) and The Nippon Foundation (TNF) have come to be involved in the Initiative. The two foundations share a common interest, that is to serve for the better health of the people in the developing world. SMHF was established in 1974, specifically to contribute toward leprosy control in the countries where leprosy is still a public health problem. It's establishment was a product of a dream of two prominent leaders in Japan; one being Mr. Ryoichi Sasakawa, the founder of TNF, and the other was Professor Morizo Ishidate, a prominent pharmacological scientist, a dedicated Christian, who for the first time in Japan synthesized Promin, the then miracle cure of leprosy, in late 1940s and opened a new era of leprosy treatment in Japan. Prof. Ishidate later became the first board chairman of SMHF. These two gentlemen were born at the very final decade of 19th century and thus personally witnessed the widespread misery of leprosy patients in Japan. Each in his own way committed to leprosy relief. As a natural development of the time, they met and joined hands to work for the cause.

After 25 years since the, we are now looking ahead of the day when we can talk about elimination of leprosy, although intensified efforts are needed if we are to successfully achieve this goal. A number of people present here, including Dr Neira and Prof. Grosset are fully aware of this. The two pioneers left us before we could report to them that their dream is becoming a reality, but they knew it was the right path for the world to place priority to deliver the cure as quickly and as far away as possible to the people who need it. At the final stage of leprosy elimination effort, the commitment of TNF and SMHF remain intact, as WHO is well aware of.

BU was not an agenda of neither of the two foundations until recently but because of the already established channel between WHO and SMHF, and also the involvement of quite a number of leprosy experts and NGOs to BU, it came natural for SMHF to be a coordinator with WHO on behalf of TNF, although it is not likely for TNF to establish two funding channels for BU, one direct and one through SMHF, as in the case of leprosy.

For both foundations, BU was totally unknown until one afternoon in October 1996, when we organized a small meeting over lunch in Tokyo where several leprosy experts along with Mrs. Ayako Sono, the chairperson of TNF and Mr. Yohei Sasakawa, President. Mrs. Sono is a well-known novelist and an essayist but she is also a frequent visitor to African countries. She had visited Côte d'Ivoire and while visiting a clinic in Zoukougbeu she saw devastating skin ulceration in many children. She said to the guests at lunch, "I wonder if anyone of you know about what they call locally Daloa ulcer. Is there any cure or prevention?" Leprosy specialists Prof. Lechat and Dr Noordeen were among the guests and they said, "It must be Buruli ulcer. The best persons to contact were Dr Wayne Meyers and Prof. Françoise Portaels." I am

sure Dr Meyers remembers that I contacted him immediately and he responded to me with a whole lot of documents and saying he was very happy that at last some one has shown interest in Buruli ulcer.

However, TNF's interest did not go very far from that stage until April 1997 when, at leprosy meeting held in WHO HQ, the then Director-General of WHO, Dr Hiroshi Nakajima, approached representatives of SMHF and TNF who were at the meeting with a news of alarming increase of BU cases in Western African countries and asked to explore a possible funding from TNF to WHO.

The initial interest of Mrs. Sono and WHO's initiative were joined, which later developed to formulate a forum for international effort against Buruli ulcer. After some negotiations TNF agreed to release US\$500,000 over two years as seed money for WHO to review the situation and raise awareness in the scientific and medical community world-wide.

The initial two years that followed have seen a number of developments, which we have heard today and will hear during this meeting. Although the definite breakthrough is still to be waited, it is no doubt that the initial funding was effectively utilized to mobilize interest and actions. WHO BU unit should be congratulated for successfully utilizing this fund as a catalyst to mobilize and coordinate the wider actions.

During the leprosy conference held in Abidjan last November, Mr. Sasakawa visited Raoul Follereau Center in Adzopé and observed BU cases and its treatment. Dr Kingsley Asiedu and myself accompanied him together with another officer from TNF. We also visited Manikro center and Kongouanou center, although Mr. Sasakawa could not join this part. It was not a pleasant scene to see so many young people suffering from such a devastating physical damage. It left a deep impression on Mr. Sasakawa that something has to be done and done urgently. Mr. Sasakawa was pleased to be told that the initial two years of BUI enabled to interest more partners and together they are developing a strategy to address various aspects of BU from scientific research, community education and support to the field units. Subsequently TNF agreed to continue support toward WHO to coordinate and accelerate the actions against BU.

For the year 2000, TNF support to WHO will be US\$300 000 and it is likely they will continue their support for another two more years.

As NGOs with an interest for better quality of the life of the people, we know that statistics quoted in public health reports are not just numbers but they represent the lives and suffering of individuals. We are naturally interested in reducing the so-called 'burden' but at the same time we would like to see improvement in the lives of the people who suffer. In this regard, I would like to share with you one small attempt which we are looking into. We are wondering whether or not the application of cultured epithelium or bioskin to BU patients who have had an extensive excision of skin tissue may have some advantage in surgical treatment of severely ulcerated patients. We know the technology exists and we also know that the products, both cultured auto-grafts and hetero-grafts are commercially available in the market, but often with prohibitive prices. In Adzope and Manikro centers we saw many young

people with extensive skin excision waiting to be grafted with their own skin. They have to spend many months before they can be released from the hospital. We also assume there are many more who are left with contractures and deformities which they have to endure and live with for life. We know that the product of 'tissue engineering' is a cost thing. It is one of many other 'unreachable items' for those who do not have means. But we feel if it makes a difference to the lives of people why not explore the possibility. We have found that the process of culturing grafts does not require a prohibitively sophisticated set up. I would be very much interested to know if any treatment centers have attempted this. I would also like to know any possible venues that may be able to do this on an experimental basis.

In front of us today we have a newly published monograph on BU, the first of its kind with comprehensive information. I would hope to see its revised edition in the very near future with the latest news and findings of the breakthrough. I am sure both Follereau Foundation and The Nippon Foundation will be happy share the cost once again.

Case management of patients at the specialized centre in Lalo, Mono department, Benin, Médecins sans Frontières Luxembourg's activities in Benin

Dr Antoinette Kapinga, Dr Pierre Humblet and Dr Christian Johnson, Médecins Sans Frontière Luxembourg

Title

“Assistance to the National Buruli Ulcer Control Programme in Mono department, Benin”

Description

Mission context (See, geographical map.)

Benin is in West Africa, on the Gulf of Guinea.

Area: 112 622 km² (Benin is 670 km long and 126 wide).

Population of Benin: 5.2 million

Administrative subdivisions 6 departments.

The two northern departments, ATAKORA and BORGOU cover 75% of the country's total area but are home to only 30% of the population.

The four southern departments, ZOU, MONO, OUEM and ATLANTIQUE cover 25% of the area of Benin and are home to 70% of its population (high population density: 150 persons per km² against 21 per km²).

These are the regions most affected by Buruli ulcer.

Location of Médecins Sans Frontières Luxembourg (MSF L):

Mono department, Lalo district.

Beneficiaries

Population of Mono department: **820 000 people**

However, the actual number of beneficiaries of the information and active case detection campaign is **77 497** – the population of Lalo district itself.

Mission history:

- The mission follows the suggestion made to MSFL by the Antwerp Institute of Tropical Medicine (Professor F. Portaels).
- **May 1997**, exploratory mission: carried out by the Medical Director of MSF Luxembourg, Professor Portaels and Dr Meyers of the United States. The mission confirmed the presence and development of this endemic disease which is caused by a skin infection with *Mycobacterium ulcerans*.

- **July 1998**, a three-year agreement was signed by MSF and the Government of Benin.
- **14 December 1998**, Inauguration of the specialized treatment centre at Lalo and official launch of the National Buruli Ulcer Control Programme in Benin.

The BU situation in Mono at the outset of the project

Prevalence/incidence: unknown

Availability of services:

- **Curative:** not standardized;

Possibilities: primary health care services, traditional practitioners, no use of services.

Patients have to travel to the Zagnanado centre in Zou department.

Problems of accessibility, a long stay away from their family.

-Preventive:

Not organized; the population and health care staff are ignorant about the disease.

-National policy:

Strategies under preparation, a system of case management: specialized facilities? integration within existing care facilities?

MSF PROJECT

1. Initial objectives

General objective

- To contribute to Buruli ulcer control in the Republic of Benin.
- To improve curative case management of patients and to develop information and research aspects.

Specific and operational objectives

- *Curative:* To set up a specialized treatment centre to improve case management of BU in Benin by early detection and treatment of Buruli ulcer patients.
- *Preventive:* To initiate health education and information activities among the population and health personnel.
- *Research:* To contribute to research into the optimal organization of services, essentially as regards case management; in particular, to validate the “postulate” that the option of a Specialized Treatment Centre represents a sound strategy.

2. Strategies

The curative component:

Establishment of a specialized treatment centre at Lalo and in-service training for BU health workers.

Preventive component:

Information of the population, training community relay BU teams.

Early detection of the disease would make it possible considerably to shorten hospitalization and the cost of care.

Scientific component:

Several “operational” research protocols to develop sound knowledge of the disease and of control measures, in collaboration with the Antwerp Institute of Tropical Medicine.

3. Contributions and achievements

Curative case management

- *Building and fitting out the facilities:*
Lalo specialized centre, wards, rooms (pharmacy, sterilization, laboratory etc.) to optimize the case management of patients and improve the quality of care. Procurement of equipment and medical materials.
- *Training for health personnel:*
Some topics: BU detection, anaesthesia using ketamine, the basic gestures in physiotherapy for re-educating patients; dressing techniques (30 nurses in 1998 and 36 community health workers in 1999).
- *Direct assistance for patients:*
Complete payment of medical expenses: drugs, dressings during the pre- and post-operational periods and surgical operations on patients (excision and graft).

Information and training

- Information and active case detection are the responsibility of community Buruli ulcer control teams in Lalo district (11 villages visited out of 31).
- Supervision: logistical resources to supervise and manage the community Buruli ulcer control teams and to facilitate access to hyperendemic villages during the rainy season.

4. Results

- Collaboration in the field has made it possible to draft and publish a basic protocol on surgical treatment for case management of Buruli ulcer patients.
- Research protocols are under way with the Antwerp Institute of Tropical Medicine and the National Buruli Ulcer Control Programme; they concern in particular, triple therapy based on anti-tuberculosis chemotherapy to control the disseminated forms of BU.

Medical statistics

Number of cases managed at Lalo during 1998:

New cases: 68

Number of cases managed at Lalo during 1999:

New cases: 86 (and three recurrences)

1999 STATISTICS

1. New cases and recurrences

	Confirmed						Unconfirmed						Sub-total		Total	
	< 15 years		15-49 years		> 49 years		< 15 years		15-49 years		> 49 years					
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
New cases	4	3	0	0	0	0	16	14	21	15	6	7	47	39	48	41
Recurrences	0	0	0	0	0	0	1	0	0	2	0	0	1	2		

2. Clinical forms

Nodule	Papule	Plaque	Oedema	Ulcer	Osteomyelitis	Disseminated	Total
1	0	3	3	68	9	5	89

<i>Activities</i>	1998	Jan.	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	TOTAL
Patients programmed		32	30	9	6	22	15	-	25	9	21	9	29	207
Patients operated		20	20	9	6	22	15	4	20	7	16	8	21	168
Excisions		16	9	2	5	10	10	1	10	4	8	5	9	89
Grafts		4	11	7	-	6	5	2	9	3	7	3	7	64
Bone curettage or mobilizations		-	-	-	1	6	-	1	1	-	1	-	5	15
New cases	68	10	3	8	5	6	5	5	8	10	10	10	9	89
Discharged		-	3	2	9	7	3	1	7	2	3	-	4	41
Operating days		3	2	2	1	4	3	1	4	1	2	1	3	27

5. Difficulties encountered

1. Those linked to the choice of structure - “district health centre”: limited capacity (22 beds), discontinuous surgical and medical coverage.

2. Average length of hospitalization: 76 days.

Prospects

- Development of operational research into the organization of services for early case management of patients, integrated, quality and cheaper care.
- Better standardization of treatment protocols, management tools and patient monitoring.
- Study of practical means of external subsidizing of case management, which is currently costly and beyond the means of most patients and of the local health care system.

Contribution of the Kobe International University, Making of a new option to the Worldwide Movement for the Children of Buruli Ulcer: a case of Kobe International University

*Professor Yuki Shimomura, International Center, Kobe International University,
Kobe, Japan*

Awareness

How KIU came to learn about Buruli ulcer

We at Kobe International University (KIU) knew nothing about Buruli ulcer when we learned it for the first time from Dr Yukiko Fukunishi of National Sanatorium, Aomori, Japan and Mr Kazuyuki Fukunishi, who was my student and is currently a Ph.D. Student at University of Wales. Then, we turned to WHO homepage and asked Dr Fukunishi to pass on any available information on Buruli ulcer. In doing so, what came to our thought first then, was exactly what we could do for the children of Buruli ulcer (BU).

Raising awareness about Buruli ulcer in Japan

Our first task needed was to raise awareness about the disease, since virtually no one know about it except few medical specialists in Japan. I, as Director of International Center, called upon a meeting of selected teaching staffs and together formulated an action plan for an international symposium on BU in Kobe. There were two main reasons for planning of an international symposium: (1) such event would be appropriate for an international university and thus educational to the students and (2) also could approach wider audience outside the university to fulfill the objective of raising awareness about the disease in the region.

With the full supports from Reverend Miizutani, the Chairperson of Governing Board of Trustees and Dr Sasaki, president of KIU, the action plan was implemented. The administrative and planning committee was organized and named Project SCOBUR (Save the Children of Buruli ulcer). The project consists of teaching and administrative staffs and university students. The most important supports came from KIU Student Volunteer Project (V Project) which was originally organized to assist the suffering people of the Great Hanshin-Awaji Earthquake in 1995 and KIU Graduates Volunteer Group.

Action

Photo-Exhibition and Fund-Raising Campaign

To take the issues of BU to the people of Kobe, if not Hanshin Area (the area includes Kyoto, Osaka and Kobe), the Project SCOBUR planned a series of photo-exhibitions. To those who have no knowledge of BU and what it does to the patients, “a picture is worth a thousand words”. Dr Yukiko Fukunishi and Dr Kingsley Asiedu of WHO kindly provided us photos at my request. 36 photos were displayed at three different places like shopping center and stations plaza. Over one hundred people visited the photo-exhibitions. The byproduct of the first exhibition was a drive to raise funds, which was initiated by the visitors who thought that there should be a donation box. It is incredible to think that the total number of contributors reached over 3,000 within

four months from mid-September to mid-December, no matter how individual donations were small.

Publicity

(1) Homepage: We put up the first homepage on Buruli ulcer in Japanese.

<http://www.kobe-kiu.ac.jp/~buruli>

With permission from Dr K. Asiedu, the homepage was officially linked with WHO BU Homepage.

(2) Press Coverage: Asahi Newspaper (September 30th), Kobe Newspaper (October), Mainichi Newspaper (November 3rd and 27th)

NHK (National Broadcasting Association) gave coverage in primetime news.

Other Coverage: Anglican Church News (October 25th), Christian Newspaper (November 6th)

International Center News: Special Report from Ghana (October Edition),

Yashiro Gakuin News (November 1st)

(3) Over 2,000 posters for the symposium were distributed to:

1. every train stations from Osaka to Himeji (West of Kobe) with permissions of major railroad companies in the region (including JR West, Hankyu, Hanshin and Sanyo),
2. medical and nursing schools in Kansai area
3. universities and high schools in Kobe

International Symposium 1999

Title: Challenge to Disabling Disease: Save the Children of Buruli Ulcer

Place: Kobe Sangyo Shinko Center, Kobe

Date and time:

Invited Dr Kingsley Asiedu of WHO as a keynote speaker, His Excellency Mr W.R.E. Ouedraogo, Ambassador of Burkina Faso in Japan, Dr Yukiko Fukunishi, Dr Milanga Mwanatanbwe of Nippon Medical School as panelists/discussants. His Excellency Ngambani Gatton Zimileze, Ambassador of the Democratic Republic of Congo in Japan, Dr Goro Asano of Nippon Medical School as guests of honor.

In a 392-seat theater, over 360 people attended. Unfortunately other invited embassies of Africa were not able to attend the symposium, but kindly gave patronage to the event. Prefectural Government of Hyogo and City of Kobe also expressed their supports along news companies listed above.

Aftermath

The growing memberships of Project SCOBUS actively campaigned individually after the symposium.

Other organizations

Donations from Schools and Church Organizations

200 set of student produced-BU Calendar were sold as part of fund-raising efforts.

Planning Ahead

Publication

Collected speeches and discussions of International Symposium 1999 will be published by June 2000.

NPO (Non-Profit Organization)

In addition to membership fees, Project SCOBU will be able to sell some novelty goods such as calendar and telephone cards. The Project hopes to establish worldwide BU network with universities and colleges in addition to the already established African-net in Japan.

Introduction of New Subjects in University Curriculums

KIU will invite lecturers and provide series of lectures on international volunteer and practical programs as a student internship.

KIU International Symposium 2000

International Symposium 2000 will be held in October. The topic will be on BU to enforce the movement that begun in Japan.

Objectives of year 2000

1. medical assistance
2. shelters for BU children
3. educational services

Kobe International University as an educational institution hopes to contribute, no matter how small it would be, to the great movement you, the distinguished participants to this meeting, have already started. As an institution of economics, we cannot do so in medical field, but we hope to present an option to the movement to save the children of Buruli ulcer not just in Africa but other areas of the world.

Thank you.

Social mobilization for Buruli ulcer

Dr Elil Renganathan, Social Mobilization Team, Communicable Diseases Control, Prevention and Eradication, WHO Headquarters, Geneva

The Social Mobilization Challenge

The social mobilization and public communication challenges posed by Buruli Ulcer (BU) are special and will require skilled and sensitive handling.

There is a dearth of good information about BU. We do not know how it spreads; we therefore cannot offer the public recommended preventive actions.

We do not know who is susceptible to infection; we therefore cannot forewarn the public.

There is at this time no diagnostic tool for detecting the presence of an infection; we therefore cannot promote a health-seeking behaviour such as “Come to our clinic for a definitive diagnosis.”

We have no ready treatment for BU except to suggest surgery with all the alarm bells blasting away in the public mind with the word “surgery.”

And if we insensitively broadcast the incidence and prevalence of BU in certain communities and countries, we can promote behaviour-inhibiting fears, in addition to prompting a global alarm affecting trade, investment and tourism sectors of countries specified. To put it mildly, BU is not pretty, and in the absence of good remedies, the possibility for an alarmist take on the situation is very likely.

So we are stuck, it would appear. What we have to tell the public and donors and government officials is not very re-assuring. And the crisis slowly and quietly builds.

And yet, if we are to make any headway in responding to this disease, our singular goal remains one of prompting specific behavioural responses on the part of donors, researchers, government officials and the public.

WHO wishes to emphasize the behavioural outcomes of any attempted social mobilization/public communication intervention.

It is not going to be sufficient to simply make people aware of the disease and hope for behavioural impact. Increasing awareness is notoriously insufficient for prompting action though an essential basis for it.

It is clear that if we are to embark on a large-scale effort to contain and eventually eradicate BU, achieving specific behavioural goals are paramount:

- We need action-expressed commitment of government leaders to embark on nationwide campaigns to educate the public and prompt behaviours to seek treatment,

limited as these options are at this time. (Action-expressed commitment is a commitment which goes beyond the nod of the head and the acknowledgment that “Yes, we have a problem” to one which provides a direct mandate for field action.)

- We need strategically targeted donors, with a sharper awareness of the extent of the problem, to act promptly with specific financial support for country-level interventions.
- We need members of the public in affected countries and communities to take deliberate action to seek diagnosis and treatment of BU, despite our current limitations in both areas.

These are just a few of the key behavioural responses we seek. And we need to do all of the above without creating unnecessary public alarm and possible harm to trade, investment and tourism of affected countries.

WHO’s Approach to Social Mobilization/Communication for Behavioural Impact

WHO has just begun this year the development and implementation of a new concept of social mobilization (SM) which advances SM to a point beyond “advocacy” with a sharpened emphasis on SM which has behavioural impact. We have adopted the rather cumbersome term of SM/COMBI, with COMBI being the acronym for “Communication for Behavioural Impact.” The strategy being used is a modified form of the private sector’s Integrated Marketing Communication (IMC) approach which focuses on the behavioural outcomes and a “market” analysis to determine what are those factors which foster or hinder desired behavioural responses.

In general the SM/COMBI approach calls for five lines of communication actions, appropriate to the “market” circumstances:

- Public relations/advocacy (via the mass media – news coverage, talk shows, soap operas, discussion programmes; meetings with various categories of government and community leadership, service providers, administrators.)
- Sustained Appropriate Advertising (in M-RIP fashion – Massive, Repetitive, Intense, Persistent)
- Community Mobilization (including use of folk media, music, song and dance, road shows, community drama, leaflets, posters, pamphlets, videos).
- Personal Selling/Interpersonal Communication (at the community level and particularly at service points, with appropriate patient literature)
- Point-of- Service Promotion (emphasizing easily accessible and free availability of treatment and diagnosis).

The key in planning SM/COMBI programmes is to strive for an integrated approach with a judicious blending and selection of communication actions appropriate to the behavioural outcome desired, and not believing that one single kind of intervention is all-powerful.

Applying SM/COMBI to Buruli ulcer

WHO proposes to apply the SM/COMBI approach to Buruli Ulcer in the following two ways to begin with:

1. SM/COMBI Programmes in Selected Affected Countries

We will facilitate the design and implementation of SM/COMBI programmes in selected countries and communities directed at increasing public awareness of the disease, promoting a better understanding of the only treatment option available at this time, and prompting the behavioural response of seeking diagnosis and treatment at health facilities. Such an effort presupposes the availability of trained health service providers and the services for diagnosis and treatment.

These country programmes will have three dimensions (details to be developed at a later stage):

- a. SM/COMBI interventions for securing action-expressed Leadership Commitment. (This will include, for example, the production of a short 8-minute local video on BU, and a series of structured sessions with government leaders, etc.).
- b. SM/COMBI interventions for securing action-expressed support of key implementation officials and staff in appropriate Ministries and NGOs.
- c. SM/COMBI interventions, using the SM/COMBI approach described earlier with its five potential communication action lines, for securing community support and individual behavioural responses with regard to seeking diagnosis and treatment, with due attention to the “cost” vs value calculation individuals will make in weighing the decision to seek diagnosis and treatment, limited as both of these are at this time. In addition, special attention will need to be paid to the delicate task of conducting public education on BU without raising behaviour-inhibiting community fears and widespread public alarm. The blend of communication actions will need to be determined country by country and so too decisions about what communication materials would be appropriate in each country and community.

2. SM/COMBI Strategy for Targeted Donor Advocacy and Action

We would eschew a large-scale global advocacy initiative for BU (with its attendant global alarm-creating possibilities) and instead focus on a targeted number of key donors. A special 8-minute video on BU would be produced for use in structured presentation/discussion sessions with donors, together with other audio-visual support materials. As the situation develops, there might be need for some global media attention to the problem. This sort of coverage will need to be sensitively pursued with key global media institutions.

The above provides the general framework within which WHO proposes to start applying SM/COMBI techniques to the task of BU control and eradication.

ANNEXES

Annex 1 - Agenda

3RD WHO AD HOC ADVISORY GROUP MEETING ON BURULI ULCER 1-3 March 2000, WHO Headquarters, Geneva

Objectives of the Meeting

1. To define the research agenda for Buruli ulcer;
2. To define modalities for surveillance, surveys and estimation of the burden of the disease;
3. To define modalities for the use of drugs for the prevention of recurrences; and
4. To define training needs for Buruli ulcer.

Expected Outcome

Conceptualization of a WHO strategic framework document and a 5-year plan of work on Buruli ulcer in the following areas:

- Research priorities;
- Modalities for surveillance, surveys and estimation of disease burden
- Training.

Wednesday, 1 March 2000

Update on country and research activities

Chairpersons: Dr Maria Neira and Professor Jacques Grosset

09:00 – 09:20	Welcome Remarks	Dr David Heymann, Executive Director, Communicable Diseases Dr Maria Neira, Director, Communicable Diseases Control, Prevention and Eradication
09:20 – 09:30	Progress report on GBUI Rationale and objectives of 2000 meeting	Dr Mario Raviglione, Coordinator, Endemic Bacterial and Viral Diseases
09:30 – 09:45	Planned activities for 2000	Dr Kingsley Asiedu
09:45 – 10:00	AFRO Buruli ulcer efforts	Dr Eugene Nyarko
10:00 – 10:20	Clinical presentations and cytological diagnosis of MUI	Dr John Hayman
10:20 – 10:40	Update on control activities in Benin	Dr Augustin Guédénon
10:40 – 11:00	<i>Coffee Break</i>	

11:00 – 11:20	Update on control activities in Côte d’Ivoire	Dr Edgard Kacou
11:20 – 11:40	Update on control activities in French Guiana	Dr Roger Pradinaud
11:40 – 12:00	Update on control activities in Ghana	Dr George Amofah
12:00 – 12:20	Update on control activities in Papua New Guinea	Sister Joseph
12:20 – 12:40	Update on control activities in Togo	Dr Napo Tignokpa and Dr Battista Priuli
12:40 – 14:00	<i>Lunch</i>	
14:00 – 14:15	Update on research activities	Professor Françoise Portaels
14:15 – 14:30	Update on research activities	Dr Paul Johnson
14:30 – 14:45	Update on research activities on drug treatment	Professor Jacques Grosset
14:45 – 15:00	Update on research activities on the toxin	Dr Pamela Small
15:00 – 15:15	CDC's role in the Buruli ulcer activities	Dr Jordan Tappero
15:15 – 15:30	Update on research activities on serology	Dr Harold King
15:30 – 16:00	<i>Tea Break</i>	
16:00 – 16:15	Update on research activities on histopathology	Dr Wayne Meyers
16:15 – 16:30	Update on research activities on immunology	Dr Mark Wansbrough-Jones
16:30 – 16:45	Conceptual framework for estimation of disease burden related to Buruli ulcer	Mr Frank Dadzie
16:45 – 16:55	Nippon Medical School, Tokyo, Japan	Dr Mwanatambwe Milanga
16:55 – 17:05	Role of Noguchi Memorial Institute for Medical Research (NMIMR), Accra, Ghana in Buruli ulcer research	Professor David Ofori-Adjei
17:05 – 17:15	Sasakawa Memorial Health Foundation, Tokyo, Japan	Mrs Kay Yamaguchi
17:15 – 17:25	MSF Luxembourg's work in Benin	Dr Antoinette Kapinga
17:25 – 17:35	Pfizer Pharmaceutical Inc., New York, USA	Dr Ann Kolokathis
17:35 – 17:45	Contribution of Kobe International University, Kobe, Japan	Professor Yuki Shimomura

Thursday, 2 March 2000*Working groups***Chairperson: Dr Eugene Nyarko**

09:00 – 09:15	Social mobilization and advocacy approach to Buruli ulcer	Dr Elil Renganathan
09:15 – 10:30	Working groups:	
	1. Research agenda (excluding drug treatment)	Dr John Hayman
	2. Modalities for surveillance, surveys and burden of disease	Dr Jordan Tappero
	3. Drug treatment	Professor Jacques Grosset
	4. Training needs	Dr Eugene Nyarko
10:30 – 11:00	<i>Coffee Break</i>	
11:00 – 12:30	Continuation of working groups	
12:30 – 14:00	<i>Lunch</i>	
14:00 – 15:30	Continuation of working groups	
15:30 – 16:00	<i>Tea Break</i>	
16:00 – 17:30	Presentation of working group discussions and recommendations at plenary	

Friday, 3 March 2000**Chairpersons: Dr Augustin Guédénon and Professor Françoise Portaels**

09:00 – 10:30	Finalization of working groups recommendations	
10:30 – 11:00	<i>Coffee Break</i>	
11:00 – 12:30	Presentation of final recommendations of the working groups	All
12:30 – 14:00	<i>Lunch</i>	
14:00 – 15:30	Donors, NGOs activities, funding issues Any other business General recommendations for WHO, endemic countries and donors/NGOs	All
15:30 – 16:00	<i>Tea Break</i>	
16:00 – 16:15	Closing Remarks	Dr Maria Neira, Director Control, Prevention and Eradication

Annex 2 - List of participants

Sister Julia Aguiar, Mission Catholique Zagnanado, Zagnanado, Benin

Dr George Amofah, Public Health Division, Ministry of Health, P. O. Box M-44, Accra, Ghana

Sister Nosella Domitilla, Dispensaire de Kongouanou, Kongouanou, Côte d'Ivoire

Prof. Jacques Grosset, Bactériologie et Hygiène, Faculté de Médecine, Pitié-Salpêtrière, 91 Boulevard de l'hôpital, F-75634 Paris, Cedex 13, France

Dr Augustin Guédénon, Dermato-Vénérologue, 06 BP 2572, Cotonou, Benin

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Dr Maria Neira, Director, Communicable Diseases Control, Prevention & Eradication

Dr Mario Raviglione, Coordinator, Strategy Development and Monitoring for Endemic Bacterial and Viral Diseases, Communicable Diseases Control, Prevention & Eradication

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Invited but unable to attend

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