

**WHO ANNUAL MEETING ON
BURULI ULCER**

31 March – 2 April 2009

ABSTRACTS

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Printed by the WHO Document Production Services, Geneva, Switzerland

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AGENDA - Common and Control Sessions

Tuesday, 31 March (Common Session)

09:00 – 10:30: Country updates I

1. Benin (*Christian Johnson*)
2. Australia (*Paul Johnson*)
3. French Guiana (*Pierre Couppié*)
4. Togo (*Salomon Hainga*)
5. Cameroon (*Charles Nsom Mba and Earnest Njih*)

11:00 – 12:30 : Country updates II

1. Ghana (*Edwin Ampadu*)
2. Côte d'Ivoire (*Henri Assé*)
3. DRC (*Anatole Kibadi*)
4. Gabon (*Louis Bayonne Manou*)
5. Congo (*Damas Obvala*)
6. Guinea (*Kesso Bah*)

14:00 – 15:30: Antibiotic treatment I

1. Impacts of dosing frequency of the combination rifampin-streptomycin on its Bactericidal and Sterilizing Activities Against *Mycobacterium ulcerans* in mice (*Baohong Ji*)
2. Comparison of rifapentine and rifampin based oral regimens in treatment of *Mycobacterium ulcerans* infection in mice (*Deepak Almeida*)
3. Dynamics of serum neopterin concentration during antibiotic treatment of Buruli ulcer disease; evidence of macrophage activation (*Steven Sarfo*)
4. Analysis of histopathological changes and local immune responses in the course of R/S chemotherapy in the experimental Buruli ulcer mouse model (*Marie-Thérèse Ruf*)
5. Severe multifocal form of Buruli ulcer after streptomycin and rifampicin treatment: a case report with comments on possible dissemination mechanisms (*Ange Dossou*)

16:00 – 17:30: Antibiotic treatment II

1. Preliminary results of a clinical trial of eight-week daily treatment with the combination rifampin-clarithromycin for patients with Buruli ulcer (*Annick Chauty*)
2. Prognostic indicators associated with the clinical response after 4 weeks of treatment of suspected Buruli ulcer cases with rifampicin and streptomycin in Allada, (*Ghislain Sopoh*)
3. Response to treatment with the combination rifampicin-streptomycin for 5 days per week for 8 weeks for Buruli ulcer (*Richard Phillips*)
4. Antimicrobial treatment for Buruli ulcer: results of the Burulico trial evaluation of a switch to oral treatment to reduce streptomycin injections for early, limited buruli ulcer (*Tjip van der Werf*)
5. Patterns of healing and paradoxical reactions during antimicrobial treatment of Buruli ulcer – data from a drug trial in Ghana (*Willemien Nienhuis*)

Wednesday, 1 April (Control Session)

08:30 – 10:30: Laboratory confirmation of cases (10 minutes each)

1. The value of diagnosis of *M. ulcerans* infection by Fine Needle aspiration (*Viviane Cassisa*)
2. Confirmation of cases of Buruli ulcer at the National Buruli Ulcer Reference Laboratory (LNRUB) of the Institut National de Recherche Biomédicale (INRB-Kinshasa) in the Democratic Republic of the Congo (*Anatole Kibadi*)
3. Buruli ulcer molecular diagnosis routinely performed in Cotonou, Benin (*Dissou Affolabi*)
4. Confirmation of Buruli ulcer in Central African Republic (*Fanny Minime-Lingoupou*)
5. Overview and prospect for the National Buruli Ulcer Reference Centre (CNR-BURULI) in the Buruli ulcer control effort in Côte d'Ivoire (*N'Guetta Aka*)

10:30 – 12:30: NGOs

1. ANESVAD, Spain (*Almuneda Mendez Morante*)
2. Raoul Follereau Foundation, Luxembourg (*Emile China*)
3. SCOBU, Japan (*Yuki Shimomura*)
4. Health Foundation, Ghana (*Lynda Arthur*)
5. MSF - Buruli Ulcer project at Akonolinga (*Eric Comte*)

14:00 – 15:30: Health system

1. Integration of Buruli ulcer control activities into primary health care: the case of the control programme of the Institut Médical Evangélique (IME)/Kimpese in the Democratic Republic of the Congo (DRC) (*B. B. Imposo*)
2. Decentralization in Akonolinga (*Felix Sagno*)
3. Organization of case management for Buruli ulcer patients in Kouilou department in the Republic of the Congo (*Jean-Martin Mabiala*)
4. 3 years of implementation of early detection activities in Amansie West District of Ghana (*Joseph Adomako*)
5. Early case detection and management of Buruli ulcer in the Upper Denkyira district of Ghana (*Erasmus Klutse*)

16:00 – 17:30: Health system

1. Functional limitations after surgical or antibiotic treatment for Buruli ulcer in Benin (*Yves Barogui*)
2. Training in basic rehabilitation: an overview of three years' experience in Cameroon (*Valarie Simonet*)
3. Buruli ulcer in Togo: Prevention and treatment of disabilities from Buruli ulcer in the Maritime region (*Pauline Falipou*)
4. Wrist contractures in sequelae of Buruli ulcer: the place of resection of the 1st row of carpal bones (*Patrick Meredith*)
5. Multicenter Surgical Outreach for Management of Buruli ulcer (*Pius Agbenorkou*)
6. Modern dressings (*Felix Sagno*)

Thursday, 2 April

09:00 – 10:30: Surveillance

1. Analysis of the BU 01 in Benin for 2008–lessons learnt (*Yves Barogui*)
2. Contribution of mapping to epidemiological surveillance of Buruli ulcer in Benin : Distribution of the disease by foci (*Ghislain Sopoh*)
3. Buruli Ulcer Surveillance in Ghana: Current Practices and Future Priorities (*William Opare*)
4. Analysis of factors associated with seeking treatment among Buruli ulcer patients (*Alphonse Um Boock*)
5. New foci of Buruli ulcer, Angola and Democratic Republic of Congo (*Anatole Kibadi*)

11:00 – 12:30: Other presentations

1. Cost of case management of Buruli ulcer cases at the Buruli ulcer Detection and Treatment Centre (CDTUB) at Allada in Benin (*Patrick Makoutode*)
2. Buruli ulcer: Perception of the disease and study of risk factors in endemic and non-endemic zones in Côte d'Ivoire (Emmanuel Tia)
3. Exploration of Haematological Parameters in Suspected Buruli Ulcer Patients: Case-Control Study in the Endemic Regions of Allada and Lalo in Benin (*Evelyne Lozes*)
4. Extra Cutaneous Manifestations Of Buruli Ulcer (*K. Kadjo*)
5. Activities to Control Endemic Treponematoses in the Congo (*Damas Obvala*)

14 :00 – 15 :30 : Finalization of report

1. Preparations of control and research reports (*Chair and Rapporteurs*)
2. Group work to finalize a draft roadmap for implementation of the *Cotonou Declaration*

16:00 – 17:30: Closure

1. Plenary: presentation of conclusions and recommendations
2. Closing remarks: *TBA*

AGENDA - Research Session

Each Speaker has 15 Minutes Plus Five Minutes for Questions

Wednesday, 1 April

09:00 – 10:30: *M. ulcerans* in the environment and transmission to humans (I)

09:00 – 09:20

Paul Johnson

Vector borne diseases, mosquitoes and Buruli ulcer in Victoria,

09:20 – 09:40

Janet Fyfe

A role for small mammals in the ecology of *Mycobacterium ulcerans*

09:40 – 10:00

Eric Benbow

Environmental sampling for *Mycobacterium ulcerans*: important considerations to understanding transmission

10:00 – 10:20

LP Campbell

Exploring Environmental Factors Related to Buruli Ulcer Disease within the Couffu and Oueme Watersheds in Benin, Africa

10.20-10.40

Eric Elguero

Risk factor analysis of Buruli ulcer cases in French Guiana. A case-control study

11:00 – 12:30: *M. ulcerans* in the environment and transmission to humans (II)

11:00 – 11:20

Lydia Mosi

Experimental infection of Medaka (*Oryzias latipes*) with *Mycobacterium ulcerans*: A model for transmission, pathogenesis and toxicity to fish.

11:20 – 11:40

Laurent Marsollier

Dynamic population of water bugs in a Buruli ulcer endemic area and their rate of colonization by *M. ulcerans*

11:40 – 12:00

Julien M.C. Doannio

Biological diversity and implication of water bugs in the transmission of *M. ulcerans*, the cause of Buruli ulcer in Côte d'Ivoire (West Africa)

12:00 – 12:20

Yao Télesphore Brou

Land use and land cover changes and Buruli Ulcer in Côte d'Ivoire and French Guyana

12:20 – 12:40

Yao Télesphore Brou

Study on a local spatial scale in Cayenne (French Guyana)

12:40 – 13:00

Lance Waller

Linking Surveillance, Epidemiology, and Ecology for Buruli ulcer Disease in Ghana

14:00 – 15:30:

***M. ulcerans* in the environment and diagnostic methods**

14:00 – 14:20

Pam Small

Why does culture fail? Molecular Analysis of *Mycobacterium ulcerans* culture positive and culture negative Buruli ulcer

14:20 – 14:40

Heather R Williamson

Quantitative Studies on the Presence of *Mycobacterium ulcerans* DNA in Environmental Samples from Ghana

14:40 – 15:00

Caroline Lavender

Report on pilot quality assurance program for molecular detection of *M. ulcerans* in environmental samples

15:00 – 15:20

16:00 - 17:30:

***M. ulcerans* genetic variation**

16:00 – 16:20

Gerd Pluschke

Genetic diversity of *M. ulcerans*

16:20 – 16:40

N Coulibaly

Molecular Study Of The Biodiversity Of *M. ulcerans* Strains Isolated In Côte D'Ivoire Using Miru Vnt

16:40 – 17:00

Katharina Röltgen

Genetic diversity of *Mycobacterium ulcerans* strains from Ghana

17:00 – 17:20

Tim Stinear

Insights from comparison and analysis of multiple *M. ulcerans* genome sequences

Thursday, 2 April NOTE: 10min EARLIER START TODAY

08:40 – 10:30: Mycolactone and its role in disease (I)

08:50 – 09:10

Caroline Demangel

Signature of the immunosuppressive action of mycolactone in the peripheral blood of Buruli ulcer patients

09:10 – 09:30

Steven Sarfo

Kinetics of mycolactone concentration in human *M. ulcerans* lesions during antibiotic treatment

09:30 – 09:50

Paul Converse

Mycolactones in *Mycobacterium ulcerans* strains: expression and cytotoxic activity quantification

09:50 – 10:10

E. Zavattaro

Seric cytokines detection in different clinical conditions of Buruli Ulcer: preliminary results

10:10 – 10:30

11:00 – 12:30: Mycolactone and its role in disease (II)

11:00 – 11:20

Germain Mabèrou Hounghbedji

Buruli ulcer, an infection that goes far deeper than the skin: the impact of *Mycobacterium ulcerans* and its toxin on muscle tissue

11:20 – 11:40

Laure Guenin-Macé

Dynamics and molecular basis of the cytoskeletal rearrangements induced by mycolactone in human cells

11:40 – 12:00

Alvar Grönberg

The toxicity of mycolactone on keratinocytes and means of its reversal

12:00 – 12:20

G Leigheb

Mycolactone damages also human keratinocytes

ABSTRACTS - Common and Control Sessions

An overview of the effort to improve control of Buruli ulcer in Benin

Roch Christian Johnson

The first cases of Buruli ulcer in Benin were diagnosed in 1977 by the Franciscan nuns at the St Camille hospital in Dogbo. It was not until 1988 that the first publication on the disease in Benin came out. In the light of the growing importance of this health problem, the Beninese Ministry of Health developed its first plan of action covering the period 1997 to 1999. The objectives of this initial plan were to draw the attention of the national and international community to the disease, to provide training for social and health workers, to set up treatment facilities, to carry out detection of cases and provide treatment for patients and to contribute to operational research. As a result of the plan, 2330 cases were detected over 3 years - 36% of them non-ulcerative forms and 64% ulcerative, disseminated or scar forms and 1310 cases received treatment (i.e. 56%) with 22% presenting sequelae. It was possible to provide training for only 20% of physicians and 4.5% of nurses practising in the endemic areas.

A second plan with more ambitious objectives was drawn up for the period 2000 to 2005; its objectives included increasing by 50% the rate of detection of non-ulcerative forms, treating 95% of the active forms detected, reducing the defaulter rate to 5%, providing rehabilitation for 10% of patients with disabilities, training 80% of health workers in areas in which the disease is endemic and fostering research. However, the introduction of antibiotic treatment led to a revision of the plan and the introduction of another plan for the period 2004 to 2008.

After the plan's implementation, there was an exponential increase in case detection, with some 1000 cases being detected annually, 50% of them at an early stage. Confirmation by laboratory examination is provided locally using direct examination, culture, PCR and histopathology, within a deadline that has been reduced to two weeks. As regards case management, there are five operational Buruli ulcer detection and treatment centres (CDTUB), and 35 peripheral health centres provide decentralized case management of Buruli ulcer cases. Treatment is well integrated within the health system, private and faith-based health centres play their part and skills and treatment protocols are readily available.

In 2008, the relapse rate was 3%. All cases received treatment with antibiotics and 32% of all patients in the country were cured without the need to resort to surgery. However, despite this progress, there are several areas requiring improvement: Information, Education and Communication (IEC), epidemiological surveillance and case detection.

The community intermediaries have no means of transport, and this makes it difficult for them to reach some villages. The audiovisual equipment used to provide information is hard to transport. As regards treatment, a large proportion of patients refuse to be admitted to hospital, largely on account of the remoteness of certain villages and apprehension about the indirect costs. The CDTUB have health-centre status, even though they operate as hospitals and psychosocial support is inadequate in all health centres.

All these aspects need to be improved within the framework of future plans of action.

Buruli ulcer in Australia, 2008

Paul Johnson,^{1,2} Caroline Lavender,² Lynne Browne,³ Carolyn O'Brien,⁴
Kathrine Handasyde,⁵ Janet Fyfe.²

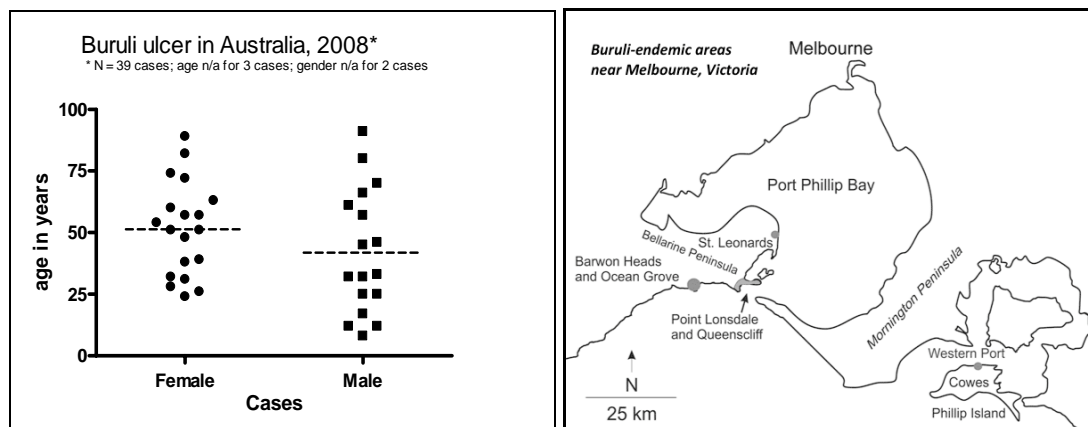
1. Department of Infectious Diseases, Austin Health & University of Melbourne, Victoria, Australia
2. Victorian Infectious Diseases Reference Laboratory and WHO Collaborating Centre for *Mycobacterium ulcerans*, Melbourne, Victoria, Australia
3. Department of Primary Industry, Atwood, Victoria, Australia
4. Tuberculosis Program, Department of Human Services, Victoria, Australia

In 2008 there were 39 new human cases of Buruli ulcer notified to the WHO Collaborating Centre for *Mycobacterium ulcerans* in Melbourne, compared with 17 cases in 2007. For 2008, 35/39 cases (90%) were from Victoria, the remaining cases were from Queensland (3 cases) and the Northern Territory (1 case). In Victoria, 27/35 (77%) were exposed on the Bellarine Peninsula, and 13 of these were linked to one town, Point Lonsdale. Of the remaining 8 Victorian cases, 3 were exposed in East Gippsland, one on Phillip Island, one on the Mornington Peninsula and there were two cases that have not yet been definitively linked to known endemic areas.

For all Australian cases, ages ranged from 8-82 years; 19 were females, 18 were males and gender was unavailable for two. Four cases were children, all of whom were males (ages 8, 12, 12 and 17 years).*

Three recurrent human cases were also recorded (defined as a new PCR or culture positive lesion occurring in a case recorded in a previous report). There were also 8 laboratory confirmed cases in animals, all from Victoria (one common rat, one dog and 6 ringtail possums). The rat, dog and 5 ringtail possums were from the Bellarine peninsula; the remaining ringtail possum was from Phillip Island.

The Bellarine Peninsula, 60-80 km south of Melbourne, is the main endemic focus for Buruli ulcer in Australia at present. There is also significant year-to-year variation in the incidence of Buruli ulcer which may relate to climatic conditions, particularly higher rainfall in Victoria. This year's report includes the first known case of Buruli ulcer in a domestic dog.



* Female children have been notified in previous years

***Mycobacterium ulcerans* infection in 2008 in French Guyana; HIV immune restoration syndrome; increasing use of two drug therapy rifampicin-clarithromycin treatment**

Pierre Couppié,¹ Dufour J,¹ Fior A,² Queuche F,³ Clyti E,¹ El Guedj M,⁴ Sainte-Marie D,¹ Vantilke V,⁴ Nacher M.⁴

1. Dermatology service, Centre Hospitalier de Cayenne
2. Pathology service, Centre Hospitalier de Cayenne
3. Institut Pasteur de la Guyane
4. COREVIH-Guyane, Centre Hospitalier de Cayenne

Eight new cases of infection with *M. ulcerans* (MUI) were diagnosed in French Guyana in 2008. It is noteworthy that none of them affected children, as has been the case in French Guyana for 10 years.

From the clinical angle, one remarkable observation is noteworthy. It concerns a 54-year old HIV-positive patient who had consulted some years previously for cutaneous leishmaniasis of the arms. At the time, he was found to be HIV positive. After his leishmaniasis was cured, he was lost track of. In December 2007, monitoring of his HIV infection was resumed. Because of his CD4 lymphocytes count of 14/mm³ and a viral load of 162 000 copies/ml, triple drug antiretroviral treatment (tenofovir, emtricitabine and efavirenz) was begun in January 2008.

In March, the patient consulted a dermatologist for an ulcer on his right knee which had been developing for a fortnight, and which had been preceded by a plaque that had appeared about a month after he had started the triple therapy. His CD4 count had improved (177/mm³ à M1), as had his viral load (132copies/ml at M1). A clinical examination found a 4x6cm diameter ulcer with undermined edges along 4cm. Pathological examination (4 mm punch) revealed acidophilic necrosis with a number of Ziehl-Neelsen stain AFB. Both PCR and culture were negative.

The conclusion pointed to a probable surviving MUI against a background of immune restoration syndrome described among highly immune-compromised HIV-positive patients after administration of triple therapy, in particular in association with numerous mycobacterial infections (*M. tuberculosis*, *M. avium-intracellulare*, *M. leprae*). Investigation for Leishmania (direct examination, culture) was negative. The condition evolved satisfactorily under treatment with antibiotics associating oral rifampicin 10 mg/kg/d and intramuscular amikacin 15 mg/kg/d for two months.

This is the first observation of immune restoration syndrome involving *M. ulcerans*.

In 2008, our pharmacists started to apply stricter criteria for prescribing amikacin. In France, use of this antibiotic is restricted to hospitals. It became impossible for us to prescribe it outside a hospital environment (conventional admission to hospital, admission as day patients or domiciliary hospitalization). As a result, when patients are not willing to accept the constraints of hospital treatment, two-drug treatment with rifampicin and clarithromycin has been prescribed with good results.

Overview of Buruli ulcer control activities in Togo in 2008

Salomon Hainga

2008 was a period of intense activity for Buruli ulcer control in Togo. Activities in the fields of case-detection, Information, Education and Communication (IEC) and community-based surveillance made it possible to confirm 95 new cases of Buruli ulcer.

Case-detection activities were successful on account of the measures implemented in support of them, including training, capacity-building for health facilities and monitoring/supervision. The breakdown of the 95 new cases confirmed in 2008 is as follows:

*** Age:**

42% of the cases were under 15 years of age;
43% were between 15 and 45 years of age;
15% were over 45 years of age.

*** Sex:** 58% of the patients were male and 42% female.

*** Classification by category:** the majority of patients were in category 2 (46%).

*** Clinical forms:** ulcers were the most common clinical form (62 cases).

*** Site:** the lesions were most frequently located on the lower limbs (45 patients).

*** Origin:** 86 of the 95 cases confirmed were from the Maritime region (the region of highest endemicity and where the National Referral Centre is located).

*** Case confirmation:** all 95 cases were confirmed by PCR, with a positive rate of 43%.

*** Case management:** 64 cases were admitted to hospital for treatment and 31 treated as outpatients. Of the patients admitted to hospital, 29 were treated solely with antibiotics and 19 of them were cured without sequelae limiting their movement or amputation. The patients were also provided with nutritional and psychosocial support.

*** Prevention of disabilities and physical rehabilitation:** Of the patients admitted to hospital, 35 were cured with no sequelae.

The performance achieved in 2008 was possible thanks to the support of the Government of Togo and its development partners (OMS, GLRA and Handicap International).

Further strengthening of this support will enable the Togolese National Buruli Ulcer Control Programme to carry out mapping of cases and to improve early detection and treatment of Buruli ulcer cases in all those parts of the country in which the disease is endemic.

Summary of the presentation by Cameroon

Charles Nsom Mba and Ernest Njih

Buruli ulcer is an authentic public health problem in Cameroon. Since 2000, the response provided to it by the health system has produced satisfactory results. The response is based on the strategies defined by the World Health Organization and is implemented in close collaboration with our partners: WHO, Aide aux Lépreux Emmaüs-Suisse, Médecins Sans Frontières and the Centre Pasteur in Cameroon.

The aggregate number of cases has been constantly increasing since then, and in 2008, 314 new cases were detected and provided with treatment in accordance with the WHO protocols. Operational research is under way, and in 2009 it is planned to continue activities in known disease foci and to identify new foci in order to expand activities.

National programme presentation, 2009, Ghana

Edwin Ampadu

The national programme continues to offer the needed technical support in terms of logistics mobilization and policy direction to ensure the sustainability of control activities particularly in the endemic areas and the country at large are held high.

However, the programme is further challenged with low awareness of the disease both within the medical community and the public in spite of the various institutional and districts awareness interventions pursued over the years .

In the year 2008, the impact of the external support was tremendous. Some key areas of interventions, early case detection and referrals, prevention of disability and capacity development and health system strengthening have seen tremendous improvement. This adds up to much needed comprehensive care to Buruli ulcer patients and health system strengthening.

National objective

To minimize the morbidity and disability associated with Buruli ulcer disease through all strategic interventions.

Key interventions areas

- Early detection and standardized treatment
- Health system strengthening
- Advocacy for Buruli ulcer in the context of neglected tropical diseases
- Research intervention
- Monitoring and advocacy activities

Early case detection

- Through community screening and Information, Education & Communication [IEC]
- Active case search by community volunteers and health workers
- Health facility based skin diseases surveillance activities
- 4 main endemic districts carried out active interventions on case detection and referral and management

Achievements

Over 67% of total cases reported were as a result of early case activities carried out in most endemic areas. During that time close to 57% of cases reported were of Cat I lesions. The strategy adapted has some synergism for other programme activities. It was mainly screening for any skin lesions.

The way forward is to use the new approach of skins lesions to serve as community case identification and report.

Standardized case management

- The use of a combination therapy of streptomycin and rifampicin as first line treatment for all forms of Buruli ulcer and surgery as adjunct
- Best wound care management, physiotherapy and prevention of disability
- Specimen collection for laboratory confirmation by PCR (Use of FNA for non-ulcerated forms and wound swabs for ulcerated cases)

Achievements

Case confirmations were systematically carried out for both Ziehl-Neelsen and PCR in the 3 national supportive laboratories, KCCR, Noguchi and KATH. These centres provided reagents to support the programme.

The laboratory confirmation covered 78% of total cases reported, a dramatic improvement over the previous year.

The litmus test was PCR+ and this gave a total of 51.6%

The disease burden

Currently 426 communities from the 6 regions have been mapped as reporting on the disease giving a total of 986 cases.

Community reporting	No.	Total # of cases reported
> 30 cases	1	21
20–29 cases	3	68
10–19 cases	4	69
5–9 cases	11	89
1–4 cases	407	They are many [729]

Standardized case-based reporting and surveillance

- Use of BU01 & BU02 forms for case-based recording and reporting respectively
- Nationwide community based surveillance using the HealthMapper
- Incorporate Buruli ulcer surveillance into mainstream National Integrated Disease Surveillance and Response

Human capacity development

- Training of community based agents (CBSVs, school teachers, herbalists and chemical sellers) on suspecting and reporting the disease for treatment
- Training of health workers on diagnosis, use of combination therapy, specimen collection and transportation, wound care, surgery and prevention of disability.
- Provision of educational materials for awareness creation
- Staff moral to programme control activities gradually improving

Infrastructure development

- Construction and renovation of hospital wards, surgical theatres, laboratories and physiotherapy blocks/units

Supply of surgical and physiotherapy equipment

- Transport and ICT support to some centres
- These supports and interventions have placed control activities on a better scale within the ministry and the endemic areas

Operational research

- Antibiotics expansion with the enhancing wound healing
- Why late reporting of BU ?

Monitoring, supervision and technical support

- Direct technical support to some endemic districts: 18 carried out
- Integrated monitoring, supervision and technical support through disease control and prevention department framework.

Collaboration and advocacy

- Collaborate with Yaws, leprosy, guinea worm and onchocerciasis, etc. (Integrated Skin Diseases Programme).
- Advocate for visibility of Buruli ulcer in the context of neglected tropical disease
- Some programme achievements include provision of surgical theatre, wards, physiotherapy units and laboratory facilities

Special interventions

- Wound care and lymphoedema control
- This was initiated as a way of improving treatment outcome for all patients with wounds
- The national programme is spearheading this initiative to improve wound care in Ghana
- This initiative was sponsored by WHO and the ministry of Health, Ghana

General challenges to the programme

- Late detection and treatment
- Financial support to BU treatment in health facilities stand in limbo
- Provision of recommended dressing materials to support case management needs policy direction
- Partnership issues – few local and external NGOs are interested in Buruli ulcer in spite of the advocacy works

Reasonably resourced: onchocerciasis, lymphatic filariasis, guinea worm, soil-transmitted helminthiasis

Wide disparity in Programme resources - grossly inadequate resources [BURULI ULCER, YAWS]

Funding urgently needed to assist in case control

Way forward

- Advocate for continuous community education on skin lesions as a means of early case detection and referrals.
- Research to determine the critical time to carry out surgery whiles on antibiotics treatment, a way of improving treatment outcomes
- Other research interventions on transmission and case management
- Resource mobilization with corporate bodies in the country

Buruli ulcer situation in Côte d'Ivoire: Activity overview 2008

Henri Assé

Control strategy in 2008

Early case detection at the community level and IEC

Awareness-raising and case detection campaign in three (3) health districts
Mobile awareness-raising campaign in three (3) wards of Abidjan.

Training for 10 district management teams with the support of our partners: Anesvad and Mission Chirurgicale D'afrique ; and for 3 district management teams with the support of Map International.

Training for health professionals and community intermediaries in 4 districts with the support of the Fondation Raoul Follereau and in 3 districts with the support of Map International.

Standardization of case management

Treatment with antibiotics is provided in the 64 treatment facilities. Surgery is carried out in 6 health facilities.

Case confirmation

Is carried out by PCR at the Institut Pasteur in Côte d'Ivoire. So far, 840 samples have been confirmed.(83.58% positive rate)

Improving technical facilities with the help of partners

Partners	Details	Beneficiaries
WHO	Box of dressings, computer equipment, Audio-visual equipment	4 districts and four treatment facilities
ANESVAD	Laboratory and operating theatre equipment	3 treatment facilities
MAP INTERNATIONAL	Computer and Audio-visual equipment	3 districts

Standardization of case notification

Use of forms BU01 and BU02 recommended by WHO in all treatment facilities

Coordination, follow-up and evaluation of Buruli ulcer control activities

acquisition of a headquarters for PNLUB reinforcing the coordination team organization of monthly meetings attended by all those involved in the control effort (investigators, practitioners and partners) visit by Dr Asiedu, Coordinator of the Global Buruli Ulcer Initiative.

Advocacy and development of partnership

visit by an evaluation team from the NGO ANESVAD for the purpose of strengthening its partnership visit by a team of experts from the Republic of Korea to carry out a feasibility study into a project submitted by PNLUB

Social and economic rehabilitation

Educational support (literacy and refresher courses) in 3 health facilities.

Operational research

Two (2) State Doctoral theses in medicine have been :
Evaluation of rifampicin – streptomycin combination for treatment of Buruli ulcer.
Buruli ulcer – HIV-AIDS coinfection

Epidemiological, Clinical And Treatment Aspects

Number of BU cases detected → 2178 New cases → 2178 Relapses → 0
Number of health facilities having treated patients in 2008 → 64
Number of districts where the disease is endemic having reported cases → 25
Number of districts from which patients originate → 33

Age of patients

≤ 15 years 40.69%
> 15 years and ≤ 49 years 42.35%
≥ 50 years 16,96%

Sex

male → 49.24%
Female → 50.76%

Made some use of traditional medicine

yes → 57.92%
No → 42.08%

Presence of a disability on admission

Yes → 31,40%
No → 68,60%

Clinical form

Nodule → 9.49%
Edema → 13.94%
Plaque → 11.76%
Osteitis → 2.07%
Ulcer → 62.82%
Non-ulcerative forms → 37.18%
Ulcerative forms → 62.82%

Laboratory

Out of 1005 samples so far examined, 840 (83.58%) were positive under PCR. A total of 766 samples are still being tested.

Category of lesion

Category 1 → 26.98%
Category 2 → 44.54%
Category 3 → 28.48%

Site of lesion

UL → 26.08% Back → 1.40%
LL → 61.81% Butt. → 1.21%
Gen. org. → 0.18% Thor. → 1.34%
Breast → 0.30% H & N → 2.91%
Eye → 0.43% Abd. → 2.37%

Medical treatment

Yes → 94.92% 27.96%
No → 5.08 %

Surgical treatment

(609 operations out of 338 patients, i.e. 2 operations per patient)

Democratic Republic of the Congo (DRC): National Buruli Ulcer Control Programme (PNLUB): Annual report for 2008

Kapay Kibadi Anatole, Singa Nyota Jackie, Imposo Hubert-Désiré, Phanzu Delphin, Minuku Jean-Bedel, Kayinua Edouard, Kongawi Jacques, Ndombe Martin, Muyembe Jean-Jacques, Suykerbuy Patrick, Portaels Françoise, Tiendrebeogo Alexandre

Background

Mycobacterium ulcerans infection, also known as « Buruli Ulcer» (BU) affects at least 27 countries on four continents. Most of them, 16, are in Africa and they include the Democratic Republic of the Congo.

Mycobacterium ulcerans infection, also known as « Buruli Ulcer» (BU) affects at least 27 countries on four continents. Most of them, 16, are in Africa and they include the Democratic Republic of the Congo.

The National Buruli Ulcer Control Programme was created in 2002 within the Ministry of Health. Between 2002 and 2007, a total of 1166 cases of the disease were reported at the annual meetings of WHO on Buruli ulcer.

Overall objective for 2008

To expand control activities in areas of endemicity and to prevent the disabilities caused by the disease, by means of better case management

Results achieved

Community-level activities

Distribution of the new management tools produced by WHO, including the BU01, BU02, BU03 and BU04 forms in Nsona-Mpangu and Kimpese rural health zones (ZSR).

Building up the rural health system

Strengthening activities to decentralize the control effort already begun in 2006 in Nsona-Mpangu rural health zone, and in 2008 in Kimpese rural health zone.

Number of cases of Buruli ulcer declared in 2008 : 963 suspected cases

- The IME Hospital in Kimpese declared 846 cases of Buruli ulcer, 793 of which were detected by the prevalence survey carried out during the third quarter of the year in Nsona-Mpangu (411 cases) and Kimpese (382 cases) ZSR and 53 declared during the last quarter.
- INRB declared 170 cases of Buruli ulcer, 120 of them from Nsona-Mpangu ZSR and 50 from the city of Kinshasa. On 2 and 3 may 2008, the Institute organized a meeting at Songololo in Bas-Congo province to set up a national Buruli ulcer case confirmation network.

Treatment of Buruli ulcer patients in accordance with the WHO-recommended protocol:

- The IME hospital in Kimpese declared 29 cases admitted to hospital and treated with rifampicin and streptomycin in association with surgery.

- INRB declared 56 cases treated in Nsona-Mpangu ZSR in accordance with the same protocol.
- Between 8 and 13 December 2008, operations were performed at Nsona-Mpangu hospital on 25 Buruli ulcer patients with sequelae by a United States surgical mission.

Case confirmation by the National Buruli Ulcer Reference Laboratory (INRB)

In 2008, efforts were made to develop the activities of this national laboratory, which received 234 surgical biopsies, 169 swab samples and 6 fine-needle aspirations.

Results (INRB): 55 patients confirmed by positive ZN stain, 40 by histology, 10 by culture and 10 by PCR. IMT in Antwerp, Belgium has already analysed biopsies from 8 patients. All 8 have been confirmed as BU by PCR + and ZN + . Other analyses are under way.

Staff supervision, monitoring and evaluation of control activities

From 3 to 6 December 2008, a supervisory mission was carried out in Bas-Congo province by PNLUB, WHO, ALM and the TLMI.

Conclusion

Efforts are under way to build up and improve the Buruli ulcer control system in DRC. However, the National Programme is handicapped by lack of funding and of a partner. A further effort is required in respect of data management, using the BU01, BU02, BU03 and BU04 forms throughout the country, as it is impossible to use some of the data currently available. We should like to express our thanks to WHO, ALM, IMT Antwerp, INRB and IME-Kimpese.

Buruli ulcer in Gabon: an overview of four years' work

Louis Bayonne Manou

Introduction

Buruli ulcer is an emerging disease in equatorial Africa. The first cases of *Mycobacterium ulcerans* in Gabon were described in 1986. Since the establishment of the National Buruli Ulcer Control programme in 2005, more than 247 cases have been registered and treated. Activities were carried out in the provinces of Moyen Ogooué, Woleu Ntem, Ogooué Ivindo and Ngounié

Activities carried out

National level

- Coordination and monitoring of activities for the implementation of the operation plan
- Validation of the National and Strategic plans 2008 – 2012
- Capacity-building for health workers through training
- Organization of surveys in Moyen Ogooué, Woleu Ntem and Ogooué Ivindo provinces
- Raising awareness among the populations at risk
- Distribution of Information, Education and Communication aids

Provision of specific antibiotics and of consumables to hospitals

At the operational level

1. Community-based early detection

This activity was carried out in provinces in the centre, north and south-central part of the country by health workers and community intermediaries; a total of 247 cases were reported, with the following distribution:

Distribution of new cases by age group and sex				
	Number			Total
	< 15 yrs	15 – 49 yrs	> 49 yrs	
Male	63	41	29	133
Female	58	37	19	114
Total	121	78	48	247

2. Information- Education – Communication

Awareness-raising sessions were organized for the target populations, involving:

- Projection of the film on Buruli ulcer;
- Radio broadcasts;
- Talks with question-and-answer sessions and distribution of brochures and leaflets to school children in Lambarené commune.

3. Laboratory confirmation

A total of 139 samples taken from 247 suspected patients (56,27%) were confirmed by PCR or Ziehl-Neelsen stain at the laboratory of the Institute of Tropical Medicine in Antwerp.

4. Observance of the case-management protocol (antibiotics, surgery, prevention of disabilities)

The National Buruli Ulcer Control Programme has adopted the WHO strategy and protocol. Accordingly, all our patients received specific antibiotics (streptomycin, rifampicin). These molecules made possible rapid cure and a reduction in the length of hospital stay.

5. Training for health workers

During these four years of activity, and thanks to the multifaceted assistance provided by WHO and ALES, the programme provided training for health workers, community intermediaries and technicians (two laboratory technicians and one occupational therapy technician to reduce disabilities).

6. Standardization of the case registration and reporting system

This is assured by the use in hospitals and health centres of the forms proposed by WHO (BU01, BU02, BU03 and BU04).

7. Monitoring and evaluation of health workers

Monitoring of the peripheral level is carried out every three months by the central level.

Current situation of Buruli ulcer in Congo

Damas Obvala

The disease affects four departments: Kouilou, Pointe – Noire, Niari and Bouenza. There are reported to be suspected cases not yet confirmed by laboratory tests in other departments, in particular Pool and Cuvette.

Since 2005, activities have been carried out as part of a joint leprosy, Buruli ulcer and yaws programme. They have consisted of community awareness-raising, supervision of centres providing treatment, active and passive community case detection, training for health workers and programme managers and systematic collection of samples from cases for PCR.

As regards epidemiology, 126 cases have been detected and treated, including 124 new cases and 2 relapses. Ulcerative forms account for 72.2 % of cases and 65.8% of cases affect adults.

Category 2, lesions account for 47.6% of lesions, and 70.6% of lesions are on the lower limbs.

As regards medical treatment, 104 cases (84.9 %) were treated with specific antibiotics and 49.2% of cases were cured without sequelae; other patients are still under treatment.

Twelve new communities (villages), in districts known to be disease-endemic, reported cases of Buruli ulcer during the year, indicating that the disease is expanding.

Collection of samples for confirmation by PCR marked an innovation during the year; samples were taken from 81 cases (64.2 %) and 68 of them (59.3%) were confirmed by PCR; most of the samples were from Kouilou department.

In most cases, the lesions responded satisfactorily to treatment.

Surgical treatment of patients was provided at Nkayi base hospital (13 cases)

The main constraints encountered may be attributed to the limited budgets and lack of logistic resources.

Prospects for 2009 enhanced awareness-raising activities among communities, training for community intermediaries, supervisory training for health workers responsible for case management, surgical treatment at the Madingo-Kayes national referral centre.

Annual Report on the activities of the National Buruli Ulcer Control Programme (PNLUB) in 2008

Kesso Bah

Introduction

Buruli ulcer is an endemic skin disease caused by *Mycobacterium ulcerans*. The disease takes various forms, the most spectacular of which are extensive ulcers and bone involvement whose sequelae are often disabling. In terms of frequency, it ranks third among mycobacterial diseases after leprosy and tuberculosis. The populations most affected are poor people in rural areas.

As a rule, the disease is detected at a late stage because most health workers are unfamiliar with it and because factors associated with taboos mean that patients first of all consult traditional healers.

In Guinea, surgery is the only treatment available, in spite of its high cost and the relatively long period of hospitalization required.

The National Buruli Ulcer Control Programme (PNLUB) has conducted a number of activities, albeit limited, in order to control the disease in the country.

Overall objective for 2008

To reduce morbidity and disability from Buruli ulcer.

Specific objectives

- to carry out an evaluation of the National Buruli Ulcer Control Programme, with the assistance of an outside consultant;
- to mobilize the resources needed to implement the activities of the plan of action 2008;
- to draw up an operational plan of action (OPA) for 2009-2013;
- to organize a consensus meeting on the OPA 2009-2013;
- to promote early detection of at least 10% of cases;
- to provide laboratory confirmation of at least 50% of cases;
- to provide comprehensive case management for at least 50% of cases detected in 2008;
- to improve and ensure smooth running of logistics;
- to enhance the skills of human resources;
- to build up the infrastructure and equipment of treatment facilities;
- to supply treatment facilities with drugs, laboratory reagents and other consumables;
- to organize a coordination meeting to galvanize partnership among the different actors involved;
- to organize a meeting to provide feedback;
- to organize supervision of activities in the field.

Expected outcomes

Capacity-building for Buruli ulcer control

Activities carried out

The activities carried out are described in their order of priority as key components of the strategy recommended by WHO for Buruli ulcer control.

Community-level activities

The activities making up this component include early case detection at the community level, communication activities to bring about behavioural change and improving the community-based surveillance system by training village health workers.

During 2008, two active case-detection campaigns were organized: the first in Kindia, Boffa and Forécariah prefectures from 22 to 30 April thanks to funding from MSF Switzerland, and the second in Macenta, N'Zérékoré and Lola prefectures from 5 to 14 July, made possible by funding from WHO. During these campaigns, a total of 18 suspected cases were detected and referred to CDTUB and to the national health facilities providing treatment for Buruli ulcer in the region. Late forms were the most common among the suspected cases.

A total of 22 samples were sent to the Institute of Tropical medicine in Antwerp, Belgium for detection of *Mycobacterium ulcerans* by culture, PCR and et histopathology. No cases were confirmed by the preliminary findings of PCR and culture. However, four samples are still undergoing histopathological tests.

During these activities, PNLUB distributed the new management tools produced by WHO, including the BU01, BU02, BU03 and BU04 forms.

In the course of the same campaign, communication activities were carried out in rural health centres in the prefectures concerned by the active case-detection campaign, to bring about changes in behaviour (CBC). The village health workers and staff of the community health centres concerned were also given basic information on CBC activities.

Strengthening the health system

This involves improving health infrastructures and their equipment, providing training for health workers, securing commitment to the control effort from officials at the intermediate level of the health pyramid and reporting and registration of cases of Buruli ulcer using the new management tools produced by WHO.

The Luxembourg Raoul Follereau Foundation provided CDTUB with drugs, laboratory reagents and other consumables.

No training activities were carried out during the year, for lack of funds.

Case management

In Guinea, providing laboratory confirmation still poses a real challenge. During the year, no cases were confirmed by laboratory tests.

Surgery is the treatment of choice for all patients. Apart from the activities of the medical centre of the Mission Philafricaine, there are no disability prevention or physical rehabilitation activities, even at CDTUB. Providing training for the staff of the physiotherapy unit at N'Zérékoré CDTUB is a matter of urgency.

Analysis of the epidemiological situation in the country is based on the administrative region of N'Zérékoré, where the Buruli ulcer is located. This region is in the south-east of the county and is an area in which Buruli ulcer is known to be endemic, in the absence of a nationwide prevalence study.

For the purposes of our calculations, the population of the regions is estimated to be 2 427 010. Analysis of the results for 2008 yields the following findings:

Number of new cases and relapses (breakdown by age, sex and location)

Table 1. Total number of cases diagnosed during the reporting period

Category	Number	Number with joint involvement
New cases	80	9
Relapses	0	0
Total	80	9

Table 2. Analysis by location

Category	Number
Communities	
Total number of communities reporting cases of BU	9
Number of new communities reporting cases of BU during the year of the report	3
Number of communities previously identified reporting no cases of BU during the year of the report	2
Districts	
Total number of districts reporting cases of BU	9
Number of new districts reporting cases of BU during the year of the report	3
Number of districts previously identified reporting no cases of BU during the year of the report	2

Table 3. Distribution of new cases by age-group and sex

Sex	0 à 15 years	16 – 49 years	> 49 years	Total
Male	9	23	9	41
Female	3	21	15	39
Total	12	44	24	80

Table 4. Laboratory confirmation of cases

Category	Number
Total number of cases confirmed by ZN	1
Total number of cases confirmed by molecular biology (PCR)	0
Total number of cases confirmed by histology	NK
Total number of cases for which confirmation was not possible	0
Total number of cases confirmed by at least one of the above methods	1

Table 5. Analysis of clinical forms and treatment categories for all cases detected

Category	CAT I	CAT II	CAT III	TOTAL (%)
Non ulcerative	2	3	2	7
Ulcerative	7	30	36	73
Total	9	33	38	80

Table 6. Indicators

Indicators	Results
New case detection rate	3,29
Percentage of new cases with joint involvement	11,25
Percentage of persons aged under 15 years among new cases	15
Percentage of females among new cases	48,75
Percentage of all cases that were confirmed	1,25
Percentage of new cases with ulcers	91,25

Staff supervision, monitoring and evaluation of control activities*Supervision*

A supervisory mission was carried out in N'Zérékoré administrative region from 1-13 March 2008.

The mission had the following aims:

- To stimulate case detection and treatment of patients;
- To improve care quality in facilities providing treatment for Buruli ulcer patients;
- To assess the extent of use of the new data-collection tools.
- To assess the degree of commitment to disease control among officials in administrative entities and health districts;
- To provide preliminary information on the results of the case-detection campaign.

The results of this supervisory mission were as follows:

- Early detection of cases is poor;
- Collection of samples for laboratory testing has improved;
- No cases were confirmed by laboratory tests,
- Commitment on the part of health officials is increasing at some levels;
- Health workers in some sites are demotivated.

Meeting to provide feedback.

A meeting to provide feedback was organized in N'Zérékoré prefecture from 11 to 16 October 2008.

The meeting was organized for the following purpose:

- To disseminate information on the disease's epidemiological situation and on the control activities carried out;
- To identify the problems and constraints that exist in the field;
- To put forward potential solutions to the different problems identified;
- To organize follow-up to and supervision and evaluation of Buruli-ulcer control activities;
- To advocate on behalf of the recruitment of new partners to finance and implement activities.

After the meeting, the operational plans of action were discussed, amended and adopted by all the prefectures in N'Zérékoré administrative region.

Advocacy, social mobilization and partnerships

Thanks to the advocacy carried out during the year by the coordination office of PNLUB, it was possible to:

- Assign an anaesthetist to N'Zérékoré CDTUB, who took up his post;
- Inclusion of PNLUB in the national development budget for 2009;
- Inclusion of PNLUB in the activities of the WHO Representative Office for 2008-2009 ;
- Inclusion of Buruli ulcer on the agendas of the different prefectural health committees and of the N'Zérékoré region health committee;

Research

None of the research activities planned for 2008 were carried out.

Difficulties

The main difficulty is the lack of financial and material resources.

Outlook for 2009

In order to improve control of Buruli ulcer in 2009, the following measures are needed:

- Evaluation of the performance of the National Buruli Ulcer Control Programme, with the assistance of an outside consultant;
- Advocacy, in order to mobilize the resources needed to carry out activities in 2009 and organization of logistics.
- Promotion of early case detection;
- Promotion of laboratory confirmation of clinical cases and quality assurance in laboratories;
- Provision of technical support for N'Zérékoré CDTUB and for the centres of excellence, including N'Zérékoré regional hospital and the medical centre operated by the Mission Philafricaine at Macenta;
- Improving the skills of human resources;
- Supplying health facilities that provide treatment with drugs, laboratory reagents and other consumables;
- Organization of a coordination meeting to develop a more fruitful partnership with the different actors;
- Organization of feedback;
- Supervision of activities in the field.

Conclusion

Buruli ulcer is a disease that is still largely unfamiliar to most health workers. In spite of the progress made towards control of the disease in Guinea, many challenges still have to be taken up; these include early detection of cases and laboratory confirmation of clinical cases. This latter element is an essential prerequisite for enhancing the credibility of the national programme.

The large number of activities required to control this disabling disease and the challenges to be faced call for financial and material resources. Further commitment is required from the Government of Guinea and its partners in order better to control the disease.

We should like to express our thanks to all of our partners, and in particular to the World Health Organization, the Luxemburg Raoul Follereau Foundation, the Guinean Raoul Follereau Association the Spanish NGO ANESVAD, the Nippon Foundation and the facilities providing patients with treatment.

Impacts of dosing frequency of the combination rifampin-streptomycin on its bactericidal and sterilizing activities against Mycobacterium ulcerans in mice

Baohong Ji

Because of operational limitations, a significant proportion of the health centres at the peripheral level are able to provide treatment to Buruli ulcer patients with the combination rifampin-streptomycin (RIF-STR) only five-times-weekly (5/7), instead of seven-times-weekly (7/7), as recommended.

The objective of this experiment is to assess the impacts of various dosing frequencies of the combination on its bactericidal and sterilizing activities against *M. ulcerans* in mice. The results demonstrated that the bactericidal activities did not differ significantly among five dosing frequencies of the combination, ranging from 7/7 to 2/7 administration weekly, but the sterilizing activities varied widely. RIF-STR 7/7 was the only regimen which was able to sterilize infection after 4 to 8 weeks of treatment; the sterilizing activity of reduced dosing frequencies was significantly compromised, and 8 weeks of 5/7 administration yielded a relapse-rate greater than the generally accepted level of 5%.

We recommend that the duration of treatment with 5/7 administration be prolonged beyond 8 weeks, and that additional experiments in mice with sufficient statistical power to compare the relapse-rates of *M. ulcerans* infection between 8 weeks of 7/7 administration and 10 and 12 weeks of 5/7 administration of RIF-STR be carried out.

Comparison of rifapentine and rifampicin based oral regimens in treatment of experimental *M. ulcerans* disease using the kinetic mouse model

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Rationale

The recommended treatment for *M. ulcerans* disease or Buruli ulcer (BU) includes daily treatment with an aminoglycoside, usually streptomycin (SM), and rifampicin (RIF) for two months followed, if necessary, by surgical excision and/or skin grafting. Since many patients with BU reside in remote areas with limited medical facilities, development of a completely oral drug regimen might make treatment easier to implement. Previously RIF + Clarithromycin (CLR) based oral regimens were tested but were not found to be as effective as RIF + SM in the mouse footpad model. Use of rifapentine (RPT), a rifamycin derivative with a longer half life than RIF, may enable greater rifamycin exposure and better activity. Previous studies conducted by us showed encouraging results but the ATCC strain Mu1617 that we used was found to be poorly virulent. Therefore we compare the activity of 10mg/kg rifapentine and 10mg/kg rifampicin based oral regimens in the treatment of Buruli ulcer in mice infected with the recent clinical isolate from Ghana, Mu1059.

Methods

320 Balb/C mice were infected in the right hind footpad with 3.24 log₁₀ CFU of *M. ulcerans* 1059 strain. Treatment was started 11 days later when the CFU count was 3.35 log₁₀ cfu/footpad. All mice were treated 5 days a week for 4 weeks. The treatment groups were as follows: untreated negative controls (n=30), positive control, RIF+SM (n=55); and test regimens, SM alone (150 mg/kg) (n=25); RIF alone (n=25); RPT alone (n=25); CLR alone (100 mg/kg) (n=30); RIF+CLR (n =55); and RPT+CLR (n=55). Upon completion of treatment 5 mice from each group were sacrificed for CFU counts and the rest were kept for foot pad swelling. The relative bactericidal activity of the different drug regimens was assessed by the delay in median time to footpad swelling in test mice compared with control mice, using kinetic method developed by Shepard & Mc Rae.

Results

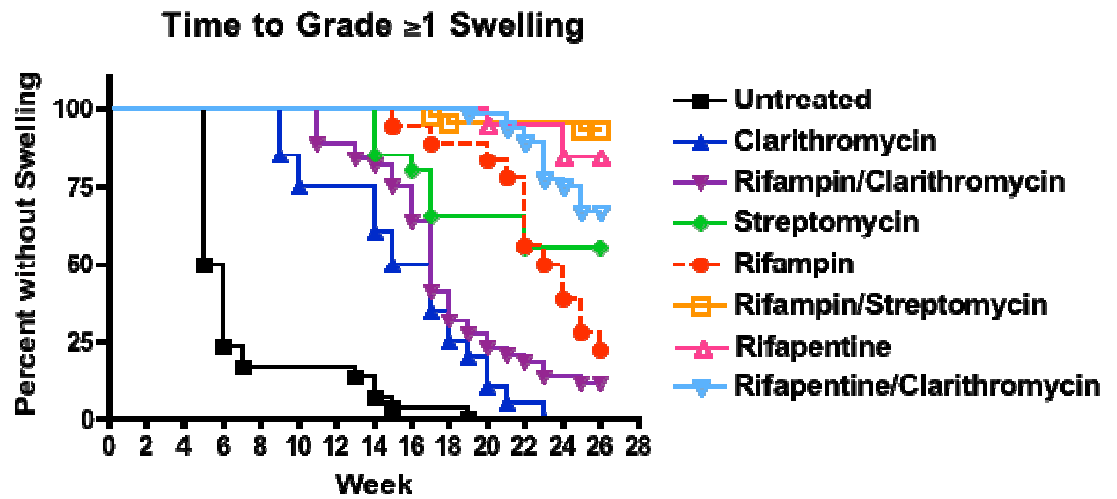
After 4 weeks of treatment, the CFU counts in negative control were 5 log₁₀ CFU/footpad, for those treated with RIF+SM were 0.52 log₁₀ CFU; RIF+CLR were 1.26 log₁₀ CFU; RPT+CLR were 0 CFU; S alone, 0.35 log₁₀ CFU; R alone, 0.76 log₁₀ CFU, P alone, 0.12 log₁₀ CFU and CLR alone, 3.54 log₁₀ CFU. The time to 50% swelling (Fig 1) was the shortest (16wks) for CLR alone, followed with RIF+CLR (17wks) and RIF alone (23wks). Other regimens did not yet reach 50% swelling.

Conclusion

From the results available so far, the activity of RPT alone was close to that of RIF+SM combination which still appeared the most active. CLR alone was the least potent. All combinations of a rifamycin with CLR were less active than the rifamycin alone. PK analysis showed that giving CLR together with RIF reduced the RIF serum levels in mice. Therefore

further studies need to be done to evaluate the PK interaction and to determine if this problem is a mouse artifact.

Figure 1.



Dynamics of serum neopterin concentration during antibiotic treatment of Buruli ulcer disease: evidence of macrophage activation

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Introduction

Mycolactone, which is central to the pathogenesis of *M. ulcerans* (Mu) disease, suppresses macrophage function at low concentration. We have recently shown that during antibiotic treatment of patients with Mu disease there is an increase in interferon γ (IFN γ) secretion in a whole blood stimulation assay suggesting improvement in Th-1 responses (Ref). Neopterin is a pteridine compound released by activated monocytes upon stimulation by interferon γ . The object of this study was therefore to look for evidence of macrophage activation in patients with Mu disease during antibiotic treatment by measuring the serum concentration of neopterin alongside CRP as an inflammatory marker.

Methods

30 patients with Mu disease were recruited from villages near Tapa in the Ahafo Ano North district of Ghana. The diagnosis of Mu infection was confirmed by PCR for IS2404 on a 4mm punch biopsy. All patients were treated with rifampicin 10mg/kg by mouth and streptomycin 15mg/kg I/M daily for 8 weeks. After obtaining informed consent 5ml of venous blood was collected in endotoxin free tubes before treatment and after 4, 8 and 12 weeks. Serum was separated and stored at -200C until analysis. Serum neopterin was measured by ELISA (Genway,US) according to manufacturer's instructions and CRP measured at St. George's, University of London by ELISA. Samples were taken from 10 TB patients and 5 normal controls. Mann-Whitney's U-test was used to compare the medians of serum neopterin and CRP at various time points with $p < 0.05$ taken as level of significance.

Results

Mu disease was confirmed by PCR in 16 patients with pre-ulcerative and 14 with ulcerative disease. All lesions healed within 24 weeks of starting antibiotics and there were no recurrences after follow up for a year. Median serum neopterin concentration in 5 normal controls, 30 untreated Mu disease patients and 10 patients with pulmonary tuberculosis were 7.9 nmol/l (range 3.9-15.12), 11.0 (4.5-43.0) and 53.5 (13.1-85.1) respectively with a significant difference between normal controls and patients with tuberculosis ($p < 0.05$) but not between normal controls and Mu infected patients. During antibiotic treatment of Mu disease, serum neopterin increased to 18.9 nmol/l (2.6-43.7; $p < 0.005$ compared to pre-treatment concentrations) after 4 weeks but declined at 8 weeks to 15.3 (8.6-39.5; $p < 0.05$) and at 12 weeks to 15.9 (5.7-40.5) ($p > 0.05$). With few exceptions, serum CRP concentration remained within normal limits before, during and after antibiotic therapy.

Discussion

The change in serum neopterin concentration during antibiotic therapy of Mu disease followed the same pattern as the recovery of gamma interferon secretion reported recently (Ref).

A possible interpretation of these findings is that when mycolactone secretion by Mu is reduced by antibiotic treatment, IFN γ secretion is induced by killed Mu and macrophages secrete neopterin. If this is the case measurement of serum neopterin could be a useful method of monitoring the response to antibiotic treatment. In contrast, serum CRP did not reflect either disease activity or treatment response.

Reference

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Analysis of histopathological changes and local immune responses in the course of R/S chemotherapy in the experimental Buruli ulcer mouse model

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Directly observed treatment with a combination of rifampin and streptomycin, administered daily for 8 weeks is the current recommendation of the WHO for chemotherapy of Buruli ulcer. To gain better insight into the mode of action of these antibiotics against established *Mycobacterium ulcerans* infection foci and to characterize recovery of local immune responses, we conducted a detailed histopathological study with *M. ulcerans* infected and R/S treated mice.

To monitor (i) the establishment of infection foci, (ii) time dependent changes in bacterial load (iii) pathogenesis and (iv) cellular immune responses, mice were inoculated with *M. ulcerans* in the footpad and eleven weeks later treated with R/S five times weekly. Development of lesions during the first eleven weeks and subsequent differences in disease progression between R/S treated and untreated mice were analysed. Groups of mice were sacrificed at different time points; footpads were collected and microscopically analyzed. Additionally the lesion index was macroscopically determined and CFU counts per footpad were recorded.

Already five weeks after inoculation with *M. ulcerans*, massive leukocyte infiltration throughout the entire footpad was observed. In this early stage of the infection acid-fast bacilli were localised both extracellularly and intracellularly. During further progression of the infection a steady increase of the bacterial load was found. 15 weeks after inoculation huge clusters of extracellular bacteria located in large necrotic areas and surrounded by dead host cells were visible in untreated mice. Already two weeks after start of the chemotherapy bacilli started to appear as beaded rods and the bacterial load started to decrease. While in untreated footpads a neutrophilic immune response was primarily observed, a more structured immune response with the development of B lymphocyte clusters and macrophage accumulations around beaded bacteria took place in the lesions of R/S treated mice. Results demonstrate that histological studies will be a useful tool to investigate treatment efficacy with alternative antibiotic combinations.

Severe multifocal form of Buruli ulcer after streptomycin and rifampicin treatment: a case report with comments on possible dissemination mechanisms

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We report a severe multifocal Buruli ulcer case with osteomyelitis in a six year –old HIV-negative boy.

Such forms are poorly documented and generally occur in patients with HIV co-infection. The dissemination process is sometimes attributed to the surgery and the advent of the antibiotic treatment by streptomycin (S) and rifampicin (R) raised the hope that these cases be reduced.

This case raises two relevant aspects of multifocal BU. One is the mechanism of the dissemination process behind the development of the multiple foci and the second is related to the difficulties of treatment of the multifocal forms of BU.

Biochemical (hypoproteinemia) and hematological (anemia), as well as clinical (traditional treatment) and genetic factors are discussed as possible risk factors for dissemination. A probable bacteremia of extracellular or intraphagocyte *M. ulcerans* are suggested as possible dissemination mechanism.

Disseminated lesions are concomittent or followed intensive inflammatory symptom, suggesting the occurrence of an immune reconstitution inflammatory syndrome (IRIS) in the new lesions

Preliminary results of a clinical trial of eight-week daily treatment with the combination rifampin-clarithromycin for patients with Buruli ulcer

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Effective, patient-friendly, and orally administered combined regimens that would greatly simplify the treatment of Buruli ulcer under field conditions are urgently needed. Mouse experiment had demonstrated that the bactericidal and sterilizing activities of the combination rifampin (RIF)-clarithromycin (CLR) were quite similar to those of the combination RIF-streptomycin (STR), the only drug regimen recommended by the World Health Organization for treatment of Buruli ulcer. We have therefore launched a prospective but non-comparative clinical trial with the combination of RIF-CLR for treatment of Buruli ulcer.

The objectives of the trial are to determine if 8-week daily treatment with the combination: i) is able to cure patients of Buruli ulcer with a single lesion ≤ 10 cm in diameter with a negligible recurrence rate; and ii) is well tolerated by the patients, especially by the pediatric patients.

Twenty-three patients, whose diagnosis of Buruli ulcer was confirmed by PCR, were recruited into the trial. Sixteen (16) of these patients were females and 7 males; 13 in the age between 5 and 15, and 10 above 15 years old; 16 had ulcerative lesions and 7 non-ulcerative lesions; the lesions of 9 cases belonged to Category I (with lesion <5 cm in diameter) and 14 cases to Category II (with lesion >5 cm in diameter). Each patient was treated with the combination of RIF-CLR for 8 weeks, and the daily dose consisted of RIF 10 mg/kg body weight and CLR 12 mg/kg body weight. RIF was formulated either in capsule (150 mg each) or in syrup (20 mg/ml), CLR was formulated either in tablet (250 mg each) or in oral suspension (25 mg/ml). Every dose of treatment was administered by the patients under directly supervision by a health worker.

Twenty (20) of the 23 patients had already completed their 8-week treatment: 7 of them had Category I lesions and 13 had Category II lesions before treatment. Various degrees of definite clinical improvements were observed in all 20 cases during the first few weeks after starting treatment, and oedema of the lesions had disappeared before day-30. The Category I lesions of all 7 cases were healed within 3 months after starting treatment; the intervals between starting treatment and occurrence of healing in this subgroup ranged from <30 days to 76 days, with a median value of 30 days. Curettage was necessary for one of the 7 cases in this subgroup. Among the 13 cases with Category II lesions, the non-ulcerative lesions of all 4 cases were healed at day-90 to day-140 after either excision-skin grafting or curettage; 6 of the 9 cases with ulcerative lesions were healed at day-56 to day-180 without surgical intervention, and 3 were healed at day-90 to day-120 after curettage. The intervals between starting treatment and healing in the subgroup with Category II lesions were significantly longer than those in the subgroup with Category I lesions.

In summary, the lesions of all 20 cases were healed within 6 months after starting RIF-CLR treatment: 12 cases, 6 each had either Category I or II lesions, were healed with chemotherapy alone, but healing of the lesions in 1 case with Category I and 7 cases with Category II required certain surgical intervention, either curettage (6 cases) or excision-skin grafting (2 cases). After 8 months of follow-up after healing, no recurrence has been observed among these patients.

Paradoxical reactions were observed in 6 (30%) of the 20 cases who had completed their 8-week treatment with RIF-CLR. One of these 6 cases had a Category I lesion (non-ulcerative plaque), and 5 had Category II (3 non-ulcerative and 2 ulcerative) lesions before treatment. The paradoxical reactions occurred at 4 to 8 weeks after starting chemotherapy, characterized by abrupt flaring up of signs and symptoms of the Buruli ulcer after initial improvements, such as pain, enlargement of lesions, increasing in local temperature and intensity of induration, and, eventually, necrosis of the lesions. Histopathological analyses of the affected tissues removed by curettage or excision revealed leukocytes infiltration and development of haemorrhages in 5/5 cases analysed and of granulomas in 3/5 cases. Acid-fast bacilli were found either partially or predominantly located inside macrophages and had developed a beaded appearance, as is typically observed during effective antibiotic treatment. Presence of *M.ulcerans* DNA in the specimens was confirmed by PCR. Histopathological examinations provided no evidence for the development of new mycobacterial infection foci, and cultivation of *M.ulcerans* was positive only in one of the 6 cases. Taken together these results indicate that the paradoxical reactions were not related to treatment failure or relapse, but rather to a rapid recovery of the local immune reactivity following the chemotherapy-induced killing of the mycolactone-producing *M.ulcerans*. After surgical intervention, the lesions of all 6 cases with paradoxical reactions were gradually healed.

Adverse events were closely monitored during treatment with RIF-CLR, but were not detected in any of these cases either through clinical observation or laboratory examinations.

The preliminary results of the trial indicate that 8-week daily treatment with the combination RIF-CLR is effective for patients with Buruli ulcer, and that patients were well tolerated to the treatment.

Prognostic indicators associated with the clinical response after four weeks of treatments of suspected Buruli ulcer cases with streptomycin and rifampicin in Allada

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Background

Surgery was the only therapeutic management of *Mycobacterium ulcerans* disease.

In 2004 the WHO advisory group on BU recommended the use of the combination of Streptomycin (S) and Rifampicin (R) for the treatment of lesions.

This survey aim to document the clinical response of BU lesions to the administration of S and R, and to identify prognostic indicators associated with this response after 4 weeks, the need for surgery and the healing of lesions.

Method

A cohort study was carried out from January 1, 2005 to March 31st, 2008. A total of 263 patients were recruited based on clinical diagnosis and treated by S + R. Among them, 229 patients matched the inclusion criteria. The measure of the clinical response to treatment was based on the decrease of the surface (D) of lesions.

Results

110 out of the 229 patients assessed (48%) had a D>50% after 4 weeks S+R. Variables associated with this outcome are a patient delay > 2 months (OR 0.41), an ulcerated lesion (OR 0.50) and the mean diameter of the initial lesion. Variables associated with the need of surgery for patients with D >50% were a patient delay of > 2 months (OR 2.45) and the mean diameter of the initial lesion. The same variables were associated with the healing duration. A D>50% was associated to a significant reduction of sequelae compared to a D<50%.

Conclusion

These results highlight the possibility to cure BU without surgery by using S+R therapy and its advantage in reduction of sequelae. Its also emphasizes the importance of early detection on the management of cases and the treatment' result.

Response to treatment with the combination rifampicin-streptomycin for 5 days per week for 8 weeks for Buruli ulcer

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Introduction

The combination of Rifampicin and streptomycin is the drug regimen currently recommended by the WHO for treatment for humans with Buruli ulcer caused by *Mycobacterium ulcerans* (Mu) infection. In African countries where Buruli ulcer is endemic, ambulatory treatment with daily intramuscular injections of Streptomycin may be difficult to maintain for 8 weeks especially on Saturdays and Sundays when small clinics are closed. The aim of this study is to determine healing, viability of *M. ulcerans* and recurrence of *M. ulcerans* disease in subjects treated with Streptomycin (STR) and Rifampicin (RIF) for 5 days per week for 8 weeks.

Methods

From October 2007 to February 2009 in a prospective study patients with active Mu disease recruited from the Ahafo Ano North district of Ghana were administered STR-RIF 5 days a week for 8 weeks after swabs, 4 mm punch biopsies and fine needle aspiration (FNA) were obtained to establish the diagnosis of Mu disease by microscopy, culture and PCR. Further biopsies or swabs where possible were obtained at 6 weeks for culture. Clinical response to antibiotic therapy was assessed 2 weekly by measuring the surface area of lesions serially until complete healing. Subjects with large lesions (Cat II and Cat III) were given the option for skin grafting after completion of treatment. Photographs of lesions were also taken at review. Subjects were followed up after completion of treatment for 12 months to determine recurrence.

Results

46 patients clinically diagnosed with *M. ulcerans* disease underwent eligibility assessments. Of 46 patients recruited for SR5 treatment, 4 were retrospectively found to be ineligible on the basis of negative laboratory confirmation tests. 42 subjects received rifampicin and streptomycin but 36 completed treatment. Among the 36 patients: 9 (25%) subjects had category 1 (<5cm diameter), 13 (36%) Category II (5-15cm diameter) and 14 (39%) had Category III lesions.

After 4 weeks of treatment, 3 (8.6%) lesions (2 Cat I, 1 Cat II) were completely healed. After completion of antibiotic therapy at 8 weeks, 10 more lesions (4 Cat I, 4 Cat II and 2 Cat III) were healed bringing the cumulative total number of healed cases to 13 out of 36 (36.3%). Between week 8 and week 24 an additional 21 lesions went on to complete healing (7 at week 12, 7 at week 16, 2 at week 20 and 5 after week 24) with the cumulative healing rising to 34 (94.6%) out of 36 patients. Two subjects were lost to follow up (1 Cat II and 1 Cat III).

Of 6 subjects referred for skin graft (1 Cat II and 5 Cat III), 4 completely healed but two of these disappeared after surgery was proposed.

5 subjects healed with some limitation of movement despite encouraging simple exercises. A One subject had a positive culture result at 8 weeks of treatment but so far, no recurrence has been demonstrated 12 months after follow up.

Conclusion

Preliminary observations suggest that STR-RIF combination administered 5 day a week may be effective in treating Buruli ulcer and further studies are needed to confirm these findings.

Support is gratefully acknowledged from the World Health Organisation.

**Antimicrobial treatment for Buruli ulcer:
results of the Burulico trial evaluation of a switch to oral
treatment to reduce streptomycin injections for early, limited
buruli ulcer**

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Objectives

To evaluate the efficacy of antibiotic therapy with rifampicin and streptomycin given for 8 weeks, and with rifampicin (R) and streptomycin (S) given for 4 weeks followed by a 4 week oral combination of clarithromycin (C) and rifampicin, in confirmed, early stage *M. ulcerans* infection (BU) in patients over five years of age. The ultimate goal is to search for an effective alternative treatment to radical débridement surgery, and to explore possibilities to minimize the use of injectable antimicrobial therapy.

Study design

- Inclusion criteria: patients ≥ 5 yrs with early, limited and confirmed BU disease (onset < 6 months and diameter < 10 cm);
- Confirmation testing: 3 punch biopsies for 1) PCR, 2) culture and ZN staining, 3) histopathology. In ulcerative lesions, also 2 swabs for 1) PCR and 2) culture and ZN staining;
- Primary clinical end point: cure at 12 months after starting antimicrobial treatment;
- Secondary clinical endpoints: time to wound healing; time to wound closure;
- Failure: increase in size of lesion ($> 150\%$ of initial surface area); non-closure at 12 months after starting treatment; recurrence; need for large débridement surgery;
- Sample size calculation: 80% power to detect $>20\%$ difference ($\alpha = 0.05$) in cure / failure rate between two treatment arms after follow up = 12 months - 148 fully evaluable patients with confirmed early, limited *M. ulcerans* infection;
- Study sites: Nkawie-Toase Governmental Hospital and Agogo Presbyterian Hospital, serving BU-endemic areas in Ashanti Region, Ghana;
- Treatment and follow up: ambulatory Directly Observed Therapy strategy in nearest health post. Weekly clinical assessment by BU team with digital photography. Regular follow up with assessment of diameter and surface area of lesion – initially, during antimicrobial treatment, blood tests and hearing tests for toxicity screening – total follow-up 12 months from start of treatment.

Results

Of 239 individuals screened, 180 patients started on treatment, 151 were randomized (146 PCR-confirmed); 146 completed follow up; 5 were lost to follow up - one patient died of unrelated cause, one defaulted and 3 moved out. All these 5 participants were healed before being lost to follow-up. 10 patients failed on treatment - 5 had lesions that had not healed at one year follow up, 4 that had large débridement surgery, and one was treated with an additional 4 weeks of SR. No recurrences were seen at one year follow up.

Healing at one year follow up - the primary endpoint – was similar: 96% in the SR4CR4 group vs 91% in de SR8 group ($p=0.21$). Also, secondary endpoints were similar: mean time to complete healing: 25.6 wks vs 25.6 wks ($p=0.53$); mean time to wound closure: 21.2 wks vs 21.3 wks ($p=0.76$). Post-hoc analysis showed large differences in mean time to healing for different lesion size (category I vs category II&III: 19.3 wks vs 29.4 wks, $p=0.000$).

No hearing impairment, nephro- or hepatotoxicity was detected. 3 adult patients complained of vertigo while on streptomycin - one remained having symptoms of imbalance at the end of follow up. 2 patients had abdominal discomfort after starting clarithromycin.

Conclusions

Antimicrobial therapy appears highly effective and is well tolerated, but healing is slow; switch to oral CR after 4 weeks of SR is non-inferior to continued SR therapy.

Funding: EU FP6 2003-INCO-Dev2-015476

Patterns of healing and paradoxical reactions during antimicrobial treatment of Buruli ulcer - Data from the Burulico drug trial in Ghana

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Introduction

In tuberculosis and other mycobacterial infections, effective antimicrobial killing may be accompanied by transient clinical deterioration; this response pattern is known as paradoxical reaction. Earlier observations in Buruli ulcer that lesions may progress during antimicrobial treatment may have been mis-interpreted as lack of antimicrobial killing. The BURULICO drug trial confirmed earlier observations that Buruli ulcer heals with antimicrobial treatment in over 90% of cases without additional débridement surgery. In the present study, we analyzed the subset of patients that were followed without surgical intervention, to search for patterns that may reflect paradoxical reactions during treatment and follow-up.

Methods

(1) Acetate sheet recordings of lesional size data measured over time were scanned, and surface area was calculated and plotted over time, after start of antimicrobial treatment; (2) pre-ulcerative lesions were studied separately, and subsequent ulceration was recorded; and (3) digital images of the lesions were also studied for comparison. As no differences between study arms were detected for any of the end points, all data were pooled for the present study.

Results

136 patients were included in the acetate sheet analysis. (1) The largest and fastest decrease in surface area (> 50%) occurred in the first 6 weeks after start of treatment. Hereafter (week 6 – 10) a small increase in surface area was observed. Then, healing was steady, but slow. This pattern of healing was similar for all different lesional types. (2) Out of the 92 pre-ulcerative lesions, 15 (16%) never ulcerated but gradually continued to heal; 77 (84%) of these lesions however first ulcerated before they finally healed, with a mean time 6 (\pm SD 4) weeks. A total of 20 lesions (22%) ulcerated after completion of antimicrobial treatment, yet finally healed. Although punch biopsies preceded ulceration in most cases, ulceration occurred likewise in 12 lesions in 11 patients that did not have earlier punch biopsies. Patients typically experienced pain at the lesion site just before and at the time the lesion started to ulcerate. (3) 4 out of 151 patients had more than one lesion at start of treatment; 9 patients (6%) developed a second lesion clinically diagnosed as Buruli ulcer during follow-up; 4 of these were confirmed by PCR or ZN. In 6 from those 9, the second lesion became evident during the 8 weeks of antimicrobial treatment; in 3 patients the second lesion appeared after treatment was completed. One of them also developed a third lesion. One of the 9 lesions was excised. The other lesions ulcerated spontaneously, and healed subsequently without further intervention. In the 4 patients enrolled with more than one lesion, the second (smaller) lesion was not punch-biopsied. These lesions also spontaneously ulcerated and healed, though the ulceration occurred later than the lesions that were punch-biopsied.

Conclusions

Analysis of surface area using acetate sheet tracings of lesions provides important information on the pattern of healing. 1) The fastest and largest reduction in surface area occurred during the first 6 weeks of treatment. 2) A paradoxical response between week 6-10 is the usual, not an exceptional response pattern. The evolution of lesions after start of antimicrobial treatment could only be detected by careful observation avoiding early referral for surgery. 3) Most of pre-ulcerated lesions ulcerate during or after treatment. We believe this too is a paradoxical response and should not be considered as failure of antimicrobial treatment. Additionally, lesions appearing only during or after treatment probably reflect an inflammatory response to microbes present in such lesions that initially failed to elicit a host immune response. Finally, we believe these observations should help design future drug trials for Buruli ulcer.

Funding: EU FP6 2003-INCO-Dev2-015476

The value of diagnosis of M. ulcerans infection by Fine Needle aspiration

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In the case of lesions that have been active for a long time (oedema, ulcers with undermined edges) clinical diagnosis of Buruli ulcer on the basis of clinical signs is relatively easy; however, it is often still problematic in the case of early forms (nodule) when it may be confused with other chronic skin lesions (cutaneous leishmaniasis, tumorous nodules etc...). Confirmation by laboratory diagnosis essentially relies on detection of the bacteria (by culture, Ziehl-Neelsen stain and PCR).

These analyses are carried out using biopsies taken from the lesion. In order to take these samples, which can be a painful process, patients must be admitted to well-equipped hospital facilities. Swab samples, which are also used, are very painful for patients and may be taken only from ulcerative forms of the disease. One alternative that has been adopted relies on fine needle aspiration. No specialized facilities are required to take these samples, which may be collected directly from patients at home or at peripheral health facilities.

During the last three years, we have evaluated the efficacy of bacteriological assays using fine needle aspiration from ulcerative and non-ulcerative lesions. Our results from analysis of 210 samples show that bacteriological assays using fine needle aspiration provide a high-quality diagnosis, in particular where closed lesions are concerned (nodule, plaque and oedema).

This work was supported by the Fondation Française Raoul Follereau, and the European Community (FEDER 10250).

Confirmation of cases of Buruli ulcer at the National Buruli Ulcer Reference Laboratory (LNRUB) of the Institut National de Recherche Biomédicale (INRB-Kinshasa) in the Democratic Republic of the Congo

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Introduction

On the basis of the resolutions adopted by the 1st national congress on Buruli ulcer (BU) in the Democratic Republic of the Congo (DRC), held at Kinshasa from 28 au 29 September 2004, and jointly organized by the World Health Organization (WHO) and the Ministry of Health of the Democratic Republic of the Congo, whereby the Institut National de Recherche Biomédicale (INRB) was designated as the National Buruli Ulcer Reference Laboratory, we carry out microbiological and histopathological analyses to confirm cases of Buruli ulcer in the Democratic Republic of the Congo.

As regards microbiological analyses:

- Direct microscope examination is the most common procedure;
- Polymerase chain reaction (PCR) : the first analyses began in February 2008; however, supply of reagents poses problems and hinders continuation of the activities;
- Culture: is carried out if the result of the direct microscope examination is positive;
- Histopathology: for confirmation and differential diagnosis.

Results

2.1. Microbiological analyses

- a) Types of sample taken
 - Surgical biopsies in semi-solid medium (Panta) for direct microscope examination
 - (ZN), culture and PCR and in 10 % formaldehyde solution for histopathological analyses
 - Swabs for microbiological analyses (ZN, culture and PCR)
 -
- b) Number of samples taken and results obtained
 - b.1) Nsona-Mpangu rural health zone (Bas-Congo province)
 - 234 surgical biopsies from 88 BU patients; ZN was positive in 49 cases under direct microscope examination;
 - 59 swabs from 27 BU patients: ZN was positive in 6 cases under direct microscope examination;
 - 6 fine needle aspirations from 5 patients, none of which were ZN positive under direct microscope examination

In all: out of 120 patients suspected of being infected by *M. ulcerans* in Nsona-Mpangu rural health zone, 55 (45 %) were confirmed by direct microscope examination (ZN positive) and culture was positive in 13 (23 %) of these cases

b.2) City of Kinshasa

110 samples taken from 50 patients with suspected *M. ulcerans* infected skin ulcers; no laboratory tests were positive for *M. ulcerans*.

2.2. Histopathological analyses

We received 75 surgical biopsies set in 10 % formaldehyde and taken from patients being treated in the BU-endemic focus in Nsona-Mpangu rural health zone (Bas-Congo province).

In 2008, we were able to conduct histopathological analyses on only 50 biopsy specimens, 41 of which presented histological lesions compatible with *M. ulcerans* (BU) infection (presence of AFB). Nine other specimens presented signs of chronic, non-specific inflammation.

Results of histopathological examination of the 50 specimens (surgical biopsies of the suspected BU)

Histopathological lesions compatible with BU	41 (82 %)	-
Histopathological lesions not compatibles with BU	9 (18 %)	These 9 specimens present signs of chronic non-specific inflammation.

Other activities carried out

- Training workshop on molecular diagnosis of human African trypanosomiasis and of Buruli ulcer at INRB, from 26 to 29 February 2009.
- Extension of the national network for case confirmation of Buruli ulcer to Nsona-Mpangurural health zone, Bas-Congo province, 2 to 3 May 2009.
- Surgical mission to treat sequelae of Buruli ulcer, Nsona-Mpangu hospital, 8 to 13 December 2008.
- Seminar at INRB on collecting, conservation and transport of specimens of Buruli ulcer, 12 to 13 December 2008.

Conclusions

During 2008, the National Buruli Ulcer Reference Laboratory was able to confirm cases of BU in DRC thanks to microbiological and histopathological examinations. The results are both satisfactory and encouraging.

In 2009, we intend to train laboratory technicians in rural areas and to decentralize direct microscopy examinations for AFB to the rural health zones which already carry out examination for Koch's Bacillus. We also intend to revive PCR to diagnose *M. ulcerans*.

The LNRUB operates thanks to the direct financial support of INRB, which remains insufficient in spite of a partial contribution from the Institute of Tropical Medicine in Antwerp towards microbiological activities and from the Cytologie Développement (PCD/ France) programme towards histopathological activities.

We request outside support in order for INRB to become a fully operational national reference laboratory for Buruli ulcer in the Democratic Republic of the Congo.

Buruli ulcer molecular diagnosis routinely performed in Cotonou, Benin

Affolabi Dissou

Laboratory confirmation of Buruli ulcer (BU)-suspected cases has become important since the clinical diagnosis in endemic settings is not always accurate. The importance of laboratory confirmation of cases is further strengthened following the introduction of antibiotic treatment in 2004. Polymerase chain reaction (PCR) is the recommended test but it is not routinely performed in many countries due to costly equipment and infrastructure needed. To manage microbiological activities on BU in Benin, the Mycobacterial Reference Laboratory in Cotonou was reinforced in 2002 to carry out microscopy and culture for BU. Since the beginning of 2008, the laboratory has been equipped to perform PCR following the training of a microbiologist and a technician at the Institute of Tropical Medicine, Antwerp, Belgium.

Every fortnight (not always respected), specimens were sent from three main treatment centres (Allada, Lalo and Zagnanado) to the national reference laboratory and analyzed by microscopy, culture and PCR. PCR and microscopy results were available in 10 days in average and these results were immediately sent to physicians by e-mail. Quality control performed at the Mycobacteriology Unit of ITM showed no particular problem. At the end of 2008, 436 specimens (swabs, tissue fragments, fine needle aspiration) from suspected cases were analyzed. Results are summarized in Table 1.

Table 1. Microscopy and PCR results in 2008

	PCR		Total N (%)
	Positive N (%)	Negative N (%)	
Microscopy			
Positive	126 (53.8)	9 (4.4)	135 (31.0)
Negative	108 (46.2)	193 (95.6)	301 (69.0)
Total	234 (100)	202 (100)	436 (100)

Thus, PCR has added 46.2% of positive specimens to microscopy.

For culture, we faced in 2008 contamination problems now solved but culture results are not yet available.

In conclusion, PCR is useful for BU diagnosis and is feasible in a low resource country; however its usefulness for follow-up of treatment should be further studied.

Since there is a good concordance between microscopy and PCR in smear positive specimens, it would be cost-effective to use microscopy in peripheral laboratories for screening and PCR as a second test reserved only for smear negative specimens. It is also important to establish a network involving peripheral, national and supranational laboratories and to ensure the quality of the diagnosis at each level of the network.

Acknowledgments. PCR has been set up in Cotonou thanks to Association Française Raoul Follereau and Directorate General of Cooperation Development (DGCD, Belgium).

Confirmation of Buruli ulcer in Central African Republic

Fanny Minime-Lingoupou

Buruli ulcer (BU) is an important skin infection due to *Mycobacterium ulcerans*. It is linked to contact with hydric environment. BU are endemic throughout African, Americas, Australia and Asia and is almost limited to rural communities. In Central Africa, foci of BU have been described in Gabon, Equatorial Guinea, Cameroon, Congo, Democratic Republic of the Congo and Sudan, neighbour of Central Africa Republic (CAR). Surprisingly, in this latter country, no cases of BU have been reported so far. Its presence was suspected in 2006 but complete diagnosis was not obtained leading to passive survey in the hospitals of Bangui (capital of CAR).

This is the first description of BU in Central African Republic: two patients have been diagnosed as BU because of positive Ziehl-Neelsen (ZN) staining and genetic amplification; Six suspected cases were obtained using PCR IS2404 alone. The positive results have been confirmed using Real time PCR specific of IS2404 sequence.

In CAR, the search of BU remains difficult in a country where this disease is not taken into account seriously. Although ulcers sometimes of gigantic size, are observed, the patient's condition do not permit to achieve a biological diagnosis. Further effort must be done to detect the disease in the early stage and thus to cure patients before appearance of extensive lesions.

Overview and prospect for the National Buruli Ulcer Reference Centre (CNR-BURULI) in the Buruli ulcer control effort in Côte d'Ivoire

Aka N'Guetta, Ekaza E, Coulibaly B, Coulibaly D, N'guessan R, Yapo-Crezoit A. and Dosso Mireille

Introduction

The interest generated by *Mycobacterium ulcerans* infection may be explained by the strong global resurgence of the disease in the last ten years, and especially in Africa. In Côte d'Ivoire, the number of cases is increasing regularly and all the country's regions are now affected by the disease. This has an enormous social and economic impact, in particular because the population concerned mainly comprises farmers and children. Until 2005, diagnosis relied essentially on clinical criteria. The WHO Technical Advisory Group on Buruli ulcer has recognized that the adoption and extension of antibiotic treatment calls for a highly skilled clinical diagnosis, based on case confirmation by a laboratory, and has recommended that at least 50% of declared cases should be confirmed by PCR. These new provisions are in line with the missions of the CNR-Buruli, which has gradually introduced tools for laboratory case confirmation of Buruli ulcer at the Institut Pasteur in Côte d'Ivoire,.

Material and methods

This presentation provides an overview of four years' work by CNR-Buruli in case confirmation of Buruli ulcer in Côte d'Ivoire by PCR from 2005 to 2008. The samples analysed were collected in the different regions of the country. They were transported in a transport medium made up of Middlebrook 7H9 broth supplemented by 0.75% cetylpyridinium chloride (CPC). The sample DNA was extracted using the phenol-chloroform method. The IS2404 sequence was amplified by Nested PCR.

Results

Between 2005 and 2008, a total number of 1758 samples were analysed by PCR. The number of samples received for confirmation has been increasing constantly each year since 2005, and had increased 10.46 times in 2008. Confirmation rates varied each year: 76.2%, 42%, 49.7% and 83.86% respectively in 2005 (168), 2006 (176), 2007 (348) and 2008 (1066). The samples sent to CNR in 2006 and 2007 were taken by persons without the proper training for the task.

Conclusion

The CNR-Buruli is fully committed to the control effort. It possesses the necessary human and technical resources to perform case confirmation of Buruli ulcer. In order to maximize diagnosis for proper implementation of antibiotic treatment, those responsible for taking samples for analysis need to be trained. The CNR-Buruli needs financial and logistic support. Buruli ulcer case confirmation is an ongoing activity, calling for motivation of the staff concerned and the assistance of an experienced outside reference laboratory for monitoring purposes.

Outcomes of two evaluations on Buruli ulcer supported by ANESVAD Foundation in Benin and Ghana in 2008

Almudena Morante Méndez

Health is a sectorial priority for ANESVAD Foundation. Since 1999, its primary goal in Africa has been to reduce the morbidity and disability related with Buruli ulcer. Ghana and Benin, where ANESVAD started its first interventions in 2001 and 2002 respectively, are therefore considered priority countries for ANESVAD.

Since 2003, ANESVAD has supported a programme to improve the early detection of Buruli ulcer in Amansie West District, in Ghana. The programme spans its activities on three phases, until August 2008.

On the other hand, ANESVAD has contributed for three years (2006-2008) to the five-year Action Plan of the National Programme to fight against Buruli ulcer (PNLUB) in Benin 2004-2008.

In this context, in 2008 ANESVAD has carried out two external evaluations, one at district level in Ghana, and the other one, at national level in Benin upon request of the PNLUB. Both evaluations answer to the relevance, efficiency, effectiveness, impact and sustainability of the programmes. Outcomes of these evaluations have contributed to obtain significant conclusions for lessons learnt, best practices and working methodologies and set up recommendations for future actions.

The extended presentation will include the following aspects of both evaluations:

- Background;
- Goals of the evaluations;
- Methodology;
- Evaluation team;
- Impact of evaluation;
- Major strengths and weaknesses; and
- Main conclusions and recommendations.

As a consequence of the results obtained, ANESVAD future perspectives in the field of Buruli ulcer include:

- to support public health policies directed to early detection in the endemic districts;
- to consolidate the peripheral health system to increase the accessibility to adequate treatment and clear the referral centres;
- to strengthen the capacity building of local partners on the management of projects;
- to increase collaboration with partners of the civil society;
- to consolidate the programme of prevention of disability;
- to promote long term collaboration programmes;
- to support other Buruli ulcer evaluation initiatives.

Collaboration between the Fondation Luxembourgeoise Raoul Follereau and Benin

Emile China

Since 2002, FFL/ARFB has provided assistance to PNLLUB by setting up and supporting the CDTUB in Allada.

This assistance has made it possible to provide infrastructure and equipment and to operate the Centre, which has provided treatment for 250 patients each year since it was founded.

Bolstered by its success and by the achievements made possible thanks to this collaboration, FFL/ARFB has committed itself to reinforce CDTUB to raise it to the level of an international training centre for research into and control of Buruli ulcer.

A report on volunteer actions for Buruli ulcer children by SCOBU

Yuki Shimomura*, Tetsuya Fujikura, Kazuyuki Fukunishi[†], Tomoki Niiyama[‡]**

Project SCOBU

For the past four years, Kobe International University Project SCOBU has developed a pilot educational program for BU children in Benin. The program provides BU children a proper primary education. With the rigid administration and control by the Ministry of Health of Benin and Dr. Roch Johnson, National Program Coordinator for Leprosy and Buruli Ulcer, the four years of Project SCOBU Educational Pilot Program made over 300 children in total possible to receive a primary education. In Cameroon, the program support also went for a BU student to enable to further his education.

Project SCOBU will start a pilot educational program in Togo in cooperation with the German Leprosy and Tuberculosis Relief Association (DAHW) this year. We will provide the financial support for the action by DAHW to create a social and education unit for the children living with BU during their hospital time.

We are continuing advocacy programs in Kansai, Western Japan area. Advocacy programs have progressed considerably over the time and always made strength our fund.

Throughout our activities, we can clearly confirm the theory how small NGO or NPO such as our group can do effective activity or support for the area where need help, is cooperation with International Organization such as United Nation or World Health Organization and the Government where the organizations wishes to support. Project SCOBU as a small non-medical group will continue our socio-economic challenges and wishes our small support can help BU Children.

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Health Foundation Of Ghana

Lynda Arthur

Introduction

Health Foundation of Ghana (HFG) is an issue oriented, not for profit, non-governmental organisation, committed to assisting Ghanaians to achieve better health through the design and implementation of creative solutions to local health problems. The Foundation focuses on advocacy, capacity building through training, development of rural communities, research and information dissemination.

HFG is strongly committed to assisting the Government of Ghana in its efforts to improve health delivery for the much needed socioeconomic development of the nation.

Formed in February 1998 out of the Dreyfus Health Foundation Office in Accra, which was established in 1991, the Foundation works in partnership with donor organisations, local and international non-governmental agencies, government agencies and community based organisations.

Health Foundation of Ghana runs four (4) major programmes.

- Buruli Ulcer Control and Support
- Sexual Reproductive Health & HIV/AIDS Prevention, Advocacy & Behavioural Change Communication
- Capacity building for Community Health and Development
- Health Information Research and dissemination.

HFG's efforts are focused on approaches that stress individual and group responsibility, ideas and action. Monitoring and Evaluation is an integral part of all our programs.

Visit us at our office in Accra, Ghana.



HFG's Buruli ulcer programme activities (2002- 2009)

Buruli Ulcer (BU) is a disease endemic in parts of Ghana including the Amansie West, Amansie Central, Upper Denkyira, Suhum Kraboa Coaltar, Asunafo South and Asunafo North districts. Early Detection, Reporting and Treatment of the disease is needed to prevent deformities and even death of victims. New treatment recommendations by the World Health Organisation mean that there is hope for victims.

Since 2006, Health Foundation of Ghana has partnered with Fontilles Lucha Contra La Lepra (Spain) and The National Buruli Ulcer Control Program to implement Buruli Ulcer control and support projects in Suhum Kraboa Coaltar, Asunafo South Asunafo North and Amansie Central Districts in Ghana. The projects have provided:

- Training in Buruli Ulcer Early Case detection and reporting, case management, documentation and data processing, to over 480 Community Based Surveillance Volunteers (CBSVs) and Teachers, 120 Community Health workers, 120 Hospital Health workers.
- Support to district hospitals in the form of medical & theatre supplies and consumables.
- Surgical-out-reach services and technical support to the Suhum Government Hospital.

From 2002-2003, HFG partnered with the Dreyfus Health Foundation (DHF), USA and the NBUCP to under take a Buruli Ulcer Project in Amansie West District, and the Upper Denkyira Districts of Ghana. 400 CBSVs in total were trained in early case detection and reporting. The project provided two motor bikes, a dressing shed (featured in the WHO Buruli Ulcer Documentary) and medical supplies to the districts to support surveillance and treatment activities

Into the future HFG will partner with International and local organizations to:

- Continue early case detection and treatment activities
 - Epi Info & HealthMapper for disease surveillance to be incorporated
 - Prevention of disabilities in Buruli ulcer Disease
- Scale up and support 10 more endemic districts by 2013
- Assist endemic districts to refurbish/establish Buruli Ulcer Centers, theatres and skill training facilities for social re-integration of former BU patients.
- Research; pilot “Enabler’s Package” in Amansie Central district
- Advocate for policies that will assist endemic districts and victims of Buruli Ulcer.

Buruli Ulcer project at Akonolinga

Eric Comte, François Sihom

The BU project which MSF-CH has been operating since 2002 at Akonolinga progressed quite satisfactorily, despite the numerous difficulties associated with its implementation.

The inspiration for the MSF-CH project comes from the fact that between 1975 and 2001, the Nyong valley was strangely affected by this disease, an increasing number of cases being detected by an epidemiological survey. The health districts most affected were Ayos, Akonolinga and Abong Mbang where prevalence was 4.4 per thousand population.

Like ALES (Aide aux Lépreux Emmaus Suisse) in Ayos health district, MSF-CH decided to provide treatment for cases of Buruli ulcer in Akonolinga health district by setting up a project entirely funded by and managed in partnership with the Ministry of Public Health; the objectives of the project were to reduce disabilities by providing early treatment and rehabilitation for patients under treatment.

In 2007, the prevalence survey found that prevalence was markedly higher in Akonolinga health district than in the three other health districts.

Together with its banks, the Nyong river, a sluggish water course provides an ideal environment for the disease. The population is settled and works in farming, forestry and fishing.

From 2002 to 2008, MSF-CH carried out improvements to the quality of care for Buruli ulcer patients: construction of a new multi-purpose building, nutritional support for patients under treatment, educational support for children with Buruli ulcer, technical support, infrastructure refurbishment, referral of severe cases at the expense of MSF-CH, defraying the cost of drugs and medical consumables and introduction of modern dressings. Since the project was implemented, MSF-CH has provided treatment for more than 750 patients and the occupancy ratio of the 65 beds has been more than 93%. The annual budget amounts to SF 900 000.

MSF-CH employs 40 persons (26 MSF-CH personnel, including 2 expatriate managers and 15 MOH personnel).

The cases originate from all areas in the district, although cases from Akonolinga and Abem predominate, regardless of age or sex.

A process of decentralization, which has been planned since 2008, is being implemented in Abem health area, where a full range of treatment is being provided on an out-patient basis for 17 new cases (antibiotics, rehabilitation, raising awareness and active case detection). We plan gradually to extend decentralization to the other health areas.

Integration of Buruli ulcer control activities into primary health care: the case of the control programme of the Institut Médical Evangélique (IME)/Kimpese in the Democratic Republic of the Congo (DRC)

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3. Nsona-Mpangu health zone, Songololo territory, Bas-Congo, DRC.
4. National Buruli Ulcer Control Programme, Kinshasa, DRC.
5. American leprosy Mission, Gemena, Equateur, DRC.
6. Medical Assistance Program (MAP) INTERNATIONAL, Abidjan, Côte d'Ivoire.
7. Institute of Tropical Medicine, mycobacteriology unit, Antwerp, Belgium.

The Buruli ulcer control programme at the general referral hospital (HGR) of the Institut Médical Evangélique (IME) in Kimpese started in 2001.

Its facilities have gradually been reinforced, thanks to the support of both national (National BU Control Programme, National Institute for Biomedical Research) and international (American Leprosy Mission, Institute of Tropical Medicine, Antwerp, Fondation Damien and European Union) partners.

The programme's team, which comprises physicians, nurses and paramedical staff working at the IME's HGR have taken various training courses and internships. This specialized team has operated the programme and been responsible for all its activities, whether at the HGR or at the community level (Songololo territory), in accordance with the approach recommended by WHO.

At the hospital itself, case management of patients has become highly developed. However, at the community level and despite the efforts made, decentralization of activities had been somewhat at a standstill on account of two major difficulties: the first concerned logistics, and the other the difficulties of performing surgery in rural health centres that lack appropriate equipment.

Nevertheless, health workers have been trained; 13 health centres have been chosen as local treatment centres and as focal points for community-based control activities.

Administration of treatment with specific antibiotics, which has proved to be highly effective, has facilitated integration, notwithstanding a number of logistic problems.

Thanks to the commitment of community-health officials (chief medical officers in the health zones) of Songololo territory and the contribution from all those concerned, the BU control programme at the IME/Kimpese hospital is now integrated into the primary health care facilities.

The results of this integration have rapidly become apparent: the number of BU patients admitted to hospital fell from 75 in 2007 to 29 in 2008; at the same time, 303 new cases were detected and treated in 2008, in comparison with 98 in 2007. These results hold out hope that the disease will be stabilized and brought under control in Songololo territory.

Decentralization at Akonolinga

Felix Sagno

In order to provide case management for Buruli ulcer, in partnership with Akonolinga health district, MSFCH has explored an approach designed to involve all health areas in case management of the disease.

The purpose of this effort is:

1. To broaden the search for new cases, to reduce the number of defaulter, to lessen the burden of work on hospitals, to shorten patients' stay in hospital, to transfer skills to community health workers and to disseminate information on this disease which the population still considers as a mystery.
2. In order to achieve these objectives, MSF and its partners have adopted a strategy: rapid evaluation of high-risk areas, a mobile dispensary and a forward post, all of which are capable of changing, taking into account a number of key criteria.
3. In order to measure the results, a monitoring system has been set up, based on the following: a register, a referral and antibiotic treatment form, evaluation of functional disability and a patient monitoring form.
4. The use of specific indicators: percentage of cases detected, cases confirmed as BU or not, duration of stay in hospital, discharged as cured, number of cases referred and admitted to hospital.

Organization of case management for Buruli ulcer patients in Kouilou department in the Republic of the Congo

Jean-Martin Mabiala

Outline

1. Maps: Congo, Kouilou
2. Administrative set up and populations
3. Health structure in Kouilou
4. Background to Buruli ulcer in Kouilou
5. Endemic zones: features
6. Organization of case management for patients: case management centres, staff training, quality of case management (medical, surgery)
7. Results
8. Constraints
9. Prospects
10. Conclusion

Summary of the presentation

Kouilou is one of the departments of the Republic of the Congo in which Buruli ulcer is endemic. It has a rural population of 97 000, and the urban population of the town of Pointe-noire is 750 000.

There are six administrative districts in Kouilou: Nzambi, Madingo-kayes, Kakamoeka, Hinda, Mvouti and Tchiamba zassi, together with the town of Pointe-noire, which forms a department within Kouilou.

The districts of Madingo-kayes and of Kakamoeka are the zones where endemicity is highest. A few cases of Buruli ulcer have been reported in the district of Hinda as well as in Pointe-noire. There are 23 health centres in Kouilou, 5 of which provide case management for Buruli ulcer, while Pointe-noire has 15 health centres, with 5 of which provide case management.

There is currently a national centre for treatment of Buruli ulcer, which is located at Madingo-kayes and which has been refurbished with the help of the Raoul Follereau Foundation.

Medical case management of patients began in September 2006 using rifampicin and streptomycin.

Surgical treatment is being introduced with cautiously. Its shortcomings have been responsible for a number of treatment failures.

The lack of nutritional support also discourages patients from going to Pointe-noire to undergo surgery (constraints).

- The outlook is favourable thanks to:
- Fitting out of the National Buruli Ulcer Treatment Centre in Madingo-kayes by the Raoul Follereau Foundation
- The training provided in Benin for the physician from the National Buruli Ulcer Treatment Centre in Madingo-kayes
- The training provided for a nurse-anaesthetist
- The development of surgery at Madingo-kayes, in an area of endemicity
- The contacts established by the Minister of Health, with a view to obtaining nutritional support for Buruli ulcer patients from a number of local partners.

Three years of implementation of early detection activities in Amansie West District, Ghana

Joseph Adomako

Background

Buruli ulcer management and control had been one of the major public health intervention challenges in the Amansie West District before 2003. The district used to be the worst affected district in Ghana with a crude prevalence rate of 150.8/100,000 as compared to the national average of 20.7/100,000 (1999 national case search).

Numerous competing health challenges including high malaria prevalence rate (52% of OPD attendance), low tuberculosis detection rate (7%), increasing HIV/AIDS prevalence (4.5%), inaccessible health care, bad roads, and inadequate health professionals and facilities, and general poverty compounded the difficulty in Buruli ulcer management and control.

In 2003 however ANESVAD accepted a proposal to support the district to implement a project to improve early detection of the disease with the aim of reducing the severity and complications of the disease, particularly among children in the Amansie West District. From 2003 to date, there have been three phases of the project:

Project Design

The project was designed to focus on communities, school system and health system. With communities, working with them by training volunteers to detect cases, dress small ulcers and refer complicated cases to the health facilities. The training involved also traditional healers including traditional birth attendants (village midwives), and chemical sellers (village pharmacists) who are very important health care providers at the village level.

With school system, working closely with teachers and school children, and training teachers to detect and refer suspicious cases to the health facilities. Improving knowledge about the disease among school teachers and allaying their fears about the disease being infectious – transmitting the disease from cured patients to other students.

With the health system, improving knowledge among health workers at the peripheral health facilities (private and public) to enhance case detection, managing simple cases and referring complicated ones to the district hospital. They will also support and supervise the school and community level activities in their respect areas.

In addition, outreach activities are organised in the communities to increase awareness on the disease and detect and manage cases at the community level.

Impact

There has been increased awareness of the disease among the general population which has led to early reporting for treatment and also minimised the use of herbs for treatment.

Additionally there has been massive improvement in the knowledge and skill of health workers at the peripheral facilities in the management of the disease. Consequently early case detection has increased from as low as 20% in 2003 to 53% in 2007.

Conclusion

Improving Buruli ulcer management and control, like all Public Health interventions, should not be the preserve of only health workers but requires the concerted efforts of all--the health system, the community, government, NGOs, etc

Early case detection and management of Buruli ulcer cases in the Upper Denkyira District of the Central Region of Ghana

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Introduction

The Upper Denkyira District is one of the endemic districts in Buruli Ulcer in the Central Region of Ghana with a population of 128,059.

Buruli ulcer cases reported in the District accounted for the highest number of reported cases in the Region. Most of the Buruli ulcer cases come from remote and inaccessible communities along the banks of the River Offin. Nearly 85% of all reported cases in the District were diagnosed in the late ulcerative stage. This situation did not augur well for the control of the disease in the district because of the high cost in the management of ulcerative and late stages of Buruli ulcer.

In view of these problems, the District was fortunate to have received funding from ANESVAD to implement an early case detection project from October 2007 to September 2008. We present the activities carried out and results achieved.

Key activities carried out

The following activities were carried out:

- Training of 60 Community Based Surveillance Volunteers (CBSV's) from 30 endemic communities.
- Practical training of 30 selected health workers in the management of Buruli ulcer cases.
- Sensitization and video shows in 15 endemic communities.
- Active case search through screening of people especially school children in the 15 communities.

Before the start of the project, a stakeholders' meeting was held to define roles and responsibilities. We developed 'T' shirts and caps for health workers and village volunteers in the communities both as incentives and part of sensitization. In pursuit of the project, we also acquired a new Toyota Hilux 4x4 and audio-visual equipment.

Results

- A total of 225 Buruli ulcer suspected cases were detected during the project period.
- 83 (37.0%) cases were pre-ulcerative and 134 (60.0%) were ulcerative. Others, mixed and osteomyelitis constituted 3% of the cases.
- 53(23.6%) of the cases were children aged 15 years and below, 99 (44.0%) were between 15-49 years of age and 72 (31.0%) of cases were above 49 years of age.
- In all 6081 were screened in 15 communities by the outreach team. 106 (46.9%) out of the 225 detected cases were identified and referred during the community sensitization activities.
- Samples taken for PCR were 118 and 50(42.4%) were confirmed positive.

Indirect Benefits

2311 other conditions were detected:

- Itching skin rashes – 1065, yaws – 42, ring worm – 169, chicken pox – 333, onchocerciasis – 247, schistosomiasis – 84, tinea capitis – 177, boils – 4, scabies – 168, leprosy – 15, suspected AFP – 3, yellow fever – 2, measles – 2.
- Increased awareness and knowledge on Buruli ulcer in the communities.
- Improved community support for volunteers and community commitment for health activities.
- Improved community surveillance on Buruli ulcer, TB, yaws, onchocerciasis, leprosy, poliomyelitis, yellow fever and neonatal tetanus.
- Use of the vehicle and audio-visual equipment in support of other health activities eg, anti-polio campaigns.

Conclusion

- Early case detection of Buruli ulcer cases did not only help improve the surveillance of Buruli ulcer but also helped with efficient integration of surveillance of other diseases.
- Improved surveillance of epidemic prone diseases and diseases of public health importance such as polio, yellow fever and neonatal tetanus.
- Enhancement of IE&C and BCC activities in the communities.

Acknowledgements

GBUI - WHO

ANESVAD - Spain

NBUCP - Ghana

MHD – DUNKWA-OFFIN

Stakeholders/Communities/Cbsv/Staff/Patients

1* Municipal Health Directorate

2* National Buruli Ulcer Control Programme

Functional limitations after surgical or antibiotic treatment for Buruli ulcer in Benin

Yves Barogui, Roch Christian Johnson, Tjip van der Werf, Ange Dossou, Pieter Dijkstra, Ymkje Stienstra

Almost half of patients have functional limitations after treatment for Buruli ulcer disease. Antibiotic treatment (along with surgery) was introduced in the National Program for Buruli ulcer in Benin in 2005. Aim of this study was to compare functional limitations in patients who were treated by antibiotics, surgery or both, using a validated questionnaire. 179 former patients in Lalo, Benin were retrieved, and interviewed in their village. Hospital records were used to gather data about size of lesion at presentation and treatment provided. No significant differences in resulting functional limitations were found between the different treatments.

Larger lesions (>15 cm cross sectional diameter) at presentation, lesions on a joint; muscular atrophy; and amputation were all associated with a higher risk for functional limitations. Advantages of antibiotic treatment may involve other domains, like costs of treatment, or a change in help seeking behaviour.

Training in basic rehabilitation: an overview of three years' experience in Cameroon

Valérie Simonet

Learning how to fish...

Training occupational therapists who are in turn capable on their own of training others is one of the objectives set by ALES (now FAIRMED) since 2004.

With the help of an outside specialist in charge of training, the team specialized in prevention of disabilities from Buruli ulcer has started to train health workers from peripheral health centres in Ayos. The practical field guide recently published by WHO sprung from the need to provide them with a teaching aid for their training activities.

A second objective of FAIRMED is to provide access to quality care to as many people as possible; by means of this training in basic rehabilitation, which lasts approximately 10 days, FAIRMED intends to make it possible for certain peripheral health centres in regions where BU is endemic to acquire the skills needed to provide case management for the most common types of Buruli ulcer cases.

The training has been repeated three times from 2006 to 2008, each time under slightly different circumstances, while preserving basic elements that are sufficiently similar for the different sessions to be compared. By analysing the data gathered during the training sessions, we have been able to identify the weaknesses, bring out the strengths and make recommendations to enhance their efficacy.

... is far better than being given a fishing rod

Although not initially so planned, for a number of reasons the occupational therapists who were to become trainer-practitioners found themselves having to cope unassisted during the first training session in 2006.

The results of this training session showed that it had scant impact on the management of Buruli ulcer patients and underscore the very real danger of training that involves simply handing out a manual or guide. Without a certain level of investment, the results achieved do not justify the effort. In other words, badly supported and ill-prepared training is sometimes hardly worth the effort.

From analysis to adaptation

The main obstacles encountered during the different sessions were:

- Lack of the teaching skills required to run a training session and to set up an appropriate training programme, too little time allowed for training (practical sessions lasting less than ten days)
- too few trainees (not enough of them during the training session and /or trainees isolated in their region), too little or, on the other hand, too much outside help, (those responsible for training provide either too little or too much input, thus stifling the dynamics and involvement of the trainers)
- beliefs, ideas or habits linked to the culture of the trainers and trainees (primacy of oral rather than written communication, of theoretical knowledge rather than know-how, perception of the person in their hands as an object receiving care rather than an active partner).

On the strength of the experience acquired from previous sessions, the 2008 training session turned out to be the most effective, both from the angle of the trainees (knowledge of basic rehabilitation) and from that of the practitioners providing the training (development of teaching skills and understanding of the training programme). The following elements were probably decisive to the satisfactory outcome of this training session:

Teaching aids provided to the trainers during preparations for the training session (how to run training for adults, how to produce a suitable training programme)

Allowing sufficient time for the acquisition of new skills (10 whole days in the case of this training session)

- Using the group as an active contributor to the training
- Carefully measuring and varying the input from the training officer so as to encourage involvement by the trainers and strengthen their teaching role
- The right mix of «universal» teaching principles (what is it, in general, that helps adults to learn?) and of cultural considerations (how is knowledge transmitted in this region, among this population?)

Thanks to these adjustments, the trainer-practitioners were able as well as possible to adapt the way they passed on their knowledge and know-how, while preserving their individual style. This approach made it possible to avoid some all-too-common pitfalls and to ensure the intervention's sustainability.

Buruli ulcer in Togo: Prevention and treatment of disabilities from Buruli ulcer in the Maritime region

Pauline Falipou, Denis Gadah

Introduction

Buruli ulcer is a serious skin disorder caused by *Mycobacterium ulcerans*. In Togo, the region most affected by the disease is Maritime region. The purpose of our activity, which was carried out in 2008, was to reinforce prevention and treatment facilities and the skills of health workers.

Methods

The Buruli ulcer project operated by Handicap International in Togo focused its efforts on prevention of disabilities, with the three following lines of action:

- Improving assessment to facilitate follow-up
- Improving treatment and rehabilitation to generate a case-management dynamic
- Improving information and education of patients and their families to facilitate reinsertion

New tools have been developed for each of these lines of action, in collaboration with the CNRTUB team :

- Line of action n° 1: a new assessment form in association with a computerized data base (generation of indicators for follow-up)
- Line of action n° 2: providing equipment for rehabilitation rooms, training staff and development of a new reference manual, organization of group gymnastics sessions
- Line of action n° 3: introduction of rounds to the villages by the roving physiotherapist, creation of educational aids for disability prevention (posters, PowerPoint presentations and exercise cards for patients)

Results

- 6 physiotherapists received training and supervision in treatment of BU patients
- 18 nurses were trained in disability-prevention techniques
- 30 community health workers were provided with basic information on disability prevention
- decentralized follow-up was provided for 92 patients with BU sequelae
- 195 attended consultations during the three rounds organized
- organized and scheduled case management of rehabilitation was provided for patients (assessments, information sessions, group gymnastics sessions) at the National Buruli Ulcer Referral and Treatment Centre (CNRTUB)
- The different information aids for disability prevention were distributed

Conclusion

As far as possible, we try to avoid excessively long periods of hospitalization at CNRTUB and encourage decentralized treatment to enable patients to return as quickly as possible to their home environment and avoid their becoming isolated within their community.

The key to reinsertion of patients in their communities lies in raising awareness (information on the disease and the means of curing it) and education (learning the simple treatment procedures) of all those involved (patients, families, the community and chief health post nurses...)

The challenge facing the next international conference will be to present, thanks to the computerized data base available, rather than just the number of patients consulted for rehabilitation, the percentage of patients whose joint mobility has improved or skin become more supple as a result of regular treatment.

Wrist contractures in sequelae of Buruli ulcer: the place of resection of the 1st row of carpal bones

Patrick Meredith, Henri Assé

Buruli ulcer destroys much more than skin and subcutaneous tissue. Exposed muscle tissue is the site of an inflammatory reaction during the infection and of necrosis from desiccation, resulting in contractions of muscle fibre resembling Volkmann syndrome. In addition, if the site of the Buruli ulcer is close to a joint, septic arthritis will develop in the joint. As the majority of patients are children, growth cartilage will also be affected.

On the upper limb, the combination of these factors is responsible for contracture of the joints in flexion or extension, depending on the muscle compartment involved. As regards hand function, in addition to shoulder and elbow mobility, wrist position is of greatest importance for grasping. In hyper-extension, the fingers are clawed, and in hyper-flexion, pinch position with the thumb is deficient. If this is compounded by impotence of finger flexion or extension on account of the muscles fibrosis, the result is a disabled hand. This makes it important to correct the position of the wrist before dealing with finger function, although ideally, this should all be done at the same time.

The wrist should be at least stable when in a neutral position; if it is possible also to preserve a degree of movement, this is all the better.

Correction concerns all the tissues: bones, joint capsules, tendons, muscles and skin, while preserving vascularisation and innervation.

Correction using elongation of the tendon muscles involved runs a considerable risk of the suture giving way, on account of the poor quality of the tissues. Correction using displacement of the whole muscle compartment involved is highly traumatic for a muscle that is already poorly vascularised and poses a risk for the inelastic motor nerves. The drawback of reducing forearm length by osteotomy of the radius and cubitus is that it requires the use of material for osteosynthesis on a site that is not always sterile, in operating theatres which are not always suitable - hence the risk of infection and pseudoarthrosis. Moreover, the equipment is costly, and a second operation needs to be scheduled in order to remove it - involving additional cost, transport and upheaval.

We have opted for carpal correction by resection of the 1st row of carpal bones, associated with, capsulolysis and capsuloplasty, elongation of the tendons and liberation of the synechia of the superficial fascia, and filling the defects in the capsules and tendons with local vascularised flaps. The resulting wrist is stable in neutral position while preserving partial flexion-extension function. Neither osteotomy nor any costly equipment are required, and there is no need for a second operation.

The technique and results are presented with examples of cases having undergone operations at the Institute of Reconstructive Surgery in Abidjan.

Multicenter Surgical Outreach for Management of Buruli ulcer

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Background

Ghanaians living outside Accra and Kumasi, where the country's main teaching hospitals are located, find it difficult to access specialized medical services. Therefore, many patients in rural areas depend on medical outreach teams for specialized treatment, including surgical treatment for Buruli ulcers and their related pathologies. This paper describes efforts made by one surgical outreach team to identify and manage Buruli ulcers in patients from less endowed areas in Ghana.

Methodology

Record review of Buruli ulcer cases treated during outreach visits to underserved areas in Ghana by a reconstructive surgical outreach team during a fourteen year period from 1995 – 2008.

Results

Out of a total of 2284 patients treated during 84 visits to 8 centres, 933 were treated for Buruli ulcers and related conditions during the 14 year period.

Conclusion

Surgical outreach to underserved areas in Ghana has decreased in recent years, while the need for such work remains very high. More surgical outreach teams should be formed to manage surgical cases such as treatment for Buruli ulcers in these rural areas, where specialized medical services are otherwise unavailable.

Modern dressings

Felix Sagno

For two years now, in partnership with Akonolinga district hospital, Médecins sans frontières Switzerland has introduced a range of essential modern dressings into the Buruli ulcer treatment programme: hydrogel, calcium alginate (Kaltostat®), charcoal with silver (Actisorb silver®), hydrocellular (Biatin®), tulle gras, Corticotulle®, Bétadine and saline.

General principles

1. Assessment of patients and their lesions
2. The lesion assessment and monitoring form is completed
3. Dressing protocol is proposed on the basis of the clinical state of the lesion.

The purpose of these principles is :

1. To describe the lesions: infected, fibrinous, budding, hyper budded and epithelial.
2. For each type of wound, there is a dressing protocol suited to the different stages: cleansing, budding, formation of epithelial tissue.

The following protocols are currently in place

1. Calcium alginates: Cleansing of fibrinous, necrotic, undermined and haemostatic wounds (ion calcium is a coagulant), bacteriostatic.
2. Charcoal with silver: (Actisorb silver®): infected, odorous wounds
3. Hydrogel: cleansing of fibrinous, dry, soft wounds, necrosed plaques and promoting scarring of non-exudative wounds.
4. Hydrocellular : (Biatin) : absorbent while preserving a humid medium for wounds that are forming granulation and epithelial tissue.

Analysis of the BU 01 form: main lessons learned

Yves Barogui

This initial evaluation of the BU 01 form has shown it to be an excellent tool. Not only does it provide all the information to be found in the BU 02 form, it also provides information on the disease history, laboratory confirmation, treatment monitoring and treatment outcomes.

It is simple, succinct and easy to complete. Use of the BU 01 form in Benin has enabled us to determine that during 2008, 39.28% of patients resorted to traditional medicine before attending hospital. More than half the patients (56.46 %) consulted 8 weeks after the onset of the disease. More than one out of four patients (27.88%) were referred to the health centre by a former Buruli ulcer patient.

It is nonetheless important for the different actors to redouble their efforts to ensure that data are even more complete, especially as regards confirmation by a laboratory.

It would be desirable for measurement of the lesions to be included in the form, to provide an even better tool for monitoring patients.

Contribution of mapping to epidemiological surveillance of Buruli ulcer in Benin : Distribution of the disease by foci

Ghislain Sopoh

Data collection for purposes of epidemiological surveillance in Benin relies on the BU 02 form, which is in the form of a three-leaf register available in the country's health facilities responsible for detection and treatment of Buruli ulcer. Thanks to this tool, information on 4988 cases was collected between 1 January and 31 December 2007.

The data thus collected allow us to describe the epidemiological situation in time, space and terms of the individuals affected.

An average of 80 cases were detected and provided with treatment each month in Benin.

Mapping allows the situation to be portrayed spatially, in each department, commune and village and from one year to the next. Mapping shows that:

- the level of endemicity varies from one department to another;
- within a single department, there are:
 - communes in which endemicity is very high along with others in which it is low;
 - communes which remain highly endemic from one year to the next, while there are others in which endemicity is always very low.
- single communes (such as Zê), where some villages remain highly endemic along with others in which endemicity is always low.

Moreover, spatial description allows us to show that those communes in which the disease is permanently endemic in Atlantique (Zê), Zou (Quinhi) and Ouémé (Bonou) departments in fact border on one another, thus forming a permanent disease focus centred on the village of Dasso-Quinhi.

Mapping thus makes it possible to show that distribution of cases of Buruli ulcer is by disease focus and that it is geographically heterogeneous and that regardless of the administrative division of territory, transmission is permanent within an unbroken geographical area.

Buruli ulcer surveillance in Ghana: current practices and future priorities

William Opare

Official system for surveillance of Buruli ulcer in Ghana started around 1994. This was a sequel to periods of uncoordinated focus on the disease since its first description in 1971 in the Greater Accra region.

Reporting period 1994-2006.

Description of system

Buruli ulcer surveillance data are reported to NBUCP through the public health system of the Ghana Health Service quarterly. From 1994-2006, data regarding reported cases of Buruli ulcer to the national office were regional aggregates for districts reporting, age, sex, clinical form(s) and presence of disability upon diagnosis of cases. Descriptive analyses were performed, and cumulative incidence by region, age group, and sex were calculated.

Results

During 1993-2006, a total of 8190 cases of Buruli ulcer were reported to the NBUCP by 51 districts from 7 regions. During the same period, reporting endemic districts increased to 36 by 2007 from 9 in 1994. The number of cases also increased from 214 in year 1994 to 1202 by year 2005. Between 67-70% of total national cases are reported by six districts from 3 regions. The Ashanti region alone reports over 50% of national cases. Laboratory of confirmation of cases were marginal during this period.

Reporting Period 2007-2008

A more flexible reporting system was introduced in year 2007. Through this system, standardized forms for case treatment, line register of cases and laboratory request were introduced. Reporting became monthly instead of quarterly. Through this system community data was captured and mapped geographically.

In 2008, 426 communities nationwide were reporting Buruli ulcer. Four (4) communities reported between 20-31 cases yearly giving an incidence rate of about 96/10000 population. . 76 communities reported the disease for the first time using number of communities reporting in year 2007 as a reference point. 51.6% of cases were PCR positive.

21.9% of cases reported were self referrals as against 17.8% and 13.5% by health workers and community volunteers respectively.

Future Priorities

- Migrate current reporting system to a Buruli ulcer registry : Collect complete data on all BU cases diagnosed through high quality control and improvement programme from diagnosis to treatment outcome.
- Deploy electronic reporting for 50% of endemic districts by end of year 2009
- Begin Sentinel Surveillance in 4 high incidence communities and 3 treatment centres
- Build capacity for district staff to use health mapper

Analysis of factors associated with seeking treatment among Buruli ulcer patients

Alphonse Um Boock

Introduction

This study was carried out in Ayos health district, which is a referral centre for Buruli ulcer treatment in Cameroon. The disease, which is still referred to as "atom" has been present for a long time, but it was only in 2002 that control strategies were developed, marking the beginning of action to provide treatment.

"Atom" is viewed as a curse, a practice associated with witchcraft and affecting anyone who breaches tradition or who is guilty of an act proscribed by society. Accordingly, "Atom" cannot be treated in hospital; the sorcerer alone was capable of curing it. This explains the reluctance to use drugs and the absence of patients from hospitals.

Since activities to control the disease began, a major effort has been made to educate the populations. As a result, a large part of the population now understands that "atom" can be treated in hospital and that it is unconnected with witchcraft. At present, passive case detection of Buruli ulcer operates in Ayos and the vast majority of the population are satisfied with the care provided for Buruli ulcer at the hospital.

In terms of diagnosis, the Centre Pasteur in Yaoundé provides case confirmation by PCR free of charge. At the same time, staff in health centres systematically provide first-line confirmation with Ziehl-Neelsen stain.

Generally speaking, considerable progress has been made with case management of Buruli ulcer, especially since the introduction by WHO of antibiotic treatment in 2004. Just a few years ago, the only form of treatment was surgery. At the same time, management tools have improved considerably and provide a far better epidemiological picture of the disease; the BU 01 form is a good example of this.

In spite of the progress made, there are still many grey areas as far as understanding of the disease is concerned, and in particular the incubation period. Other concepts, such as "early lesion" are still somewhat vague and ill-defined. However there is no doubt that the nodule is par excellence the early lesion of Buruli ulcer. Fortunately, the new classification of lesions by category has further improved the definition of early lesion, thanks to which national programmes are able better to measure their achievements as regards early detection. The new classification is based not only on the size of the lesion, but also on its response to antibiotic treatment.

This gives the following categories:

- Category I lesions: a single lesion ≤ 5 cm in diameter
- Category II lesion: a single lesion 5–15 cm in diameter
- Category III lesion: a single lesion >15 cm in diameter, multiple lesions, lesions at critical sites and osteomyelitis.

Recent studies have shown that category I and II lesions respond better to medical treatment (specific antibiotics) than category III lesions.

However, a number of questions are still unanswered:

- How long does it take for an ulcer to appear after a lesion has closed?
- Until when should a lesion be considered as early?
- How long does the change from one category to another take?

We shall attempt to answer some of these questions using data from the new BU 01 form.

We have adopted the following research hypothesis: «There is a relationship between the time take to seek treatment and certain variables, such as category of lesion».

Methodology

a) Type of study:

Prospective and descriptive study.

b) Sampling:

We included all Buruli ulcer patients received during 2008, with the following recruitment criteria:

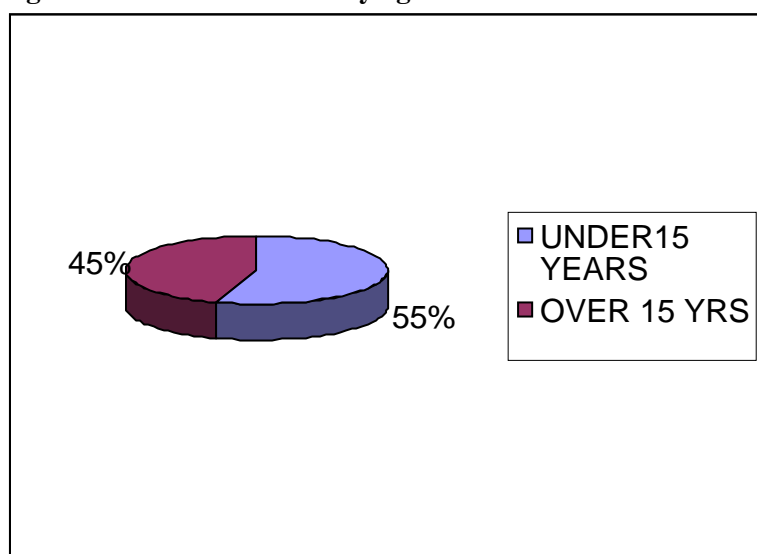
- Age of more than 4 years
- Domiciled in Ayos health district
- Agreeing to be treated at Ayos hospital

c) Data processing:

Data from the BU 01 forms were entered into Epi info, version 6.0 and statistical analysis performed using SPSS-Windows 12. We used bivariate analysis (chi 2 and p value) to explore the relationship between time and the symptoms and categories. Proportional differences were estimated at a 5% confidence level.

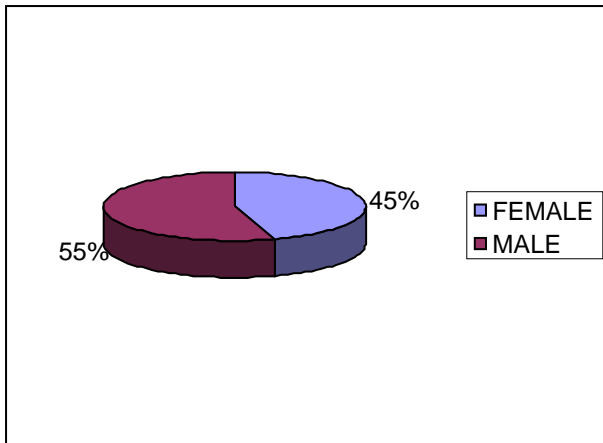
Characteristics of the patients in the Study

Fig. 1: Disease distribution by age



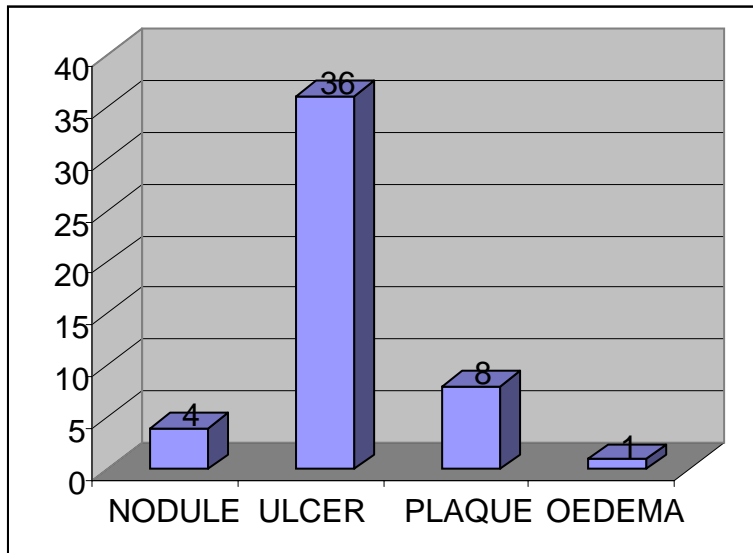
In our sample children aged under 15 years seem to be more affected by the disease.

Fig. 2: Distribution by sex



There seem to be more women than men in our sample. (Significant difference,)

Fig. 3 : Clinical forms observed



Our sample contains a higher number of ulcers

Analysis of relations between variables

a. Clinical forms

	Nodule		Ulcer		Plaque		Oedema		Total	
	N°	%	N°	%	N°	%	N°	%	N°	%
Period 1										
0–1 months	2	50.0	0		6	75.0	1	100.0	9	19.1
More than one months	2	50.0	34	100.0	2	25.0	0		38	80.9
<i>P value</i>	<i>0.000</i>									
Period 2										
0–2 months	2	50.0	6	17.6	7	87.5	1	100.0	16	34.0
More than two months	2	50.0	28	82.4	1	12.5	0		31	66.0
<i>P value</i>	<i>0.001</i>									
Period 3										
0–3months	3	75.0	12	35.3	8	100.0	1	100.0	24	51.1
More than three months	1	25.0	22	64.7	0		0		23	48.9
<i>P value</i>	<i>0.005</i>									
Period 4										
0–4 months	3	75.0	14	41.2	8	100.0	1	100.0	26	55.3
More than four months	1	25.0	20	58.8	0		0		21	44.7
<i>P value</i>	<i>0.014</i>									
Period 5										
0–5 months	3	75.0	19	55.9	8	100.0	1	100.0	31	66.0
More than five months	1	25.0	15	44.1	0		0		16	34.0
<i>P value</i>	<i>0.097</i>									
Total	4	100.0	34	100.0	8	100.0	1	100.0	47	100.0

Globally, ulcers (72.3% and n=36) are the most common clinical form, followed by plaques (17.0% n= 8). As regards the time taken by patients to seek treatment, the above table shows that whatever the period, there is a significant link with the clinical form with a 10% confidence level (p<5%).

b. Site of the lesion

In all, 47.9% of the lesions diagnosed were on the upper limbs and 52.1% on the lower limbs. There is apparently no significant association between the site of the lesion and the time taken by patients to seek care (p>10%). In other words, whether the lesion is located on the upper or lower limbs does not affect the time taken to seek treatment. However, it is worth noting that regardless of the site of the lesion, almost 7 patients out of 10 take at least 2 months to seek treatment.

Table 2: Distribution of patients by location of lesion and time taken to seek treatment

	Upper Limb		Lower limb		Total	
	Number	%	Number	%	Number	%
Period 1						
0-1 months	6	26.1	3	12.0	9	18.8
More than one months	17	73.9	22	88.0	39	81.3
<i>P value</i>	<i>0.212</i>					
Period 2						
0- 2months	9	39.1	7	28.0	16	33.3
More than two months	14	60.9	18	72.0	32	66.7
<i>P value</i>	<i>0.414</i>					
Period 3						
0- 3months	14	60.9	10	40.0	24	50.0
More than three months	9	39.1	15	60.0	24	50.0
<i>P value</i>	<i>0.149</i>					
Period 4						
0- 4 months	15	65.2	11	44.0	26	54.2
More than four months	8	34.8	14	56.0	22	45.8
<i>P value</i>	<i>0.141</i>					
Period 5						
0- 5 months	18	78.3	13	52.0	31	64.6
More than five months	5	21.7	12	48.0	17	35.4
<i>P value</i>	<i>0.057</i>					
Total	23	100.0	25	100.0	48	100.0

From an analysis of the above table, it is clear that there is a significant association between the location of the lesion and the patients' age at the 5% confidence level ($p < 5\%$). Accordingly, among children and adolescents (aged from 0 to 15 years), the majority of lesions are location on the upper limbs (73.9% in comparison with 26.1 among those over 15 years). In contrast, the lesions are located on the lower limb in a majority of those aged over 15 years.

In terms of the patients' sex, there is a higher proportion of men among patients with a lesion located on the upper limbs (52.2% in comparison with 47.8%).

The opposite is true of patients whose lesion is located on the lower limbs, with a much higher proportion of women than men.

Table 3: Distribution of patients by location of lesion, age and sex

	Upper Limb		Lower limb		Total	
	Number	%	Number	%	Number	%
Age of patient						
0-15 years	17	73,9	10	40,0	27	56,3
More than 15 years	6	26,1	15	60,0	21	43,8
<i>P value</i>	0,018					
Sex of patient						
Male	12	52,2	9	36,0	21	43,8
Female	11	47,8	16	64,0	27	56,2
<i>P value</i>	0,259					
Total	23	100,0	25	100,0	48	100,0

c. Category of treatment

Our sample is marked by a predominance of category I lesions (42,9%), followed by category II lesions (38.8%). Only 18.4% of patients presented category III lesions.

Moreover, our analyses show that there is a significant link between the category of lesion and the time taken to seek treatment ($p < 5\%$). The above table shows that patients with category I lesions take a relatively short time to seek treatment in comparison with category II and III lesions. Almost 95.2% of patients with lesions in this category took less than 4 months to seek medical treatment. All the patients with category III lesions who consulted within three months had either plaque or ulcerative oedemas.

However, as regards category II lesions, patients took less time to seek treatment. 42.1% of people took more than 5 months to seek treatment. However, plaques and oedemas were exceptions, as all the cases observed (73.7%) consulted in less than three months, as in the case of patients with category I lesions.

Patients with category III lesions took a relatively long time to seek treatment. Almost all of them took more than 5 months (88.9%) while among patients with category I lesions, the proportion was just 4.8%.

Finally, it is clear that patients with category I lesions seek treatment relatively quickly, while those with category III lesions take much longer. This allows us to conclude that a lesion which has been developing for less than four months may be considered as an early lesion, regardless of its size, whereas detection after more than five months may be considered as late.

Table 4: Distribution of patients by category of lesion and time taken to seek treatment

	Category I		Category II		Category III		Total	
	Number	%	Number	%	Number	%	Number	%
Period 1:								
0-1 months	4	19.0	5	26.3	0		9	18.4
More than one months	17	81.0	14	73.7	9	100.0	40	81.6
<i>P value</i>	0.243							
Period 2:								
0- 2months	11	52.4	6	31.6	0		17	34.7
More than two months	10	47.6	13	68.4	9	100.0	32	65.3
<i>P value</i>	0.021							
Period 3:								
0- 3 months	18	85.7	7	36.8	0		25	51.0
More than three months	3	14.3	12	63.2	9	100.0	24	49.0
<i>P value</i>	0.000							
Period 4:								
0- 4 months	20	95.2	7	36.8	0		27	55.1
More than four months	1	4.8	12	63.2	9	100.0	22	44.9
<i>P value</i>	0.000							
Period 5:								
0- 5 months	20	95.2	11	57.9	1	11.1	32	65.3
More than five months	1	4.8	8	42.1	8	88.9	17	34.7
<i>P value</i>	0.222							
Total	21	100.0	19	100.0	9	100.0	49	100.0

Conclusion

Form BU 01 is a valuable management tool for data on Buruli ulcer. It has made it possible for us to determine the following.

Whatever the time taken to seek treatment, there is a significant association with the clinical form of the lesion, with a 10% confidence level ($p < 10\%$). However, this conclusion does not hold for a 5% confidence level. There is a significant association between location of the lesion and the patients' age, with a 5% confidence level ($p < 5\%$). There does not seem to be a significant association between location of the lesion and the time take by patients to seek care ($p > 10\%$). Among young people, (aged from 0 to 15 years), the majority of lesions are on the upper limbs

(73.9% in comparison with 26.1% among those aged over 15 years). However, patients with a lesion on the lower limb are mostly aged over 15 years (i.e. 60%).

As regards the patients' sex, we found that there were proportionally more men than women with lesions located on the upper limbs (52.2% vs 47,8%). However, it is not possible to determine a significant variation in the location of lesions on the basis of sex ($p>5\%$).

Our analyses also show that there is a significant association between the category of the lesion and the time patients take before consulting, with a 5% confidence level. The time taken by patients with category I lesions before consulting is relatively short in comparison with those with lesions in the other categories.

A lesion which has been developing for less than four months may be considered as early, regardless of its size, while a lesion detected after more than five months may be considered as late.

This study paves the way towards an understanding of the concepts of early or late detection and also allows us to show the importance of determining the category of Buruli ulcer. However, the small scale of our study compels us to put our conclusions into perspective; they need to be checked by studies involving larger samples.

Given the lack of precise data on the prevalence of the disease, if we assume that at least 50% of the population is at risk, and assuming an alpha risk of 5% and an accuracy of 5%, we come up with a sample of 382 cases. Moreover, 15% of the total population are estimated to attend hospital.

If we apply the hospital attendance rate to our theoretical sample, we find an expected number of 58 new cases at Ayos. Consequently, our sample represents only 86% of the expected number of patients.

New foci of Buruli ulcer: Angola and Democratic Republic of the Congo

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Here we present the first laboratory confirmed cases of *Mycobacterium ulcerans* infection (Buruli ulcer) (BU) which were infected near the Kwango/Cuango River in Democratic Republic of the Congo (DRC) and in the Republic of Angola. Two patients were infected at Kafufu/Luremo in Angola, and another at Kasongo-Lunda in DRC. The medical treatment (rifampin and streptomycin), presently recommended by the World Health Organization for the management of *M. ulcerans* was effective in association with surgery after a follow-up of 42, 30 and 28 months, respectively. Areas along the Kwango/Cuango River between the DRC and the Republic of Angola are newly discovered endemic foci for BU but the spread of the disease needs to be determined. Risk factors for BU along this river and the possible influence of artisanal alluvial mining on BU outbreaks deserve further investigation.

Cost of case management of Buruli ulcer cases at the Buruli ulcer Detection and Treatment Centre (CDTUB) at Allada in Benin

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2. Buruli ulcer Detection and Treatment Centre (CDTUB), Allada
3. Buruli ulcer Detection and Treatment Centre (CDTUB), Lalo
4. National Leprosy and Buruli Ulcer Control Programme

Summary

Objective: This study examines the cost of treatment of cases of Buruli ulcer at the CDTUB in Allada. It uses three categories for Buruli ulcer cases, based on the WHO classification.

Method adopted for the study

The study is a horizontal, retrospective evaluation. A total of 100 files on patients, selected using the inclusion criteria adopted for the period, were examined. Additional interviews with technical (from the technical departments) and administrative staff were organized to obtain more precise cost estimates. The data were entered into an Excel chart and analysed using SPSS 11.5 for Windows, Chicago, USA.

Results

Median costs vary depending on the category; they are US\$ 1199.7, US\$ 1630.4 and US\$ 2375.7 for categories 1, 2 and 3.

Expenditure on drugs and consumables represents 19%, 21% and 19.1% respectively of the median total cost of treatment for each category. The median total cost of treatment for all the patients included was US\$ 1791.7.

The estimated total cost of treatment for the 100 patients treated at the Centre between 1 June 2006 and 31 December 2007 was CFA francs 94 498 548.88 or US\$ 188 997.1. Institutional costs (costs linked to service provision and administrative costs) accounted for 28% of the total cost of case management of Buruli ulcer at the Allada CDTUB; this means that a considerable effort is needed for advocacy permanently to cover the 72% of expenditure represented by technical costs.

Lastly, as regards itemized expenditure on technical case management, six items are relatively expensive: total cost of drugs and consumables, wages and administration, physiotherapy, anaesthesia-intensive care, hospital care and surgery.

Conclusion

The cost of case management of Buruli ulcer at the CDTUB in Allada is high because patients delay seeking treatment in health facilities. There is an urgent need for action at the community level to develop early case-detection in areas of endemicity and to re-examine a number of tools in order gradually to introduce analytical accounting to ensure efficient resource management.

Buruli ulcer: Perception of the disease and study of risk factors in endemic and non-endemic zones in Côte d'Ivoire

Emmanuel Tia*, Yapi Y. G.* Kadjo K. A.*

The perception by the population of Buruli ulcer and the role of insects and other aquatic invertebrates were studied from 18 to 30 October 2007 and from 14 to 16 March 2008 in five villages in Taabo (an area in which the disease is endemic and in Dabou (where it is not).

The survey of knowledge, attitudes and practices (KAP) involved 535 people, 58% of them from Taabo and 42% from Dabou. The investigation found that 83% of people living in endemic zones were familiar with the disease and 5% in non-endemic zones.

On the basis of sociological data, more than 88% of the population living in the zones concerned by the investigation are in contact with water.

Ignorance of the mode of transmission of the disease is poor (96% and 100%) among the populations investigated.

Ulcers, which are perceived as mysterious ailments, are essentially treated by traditional medicine.

Nonetheless 83% of the population living in endemic zones and 54% of those living in non-endemic zones were willing to live with people affected by the disease.

The study into risk factors (insects belonging to the families Naucoridae and Belastomatidae, aquatic flora, the physical and chemical composition of water and soil) some elements of which are still at the stage of laboratory analysis, should make it possible to locate *Mycobacterium ulcerans* in our environment.

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Exploration of haematological parameters in suspected Buruli ulcer patients: case-control study in the endemic regions of Allada and Lalo in Benin

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This case-control study, with artificial matching, was conducted on subjects living in areas of Benin in which Buruli ulcer is endemic. The purpose of the study was to identify a possible modification of biological parameters that might account for the change in the overall state of health of Buruli ulcer patients on admission.

The study concerned suspected Buruli ulcer patients admitted to the Buruli ulcer case-detection and treatment centres. The cases were matched with controls selected in their neighbourhood who satisfied the selection criteria.

The sampling method consisted of recruiting all patients with suspected Buruli ulcer during the study period. The cases were then matched with controls selected and chosen on the basis of probability.

On completion of the study, it appears that 84.4% of the patients admitted carried category II and III ulcers and presented modifications to their para-clinical and clinical parameters.

In particular:

- a lower body-mass index ($p < 0.01$)
- anaemia, measured by mucous membrane colour, ($p < 0.0001$)
- anaemia, measured by haemoglobin level ($p < 0,01$)
- hypochromic ($p < 0.001$) and other iron deficiency ($p < 0,0001$) anaemias probably attributable
- to capture of iron by *M. ulcerans* and blood loss from micro haemorrhage in the ulcers
- reticulocytopenia ($p = 0.01$) related to the iron deficiency anaemia.

These results show that haematological parameters of BU patients deviate from the norm more than those of healthy subjects. They provide indications for better case management of BU patients following their admission.

Keywords: Buruli ulcer– Anaemia – Case - Controls

Extra cutaneous manifestations of Buruli ulcer

Kouamé Kadjo, Ouattara B, Koffi F, Koffi N

Objectives

To determine the epidemiological, clinical and haematological profiles of patients.

Methods

This was a comparative study conducted at the Institut Raoul Follereau between January 2000 and July 2007. It concerned 221 patients with Buruli ulcer and 221 other patients without the disease. All the patients shared the same social, economic and cultural characteristics.

Results

The average age of the patients was 25 years, with extremes of 2 and 78 years; the sex-ratio was 3M/2F. The average age of the control group was 23 years (with extremes of 2 and 78 years). The sex ratio in this group was identical to that of the first group.

In 67% of cases, the Buruli ulcer had been active for two months prior to admission. In 75% of cases, it was at the ulcerative stage.

Anaemia was present in 72% of the patients; in 50% of cases, it was normocytic normochromic, and microcytic hypochromic in 47.5% of cases. Anaemia was found among 21.2% of the control group. In 66% of cases it was microcytic hypochromic, and normocytic normochromic in 25.5% of cases.

Conclusion

Buruli ulcer is a disorder which causes anaemia, whose mechanism is certainly attributable to several factors.

Activities to control endemic treponematoses in Congo

Damas Obvala

Cases of yaws in two (2) departments where the disease is endemic in northern Congo.

Yaws, a non-venereal treponematoses is currently considered to be a disease that has disappeared since time immemorial from several countries in the world.

The infection still occurs in three departments of the Congo, Congo, Likouala, Sangha and Lékoumou.

The populations most affected by the disease are the pygmies or Babenga, who make up almost one third of the population in these departments. These indigenous populations live in warm, humid forests, where living conditions and hygiene are poor.

In December 2008 and January 2009, an integrated joint mission was carried out in the two departments of Likouala and Sangha with the following objectives; to inform the target populations about the disease, to detect and treat any cases and to promote hygiene among these deprived communities.

In the two departments, 646 clinical cases of yaws and 83 contacts were treated along the stretches of the five rivers visited.

A total population of 8281 inhabitants was examined, with a participation rate of 51.68 %

Case distribution by age, sex and type of lesion was as follows:

- Infants: 36 cases (5.5 %)
- Children: 169 cases (26.1 %)
- Adults: 441 cases (68.2 %)
- Primary yaws: 582 cases (80.8 %)
- Secondary yaws: 122 cases (18.8 %)
- Tertiary yaws: 2 cases (0.3 %)

All the cases were treated with proper doses of depot penicillin (Extencillin), in accordance with the WHO protocol.

Providing these communities with information and encouraging good hygiene was an important component of the mission.

The main difficulties encountered were the inaccessibility of the target populations, their nomadic way of life in the forests, the poor health infrastructure and the prohibitive cost of the activity.

The populations attachment to their forests, geographical and climatic factors and poor hygiene account for the persistence and perennial nature of the disease among these communities.

Under these conditions, the most realistic approach would be to raise awareness of the disease among the communities and to conduct roving missions among them.

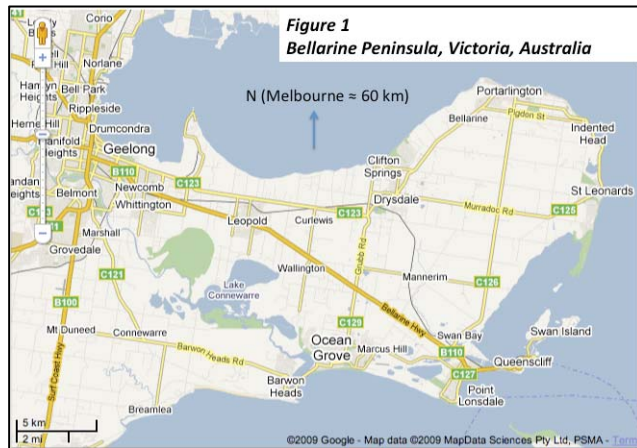
ABSTRACTS - Research Session

Vector borne diseases, mosquitoes and Buruli ulcer in Victoria, Australia

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Buruli ulcer typically occurs in association with swamps or rivers but the mode of transmission to humans remains unknown. The Bellarine Peninsula, 60-80 km south of Melbourne (figure 1), is highly endemic for Buruli ulcer and there were 27 new human cases and 7 animal cases linked to this region during 2008.



Mosquitoes captured on the Bellarine peninsula are more likely to test positive by PCR for *Mycobacterium ulcerans* DNA than those captured in non-endemic areas (1). Furthermore, residents of the Bellarine peninsula who report being bitten by mosquitoes have a higher likelihood of being diagnosed with Buruli than those from the same region who report fewer bites from mosquitoes or use insect repellent (2). During our investigations into the mode of transmission of *Mycobacterium ulcerans*, we have

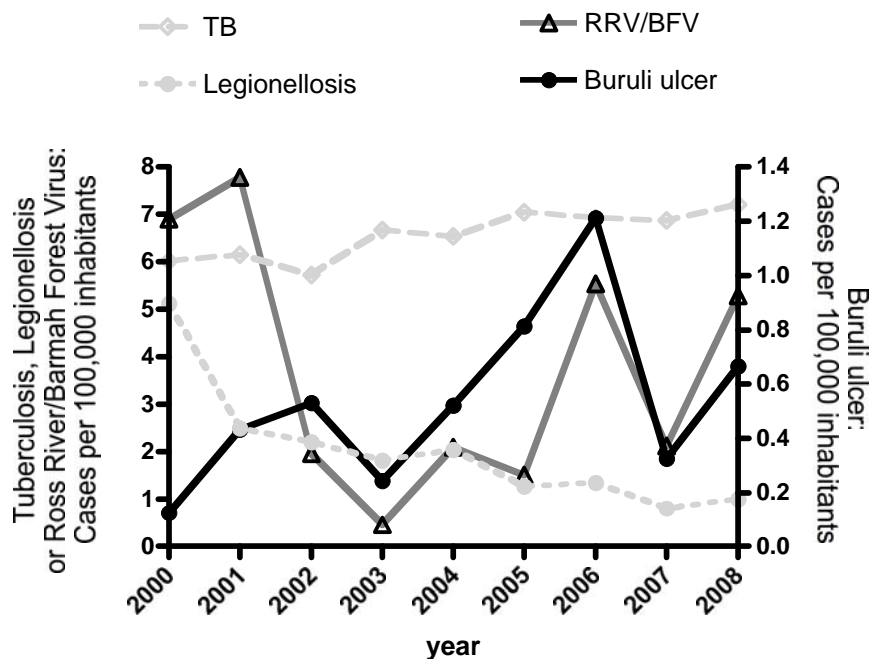
continued to trap and test mosquitoes and now have data over a 40-month period from 8 different Bellarine peninsula locations. Captured mosquitoes were tested in pools by real-time PCR as previously described (1,3). During the same period we investigated newly diagnosed cases of Buruli ulcer and attempted to identify their most likely place of exposure. When compared by non-parametric correlation, we observed a significant association between the proportion of mosquitoes in a particular location that were PCR-positive for *M. ulcerans* DNA and the number of locally acquired human infections.

We have also compared rates of notification of Buruli ulcer for the whole of Victoria with other notifiable diseases using publicly available public health data (4). We noted a striking association between notifications of Buruli ulcer* and combined Ross River Virus/Barmah Forest Virus infections (RRV/BFV), both of which infections are transmitted by mosquitoes (figure 2). From 2002-2008 this association approached statistical significance ($r = 0.73$; $p = 0.06$) (figure 2) but there was no similar correlation with any other notifiable disease during the same period, including tuberculosis--the most common mycobacterial disease in Victoria ($r = 0.3$; $p = 0.48$) or with infections caused by Legionella, a non vectored water-associated environmental pathogen ($r = 0.04$; $p = 0.66$). These data strongly suggest that conditions that favour mosquito transmission of RRV/BFV also favour transmission of *M. ulcerans*.

* Buruli ulcer was not made notifiable in Victoria until 2004; we have relied on our own laboratory information prior to this. Other diseases with which Buruli ulcer was compared have been notifiable and publicly reported for many years.

There is now considerable circumstantial evidence to support the hypothesis that *Mycobacterium ulcerans* is transmitted to humans by mosquitoes in Victoria. Mosquitoes may not be the only mode of transmission and we cannot exclude a role for non-vectored transmission from soil or aerosol. We are actively investigating the possibility that possums or other small animals are the environmental reservoir of *M. ulcerans* and that mosquitoes which breed or rest in drains contaminated with their excreta transmit the infection to humans.

Figure 2
Selected notifiable diseases, Victoria, Australia; 2000-2008.
(Johnson PDR and Lavender CJ; in press Emerging Infectious Diseases 2009)



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A role for small mammals in the ecology of Mycobacterium ulcerans

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Following the discovery of *Mycobacterium ulcerans* DNA in the excreta of common ringtail (*Pseudocheirus peregrinus*) and brushtail possums (*Trichosurus vulpecula*), collected from a location associated with ongoing human infections, a study was initiated to investigate the potential role of these native Australian mammal species as wildlife reservoirs of *M. ulcerans*.

Over a 9 month period in 2008, a total of 20 common ringtail and 12 common brushtail possums were trapped in cage traps, or by hand, in Point Lonsdale, a Victorian coastal town from which at least 96 human cases of Buruli ulcer have been laboratory confirmed since 2002. The animals were examined for skin lesions (swabbed if present) and morphologic data and samples, including blood and fresh faeces, were collected for analysis. They were then permanently marked for ongoing identification (micro-chipped and tattooed) and the majority were re-released at the point of capture. While all of the common brushtail possums were free of lesions, one had traces of *M. ulcerans* DNA in a faecal sample. However, five of the common ringtail possums had laboratory confirmed *M. ulcerans* lesions on their tails, feet or faces and two additional animals had *M. ulcerans* DNA detected in their faeces, but had no obvious skin lesions. Four of these *M. ulcerans*-positive common ringtails were sacrificed and full necropsies performed to determine the extent of infection. *M. ulcerans* was detected in the gut contents of all four animals. Evidence of systemic infection, involving the liver and lungs, was observed in one individual that also had multiple ulcerative and oedematous external lesions.

Thirty one common rats (*Rattus rattus*) were also captured, in possum traps, in the same location. PCR analysis of the gut contents of these animals revealed that 7 (23%) were positive for *M. ulcerans*, suggesting recent ingestion, and one had a PCR-positive lesion on a foot.

These results confirm that both possums and rats can be naturally infected with *M. ulcerans*, and could potentially act as reservoirs from which direct or indirect transmission to humans could occur. Studies are continuing to establish whether *M. ulcerans* is able to replicate in the gastrointestinal tracts of mammals and the precise role that small mammal colonization/infection plays in the ecology and human epidemiology of *M. ulcerans*.

Environmental sampling for Mycobacterium ulcerans: important considerations to understanding transmission

Eric Benbow, Heather R. Williamson, Mollie D. McIntosh, Ryan Kimbirauskas, Charles Quaye, Charles Yeboah, Stephanie Miller, Daniel Boakye, Pamela L.C. Small, Richard W. Merritt

Understanding the transmission of *Mycobacterium ulcerans* has, in part, been hampered by difficulties of identifying and quantifying the organism in the environment. In addition, few studies related to transmission have employed standardized sampling programmes and replicated study designs, both necessary for a more complete scientific description of where and how to sample for the potential pathogen. For any environmental organism that also acts as a pathogen, it is important to identify habitats where its populations are relatively more abundant compared to less hospitable areas where it is in lower abundance or absent. This information facilitates detection of relevant reservoirs and/or vectors of the pathogen, something necessary for determining the route of transmission of Buruli ulcer disease, particularly in Africa.

In this paper we address the difficulties and considerations of identifying the ecological niche of *M. ulcerans* from Ghanaian aquatic habitats that range in size, structure and duration. Using standardized descriptive and manipulative experimental studies we examined the relative abundance and distribution of *M. ulcerans* at multiple spatial and temporal scales on various environmental substrates. Employing both dichotomous (i.e., presence/absence as positivity rates) and quantitative (i.e., qPCR as cell population abundance) approaches to describing the extent of organism occurrence, we report that populations of *M. ulcerans* were relatively widespread, but not found in every habitat or location. This variation occurred both within and among substrates of the following: suspended particulate matter in the water column; dominant aquatic and riparian plants; glass and plastic slides incubated in aquatic habitats; nutrient-diffusing substrates; dry and wet surface soil samples; and various aquatic and terrestrial invertebrate taxa.

Spatially, *M. ulcerans* populations on these substrates were highly variable at the country-scale (southern Ghana), local-scale (among waterbodies in the same region or district), habitat-scale (within a single waterbody), and microcommunity-scale (on a single plant or among individuals of a single invertebrate species). To understand the temporal variation in *M. ulcerans*, six waterbodies were monitored about every two months for a year. We found that populations significantly varied over the course of the year, with highest relative abundance occurring during the summer months. Based on these studies, we recommend that future environmental sampling for *M. ulcerans* include spatial and temporal consideration, high substrate/sample replication and qPCR confirmed by multiple labs. Furthermore, we advocate that environmental studies be designed within a framework of microbial ecology, attempting to understand what biotic and abiotic factors regulate the dynamics of *M. ulcerans* populations. This approach will provide a logical and essential direction of data acquisition that can be used for identifying transmission pathway(s), and consequently, management strategies for disease prevention.

Exploring environmental factors related to Buruli ulcer disease within the Couffu and Oueme Watersheds in Benin, Africa

Lindsay Campbell, van Ravensway J, Benbow ME, Small P, Johnson RC, Soppin G, Merritt R, Qi J

Landscape disturbance and changing environmental variables may contribute to an increase in Buruli ulcer disease (BU), particularly in West Africa. Our previous studies have analyzed different land cover classes in relation to BU incidence and prevalence in Benin; however, specific environmental attributes were not studied. For example, landscape fragmentation, or the degree to which the landscape is divided into smaller and more numerous areas of different land covers, has important ecological ramifications that may be associated with microhabitats conducive to the growth of *Mycobacterium ulcerans* (MU) resulting in ecological pathways through which the pathogen infects humans. There are other environmental factors that may impact BU/MU occurrence, including landscape wetness, fraction of vegetative cover, and water quality.

This study builds upon knowledge gained from previous land use and land cover research in Benin by quantifying landscape fragmentation, land cover class adjacency, and landscape diversity in relation to BU positive and BU negative communities along the Couffu and Oueme Rivers. Future research goals include the use of high resolution satellite imagery to discern specific vegetation types, to better quantify landscape wetness, and to help determine water quality and inputs from human activities that may alter the environmental attributes associated with BU prevalence.

Risk factor analysis of Buruli ulcer cases in French Guiana. A case-control study

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Buruli ulcer (BU) is an endemic disease in French Guiana, a French overseas territory located north of Brazil, where BU cases have been recorded since 1965. In order to better understand the role of contacts with the environment in *Mycobacterium ulcerans* transmission, a case-control study was set up within the dermatology department of Cayenne Central Hospital. The study included every BU patient admitted to Cayenne Hospital from January 2002 to July 2004. For each BU patient, two controls were selected among hospital patients treated for other disease. Cases and controls were matched on age and date of admission. Covariates included occupation, leisure activities, ethnic group, type of residence, geographical distance to several types of water bodies from living place and workplace, making a total set of about 100 distinct covariates. The study was analyzed via conditional logistic regression, a method able to take into account several covariates. In this oral communication, we discuss the influence of the main factors that may explain BU disease transmission among French Guiana citizens, in a Latin American region for which the disease may be considered to be an environmentally-persistent endemic phenomenon.

***Experimental infection of Medaka (Oryzias latipes) with
Mycobacterium ulcerans:
A model for transmission, pathogenesis and toxicity to fish***

Lydia Mosi, Nadine Mutoji, Don Ennis, Pamela L.C.Small.

Mycobacterium ulcerans is an aquatic environmental mycobacterium that causes the disease Buruli ulcer. Molecular analysis reveals that *M. ulcerans* is closely related to *M. marinum*, which causes disease in both fish and man. In addition to its chromosome, *M. ulcerans* has a 174-kb plasmid that produces a virulent macrolide toxin, mycolactone.

It is unclear the nature of *M. ulcerans* infection in fish other than the presence of the bacterial DNA. Based on this evidence we proposed to investigate the capability of *M. ulcerans* to produce an infection in Medaka (*Oryzias latipes*) and explore the capability of infected fish to support the replication of the bacteria following direct inoculation.

Thus far we have shown that *M. ulcerans* with or without the toxin is not lethal to Medaka even at high doses. Over time, infected Medaka do not exhibit any visible signs of infection or toxicity. Histopathological sections of infected medaka do not reveal significant gross pathogenesis however at both 7 and 60 days p.i., *M. ulcerans* DNA can be detected in all anatomical sections of infected fish.

Work is still in progress to determine if *M. ulcerans* can replicate in infected medaka over time. Preliminary invitro work suggests that goldfish leukocytes are susceptible to nanogram amounts of purified mycolactone. This is the first study to demonstrate the possibility of fish as a reservoir for *M. ulcerans* within the aquatic environment.

Dynamic population of water bugs in a Buruli ulcer endemic area and their rate of colonization by M. ulcerans

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Buruli ulcer is an emerging disease in tropical zones, especially in West Africa. The etiological agent is *Mycobacterium ulcerans*, which is an environmental mycobacteria. Populations affected by this disease are those working or living close to humid and swampy zones. The transmission is still not completely clear, but some studies show the implication of water bugs as host and vector of *M. ulcerans*. The knowledge of these insects in their environment is limited.

The aim of this study was to determine the dynamic of water bugs population in non endemic and endemic zones and to estimate their rate of colonisation by *M. ulcerans* into their tissues and saliva. Between October 2007 and July 2008, water bugs were collected in the Nyong River in Akonolinga, an endemic zone in Cameroon. Height families (16 morphotypes) of water bugs were identified and presented a large seasonal variation of density.

Detection of *M. ulcerans* DNA in insect tissues and saliva was performed using real time PCR. Results showed that all water bug families in endemic area for Buruli ulcer were permissive to colonization by *M. ulcerans*. However, the rate of colonization by *M. ulcerans* varied between 1% to 20 % in the same area depending on the season. Moreover, direct detection of *M. ulcerans* DNA in insect saliva suggests that water bugs are able to transmit *M. ulcerans* by bite.

This work was supported by Fondation Française Raoul Follereau, Fondation Pierre Ledoux, Pasteur Institute Network (PTR 212), Inserm, IMEA and European Community (FEDER 10250).

Biological diversity and implication of water bugs in transmission of *Mycobacterium ulcerans*, the pathogen of Buruli ulcer, in Côte d'Ivoire (West Africa)

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Buruli ulcer, which counts among the neglected tropical diseases, was declared an emerging disease by WHO in 1998.

In recent years, Buruli ulcer, whose causative agent is *Mycobacterium ulcerans*, an environmental mycobacterium found in soil and water, has become the third mycobacterial disease after leprosy and tuberculosis. It is developing at a disturbing rate in West Africa, and in particular in Côte d'Ivoire which, with an aggregate number of 25 000 cases and more than 2000 cases detected each year, is the country most affected not just in Africa but in the world.

The disease is particularly common in specific areas and spreads successfully in marshes and grassland in the vicinity of streams and rivers. In order to control the disease, it is fundamental to understand its epidemiology.

Although it has been firmly established that the bacillus is not transmitted from human to human, and that people seem to be contaminated through contact with the aquatic environment, the mode of transmission of *M. ulcerans* to humans is not yet well understood.

Recent studies have indicated that aquatic insects, and in particular water bugs, might be implicated in transmission of *M. ulcerans* to humans via accidental bites. In 2008, a study of the species diversity, biology, ecology of water bugs and their role in transmission of *M. ulcerans* to humans was carried out in Côte d'Ivoire in 2008. Water bugs were collected each month in different aquatic environments in the regions of Dabou and Tiassalé and then in Bouaké, which are respectively located in the south and centre of the country. The insects were identified by family, genus and occasionally species. Correlations were established between their distribution, frequency of occurrence and monthly variation in their distribution in the ecosystem at the water points investigated and human activities. Mono-species batches of water bugs were regularly made up for detection of molecular signatures of *M. ulcerans* using PCR. Eighteen (18) species of bug belonging to 8 families were inventoried.

The most common species which were present at all sites in significant numbers belong to the genera *Diplonychus*, *Micronecta*, *Naucoris*, *Ranatra* and *Laccotrephes*. A wide diversity of human activities was observed around the water points. Out of 289 mono-species batches of water bugs examined using PCR, 26 samples were positive. They belonged to the following families: *Belostomatidae*, *Naucoridae*, *Nepidae*, *Ranatridae* and *Notonectidae*. The species diversity of water bugs, their distribution and confirmation of the presence of *M. ulcerans* in certain species which accidentally bite humans in water point to their implication in transmission of Buruli ulcer, which is closely linked to human activity around water points. Moreover, species of the genus *Diplonychus* are excellent fliers and could bite humans in and outside their homes when attracted there by light sources.

Land use and land cover changes and Buruli Ulcer in Côte d'Ivoire and French Guyana

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1. Dynamique des Réseaux et des territoires
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Study on a national spatial scale in Côte d'Ivoire

As many areas in tropical zone, the environment in Côte d'Ivoire in West Africa and French Guyana in South America have been subjected to high modification in the last 30 years. The analysis of climatic data clearly shows a stark decrease in rainfall during this period. At the same time, changes in the land use and the land cover are observed. These environmental modifications affect rural urban ecosystem and can increase health risks like Buruli ulcer. The main objective of this study is to investigate the relationships between the incidence of Buruli ulcer disease and a group of environmental variables in Côte d'Ivoire (the most contaminated country in the world) and in Cayenne in French Guyana (the most contaminated area in South America).

In this study we have intersected the percentage incidence of Buruli with environmental data. These environmental data concern vegetation, crops (rice and banana), dams and lakes. Using a geographical information system and multivariate analyses we showed a link between cases of Buruli ulcer disease and different environmental factors for the first time at a country-wide scale. As result, irrigated rice field cultures areas, and, to a lesser extent, banana fields as well as areas in the vicinity of dams used for irrigation and aquaculture purposes represent high risk zones for human population to contract Buruli ulcer in Côte d'Ivoire. This is much more relevant in the central part of the country. As already suspected by several case-control studies in different African countries, we strengthen in this work the identification of high risk areas of BU at a national spatial scale. This first study should now be followed by many others in other countries and at a multi-year temporal scale. This goal implies a strong improvement in data collection and sharing, in order to achieve a global picture of the environmental conditions which drive the Buruli Ulcer emergence and persistence in human populations.

Key words: Land use and land cover, wet land, sanity risk, Côte d'Ivoire

Study on a local spatial scale in Cayenne (French Guyana)

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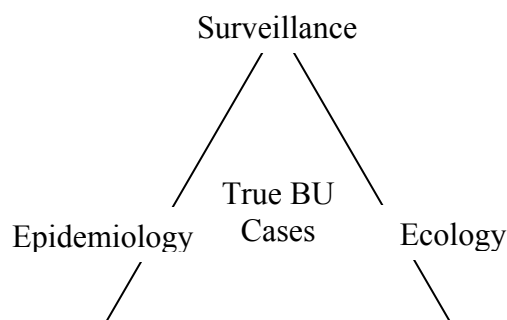
In Cayenne area, studies of relationship between health and environment have become important because of high climate variability and land cover changes. The monitoring of Hydro-climatic and land cover dynamics can help us to improve knowledge of infectious diseases emergency conditions. In the Cayenne area, we used the GPS to localise patients. Then, we generated a map of points with the geographic coordinates of the patients. We also produced a map of wet zone using remote sensing data. The overlaying of both maps shows that Buruli ulcer's patients are localised near from the town's water evacuation channels and periodic inundation zone. In the same time, we studied the relationships between rainfall's variability and Buruli Ulcer's patient cases. We observed, in general, an increase of patient's cases during the year of rainfall deficit and conversely.

Based on these interactions, we proposed the hypothesis that, due to decrease of the rainfall some years, clean water and polluted water can stagnate in the evacuation channels and in the periodic inundation zone, and then constitute potential zone of buruli ulcer emergence. The risk to contract this disease is important for the populations living around these wet areas, because some of them are used to entering in contact with these areas.

Key words: Climate, wet land, sanity risk, Cayenne

Linking surveillance, epidemiology, and ecology for Buruli ulcer disease in Ghana

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Edwin Ampadu, and William Opare**



Buruli ulcer, caused by the bacterium *Mycobacterium ulcerans*, can result in devastating disease, and is endemic in many countries along Africa's western coast including Ghana. Although Buruli ulcer was first described in 1897 by Sir Robert Cook, the reservoir and mode of transmission remain unknown. Research into Buruli ulcer prevention, transmission, and treatment often falls into one of three categories:

The surveillance of human cases of Buruli ulcer to quantify the burden of disease and allocate prevention and treatment efforts within countries and across the world;

The epidemiology of Buruli ulcer identifying the risk factors driving disease incidence, the progression of disease, the effectiveness of treatment, and the burden and cost of care; and the ecology of *M. ulcerans* defining the life cycle of the causative pathogen in the environment, relevant hosts and/or vectors, and contact patterns leading to human cases of Buruli ulcer.

All three areas reflect vibrant areas of research, but these often operate independently of one another. Our research program aims to operate at the intersection of all three aspects of Buruli ulcer research and we report on progress to date on our developing field work in Ghana in cooperation with collaborators in all three areas.

More specifically, public health surveillance for Buruli ulcer is the ongoing, systematic collection, analysis, interpretation, and dissemination of data. The primary goal for the use of this data is for public health action to reduce morbidity and to improve the health of affected populations. During the summer of 2008, the WHO Global Buruli Ulcer Initiative, in conjunction with Ghana Health Service, invited a team of evaluators from Emory University to assess the current Buruli ulcer surveillance system in Ghana and to make recommendations for its improvement and expansion.

We will provide a brief report on the evaluation team's findings with respect to:

- Describing and assessing the collection and management of Buruli ulcer surveillance data;
- Describing and assessing the integration of surveillance and disease control efforts for Buruli ulcer and other diseases, including Integrated Disease Surveillance and Response;

- Describing and assessing community-based surveillance efforts for Buruli ulcer and their overlap with similar efforts for other diseases; and
- Describing and assessing the system for laboratory confirmation of Buruli ulcer cases.

Next, we place these results in context of ongoing environmental surveys and plans for coordination of future efforts to expand linkages between surveillance, epidemiology, and ecology of Buruli ulcer.

"Why does culture fail? Molecular Analysis of Mycobacterium ulcerans culture positive and culture negative Buruli Ulcer"

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Successful culture of *Mycobacterium ulcerans* from infected tissue has low sensitivity as a diagnostic method. The inability to culture *M. ulcerans* from a lesion may be due to the fact that the tissue sample does not contain viable *M. ulcerans*, the numbers of *M. ulcerans* may be insufficient to yield a culture or some biovars of *M. ulcerans* may be more readily cultured than others.

In order to investigate these possibilities, we compared molecular profiles of *M. ulcerans* from cultures obtained from Buruli ulcer patients with results obtained from analysis of DNA extracted from BU patient tissue which was culture negative but IS2404 positive. Analysis of 27 cultures taken from patients near Tepa, Ghana showed that 23/27 (85%) isolates VNTR- typed as Profile C (profile of the Agy99) , 1 matched Profile A, and VNTR profiles could not be obtained from 3.

In contrast analysis of DNA from patient tissue where culture was not obtained showed a much broader distribution of *M. ulcerans* biovars. Of the 15 samples in the "No culture" group 1 typed as Profile A, 3 as Profile B, 8 as profile C , 1 as Profile D and one had a VNTR profile consistent with a mycolactone-producing mycobacteria other than *M. ulcerans*. Results from quantitative PCR suggest that the ability to obtain positive cultures from the same biovar is dose dependent. In summary our results suggest that the failure to obtain a culture from a patient may be due either to a low bacterial load, or to the presence of *M. ulcerans* biovars which are readily cultured. These results support earlier findings that the *M. ulcerans* biovars most common in the environment, are not those most often isolated from patients.

Quantitative Studies on the Presence of *Mycobacterium ulcerans* DNA in Environmental Samples from Ghana

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Though *Mycobacterium ulcerans* has been widely associated with aquatic habitats, attempts to culture the organism from an environmental sample have occurred only once. Because of this, identification of *M. ulcerans* from environmental samples has largely relied upon exploitation of molecular tools for detection of *M. ulcerans* DNA. While conventional PCR has provided evidence for the presence of *M. ulcerans* in soil, macrophytes, aquatic insects and vertebrates, water filtrate, and biofilm, quantitative PCR (qPCR) has only recently been employed to determine the quantity of *M. ulcerans* in these samples. *M. ulcerans* target DNA in environmental samples occurs in the context of complex and unknown populations of microflora. Because of this the specificity as well as sensitivity of PCR is problematic.

The potential for PCR inhibition, the low proportion of target DNA in some samples and the problems in determining specificity are of a particular concern when evaluating samples collected from aquatic habitats. The degree of PCR inhibition is highly dependent on the type of sample. This raises questions regarding the value of comparative quantitative PCR of environmental samples. The methods of DNA extraction as well as choice of PCR targets and reagents used are also important variables.

In order to determine the role of PCR inhibition in different environmental matrices, environmental samples were spiked with dilutions of *M. ulcerans*. In these studies we evaluated the role of DNA extraction methods, and reagents used for qPCR in order to optimize environmental PCR. Because environmental samples must often be stored for a considerable period of time before analysis, we have also conducted studies to optimize protocols and time framework for storage and sample processing. Results from this work represent a small step toward the determination of the environmental niche of *M. ulcerans* in aquatic habitats.

Report on pilot quality assurance program for molecular detection of *M. ulcerans* in environmental samples

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Background

At the 2008 WHO Annual Meeting on Buruli ulcer, the Technical Advisory Group (TAG) agreed to establish quality assurance (QA) programs for the molecular detection of *M. ulcerans* in clinical and environmental samples. The WHO Collaborating Centre for *M. ulcerans* based in Melbourne, Australia, agreed to coordinate a QA program for environmental samples.

Objectives

To determine the feasibility of an environmental QA program (e.g. cost, workload, export/import permit issues etc)

- To develop and carry out a pilot QA program
- To report the results of the Program to participants
- To help participants with technical difficulties if required
- To develop recommendations for future programs in consultation with participants

Program overview

Eight laboratories based in Australia, Cameroon, Belgium, France, French Guiana, Japan and the USA took part in the Program. Participants were sent eight heat-sterilised environmental samples collected from an endemic region for analysis (i.e. samples were not spiked). Participants tested the samples using the DNA extraction and PCR methods they routinely use for environmental samples in their own laboratories. The program organisers covered the cost of preparing and shipping the samples. Participants were required to supply their own equipment and reagents.

Results

There was a high level of interest in the Program, with 13 laboratories responding to the invitation to participate. Samples were received by all participants with minimal delay and in good condition. There was good agreement between the expected results and the results generated by participants, with five laboratories reporting the correct result for all eight samples only three labs experiencing contamination and/or PCR inhibition. Of the four laboratories that obtained the correct result for every sample, four used the Mo Bio Soil Kit for DNA extraction and four used real-time PCR targeting IS2404 for sequence detection. Feedback was provided to all participants and technical advice given to those laboratories with one or more incorrect result. A written report will also be distributed to participants and members of the TAG. The cost of running the Program was estimated at €625/US\$8271.

¹ Figure includes preparatory testing, sample preparation and postage, but excludes labour

Conclusion

A QA Program for molecular detection of *M. ulcerans* in environmental samples is both useful and feasible. Most laboratories which participated in the program obtained the expected results. Discussion points for future programs include: (i) varying the samples type, (ii) using lower concentrations of *M. ulcerans* DNA (in order to test PCR sensitivity), (iii) rotating the organising laboratory, and (iv) ongoing funding for the Program.

Genetic diversity of Mycobacterium ulcerans

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Acquisition of the virulence plasmid pMUM001 (encoding polyketide synthases that produce the immunosuppressive macrolide toxin mycolactone), massive gene decay and pseudogene formation are hallmarks of the development of *M. ulcerans* from *M. marinum* into a pathogen that causes chronic infections (Stinear et al. 2007).

Our comparative genomic hybridisation analysis of *M. ulcerans* clinical isolates of diverse geographic origin revealed extensive large-sequence polymorphisms. The identified transposable element-associated insertional/deletional recombination events are indicative of progressive genome shrinking. Reductive evolution indicates that *M. ulcerans* is adapting to a new niche environment. Results suggest a preferential loss of immunodominant proteins, such as ESAT-6, CFP-10 and HspX. Analysis of the large InDel polymorphism allows distinguishing between two distinct lineages: (i) the “classical” lineage representing the most pathogenic genotypes – those that come from Africa, Australia and South-East Asia; and (ii) an “ancestral” lineage comprising strains from China and Japan, South America and Mexico.

Although continental types of *M. ulcerans* strains have been well established, to differentiate between isolates within geographic regions, such as strains from African countries, has remained a challenge. Many conventional genotyping methods have been applied for *M. ulcerans*, but only a few, such as variable-number tandem repeat (VNTR) typing have provided at least limited resolution among clinical isolates from Africa.

Genome wide analysis of single nucleotide polymorphisms (SNPs) appears to be the only method that will allow developing genetic fingerprinting methods for the genetically largely monomorphic local populations of *M. ulcerans*. The complete genome sequence of *M. ulcerans* strain Agy99 (Stinear et al. 2007), can be used as the reference for comparative genome analysis and the ongoing revolution in massive parallel sequencing technologies makes this approach feasible. Based on SNP analyses the evolutionary time frame for the emergence of *M. ulcerans* lineages can be estimated and SNP typing assays can help to identify transmission pathways.

Molecular study of the biodiversity of M. ulcerans strains isolated in Côte d'Ivoire using MIRU/VNTR

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Introduction

Buruli ulcer is an endemic disease in Africa, and Côte d'Ivoire, where there are some 2000 new cases each year, is the country most affected. In order to study the disease's mode of transmission and to determine the diversity of the strains circulating in the country, a preliminary study has been carried out for the purpose of evaluating the genetic biodiversity of Ivorian strains of *M. ulcerans* by molecular typing using minisatellite markers: MIRU VNTR.

Material

This preliminary study was carried out using a total of 79 samples from various regions in Côte d'Ivoire and from different sources: 40 strains, 33 of which were isolated at the Typical and Atypical Mycobacteria Unit of the Institut Pasteur in Côte d'Ivoire and 07 reference strains; 28 clinical samples comprising samples from operations and from exudate and 11 samples collected in the environment, mainly from aquatic insects belonging to the order of the Hemiptera.

Methodology

The different samples were selected for their positive results in tests to detect the presence of the *M. ulcerans* genome. After confirmation, molecular typing was performed by detection of the molecular markers targeting the number of MIRU/VNTR repeat tandems. This preliminary study concerned loci 1, 2, 5, 6, 9, 33 and Mul_0583. The PCR products obtained for each target were then sequenced and analysed using CLC viewer 5.1.2 and Geneious Biomatters 3.8.4 software.

Results

Not all the strains analysed presented the 3113 repeat profile characteristic of African strains. It was not possible to amplify 16 of the 33 strains on at least one of the following loci: 1, 6, 9 and 33.

In the clinical samples, the 311 repetition profile was found on loci 1, 6 and 9. On locus 33, the size of the amplification products was 300bp more than the expected band of 845 bp.

The environmental samples produced different sized amplification products at each locus, making it impossible to evaluate the number of repeats on them.

Analysis of sequences on loci 6, 9 and 33 after alignment showed no significant variations; this shows the conservation of the sequences from the Ivorian strains at these loci. However, one strain did present numerous mutations on locus 1.

Conclusions

This preliminary study shows that there are few variations among the Ivorian strains; this would seem to indicate that they are genetically indistinguishable with the markers used. A new set of markers could shed light on genetic diversity among the Ivorian strains.

Key words : Buruli ulcer - *Mycobacterium ulcerans*- Molecular typing- MIRU VNTR- Côte d'Ivoire.

Genetic diversity of *Mycobacterium ulcerans* strains from Ghana

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Mycobacterium ulcerans strains of world-wide origin could be differentiated by analysis of large sequence polymorphisms and other genetic typing methods into five haplotypes and two distinct lineages (1). In contrast, *M. ulcerans* isolates coming from the same geographical location are genetically highly monomorphic (2). Lack of genetic fingerprinting methods for such closely related strains has hindered studies on environmental reservoirs, transmission pathways and evolution of *M. ulcerans*.

Monomorphic bacterial populations exhibit so little sequence diversity that sequencing of a few gene fragments is not informative. However, comparison of complete genome sequences of two *M. ulcerans* isolates from Ghana with the published genome of strain Agy99 isolated in 1999 from a patient from the Ga district of Ghana (3) revealed the presence of Single Nucleotide Polymorphisms (SNPs) between these isolates. Detected SNPs were used for the establishment of a high-throughput genetic fingerprinting method for Ghanaian isolates. The method chosen for this purpose was amplification refractory mutation assays carried out by real-time polymerase chain reactions and improved by using hairpin-shaped instead of linear primers. Analysis of 53 disease isolates from the Ga district at 73 SNP locations revealed the presence of six haplotypes. This method enabled a phylogeographic analysis based on the domicile of the patients from which the strains were isolated.

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This study was supported in part by the 'Stop Buruli' initiative funded by the UBS Optimus Foundation.

Insights from comparison and analysis of multiple M. ulcerans genome sequences

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In 2007 the first *M. ulcerans* genome sequence was published. We have now used Illumina high throughput sequencing technology to sequence a further five genomes in the last three months. Studies of the spectrum of activity of mycolactones and discoveries of new potential animal reservoirs of *M. ulcerans*, indicate that although *M. ulcerans* disease is related to aquatic environments, *M. ulcerans* is not necessarily an environmental *Mycobacterium* associated with “swamps and slow-flowing water”, but a species adapted to certain mammalian hosts. We present preliminary data from our high resolution genomic comparisons to suggest that while the bacterium might be widespread in certain animal hosts, transmission is occurring at a local level.

Signature of the immunosuppressive action of mycolactone in the peripheral blood of Buruli ulcer patients

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In a previous study, we have shown that mycolactone suppresses the capacity of human dendritic cells to produce inflammatory chemokines *in vitro*, with a selective effect on the macrophage inflammatory protein (MIP) 1a, MIP-1b and the monocyte chemoattractant protein 1 (MCP-1). To investigate the physiological relevance of this finding, we have compared the circulating levels of a large array of cytokines and chemokines in Buruli ulcer (BU) patients and endemic controls. Despite the presence of proliferating bacteria and tissue destruction within BU lesions, the circulating levels of most inflammation markers were not augmented in patients compared to healthy controls. In fact, the four inflammatory chemokines MIP-1b, interleukin (IL) 8, MCP-1, and to a lower extent fractalkine, were significantly suppressed. Notably, the serum levels of IL-8 and MCP-1 were not reduced in tuberculosis patients, suggesting that their suppression is specific to BU disease. Down-modulation of MIP-1b, IL-8 and MCP-1 was induced at the nodular stage of the disease, persisted during the ulcerative stage, and resolved after anti-BU therapy. These observations are consistent with the hypothesis that mycolactone limits the development of inflammatory responses to infection *in vivo*. Moreover, they highlight the potential interest of measuring MIP-1b, IL-8 and MCP-1 blood levels for monitoring efficacious patient responses to antibiotic treatment.

Kinetics of mycolactone concentration in human M. ulcerans lesions during antibiotic treatment

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Introduction

Mycolactone, which is central to the pathogenesis of *M. ulcerans* (Mu) disease, suppresses macrophage function at low concentration. We have recently shown that during antibiotic treatment of patients with Mu disease there is an increase in interferon γ (IFN γ) secretion in a whole blood stimulation assay suggesting improvement in Th-1 responses (Ref). Neopterin is a pteridine compound released by activated monocytes upon stimulation by interferon γ . The object of this study was therefore to look for evidence of macrophage activation in patients with Mu disease during antibiotic treatment by measuring the serum concentration of neopterin alongside CRP as an inflammatory marker.

Methods

30 patients with Mu disease were recruited from villages near Tepa in the Ahafo Ano North district of Ghana. The diagnosis of Mu infection was confirmed by PCR for IS2404 on a 4mm punch biopsy. All patients were treated with rifampicin 10mg/kg by mouth and streptomycin 15mg/kg I/M daily for 8 weeks. After obtaining informed consent 5ml of venous blood was collected in endotoxin free tubes before treatment and after 4, 8 and 12 weeks. Serum was separated and stored at -200C until analysis. Serum neopterin was measured by ELISA (Genway,US) according to manufacturer's instructions and CRP measured at St. George's, University of London by ELISA. Samples were taken from 10 TB patients and 5 normal controls. Mann-Whitney's U-test was used to compare the medians of serum neopterin and CRP at various time points with $p < 0.05$ taken as level of significance.

Results

Mu disease was confirmed by PCR in 16 patients with pre-ulcerative and 14 with ulcerative disease. All lesions healed within 24 weeks of starting antibiotics and there were no recurrences after follow up for a year. Median serum neopterin concentration in 5 normal controls, 30 untreated Mu disease patients and 10 patients with pulmonary tuberculosis were 7.9 nmol/l (range 3.9-15.12), 11.0 (4.5-43.0) and 53.5 (13.1-85.1) respectively with a significant difference between normal controls and patients with tuberculosis ($p < 0.05$) but not between normal controls and Mu infected patients. During antibiotic treatment of Mu disease, serum neopterin increased to 18.9 nmol/l (2.6-43.7; $p < 0.005$ compared to pre-treatment concentrations) after 4 weeks but declined at 8 weeks to 15.3 (8.6-39.5; $p < 0.05$) and at 12 weeks to 15.9 (5.7-40.5) ($p > 0.05$). With few exceptions, serum CRP concentration remained within normal limits before, during and after antibiotic therapy.

Discussion

The change in serum neopterin concentration during antibiotic therapy of Mu disease followed the same pattern as the recovery of gamma interferon secretion reported recently (Ref).

A possible interpretation of these findings is that when mycolactone secretion by Mu is reduced by antibiotic treatment, IFN γ secretion is induced by killed Mu and macrophages secrete neopterin. If this is the case measurement of serum neopterin could be a useful method of monitoring the response to antibiotic treatment. In contrast, serum CRP did not reflect either disease activity or treatment response.

Reference

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Mycolactones in Mycobacterium ulcerans strains: expression and cytotoxic activity quantification

**Paul J. Converse, Deepak V. Almeida, Radhika Gupta, Eric L. Nuermberger,
Jacques H. Grosset**

Mycobacterium ulcerans infection in the footpads of mice results in gradual swelling first apparent 4-6 weeks after infection and progressing to footpad ulceration and loss of the foot. The type (ATCC 14188, DSM 44154, RT, TMC 1617) strain of *M. ulcerans*, isolated in the 1940s in Australia and available through the American Type Culture Collection (ATCC) was used in our experiments examining the effects of BCG vaccination in BALB/c and C57BL/6 mice as well as in chemotherapy investigations. The organism did induce progressive swelling and ulceration but BCG was markedly more effective in protecting BALB/c than C57BL/6 mice, although the latter strain is a typically mycobacteria-resistant mouse strain, and in some cases self-healing was observed. Colleagues informed us that the type strain has lost the ability to produce mycolactone (ML). We, therefore, investigated this issue in the ATCC strain, Mu1617, in comparison with a Malaysian strain, Mu1615, that stably produces ML, a recent clinical isolate from Ghana, Mu1059, and purified ML. Ethanolic extractions of the Mu strains were carried out. Thin layer chromatography analysis revealed the presence of ML in all strains except Mu1617. Cytotoxicity assays using either the J774 macrophage cell line or the L929 fibroblast cell line determined that ethanolic extracts of all strains, including Mu1617, were active against the cells. However, serial dilution of the extracts showed that activity was rapidly lost with increasing dilutions in Mu1617 but not in the other strains. Using tetrazolium (MTT) and neutral red staining approaches, we have been able to correlate extract activity both by microphotography and by determination of optical density, most efficiently with MTT, using an ELISA reader. This approach may enable a simple evaluation of drugs that target ML production without necessarily killing *M. ulcerans*.

Acknowledgement: We would like to thank Dr. Pamela Small and colleagues for provision of strains as well as advice on TLC and cytotoxicity assays. Radhika Gupta was very helpful in carrying out the TLC assays.

Seric cytokines detection in different clinical conditions of Buruli ulcer: preliminary results

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Background

Buruli Ulcer (BU) is a severe disease caused by *Mycobacterium ulcerans* (Mu) characterized by polymorphic cutaneous lesions, ranging from small nodules to wide ulcers and secondary skin or bone involvement. In the last years, several studies have been published investigating also the immune response in BU patients with some controversial results.

Aim

The aim of the present study was to investigate *ex vivo* the Th1 and Th2 cytokine expression in the serum of young patients of endemic areas of Benin, affected by different stages of BU, and to compare it with the seric values of healed subjects and healthy controls.

Materials and Methods

Thirty-four Beninese subjects were enrolled and divided into the following three groups: i) sixteen patients affected by BU (11 males, 5 females; mean age 13,6 years) ii) four patients previously affected by BU, but healed after specific therapy (3 males, 1 female; mean age 18,2), and iii) fourteen healthy subjects (8 males, 6 females; mean age 12,4 years). Furthermore every BU patient was clinically classified according to the lesional morphology (nodule, plaque, ulcer, oedema), duration of the illness, administration period of the standard antibiotic therapy (associated rifampicin and streptomycin) with or without surgery. All the subjects in the study underwent to a 3 mL of whole blood withdrawal, that was immediately processed to obtain serum. The following seric cytokine dosages were detected by a cytometric bead assay: IFN γ , TNF- α , IL-2, IL-10, IL-4, IL-5.

Results

Our study did not show significant variations in the expression of TNF- α , IL-2, IL-10, IL-4 and IL-5, but revealed a significant difference of IFN γ level in patients affected by various clinical situations: in fact, IFN γ reached higher values in the ulcerative than in the pre-ulcerative stage and once more increased values in the group of the recently healed patients; while healthy subjects had a mean level similar to those affected by pre-ulcerative cutaneous lesions ($p=0.02$). We further investigated the cytokine production in relation to the persistence period of the illness, and significant results were seen only for IFN γ levels, that were highest in healed patients compared to affected patients and healthy subjects ($p=0.01$). Interestingly, patients affected by BU by more than 2 months, showed a higher IFN γ level, with a mean value similar to recently healed subjects ($p=0.01$). No correlation was observed between cytokine level and days of standard therapy.

Conclusion

Our preliminary results, even if related to a small number of subjects, confirmed a different cytokine secretion in different clinical stage in BU patients and confirmed a correlation with the length of the illness. In particular, IFN γ was the only cytokine that could be a marker of a more favorable prognosis.

Buruli ulcer, an infection that goes far deeper than the skin: the impact of *Mycobacterium ulcerans* and its toxin on muscle tissue

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Buruli ulcer (BU) is an emerging tropical disease caused by a slow-growing environmental pathogen, *Mycobacterium ulcerans* (*M. ulcerans*). The pathologies caused by it are strongly linked to the cytotoxic effect of the mycolactone secreted by *M. ulcerans* and its modulation of immune response. Biologically, the toxin is responsible for extensive necrosis of cutaneous and subcutaneous tissue, which may evolve towards cure of the tissue by scarring and fibrosis, restricting movement and impoverishing the quality of life of those affected. Empirical observations have also shown that the muscle tissue underlying the necrosis may also be involved. This study was designed to study the impact of *M. ulcerans* and of its toxin on muscle tissue, using mice.

Method

C57BL/6 strain mice were used in two types of experiment. Under one protocol, mice were infected with 10⁵ *M. ulcerans* injected subcutaneously proximate to the biceps muscle on the foreleg. The biceps muscle was chosen because it is a superficial tissue and can as closely as possible mimic the physiopathology of BU. In a second type of experiment, 300 µg of mycolactone were injected into the soleus, a calf muscle. This muscle was chosen because our laboratory is highly familiar with its physiological, histological and immunological characteristics. The mice were then sacrificed after different periods post injection and the biceps and solei muscles dissected and then incubated in physiological solution to analyse their contractile and passive properties, or sectioned for analysis of muscle damage and aggregate leukocyte concentration. Levels of hydroxyproline, a fibrosis indicator, were also measured in certain muscles.

Results

The presence of *M. ulcerans* entailed a reduction of approximately 30% in maximal strength in comparison with the control group. More significant loss of strength (approximately 68%) was registered in the presence of mycolactone. The presence of *M. ulcerans* and of mycolactone was also responsible for a chronic inflammatory response, muscle stiffness and a significant increase of hydroxyproline concentration. Another noteworthy feature is that the presence of mycolactone was responsible not only for muscle damage, but also prevented regeneration of muscle tissue.

Conclusion

Our results indicate that *M. ulcerans* and mycolactone alter the physiological, histological and biochemical properties of the biceps and solei muscles. Other studies will be needed to shed light on the molecular mechanisms underlying the inability of the skeletal muscles to repair themselves in the presence of mycolactone. These experimental results in mice may account for the contractures and other functional sequelae observed in certain subjects affected by Buruli ulcer.

Dynamics and molecular basis of the cytoskeletal rearrangements induced by mycolactone in human cells

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Previous studies have reported that mycolactone induces dramatic changes in the morphology of mouse fibroblasts, resulting from cytoskeleton rearrangements that are detectable within 4 hours of exposure to the toxin (George et al. 1998). Here we show that mycolactone indeed causes profound alterations of the actin dynamics, in multiple human cell types. Cytoskeletal modifications are diverse and include the production of cell surface protrusions (filopodia, lamellipodia, and membrane ruffles), as well as the alteration of focal adhesions and stress fibers. In vitro measurements of actin monomer assembly in the presence or absence of the toxin showed that these effects do not result from a direct interaction of mycolactone with actin, or with the mediator of actin fragmentation gelsolin. In fact, we found preliminary evidence that mycolactone stimulates the activity of the small GTPase-binding protein Rac, a universal regulator of cytoskeletal remodeling. The molecular mechanisms leading to Rac activation by mycolactone are currently investigated.

The toxicity of mycolactone on keratinocytes and means of its reversal

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Mycolactone is an important virulence factor in ulcer formation. Its presence is associated with cell death, extracellular infection and pathology. Mycolactone is cytotoxic to fibroblasts and adipocytes in vitro and has modulating activity on immune cell functions. Fibroblasts and adipocytes undergo cell death involving apoptosis and necrosis after 3-5 days when exposed to mycolactone. The effect of mycolactone on keratinocytes has not been reported previously.

We have investigated effects of mycolactone on human primary skin keratinocyte growth and cell numbers in serum free culture medium. A concentration and time dependent reduction in keratinocyte cell numbers was observed after exposure to mycolactone. This was associated with an altered cell morphology involving cell rounding and detachment. The effect was evident after 48 h of treatment with >100 ng/ml mycolactone. In conclusion, mycolactone is toxic to keratinocytes and this may contribute to the ulceration and poor healing of Buruli ulcers. Studies on the contribution of necrosis, apoptosis and growth arrest in the effect of mycolactone on keratinocytes will be presented as well as the identification of known drug substances that interfere with these effects.

Mycolactone damages also human keratinocytes

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Background

The effect of mycolactone produced by *Mycobacterium ulcerans* on different cell types including inflammatory cells such as neutrophils and macrophages, T cells, fibroblast cell lines and adipocytes has been investigated but no data exists on its effect on human keratinocytes.

The human epidermis maintains a constant cellular turnover based on the presence in the basal layer of a population of keratinocyte stem cells that retains a high capacity of self-renewal throughout life. Stem cells (KSC) generate transit amplifying cells (TA) that terminally differentiate after a discrete number of cell divisions in terminally differentiated TA cells.

Apoptosis plays a fundamental role in epidermal homeostasis

Aim

In our study, we investigate the apoptotic effect of mycolactone A/B in human stem and TA keratinocytes and in HaCat cells (spontaneously transformed human keratinocyte cell line).

Material and method

Normal human keratinocytes were obtained from biopsy specimens from dorsal skin of healthy donors were separated in three populations, cultured and then treated with increasing concentration of mycolactone A/B. We detect apoptosis in KSC and TA cells and in HaCat cell line.

Results

Treatment of KSC and TA cells with mycolactone A/B induced severe apoptosis in dose-dependent manner.

TA keratinocytes were the more sensitive to mycolactone toxic effect.

Mycolactone A/B is less toxic on HaCat.

Conclusion

On the basis of our preliminary research it seems that not only the connective and adipose cells tissues are the target of the toxic action of mycolactone, but that epidermal keratinocytes may be directly involved in the mechanism of *M. ulcerans* infection too.

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