WHO Meeting on Buruli ulcer and other skin NTDs

Final report

25–27 March 2019

WHO Headquarters
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World Health Organization

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Report of the WHO Technical Advisory Group on Buruli ulcer

Geneva, 27 March 2019

1. Introduction

The World Health Organization (WHO) convened a meeting of the Technical Advisory Group on Buruli ulcer at its headquarters in Geneva, Switzerland on 27 March 2019. Dr Mark Wansbrough-Jones (St George's Hospital Medical School, UK) chaired the meeting. Dr Lise Grout, Dr Kingsley Asiedu and Dr Alexandre Tiendrebeogo (WHO) were observers.

2. Membership of the Group

Dr Wansbrough-Jones has decided to step down from chairing the Group but intends to continue participating in future meetings, if invited. Dr Asiedu explained that other members have already stepped down, including Professor Jacques Grosset and Professor Pamela Small, and extended thanks to all past members for their immense contributions.

Membership of the Group should be reviewed and extended to reflect the shifting focus towards integration of activities. All current members were invited to re-express their interest in continuing to serve on the Group; Dr Asiedu has received some new names for consideration. A new Chair will be appointed once the Group has been reconstituted.

Action: Kingsley Asiedu and Group members

3. Integration of activities

Dr Christian Johnson (Fondation Raoul Follereau, France) reported that all endemic countries have initiated integration projects but there is considerable variation among countries. It was recommended that WHO should coordinate the preparation of guidelines on the basis of experience to date and implement them before the next meeting in 2021.

Professor Roderick Hay (International Foundation for Dermatology, UK) pointed out that dermatologists working in sub-Saharan Africa could be persuaded to assist in providing training; the International Foundation for Dermatology (London, UK) holds a list of such individuals. The University of Catalonia (Barcelona, Spain) conducts online training courses for four skin NTDs (Buruli ulcer, cutaneous leishmaniasis, leprosy and yaws), but they would be too expensive for health personnel from endemic countries in Africa (the cost per participant is € 800). This course does not include the other skin diseases (non-NTDs) which account for 90% of the burden. WHO will explore free online courses to reach millions of health workers around the world.

Action: Kingsley Asiedu, Roderick Hay, Lise Grout

4. PCR confirmation of cases

Data presented at the meeting showed a continuing poor rate of confirmation of Buruli ulcer cases by PCR. In the known areas with consistently poor performance, achieving improvement has proven difficult. The Group strongly recommended that the causes of poor performance be thoroughly investigated and resources increased in such areas since unconfirmed case reports are of little value.
In future, supplies of antibiotics will be linked to the number of laboratory-confirmed cases of Buruli ulcer.

Action: Kingsley Asiedu, National Programme Managers

5. Category III lesions

A disappointing increase in reports of Category III lesions was noted. The Group recommended that the reasons for this be carefully analysed in affected countries to involve districts with similarly low rates of case confirmation. National Programme Managers are responsible for ensuring that such districts are identified urgently and resources including further training are provided.

Action: Kingsley Asiedu, National Programme Managers

6. External Quality Assessment Programme

The results of the fourth round of the External Quality Assessment (EQA) Programme were reported during the meeting. Unfortunately, Dr Miriam Eddyani's contract at the Institute of Tropical Medicine (ITM; Antwerp, Belgium) is due to expire in the autumn and she will not be replaced. Professor Bouke de Jong (ITM, Belgium) reported that ITM will be unable to provide further rounds of EQA and recommended that this function be taken on by a laboratory in an African country endemic for Buruli ulcer for a future three yearly rounds. Dr Eddyani expressed her willingness to provide ongoing support in the form of a consultancy. Thanks were extended to Dr Eddyani and Professor de Jong for their input to the EQA programme. The Group recommended that funding be sought from nongovernmental organizations to maintain this vital function. (The cost of the last round was reported as € 68 000 of which € 55 000 was attributed to staffing).

Action: Kingsley Asiedu

7. Fully oral antibiotic therapy

Further support was given during the meeting to the change in recommended antibiotic therapy to the fully oral regimen presented in the trial report. This change has been fully implemented because streptomycin is not available; the information on the WHO website will be updated accordingly when the trial data are published.[1] Professor Tjip van der Werf (University of Groningen, Netherlands) reported the availability of a new formulation containing the combination of rifampicin and clarithromycin.

Action: Kingsley Asiedu to check current information on the website and explore the possibility of supplying the new formulation routinely. Professor van der Werf and Dr Richard Phillips to move towards early publication of data.

8. Funding for research

Researchers have experienced increasing difficulty in raising funds for research. Professor Tim Stinear (University of Melbourne, Australia) noted that a contributing factor could be the lack of major political advocacy since the Yamoussoukro meeting in 1998 attended by three West African Heads of State. A further problem may be a perception by funding bodies that the incidence of Buruli ulcer disease is in decline. It was agreed that this false perception should be countered at every opportunity.
Action: Kingsley Asiedu to consult on the best way forward.

9. WHO electronic data reporting system

It was recommended that data reported to WHO from endemic countries should be submitted entirely through the electronic data system, as reported by Dr Lise Grout (WHO), by the time of the meeting in 2021.

Action: National Programme Managers, Kingsley Asiedu, Lise Grout

10. GeneXpert

The Group recommended that the possibility of adapting GeneXpert to detect *Mycobacterium ulcerans* should be explored.

Action: Kingsley Asiedu to check with FIND (the Foundation for Innovative New Diagnostics).

Members

Pierre Couppié, Bouke de Jong, Gabriel Diez, Miriam Eddyani, Roderick Hay, Christian Johnson, Paul Johnson, Richard Phillips, Gerd Pluschke, Françoise Portaels, Paul Saunderson, Ghislain Sopoh, Ymkje Stienstra, Tim Stinear, Alphonse Um Boock, Tjip van der Werf, Mark Wansbrough-Jones (Président)

Observers

Kingsley Asiedu, Lise Grout, Alexandre Tiendrebeogo

[1] Treatment. In: Buruli ulcer (*Mycobacterium ulcerans* infection) [WHO fact sheet] (https://www.who.int/en/news-room/fact-sheets/detail/buruli-ulcer-(mycobacterium-ulcerans-infection).

Summary of the control sessions

Integrated approach to skin NTDs

- The meeting noted with satisfaction the progress being made in countries to implement an integrated approach to skin NTDs (e.g. for cutaneous leishmaniasis, Buruli ulcer, leprosy, scabies and yaws) as well as other common diseases of the skin (e.g. fungal skin infection). Experiences were reported from Benin, Cameroon, Côte d'Ivoire, Ghana, Liberia and Togo.
- To accelerate integration, WHO should coordinate the preparation of guidelines to assist countries in standardizing the approach (implementation, data collection, reporting) to achieve comparable results from one country to another.
- Free online training courses targeting millions of frontline health workers should be developed to build capacity for diagnosis and management of skin diseases.
- National programmes are encouraged to collaborate with national networks of dermatologists to benefit from their expertise and support.

Buruli ulcer

- The number of new cases of Buruli ulcer appears to be decreasing in most countries in Africa, but not in Australia (635 cases in 2017 and 2018). The causes of this decline should be investigated while simultaneously enhancing active surveillance to ensure that cases are not just being missed.
- The high proportion of category III lesions in most countries reflects inadequate early case detection activities.
- Confirmation of cases by PCR is still poor, and much work remains to be done. Given the decreasing number of new cases and the resources available for control activities, the low rate of confirmed cases reported by national control programmes is no longer acceptable.

Yaws

- Cases of yaws confirmed by the dual path platform (DPP) test are reported from Benin, Cameroon, Central Africa Republic, Côte d'Ivoire, Ghana and Liberia, demonstrating active efforts to confirm cases.
- Countries are encouraged to continue active and passive surveillance and to confirm suspected cases by rapid tests (SD Bioline and DPP). If cases test positive, it is recommended to collect samples for PCR (to monitor resistance at baseline).
- Countries that have already confirmed cases and mapped the endemicity of yaws should develop and implement national eradication plans. These countries can request technical support from WHO for this purpose.

DHIS2

- National programmes are encouraged to use the DHIS2 data management platform for case reporting.
- WHO is available to assist national control programmes for this purpose if requested.
- Starting from January 2020, data for Buruli ulcer and yaws will be reported through a DHIS2 platform.

Recommendations

WHO

- Provide technical support for:
  - development and implementation of yaws eradication plans adapted to national contexts;
  - effective use of the DHIS2 platform; and
  - coordination of standardization of tools used by countries in integrated screening (planning, implementation, reporting forms, wound management, etc.).

Partners

- Continue support to countries including for:
  - confirmation of BU cases;
  - supply of rapid diagnostic tests for yaws; and
  - planning and financing of integrated activities

National programmes

- Note the importance of laboratory confirmation of Buruli ulcer cases: countries are strongly recommended to increase the rate of laboratory confirmation (at least 70%). In future, supplies of antibiotics will be linked to the number of laboratory-confirmed cases.
- Use the DHSI2 platform for case reporting.
- For countries that have notified yaws, develop and implement the National Yaws Eradication Plan.
- Continue integration activities.

Summary of the research sessions

There was a total of 28 research presentations covering diagnostics, transmission, treatment and pathogenesis.

There has been steady progress towards a point-of-care antigen detection test, based on antibodies specific to mycolactone. Diagnostic advances also include a portable laboratory set-up, based on an isothermal DNA amplification assay and all necessary equipment packed into two "suitcases". Such equipment could be deployed in medical centres at the periphery to support BU diagnosis.

Studies of transmission continue with a report confirming known environment risk factors for BU, but notable because the study was conducted in Nigeria, reflecting growing BU activities in that country. A case-control study in Benin linked access to fresh-water bores to reduced BU risk. An Australian research team reported on a cluster randomized controlled field mosquito intervention trial currently underway to try and disrupt BU transmission. The trial has just begun and results will become available over the next 24 months.

Compared to 2017, there were relatively few presentations on fundamental research to understand pathogenesis of *M. ulcerans* infection, with data presented reinforcing previous research that has shown mycolactone binds a host protein called Sec61 and that this interaction substantially explains the immune dysfunction and cytotoxicity of mycolactone. There is growing evidence too that mycolactone disrupts the endothelium and is involved in coagulative necrosis.

New options for antibiotic treatment were also presented. The findings from a large RCT to test an all-oral antibiotic combination of clarithromycin and rifampicin (CR8) showed non-inferiority to streptomycin and rifampicin (SR8). Data on a new antibiotic called Q203 were also presented, showing the exquisite sensitivity of *M. ulcerans* to this compound. This new antibiotic appears to synergise well with rifampicin (rif).

There were data presented too on antibiotic course shortening regimens involving Q203 with rif, or high dose rif alone, and also the potential for triple-oral beta-lactam regimens to treat *M. ulcerans* infection.

Day 1

Plenary sessions

In memoriam: Dr Wayne Marvin Meyers

Presented by Professor Françoise Portaels

It is with deep sadness that I inform you of the passing of Dr Wayne Marvin Meyers at Laurel, Maryland, on 12 September 2018.

Born at Huntingdon in rural Pennsylvania, he graduated with a BSc in chemistry in 1947, a Master's and PhD in Microbiology from the University of Wisconsin in 1953 and 1955, and a degree in medicine from Baylor College of Medicine (Houston, Texas) in 1959.

His great interest in humanitarian medicine led him to engage in missionary work for the American Leprosy Missions (ALM) with his wife, Esther Kleinschmidt, In 1961, Dr. Meyers was appointed Medical Director of the Nyankanda Leprosarium (Burundi), and in 1962 he took charge of the leprosarium at Oicha Hospital in Kivu (Congo). In 1965, ALM sent Dr Meyers and his family to Bas-Congo, where until 1973 he was director of the Kivuvu Leprosarium attached to the Evangelical Medical Institute (IME) at Kimpese. During this time, Dr Meyers developed outpatient services and decentralized the management of leprosy to 20 centers that he visited regularly. In addition to leprosy, Dr Meyers also dealt with other tropical diseases such as Buruli ulcer (BU), filariasis, yaws and onchocerciasis. At the IME, Dr Meyers set up a laboratory where *Mycobacterium ulcerans* was first cultivated in a rural setting.

I made the acquaintance of Dr Meyers and his family in 1971 when I was conducting a doctoral research project on mycobacteria in the environment and the reservoir of *M. ulcerans*.

In 1973, the Meyers family left Congo to settle in Honolulu where Dr Meyers was appointed Professor of Pathology at the University of Hawaii.

In 1975, he was hired by the Armed Forces Institute of Pathology (AFIP) at the Walter Reed Medical Center in Washington, DC. He was appointed Director of the Microbiology Division and head of the Leprosy Registry for the American Registry of Pathology. Through his efforts, the American Registry of Pathology now contains the world's largest collection of well-documented tissues of leprosy patients.
In 1988, Dr Meyers was elected President of the International Leprosy Association (ILA) for a period of 5 years.

He retired in 2005 but remained active as a visiting scientist in research and the writing of scientific works, as well as in teaching.

At AFIP, Dr Meyers focused mainly on the histopathology of infectious diseases. Together with other colleagues including myself, he was involved in research on leprosy in wild animals (monkeys and nine-banded armadillos). For the first time, it was postulated that leprosy might be a zoonosis. We now have have sufficient microbiological and epidemiological evidence to consider leprosy a zoonosis, at least in the southern United States.

In addition to leprosy and other tropical diseases, Dr Meyers took a keen interest in BU. With his AFIP colleagues, he discovered that *M. ulcerans* produces a toxin with cytotoxic and immunosuppressive properties, an important factor in virulence.

In 1991 Dr. A Guédénon, Director of the Beninese Leprosy Control Program, informed us of a recrudescence of BU in Benin. An important body of research was then being undertaken in collaboration with Dr. Guédénon, AFIP, the Antwerp Institute of Tropical Medicine (IMT), the Gbemontin Health and Nutritional Centre of Zagnanado and a number of Beninese researchers, covering such diverse areas as geographical distribution, disease incidence and prevalence, mode of transmission, pathogenesis, clinical manifestations, differential diagnosis and laboratory diagnosis.

Dr Meyers (co) authored more than 400 scientific works including publications in peer-reviewed journals, and a number of chapters and monographs.

In Africa and the United States, Dr Meyers trained generations of students, doctors, researchers and health professionals with skill, patience and humility, regardless of the level of his students. His encouragement and advice, always constructive, as well as his considerable generosity, approachability and his qualities as a teacher always impressed me.

Those who had the privilege of knowing and working with him will remember Wayne Meyers as a man open to the world, with a great sense of humour, even in sometimes difficult situations, which I personally witnessed on a number of occasions.

A great man has passed away, an endearing personality, an outstanding pathologist, a doctor at the service of the poor and dedicated to his patients, from whom we can all draw inspiration. In addition to making medical and scientific contributions, Wayne deepened his knowledge of different cultures through his numerous travels, stays and residence in many countries.

As Dr Asiedu recently wrote: *"He touched our lives in many ways and we are profoundly grateful for his decades' long devotion to BU and leprosy"*.

With his passing we have lost a great doctor, a brilliant scientist and, for me personally, a valued collaborator and friend of almost 50 years.

Françoise Portaels, Emeritus Professor, Antwerp Institute of Tropical Medicine and Brussels Free University (VUB), Belgium.

Buruli ulcer in Australia, 2017-18

Presented by Paul Johnson

Paul Johnson,[1,3] Ee Laine Tay[2, 3], Maria Globan[3], Caroline Lavender[3], Janet Fyfe.[3]
1. Department of Infectious Diseases, Austin Health & University of Melbourne, Australia
2. Department of Health and Human Services (Victorian State Government)
3.Victorian Infectious Diseases Reference Laboratory and WHO Collaborating Centre for Mycobacterium ulcerans, Peter Doherty Institute for Infection and Immunity, Melbourne, Australia.
Acknowledgement: We thank Bridget O'Connor and her colleagues; Mycobacterial Reference Laboratory, Brisbane, Queensland.

Overview

635 incident human cases of Buruli ulcer were diagnosed in 3 Australian states in 2017-18; all but 15 were acquired in Victoria (temperate southeastern Australia). One additional case from Tabubil in PNG was confirmed by PCR at the Mycobacterium Reference Laboratory in Brisbane in 2017 (6 cases from the same region were reported in 2015-16). There were 3 confirmed Buruli cases in animals, all from Victoria in 2018 (2 ringtail possums, 1 domestic dog).

Figure 1.
Map of Australia showing established areas of M. ulcerans transmission. Graphs show activity by year 2014-2018 in the two most active endemic regions.

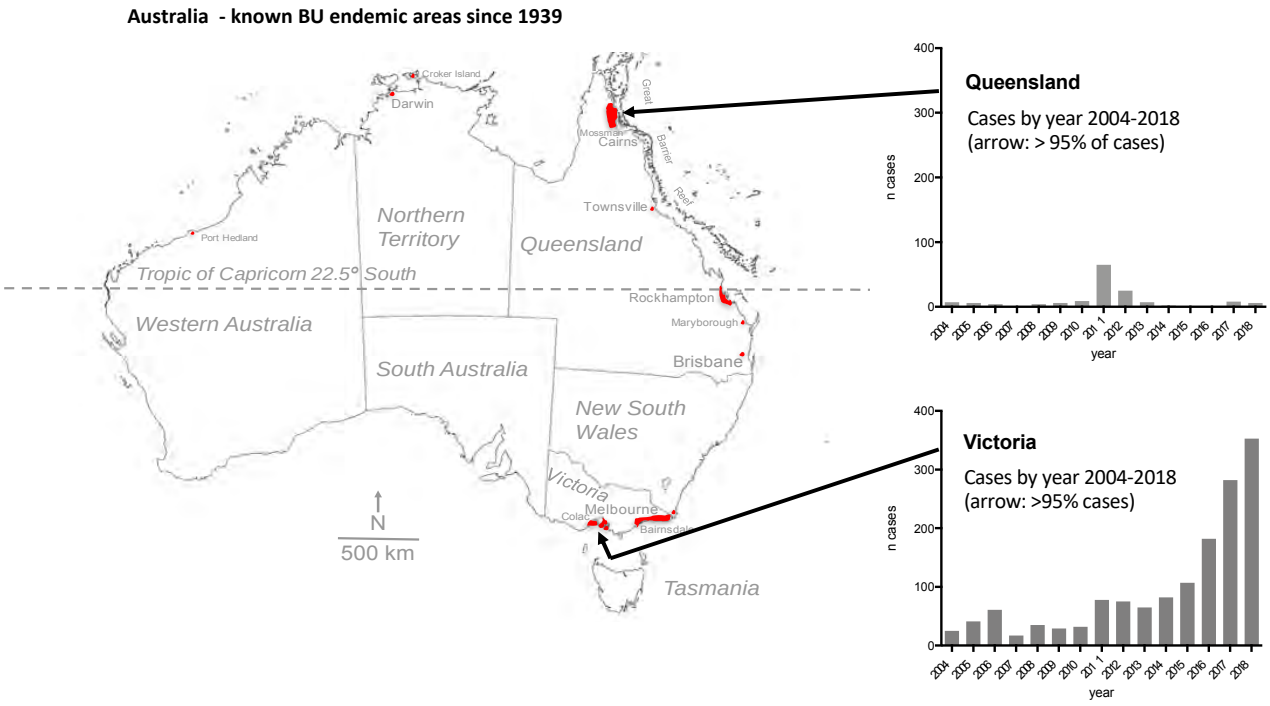
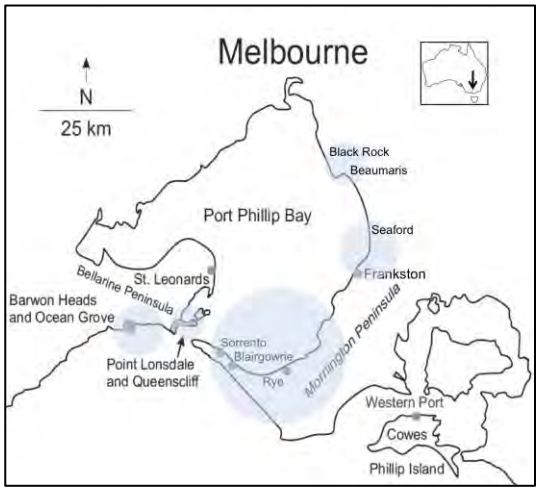


Figure 2. *Main endemic areas near Melbourne. Circle-areas are proportional to notifications 2017-18.*



In **Victoria** the exponential increase in cases that began in 2014 has continued with 282 diagnosed in 2017 and 353 in 2018. The rapid increase in Victoria has caused significant local concern in affected endemic areas – predominantly on the Mornington Peninsula, Frankston and surrounds, and the southeastern bayside suburbs of Melbourne as far north as Black Rock and Beaumaris. Cases are still being linked to towns on the Bellarine Peninsula (Point Lonsdale, Queenscliff, Ocean Grove, Barwon Heads, St Leonards) although Buruli may now be declining in this region. For example in 2011, 27 cases were linked to Point Lonsdale compared with only 5 in 2018. Most diagnoses are made in the southern winter but when adjusted for a median incubation period of 4.5 months and an estimated diagnostic delay of 1-2 months, transmission appears to peak in mid to late summer. Buruli ulcer on Phillip Island, scene of a significant local outbreak 1992-98, has become rare. Possum excreta surveys have demonstrated widespread *M. ulcerans* contamination of the local environment in human outbreak areas.

Buruli ulcer in the endemic region in far north Queensland Australia

Presented by Dr Christina Steffen

Cairns & Hinterland Hospitals and Health Service District, Queensland, Australia.
(Queensland Health)

Twenty-one cases of *M. ulcerans* were confirmed from 1/1/2013 to 31/12/2018. Numbers ranged from no (0) cases in 2016 to 8 cases in 2017, exemplifying the sporadic but persistent manifestation of *M. ulcerans* infection in this endemic area.

Nineteen of 21 cases were residents of the endemic area, with three from Julatten, a new focus within the endemic area.

All cases were confirmed with PCR. There were 3 nodules, 14 ulcers and 4 ulcerated plaques. One patient had two nodular lesions. All ulcers were less than 5cm in diameter. All ulcerated plaques were 5-15cm. Age range was 7 to 88 years, average 50 years, median 50 years. Twenty of the 22 lesions were located on extremities (lower limb 14, upper limb 7, trunk 2).

All patients were offered antibiotic treatment consisting of oral Rifampicin and Clarithromycin with intention to treat for eight weeks. Eleven (11) patients completed antibiotic treatment with two agents. A further 5 patients received partial antibiotic treatment only, 3 due to intolerance and 2 for other reasons. Antibiotics were contraindicated in one patient with recent *Clostridium difficile* colitis. Four refused antibiotics and requested primary excision of their ulcer.

Eight patients healed their lesions with antibiotics alone. Narrow excision was performed in 11 patients, (5 primary excisions and no antibiotics, 4 in conjunction with partial antibiotic treatment, and 2 for wound closure). Two cases (2017) underwent debridement and skin grafting and a further two from 2018 require debridement and grafting for large ulcerated plaques.

Universal access to surgical intervention results in prompt management of small lesions where antibiotics are contraindicated or not tolerated, and of larger lesions following antibiotic treatment to expedite wound healing and return to full physical and social functioning.

No recurrences at twelve months have been recorded for the 2013-2016 cohort. Twelve month follow up is not complete for the 2017 and 2018 cohort.

Buruli ulcer in Australian children

Presented by N. Deborah Friedman

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Introduction

To date, there have been no large-scale studies of Australian paediatric Buruli Ulcer (BU). We aimed to describe the epidemiology, clinical presentation, diagnosis, treatment and outcomes in paediatric BU patients in a large Australian prospective cohort.
Methods:
Analysis was performed of a prospective cohort of all BU cases managed at Barwon Health, Victoria, from 1/1/1998-31/5/18. Children were defined as ≤ 15 years of age. Severe lesions included those categorized as WHO II or III.

Results

The study population included 565 patients: 52 (9.2%) children, 289 (51.2%) adults aged 16-64 years and 224 (39.7%) adults aged ≥ 65 years. For children, 26 (50%) were female and the median age was 8.0 years (IQR 4.8-12.3 years), although cases occurred across all age-groups; 20 (38.5%) were aged 0-5 years, 12 (23.1%) aged 6-10 years and 20 (38.5%) aged 11-15 years. Six (11.5%) cases were diagnosed from 2001-2006, 14 (26.9%) 2007-2012 and 32 (61.5%) 2013–2018. Although the total case numbers increased, the proportion of children in the cohort was stable over time.

In children, lesion position was similar to adults with 69.2% on lower limbs, 28.9% on upper limbs and 1.9% on the head or trunk. Children had a significantly higher proportion of non-ulcerative lesions compared to adults [32.7% compared to 8.7% for adults aged 16-64 and 17.9% for adults aged ≥65 ($p<0.001$)] and a higher proportion of severe lesions [(26.9%) compared with adults aged 16-64 years (19.8%), $p<0.01$]. The median duration of symptoms prior to diagnosis was shorter for children (42 days, IQR 28-60 days) compared with adults aged 16-64 years (56 days, IQR 30-84 days, $p=0.04$). Children had a significantly lower proportion of multiple lesions (1.9%) than adults (5.5%, $p=0.04$).

There was a significantly lower proportion of children who experienced antibiotic complications (6.1%) compared to adults (20.6%, $p<0.001$). Children had a significantly higher rate of paradoxical reactions (38.8%) compared to adults aged 16-64 (19.2%) ($p<0.001$) and paradoxical reactions in children occurred significantly earlier than in adults (median 17 days, IQR 14-62 days, compared to 56 days, IQR 29-80 days, $p<0.01$).

Cure rates were similarly high for children compared to adults treated with antibiotics alone (96.4%, $p=0.18$) or with antibiotics and surgery (100%, $p=0.52$). However cure rates were significantly higher for children compared with adults when treated with surgery alone (100% compared with 44.4% for adults aged ≥65, $p<0.01$).

Conclusions

BU cases in Australian children are increasing and represent an important but stable proportion of Australian BU cohorts, although a smaller proportion compared with Africa. Compared with adults, there are significant differences in clinical presentation and treatment outcomes that are important to understand for optimal BU diagnosis and treatment in Australian children.

Buruli ulcer control activities in Côte d'Ivoire in 2017-2018

Presented by Henri Assé

National Buruli Ulcer Control Programme, Côte d'Ivoire

Key activities in 2017 and 2018

1. Integrated epidemiological surveillance

Passive, community-based Buruli ulcer screening is a routine activity carried out by community liaison workers who refer suspected cases to peripheral health centres for clinical confirmation and appropriate case management. Epidemiological surveillance activities include regular active integrated screening for neglected tropical diseases with skin manifestations. Over the last two years, eight integrated screening campaigns for neglected tropical diseases with skin manifestations have been carried out in the six health districts of Divo, Yamoussoukro, Sakassou, Beoumi, Soubré and Gagnoa. These campaigns were launched in collaboration with the National Programme to Eliminate Leprosy and targeted Buruli ulcer, leprosy and yaws.

2. Managing screened cases of Buruli ulcer

Screened cases of Buruli ulcer are managed at peripheral health facilities in endemic health districts. We believe that community-based care is an important component of Buruli ulcer control. Only complex cases are referred to specialist centres for medical care or surgery.

Results

1. Results of Buruli ulcer control activities in 2017 and 2018

The epidemiological variables are summarized in the table below.

YEAR	BU cases	Antibiotics (%)	Child aged 15 or under (%)	Joint limitation (%)	Ulcerative (%)	Category I (%)	Category II (%)	Category III (%)
2018	261	100	44.44	10.63	75.1	34.87	38.7	26.43
2017	344	100	48.25	9.59	67.44	32.26	40.12	27.62

2. Results of integrated control activities

Eight screening campaigns were carried out in the form of mobile consultations within health districts. Twice as many cases of leprosy were screened during these campaigns in comparison to cases of Buruli ulcer. We also confirmed cases of yaws in all six health districts.

Health district	Number of individuals presenting with skin lesions observed	**DDP-confirmed yaws**	**Buruli ulcer**	**Leprosy**
Divo	1268	**6**	**3**	**4**
Yamoussoukro	458	**5**	**0**	**1**
Sakassou	764	**3**	**1**	**2**
Béoumi	344	**3**	**2**	**4**
Soubré	1163	**6**	**1**	**3**
Gagnoa	1301	**21**	**2**	**5**
Total	**5298**	**44**	**9**	**19**

Analysis

Strategy for the control of NTDs with skin manifestations

Integrated activities aiming at controlling NTDs with skin manifestations, namely Buruli ulcer, leprosy and yaws, have allowed us to pool resources and expand the provision of care to the community, strengthening and sustaining the epidemiological surveillance of these diseases.

Incidence of Buruli ulcer

The number of reported cases of Buruli ulcer has steadily declined in Côte d'Ivoire on the whole and in all endemic districts since 2010. Half of all Buruli ulcer cases reported in endemic districts in 2018 were recorded in the districts of Sinfra, Daloa and Oumé. Since 2016, six health districts in which Buruli ulcer was initially endemic have reported no cases of Buruli ulcer.

Clinical forms of Buruli ulcer at screening

Despite the significant uptake in early screening, we continue to note a relatively high proportion of ulcerative forms. Efforts should be made to reduce ulcers, which are the worst effect of this disease.

Discussion

Over the next few years, Buruli ulcer control should focus on:

- Intensifying the integrated surveillance of neglected tropical diseases with skin manifestations;
- Reducing the prevalence of ulcerative forms;
- Finalizing the mapping of yaws;
- Implementing other interventions towards yaws eradication; and
- Preserving gains made in the fight against Buruli ulcer, in particular the decline in the incidence of the disease.

Six versus eight weeks of antibiotics for small *Mycobacterium ulcerans* lesions in Australian Patients.

Presented by Daniel P. O'Brien

Daniel P O'Brien[1,2,3#], N Deborah Friedman[1], Raquel Cowan[1], Aaron Walton[1], Eugene Athan[1,4].
Department of Infectious Diseases, Barwon Health, Geelong, Victoria, Australia[1]; Department of Medicine and Infectious Diseases, Royal Melbourne Hospital, University of Melbourne, Melbourne, Victoria, Australia[2]; Manson Unit, Médecins Sans Frontières, London, United Kingdom[3]; School of Medicine, Deakin University, Geelong, Australia[4].

Aim

M. ulcerans causes necrotizing infections of skin and soft-tissue. Antibiotics are highly effective in curing lesions, but in Australian populations are associated with significant toxicity. We aimed to assess in those not undergoing surgery whether six weeks compared with the currently recommended eight weeks duration of combination antibiotics was effective treatment for small *M. ulcerans* lesions.

Methods

M. ulcerans cases from a prospective observational cohort at Barwon Health, Victoria, treated with antibiotics alone from 1/10/10-31/3/18 were included in the study. Patients were included in the six-week antibiotic group if they received ≥ 28 days and ≤ 42 days of antibiotics and were included in the 8-week antibiotic group if they received ≥ 56 days of antibiotics. Only WHO category 1 lesions and lesions ≤ 1600 mm^2 in size were included. Treatment cure was defined as complete healing of the *M. ulcerans* lesion following treatment without the occurrence of a culture positive *M. ulcerans* recurrent lesion within 12 months of commencing antibiotic treatment.

Results

Two hundred and seven patients were included in the study; Fifty-three (25.6%) in the six-week group and 154 (74.4%) in the eight-week group. The median age of patients was 53 years (IQR 33-69 years) and 100 (48.3%) were female. 41.7% of patients had lesions ≤ 400 mm^2 in size and 93.2% of lesions were ulcerative. Initial antibiotic regimens used were rifampicin and clarithromycin in 66.7% and rifampicin and ciprofloxacin in 31.4% of cases respectively. Patients in the six-week group were significantly more likely to be female (62.3% compared with 43.5%, p=0.02), and have significantly smaller lesions at diagnosis (65.1% compared to 26.2% ≤ 400 mm^2 in size, p<0.001).

Fifty-three patients (100%) achieved treatment cure in the six-week group compared with 154 (99.4%) in the eight-week group (p=0.56). No patients died or were lost to follow-up during the study. Median time to heal was 70 days (IQR 60-96 days) in the six-week compared with 128 days (IQR 95-173 days) in the eight-week group (p<0.001).

Conclusions

For small *M. ulcerans* lesions in Australian patients, six weeks may be as effective as the currently recommended eight weeks duration of combined antibiotic therapy in curing lesions without surgery. This offers the potential to reduce treatment toxicity without compromising effectiveness.

Fourth round of External Quality Assessment Program (EQAP) of molecular detection of *Mycobacterium ulcerans* in clinical specimens

Presented by Miriam Eddyani

Miriam Eddyani, Wim Mulders, Kristina Fissette, Willem-Bram De Rijk, Francoise Portaels, Bouke C. de Jong

Institute of Tropical Medicine, Antwerp, Belgium

In 2018, we organized the fourth round of the biennial External Quality Assessment Program (EQAP), with the objective to assess the proficiency of laboratories in the detection of *Mycobacterium ulcerans* DNA. Laboratories could also compare their performance with the three previous rounds, organized since 2009.

While not accredited, this proficiency testing scheme is designed following the ISO/IEC 17043:2010(E) standard for proficiency testing. All information supplied by participants is treated as confidential and participants are encouraged to provide their results to relevant stakeholders such as their National BU Control Programs, WHO, and any clinical trial teams they may support with BU diagnostic services.

The panel consisted of 34 suspensions of clinical specimens, which had been selected to allow assessment of sensitivity (false negatives), specificity (false positives), and inter-laboratory reproducibility. All suspensions were sent in duplicate to assess intra-laboratory reproducibility. Consensus values of four expert participants who had ≥97% concordant results in the 3 previous rounds were used as reference standard. We also distributed serial dilutions of genomic *M. ulcerans* DNA. Testing both specimen suspensions and DNA extracts allowed laboratories to evaluate the performance of DNA extraction and PCR amplification separately. Participating laboratories were asked to process the EQAP panel by the method routinely used in their laboratory for molecular detection of *M. ulcerans* in clinical specimens.

In this fourth round, 18 laboratories participated which was more than in any of the previous rounds. Five laboratories had participated in all 4 EQAP rounds. The participating laboratories were located in 13 countries on 3 continents and represented reference-, academic-, private- and hospital laboratories.

Nine (50%) laboratories reported a concordance of ≥97%. The proportion of correct qualitative results varied between 44% and 100% by laboratory. Nine (50%) laboratories reported false positive results, indicating problems of specificity most probably due to DNA contamination. More laboratories than usual reported a worrisome number of false positive results. These laboratories had all processed more than 100 clinical samples in 2017. Four (22%) laboratories reported a concordance in microscopy positive samples < 95%, indicating problems of sensitivity. Six (33%) reported both false positive and false negative results. Reproducibility within laboratories (intra-laboratory reproducibility) ranged from 50% to 100%. Two participants made clerical errors.

The trend towards an improved median performance of participating laboratories over the four rounds is encouraging, suggesting that patients are now more likely to receive correct diagnostic results. However, in this fourth round some laboratories had an unusually weak performance.

While PCR has much enhanced the sensitivity of BU diagnostics, quality assured microscopy remains an indispensable technique. Not only is microscopy available at the peripheral level, the monitoring of qPCR results also requires the interpretation alongside microscopy results. Moreover, since in four laboratories PCR results are no more sensitive than microscopy results, PCR has no added diagnostic value unless the sensitivity of the technique is increased. Similarly, laboratories that reported false positive results may resort to microscopy while resolving contamination issues.

The results of this sequential multicenter EQAP emphasize the importance of sustaining this program on a regular basis. For future rounds, a new organizer in a BU endemic country will be appointed by WHO among the two consistently best performing laboratories. Increased technical assistance for improved performance of selected laboratories by the best performing laboratories is another priority.

Rationale approach for effective wound care in Benin and Côte d'Ivoire: towards a multidisciplinary approach for the integrated management of Neglected Tropical Diseases with cutaneous manifestation.

Presented by Christian Johnson

Roch Christian Johnson[1]; Gabriel Diez[2]; Silvia Santos[2]; Jean Gabin Houezo[3] ; Henri Asse[4] ; Simplice Djakeaux[5] ; Ghislain Emmanuel Sopoh[6] ; Mark Nichter[7]

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Introduction

Wounds are the manifestation of several Neglected Tropical Diseases (NTDs) such as Buruli ulcer (BU), leprosy and yaws as well as several non-communicable diseases (diabetes, sickle cell disease). Wound care is recognized by the World Health Organization (WHO) as a cross-cutting issue of the control of NTDs. Those wounds are an important public health problem in West Africa due to their high prevalence, degree of suffering and socio-economic consequences for both households and health system. During a BU outreach program in Bénin, in the course of detecting 300 cases of BU, over 2000 wounds were detected. Inadequate management of wounds threatens significant gains in the fight against NTDs. The current project "rationale approach for effective wound care in Benin and Côte d'Ivoire" aims i) to collect baseline data on existing wound care practices in clinics, as well as data on home-care and health care seeking behaviour for wounds in community settings in Bénin and Côte d'Ivoire; ii) to develop basic wound care guidelines; instruments and interventions for wound management; iii) to develop training in wound care management and outreach education for community members leading to better self-care practices; iv) to conduct a proof of concept (feasibility) study followed by a pilot study to test the effectiveness of clinic-based training and community based wound care outreach education.

Method

This project has been developed with a transdisciplinary approach by bringing together the both medical and social sciences. The methods used during this research are structured into 2 components: a multi stage formative research was conducted using a variety of qualitative data collection methods to gather information on wound management in community and clinical settings in Benin and Côte d'Ivoire. Methods employed include free listing, semi-structured interviews, collection of illness narratives, case studies, card sorts using photographs of wounds and medications, observations of wound care practices and a confederate study where patient-actors will ask healers and medicine sellers for treatment advice for afflicted family members. In addition; an intervention-oriented research were designed to develop, validate and implement a wound care awareness and training program. Pre and post wound care knowledge and practices were also evaluated.

Results

In the course of this project, using baseline informations collected through a multidisciplinary approach, instruments were developed for interventions to address issues related to wound care and skin related NTDs management. The direct results of this project can be summarized in 4 points :i) an evidence based culturally sensitive wound care guidelines and skin NTDs modules for communities and health centers were developed; pretested and validated. ii) The instruments developed were used to organize 28 outreach educations for communities and training of 18 health staff on wound care management and skin NTDs in the both two countries. iii) A cohort of 305 cases of wounds were recorded and followed (70% of healing during midterm assessment). During the implementation of the project 1582 skin conditions; 70 leprosy patients; 38 BU and 7 yaws were also detected and managed. The results of this project are not limited to the number of patients screened. It also helped to network the community, health workers and researchers which allowed for a strengthening of the health system. iv) As far as capacity-building concerned; 2 PhD and 4 masters students were enrolled in the project. These students will strengthen the program staff of both countries, thus contributing to the sustainability of the national programs of the two countries. In addition, this project allowed rich exchange of experiences between the PNLLUB of Benin and that of Côte d'Ivoire. It has also enabled the various partners supporting the two countries to develop collaborations and pool their resources for the fight against cutaneous NTDs in both countries.

Conclusion

This project brings together the community, researchers in medical and social sciences, health workers; the ministries of health of two countries, universities of the North and of the South and international NGOs in the same process to jointly address a health problem in an evidence-based approach.. It allowed developing and testing a community and clinic-based wound care management pilot interventions in Benin and Côte d'Ivoire. After conducting training and community outreach in both two countries and evaluating the effectiveness of the intervention, we believe that the model tested in this project can serve as an example for developing regional interventions in the fight against cutaneous NTDs in West Africa.

Wound management in communities in Benin and Côte d'Ivoire: findings from the pilot study

Presented by Anita C. Wadagni

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Introduction

Wounds are a public health problem in West Africa and are associated with several neglected tropical diseases. Patients with wounds tend to opt first for self-care and later access peripheral health centres as their first point of contact with the health system. Here we report the findings and perspectives obtained through a pilot study on improving wound management at the community level and in primary health care centres.

Method

This is a quasi-experimental "before-and-after" study involving the implementation of interventions in Benin and Côte d'Ivoire between January 2017 and December 2018. The study was carried out in several stages:

1. Initial data collection;
2. Development of training and follow-up tools;
3. Implementation of interventions; and
4. Post-intervention evaluation.

This study reflects on the presentation of findings resulting from the implementation of interventions, which process consisted of the following activities:

- Training health workers in diagnosis;
- Treating and monitoring wounds;
- Raising awareness among the community of good home-based wound care practices; and
- Organizing mobile consultations with a cohort of patients presenting with wounds divided into three groups (those with simple wounds that could be treated at home, those with wounds that could potentially be treated at home and those with wounds that should be treated at a health centre) and monitoring the evolution of their wounds.

Results

Eighteen health workers were trained in 11 modules. An analysis of tests taken before and after training revealed improvements in the overall awareness of health workers trained in both countries. Ten awareness-raising sessions were held in both countries and targeted 2224 individuals. These were followed by ten mobile consultations that permitted the diagnosis of 850 people with skin diseases, of which 303 (35.65%) presented with wounds. These were grouped into three categories: 194 simple cases, 62 suspicious cases and 47 cases to be followed up at a health centre. By the end of the follow-up period conducted one month after the mobile consultations, 191 of the 194 simple cases treated at home were followed up and the wounds of 152 of those patients (79.58%) had healed. Sixty of the 62 suspected cases to be treated at home were followed up and the wounds of 46 of those patients (76.66%) had healed. Forty of the 47 patients referred to health centres had received medical attention and the wounds of 26 of those patients (65%) had healed. The main reason for failure to follow up with a patient was their movement to another area. Regarding changes in behaviour, 83% (209 out of 251) of patients followed up at home (simple and suspicious cases) had cleaned their wounds with soapy water; 82% (205) had not applied products (such as home remedies, antibiotics and powders) to the wound to ensure that it remained dry; and 81% (203) had correctly applied shea butter to their wounds. However, only 55.37% (139) had appropriately dressed their wounds.

Conclusion

Wound management at the community level has positive effects on healing, helps to avoid complications and relieves the burden on the health system.

Keywords: Wounds, neglected tropical diseases, Benin, Côte d'Ivoire

Skin NTDs – new initiatives

Presented by Roderick Hay

Roderick Hay

Kings College London and the International Foundation for Dermatology

The skin is the first and most readily available source of clues to diagnosis of many conditions including NTDs; helping disease recognition through skin signs has important implications for diagnosis, mapping, disease control and minimisation of stigma. The development of a new WHO guide to Skin NTDs and common skin conditions is an important step in empowering field teams to recognise the common morphological signs through four diagnostic pathways, take steps to confirm the diagnosis and, in the case of common skin disease, initiate treatment. It is available in English http://apps.who.int/iris/bitstream/handle/10665/272723/9789241513531-eng.pdf?ua=1 , French, Spanish, Portuguese and Arabic. The range of possibilities that have now arisen has been summarised in a special, issue of Tropical Medicine and Infectious Disease . It demonstrates the different methods of training local health care workers, supporting their diagnoses through devices and telemedicine, it provides updates on dilemmas in laboratory diagnosis of key disease such a leprosy and the reality of mass or individual treatment.

The issue can be found at this site - https://www.mdpi.com/journal/tropicalmed/special_issues/Skin_NTDs. It is intended that these developments will lead on to further work on training techniques, evaluation and data mapping as well as revising treatments to ensure that affordable but high quality products are available globally.

The main assessment criteria were changes in behaviour and wound healing time. Data collected during training, awareness-raising activities and mobile consultations were used to conduct a descriptive analysis.

Update on AFRO integrated strategy for case management of five neglected tropical diseases (Buruli ulcer, human African trypanosomiasis, leishmaniasis, leprosy and yaws) in the WHO African Region

Presented by Alexandre Tiendrebeogo

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Objectives

Further to the adoption of resolutions on Neglected Tropical Diseases (NTDs) by the World Health Assembly and the Regional Committee for the WHO African Region, an integrated strategy for addressing five Case Management (CM) NTDs: Buruli ulcer, Human African Trypanosomiasis, Leishmaniasis, Leprosy and Yaws, was promoted by the WHO Regional Office for Africa (AFRO). The objective of this integrated strategy was to contribute to the achievement of the Global NTD roadmap, the targets and goals of the Regional NTD Strategy and Strategic Plan 2014-2020 by 2020, which include eradication of Guinea worm disease and yaws, sustained elimination of leprosy as a public health problem, elimination of human African trypanosomiasis as a public health problem, and control of Buruli ulcer and leishmaniasis.

Methodology and processes

In chronological order the following activities were carried out:

- 2013: WHO WHA and RC Resolutions on NTDs (WHA66.12 and AFR/RC63.R6) and AFRO Regional NTD Strategy and Strategic Plan 2014-2020 and Country NTD Master Plans for 2011-2015 and 2016-2020
- 2014: Development of the Integrated CM Strategy in Lomé, Togo and ToR of the CM-NTD RPRG
- 2015: Development of a Manual on integrated CM of NTDs for Peripheral Health Workers and two guides for Supervision of PHWS by District health Management Teams and on integrated M&E of CM-NTDs, in Douala, Cameroon
- 2016: 1st Meeting of CM-NTD NPMs and Stakeholders in Cotonou, Benin
- 2017: 1st Joint Meeting of CM and PC NTD NPMs and Stakeholders in Libreville, Gabon
- 2018: Meeting of 10 BU-LEP-Yaws co-endemic countries in Abidjan, Cote d'Ivoire
- 2018: Meeting of Leprosy Low Burden Countries in Gaborone, Botswana

Results

Five documents were developed and finalised in French and then translated into English and Portuguese and disseminated for adaptation and use to all Member countries of the African Region.

Implementation of this integrated strategy started with the support of AFRO in 10 countries: Burkina Faso, CAR, Cote d'Ivoire, DRC, Guinea, Liberia, Malawi, Nigeria, Sierra Leone and Togo.

Reduced burden of CM-NTDs from 2015 to é017 or 2018 in the Region as follows:

- BU: from 1996 (2016) to less than 1,500 in 2018
- HAT, from 300 (2015) to 1447 (2017)
- Leishmaniasis from 30,000 (2015) to 20,000 (2017)
- Leprosy from 23,000 (2015) to 21,616 (2017)
- Yaws Still estimated at 20,000 annual cases but may be less with DPP confirmation

Next steps

- Joint CM NTD Interventions in more countries
- Joint CM and PC NTD Interventions in more countries
- Regional NTD Strategy and Strategic Plan 2021-2030
- Country NTD Master Plans 2021-2025

Conclusion

With the adoption of the integrated strategy for case management neglected tropical diseases and dissemination of guidance documents, the WHO Regional Office for Africa aims to implement more effective and efficient approaches for addressing these five diseases and achieve the 2020 NTD goals in the Region and target the post 2020 goals, including HSS for UHC, the Triple billion goal of the GPW13 and the SDGs by 2030.

Skin disease prevalence survey as a part of integration activities for skin NTDs in Côte d'Ivoire: results from the Adzopé and Gagnoa health districts and implications for future implementation

Presented by Rie Roselyne Yotsu

Rie Roselyne Yotsu[1) 2)], Kouamé Kouadio[3)], David Coulibaly N'Golo[3)], Aka N'Guetta[3)], Koffi Landry Kouadio[4)], Emma Yeboue[5)], Kadio Augustin Kouakou-Adonis[6)], Kadio Constance[7)], Amari Akpa[4)], Konan N'Guessan[4)], Norihisa Ishii[8)], Djakeaux Simplice[5)], Henri Assé[6)], Aubin Yao[4)], Bamba Vagamon[9)]

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Introduction

Many neglected tropical diseases – including Buruli ulcer, leprosy, and yaws present with skin symptom(s) (skin NTDs). This characteristic feature may facilitate early detection by health-related fieldworkers in endemic areas. We aim to leverage fieldworkers to implement an integrated skin survey in early detection of skin NTDs in Côte d'Ivoire; a country with the highest reported number of Buruli ulcer cases globally. We are presenting our program implementation, results, and challenges to date since initiation of the project in May 2014.

Objectives

To establish integrated skin survey for early detection and treatment of skin NTDs and to describe the distribution and the disease burden of these diseases in Côte d'Ivoire.

Methods

During the four years, we have conducted school skin surveys in two health districts, Adzopé and Gagnoa, and for the latter, we further conducted community survey where we identified as highly endemic with skin NTDs during the school survey. Our surveys consisted of two phases: 1) screening by nurses of primary schoolchildren aged 5 to 15 and selection of those presenting with any skin lesion(s); and 2) in-school examination and management of screened children by medical teams including dermatologists. Sensitization was done during phase 2 to invite any individuals with skin lesion(s) missed during phase 1. Along with the surveys, we assessed personal hygiene practices and children's dermatology life quality index (CDLQI).

Results

In Adzopé, we covered a total of 13,019 schoolchildren among which we found 1 case of leprosy and 36 cases of scabies. In Gagnoa, we covered a total of 9,930 schoolchildren among which we found 1 case of leprosy, 5 cases of Buruli ulcer, 2 cases of yaws, and 68 scabies. In both districts, the prevalence of skin diseases was 26% of which mostly were fungal infections. Further community survey enabled further detection of cases. For personal hygiene practices, significant differences between skin NTDs and non-skin NTDs were observed in frequency of taking a shower and changing clothes. Increase in CDLQI, indicating the impact of skin diseases on children's daily lives, was observed regardless of disease type. Prescriptions or, in severe cases, medications and follow-up were provided to those diagnosed.

Conclusions

Few number of patients for each skin NTDs detected during the surveys justifies the need for skin NTDs integration. High prevalence of skin diseases was observed in communities with skin NTDs endemicity, which may lead to delayed detection of skin NTDs. Further strategies targeting skin NTDs should be formulated in a way that they can also reach out to the patients with skin diseases, which may be done through good training, establishing referral pathways, etc. With the lessons learnt, we plan to expand the project to a wider region in Côte d'Ivoire.

Buruli ulcer – where are we now? 2014 WHO programmatic targets and global epidemiology

Presented by Till F. Omansen

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Buruli ulcer (BU) is a neglected tropical disease (NTD) caused by the *M. ulcerans.* It results in skin lesions that can lead to extensive scarring, disability and stigma. In 2013, WHO had defined programmatic targets to be reached at the end of 2014 to address Buruli ulcer disease control. Four programmatic targets were defined 1) PCR confirmation in ≥70 % cases, 2) <25 % of cases having category III (large) lesions, 3) ≤60 % ulcerative lesions and movement limitation in ≤ 15 % of cases. Here, we analyzed BU epidemiological data reported to WHO between 2010 – 2017. We used the results to assess the global status of the four targets formulated by WHO for 2014. During the study period, a total of 23,206 of cases were reported to WHO. In 2017, 2217 cases were noted with the main epidemic countries being Australia, Benin, Côte d'Ivoire, Ghana, Liberia and Nigeria. In general, BU cases declined greatly within the past years. However, in Australia, Ghana, Liberia, and Nigeria, an increase of cases reported was noted recently. Regarding the global targets set for 2014, some progress was made between 2012 (baseline year) and 2014. However, only goal 4 (movement limitation) was attained by 2014. Up to date, progress made towards all four targets was lost by 2017 and several countries since deteriorated below levels of the initial assessment in 2012. Even though cases declined globally over the past years, the status on the programmatic targets highlights the challenges still associated with the disease. With *M. ulcerans* being an environmental pathogen with an unclear transmission pathway, disease eradication is impossible. Disease control therefore must focus on early and rapid diagnosis and adequate, fast treatment. This study demonstrates the gaps in BU disease control and provides a basis to repeat a discourse on BU policy and for formulating 2020 programmatic targets.

Day 2 – Control

Integration

Review of Buruli ulcer surveillance data in Victoria, Australia, 2004 to 2018

Presented by Ee Laine Tay

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Background

The state of Victoria in southeastern Australia is currently experiencing the highest number of Buruli Ulcer (BU) cases on record. The trend is not uniform across the five recognised BU-endemic areas: Bellarine Peninsula, Mornington Peninsula, Frankston region, the southeastern Bayside suburbs (Bayside suburbs) and East Gippsland. The increase is associated with a shifting epidemiology of disease from the Bellarine to the Mornington Peninsula since 2012. This study aims to detail the epidemiology of BU in Victoria, and in the interest of ensuring prompt management of cases, characterise the timing of presentation and diagnosis for BU cases.

Methods

Retrospective descriptive analysis of laboratory confirmed BU cases notified to the Department of Health and Human Services in Victoria between 2004 and 2018.

Results

There were 1477 BU cases notified in Victoria from 2004-2018, with 341 cases notified in 2018 (rate 5.3 per 100,000), the highest on record. Marked variations in notification rates were noted between postcodes of residence, with the highest rate found in residents of Rye and surrounding townships of Tootgarook and Blairgowrie (113 cases, rate 780 per 100,000 in 2018) on the Mornington Peninsula. Case numbers and notification rate increased over the period in three BU-endemic areas (Mornington Peninsula, Frankston region and Bayside suburbs), declined in the Bellarine Peninsula and fluctuated in East Gippsland (Figure 1).

In the period 2011-2018, the peak notification month was October and the first health presentation peaked in August. Symptom onset month peaked in July (lowest in January) and was similar between residents and non-residents of known endemic areas.

Evaluating the time from symptom onset and first health care presentation in 2011-2017, the median presentation delay across all areas was 30 days (IQR 14-60 days). There was no significant change over time. Evaluating the time from first health presentation and first clinical suspicion of BU, the median diagnosis delay was 10 days (IQR 0-40 days), shortest in the Bellarine (median 0 days for all years) and longest in non-endemic areas. A significant decrease in diagnosis delay was observed only in the Mornington Peninsula over time.

Conclusion

The incidence of BU is not uniform across Victoria and outbreak dynamics vary by endemic area. Delays in presentation and diagnosis highlight the need to continue efforts to improve disease awareness.

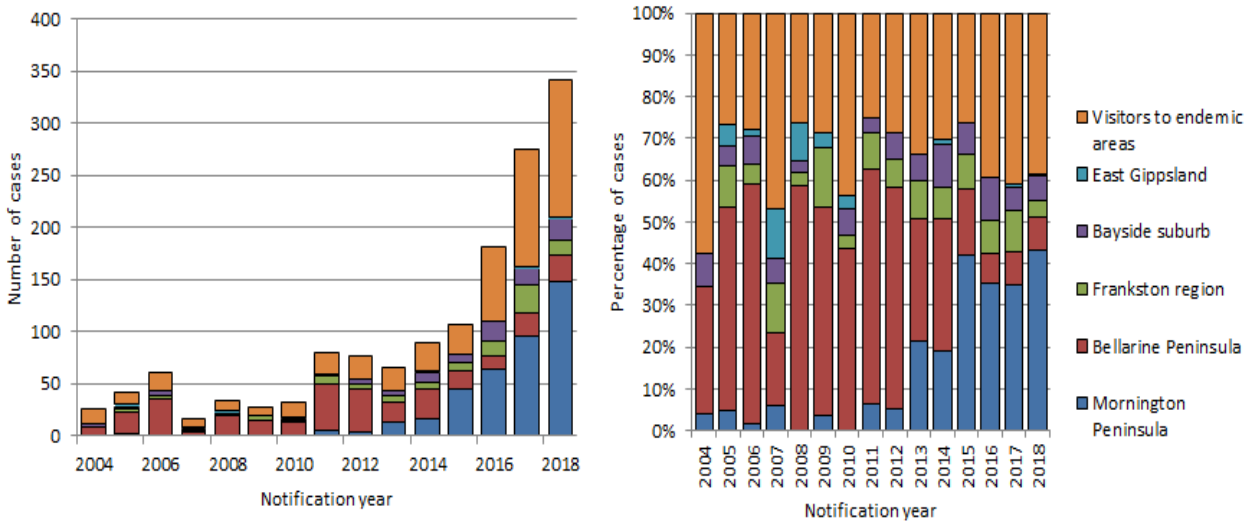

Figure 1: Number and proportion of Buruli ulcer cases notified in Victoria, by area of residence at time of notification, 2004 to 2018

Infection with *Mycobacterium ulcerans* (Buruli ulcer) and other neglected tropical skin diseases in French Guiana in 2017 and 2018

Presented by Pierre Couppié

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Over the period 2017–2018, we documented nine new cases of infection with *Mycobacterium ulcerans* in French Guiana (four in 2017 and five in 2018). Five of these patients were female and four were male, two were children aged under 15 years and the average age was 37.6 years. Six of the patients lived in eastern and central coastal regions (Cayenne and Kourou) and three lived in the western coastal region (Mana and Javouhey). All patients presented with ulcerative skin lesions and seven of the nine patients presented with ulcers with undermined edges. The ulcers were located in the usual areas: on the lower limbs in five patients and upper limbs in four patients. All cases were classified under Category I. Seven of the nine patients tested positive using Ziehl-Neelsen staining, PCR confirmed positivity in four out of six patients tested and one out of seven patients tested positive using cultures. Antibiotic therapy in the form of concomitant rifampicin and clarithromycin was administered to eight patients (one patient was lost to follow-up before therapy was administered). No patients required surgery and no patients were treatment failures. Genome sequencing analysis of the strain observed in one patient indicated genomic proximity to *M. ulcerans subsp. liflandii*.

Other neglected tropical skin diseases diagnosed in the same period (2017–2018) in French Guiana were 324 cases of cutaneous leishmaniasis, most of which were *Leishmania guyanensis* or *L. braziliensis*; 25 cases of leprosy; three cases of eumycetoma; two cases of chromoblastomycosis; and three cases of lobomycosis. Among the systemic mycoses with skin foci were two cases of paracoccidioidomycosis and one case of HIV-positive histoplasmosis with mucocutaneous lesions. No cases of lymphatic filariasis were reported.

Buruli ulcer in Japan: update 2017-2018

Presented by Chiaki Murase

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Epidemiology of Buruli ulcer (BU) in Japan, up to 2018

Japan is one of the few non-tropical countries with cases of BU, reporting a total of 70 cases to date. Starting with the first case report in 1982 by Mikoshiba *et al.* there have been sporadic reports in a wide geographic area, including seven and three in 2017 and 2018, respectively. To date, BU cases have been reported in 20 out of the country's 47 prefectures (43%). Among the patients, fifty (71%) cases were confirmed as caused by *Mycobacterium* (*M.) ulcerans* subsp. *shinshuense*, a subspecies of *M. ulcerans* exclusively isolated in Japan. No BU case was reported from Hokkaido prefecture (the northernmost island of Japan) and Okinawa prefecture (the southernmost island of Japan) so far.

Characteristics of the new BU cases: 2017 and 2018

Most of the new cases (7 of 10) were over 60 years old. The other 3 cases were 4, 5, and 40 years old. Sex ratio was 1:1. The geographic distribution was again wide, with no obvious clustering. There was again no clear epidemiologic association: 3 cases had known contact with some water source. Two cases had episodes of an injury at the site of BU lesion. All 10 cases were ulcerated. Eight cases were in BU category I, and 2 cases were in the category II.

Treatment

Most BU cases in Japan have been successfully treated with combination of oral rifampicin, clarithromycin and levofloxacin (replaced by tosufloxacin for children). There is no specific recommendation for treatment based on the sizes of BU lesions, but treatments besides antibiotics may be needed in severe cases. These include radical resection, skin grafting, and sometimes new wound care methods, such as negative pressure wound therapy. Relapses of the disease after surgeries frequently occur due to insufficient resections and residual bacteria.

All the 10 new cases were treated or under treatment with the combination oral therapy, with clinical improvement. Three of them received skin grafting. These surgeries were conducted mainly with the aim to debride the necrotic tissue or to reduce of the number of pathogen. The lesion of one case expanded even under the oral regimen, therefore surgical debridement was performed.

Problems

Until 2017, all BU cases in Japan were diagnosed at the Leprosy Research Center (LRC), National Institute of Infectious Diseases (NIID) therefore it was possible to obtain information on accurate number of BU

cases. However, recently it has become possible to diagnose BU (even to confirm the subspecies of *M. ulcerans* subsp. *shinshuense*) in facilities other than LRC, NIID. BU is not set as a mandatory disease for reporting under the Japanese Infectious Diseases Control. This poses a challenge in obtaining information on accurate number of BU cases.

Challenges and way forward

We identify the following as our challenges and way forward:

- Need for increased awareness among physicians and health care professionals.
- Involvement of more physicians, health care professionals, and other actors in BU
- Search for mode of transmission in Japan
- Further research on diagnosis and treatment
- Obtain accurate information on the number of new BU cases in Japan

Skin NTDs in Japan

Presented by Mariko Sugarawa-Mikami

Mariko Sugawara-Mikami[1)2)], Nao Yamamoto[3)], Chiaki Murase[4)], Rie Roselyne Yotsu[5)6)], Koichi Suzuki[7)], Norihisa Ishii[8)], Michiko Aihara[1)]

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We analyzed the cases of skin NTDs that were reported in Japan from 2000~2018. In particular, we focused on patients with leprosy, cutaneous/mucocutaneous leishmaniasis and Buruli ulcer. The search was performed using: Japan Medical Abstracts Society and database at the Leprosy Research Center, National Institute of Infectious Diseases (NIID), Japan was also used for this analysis. A few cases of leprosy and leishmaniasis were reported in Japan during the given period, which mostly were imported cases. Interestingly however, for leprosy, there still were cases domestically acquired. These cases were in aged individuals mostly from Okinawa, the most southern islands of Japan, which was the last endemic site. Conversely, all patients with Buruli ulcer had been infected in Japan as they had no travel history overseas and the causative bacteria was isolated to be *Mycobacterium ulcerans* subsp. *shinshuense*, a characteristic strain domestic to Japan. We performed sub-analysis on sex, age, type of lesions, diagnostic methods, and treatments.

Epidemiological surveillance of Buruli ulcer in Gabon in 2015 and 2016

Presented by Dr Annick Mondjo[1]

Infectious Disease Control Programme (PLMI) – Ministry of Health, Social Welfare and National Solidarity (Libreville, Gabon)

Introduction

In Gabon, most cases of Buruli ulcer recorded each year are located in **Lambaréné**, **the main focus of infection** with *Mycobacterium ulcerans* since 1961, or its surroundings. Patients living outside Moyen-Ogooué province (the central health region) have also been diagnosed with the disease in the last 15 years. The health departments of Woleu, Oyem, Woleu-Ntem province (the northern health region) and Bendje, Port Gentil, l'Ogooué Maritime province, have now been recognized as **new foci of Buruli ulcer infection** on the basis of epidemiological records of young patients diagnosed using histological tests and/or PCR.

Organization of the epidemiological surveillance of Buruli ulcer

The characteristics of new cases of Buruli ulcer are reported to the central level, on a monthly basis in the case of referral facilities in the central health region that keep a UB02 register, and on a case-by-case basis for other health facilities. Specimens for diagnosis are transmitted centrally through the Infectious Disease Control Programme (PLMI) and are anonymized before being deposited at the administrative branch of the Franceville International Medical Research Centre (CIRMF) in the capital. PCR-confirmed diagnosis is performed free of charge by the CIRMF bacteriology unit. In 2018, this service was subjected to a quality control assessment organized by the Antwerp Institute of Tropical Medicine (Belgium) with the support of WHO.

Characteristics of new cases of Buruli ulcer

Twenty-six new cases of Buruli ulcer were reported in 2018 in comparison to 45 in 2017. The main characteristics of these new cases are shown in Table 2 below. All patients received medical attention in the region where they lived. Nearly all new cases of Buruli ulcer recorded in the last two years were located in the central health region, mainly in Lambaréné or in the second hotspot of Makouke, the village in which 11 (one in four) cases were reported in 2016. However, in contrast to the two previous years, no cases were identified by health facilities in the Maritime and northern health regions. Between 2017 and 2018, the proportion of women in the total number of new cases rose from 49% (22 out of 45) to 58.7% (17 out of 29) and new cases among children under 15 years of age rose from 40% (18 out of 45) to 48.3% (14 out of 29). The proportion of ulcerative forms continued to exceed 90% over this period. The increased proportion of category III forms and the frequency at which patients were unable to access screening services also favoured late and incomplete diagnoses, although the increase in these percentages is partly linked to the fall in the total number of cases screened.

PCR-confirmed diagnosis

The proportion of **PCR-confirmed Buruli ulcer diagnoses** performed by the CIRMF continues to rise, increasing from 25.6% in 2015 to **72.4% in 2018** (provisional data), compared with 57.8% in 2017. This increase is primarily attributable to the fact that specimens were taken from nearly all patients using swabs or fine-needle aspiration (FNA) in non-ulcerative forms. Over the last two years, the confirmation rate of Buruli ulcer has consequently been the same as the CIRMF positivity rate. In 2018, the CIRMF participated for the first time in an External Quality Assessment Project (EQAP) on *M. ulcerans* detection as recommended by the Antwerp Institute of Tropical Medicine (Belgium); this in itself represented progress, regardless of the results obtained.

Comments

The fall in the number of cases of Buruli ulcer reported in the different health regions is a complex issue. The situation reflects shortcomings in the integration of control activities carried out at the different levels of the health pyramid; poor awareness of Buruli ulcer among the public and health workers, in particular in the central health region; and geographic and financial barriers to early screening and quality care, including skin grafts required by patients with extensive ulceration (category III). A series of new specific global objectives aiming at controlling Buruli ulcer issued by WHO in 2013 have been adopted in the framework of the National Health Development Plan (PNDS) 2017–2020, primarily addressing **the PCR-confirmed Buruli ulcer diagnosis rate, which currently exceeds 70%,** and **the proportion of category III forms of the disease** (see figure 2).

Discussion

Since 2005, with the support of WHO and the Raoul Follereau Foundation, Gabon's Infectious Disease Control Programme has implemented **integrated control activities targeting NTDs with skin manifestations** that include training sessions focusing on dermatology, leprosy and Buruli ulcer. The inclusion of scabies (*Sarcoptes scabeis*) in the 2017 revision of the WHO list of neglected tropical diseases and the emerging phenomenon of the disease known as "gratti-gratta" in Libreville and other parts of Gabon in 2018 means that this strategy is needed now more than ever.

One consequence of the increased awareness of this relatively common skin disease among the public and health workers is the clear improvement in the reception of information and training on macules, papules and nodules as well as ulcers, especially the advice to avoid damaging and scratching ulcers, provided during awareness-raising meetings held during the 66th World Leprosy Day in Libreville in 2019. Heightened awareness of pruritic and nonpruritic skin diseases should lead to an increase in self-referrals and help trained general health workers to recognize rarer neglected diseases such as leprosy or Buruli ulcer. With this in mind, the Infectious Disease Control Programme has sought to strengthen capacities among laboratory workers experienced in tuberculosis diagnosis to enable them to routinely investigate *M. leprae* and *M. ulcerans* (Libreville, October 2018). To improve outcomes in Buruli ulcer control at the national level in the next few years, efforts should be made to integrate skin NTD referral pathways into standard pathways; formalize dispatch procedures for specimens, results and specific medicines; and implement regular quality control processes for PCR diagnostic tests in collaboration with the CIRMF and support from partners.

Table 1: Main characteristics of new cases of Buruli ulcer in Gabon (2015–2018)

Year	New cases of BU	% ulcerative forms	% Category III forms	% forms with functional limitation	% PCR-positive tests	% IS*2404*-based confirmation MU1/MU2
2015	**43**	**90.7% (n=39)**	**42.9% (n=18)**	**16.3% (n=7)**	**45.8% (=11/24)**	**25.6% (=11/43)**
2016	**39**	**92.3% (n=36)**	**27.0% (n=10)**	**5.3% (n=2)**	**53.6% (=15/28)**	**38.5% (=15/39)**
2017	**45**	**100% (n=45)**	**44% (=20/45)**	**16% (=7/45)**	**57.8% (=26/45)**	**60.4% (=26/43)**
2018	**29**	**89.7% (n=26)**	**51.7% (=15/29)**	**20.7% (=6/29)**	**75% (=15/21)(*)**	**72.4% (=15/29)(*)**
Buruli targets in PNDS 2017–2021	**n/a**		**<25%**			**>70%**

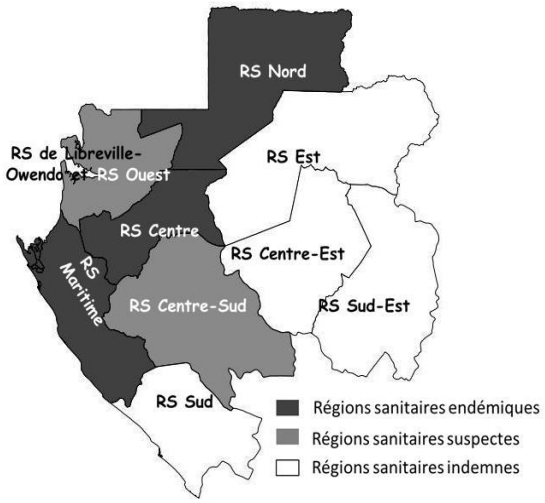
(*) Provisional data

Sources: Infectious Disease Control Programme, UB02 reports from health regions and results of PCR tests carried out by the CIRMF bacteriology unit.

Table 2: Geographic origin of new cases of Buruli ulcer in Gabon according to residence (2016–2018)

Health regions	Administrative capital	*Number of health departments*	**2015**	**2016**	**2017**	**2018**
Libreville-Owendo	Libreville	*4*	**6**	**3**	**1**	**1**
West	Ntoum	*3*	**1**	**1**		
South-East	Franceville	*11*				
Centre	Lambaréné	*2*	**32**	**27**	**44**	**28**
Centre-South	Mouila	*9*		**1**		
South	Tchibanga	*6*				
East	Makokou	*4*				
Centre-East	Koula-Moutou	*4*				
Maritime	Port Gentil	*3*	**4**	**1**	**0**	**0**
North	Oyem	*5*		**6**	**0**	**0**
TOTAL (*)		*51*	**43**	**39**	**45**	**29**

Sources: Infectious Disease Control Programme, UB02 reports from central health region (data correct as at 31 January 2019)



Map A - Map of Buruli ulcer in Gabon, 2017

Translation of text in image:
- RS = health region
- Endemic health regions
- Health regions with suspected cases
- Non-endemic health regions

Update: Buruli ulcer control activities in Ghana 2017 – 2018 and the implementation of a start-up projecting integrating other skin-related neglected tropical diseases

Presented by Dr Nana Konama Kotey

Public Health Specialist & Program Manager, National Buruli Ulcer Control and Yaws Eradication Programme

Introduction

Buruli ulcer control activities in Ghana are overseen by the National Buruli Ulcer Control Program (NBUCP). The NBUCP has continued to work with its various partners to support the diagnosis and treatment of the disease, maintain surveillance of the disease and undertake capacity building. The past 2 years has also seen Ghana take practical steps towards increasing the level of integration in the control and management of various skin-NTDs prevalent in country, including leprosy and Yaws. The country is in its initial stages of piloting the integrated skin-NTD strategy in 15 administrative districts, with the support of Anesvad.

Epidemiological Situation

For several years, routinely reported cases came from only six administrative regions despite the finding of cases in all the country's 10 regions during a National Survey in 1999. Between 2017 and 2018, the number of known reporting districts continued to increase, including some in hitherto non-reporting regions (now 8 out of 10). The decreasing trend of reported BU cases from 2014 to 2016, has also reversed. The country detected 371, 538 and 461 cases of *M. ulcerans* infections in 2016, 2017 and 2018 (by 31st October) respectively. **In 2018, cases 15 years and above continued to be high (83.3%) in keeping with the recently observed epidemiological trend in the age distribution as seen in 2016 (77.6%) and 2017 (82.9%). In both 2017 and 2018, there were 9 recurrent BU cases.**

Characteristics of new BU cases: 2017 and 2018

Although CAT III cases continue to be high (25.1% and 34.1% in 2017 and 2018 respectively), the proportion of CAT I cases has not reduced significantly in the period under review. From a proportion of 38.3% in 2016, the country has recorded 43.1% and 42.1% CAT I cases amongst cases reported in 2017 and 2018 respectively. Ulcerative clinical forms continue to be predominant – comprising 94.2% of all cases in 2017 and 84.6% in 2018 – and majority of lesions (84.8%) continue to affect the lower limb. Significantly, the proportion of cases with limitation of joint movement has continued to decline – 20.5% in 2016, 16.2% in 2017, and 15.4% in 2018.

Diagnosis and Treatment

Samples are transported by districts to a number of specialized laboratories which support the National Program with PCR confirmation: 406 (75.5%) in 2017 out of which 170 (41.9%) were positive; and 363 (78.7%) in 2018 out of which 199 (54.8%) were positive. 120 (22.3%) and 111 (24.1%) of cases completed antibiotic treatment in 2017 and 2018 respectively.

Other skin NTDs in Ghana

We will also briefly report on case numbers for other skin-NTDs in Ghana. For both 2017 and 2018, only 75 out of the 216 districts routinely reported on Yaws. There were 1687 cases of Yaws and 3053 contacts in 2017, and 2568 cases of Yaws with 2791 contacts in 2018. The country continued to record about 250 new cases of leprosy annually in both years under review with an increasing trend of grade-2 disability proportion.

The Integrated Skin-NTD Strategy

The NBUCP, National Yaws Elimination Program (NYEP), and National Leprosy Elimination Program (NLEP) have been collaborating in 15 start-up project districts since January 2018 to pilot this strategy using Ghana Health Service structures. Beyond the resource provision within this project and anticipated increased efficiency with control activities, the strengthening of the laboratory support systems and strong advocacy and research component promises to improve control activities for all skin-NTDs nationwide. Already, the Case Identification and Reporting training and the following active case searches have revealed increased numbers of all 3 skin-NTDs in districts, some of which were hitherto not reporting any new cases. We will present data from these activities within our presentation.

Evidence of the high endemicity of leprosy and yaws in Bale Loko commune, Central African Republic

Presented by Alphonse Um Boock

Um Boock Alphonse,[1] Ntozo J.P.,[3] Boua,[4] Bart Vander Plaetse[2]

Introduction

The Government of the Central African Republic wishes to provide updated and reliable data on neglected tropical diseases (NTD) in the scope of health service strengthening and revitalization.

Materials and methods

In collaboration with FAIRMED, the Ministry of Health launched a cross-cutting survey in the village of Scad.
The study was conducted between 11 and 20 June 2017. Specimens taken from 616 subjects were analysed using Epi Info software, as were the survey data.

Results and discussion

A total of 137 cases of yaws were clinically diagnosed, of which 102 of which tested positive in rapid biological tests and 79% were very contagious forms. The prevalence of yaws in this study was 22.24%, which is higher than that reported by Walter M. Kazadi in a 2012 study that revealed a prevalence of 11% in the Lobaye region. [4]

Fifty-seven cases of leprosy were screened, of which 68.42% (39 cases) were the multibacillary form. Eight children aged under 15 years (16.66%) presented with category II disabilities. The screening rate of new cases (9.25%) was much higher than in 121 other WHO countries and territories, in which the average rate was 2.9% in 2016. [6] Twenty-nine of the 57 cases (51%) screened during the survey were already known to the health services. This study demonstrates the wide spread of NTDs in the Lobaye region of the Central African Republic.

Conclusion

This study shows that leprosy and yaws remain endemic in the Central African Republic, at least in certain hotspots.
In the scope of health system strengthening, the different NTD control programmes need to be integrated to ensure their effectiveness.

Keywords: Leprosy, yaws, Bale Loko

Integrated approach to the control of neglected tropical diseases with skin manifestations in Benin

Presented by Yves T. Barogui

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Introduction

Africa bears nearly half the global morbidity burden of neglected tropical diseases, which are most widespread in tropical and subtropical regions and mainly affect low-income populations. Some NTDs have a skin manifestation. Only Buruli ulcer and leprosy have been definitively proven to be skin NTDs endemic in Benin and the presence of yaws in Benin had not been proven until 2017. In recent years, the number of cases of Buruli ulcer and leprosy has decreased considerably in Benin as in most African countries. Given the reduction in the number of cases and the scarcity of resources, the World Health Organization has recommended an integrated approach to the control of NTDs. Here we share our experience of the integrated control of NTDs with skin manifestations in Benin.

Method

Between October 2017 and December 2018, the following initiatives were organized:

- integrated training of health workers, community intermediaries, teachers and former Buruli ulcer patients in recognizing the signs of leprosy, Buruli ulcer and yaws; and
- integrated awareness-raising campaigns and screening for these three diseases in villages by medical teams formed of nurses, physicians and dermatologists;

Suspected cases of Buruli ulcer were confirmed by PCR and cases of leprosy were clinically confirmed by experienced workers.

All children with skin lesions and all adults with suspected yaws-induced skin lesions were subjected to systematic rapid diagnostic tests.

Patients' sociodemographic and clinical data were collected using comprehensive data collection forms developed for that purpose. The data were subsequently analysed using IBM SPSS Version 20 software.

Results

In total, 7262 individuals (53% of whom were women) with skin lesions were examined in more than 300 villages in areas in which Buruli ulcer and leprosy were endemic. The median age (IQR) of the subjects was 16 years (range: 7–35). The main clinical presentations screened were:

- 144 (2.0%) suspected cases of Buruli ulcer, of which 108 were confirmed;
- 118 (1.6%) suspected cases of leprosy, of which 77 were confirmed;
- 3848 (53.0%) cases that were subjected to systematic rapid diagnostic testing for yaws, of which four were confirmed by DPP;
- 218 (3.0%) cases of scabies;
- 12 (0.2%) cases of lymphatic filariasis; and
- 6843 (94.3%) cases of of other skin presentations, in particular fungal infections, eczema, cellulitis and other chronic ulcers.

Conclusion

Integrated NTD screening provides optimal screening and management for NTDs with skin manifestations. However, the sustainability of this approach will depend on the training of peripheral health workers not only in NTDs with skin manifestations but also in basic dermatology.

Keywords: Neglected tropical diseases, integrated screening, Buruli ulcer, leprosy, yaws, Benin

Pilot project on integration in the control of neglected tropical diseases with skin manifestations in Togo's Maritime region

Presented by Charlotte Amedifou

Charlotte Amedifou,* Denis Gadah,* Judith Patchali,** Sossinou AwoussiI,** Beatriz Gomez,*** Gabriel Diez***

*German Leprosy Relief Association (DAHW), Togo; **National NTD Control Programme, Ministry of Health, Togo;
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Introduction

The World Health Organization has categorized 20 diseases as neglected tropical diseases (NTDs). Togo has chosen ten of these to prioritize in control, elimination and eradication activities towards 2020 and will follow the WHO Roadmap on neglected tropical diseases in accordance with local epidemiology. Activities to control these diseases are coordinated by national control programmes on NTDs requiring preventive chemotherapy and control programmes on NTDs requiring intensive case management. Diagnosis and case management focus on each disease individually. In 2015, the Ministry of Health, the German Leprosy Relief Association (DAHW) and the ANESVAD Foundation came together to develop a strategic approach to integrate NTDs requiring case management into the primary health system in Togo, in particular at the community level, through a pilot project named "Promoting the right to health of rights-holders in Togo's Maritime region".

Method

The project was launched in the Maritime region of Togo, specifically in 15 health areas of the Zio, Yoto and Avé districts, where Buruli ulcer and leprosy were endemic and suspected cases of yaws had been reported. We adopted a strategy that involved integrating the diagnosis of all NTDs with skin manifestations requiring case management with the direct involvement of local health facilities and the community (coordination, awareness, screening, stakeholder training, diagnosis and treatment of NTDs) as part of the global fight against dermatological diseases. Between 1 January 2016 and 30 September 2018, we implemented a set of interventions including: (1) the comprehensive training of district teams, health training officers, community health workers, laboratory technicians, physiotherapists, traditional practitioners, primary school teachers and women's groups; (2) awareness-raising activities and comprehensive active detection of dermatological diseases including skin NTDs in communities, schools and homes; and (3) medical and surgical treatment and post-treatment follow-up of patients with skin NTDs and non-NTDs. These data were analysed using Epi info version 7.2.2.6 software.

Results

The project covered 168 villages and settlements not served by the 15 peripheral care units. In total, 337 male and 118 female medical and paramedical practitioners were trained in the comprehensive control of NTDs requiring case management through a dermatological approach, covering community education, early detection, management, case referrals and counter-referrals.

Fifteen women's groups composed of 35 women on average were trained and equipped to support community awareness by conveying messages relating to NTDs requiring case management through traditional cultural practices.
Case management and follow-up was conducted in peripheral care units covered by the project. These facilities were supplied with diagnostic devices and first aid equipment.

Some 144 874 individuals received attention for various pathologies across the 15 health areas covered by the project. Children under 15 years of age represented 50.61% of medical consultations for all causes and the male-to-female ratio was 1:1.2. Dermatoses such as eczema, staphylococcus, hives, insect bites and scabies represented 19 297 of cases, 10 887 of which were referred in the community (through mobile consultations and community health workers). Some 14 590 ulcers and other skin lesions were reported.

As regards NTDs requiring case management, 218 new cases of Buruli ulcer were screened and managed with a PCR confirmation rate of 95.76%. Among these cases, 85.18% were category I or II cases and the median time before consultation was four weeks. Twenty-seven new cases of leprosy were diagnosed, of which 20 were multibacillary and four were paucibacillary. Fifty-three suspected cases of yaws tested negative for the disease using the One Step Anti-TP Syphilis test. The routine use of RDT followed by DPP will continue in active studies. At least 26 serious cases of other dermatoses were treated, three of which were cases of cancers subsequently referred to a specialist in the capital Lomé.

The Ministry of Health, with the support of WHO, DAHW and the ANESVAD Foundation, has developed a national strategic plan for the integrated control of Buruli ulcer, leprosy and yaws for 2018–2020 on the basis of lessons learned from interventions in this project.

Conclusion

The findings obtained in this pilot project on the integrated screening of dermatological diseases, in particular NTDs requiring case management, through IEC campaigns and mobile consultations demonstrates the relevance and effectiveness of the approach and the interventions implemented. The integrated approach allows for early screening for NTDs with skin manifestations and other dermatological diseases and hinders stigmatization. It can also be used to support effective political advocacy to encourage national and international institutions to combat NTDs and strengthen health systems. Given the increase in the number of new cases, these activities should be continued and intensified and sustainable mechanisms should be implemented.

Epidemiological facies of leprosy in Benin between 2006 and 2018

Presented by Ronald Gnimavo

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Introduction

Leprosy (also known as Hansen's Disease) is a chronic infectious disease caused by *Mycobacterium leprae* and is endemic in Benin. This study aims to describe the epidemiological characteristics of leprosy in Benin between 2006 and 2018.

Method

This is a retrospective and descriptive study. Demographic and clinical data of all patients treated at leprosy treatment centres in the Republic of Benin and by senior leprosy nurses between 2006 and 2018 were recorded and subsequently analysed using Stata/SE 11.0 software. QGIS version 2.18.23 software was then used to map these data. The main indicators of leprosy were calculated in accordance with WHO recommendations.

Results

In total, 2785 new cases of leprosy were diagnosed between 2006 and 2018 (an annual average of 214 cases). The median age of patients was 38 years (range: 6 to 88 years). The gender ratio was 1.18 (1509 men to 1276 women). Endemicity was highest in the departments of Atacora (19.17%), Zou (18.8%) and Plateau (17.2%). Between 2006 and 2018, the detection rate fell from 3.8 to 1.32 per 100 000 inhabitants; the proportion of paediatric cases fell from 8.56% to 2.67%; the proportion of multibacillary forms rose from 72.95% to 90%; the proportion of Grade 2 disabilities fell from eight to five cases per 1 000 000 inhabitants; and the polychemotherapy completion rate rose from 90.53% to 94.12%.

Conclusion

Leprosy continues to be a public health problem in Benin. It is therefore important to reinvigorate the epidemiological surveillance system to support efforts towards the eradication of the disease by 2020.

Keywords: Epidemiology, leprosy, Benin

Developments in the epidemiological situation of Buruli ulcer in Benin between 2008 and 2018

Presented by Anita C. Wadagni

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Introduction

Buruli ulcer is a chronic infectious skin disease. Its mode of transmission is unknown, but significant progress has been made in the understanding of its pathogenic mechanism of action, diagnosis and treatment. This study focuses on epidemiological developments in Benin.

Method

This is a retrospective, descriptive study conducted over the period 2008–2018 using data from the National Leprosy and Buruli Ulcer Control Programme (PNLLUB). ArcView 3.4 and Stata 14 software were used respectively to visualize geographic data and to analyse demographic and clinical data as well as the main disease control indicators.

Results

The endemic foci of Buruli ulcer are mainly located around the valleys of the Ouémé and Couffo rivers. The communes of Dangbo, Adjohoun and Bonou continued to present the highest levels of endemicity in 2018. The number of cases fell from 897 cases in 2008 to 219 cases in 2018. The most serious forms of the disease (category III) were observed in 42.14% of cases in 2008 and 58.41% of cases in 2018. The distribution of Buruli ulcer among children is comparable to its distribution among adults and the disease affects women as often as men. The persistence of ulcerative lesions is notable (52.51% in 2008 and 47.95% in 2018). The biological confirmation rate increased significantly from 46.04% in 2008 to 67.58% in 2018.

Conclusion:

Despite the fall in reported cases of Buruli ulcer, there is still work to be done to improve early diagnosis. The National Leprosy and Buruli Ulcer Control Programme has made significant progress in the biological confirmation of cases of Buruli ulcer.

Keywords: Buruli ulcer, epidemiology, Benin

Disease burden and epidemiology of skin-presenting CM-NTDs in Maryland County, Liberia: results from an integrated cluster-randomised active case search survey

Presented by Emerson Rogers

Rogers E*, Timothy J*, Mulbah T, Marks M, Halliday K, Wright A, Zaizay Z, Walker S, Wickenden A, Pullan R, Kollie K

The WHO has initiated plans promoting an integrated strategy for a sub-group of NTDs that exhibit primary clinical presentation via the skin (skin-NTDs). The conditions targeted for integration rely heavily on intensified and innovative disease management (IDM) interventions and include Buruli ulcer (BU), leprosy, lymphatic filariasis-associated morbidity (hydrocele and Lymphedema) and yaws.

A fundamental challenge for programmes targeting neglected tropical diseases requiring case by case management is a lack of epidemiological data to understand disease burden and co-endemicity. Reliable estimates are required to equitably allocate resource-intensive IDM interventions and make progress towards WHO 2020 targets. Despite a clear programmatic need, no gold-standard methods exist for integrated population-level burden estimation of skin-NTDs. This operational gap can lead to dependence on routine case reports, which are often unreliable. To address this challenge, the Liberia Ministry of Health NTD programme developed a two-stage cluster-randomised burden estimation survey strategy to concurrently estimate the population prevalence of BU, leprosy, hydrocele, Lymphedema and yaws in Maryland County (population 167,340).

The chosen strategy used a community health centred approach by employing community health workers (CHWs) as a population screening workforce, tasked withcompleting afull household censuses and screening within each for signs of NTDs requiring case management using photo-based visual aids (92 clusters, 56,795 individuals screened). Suspected cases (2,630 of 3,131 cases; 84.0%) were followed-up in their own home by mid-level health workers trained as part of a novel 5-day skin-NTD clinical training programme. The verification stage resulted in the clinical diagnosis of 287 cases of case management NTDs (55 BU, 39 leprosy, 169 LFM) including the first serologically confirmed cases (n=24) of yaws (ChemBio Dual Platform Pathway Syphilis lateral flow assay) in Liberia for over 30 years. Rigorous quality control assessments were deployed throughout all stages of the survey including door-to-door recapture surveys, full-body skin examinations of randomly selected households and real-time GPS monitoring of all CHWs and field officers. We present the final survey results andhighlight the implementation challenges associated with scale-upof activities. We also present a novel suite of tools developed for this rigorous burden estimation approach including ODK-based mobile data collection tools, mid-level health workers training packages and job aids to assist field workers in the diagnosis of skin-NTDs.

Integrating mobile phone and social media interventions into health research: A case for improving early case detection of Buruli ulcer in Ghana and Cote d'Ivoire

Presented by Charles Quaye

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Background

Early case detection, accurate diagnosis and treatment with antibiotics are currently the first line recommendations for Buruli ulcer (BU) management. The implementation of this strategy has however been challenged with problems in its integration into various national health systems. The lack of true prevalence data and logistic infrastructure to facilitate early case reportage has contributed to the waning support for Buruli ulcer management in national health budgets compared to other diseases. Active case search is extremely of essence in any control program, however in the case of BU, this appears to be research driven and hardly health systems driven. Newer technologies such as smartphones and social media offer innovative opportunities for reaching seemingly inaccessible populations with health interventions. We describe here an innovative easy to use system for BU case identification, sample taking for confirmation and the transmission of results, and the management of BU cases which can easily be adopted for district, regional or national BU programmes.

Methods

An active case search system was set up in the Amansie Central District of the Ashanti Region of Ghana and selected centers in Cote d'Ivoire. The system was mimicked in health facilities and BU treatment centers where passive reporting was expected. These were done in seven BU treatment centers in Cote d'Ivoire from June 2018 to December 2018 and two centers in Ghana from January to December 2018. This surveillance system involved the creation of WhatsApp® group platforms for all trained health personnel as well as coordinators and personnel from the National Buruli ulcer Control programme. Photos of all suspected cases of BU and other lesions were taken by the community health nurses and volunteers, appropriately coded and shared on the WhatsApp® group platform before questionnaire administration and sample taking. Samples were rapidly transported to the reference labs and case confirmations were sent to the district health directorate by email for treatment to commence.

Results

In Ghana, a total of 117 skin lesions suspected to be BU were detected during the active surveillance period, out of which 91 (77.8%) were confirmed as BU using IS*2404* PCR. A higher proportion of positive cases was observed in the Amansie Central District (50/55) with ratios of the three categories of lesions not differing significantly from categories passively reported at the health centers. All lesions were photographed and coded onto the WhatsApp® group platforms which allowed easy verification of information on BU01 forms and the tracking of confirmation results. In Cote d'Ivoire, 68 (96%) of the 71 suspected cases were confirmed to be BU with most being category II lesions (66%). The WhatsApp® group platforms worked well for both countries and achieved the expected outcomes.

Conclusion

These findings demonstrate the possibility and effectiveness of establishing a surveillance response system via simple smartphones and social media to support BU case detection and management. The system easily allows the sharing of vital information on case treatment outcomes and the tracking of samples for confirmation and confirmation results.

Using medical illustrations to aid diagnosis of neglected tropical diseases

Presented by Joanna Butler

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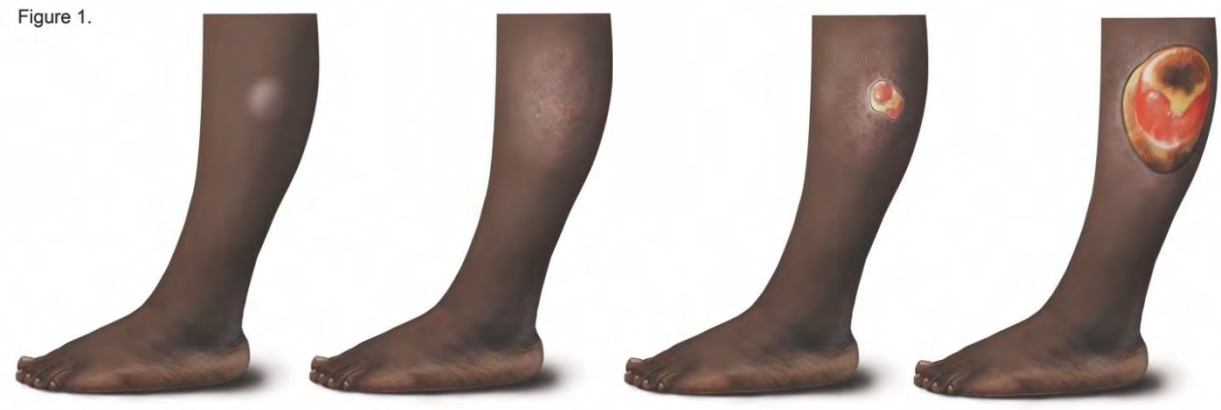
Neglected tropical diseases (NTDs) of the skin include Buruli ulcer, yaws, leishmaniasis and leprosy. First-line health workers need clear guidance to help them identify potential cases that can then be referred to specialist clinics. Currently such guidance is usually in the form of photographs. One disadvantage of this approach is that people using them tend to try and pair up the clinical lesions with the photo rather than using them to think through the diagnosis. Hence, there is an opportunity to improve diagnosis at the earliest signs of the disease by replacing these photographs with professional medial illustrations of the diseases. Ghana is one of the countries endemic for skin NTDs and current work activity is focused Buruli ulcer and Yaws, compared to more common tropical ulcers. Developing the medical illustrations involves a rigorous creation and testing process. First, a range of clinical representative photographs are used to draw a single "typical lesion". Then feedback is sought from clinical experts and those training health-workers, which is incorporated into revised illustrations.

The first draft of Buruli ulcer illustrations are complete and ready for feedback from the assembled community at this meeting (Figure 1). To date, illustrations showing the lesion on the upper calf area of the leg have been produced. For additional information on cultural and style preference, the illustrations have been produced in three different mediums to be tested along with clinical accuracy. Through survey and analysis, the illustrations providing the most consistent and measured visual experience for improving clarity and for comparable stage progression across body parts will emerge.

The ultimate aim is to provide a pamphlet that shows the diseases at various stages that can be distributed to healthcare workers in rural areas to increase case finding. It will also provide a model for how medical illustration can support low-resource-cost interventions for these under-funded diseases. By developing illustrations that may be less fearful for younger people, we hope to explore the possibility of additional preventative value by disseminating these visual resources in schools in endemic areas.

Figure 1.



Interactive mapping as a tool to investigate for lesion distribution patterns among patients with Buruli ulcer

Presented by Arvind Yerramilli

Arvind Yerramilli, Ee Laine Tay, Andrew Stewardson, Daniel P O'Brien, Paul DR Johnson

Background

The mycobacterial disease Buruli ulcer (BU) is increasing in incidence in Victoria, Australia. We aim to adapt data from previously published density maps to create an interactive web application to investigate patterns of disease.

Methods

We will be using notification data and clinical records review from a previously published article (Yerramilli et al 2017, *PLOS NTD*) which includes patients diagnosed with BU in Victoria from 1998-2015. The interactive web application will be created using the Shiny package from R (The R Foundation for Statistical Computing, version 3·3·1) in RStudio (RStudio, Boston, USA, version 0·99·893).

Findings

We aim to instantaneously filter and stratify variables including age, sex, exposure location, lesion type and WHO category and then interactively run point pattern analyses to visualise distribution patterns and identify risk factors among certain patient populations.

Interpretation

The interactive web application can be used for retrospective and prospective studies on lesion distribution. This will help researchers tackle the important question of disease transmission, readily identify risk factors, and ultimately aid in developing robust preventative measures.

Update on the further development of the SkinApp

Presented by Liesbeth Mieras

Benita Jansen and Liesbeth Mieras

NLR – the Netherlands

Background

Skin diseases are the fourth leading cause of disability worldwide. Despite the fact that these diseases are usually not fatal, they have a tremendous impact on the quality of life of affected individuals. Furthermore, skin disease manifestations can be a sign of underlying medical conditions, some of which may be life threatening. Studies have shown a tremendous shortage of dermatologists in the developing world. Additionally, present healthcare workers often lack knowledge and skills to treat skin diseases. To improve treatment of individuals affected by skin diseases, the gap between the prevalence of skin conditions and the availability of capable health care staff in peripheral health facilities should be bridged.

NLR developed a mobile phone application that supports peripheral health workers to diagnose and treat skin diseases. The development process of the SkinApp has included pilots in Nigeria and Mozambique to test the algorithm and user-friendliness. The newest, third version of the SkinApp has recently been developed and is currently being validated in several countries in Africa in preparation to use it on a larger scale. The first phase of the validation took place in Tanzania in October and November 2018.

Aim

The validation study aimed to evaluate the diagnostic accuracy and reproducibility of the NLR SkinApp (3rd edition, English version) for skin diseases, including NTDs presenting with skin lesions when used by peripheral health workers attending to persons with skin diseases, and to determine the value of the SkinApp in clinical decision making.

Objectives

1. To estimate the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the SkinApp for common skin-diseases, skin related NTDs and other included skin diseases when used by peripheral health workers.
2. To estimate the interrater reliability of the SkinApp for common skin-diseases, skin related NTDs and other included skin diseases when used by peripheral health workers.
3. To compare the treatment and referral advice for patients presenting with skin diseases as given by peripheral health workers using the SkinApp, to the treatment and referral advice that would have been appropriate according to a dermatologist (gold standard).

Method

The validation of the NLR SkinApp is a cross-sectional study amongst patients presenting with skin diseases in an outpatient dermatology clinic, of which the first phase was conducted in Mwanza, Tanzania in October and November 2018. Two peripheral health workers, without any dermatology training, field-tested the application and assessed the value of the SkinApp in clinical decision making after having received a three-hour instruction. The diagnosis of two experienced dermatologists was used as the gold standard. Individuals presenting with a skin disease at the dermatology clinic (age >18) were included in this study, after giving consent. The aim was to enrol at least 24 patients per disease listed in the SkinApp, taking into account the desired sensitivity, precision and confidence levels.

Preliminary results

During the first phase of this validation study, the peripheral health workers have provided valuable feedback to further improve the user-friendliness of the third version of the SkinApp: 1) A few changes will be made to the Body Map which is part of the algorithm to make its use more intuitive; 2) Some text adjustments will be made to correct or clarify the meaning; 3) Several photos will be added to show a greater variety of the presentation of the lesions.

Through observation of the health care workers using the SkinApp it became clear that it is an easy-to-use, supporting tool during consultation. There was a clear learning curve with a gradual increase of correct diagnoses over time during the study period.

An important and encouraging preliminary finding is that from all patients presenting with a skin disease that is part of the SkinApp, 78% (n=160) were correctly diagnosed by the health care workers.

Conclusion

The preliminary findings of the first phase of the SkinApp validation show that it is an easy to use, field-friendly tool that contributes to the peripheral health workers' capability to diagnose skin diseases.

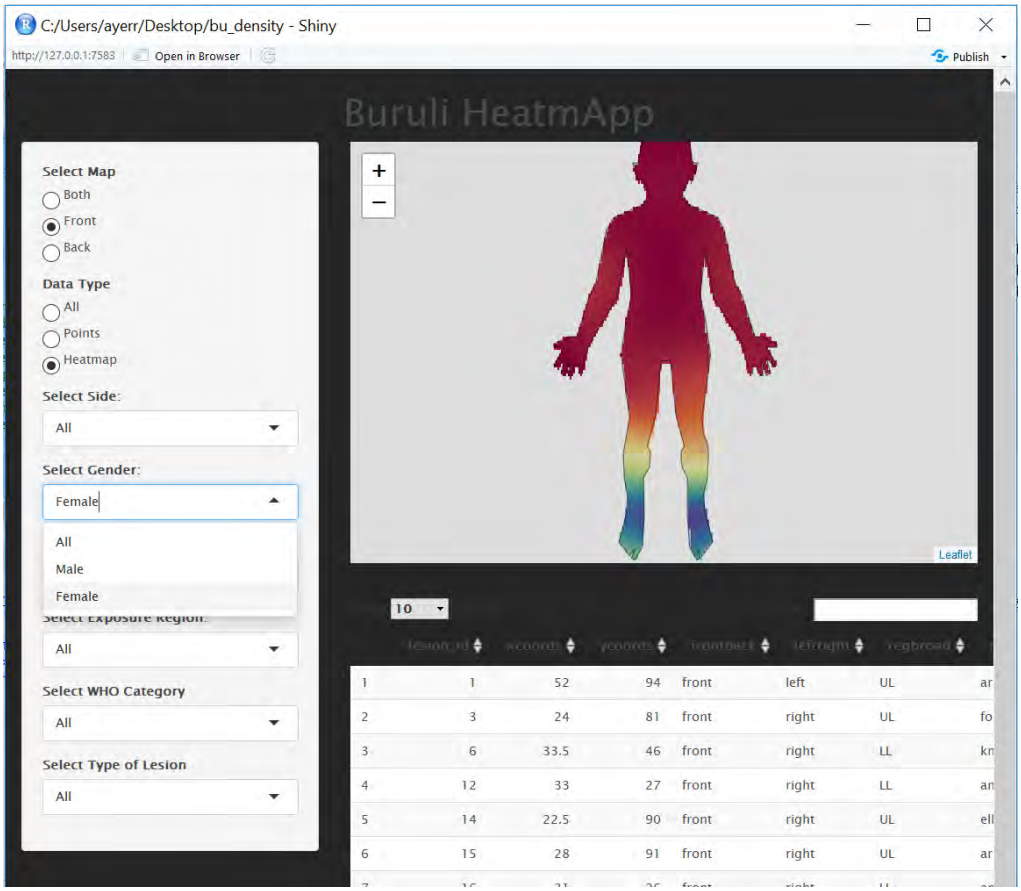


Figure 1: Screenshot of Shiny web application investigating lesion distribution among patients with Buruli ulcer.

Capacity building practical dermatology skills for NTD and other global health programmes

Presented by Claire Fuller

Dr Claire Fuller, Chair of International Foundation for Dermatology and Consultant Dermatologist

It is clear that dermatology training opportunities are limited especially in many environments concerned with NTD programmes.

A review of the impact of past, present and proposed training initiatives will facilitate the development of a coherent programme of targeted dermatology training to support integrated care of NTDs that affect the skin.

Several approaches have been tried starting with rapid needs assessment methodology to establish the local skin pathology, through one day targeted training, 2 year local diploma programmes to fully established specialist residency programmes. These will be reviewed and the impact and benefits discussed, to assist the participants in deciding the best way forward for upskilling the NTD workforce.

WHO-UOC Skin NTDs on-line training program: Lessons learnt from former editions

Presented by Carme Carrion

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Background

Neglected Tropical Diseases (NTD) cause enormous impact on individuals, families and communities in developing countries and that aggravates the cycle of poverty. Despite this fact, NTD are poorly known and rarely taught in medical schools. Skin NTDs are some of the most neglected ones. Universitat Oberta de Catalunya (UOC) together with the World Health Organization (WHO) have been collaborating to improve the case management of Cutaneous Leishmaniasis (CL), Buruli Ulcer (BU), Yaws and Leprosy in remote endemic areas by training health professionals through an interactive on-line course. The first three editions of the program were focused only on Cutaneous Leishmaniasis, while the two following ones included all 4 diseases and their common challenges. The specialization course consists of 10 ECTS (European Credit Transfer System) (250 study hours) targeted to laboratory technologists, clinicians, nurses or policy makers working in endemic areas. It lasts 16 weeks (October – February). Students receive up-to-date information on specific skin NTDs topics such as: natural history of the diseases, epidemiology, diagnosis, treatment and surveillance, data collection or differential diagnosis. Teaching strategies are on-line, asynchronous and participatory, interacting with experts in each of the topics, working on the field. It is based on scientific articles and WHO manuals, as well as the study of real cases and the sharing of the different field experiences. The
student's achievements are measured through continuous assessment activities together with a final multiple choice test which is compared to pre-test at the beginning of the course.

Once the program is successfully implemented we consider of paramount importance to assess its real social impact beyond knowledge acquisition. To do so, we performed a study that aims to determine the impact of the first 3 editions of the CL on-line course on professional practice and improve the potential impact of the current Skin NTDs on-line course.

Methodology and principal findings

Information was gathered from participants through seven semi-structured interviews. During the interview several topics were explored, covering the whole journey of the learning experience: from the expectations on the course, to experience during the program. Regarding the impact, we have considered immediate results at the end of the course, and results about one year after course completion. All the interviews have been recorded and transcribed. The analysis has been based on the transcripts and the information was coded following the different dimensions explored during the interviews. The software used was Atlas.Ti v7.

At the end of the course all the students are familiar with the WHO recommendations. A key aspect is that while students are more aware, they feel empowered and self-confident, this is extremely important in terms of guidelines spreading. Providing the knowledge to professionals directly seems to place the recommendations as the standard and thus the applicability is plausible.

Personal impacts described by the students are quite linked to emotions. The most widespread is the growth of personal motivation towards their mission and jobs. And to a lesser extent, we have found proud students. Regarding their professional performance, they are considered as the experts within their teams. Besides, we found a student who was subsequently appointed as a supervisor although it is possible that he was chosen because the bosses already planned to appoint him.

On the other hand one of the aspects where there is room for improvement is about the enrolment of students and their commitment during the course. As mentioned before, those highly motivated succeed in achieving important personal and professional impacts, but the non-motivated ones, are hardly taking advantage of the program. The selection of students might be modified in order to identify those high motivated people and who potentially can benefit more from this training experience.

Conclusions and significance

The course has proven to be a good source of social capital. Students are satisfied and still contact the teaching staff for further information about topics related to several skin NTDs. In other words, the course has provided a space to create a network of professionals with a shared focus on how to treat skin NTDs. This sense of community and belonging to a privileged elite may also reinforce the application of the concepts and methods learnt during the course.

Control

Other abstracts

General topics

Proposal of a new Buruli ulcer local treatment using the PARI Protocol

Poster by Fausto Assenza

Antonella Bertolotti°, Maria Letizia Iabichella*, Annunziata Izzo°, Fausto Assenza*, D. Dossou^, Luca Papetti°, Alessandro Stefani*.

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Background

The PARI Protocol[2] is a dossier proposed by Helios Med Onlus and Intermed Onlus concerns the Buruli ulcer local treatment for the purpose of **P**erform topical wound care, **A**void ulcer pain, **R**educe damage impact with prevention of disability and **I**mprove quality of life. The healing process[3,4]emphasized the need to avoid or reduce infection to improve the local metabolism and to balance any metabolic abnormalities. Although antimicrobial agents kill bacteria, they also damage the repairing cells. Studies have shown that the application of growth factors accelerates healing[5] but the persistence of an infection inhibits their activity[6,7]. It is known that local release of ozone has a strong bactericidal activity without any cell damage[8] and induces a better cell compliance. The stimulation of cell proliferation is due to the release of growth factors by the activation of platelets[9]. Indeed, the ozone (O3) releases a dose-dependent platelet aggregation in heparinized plasma samples, which significantly raises the amount of platelet-derived growth factor (PDGF) and activates growth factor beta1 (TGF-beta1) and interleukin-8 (IL-8). This data explains why O3 treatment, as topical ozonated autohaemotheraphy, TOA[10], is more effective and efficient when dealing with skin ulcer[11], during both debridment and wound care. Local ozone treatment also shown to be effective in the management of Buruli Ulcer[12].

Aim

To perform local ozone treatment for debridement and to improve Buruli ulcer bed healing.

Method

We developed a method where O3 is administered topically by positioning around the lesion a bag inflated with a O2–O3 mixture at a concentration of 30 mg/ml. The inflated bag is sealed just above the lesion to avoid any gas leak then it is positioned so that the gas mixture is in contact with the ulcer for about 20 minutes.

Cases presentation

Presentation of some clinical cases of Buruli ulcer treated with local ozone therapy in a short and long term.

Considerations

Evidence Based Medicine has shown that local ozone therapy succeeds in debridement in Buruli ulcer, improves healing in a lot of cases of ulcer and in different stages of the ulcer and might prevents disabilities.

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Cooperation between traditional and biomedicine to improve care for patients with Buruli ulcer

Poster by Yap Boum

Introduction

Early diagnosis and adherence to treatment are crucial to control Buruli Ulcer (BU). Unfortunately, most cases are delayed for treatment. We conducted a qualitative study in BU endemic zones in Cameroon, to assess knowledge, behaviors and perceptions of BU by patients, traditional healers and healthcare workers. We also assessed patient's perceived stigmatization.

Methods

The study was conducted in Akonolinga, Ayos, and Bankim. We gathered data through focus group discussions (FGDs) and interviews around: 1) current understanding about BU pathogenesis and treatment; 2) engagement of patients with biomedical resources to diagnose/treat BU; and 3) patient utilization of traditional medicine for treatment of BU. We designed a questionnaire to determine perceived stigmatization among current and healed patients. We selected discomfort, fear, and discrimination as indicators of stigmatization. We also assessed perceptions of the disease.

We analyzed transcripts using a content analysis framework (Krippendorf 2012 and used NVivo software V.10 (QSR International, Doncaster, Australia) data management. Stigmatization questionnaires were analyzed with SPSS Statistics for Windows, V. 24.0. (Armonk, NY: IBM Corp).

Results

Between April and December 2018 we enrolled 58 participants, with seven FGDs (17 patients, 29 traditional healers, 12 HCWs) and 12 individual interviews with physicians. The psychological assessment included 74 patients, among which 58% were males, aged from 11 to 83 years. Of these patients 42% (n=74) had open ulcers.

Regarding community perspectives on BU we found that 1) the mode of transmission is unclear with a strong mystical component, 2) biomedical treatments are considered after "failure" of traditional therapies and 3) traditional and biomedical treatments are complementary in the minds of patients and traditional healers.

Traditional and biomedicine were both used 53% of patients while when asked 80% preferred modern medicine, and 20% preferred both. In our population perceived discrimination was similarly high among healed and sick patients (58%; n=43; 55%; n=31).

Conclusion

Traditional healers are a crucial component of the healthcare seeking trajectory for BU patients and are open to collaborate with healthcare workers. Healthcare workers' are on the other side less inclined. Given patient's beliefs of BU and the important discrimination, collaborations between communities, traditional and biomedical providers are key to improve BU management and reduce the stigmatization

Monitoring and auditing in randomized controlled trials on neglected tropical diseases.

Poster by Leon Franzky, Ymkje Stienstra

Only small portion of the world's health research budget is spent on the neglected tropical diseases. Randomized controlling trials are essential to improve clinical care but they are expensive and take a long time to be carried out correctly. The limited research funding may jeopardize an appropriate monitoring and auditing system. We will analyze the availability and quality of monitoring and auditing protocols of randomized controlled trials (RCTs) studying neglected tropical diseases. The available literature will be searched for relevant RCTs published between 2016 and 2019. Results will compared to monitoring and auditing in RCTs on the big three. Corresponding authors will be contacted to give more in-depth information about the nature of the monitoring and auditing during the trials. Qualitative data will be added by interviewing different stakeholders on their perception on quality of data in RCTs and the role of auditing and monitoring.

Process of formulating a community wound management strategy in Benin and Côte d'Ivoire

Poster by Flora Houndjrebo

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Introduction

Wounds are the manifestation of several neglected tropical diseases (NTDs) such as Buruli ulcer, leprosy and yaws, as well as many noncommunicable diseases including diabetes and sickle cell disease. Wounds are a significant public health problem in West Africa given their high prevalence, the level of distress that they cause and their associated socioeconomic consequences. People presenting with wounds often receive care at reference hospitals when their lesions have reached an advanced stage. Buruli ulcer screening activities in communities reveal other chronic ulcers of varied aetiology. Most of these wounds can be treated in the home with appropriate hygienic practices. Complications reported are often due to poor management within the community and inappropriate wound management is a threat to neglected tropical disease control.
It is therefore important to educate the public about wound management on the basis of an analysis of community wound care practices.

Method

Semi-structured, individual and group interviews and direct observations were conducted with patients within the community. Images depicting different types of wound, feelings and certain products were used to facilitate the interviews.

Results

We identified the following practices: drying out the wound, poor hygiene, inappropriate wound dressing, neglect of scars, lack of knowledge of signs of clinical worsening and misuse of antibiotics. Some respondents were also under the impression that health centres did not treat certain wounds.

The first awareness-raising tool developed on the basis of these practices featured two types of message – "what to do" and "what not to do" – illustrated with images and analogies. The tool proved to be useful in several pre-tests in small groups and in the community and has subsequently been validated and implemented.

Conclusion

The messages disseminated were understood and accepted by the community. However, some of the individuals involved remained sceptical of the effectiveness of the approach and were reluctant to abandon traditional wound treatment methods. This is the biggest challenge faced in awareness-raising activities.

Keywords: wound, strategies, process, NTD

Stigmatized neglected tropical diseases and obtaining informed consent for use of patients' data in an African setting: Buruli ulcer and leprosy in focus

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Introduction

Buruli ulcer (BU) is an emerging neglected tropical disease (NTD) endemic in Nigeria but its severity and magnitude is still underestimated while Leprosy remains a disease of public health importance in Nigeria. Globally, Leprosy and Buruli ulcer are the second and third most common mycobacterium infections after Tuberculosis. Both diseases also bear a considerable degree of stigma. The act of obtaining informed consent from patients affected by NTDs regarding use of their data is an ethical principle which ought to be respected in this group of people despite their vulnerability. The current study aims to ascertain the perspective and willingness of these patients to give consent to use of their data.

Method

This descriptive cross-sectional study was carried out in three states in Nigeria between August and December 2018. Data was collected from consenting participants using researcher-administered semi-structured questionnaires.

Results

The study included 112 respondents with a mean (SD) age of 34.7 (20.3) years, ages ranging from 4 to 80 years and male: female ratio of 1.03:1. Hansen's disease patients constituted 67 (59.82%) while BU patients constituted 45 (40.18%) of respondents. A total of 33 (29.5%) respondents had suffered some form of discrimination in the course of their disease. In their response, 99 (88.39%) affirmed they would give consent for their data to be used to attract a donor individual/organization and for policy development while 100 (89.29%) would allow their data to be used for teaching/training purposes. In the pretreatment period, 89 (79.46 %) would allow their pictures, 78 (69.64%) their videos and 103 (91.96%) their recorded oral interviews to be used. Post treatment, 99 (88.39%) would give consent for pictures, 90 (80.36%) videos and 104 (92.86%) oral interviews. Among those who would not give consent, the commonest reason adduced was lack of trust.

Conclusion

Even though majority of the patients would give consent for use of their data but lack of trust was a major constraint for those not willing to give consent. Caregivers and stakeholders should hence put more effort in trying to win the patients' trust before attempting to seek informed consent.

Chronic wounds, Buruli ulcer and traditional practitioners: developing a study to better understand the realities on the ground in the central Cameroonian health district of Akonolinga

Poster by Marie Thérèse Ngo Nsoga

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Introduction

Chronic wounds pose a major public health challenge in all low-income countries as they are often a source of significant functional disabilities, pain and social stigma. They incur high medical fees as well as losses of employment and income.

Buruli ulcer, a source of particularly disabling chronic wounds, is endemic in the Nyong valley, Cameroon, where the towns of Akonolinga and Ayos are located.

Over the years, we have observed that significant numbers of patients resort to traditional medicines in line with their sociocultural perspectives. The primary impact of this choice was a considerable delay in patients' access to modern and effective care in hospital settings, which most often delayed the healing of wounds and led to an increase in disabilities.

Objectives

The main aims of this study are to outline the anthropological beliefs among the populations concerned and to identify the practices and different plants used in the traditional treatment of chronic wounds such as those caused by Buruli ulcer.

Method

A multidisciplinary team comprising care workers, anthropologists, ethnobotanists and a pharmacist conducted a survey in the Akonolinga health district in October 2018. The team interviewed 206 former patients and 26 recognized traditional practitioners, 14 (54%) of which were women. The traditional practitioners interviewed were quite happy to work closely with practitioners of modern medicine: ten (38%) believed that the two types of medicine were equally valid while eight (31%) believed that they complemented one another.

Expected results and discussion

This study enabled us to build bridges with practitioners of traditional medicine. It will be useful to maintain ongoing collaboration with these practitioners: given their influence over the routes that patients take to access treatment, they may be able to help to reduce the time taken for these individuals to seek attention at specialist treatment centres.

It will also be important to work with traditional practitioners in rural areas to promote health care practices that adhere to hygienic practices and aseptic technique, specifically through regular training sessions.

Keywords: Akonolinga, traditional practitioners, Cameroon

The paediatric participation scale measuring participation restrictions among former Buruli ulcer patients under the age of 15 in Ghana and Benin: Development and first validation results

Ymkje Stienstra

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Pieter U. Dijkstra; Yves T. Barogui; Ymkje Stienstra

Background

Buruli ulcer (BU) is a neglected tropical disease caused by *Mycobacterium ulcerans*. Former BU patients may experience participation restrictions due to physical limitations, stigmatization and other social factors. A scale that measures participation restrictions among children, almost half of the affected population, has not been developed yet. Here, we present the development of a scale that measures participation restrictions in former BU paediatric patients, the psychometric properties of this scale and the scales' results.

Methods

Items were selected and a scale was developed based on interviews with health care workers and former patients in and around the BU treatment centre in Lalo, Benin. Construct validity was tested using outcomes of interviews of a convenience sample of former BU patients aged <15 who received treatment in one of the BU treatment centres in Ghana and Benin between 2007-2012. Six a priori formulated hypotheses were tested.

Results

A feasible 16-item scale that measures the concept of participation among children under the age of 15 years was developed. In total, 109 (Ghana) and 90 (Benin) former BU patients, were interviewed between 2012-2017. In Ghana 77% of the former patients had a Paediatric Participation (PP) scale score of 0 compared to 22% in Benin. More severe lesions related to BU were seen in Benin. Most of the reported participation problems were related to sports, mainly in playing games with others, going to the playfield and doing sports at school. Five construct validity hypotheses were confirmed of which 2 hypotheses related to associations with existing questionnaires were statistically significant ($P<0.05$).

Conclusion

This is the first research to confirm that former BU patients under 15-year face participation restrictions in important aspects of their lives. The developed PP-scale is most suitable for use in patients with severe lesions.

Integrated management of Skin NTDs: a NGO perspective

Poster by Patrick Suykerbuyk

Suykerbuyk P[a], Umba P[b], El Tayeb O[c], Ramiconi V[a], Roggi A[a], Ortuño Gutierrez N[a], Demeulenaere T[a].

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Introduction

Since 1964, Damien Foundation (DF), a Belgian Medical Development NGO, makes a difference in the global fight against leprosy, tuberculosis (TB), and other neglected poverty diseases such as leishmaniasis. DF succeeds in its endeavor by (i) providing medical care through training, research and targeted medical action; (ii) facilitating the re-integration of people affected by leprosy or TB; (ii) raising awareness about the medical and social aspects of leprosy and TB; and (iv) raising the required funds to achieve its objectives.
The WHO is promoting an integrated strategy for skin-related NTDs that require active detection, management and control, and is harnessing the experience of many experts involved in skin diseases to provide guidance to implement the integrated strategy in countries where skin related NTDs are a major burden[1].

Problem statement

Such an integrated management of skin NTDs, however, forces organizations as DF to step out of its comfort zone to evolve from a historic vertical-oriented, disease-specific approach to an integrated approach whereby strategic partnerships, collaborations and synergies are key to success.

Challenges, Opportunities and Perspectives

Recently, sound scientific publications highlighted the challenges, opportunities and perspectives of an integrated skin NTDs approach[2]. During the last NTD NGO Network (NNN) Conference (2018) in Addis Ababa, Ethiopia, the main learning point was that the integration of skin diseases provides an opportunity to build the capacity of primary health care workers to detect and treat a number of diseases using the same resources. Furthermore, the NNN conference identified as main key action points (i) enhancement of advocacy for integration at national and international levels and (ii) flexibility of funding from donor's perspective needed to allow integration to succeed[3].

This presentation will provide insights in the internal kitchen of a NGO to respond to this international call to action. We will discuss the potential impact on (i) the internal organizational model of DF; (ii) capacity building of HR (e.g., training) and infrastructure (e.g., sensibilization support, diagnosis and treatment); (iii) funding challenges and opportunities; (iv) research; (v) communication and advocacy; as well as (vi) local and international partnerships. Moreover, we will present our pilot projects in DRC and discuss how the Global Partnership for Zero Leprosy (GPZL) could play a catalyzing role in the integrated approach to control skin NTDs.

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Leaving no-one behind: inclusion in patient care

Poster by Franz Wiedemann

Abstract prepared by the Togolese Federation of Associations of Persons with Disabilities (FETAPH)
Partner: GIZ (Gesellschaft für Internationale Zusammenarbeit) [German Corporation for International Development]

This abstract is based around Sustainable Development Goal 10 ("Reduce inequality within and among countries") and the Convention on the Rights of Persons with Disabilities.

Inclusion is a cross-cutting issue that affects all aspects of life in society.

Should patient care end when an individual no longer needs medication, or should it continue beyond that point?

For patients with diseases such as Buruli ulcer and leprosy, the fight begins with medical intervention. How do they reintegrate into society and how do they find their way back to community life?

Inclusion must be incorporated into patient care from the very beginning and the use of relevant organizations and services should be encouraged.

Broadening the patient care network to incorporate inclusion also influences patient health care (raising awareness, reducing disability, facilitating early management of the disease thanks to the increase in available information and strengthening integration and health and social strategies.

For example, in Togo:

- FETAPH has collaborated with the health and social services, as well as NGOs;
- A cross-cutting approach has been adopted in professional education; and
- Projects must now incorporate inclusion as a matter of course.

Details:

- Maximum of 10 slides
- 15 minutes
- Includes photographs

Integration

Off target benefits of MDAs: the benefits of improving skin health as an unintended consequence of NTD intervention programmes.

Claire Fuller

Dr Claire Fuller, Chair of International Foundation for Dermatology and Consultant Dermatologist

Controlling scabies in communities with a significant prevalence as a "side effect" of MDA has several benefits. These include increased adherence to on going MDA treatment rounds as the community experienced the benefit to their quality of life with the reduced itching, to the public health benefits of reducing the downstream effects of scabies , reducing the long term sequalae of chronic renal and heart disease. This presentation will update on the progress of the International Alliance for the Control of Scabies including consistent global diagnostic criteria, impact of advocacy on policy development and a focus on the key priorities facing scabies control in resource poor settings.

Making a case for the integrated approach to skin-related neglected tropical diseases in Ghana: an analysis of human resource barriers and opportunities within a start-up project integrating three skin-NTDs (Buruli ulcer, Leprosy and Yaws)

Poster by Dr Benedict Okoe Quao

Family Medicine Specialist & Program Manager, National Leprosy Elimination Program, Ghana

The global momentum for using general health services to control skin neglected tropical diseases (skin-NTDs), requires refinement of associated task-shifting and training, to avoid repeating failures of the premature integration of Yaws and current poorly integrated leprosy services. This study takes advantage of an ongoing start-up project in Ghana integrating the control of Buruli ulcer, leprosy and Yaws, as an implementation research to outline challenges and opportunities, necessary for this novel strategy.

Questionnaires were administered to 85 front-line healthcare workers undertaking case-identification training in 3 base-project districts with established co-endemicity and district health managers interviewed as key informants, for their prior exposure and views on intended strategy vis-à-vis existing approach. Districts were assessed for skin-NTD integration comprehensiveness using a modified grading matrix, and pre- and post-training test scores analysed for potentially modifiable factors influencing training outcomes.

All 3 districts scored highly for skin-NTD integration comprehensiveness despite an apparent non-engagement of front-line clinical staff, mostly nurses (≈62% in present study). Only 3 of the healthcare workers had worked over 10 years compared to a minimum of 9 years for district health managers. 74.1% and 62.4% had received basic and post-basic training respectively in a skin-NTD, and only 52.9% had skin-NTD clinical experience, mainly in suspecting/diagnosing cases and with majority regarding prior exposure as positive. The participant's district positively influenced both pre- and post-assessment scores, whilst basic training positively influenced post-assessment scores alone. All study participants were in favour of skin-NTD integration, with the majority anticipating no challenges with future use of integrated capacity.

The high level of integration at district level, generally positive prior experiences with skin-NTDs and positive views on integration, obviously favour the move towards integration. The problem of clinical staff moving into managerial positions with greater experience, may also inversely promote integration by reducing potential opposition from health managers. There is however a great need for comprehensive basic and post-basic training to prepare front-line healthcare workers to diagnose and manage skin-NTDs. Factors influencing the distribution of staff remain important determinants of the calibre of healthcare workers available to take up new roles and must be studied and considered appropriately to ensure the success of the integrated skin-NTD strategy.

Interregional differences in the occurrence of Skin Neglected Tropical Diseases in Southern Ghana

Poster by Matthijs van Blommestein

Background

As a means to combat neglected tropical diseases (NTD) the WHO changed their strategies from disease oriented to an intervention-based approach with the goal of eliminating these diseases. Adopting additional strategies such as mapping and screening, can be useful for better understanding and fighting this group of diseases.

Methods

This retrospective observational study focused only on NTDs with manifestations on the skin (SNTDs). We collected data from four regional hospitals and one dermatology clinic in Southern Ghana. All data was collected from patients that presented in 2017.

Results

The dataset contains information of 7425 patients, amongst which 801 (10.8%) were diagnosed with an SNTD. The SNTD that presented most frequently in these four hospitals was scabies, 620 times. These SNTDs were not distributed homogeneously; 660 of the 801 SNTD diagnoses were made in one hospital. Patients that most often presented with an SNTD were children.

Conclusion

The results presented in this study clearly highlighted interregional differences in SNTD occurrences within Ghana. These differences illustrate the importance of regional mapping to reveal SNTD distribution. Diagnostic confirmation is of vital importance to make future mapping efforts more reliable. Implementing such strategies can allow a better distribution of resources and therefore aid in the management of SNTDs.

Development of tools to train health workers and monitor patients in the scope of the community wound management initiative: processes and lessons learned

Poster by Anita C. Wadagni

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Introduction

Wounds are the manifestation of several neglected tropical diseases such as Buruli ulcer, leprosy and yaws. They can also complicate several noncommunicable diseases such as diabetes, sickle cell disease and vascular failure. Wounds are a significant public health problem in West Africa given their high prevalence, the level of distress that they cause and their resulting socioeconomic consequences. WHO has recently recognized wound management as a cross-cutting issue in the control of neglected tropical diseases.
This study describes the process followed in the development of the tools formulated in the implementation of the integrated community wound management project as well as the lessons learned.

Method

This is a quasi-experimental "before-and-after" study involving the implementation of interventions in Benin and Côte d'Ivoire between January 2017 and December 2018. The study was carried out in several stages:

1. Initial data collection;
2. Development of training and follow-up tools;
3. Implementation of interventions; and
4. Post-intervention evaluation.

This study focuses on the initial data collection stage and the process of developing the training and follow-up tools. Basic data were collected by students under the supervision of their professors. The tools were developed by an international working group composed of students and professors (physicians, public health professionals and social anthropologists). The first stage consisted of an interview with health workers on the ground to identify the prevalent aetiologies of wounds in their community, assess their knowledge of and perspectives on wound management, determine their patient referral practices and describe their patients' treatment regimens and home-based wound management practices. Training modules were developed on the basis of the aetiologies of wounds observed, taking into account any locally-available patient care products; the warning signs of each wound aetiology, including signs requiring patient referrals; and advice to give to patients regarding actions to take and avoid for the purpose of adequate wound healing. Each module contains key messages that should be remembered. The modules developed are then used to train health workers according to an iterative process based on feedback from participants over the course of training. The next stage involves the development of an algorithm to aid therapeutic decision-making.

Pre-established criteria are used to categorize patients into simple cases that can be treated at home, suspicious cases that can be treated at home and cases that need to be treated at a health centre. Follow-up tools were developed and pre-tested to assess the results of training and awareness-raising activities.

Results

Eleven modules were developed to train health workers. The tools developed include a tool to raise awareness among the public; a tool to raise awareness among children in schools; an algorithm to help health workers in therapeutic decision-making; a tool for home-based wound management; and a tool for health centre-based wound management. The lessons learned in the design and development of these tools were the following: tools needed to be flexible to allow them to be repeatedly adapted to different contexts, different stakeholders needed to be involved throughout the tool development process and local realities needed to be understood to ensure that the concepts taught will be accepted and implemented.

Conclusion

The tools created in the scope of the integrated community wound management project are innovative, unique, appropriate to the context of developing countries and easily adaptable to various contexts.

Keywords: Wounds, community, Benin, Côte d'Ivoire

Surveillance

Implementing active community-based surveillance-response system for Buruli ulcer early case detection and management in Ghana

Poster by Collins Ahorlu

Background

Buruli ulcer (BU) is one of the most neglected debilitating tropical diseases caused by *Mycobacterium ulcerans*, which causes considerable morbidity and disability. Building on earlier findings that community-based interventions could enhance case detection and reduce treatment dropout and defaulter rates, we established an active surveillance response system in an endemic sub-district in the Ga West Municipality of Ghana to enhance early case detection, diagnosis and treatment to reduce severe ulcers and its related disabilities.

Methods

We established surveillance response system, implemented in collaboration with the sub-district disease control officers, selected clinical staff and trained community-based volunteers. The active community-based surveillance- response system was implemented for 12 months. Also, pre and post intervention surveys were conducted to document any change in perceptions on BU in the study population over the period. The baseline and endline surveys were conducted in August 2016 and August 2017 respectively.

Results

On average, each person was seen 11 times in 12 months. In all 75 skin lesions were detected during surveillance rounds, out of which 17 were suspected to be BU and 12 out of the 17 were confirmed as BU using Polymerase chain reaction (PCR). Out of the 12, five, three and four were categories I, II and III lesions respectively. Physical examination was done on 94% of the people seen during the surveillance rounds. Knowledge on BU has also increased in the communities at the end of the study.

Conclusion

Findings from this study have demonstrated that, it is possible to establish surveillance-response system for BU and by extension, other neglected tropical diseases to enhance control and elimination efforts through the use of community-based volunteers.

Modelling the distribution of *Mycobacterium ulcerans* infection in Lalo commune, Benin

Esaï Anagonou

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Introduction

Climate change is causing alterations in the environment that in turn affect the geographical distribution of living organisms. Buruli ulcer is a necrotizing infectious skin disease caused by *Mycobacterium ulcerans*, an environmental mycobacterium. The disease is endemic in tropical and subtropical regions and in environmental conditions that favour the pathogen's development. Changes in the environment may affect the geographical distribution of this disease in endemic areas. This study therefore examines the influence of climate change on the geographical distribution of Buruli ulcer in Lalo, Benin.

Method

We applied the principle of maximum entropy to model the likely geographical distribution of this disease under current and future climate conditions in the comune of Lalo on the basis of environmental variables and the points of presence of the disease.

Results

Of the variables selected in the modelling process, the variable relating to precipitation in the most humid quarter contributed to the development of the final model. The climate conditions in 80% of the air in Lalo commune suggested a reduction in the prevalence of Buruli ulcer by 2050. The results of this model are consistent with national epidemiological data that show that the number of Buruli ulcer cases fell from 1203 in 2007 to 267 in 2017.

Conclusion

Our study showed that future climate conditions will hinder the prevalence of *Mycobacterium ulcerans*. In view of the scarcity of resources allocated to Buruli ulcer control, these projections will help to efficiently guide actions taken in this regard. However, these results should be interpreted with caution and in consideration of other environmental and anthropic factors.

Keywords: Buruli ulcer, modelling, distribution, Benin

Re-emergence of yaws in Benin: a study of four cases confirmed in Zè commune

Poster by Adjimon Gilbert Ayélo

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Introduction

Yaws surveillance resumed in Benin in 2012 to support the global strategy to eradicate the disease. After two unsuccessful attempts in 2012 and 2013 to survey its prevalence, in 2016 the National Leprosy and Buruli Ulcer Control Programme (PNLLUB) launched a campaign of mobile consultations to provide comprehensive screening for neglected tropical diseases requiring case management. This study describes four cases of yaws screened in Zè commune during a mobile consultation campaign carried out in 2018.

Method

In the fourth quarter of 2018, the Allada Buruli Ulcer Screening and Treatment Centre organized a mobile consultation campaign covering 15 districts of the Atlantique department. People living in these districts were advised of the activity in advance. All patients with skin lesions were examined in accordance with medical ethical guidelines. All children under 15 years of age underwent a rapid diagnostic test (RDT) for yaws and any testing positive were then tested using the DPP® Syphilis Screen & Confirm Assay.

Results

Of the 779 children presenting with dermatological lesions and who were subsequently tested, eight tested positive via RDT and four of these cases were confirmed by DPP. These children, of which three were male and one was female, were all aged 4 to 8 years. Two presented with papillomas and two had several ulcers. Three of the children lived in Gandaho village, Dodji Bata arrondissement, and one lived in Agonzounkpa village, Dawé arrondissement. The average lesion evolution time was 120 ± 34 days. All patients received a single dose of 30 mg/kg of azithromycin. The cases were reviewed two and four weeks later and all patients had recovered.

Conclusion

These cases confirm the endemicity of yaws in Benin, suggesting that in-depth research is needed to map the prevalence of the disease and determine actions to be taken towards its eradication.

Keywords: Neglected tropical diseases, yaws, eradication, Benin

Is Buruli ulcer decreasing in Cameroon ?!

Poster by Yap Boum

Introduction

Cameroon is a Buruli ulcer (BU) -endemic region, yet very few cases have been reported in recent years. In an ongoing diagnostic study, conducted by Epicentre/MSF, Fairmed, Cires and the Ministry of Health, we enrolled patients with chronic wounds in Cameroon.

Methods

Between January and December 2018, we enrolled patients affected with chronic wounds in the endemic Districts of Akonolinga, Ayos and Bankim all located along the Nyong River. We used different active research strategies including sensitization of community health workers, traditional healers and former patients to refer patients, visits to health centers and village authorities, massive awareness campaigns in key villages. Patients were enrolled at health district hospitals and medical health centers where wound samples were collected and sent to the Centre Pasteur du Cameroon for PCR analysis. Patients' demographic data were collected through the mobile data collection platform CommCare HQ – Dimagi. Basic statistical analysis was performed using R software (version 2.15.1).

Results

We enrolled 180 patients with chronic wounds. Patients age ranged from 1 to 82 years (median=30), and 64% (N=165) were males. Nearly half of the participants had PCR confirmed Buruli Ulcer (45%, N=157). Of the Buruli Ulcer positive patients, 40% were found in Akonolinga, 33% in Bankim, and 27% in Ayos. Most of the patients had wounds in their lower limbs (71%, N=172). Only 22% (N=71) of patients had wounds that were completely healed after the WHO recommended 8 weeks of treatment. We had 27% (N=116) loss of follow-up.

Conclusion

Despite the reported decrease of BU in Cameroon we have confirmed 70 cases in 2018 in only three districts. This highlights the importance of surveillance and community awareness to reach patients and ensure that individuals with chronic wounds receive proper diagnosis and treatment.

Buruli ulcer in Papua New Guinea

Wendy Houinei

Buruli ulcer was first reported in Papua New Guinea between the years 2003 to 2007 with 200 cases. From 1989 to 2002 there data was not available due to proper records not kept. Then from 2007 to 2011 PNG reported another 105 cases according to the records that were kept. All these reported cases were from only one provinces that had at least some form of awareness and sensitization of health care workers by the Program Manager for the National Leprosy Program back in 2007 and also by one of the expatriate surgeon who was working in that province who actually had done some surgical procedures and identified those cases as Buruli ulcer.

The Neglected Tropical Diseases programme started in 2012, that we started off with creating awareness and sensitization and conducted training integrated with the National Leprosy program to health care workers in three of the seven suspected provinces with Buruli ulcer. After these few trainings the National NTDs program developed a database for Buruli ulcer for the country with the three provinces reporting cases.

According to the records that the NTDs program had between the years 2007 to 2016 the reported number of Buruli ulcer cases were 136, of these 128 were new cases whilst 8 were recurrent cases. There were 102 cases with ulcers and 34 cases with oedema, 59 of these patients were males and 71 patients were females and these were all new cases. The under 15 years old that had Buruli ulcer were 75 cases, 39 males and 36 females which made up 53% of all Buruli ulcers cases reported during that period.

The activities that the NTDs program carried out between 2017 and 2018 is not much but at least we had done some work in terms of monitoring and supervisory visits to the health facilities that are reporting BU cases and distribution of the BU drugs for patients that were commenced on treatment.

For these period 2017 and 2018 PNG has reported 20 Buruli ulcer cases.

Buruli ulcer data 2017-2018

Papua New Guinea	New cases	% PCR confirmation	% completing antibiotic treatment	% children <=15 years	% females	% limitation of movement	% ulcers	% lesions location on lower limbs	% category I	% category II	% category III
2018	12	15.4	92.3	15.3	53.8	69.2	84.6	54	38.5	38.5	23
2017	7	14.3	100	85.7	57.1	85.7	85.7	43	28.6	42.8	28.6

The data analysis in the table above is summarised from the Buruli ulcer cases reports from the health facilities within the three (3) provinces currently reporting cases in the country. There were 20 reported cases between 2017 and 2018, of these cases 19 are new cases while 1 was a recurrent case.

The challenges that we have like all other countries are;

1. Improve case detection, especially early case detection
   - Develop information and awareness
   - Develop case detection in peripheral areas
   - Lack of training for health care workers

2. Inadequate Funding

3. Low commitment of government

The search for Buruli ulcer in Sierra Leone

Poster by Helen Please

Authors: Dr H Please; Prof J Scott; Dr W Bolton; Ms R Patel; Dr J Vas Nunes; Prof M Grobusch; Dr H Bolkan; Prof G Pluschke; Professor D Jayne

Group: NIHR Global Health Research Group, Surgical Technologies (GHRG-ST), University of Leeds, UK

Aims

No Buruli Ulcer (BU) cases have been confirmed in Sierra Leone since 2011 (28 cases), likely due to limited diagnostics in-country, with prior data limited to a single case in 2008 (Global Health Observatory data repository, WHO). Despite this, suspected cases are clinically identified in hospitals country-wide and pragmatically treated as BU. This lack of diagnostic certainty impacts patient care and limits the potential for BU research development in this country. This study therefore aims to establish the presence of BU in tissue samples from suspected BU cases at Masanga Hospital.

Methods

Patients with wounds clinically suspected to be BU will be identified at Masanga Hospital over a one-month period (Feb to March 2019). Tissue samples will be obtained by swab, fine-needle aspiration or biopsy, according to clinical indication. These will be stored and transported to the Swiss Tropical and Public Health Institute for analysis (including PCR, culture and histopathology) to determine the presence of BU or other neglected tropical diseases (NTDs) of the skin. As no storage method is shown to be superior in preserving samples for distant analysis when a cold-chain is lacking, samples will be subdivided between multiple storage types when possible. These include dry samples without preservative; preservation in absolute ethanol; preparation as a DSE smear; preservation in culture medium; and paraffin preservation for biopsies. In addition, clinical and examination findings will be recorded, including standard photography and a novel wound assessment smartphone application.

Expected results

In light of the clinical impression of BU at Masanga Hospital, we expect to confirm this by reliable tissue diagnosis, supported by clinical findings and medical photography. Other outcomes include recruitment rates and feasibility of storage methods, which could inform study design of future studies in similar settings. Finally, this work aims to supplement the growing clinical registry of NTDs being established in Masanga, aiming to improve monitoring, diagnosis and management of these diseases.

Impact of climate change on the epidemiology of Buruli ulcer: analysis of a hypothesis

Poster by Ghislain Sopoh

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Climate change refers to changes in meteorological conditions directly or indirectly caused by human activity. Climate change affects the health of populations, specifically by altering the composition of the air that we breathe and influencing the temperature and frequency of certain meteorological events. These changes occur in addition to natural changes in the climate. Climate change poses a significant new threat to public health. Variations and alterations in climate cause death and disease through natural disasters that result from these changes, including heatwaves, floods and droughts, as well as consequent epidemiological changes in several diseases, including prevalent vector-transmitted diseases such as malaria and dengue, malnutrition and diarrhoeal diseases and chronic diseases. Climate change affects the social and environmental determinants of health. The populations of developing countries are particularly vulnerable given the low levels of resilience in their health systems. In these countries, children under 5 are at the highest risk of climate-sensitive diseases such as malaria and diarrhoeal diseases. WHO estimates that the cost of direct damage to health (excluding costs in sectors linked to health such as agriculture, water and sanitation) will be US$ 2 billion to 4 billion per year by 2030.

In this study, we analyse the likely impact of climate change on the epidemiology of Buruli ulcer in Benin and Australia.

Diagnosis

Challenges associated with the biological confirmation of suspected cases of Buruli ulcer with negative PCR results in an African country with limited resources

Poster by N'Guetta Aka

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Introduction

Buruli ulcer is a skin NTD caused by an environmental mycobacterium named *M. ulcerans*. It is endemic in around thirty humid tropical and intertropical countries. Since 2008, WHO has recommended that 70% of suspected cases should be confirmed by PCR targeting the IS*2404* insertion sequence and ketoreductase. To this end, the Ivorian National Buruli Ulcer Control Programme (PNLUB) has collected and transferred exudate specimens from peripheral health centres to the national Buruli ulcer reference centre at the Côte d'Ivoire Pasteur Institute. Although PCR testing has detected the IS*2404* sequence in 61% of cases, thereby implicating *M. ulcerans*, no aetiology has been identified in 39% of suspicious lesions. However, in accordance with national guidelines, all patients with suspected Buruli ulcer receive antibiotic therapy regardless of the result of the confirmatory PCR test. This treatment has proven to be effective, but it is labour-intensive for medical professionals and traumatizing for the patient given the risk of accidents. It is therefore worth considering whether suspected cases of Buruli ulcer testing PCR-negative have been misdiagnosed or if these lesions were caused by pathogens other than *M. ulcerans*. In other words, should all suspected cases of Buruli ulcer receive immediate antibiotic therapy before they are confirmed by a microbiological test? This study was conducted in two health districts in Côte d'Ivoire with the aim of improving the management of skin lesions suspected to be linked to Buruli ulcer. Our objective was to improve the biological confirmation procedure and propose a clinical and biological decision-making algorithm to manage suspected cases of Buruli ulcer.

Patients and methods

Patients with suspected Buruli ulcer were recruited in the health districts of Tiassalé and Oumé using the UB01 form. Biological specimens were collected using the UB03 form and transferred to the national Buruli ulcer reference centre within two to three days. A microscopic examination was conducted, cultures were prepared and a PCR test targeting the IS*2404* sequence was carried out. The results were communicated to health care providers within 3 to 5 days. The quality of the confirmatory tests was externally assessed at the Antwerp Institute of Tropical Medicine.

Results

A total of 114 patients with suspected Buruli ulcer were enrolled: 46.5% were male and 53.5% were female; 56.1% were aged 17 years or under; and 58% of patients presented with ulcerative skin lesions and 42% presented with pre-ulcerative lesions. In total, 84.6% of cases tested positive using the three biological methods. Initial specimens tested positive in 63.2% of cases, and second and third specimens tested positive in 19.3% of cases. No mycobacteria were detected during the follow-up period in 17.5% of suspicious lesions.

Conclusion

The approach used in this study improved positivity rates, enhanced communication between screening centres and the reference laboratory during patient follow-up, reduced the time between the collection and retrieval of results, improved data quality and provided a model for the management of suspected cases of Buruli ulcer.

Biological confirmation of Buruli ulcer in Côte d'Ivoire from 2017-2018

Solange Kakou Ngazoa

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Introduction

(BU) is a neglected skin disease caused by *Mycobacterium ulcerans* and occurs in rural regions in central and in West Africa. The biological confirmation of BU required molecular diagnosis test confirmation. Since 2009, the number of BU cases was increased in Côte d'Ivoire. The surveillance was applied in the country with the implication of World Health Organization (WHO) to control and to eradicate BU. The clinical evolution of the disease has two steps by early nodula and ulcers forms. To improve the diagnosis and the surveillance of BU infection, WHO has recommended the laboratory confirmation of at least 70% of suspected BU cases. The objective of this study is to present the biological molecular diagnosis of MU in Côte d'Ivoire in 2015-2016.

Materials and methods

The samples were collected in 2017-2018 from suspected cases of BU in all sanitary districts coordinated by the national program of Buruli Ulcer. The patients were from the national program, from NGOs and other clinical structures. Briefly, 2 ml water were added to the clinical samples and well mixed. After centrifugation the pellet was resuspended in 200 µl sterile water. The alcaline lysis was applied and the extracted DNA was used in PCR methods. The real time PCR was done with 5 µl DNA and 20 µl PCR Master-mix.

Results and conclusion

The positivity rate of PCR was 46.82% and 29,5% for 2017 and 2018. Our results reveal BU endemic districts sites in the country.

The molecular diagnosis of MU has recently become a routine test for all BU cases and has improved the biological confirmation of BU in Côte d'Ivoire.

Mots clés: Buruli ulcer, *M. ulcerans*, PCR, Côte d'Ivoire, West Africa.

A simple ELISA for the detection of mycolactone in biological samples

Poster by Louisa Warryn

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The polyketide macrolide toxin mycolactone is the key virulence factor of *Mycobacterium ulcerans* and responsible for the chronic necrotising pathogenesis of Buruli ulcer (BU). All mycolactone producing mycobacteria (MPM) are considered to be members of the species *M. ulcerans,* making the toxin an ideal marker for the specific diagnosis of BU. Since the half-life of mycolactone in the affected tissue is considered to be low, determination of the concentration of mycolactone may furthermore be a suitable marker for the killing of the pathogen during treatment of the disease.

We have generated series of monoclonal antibodies (mAbs) specific for mycolactone by the B cell hybridoma technology, using spleen cells from mice immunised with protein conjugates of truncated synthetic mycolactones. Characterisation of the binding properties of these mAbs culminated in the development of a competition ELISA highly specific for mycolactone detection in biological samples. ELISA plates are coated with anti-mycolactone antibodies and the replacement of a synthetic reporter molecule by mycolactone present in the test samples is measured. Extensive optimisation of parameters of the assay, including definition of ideal coating conditions, development of a unique buffer, and selection of an optimised reporter molecule, enabled the development of a highly specific assay.

The utility of the mycolactone assay has been assessed using synthetic mycolactones, showing that all known natural variants are recognised. Mycolactone could be detected in *M. ulcerans* culture supernatants directly without extraction of mycolactone with organic solvents or other processing. In addition, we have been able to reliably detect mycolactone in footpads from mice experimentally infected with *M. ulcerans*. After final optimisation, the ELISA may be suitable as a diagnostic test for hospital settings. Furthermore, conversion of the ELISA into Rapid Diagnostic Test (RDT) format for use as a point-of-care diagnostic tool is intended.

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Related publication:
Dangy J.P, Scherr N, Gersbach P, Hug M.N, Bieri R, Bomio C, Li J, Huber S, Altmann K.H, Pluschke G. Antibody-mediated neutralization of the exotoxin mycolactone, the main virulence factor produced by *Mycobacterium ulcerans*. *PLoS Negl Trop Dis*. 2016; 10(6):e0004808.

Other skin NTDs

Applying Insects' product for treatment of cutaneous leishmaniasis

Poster by Fatemeh Ghaffarifar

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The Cantharidin is a natural compound mostly secreted by male blister beetles of Meloidae family. Cantharidin has been used for treatment warts and molluscum contagiosum by topical application.When cantharidin is applied to the skin, it causes acantholysis and blister formation. Cantharidin is absorbed by the lipid membranes of epidermal cells. In the inflammatory blister technique, cantharidin causes the skin under the lesion to be blistered. When the blister dries. The lesion peels off with the blistered skin. After the lesion is gone there usually remains no scarring. In some parts of Kerman province in Iran, meloid beetles have been used as traditional medicine for treating cutaneous leishmaniasis. Crushing only one beetle on leishmanial lesion is sufficient to heal the lesion with minimum scarring. We used cantharidin for treatment of leishmaniasis in vitro and in vivo. For in vitro we used 0.5-50 µg/ml andfor in vivo we used ointment wit 0.1 % cantharidin once a day for 2 weeks. In inflammatory blister technique we used 25 µl of 0.1 % cantharidin only once time.

One other insect products is honey that produced by bees and has antimicrobial effects. Apart from sugars, Honey attributed to the low pH (acidity) and contains several minerals such as calcium, copper, iron, magnesium, manganese, phosphorus, potassium and zinc that most of them have antileishmanial effect. In our study we shown honey has excellent results in vitro and in vivo and has apoptosis effect on promastigotes of *Leishmania major*. Experimental study have demonstrated that application of honey to severely infected cutaneous leishmaniasis alone or with other treatment accelerate the wound healing and improves tissue healing.

Nosological designations for leprosy and their impact on stigmatization in Benin

Poster by Ronald Gnimavo

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Introduction

Leprosy is a treatable infectious disease that causes serious complications in the absence of early diagnosis and treatment. This study aims to assess the level of awareness of leprosy among Beninese communities and to describe nosological designations of leprosy and their impact on stigmatization.

Method

This was a cross-cutting qualitative study conducted from 1 February to 31 March 2018 in different regions of Benin. We engaged in nonprobability sampling, specifically convenience sampling, to administer a questionnaire to individuals living in communities with people affected by leprosy. The qualitative data collected were processed manually.

Results

Sixty participants were included in the study with an average age of 33.7 ± 8.57 years, most of which were women (gender ratio: 0.54). For 85% of respondents, the earliest manifestation of leprosy was disability. Spells were reported as the cause of leprosy in 90% of cases. In some socio-ethnic groups, the name given to leprosy referred to divine retribution, fear or rejection. For example, the Yindé people call leprosy "*ouwenento*", which means "the flame of God that burns and consumes the afflicted individual". Physical appearance and fears of infection were the main reasons given for the rejection of patients with leprosy.

Conclusion

This study demonstrates the need to raise public awareness of the early signs of leprosy and the urgent need to promote interventions to dispel discrimination towards people affected by leprosy.

Keywords: Leprosy, nosology, stigmatization, Benin

Day 2

Research

Poster Session

Diagnostics

E-nose detection of Buruli ulcer in the DRC

Poster by Stan Chudy

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Introduction

Microscopy, which is the cheaper, easier and most available diagnostic method for Buruli ulcer (BU) in endemic areas, is not optimal due to low sensitivity. qPCR for the IS*2404* target has excellent sensitivity and specificity, nevertheless it requires sophisticated laboratories with strict quality control as it is prone to false positives. As patients in remote areas seldom have rapid access to molecular diagnostics, a reliable point-of-care test can save valuable time and allow for confirmation of BU during active case-finding.

For years, physicians in Sub-Saharan Africa have reported a characteristic odour of BU lesions. This provided grounds to engage in a smell-based approach towards a non-invasive point-of-care diagnostic test with an electronic nose (e-nose). Building on a pilot study conducted in autumn 2016 in Benin, the current study reflects a standardised approach using gauzes worn for 24 hours sampled in sterilized dedicated jarsto reduce background odours, compared against the clinical diagnosis and qPCR as diagnostic reference.

Materials and Methods

The sample consisted of 12 BU and 37 non-BU patients treated in the reference hospital Institut Médical Evangélique de Kimpese as well as surrounding health centres in the rural Kongo Central province in the Democratic Republic of the Congo. In the present study we used the Cyranose 320, a hand-held e-nose with 32 nanocomposite sensors, which can be operated on an external battery and solar power. Soiled gauzes were sampled in a glass jar with two outlets in the lid. The e-nose was connected to one outlet and a carbon filter to the other to limit environmental VOCs.

Results

Using a Principal Component Analysis, the output of the 32 sensors was compressed and statistically analysed by means of an independent sample t-test or a one-way ANOVA to determine whether there was a significant difference between the pattern of smell in gauzes from BU patients versus non-BU patients. The analysis was conducted using three different approaches: stratifying the samples by (i) the clinical diagnosis, (ii) the result of the qPCR analysis, (iii) or a combination of the latter, creating a BU-group (qPCR positive), a suspected BU-group (clinically positive ; qPCR negative) and a non-BU group (clinically and qPCR negative). The preliminary results do not show a statistically significant difference in the smell pattern between the groups (*p=0,34-0,93*), with poor sensitivity (0-16,7%) and high specificity (97-100%) after cross-validation, meaning that almost all samples are classified as non-BU.

Conclusion

Although e-noses have been used in an increasing number of medical research settings in recent years, they have primarily been used for breath analysis. To our knowledge, this pilot study is the first in which BU lesions are analysed by means of an e-nose. Despite a standardised smell detection method we did not identify an association with patient's disease status.

One hypothesis for the lack of statistical significance is the non-specific origin of volatiles captured in the soiled gauzes (i.e body odours, tissue debris and exudate). Using swabs or fine needle aspirates from (BU) nodules might be a valid alternative for further research, as these are easier to collect and might provide an untainted smell. When developing this smell-based method in the future, a high-sensitivity is desirable, after which quality assured qPCR analysis can be used to confirm test results. Further steps, including thermal desorption tube based VOC analysis, may confirm or refute the clinician's nasal acumen.

Molecular tools to improve the understanding of yaws in Ghana

Poster by Michael Marks

Morgan Munson, Benjamin Creswell, Cynthia Kwakye, Kofi Kondobala, Bawa Ganiwu, Rita Dede Iomotey, Paul Oppong, Frederick Opoku Agyeman, Nana Kotye, Mukaila Diwura, Ebenezer Padi Ako, Harry Pickering, Rebecca Handley, Joanna Houghton, Robert Butcher, Michael Marks

Background

Lesion swabs are required to make an accurate diagnosis of active yaws. Currently swabs are collected in transport medium and maintained in a cold chain. This is logistically challenging and adds expense. Studies of syphilis and other infections have suggested transport medium may not be needed for PCR based diagnostics.

Methods

The study was conducted in the Eastern Region of Ghana. Children with yaws-like ulcers were screened with the SD Bioline syphilis and the DPP Syphilis Screen and Confirm test. Up to 5 yaws-like lesions per individual were identified. We identified the largest, most exudative lesions first. From this lesion paired swabs were collected – one into transport medium and one as a dry swab. From a maximum of four subsequent lesions we collected additional dry swabs. Swabs in transport medium were placed into a cool box and were frozen within 6 hours. Swabs were then shipped on dry-ice for testing. Dry swabs not in transport medium were stored and shipped at ambient temperature. Swabs were tested by PCR for Treponema pallidum and Haemophilus ducreyi.

Results

A total of 55 DPP positive children with suspicious skin lesions were enrolled. Overall, 10 patients had at least 1 positive PCR result for yaws. 12 patients had at least 1 positive PCR result for *H. ducreyi*.

Of the 55 children included in this study, 53 had both a transport medium and a dry swab collected from the target lesion at baseline. There was no difference in the PCR results between swabs collected in transport medium and maintained in a cold chain and dry swabs stored at ambient temperature.

	Transport Medium Swab	Dry Swab
Positive for *T. pallidum*	9/53	9/53
Positive for *H. ducreyi*	9/53	9/53

<u>Additional non-target lesion swabs</u>

Overall we collected 111 baseline swabs across the 55 enrolled patients. 14 (12.6%) of these swabs were positive for *T. pallidum*. Of these, a total of 9 swabs were from target lesions. 4 swabs were positive from secondary lesions of patients whose target lesion was also PCR-positive for yaws. One patient had PCR confirmed yaws diagnosed based on the swab of a third lesion when both the target and secondary swabbed lesion were PCR-negative. This patient would have been missed if only the target lesion was swabbed.

Conclusions

This study suggests that storing swabs in transport medium provides no additional diagnostic benefit. Despite the small sample size, swabbing additional lesions increased the diagnostic yield in yaws in this study. This could therefore be important in the push for eradication as prevalence approaches zero and sensitive tools are required to detect the last cases of yaws.

Transmission

Buruli ulcer in two neonates: providing insight into incubation period of *M. ulcerans* disease in this age group

Poster by Yaw Amoako

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Introduction

Buruli ulcer (BU), caused by *Mycobacterium ulcerans* and endemic in parts of West Africa, is uncommon among neonates. We report on cases of confirmed BU disease in 2 HIV unexposed, vaginally delivered, term neonates from the Ashanti region of Ghana suggesting a remarkably short incubation period.

Case presentations

The clinical characteristics of the two patients from BU endemic areas are presented in table 1.
Patient 1: Two weeks after hospital delivery, her mother noticed a papule with associated oedema on the right anterior chest wall and neck which later ulcerated. There was no restriction of neck movements. The diagnosis of BU was confirmed on a swab sample which was PCR positive for the IS*2404* repeat sequence of *M. ulcerans*.

Patient 2: The mother reported noticing a swelling in the baby's left gluteal region 4 days after birth. The lesion progressively increased in size to involve almost the entire left gluteal region. Around the same time, the mother noticed a second smaller lesion on the forehead and left side of neck. The diagnosis of BU was confirmed by PCR when the child was aged 4 weeks.

Both patients were treated with oral rifampicin and clarithromycin (at doses of 10mg/kg and 15mg/kg respectively) for 8 weeks in addition to appropriate daily wound dressing. Their ulcers healed completely by the end of antibiotic treatment but they developed contracted scars. Surgery to correct the deformities is planned by the plastic surgeon.

Discussion

To the best of our knowledge, there has not been any previous report of confirmed BU in neonates from Ghana. Our report details 2 cases of PCR confirmed BU in children whose lesions appeared at age 14 and 4 days.

The mode of transmission of *M ulcerans* infection is unknown so the incubation period (IP) is difficult to estimate and is probably dependent on the infective dose and the age of exposure. New BU lesions occurred in refugees from a non-endemic area 4 - 13 weeks after their arrival in an endemic area in Uganda. In two Australian studies, the median IP were estimated as 135 and 143 days with the shortest period given as 32 days. BU has been observed in 18-day to 6-week old babies in Papua New Guinea, Democratic Republic of Congo and Uganda.

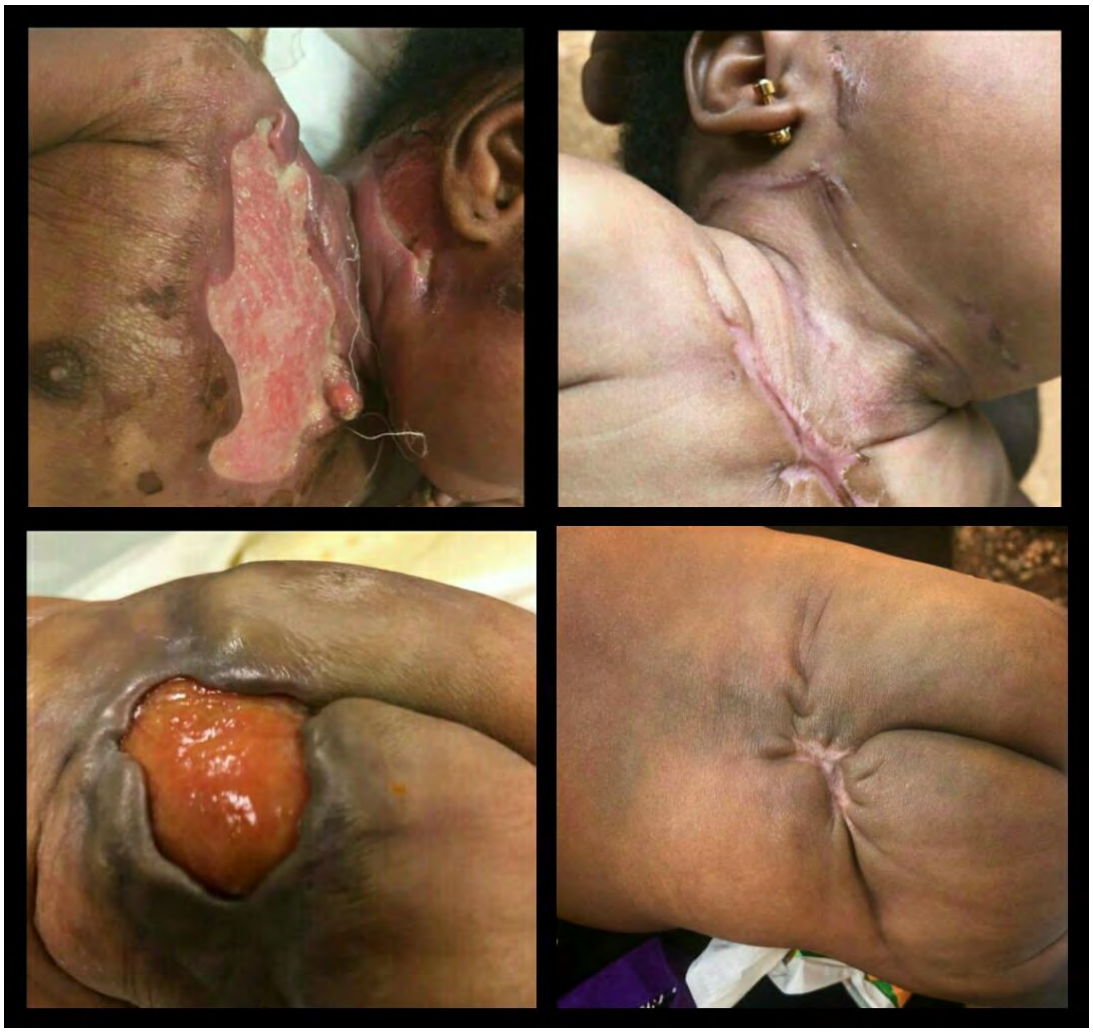
In the present study, lesions appeared 4 days after birth in patient 2. Unless infection was acquired in utero, this would be the shortest IP ever recorded. There was no evidence of BU in the mother so it must be assumed that the baby was exposed to a *M. ulcerans* contaminated water source shortly after birth. As neither the mothers nor the babies in this report were HIV infected, the short IP probably resulted from immaturity of the neonatal immune system. Another explanation would be that the babies were exposed to a high infection dose but there is no way of confirming this.

There was evidence of symptomatic secondary bacterial infection in both the patients reported in table 1. However the ulcers did not start to heal until specific therapy for *M. ulcerans* was administered. Secondary bacterial infection with *Staphylococcus aureus* and *Escherichia coli* have been reported as common isolates, usually sensitive to gentamicin as was the case in our patients.

Conclusion: BU should be included in the differential diagnosis of neonates who present with characteristic lesions especially in individuals from endemic communities. The IP of BU in neonates is probably shorter than is reported for adults.

Table 1 Clinical parameters of 2 Ghanaian neonates with Buruli ulcer disease

Characteristic	Patient 1	Patient 2
Community	Ejisu	Atwima Nwabiagya
Mode and location of delivery	Vaginal, hospital	Vaginal, home
BCG vaccination at birth	Yes	Yes
Lesion site	Chest and neck	Left gluteus, left neck
Type of lesion, WHO category	Oedema/ ulcer, category 2	Ulcer, category 3 (multiple lesions)
Age (in days) when lesion was first seen	14 days	4 days
Age of neonate at PCR confirmation of BU	5 weeks	4 weeks
Use of topical herbs	Yes	Yes
Temperature	36.3^{o}C	37.9^{o}C
Ulcer healing by end of antibiotic treatment	Yes	Yes
Development of contracture	Yes, corrective surgery planned	Yes, corrective surgery planned
Secondary bacterial infection of ulcer/ antibiotic sensitivity	*Staphylococcus aureus*/ Gentamicin	*Escherichia coli*/ Gentamicin



Before and after treatment photos of two cases of neonatal BU. Patient 1 in the upper quadrant and Patient 2 in the lower quadrant.

The influence of climatic variations patterns to the development of *M. ulcerans* infections in the Brong Ahafo Region of Ghana.

Poster by Samuel Fosu Gyasi

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Buruli ulcer is an ulcerated disease of the skin, subcutaneous tissue and sometimes the bone. This disease is caused by *Mycobacterium ulcerans*. The aim of this study was to investigate some climatic patterns to the proliferation of Buruli Ulcer in Brong Ahafo Region, Ghana. In this study, data on daily clinically confirmed cases of *Mycobacterium ulcerans* infection at the Goaso District Hospital (Brong Ahafo Region) were collected from 2008 to 2018. This was compared with daily environmental data collated from the Brong Ahafo Regional Meteorological Unit over a period of one decade. Data harvested included, daily temperature, rainfall and humidity from 2008 to 2018. A graphical presentation of the data showed that, an increase in average rainfall patterns from 2008 to 2010 showed a corresponding rise in the average Buruli Ulcer cases (25 to 50). The average relative humidity were also monitored daily where yearly means were compared with daily reported cases of BU over 10 years in the Brong Ahafo Region of Ghana. Results of this analysis also showed that, a rise in relative humidity from 8% to 15% (2008 to 2010) showed a corresponding rise in OPD reported cases of BU from 67 to 70 over the same period. There were also some correlation between thermal stratification from 2008 to 2018 and clinically confirmed cases of BU within the study area. A decline in temperature from 2013 showed a dip in *M. ulcerans* numbers over the period. It can be concluded from this study that, variations in climatic patterns in the Brong Ahafo Region of Ghana has a positive correlation with Buruli ulcer disease.

Molecular evidence of the implication of non-*M. ulcerans* pathogens in skin diseases liked Buruli ulcer using PCR targeting the insertion sequences and the ketoreductase gene

Poster by David Coulibaly N'Golo

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Introduction

Buruli ulcer (BU) is a neglected but treatable skin disease endemic in more than 30 countries. Côte d'Ivoire is the most affected country with about 1500 cases per year. *Mycobacterium ulcerans* (*Mu*), the causative agent is an environmental *mycobacterium* with an elusive mode of transmission to humans. Its virulence is related to the secretion of a toxin: the mycolactone, whose expression genes are carried by a plasmid. Today, it is recommended that at least 50% of clinical cases be confirmed by a PCR method using mainly two targets: the IS*2404* insertion sequence and the Ketoreductase gene (KR) characterizing the presence of the virulence plasmid.

Objective

The objective of this study is to use some targets referenced in the literature to detect *Mu* and show that many pathogens could be implicated in skin lesions seems to be BU cases characterizing the presence of the virulence plasmid.

Methodology

This study enrolled patients clinically diagnosed for BU because presenting skin lesions observed in the disease. Samples were cultured on Löwenstein- Jensen and 48 isolated strains diagnosed using 4 PCR targets: The IS6110 to first confirm they belong the genus *Mycobacterium sp.* , then we characterized *M. ulcerans* species by searching for the IS*2404*, IS*2606* insertion sequences consecutively (Figure 3). The presence of the plasmid involved in the synthesis of the mycolactone has been also searched. Two african reference strains ITM 97-483 and ITM 94-821(Côte d'Ivoire and Ghana) have been used as PCR control.

Results

Twenty eight out of the 48 isolated strains were positive for all the insertion sequences and the KR gene. Based on Insertion sequence and KR, three (3) profiles were found: the Profil A (IS*6110*+,IS*2404*+,IS*2606*+,Kr+)(58.5%) characteristic of *Mu* strains, the Profil B (IS*6110*+,IS*2404*+,IS*2606*-,KR+)(8.5%): specific for *M. marimum* and other *Mycobacteria producing Mycolactone (MPM)* and the Profil C (IS*6110*-,IS*2404*+,IS*2606*+, KR+)(10.5%): corresponding to non-Mycobacteria strains that carrying the insertion sequences specific to *Mu* and the Ketoreductase gene.

Discussion

Profile A is the main characteristic of *Mu* strains: they have the IS*2404* and IS*2606* insertion elements and they could have or not (losted plasmid) the polyketid synthetase (KR) gene to express virulence. Some mycobacteria strains like *M. marinum* (Profile B) possess the IS*2404* but not the IS*2606* insertion element and produce Mycolactone: they are called Mycobacteria producing Mycolactone (MPM) so they molecular identification is to be IS*2404*+ and KR+. We identified non- mycobacteria (Profile C) which not belong to the mycobacteria genus because of negative IS*6110* PCR but they possess the insertion elements IS*2404* and IS*2606* and the KR gene. On the basis of culture on Löwenstein-Jensen Those strains could be *M. ulcerans* strains which lost the IS*6110* elements but non tuberculous mycobacteria other than *M. ulcerans* could growth on Middlebrook medium.

Conclusion

This study show that other pathogens and *M.ulcerans* apparented Mycobacteria are implicated in skin lesions attributed to be Buruli ulcer cases.

Keywords : Buruli ulcer, *Mycobacterium ulcerans*, Diagnostic, PCR, profile.

Towards an Index of Biotic Integrity for use in Buruli ulcer endemic and non-endemic tropical regions

Poster by Daniel Sanhueza

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Mycobacterium ulcerans (MU) has been largely associated with freshwater ecosystems, especially anthropogenized environments (dam construction, rice culture, deforestation, etc).

In the recent years differents aspects of this infectious disease have been studied incorporating larger temporal and spatial fieldworks, collecting an extensive variety of organisms (larval and adult arthropods, snails, fishes, mammals, etc) and environmental samples (filtered water, mud, sediment, etc) from tropical regions in Africa and MesoAmerica. These new datasets revealed the presence of MU in/on a wide range of hosts/carriers belonging to highly diverse taxonomic and phylogenetic groups. Also, it has been described the existence of abiotic factors (*pH*, ions, chitin) favoring MU growth in nature. These findings have induced an important change of paradigm in MU etiology and epidemiology; it is now better described as an environmentally-persistent, multi-host pathogen emphasizing the importance of local ecological conditions for its growth, persistence and development in natural ecosystems.

Here, using two important datasets collected in Cameroon and French Guiana by our research team and based on levels of resistance of invertebrates to organic pollution, we developed different Index of Biological Integrity (IBI). Our purpose was to understand the association between the quality of certain aquatic habitats, the composition and structure of the aquatic species community, the field values of several abiotic factors and the abundance of MU. This approach pointed out the difficulty to generate a global IBI due to the very large heterogeneity of local environmental conditions observed between regions. Thus, because of the impossibility to develop a global IBI, we created various IBI's using different and more accurate spatial scales taking into account local diversity and abiotic characteristics of each region (eg. rivers flow). Our findings show that a more polluted site is not necessarily associated with a higher MU load in the aquatic environment.

Treatment

Skin microcirculation assessment in Buruli ulcer

Maria Letizia Iabichella

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Background

Skin microcirculation is responsible for wound healing[13] [14] in cases of ulcer. In our experience, a different etiology is seen after the debridement[15], and the assessment by Laser Doppler (LD) and BioMiscroscopy (BM) is reproducible[16] [17] [18]. The non-invasive study of the skin microcirculation in Buruli Ulcer (BU) is not yet been investigated.

Aim

The aim of this pilot study was the investigation of the skin perfusion and the feature of the capillary bed by Laser Doppler Fluxmetry and BioMicroscopy in BU.

Method

Perfusion was detected by non-invasive Laser Doppler Fluxmetry method on the skin near the ulcer edge. The capillary density and their feature were detected by non-invasive BioMicroscopy (video Capillaroscopy) on the skin near the ulcer edge. The assessment of LD and BM were registered into dedicated software for the subsequent quantitative analysis.

Cases. 5 BU (months age 4,6±4,2SD), painless and with granulation tissue, were investigated (3 in LL and 2 in UL) in 2 man and 3 females (years age 16,66±1,52SD). The ulcers were diagnosed and fully treated with antibiotic, according with WHO guidelines.

Results

The Laser Doppler measurement (baseline and after heating probe at 44°C) were abnormal at the edge of all investigated ulcers. The Biomiscroscopy detected a low number of capillary loops in the nutritional bed, characterized by hypocinetic erytrocytic flow, pericapillary edema, and capillary easy rupture with hemorrhaging and thrombosis in the subpapillary venous plexus.

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Conclusions

The evaluation by Laser Doppler Fluxmetry and Biomicroscopy is a reliable tool in clinical practice to monitor cutaneous microcirculation in the BU. These preliminary results show features in the cutaneous microcirculation which suggest that spontaneous recovery is very difficult in the BU. A dedicated study is needed to evaluate the changes in microcirculation related to BU healing.

Spontaneous healing of *Mycobacterium ulcerans* disease in Australian patients.

Poster by Daniel P. O'Brien

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Background

Mycobacterium ulcerans causes necrotising infections of skin and soft tissue mediated by the polyketide exotoxin mycolactone that causes cell apoptosis and immune suppression. It has been postulated that infection can be eradicated before the development of clinical lesions but spontaneous resolution of clinical lesions has been rarely described.

Methodology/Principal Findings

We report a case series of ten Australian patients who achieved healing of small *M. ulcerans* lesions without antibiotics or surgery. The median age of patients was 58 years (IQR 45-65 years) and all patients had small ulcerative lesions (median size 138mm^2, IQR 120-225mm^2). The median duration of symptoms prior to diagnosis was 87 days (IQR 56-90 days) and the median time to heal from diagnosis without treatment was 76 days (IQR 68-105 days). No patients recurred after a median follow-up of 14.4 months (IQR 9.0-21.5 months) from the development of symptoms.

Conclusions

We have shown that healing without specific treatment can occur for small ulcerated *M. ulcerans* lesions suggesting that in selected cases a robust immune response alone can cure lesions. Further research is required to determine what lesion and host factors are associated with spontaneous healing, and whether observation alone is an effective and safe form of management for selected small *M. ulcerans* lesions.

LeiProtect®, a specially approved, economic filmogenic gel, for NTD skin lesion management

Poster by Kurt-Wilhelm Stahl

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Hypothesis

LeiProtect® promotes healing of cutaneous leishmaniasis (CL) without pentavalent antimony chemotherapy.

Methods

The water-soluble LeiProtect® gel, which contains 0.09% pharmaceutical sodium chlorite (*sodium chlorosum*, prepared virtually chlorate-free from chlorine dioxide), was manufactured under GMP conditions using the Conti TDS jet-stream mixer (YSTRAL®). It is used as a collagen-free, "halal" filmogenic dressing on face lesions of complex cutaneous leishmaniasis due to *Leishmania (L.) major* (CCLLM). The quality control of LeiProtect® is at present performed by the oxidative induction of type 2 NO synthase in bone marrow-derived mouse macrophages in Western blots.

Results

After hand disinfection using WHO recommended alcohol-based hand-rub (ABHR) and daily dressings with LeiProtect® 45 complex CCLLM lesions of 34 patients from the region of M'Sila, Algeria, healed within a median period of 4 weeks (range 1-9 weeks) in the absence of systemic Sb(V) chemotherapy normally recommended by WHO for such cases. Based on these results LeiProtect® has received special approval by the Federal Institute for Drugs and Medical Devices (BfArM) according to §11 of the Medizinproduktegesetz (MPG) (BfArM Approval number 91.1.07-5640-S-006/16). The LeiProtect® batches manufactured by our GMP-certified German University Hospital are currently small (below 20 kg) and are therefore still rather expensive to manufacture. Nevertheless, the actual manufacturing and medical device costs of LeiProtect® treatment per CL lesion are already estimated at only 50% of the SSG price, which the WHO calculated in 2010 for topical antimony treatment of CL wounds.

Conclusion

In contrast to the side-effect loaded Sb(V) chemotherapy, the innovative and atraumatic approach LeiClean (ABHR + LeiProtect®) looks promising for the management of NTD skin wounds. Our nonprofit NGO looks for funding of a clinical trial with 100 to 200 CL patients, including patients with *L. tropica* lesions in order to obtain a final *CE* approval for the medical device LeiProtect®.

Implementation of a nursing protocol for the use of ozonotherapy in the treatment of Buruli ulcer

Poster by Antonio Galoforo

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Italian scientific society oxygen ozone therapy,
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Buruli ulcer (Bairnsdale ulcer, La Daintree ulcer or necrotic ulcer dermatitis) is the third most common microbacterial infection after tuberculosis and leprosy.

The causative etiologic agent, *Mycobacterium ulcerans* was identified and classified only in 1948 from Mac Callum in Australia (Costa, 2006).

Mycobacterium ulcerans, unlike other mycobacteria, produces a necrotizing exotoxin (a mycolactone) with local immunosuppressive action that destroys the tissues, (particularly the cells adipose) and blocks the capillaries.

Cytotoxic effect of mycolactone is due to its ability to stop the cell cycle, induce apoptosis and to inhibit the production of important cytokines such as TFN alpha and interleukin 10 (Torrado, 2007).

It is frequent especially in children between 5 and 15 years, the average age is 12.

Mortality is low but morbidity has very high rates.

The diagnosis is based on clinical-epidemiological and laboratory data including microscopic examination according to Ziehl-Neelsen, the positive culture of *Mycobacterium ulcerans*, the histological study of a bioethical sample excisional, the PCR (Polymerase Chain Reaction) for the DNA of *Mycobacterium ulcerans* (Agbenorku, 2001).

Ozone therapy has been established alongside surgical and antibiotic / antimycobacterial therapy and prophylaxis as a valid therapeutic aid.

Ozone has extensive applications in the medical field since (as published in Pubmed) it has the effect antibacterial, antiviral, antifungal, immunostimulant and able to improve microcirculation. An official memorandum of understanding for the study of the use of ozone therapy in the fight against the ulcer of Buruli was stipulated on 29th April 2006 at the Pasteur Institute between the institute itself, the Pnlub (National Program for the fight against the ulcer of Buruli in Ivory Coast) and O3 for Africa.

On October 30th 2006 the agreement was signed with the Ministry of Research of the Ivory Coast.
Ozone therapy has already proven to be able to deduce healing times by acting directly on the *Mycobacterium ulcerans* and on mycolactone which is inactivated and stimulating the repair processes tissue in a very short time.

The goal of this work is to develop a nursing protocol for the treatment of Buruli ulcer through the use of oxygen-ozone therapy.

The protocol includes several phases:

Step 1: Assessment

Before taking charge, each patient must undergo a clinical examination and, where possible, bacteriological; the clinical examination allows to specify the stage of the disease and the appearance of the lesions. The exam bacteriological is used to ascertain the presence of *Mycobacterium ulcerans* and any association with other superinfections.

Step 2: Equipment preparation

Gloves, distilled water, sterile gauze, plastic pipe fitting to connect to the appliance ozone therapy, polyethylene bag and patch.

Step 3: Preparation of ozonized water

Connection of plastic fitting and ozone bubbling in water for 5 minutes.

Step 4: Cleaning of the ulcer

Wash the ulcer with ozonated water and cover the ulcer with gauze soaked in ozonated water for five minutes.

Step 5: Positioning the bag

Removal of the gauzes and insertion of the limb into the bag. Hermetic sealing of the bag with the plaster.

Step 6: Ozone insufflation

Through the connection the ozone is insufflated at a concentration of 30 range until it is completely filled.

Step 7: Removing the bag

After 20 minutes the bag is removed, possibly by airing the room.

Step 8: Medication

Discussion

Advantages of ozonotherapy in the care of Buruli ulcer

- Reduction of healing times.
- Reduction of reconstructive plastic surgery.
- Reduction of the administration of antiseptics, disinfectants, antibiotics, painkillers, anti-inflammatories.
- Limitation of the cost of medications.
- Use of one device to treat up to 100 patients per day.
- Minimum maintenance of the appliance.
- Easy to apply even in difficult situations.

Vaccine

Buruli ulcer disease: the search for a mycolactone-based vaccine

Justice Boakye-Appiah

Justice Boakye-Appiah[1], Rajko Reljic[1], Mark Wasbrough-Jones[1]

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Introduction

Buruli ulcer, caused by infection with *Mycobacterium ulcerans*, is a skin disease of tropical countries, affecting predominantly children aged 5 to 15 years. The disease usually manifests itself as a painless nodule, a firm plaque, or oedematous lesion, which soon ulcerates with characteristic undermined edges. The chronic skin ulcers last months to years in the absence of treatment and cause significant morbidity. The mode of transmission however remains elusive and there is currently no vaccine against the disease. The pathogenesis of this neglected tropical disease is dependent on a lipid-like toxin, mycolactone, which diffuses through tissue away from the infecting organisms. This molecule has been intensely studied to elucidate its cytotoxic and immunosuppressive properties and is grossly known to account for much of the pathogenesis of BU.

Objective

We hypothesise that inducing a potent immune response to mycolactone may be an effective method to induce protective immunity. We aim to induce immunity to the disease by delivering mycolactone in combination with improved adjuvants and delivery systems as a vaccine. By this, we aim to understand the innate and adaptive immuno-pathological mechanisms induced by mycolactone in disease states.

Methods

We immunized mice with mycolactone based vaccine candidates and challenged these mice with wild type *M. ulcerans* strains to determine the duration of protection conferred against *M. ulcerans* disease by the vaccine candidates. We also performed various immunological assays to gain understanding of the immuno-modulatory mechanisms involved in this conferred protection.

Results

Our preliminary results showed that mycolactone can be immunogenic in mice in terms of inducing cellular immune responses. We also found that localised responses to *M. ulcerans* diseases vary from long term protection-mediated responses against the disease.

Conclusion

Mycolactone can be immunogenic and could potentially confer protection against Buruli ulcer disease.

Local humoral response during *M. ulcerans* infection: production of mycolactone-recognizing and neutralizing antibodies

Poster by Mélanie Foulon

Mélanie Foulon, Amélie Pouchin, Marie Robbe-Saule, Lucille Esnault, Amandine Durand, Fida Khater, Estelle Marion and Laurent Marsollier. Laboratoire ATOMycA, CRCINA INSERM U1232 – Angers, FRANCE

Buruli ulcer, or *Mycobacterium ulcerans* infection, remains the third most common mycobacterial disease worldwide. Children are the principal sufferers from this skin disease, and 25% of patients become permanently disabled. This chronic infectious disease is characterized by a massive skin tissue destruction leading to the development of significant ulcerative lesions. Tissue destruction is caused by a lipid exotoxin called mycolactone, which is the main virulence factor of *M. ulcerans*. At low doses, mycolactone plays a role in host colonization by modulating pain and immune response. Despite toxin secretion, major consequences of the *M. ulcerans* infection remain loco-regional. Thereon, several studies showed that in spite of recruitment of major immune actors (phagocytes cells and lymphocytes), the immune response is not able to control the lesion development. This immune failure is likely to be the consequence of immune escape strategy developed by *M. ulcerans*.

Early and non-severe stages of BU can be treated with antibiotics. Though, we have recently reported the occurrence of spontaneous healing in 5% of cases in the absence of medical treatment, suggesting a host's strategy development able to counteract the effects of *M. ulcerans*. Within this framework and in order to step forward in the understanding of this poorly characterized phenomenon, we investigated the local humoral response all through *M. ulcerans* infection stages using our spontaneous healing's mouse model. Our data showed a specific humoral response during spontaneous healing process, and we were able, for the first time to tag a subclass of immunoglobulin able to recognize *M. ulcerans* components including mycolactone. Our findings revealed that these immunoglobulins were able to neutralize the toxic activity of the mycolactone while none mycolactone-neutralizing antibodies has been found in others conventional mouse models. Completing the rational of the local humoral immune response development during *M. ulcerans* infection course, we showed a significant increase in B-cells antibodies-production during infection and more specifically during first stages of spontaneous healing process. In addition, using patients biopsies, provided from the Centre de Diagnostic et de Traitement de l'Ulcère de Buruli (CDTUB) of Pobé (Benin), we were able to identify, for the first time, mycolactone-recognizing antibodies in Buruli ulcer diagnosed patients, suggesting the potential involvement of local humoral response (characterized in mice) in the disease progression in human.

Finally, our findings pave the way for deploying innovative therapeutic strategies and protocols. Thus, it would be possible to consider the production of monoclonal antibodies able to bind mycolactone as an innovative new specific and sensible diagnosis tool. Addedly, reasoning from the fact that neutralizing antibodies broadening the treatment of some toxic components such as toxic venom, the use of mycolactone neutralizing antibodies could be a potential therapeutic strategy for Buruli ulcer.

Identifying correlates of protection for a vaccine against *Mycobacterium ulcerans* infection in a low-dose murine challenge model.

Tim Stinear

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Buruli ulcer is a neglected tropical disease caused by infection of subcutaneous tissue with *Mycobacterium ulcerans*. In this study we compared an experimental prime-boost vaccine with BCG in a low-dose murine tail model of infection. The experimental vaccine was based on a previously described TLR-2 agonist-based lipopeptide adjuvant electrostatically coupled with the enoyl-reductase (ER) domain of the *M. ulcerans* mycolactone polyketide synthases. Mice were vaccinated and then challenged via tail inoculation with an engineered bioluminescent strain of *Mycobacterium ulcerans* at a dose range of 5-20 CFU. Survival analysis showed mice that receiving either BCG or the experimental ER vaccine were equally well protected, with both groups faring significantly better than unvaccinated animals ($p<0.05$). A suite of immune parameters (response variables) were assessed in the mice across the experimental period. Logistic regression was then used to develop a model that could identify response variables predictive of vaccine protection and failure. Higher levels of cytokines IL-10 and IL-2, expressed in the local draining lymph node best predicted protection, while expression of IL-6 and TNF-alpha in the spleen were positively associated with vaccine failure. Antigen-specific CD4+ and CD8+ T cells in the spleen (including those producing IFN-gamma) only weakly influenced vaccination outcomes in this model. Antigen-specific IgG antibodies were also of low importance. This study suggests that an effective BU vaccine will need to induce a robust but well-regulated inflammatory immune response at the site of infection.

Other skin NTDs

Efficacy of ivermectin mass-drug administration to control scabies in asylum seekers in the Netherlands: A retrospective cohort study between January 2014 - March 2016.

Ymkje Stienstra

Beeres DT, Ravensbergen SJ, Heidema A, Cornish D, Vonk M, Wijnholds LD, Hendriks JJH, Kleinnijenhuis J, Omansen TF, Stienstra Y.

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Scabies is a skin infestation with the mite Sarcoptes scabiei causing itch and rash and is a major risk factor for bacterial skin infections and severe complications. Here, we evaluated the treatment outcome of 2866 asylum seekers who received (preventive) scabies treatment before and during a scabies intervention programme (SIP) in the main reception centre in the Netherlands between January 2014 and March 2016. A SIP was introduced in the main national reception centre based on frequent observations of scabies and its complications amongst Eritrean and Ethiopian asylum seekers in the Netherlands. On arrival, all asylum seekers from Eritrea or Ethiopia were checked for clinical scabies signs and received ivermectin/permethrin either as prevention or treatment. A retrospective cohort study was conducted to compare the reinfestations and complications of scabies in asylum seekers who entered the Netherlands before and during the intervention and who received ivermectin/permethrin. In total, 2866 asylum seekers received treatment during the study period (January 2014 -March 2016) of which 1359 (47.4%) had clinical signs of scabies. During the programme, most of the asylum seekers with scabies were already diagnosed on arrival as part of the SIP screening (580 (64.7%) of the 897). Asylum seekers with more than one scabies episode reduced from 42.0% (194/462) before the programme to 27.2% (243/897) during the programme (RR = 0.64, 95% CI = 0.55-0.75). Development of scabies complications later in the asylum procedure reduced from 12.3% (57/462) to 4.6% (41/897). A scabies prevention and treatment programme at start of the asylum procedure was feasible and effective in the Netherlands; patients were diagnosed early and risk of reinfestations and complications reduced. To achieve a further decrease of scabies, implementation of the programme in multiple asylum centres may be needed.

Preventive and therapeutic effects of morphine on ulcers caused by *Leishmania major* in BALB/c mice

Poster by Leila Zaki

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The parasites of genus Leishmania are the causative agents of one of the most widespread and devastating diseases**. Anti-** Leishmaniasis drugs are not sufficiently satisfactory due to their side effects .Hence, new therapeutic solutions with good efficacy and limited side effects is need. The present study was conducted to investigate Preventive and therapeutic effects of morphine on ulcers caused by Leishmania major in BALB/c mice.

In this study, we evaluated the preventive and therapeutic effects of morphine on two separate mice groups; the preventive treatment group received low doses of morphine at four intervals before being challenged with *Leishmania major* promastogotes, whereas the therapeutic treatment group received the same dosages post-challenge. To this end, immunological factors such as cytokine assay, lesion diameter and survival rate were measured. Parasitic loads were also considered for both groups by qPCR.

The parasitic load in mice received morphine before infection was lower than that in mice treated after infection and the differences were statistically significant. Moreover, no lesions were observed at the injection site in the former group. This indicates the protective role of morphine.

The results of this research showed that morphine functions better as a preventive rather than therapeutic drug.

Keywords: *Leishmania major*, morphine, ulcer, therapeutic effect, BALB/c mice.

Research

Presentations

Pathogenesis

Sec61 blockade by mycolactone: a central mechanism in Buruli ulcer disease

***Presented by Caroline Demangel*[1,2]**

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Pathology of Buruli ulcer, the necrotizing skin disease caused by infection with *Mycobacterium ulcerans,* is directly linked to the bacterial production of a diffusible macrolide called mycolactone. Recent studies have identified the Sec61 translocon as the primary cellular target of mycolactone, and shown that mycolactone binds to the core subunit of the Sec61 complex. Mycolactone binding to Sec61 inhibits its capacity to transport newly synthesized transmembrane and secretory proteins into and across the endoplasmic reticulum membrane, leading to their proteasomal degradation in the cytosol. An immediate consequence of this molecular blockade is that mycolactone-exposed cells have a reduced ability to produce a range of proteins, including cytokines, cytokine receptors, adhesion and homing molecules. In infected hosts, bacterial release of mycolactone thus impairs the generation of inflammatory and immune responses at multiple levels. Further, our global analyses revealed transcriptomic and proteomic alterations beyond Sec61 clients in mycolactone-treated cells, which result from the cascading effects of Sec61 client loss, and from the induction of cellular stress responses. Exposure to mycolactone indeed activates the ATF4/CHOP/Bim signaling pathway, eventually causing cell apoptosis. In conclusion, Sec61 blockade by mycolactone not only explains *M. ulcerans* evasion of the host immune system, it provides a molecular mechanism for Buruli ulcer pathology.

Proteomic analysis of the endothelial cell response to mycolactone

Presented by Belinda Hall

Belinda Hall[1], Yagnesh Umrania[2], Michael Deery[2], Rachel Simmonds[1]

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The pathology of Buruli Ulcer (BU) is driven by the *Mycobacterium ulcerans* toxin mycolactone, an inhibitor of entry into the ER via the Sec61 translocon. We have shown that endothelial cells are particularly sensitive to the actions of mycolactone, leading to the hypothesis that endothelial cell dysfunction may contribute to the development of BU lesions. Previous studies on the effect of mycolactone on endothelial cells have focused on analysis of individual proteins. In order to obtain a more comprehensive identification of the endothelial targets of mycolactone, we carried out quantitative proteomic analysis of membrane fractions. Human dermal microvascular endothelial cells were incubated for 24hr with DMSO or mycolactone in triplicate. After hypotonic lysis, membranes were isolated by differential centrifugation. Acetone precipitated proteins were reduced, alkylated and digested then labelled with tandem mass tags and detected by LC-MS/MS. Of 6649 proteins detected, 482 showed significant downregulation and 220 were upregulated. In corroboration with *in vitro* studies, most downregulated proteins were either secreted or surface-expressed single pass Type I and Type II membrane proteins. Gene ontology analysis showed enrichment for proteins involved in both universal and endothelial cell specific processes in the downregulated fraction while proteins associated with stress responses were enriched in the upregulated set. This dataset provides the broadest coverage yet of mycolactone targets and reveals a profound effect on endothelial cell function.

Local coagulopathy in the skin lesions of Buruli ulcer patients

Presented by Louise Tzung-Harn Hsieh

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Buruli ulcer (BU) skin lesions, caused by *Mycobacterium ulcerans* exotoxin mycolactone, display restricted infiltration of immune cells and coagulative necrosis. We have previously shown exposure to the toxin depletes expression of thrombomodulin (TM) prior to any direct effect on cytotoxicity and thus may have an impact on anti-coagulation at the endothelial cell surface. Indeed, reduced TM staining is seen in BU punch biopsy samples and is strongly associated with massive fibrin deposition. Here, we developed an unbiased approach, utilising serial sections and a sequential staining strategy to investigate whether changes in fibrin deposition around vessels correlate with endothelial TM and other haemostatic markers, platelet glycoprotein CD61, tissue factor and von Willebrand factor (vWF) in non-necrotic regions of BU lesions. In 962 vessels that were tracked and analysed from eight BU patient skin biopsies, 75.3% of unique vessels were found TM-negative. Although fibrin staining around TM-negative vessels was significantly higher than TM-positive ones, TM depletion is unlikely the only driving force of fibrin deposition. Tissue factor, the molecule that triggers extrinsic clotting cascade, was also found to be abundant in monocytes adjacent to fibrin-positive wounds and vessels in a TM-independent fashion. In addition, platelet glycoprotein CD61 was barely detectable in the analysed vessels in BU skin biopsies. Altogether, our findings demonstrate widespread disruption of coagulation pathways in BU lesions that may facilitate pathogenic fibrin deposition and also impact on tissue repair.

Understanding host interactions of mycolactone in order to improve storage and measurement, facilitating diagnostics

Presented by Harshini Mukundan

Deputy Group Leader - Physical Chemistry and Applied Spectroscopy
Team leader - Chemistry for Biomedical Applications

Mycolactone, the amphiphilic macrolide toxin secreted by *Mycobacterium ulcerans*, plays a significant role in the pathology and manifestation of Buruli ulcer. The toxin has been extensively studied as a target for the development of diagnostics and therapeutics for this disease. Yet, several challenges have deterred such development.

For one, the lipophilic nature of the toxin makes it difficult to handle and store, and contributes to variability associated with laboratory experimentation and purification yields. Our team has been working on methods to incorporate our understanding of the lipophilicity of mycolactone in order to define the optimal methods for the storage, handling and purification of this toxin. This work is a direct outcome of discussions from the previous WHO meeting on Buruli ulcer, wherein the challenges associated with measurement of this amphiphile were extensively discussed.

We present our results from a systematic correlation of variability associated with measurement techniques (thin layer chromatography (TLC), mass spectrometry (MS), and UV-Vis spectrometry), storage conditions, choice of solvents, as well as the impact of each of these on toxin function as assessed by cellular cytotoxicity. We compared natural mycolactone extracted from bacterial culture with synthesized toxin under various conditions including laboratory (solvents, buffers) and physiologically relevant (serum) matrices. Our results point to the greater stability of mycolactone in organic as well as detergent-containing solvents regardless of the container material (plastic, glass or silanized tubes).

Our studies highlight the presence of toxin in samples that may be undetectable by any one technique, suggesting that each detection approach captures different configurations of the molecule with varying specificity and sensitivity. For instance, a mass spectrometric peak and cytotoxic profile of the toxin was observed even in extracts where no UV-active TLC band was seen. This systematic assessment of impact of various experimental methodologies and laboratory practices can facilitate the development of more streamlined and reproducible methods for the characterization and measurement of the toxin.

Mycolactone is an amphiphile which is unstable in aqueous matrices such as serum. Previous work from our laboratory has shown that amphiphilic pathogen signatures associate with host lipophilic carriers, and that this association is required for their stable transportation and clearance from the host. Following along on the same assumption, we evaluated the association of mycolactone with High and Low Density Lipoproteins (HDL, LDL), in serum. Our results demonstrate -for the very first time- that amphiphilic mycolactone associates with host lipoproteins in serum, and that this association will likely impact our ability to study, diagnose and treat Buruli ulcer in patients.

Understanding the host-pathogen biology of the interaction of mycolactone with host carriers can allow for the development of better diagnostics and therapeutic approaches. Indeed, the understanding of association of pathogen amphiphiles with host carriers has lead to the development of tailored diagnostic assays for such amphiphiles in serum, which have been tested for other infectious agents such as *Mycobacterium tuberculosis*. Evaluating the feasibility of such methods for the direct measurement of mycolactone in Buruli ulcer patients is a future objective of our work.

This work was supported by an NIAID R01 award to Johns Hopkins University (Dr. Neuermberger, PI). Collaborators include Dr. Jessica Kubicek-Sutherland, Dr. Basil I. Swanson, Dr. Ricardo Marti-Arbona at LANL, Dr. Paul Converse and Dr. Eric Neuermberger at JHU, and several students and post-doctoral fellows.

Investigations into the mechanisms of action of mycolactone in Buruli ulcer pathogenesis

Submitted by Michael D. Wilson

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Introduction

Ulcers due to infections with *Mycobacterium ulcerans* if not treated worsen until surgical interventions are required. The toxin mycolactone produced by the mycobacterium is believed to be responsible and despite several studies its mode of action in BU disease remains to be elucidated. Interestingly BU patients remember experiencing previous trauma at the site of the ulcers, suggesting an impairment of wound healing processes. Mycolactone is lipophilic and passively cross cell membranes and with this knowledge we hypothesized that the toxin binds to key proteins involved in wound healing.

Methods

Blood platelets and mast cells are involved in hemostasis during early injury and both undergo degranulation upon activation. Molecular docking of mycolactone against key SNARE proteins and regulators in both cells, namely Vamp8, SNAP23, syntaxin 11, Munc13-4 (an isoform of Munc13-1) Munc18b were therefore investigated. Also investigated were published mycolactone targets Sec61, type 2 Angiotensin II receptor (AT2R) and WASP. Structural studies and MM-PBSA binding energy calculations of the mycolactone and the proteins were performed with 100 ns molecular dynamics simulations using GROMACS. Analysis of the binding interactions was performed to identify key residues involved in their binding with mycolactone.

Results

The highest binding affinity scores were -9.0, -8.9 and -8.5 kcal/mol for AT2R, sec61 and Munc18b respectively – -6.0 kcal/mol is considered the threshold. Our preliminary results showed that mycolactone binds strongly to Munc18b with an average binding energy of -247.571± 37.471 kJ/mol. The interaction also elicits changes in the structural conformation of munc18b. Arg405 was identified as an important residue of Munc18b whose mutation also result in impaired granule exocytosis.

Conclusions

The findings show mycolactone to be binding to Angiotensin II receptor (involved in cell proliferation and cell death via the ERK pathway), sec61 (important for translocation of proteins into the endoplasmic reticulum) and Munc18b (key protein of blood platelets exocytosis). The implications are that mycolactone interferes with the mechanisms of hemostasis during wounding in BU disease. The involvement of AT2R and sec61 in BU pathogenesis have been demonstrated but that for munc18b would need to be corroborated with experiments.

Diagnostics and non-antibiotic treatments

Initial serological screening test for *Mycobacterium ulcerans* exposure in Victoria, Australia

Presented by Michael S. Avumegah

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Introduction

Buruli ulcer (BU) is a subcutaneous necrotic infection of the skin caused by *Mycobacterium ulcerans*. It is the third most common mycobacterial disease after tuberculosis and leprosy. BU affects both humans and animals and is believed to have an aquatic niche. The disease has been reported in the tropics and subtropics, mainly in West Africa and in Australia. The exact mode of transmission is unknown but mammals and insects may have been involved. BU has long incubation period and the most common methods for confirmatory diagnosis are PCR, histopathology and culture of the organism. These methods have resource challenges. Development of a robust serological screening test would be beneficial to more accurately assess population exposure. This requires a designed antigen preparations specific and sensitive to *M. ulcerans*. In this study we compared cell derived preparations and four recombinant *M. ulcerans* proteins in pursuit of a serological test.

Methodology

This study has used a standardised protocol to produce and characterise 10 cell derived antigenic preparations from *M. ulcerans* (Batches: A, B, C, D, E, F, G, H and homogenate) and *M. smegmatis*. Four recombinant proteins (HSP_65, MUL_2232, MUP_057 and AT-propionate) have been partially purified. Protein composition of produced cell derived preparations were determined by comprehensive mass spectrometric analyses. These protein preparations were included in ELISA tests from which 10 confirmed BU patients, 20 healthy controls (EC) from same endemic region in Victoria and 20 non-endemic controls (NEC) from Tasmania were screened for the presence of *M. ulcerans* specific antibodies.

Results

We identified a total of 733 *M. ulcerans* proteins. A number of proteins were detected in all preparations, including known *M. ulcerans* antigens: chaperonins 1 and 2. IgG quantitation of all serum samples showed that NEC sera had low IgG concentration and unfortunately excludes any conclusion as to the validity of this comparison. Serum antibody responses to the 10 cell derived antigenic preparations were highly variable, however Batch D and recombinant protein HSP_65 showed a significant difference between BU patients and healthy controls (EC). Batch D had 90% sensitivity (CI = 55.50- 99.75%) and a specificity of 95% (CI = 75.13% - 99.87%). Using HSP_65 as test antigen had 50% sensitivity (CI = 18.71%- 81.29%) and 95% specificity (CI = 75.13%- 99.87%).

Conclusion

In this study, we produced and comprehensively characterised protein preparations derived from *M. ulcerans*. These proteins were used in a pilot serological study. Although the results are indeed promising more work is required to identify unique *M. ulcerans* antigens as well as better control samples. There is prospect of this protocol to be used for protein production from *M. ulcerans* and comprehensively characterised protein composition for the identification of unique *M. ulcerans* antigens. Such proteins if identified, could be useful as potential candidate antigen in serology, cell-mediated and/or antigen-capture assays for *M. ulcerans* exposure and surveillance in at risk populations.

Joint efforts to develop a rapid diagnostic tests for the early diagnosis of Buruli ulcer

Presented by Israel Cruz

Israel Cruz[1], Gerd Pluschke[2,3], Louisa Warryn[2,3], Jean-Pierre Dangy[2,3], Karl-Heinz Altmann[4], Marco Biamonte[5], Joseph M. Ndung´u[1].

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There are no primary measures to prevent infection by *Mycobacterium ulcerans*, the causative agent of Buruli ulcer (BU), mainly due to poor understanding of its epidemiology. The WHO target for BU in the 2012 Roadmap on neglected tropical diseases (NTDs) is that by 2020, 70% of all cases are detected early and cured with antibiotics in all endemic countries. Thus the current control strategy emphasizes early diagnosis and prompt treatment, with the goal of avoiding the complications associated with advanced stages of the disease. None of the available diagnostic tests for BU are appropriate for use at the primary health care level, where most cases are detected and treated.

In March 2018, FIND and WHO convened a consultative meeting on diagnostics for BU where experts reviewed ongoing efforts to improve diagnosis of BU and discussed progress in addressing the unmet diagnostic needs as well as the state-of-the art advances in new diagnostic approaches that could be exploited. Two of the outputs of this experts meeting were: i) a target product profile for a rapid test for diagnosis of BU at the primary health-care level, and ii) a call to coordinate efforts to detect *M. ulcerans'* macrolide toxin mycolactone with monoclonal antibodies (mAb) in order to accelerate the development of a point-of-care (POC) test.

The Foundation for Innovative New Diagnostics and the Swiss Tropical and Public Health Institute (SwissTPH) have a long-standing partnership in developing a rapid diagnostic test (RDT) for BU diagnosis. And with the aim of targeting mycolactone for the early diagnosis of BU, this partnership has been extended to Drugs & Diagnostics for Tropical Diseases (DDTD), a non-profit venture with a mission to discover new treatments and diagnostics for NTDs. The three parties are joining efforts to use mAbs generated by SwissTPH in a lateral flow assay platform developed by DDTD that includes the possibility of target enrichment, so that mycolactone can be readily detected in swab or fine needle aspirate samples from both early and advanced BU lesions.

The RDT developed will be robust and field deployable and is intended for use at the community- or public health care centre level. It could also be used at higher level (e.g. district hospital laboratories), and in active-case finding activities as well as to test patients who self-present at health centres.

With a new oral treatment for BU available it is crucial to have a drastically improved diagnostic that can make decentralized early diagnosis possible. It is therefore urgent to complete the development of a new test to enable enhanced control of the disease. A simple, easy-to-use, accurate and affordable POC test would enable identification of the disease in its early stages at community or primary healthcare facilities where the at-risk populations live and where the new oral treatment will be available. This would overcome the challenges associated with referring patients or their clinical samples long distances to reference laboratories, sometimes taking weeks before results are returned.

This project is supported by the Federal Ministry of Education and Research, Germany, UK aid from the UK Government and the Swiss Agency for Development and Cooperation.

A field-deployable recombinase polymerase amplification assay for rapid detection of *Mycobacterium ulcerans*

Presented by Michael Frimpong

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Background

Current diagnostic methods to detect *M. ulcerans* suffer from delayed time-to-results in most endemic countries as a result of prolonged time for storage and shipment of samples to a distant, centralized laboratory for PCR testing. Moreover, PCR is not always available in endemic countries in Africa due to its cost and technological sophistication. Isothermal DNA amplification systems such as recombinase polymerase amplification (RPA) have emerged as a molecular diagnostic tool with similar accuracy to PCR but having the advantage of amplifying a template DNA at a constant lower temperature in a shorter time.

Methodology and Results

In this study, a real-time recombinase polymerase amplification assay for the detection of *M. ulcerans* (Mu-RPA) was developed. The assay sensitivity, specificity and cross-reactivity were tested. After amplifying a specific fragment of IS*2404,* the Mu-RPA assay detected down to 45 genome copies/reaction in 15 minutes at a constant 42^{o}C. It successfully identified all 7 strains of *M. ulcerans* tested, and no cross reactivity was observed to other mycobacteria or clinically relevant bacterial species. Seventy-nine samples were screened both by Mu-RPA and real-time qPCR. The diagnostic sensitivity and specificity of the Mu-RPA assay were determined at 88% (95% CI, 77- 95) and 100% (95% CI, 84 – 100) respectively. A mobile suitcase laboratory applying novel DNA extraction (Genolyse) and Mu-RPA methods was evaluated for the diagnosis of Buruli ulcer in two treatment centres in Ghana. Analysing 30 samples, the Genolyse/RPA had a sensitivity of 86% (95% CI, 64-97) within an average time of 45 minutes from sample collection to results.

Conclusion

The developed RPA assay represents an alternative to PCR especially in areas with limited infrastructure.

Assessment of a field-deployable LAMP Assay for Rapid Detection of *Mycobacterium ulcerans.*

Presented by Tim Stinear

Jessica L. Porter[1] and Timothy P. Stinear[1]

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Buruli ulcer is a neglected tropical disease caused by infection of subcutaneous tissue with *Mycobacterium ulcerans*. In this study we tested an IS*2404*-based Loop-mediated Isothermal Amplification (LAMP) assay using the Optigene platform (http://www.optigene.co.uk/), as a field-deployable test for the presence of *M. ulcerans* in environmental specimens; in particular possum faecal material. As others have described, under ideal conditions the LAMP assay was sensitive and specific for *M. ulcerans*. However, bench-marking against IS*2404* qPCR showed that assay performance was substantially diminished under field conditions, with polymerase inhibition becoming an issue using crude DNA preparations, extracted using 0.6M KOH. The IS*2404* LAMP assay is a powerful test for *M. ulcerans*, but the ability to rapidly and cost-effectively prepare mycobacterial DNA of sufficient quality remains an issue for its use screening samples likely to be rich in polymerase inhibitors, such as soil or faecal material.

Potential therapeutic application of autologous Leukocyte and Platelet Rich Fibrin (L-PRF) as an alternative intervention for wound healing in Buruli ulcer

Presented by Indra B. Napit

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Buruli ulcer (BU) is an emerging chronic, debilitating, necrotizing disease of the skin and soft tissue, which is caused by *Mycobacterium ulcerans*. Roughly 90% of annual cases are in Africa; and high standards of wound care can be challenging in endemic settings for a variety of reasons including costs, hygiene and availability of resources.

A new tissue regenerative method has been evidenced in a variety of clinical trials across wound and ulcerative conditions wherein Leukocyte and Platelet-Rich Fibrin (L-PRF) is collected from patient's blood by simple centrifugation to form a matrix patch that can be directly placed on a wound to aid in healing.

At Anandaban Hospital, leprosy patients were enrolled (n=30) and treated with L-PRF therapeutic matrix applications weekly for foot ulcers ranging 2 to 18 cm^2, some of which had been non-healing, receiving ongoing routine treatment for up to 2 years without resolution or in need of amputation. The clock method was used for ulcer measurement, and high-quality photographs were recorded in each L-PRF treatment.

Across diverse sizes, 100% of ulcers were robustly healed by an average 7- 8 weeks (range=3-13), with an average 1 cm^2 wound closure per week, minimal to no scarring, utilizing on average a total 19 L-PRF matrixes (Range=4-50) per wound. L-PRF therapy is safe, cost-effective, and simple to perform even in outpatient and low resource settings by nursing or paramedic staff. After clearance of necrotic tissue, L-PRF therapy could have good potential to heal large BU wounds with less need of skin grafts with diminished scarring which could reduce related stigma.

Acute changes of skin microcirculation in Buruli ulcers after local ozone therapy

Presented by Maria Letizia Iabichella

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Background

In cases of ulcer, skin microcirculation is responsible for wound healing[19] [20]. The evaluation of acute changes in skin microvascular can be reliably assessed by Laser Doppler Fluxmetry (LDF) [21] during cold, heat or postural tests, after drug administration[22] and following local treatment[23]. Evidence-based medicine has demonstrated the efficacy of ozone treatment for the healing of cutaneous ulcers with different etiologies[24] [25] [26], including in Buruli ulcers (BU)[27] [28]. However, non-invasive LDF study of the skin microcirculation in BU after local ozone treatment has not yet been carried out.

Aim

The aim of this pilot study was to investigate skin perfusion in BU by Laser Doppler Fluxmetry during and after ozone treatment.

Method

We developed a method where O3 was administered topically by positioning around the lesion a bag inflated with a O2–O3 mixture at a concentration of 30 μg/ml. The inflated bag was sealed just above the lesion to avoid any gas leak, then it was positioned so that the gas mixture was in contact with the ulcer for about 5 minutes.
Skin perfusion was detected by Laser Doppler Fluxmetry near the ulcer edge during and after local ozone therapy administration. The assessment of LDF was registered into dedicated software for the subsequent quantitative analysis.

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Cases

5 BU (months duration 4,6±4,2 SD), painless and with granulation tissue, were investigated (3 in LL and 2 in UL) in 2 man and 3 females (years age 16,66±1,52 SD). The ulcers were diagnosed and fully treated with antibiotic, according with WHO guidelines.

Results

The Laser Doppler Fluxmetry measurements detected different reactivities of skin basal perfusion at the edge of all investigated ulcers during or after 5 minutes OT application.

Conclusions

In this study Laser Doppler Fluxmetry has been shown to evaluate reliably the efficacy of OT topical treatment in cutaneous microcirculation of the BU. These preliminary results suggest that OT promotes changes of skin perfusion reactivity in BU. A further dedicated study would be needed to evaluate the changes in microcirculation related to BU healing.

Transmission

Controlling Buruli Ulcer in Victoria: Case-Control study

Presented by Eugene Athan

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Background

Buruli ulcer (BU) has been recognised in Victoria since 1948, however efforts to control the disease have been severely limited because the environmental reservoir and mode of transmission to humans remain incompletely understood. Communities around Port Phillip Bay are experiencing a worsening epidemic of the disease with an increasing number and severity of cases, and the risk of acquiring disease is spreading into new geographical areas.

Research Question

What are the environmental and behavioural risks and protective factors associated with BU disease in the affected area in Victoria?

Aim

This case-control study aims to identify the environmental and behavioural risk and protective factors associated with BU disease in the affected area in Victoria, and to provide new details about *Mycobacterium ulcerans* (MU) environmental presence and host interface risk factors of transmission.

Objectives

- To determine what behaviours and human characteristics are associated with BU in the affected area.
- To establish which fauna, flora, water sources, and soil type are potentially involved in MU transmission in the affected area.
- To establish if samples positive for MU DNA contain viable bacteria.
- To determine if behavioural risk factors can be linked to potential environmental sources of MU.
- To establish if housing development, construction or sewage works are associated with BU in the affected area.
- To examine the association of climate and rainfall with prevalence of BU
- To determine if wounds or bites from insects are associated with BU in the affected area.

Study Design

A matched case-control study over two years comprising two components: 1) a self-administered questionnaire for all participants, and 2) a field survey conducted at the residence of a subset of cases and controls.

Study Location

The study area comprises townships surrounding the Port Phillip Bay area. All the included communities have had BU cases diagnosed among residents in the previous five years and are considered to be part of the current Victorian outbreak.

Study population

Cases consist of all adults aged ≥18 years of age notified with laboratory confirmed BU disease to the Victorian Department of Health and Human Services within the study period or three months prior to start of the study period. Controls are residents of the study area and aged ≥18 years, and will be selected from two sources: 1) the Victorian Population Health Survey (VPHS) control bank, and 2) the Victorian electoral roll. We aim to enrol 200 cases from the affected area and 5 controls per case, matched on postcode of residence.

Sample analysis

All environmental samples will be analysed for the presence of MU DNA and RNA to determine the distribution of bacteria (non-viable and viable) at each residence. Basic soil analysis (temperature, pH, salinity, etc.) will also be conducted to establish soil type.

Risk analysis

Survey responses and field survey results will be combined with climatic and environmental data in a risk framework, enabling the identification of specific risk factors for contracting MU and likely transmission routes.

A multifactorial mosquito control intervention versus standard community information for the reduction of Buruli ulcer in Victoria, Australia: a cluster randomised controlled trial.

Presented by Jane Oliver and Simon Crouch

Jane Oliver*[1], Simon Crouch*[2,3], Katherine Gibney[1,2,4], Ee Laine Tay[2], Rebecca Feldman[2], David Price[1,3], Paul Johnson[4,5], Tim Stinear[1]

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Introduction

Human Buruli ulcer (BU) cases have been reported in more than 30 countries, mostly in tropical areas; however, an epidemic is currently occurring in temperate coastal Victoria, Australia. While BU cases in Africa typically live near slow flowing waterways, environmental reservoirs and transmission are not fully understood. In Victoria, possums in BU endemic areas frequently excrete *M. ulcerans* in their faeces and some develop BU lesions. Furthermore, *M. ulcerans* DNA has been detected in several species of Australian mosquitoes including *Aedes notoscriptus* and *Aedes camptorhynchus*. It has been proposed that possums act as reservoir-amplifiers of *M. ulcerans* in the environment, and that infection could be transmitted to humans mechanically from biting insects. We hypothesise that mosquitoes are a critical mechanical vector for *M. ulcerans* transmission in the current Victorian outbreak.

The main objective of this study is to compare the impact of a multifactorial mosquito control program on the incidence of BU to standard community information about the prevention of mosquito bites alone. This study forms part of the *Beating Buruli in Victoria* partnership project, funded by the National Health and Medical Research Council, Victorian Department of Health and Human Services (DHHS) and Mornington Peninsula Shire Council (Grant GNT1152807).

Methods

The study will take place across the 2019/20 Southern Hemisphere summer. Small area clusters of around 315 people, residing in groups of geographic regions called MESH blocks, will be randomised to intervention or control arms, with 33 clusters in each arm. This sample size calculation is based on an estimated incidence of 900 cases per 100,000 population, a coefficient of variation of 0.9 and 80% power to detect a 60% reduction in BU cases between the intervention and control arms. The intervention includes residual harbourage spraying, larviciding, ultra-low volume fogging, and residential mosquito trapping. All residents in both intervention and control clusters will receive standard DHHS community information about personal measures they can take to decrease their risk of receiving mosquito bites.

The primary outcome, BU incidence among residents of intervention areas compared to control areas, will be calculated using BU notification data provided by the DHHS. The secondary outcome, the impact of the intervention on mosquito numbers, will be determined by mosquito surveillance in both intervention and control clusters.

Implications

This is the first time that a mosquito control program has been used to attempt to reduce the incidence of BU. As part of the larger *Beating Buruli in Victoria* project, this study will provide clear evidence to support public health measures and policies to address the ongoing epidemic of BU in Victoria.

Environmental control of diseases: quantitative survey of the impact of well-drilling on Buruli ulcer

Presented by Horace Degnonvi

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Background

Buruli ulcer, caused by *Mycobacterium ulcerans*, is the third most common mycobacterial disease worldwide. The number of new cases of Buruli ulcer has decreased in some endemic countries, but the factors accounting for this change in incidence remain unidentified.

Methods

We collected data for Buruli ulcer incidence and well drilling over a period of 10 years. We then performed a case-control study in 2016, to assess the effect of well drilling on Buruli ulcer incidence in a community from Benin in which this disease is endemic.

Findings

The decrease in Buruli ulcer incidence was strongly correlated with an increase in well drilling in Oueme, particularly in the community of Bonou, where 106 cases and 212 controls were enrolled for the case-control study. The regular use of well water for washing/bathing/drinking/cooking was protective against Buruli ulcer ([(aOR)] = 0.1, 95% confidence interval (CI) = 0.04 - 0.49) whereas regular contact with river water ([adjusted odds ratio (aOR)] = 19.8, 95% confidence interval (CI) = 2.56 - 25.49) was the main factor associated with the risk of contracting Buruli ulcer.

Interpretation

The use of well water in daily activities is clearly protective and linked to the decrease in the incidence of Buruli ulcer in Bonou. The drilling of wells at an appropriate distance relative to the household's place of residence, together with sensitisation and education programmes to improve practices in drinking and domestic water use, would probably be effective as a strategy for Buruli ulcer prevention.

The association of Buruli ulcer disease endemicity with major climatic, epidemiological and socio-environmental factors: a geospatial analysis from southern Nigeria

Presented by Saskia Kriebich

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Introduction

Nigeria is known to be an endemic country for Buruli ulcer (BU) in West-Africa. However, the level of BU endemicity remains ill-defined and the recently reported drastic increase in BU case numbers in Nigeria suggests a much greater burden of the disease than previously anticipated. BU is characterized as a highly focal disease with clustered geographical endemicity. The route of transmission is still not fully understood, but supposed to occur from contaminated environments to humans. In light of the limited resources and the low prioritization for combating the disease, the identification of climatic, epidemiological and socio-environmental factors predictive of BU endemicity is crucial. Thus, we analyzed the association of 164 BU cases, reported between 2012 and 2015, in four Nigerian States with a series of climatic, socio-environmental and epidemiological factors at the level of the respective Local Government Areas (LGAs).

Methodology

Through home visits of all 164 BU patients reported between 2012 and 2015, the BU cases were geocoded. Our outcome variable - the prevalence (Pr) per 100,000 - was calculated for every different LGA reporting BU cases. The independent variables - data on relevant climatic, socio-environmental and epidemiological parameters - were obtained from services based on remote Earth Observation data, OpenStreetMap, online mapping tools, literature review and geocoding of data in the field. In a first step of our analysis we developed geospatial illustrations of the reported BU cases. Secondly, we performed a Spearman rank correlation between the outcome and the independent variables. Finally, a regression analysis was performed using a generalized linear model in order to assess the most accurate predictive model for the BU Pr at the LGA level.

Results

Through our geospatial illustration, the proximity of BU cases towards different types of water bodies was clearly evident. The correlation analysis revealed an inverse correlation between BU Pr and the following factors: i) median land slope; ii) average annual rainfall; as well as iii) distance to ponds, lakes and all kinds of waterbodies (composite variable comprising ponds, lakes, rice fields and rivers). With respect to the prediction quality, the best performing model included two independent variables, i.e. distance to rivers and to all kinds of waterbodies, yielding a Root Mean Square Deviance of 3.8.

Discusssion

Our findings are in line with the existing evidences from the literature by pointing towards an association between BU Pr and the proximity to water bodies as well as to uneven landscapes. Models taking into account distance to water body related variables had the best prediction quality for the presence of BU. As systematic active case finding activities need to be intensified, geospatial analysis could serve as an important prioritization tool in planning cost-efficient BU-interventions at the subnational level. A larger-scale project encompassing regions with wider climatic, sociodemographic and epidemiological diversity and higher number of BU cases is recommended, in order to verify our results and better assess the predictive quality of a series of further factors, such as the degree of water flow and water temperature.

Mutation profiling reveals the non-random distribution of UM strains on a local scale in West Africa

Submitted by Clément Coudereau

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Buruli ulcer is found in several tropical, subtropical or temperate regions in the world but most cases are reported in rural areas from West and Central Africa. In those regions, the lack of clear understanding regarding its environmental reservoirs and mode of transmission has hampered the epidemiological monitoring and prevention strategies of the disease.

Our aim was to decipher the genetic diversity of the bacteria over a small endemic area of Benin to better our knowledge on spread and dissemination. We performed a phylogeographic analysis combining whole genome sequencing with spatial scan statistics on 179 bacterial isolates. These were obtained from human over a 10-years period and representing two endemic departments in the south-east of Benin, as well as a neighboring department in Nigeria.

We created and used a new mutational profile model with predictive capabilities for grouping bacterial strains. With this method, 8 distinct genotypes were identified. Using spatial scan statistics, we found those genotypes to be unevenly distributed over the studied area as 3 geographical clusters, associated with landscape characteristics such as hydrological and pedological features, were identified. The genotypes of 29 newly sequenced strains from those clusters were correctly predicted with an average accuracy of 90%. This work supports the idea that *Mycobacterium ulcerans* presents a differential genetic evolution conditioned by its location and that spatial scan methods can help identify Buruli ulcer risk heterogeneity at local level. Combined with the use of passive notification and active case detection, those results will be used to narrow down the location of high-risk infection sites and stamp out those hotspots of transmission, thus, strengthening disease surveillance.

Day 3

Plenary sessions

Control

Surveillance of Buruli ulcer in the Democratic Republic of the Congo: preliminary results (2016–2018)

Presented by Marie José Kibadi

Kabedi M.J, Mintsey N., Nkunku L. Lunguya O., Kimbonza S., Eddyani M., de Jong B. and Muyembe JJ.

Background

Buruli ulcer poses a real and underrecognized risk to public health that requires international mobilization. It is an emerging threat to public health in several intertropical rural regions, including in the Democratic Republic of the Congo. However, the effectiveness of disease control activities can be improved by enhancing the visibility of the disease and mobilizing resources.

Objective

To document Buruli ulcer in the different provinces of the Democratic Republic of the Congo.

Materials and methods

Specimens were taken from patients with suspected Buruli ulcer living in different provinces of the Democratic Republic of the Congo. Two techniques were employed to confirm cases, namely Ziehl-Neelsen staining and real-time PCR. Data was compared using the chi-squared test.

Results

During the three surveillance years (2016–2018), 984 specimens were taken, 86.1% of which were extracted using swabs. Seventy-two cases (7.3%) tested positive using Ziehl-Neelsen staining and 251 (25.51%) were confirmed by PCR ($p<0.001$). The highest proportion of cases testing positive per province was observed in Equateur (11 out of 19 cases, or 57.9%), followed by Central Congo (215 out of 707 cases, or 30.4%) and Maniema (16 out of 52 cases, or 30.7%). The lowest proportions of positive results were reported in Haut Uélé (3 out of 13 cases, or 23.1%) and Kinshasa (13 out of 188 cases, or 6.9%).

Conclusion

Surveillance of Buruli ulcer has been designated a public health objective to allow the measurement of its significance and the evolution of its incidence in the Democratic Republic of the Congo. Surveillance is important as it permits better documentation of the disease burden, mapping of endemic villages and better case management.

Keywords: surveillance, Buruli ulcer, Democratic Republic of the Congo, preliminary, results

Buruli ulcer treatment: antimicrobial therapy is the mainstay of treatment, but the rate of surgical intervention differs highly between treatment centres

Presented by Anita C. Wadagni

AC Wadagni, J Steinhorst, YT Barogui, PM Catraye, R Gnimavo, M Frimpong, R Phillips, TS van der Werf, GE Sopoh, ROC Johnson, Y Stienstra

Background

Antibiotic treatment proved itself as the mainstay of treatment for Buruli ulcer disease. This neglected tropical disease is caused by *Mycobacterium ulcerans*. Surgery persists as an adjunct therapy. In an earlier clinical trial, patients benefited from delaying the decision to operate. Nevertheless, the rate of surgical interventions differs highly per clinic.

Methods

A retrospective study conducted in six different Buruli ulcer (BU) treatment centers from Benin and Ghana. BU patients clinically diagnosed between January 2012 and December 2016 were included and general characteristics and surgical interventions during the follow-up period, at least one year after diagnosis, were recorded. Logistic regression analysis, was carried out to estimate the effect of the treatment center on the decision to perform surgery, while controlling for interaction and confounders.

Findings

A total of 1193 patients, 612 from Benin and 581 from Ghana, were included. In Benin, most lesions (42%) were categorized as the most severe lesions (WHO criteria, category III), whereas in Ghana most lesions (44%) were categorized as small lesions (WHO criteria, category I). In total 344 (29%) patients received surgical intervention. The percentage of patients receiving surgical intervention varied between hospitals from 1.5% to 72%. Even after adjusting for confounders, rates of surgical interventions varied highly.

Patients treated in one of the centers in Benin were much more likely to have surgery compared to the clinic in Ghana with the lowest rate of surgical intervention. (OR(crude) 163 (54 - 498) and OR(adjusted for severity and functional limitation at start of treatment) 110 (35 - 343). In one of the centers in Benin, the rate of surgical interventions has increased over the years (33% in 2014 to 89.7% in 2016 $p<0.001$).

Interpretation

The decision to perform surgery in BU varies highly per clinic even after adjusting for confounders. Evidence based guidelines are needed to guide the role of surgery and are likely to reduce the number of interventions and save resources.

The integrated control of skin NTDs is effective Cameroon

Presented by Earnest Njih Tabah

Background

Neglected Tropical Diseases (NTDs) are a group of communicable diseases associated with poverty, as they occur in remote and poverty-stricken areas of the tropics, affecting the poor and voiceless populations, and perpetuating the poverty cycle amongst them. NTDs door not attract significant resources for their control. Fortunately, a good number of these NTDs occur on the skin and are co-endemic in most areas, thus providing an opportunity for their integrated control. With this backdrop, the WHO has recently made recommendations for integrated control of these NTDs of cutaneous expression following calls for policy change by some experts in the domain. Our study aimed to show that integrated training and case search of skin NTDs are feasible in Cameroon.

Methods

We carried out a cross-sectional study within the framework of an investigation of a yaws outbreak in four health districts in the East Region of Cameroon in September 2017. Teams were constituted for each of the four health districts, comprising a least a medical doctor, a senior nurse and a laboratory scientist from the national or regional level; and local staff including four nurses, one laboratory technician, and at least 3 community health workers. The team members from the central/regional level who are part of the national yaws, leishmaniasis, leprosy and Buruli ulcer control programme team were given a one-day refresher training. They in-turn trained the local staff that joined the team while in the health districts, on skin examination and clinical diagnosis of yaws, leprosy Buruli ulcer, scabies and other common skin diseases. The laboratory technician was trained on conduction of rapid diagnostic tests for yaws. The teams visited villages and pigmy camps according to a pre-established schedule. In each village and after sensitization, children 15 years and below were gathered at the chief's palace or the village school, where they were examined in a well-lit area, that protected each participant's intimacy. Using the Open-data-kit (ODK) smart phone application, socio-demographic data of each child examined and characteristics of lesions for those with skin lesions were collected. A descriptive analysis of variables was made using SPSS version 20.

Major outcomes

A total of 1352 children 15 years and below were examined, of whom 54% were males. Their age distribution was: 47% for 0-5 years, 37% for 6-10 years and 16% for 11-15years. Of these children, 751 (55.6% had at least one skin lesion, with 480(36%) being yaws-like lesions and 271 (20%) being other types of lesions. For the yaws-like lesions, the most prominent were ulcers (54.8%), papilloma (16.1%) and squamous-macular (14.4%). Over 75% of the lesions occurred on the limbs. Sixty-two (13%) of cases of yaws-like lesions tested positive for the rapid diagnostic screening test, and 53 (11%) were confirmed by the DPP yaws confirmatory test. The other skin lesions comprised mainly scabies (49.4%), superficial fungal infections (40.2%), and impetigo (3.7%). Few cases of tungiasis, filarial skin rash, seborrheic dermatitis, and abscesses, were also seen.

Conclusion

Integration of some skin-NTDs control activities including training and case search is very feasible. It allows for a more efficient used of resources, and improvement of surveillance of these conditions. However, training of primary health care workers on skin NTDs and other common skin infections, and full implication of community volunteers would be necessary for the sustenance of this approach.

Implementation of an integrated management of skin NTDs in Ghana: Experiences from the laboratory

Presented by Bernadette Agbavor

Michael Frimpong[1], Francisca Sarpong[1], Abigail Agbanyo[1], Bernadette Agbavor[1], Abass K. Mohammed[2], Roland Miah[3], Sampson K. Addo[4], Nasas Ofosu Kwabi[5], Elizabeth Ofori[6], George Amofah[7], Justice A. Nyarko[8], Clement Tetteh[9], Yahaya Bedradeen[10], Nana Konama[11], Solomon Gyabaah[1], Richard Phillips[1*]

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Background

Task shifting of skills to Community Health Volunteers has been identified for successful implementation of the integrated skin NTD strategy. A strengthened health system including greater access to diagnostic confirmation is advocated. In 2018 an integrated case management of neglected tropical disease (CM-NTD) was implemented in Ghana through support of ANESVAD. This included support for three laboratories for diagnostic confirmation of suspected cases of Buruli ulcer (BU), leprosy and yaws. The expected outcome for this programme is establishment of improved capacity and laboratory diagnosis of these diseases through strengthening of systems at the national, district and community level. We present here a laboratory perspective of work carried out in 9 districts that provided samples for diagnostic confirmation.

Methods

A cohort of district health workers and community health volunteers from each district was trained on an integrated approach to identifying Buruli ulcer, leprosy and yaws. The teams were also trained on sampling, packaging and transport of samples to the laboratory. Communities and schools within their respective districts were visited for awareness raising and all persons with skin lesions suspected to be Buruli ulcer, yaws or leprosy were examined. The socio-demographic information and characteristics of lesions were collected using the WHO SkinNTD 01 form. All suspected cases of yaws were screened with syphilis RDT and confirmed with the DPP test on the field. Samples were also collected from lesions and sent to the reference laboratory. A descriptive analysis of the epidemiological, clinical and laboratory variables as well as mapping of all cases were done with Excel and QGIS.

Principal findings

In the study period, samples from 316 suspected cases were received between the period of August – December 2018. The median (IQR) age was 32 (13-53) for BU, 12 (10-15) for Yaws and 43 (24-59) for leprosy.

Of the 286 BU suspected cases, 76 (27%) were confirmed by PCR. There were 12 cases of clinical leprosy, 8 DDP confirmed yaws of which 2 were further confirmed as *H. ducreyi* by PCR. Interestingly, when the data was stratified according to where sampling was done for BU cases, those taken at the BU clinics had a significantly high PCR positivity rate compared to those obtained in the community, 62% versus 9%, $p < 0.0001$.

Discussion/Conclusion

There is the need for further training of health teams also targeting other more common skin disorders (e.g scabies, impetigo, fungal infections) that are likely to be captured as differential diagnosis to improve results of confirmation for Buruli ulcer. For BU and Leprosy where POC tests are not available 'clinical expert panels' consulted through mobile technology or other may help to improve clinical diagnostic sensitivity as well as reduce requests for tests thereby provide savings for laboratories.

Prevalence and profile of HIV in patients with *Mycobacterium ulcerans* infection in Nigeria

Presented by Anthony Meka

Meka AO[1], Chukwu JN[1], Ukwaja KN[2], Nwafor CC[1], Ekeke N[1], Chukwuka A[1], Eze CC[1], Adebayo PI[3], Lawanson AA[3].

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Background

Little is known about the relationship between Buruli ulcer (BU) and human immunodeficiency virus infection in Nigeria. This study investigated the prevalence and profile of HIV among BU patients in Nigeria

Methods

This was a prospective cohort study of all BU patients managed in three treatment centres in Southern Nigeria during May 2016 to August 2017. All patients were screened for HIV and underwent laboratory investigations for BU.

Results

A total of 46 BU patients registered for treatment during the period were screened for HIV. Of these, three were co-infected with HIV given a prevalence of 6.5%. The prevalence of HIV co-infection was higher among male than female patients (9.5 vs. 4.0%; $p = 0.433$) and higher among older BU patients than children i.e., ≤15 years (10 vs 0%; $p = 0.267$). The mean healing time for BU-HIV co-infected patients was 178.3 compared with 112.0 days among HIV-negative BU patients ($p = 0.265$).

Conclusions

Our findings support the hypothesis of a higher prevalence of HIV infection in persons with BU compared with the general population. Further studies are needed to clarify the association between BU-HIV co-infection and duration of wound healing.

Assessment of community understanding of the aetiology, transmission, presentation, treatment and prevention of Buruli ulcer disease (*Mycobacterium ulcerans* infection) in Southern Nigeria.

Presented by Ngozi Ekeke

Ekeke N[1], Chukwu JN[1], Ukwaja KN[2], Nwafor CC[1], Meka AO[1], Chukwuka A[1], Eze CC[1], Adebayo PI[3], Lawanson AA[3].

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2. Federal Teaching Hospital, Abakaliki, Ebonyi Stat
3. National Tuberculosis & Leprosy Control Programme, Federal Ministry of Health, Abuja Nigeria.

Background

Poor knowledge and cultural beliefs have been shown to influence timely care-seeking among persons with Buruli ulcer disease (BUD). An assessment of community understanding of the disease is crucial for the design of health education interventions. Little is known about the community understanding of aetiology, transmission, prevention and treatment of BUD as well as their attitudes to persons with BUD in Southern Nigeria, hence this study.

Methods

This was a cross-sectional survey conducted among adult community members in BUD endemic settings of Southern Nigeria in 2017. A semi-structured interviewer-administered questionnaire was administered to all participants. The influence of socio-demographic factors on these variables was investigated.

Results

Of 491 adults who completed the survey, 315 (64.2%) belonged to the ≤40 years age group, 257 (52.3%) were males and 415 (84.5%) had some formal education. The overall mean (SD) knowledge score was 5.5±2.3 (maximum 10) and only 172 (35.0%) had good knowledge of BUD. A total of 327 (66.6%) and 55 (11.2%) considered BUD as a very serious and a somewhat serious illness, respectively; 372 (75.8%) felt compassion and desire to help affected persons, 77 (15.7%) felt compassion but tended to stay away from them, 53 (10.8%) feared them because they may infect them with the disease. Having a formal education and ethnicity were independent predictors of knowledge of BUD.

Conclusions

There is poor community knowledge of BUD in endemic settings in Nigeria. Community education programmes should target the delivery of specific information on known risk factors of the disease and its preventative measures, and early recognition of symptoms and appropriate care-seeking should be emphasised.

Health seeking behaviour for Buruli Ulcer disease in the Obom sub-district of the Ga south Municipality of Ghana

Presented by Eric Koka*

Department of Sociology and Anthropology, University of Cape Coast, Cape Coast, Ghana (Email: ekoka@ucc.edu.gh)

The current biomedical Buruli ulcer case management strategies emphasise the importance of early reporting, timely and appropriate medical treatment of nodules before they ulcerate and give rise to debilitating disease sequel of osteomyelitis, contractures, deformities and disabilities However, there are a wide range of socio-cultural and demographic factors that influence health seeking behaviour for Buruli ulcer case management. The purpose of the study was to determine health seeking behaviour for Buruli ulcer by affected persons and their families. This was a descriptive study involving both qualitative and quantitative data collection designed to determine health seeking behaviour for Buruli ulcer by affected persons and their families in the Ga South municipality. Thirty (30) in-depth interviews were conducted for Buruli ulcer patients and their corresponding caregivers on barriers and facilitators to health seeking and the most preferred health seeking options and the reasons for choosing that option. Three (3) Focus Group Discussions (FGDs) were also conducted among elderly community members (Akan, Ga and Ewe) and it also centered on the factors that affect health seeking in the communities. Finally, survey questionnaire interviews were conducted with 300 community respondents in three major languages (Ga, Akan and Ewe) in the Obom sub-district of the Ga South municipality. In selecting respondents for the community survey, systematic sampling was used to select 300 respondents for the study. The study revealed that majority (71%) of respondents would seek treatment immediately they see the signs and symptoms of Buruli ulcer. However, it came to light that most respondents (41.0%) would resort to self-medication as their first treatment option when infected with Buruli ulcer disease. The study also revealed that while 166 (55.3%) of respondents said they would not combine more than one treatment regimen for the management of their condition, 128 (42.7%) said they would combine more than one treatment regimen when infected with Buruli ulcer. However, the health seeking of self-medication or visiting the drug store or herbalist before seeking biomedical treatment was alarming since it leads to delays in reporting. This is a serious public health concern since delay in reporting could lead to category three lesions that have serious financial implications on the individual and the nation at large.

Integrated approach to tropical lymphoedemas: simple interventions reduce acute episodes in all tropical lymphoedemas and improve quality of life

Presented by Claire Fuller

Chair of International Foundation for Dermatology and Consultant Dermatologist

Lessons from podoconiosis treatment programmes have taught that significant life quality improving benefit can be achieved with simple interventions. Reviewing the methods adopted and now multiplied across tropical lymphoedema communities throughout affected countries provides evidence for the reduction in frequency of acute adenolymphangitis enabling patients to commit to productive lives.

The ENDPoINT Consortium – integrating limb care and wellbeing support across skin-NTDs

Presented by Gail Davey

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Background

The skin-NTDs LF, podoconiosis and leprosy can all result in lower limb lymphoedema, and are debilitating, painful and mobility-reducing conditions which predispose affected people to poor mental health. The "Excellence in Disability Prevention Integrated across NTDs" (EnDPoINT) Consortium has been formed to integrate and scale-up a holistic, community-level care package – involving physical and psychosocial care – for patients with podoconiosis, LF and leprosy in Ethiopia.

Methods

The Consortium's work is in three Phases. Phase 1 draws together existing knowledge to finalise a holistic package of physical, psychosocial and mental health care for people affected by LF, podoconiosis and leprosy, and to develop strategies for integrating this package into the routine health care delivery system in selected districts in Awi zone in northern Ethiopia. During Phase 2, the package is piloted and evaluated in a single district. In Phase 3, following modifications, the package is scaled up across three further districts, and evaluation, including economic analysis completed.

Progress

Following situational analysis and three of Theory of Change workshops and key informant interviews with stakeholders (patient representatives, implementers, community leaders and policy makers), a Theory of Change map was developed. Subsequently, a care plan covering health care organization level, health care facility level and community level has been developed. The existing joint LF and podoconiosis care guideline has been adapted to include limb care for leprosy and mental wellbeing across the three skin-NTDs. Training materials have been developed, and training of trainers is due to commence in spring 2019.

Conclusions

Mental health and wellbeing are vital components of Disease Management, Disability and Inclusion (DMDI) for skin-NTDs. This implementation research project is the first to approach integration of mental health care with limb care for three key skin-NTDs. Our approach is likely to be applicable to a settings in which a range of skin-NTDs are co-endemic.

Funders

The EnDPoINT Consortium is funded by the UK NIHR through the Brighton & Sussex NIHR Global Health Research Unit on Neglected Tropical Diseases.

Research

Treatment

Triple oral beta-lactam containing therapy for Buruli ulcer treatment shortening

Presented by Santiago Ramón-García

María Pilar Arenaz-Callao[1, 2], Rubén González del Río[2], Ainhoa Lucía Quintana[3], Charles J. Thompson[4], Alfonso Mendoza-Losana[2] * and Santiago Ramón-García[1, 2, 3, 4] *

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Before 2004, the only treatment option for Buruli ulcer (BU) was surgery. A major breakthrough was the discovery that it could be cured in most cases with a standard treatment that involved 8 weeks of combination therapy with rifampicin and streptomycin. However, the use of streptomycin is often associated with severe side effects such as ototoxicity, or nephrotoxicity. More recently, a clinical trial demonstrated equipotency of replacing the injectable streptomycin by the clarithromycin, which is orally available and associated with fewer side effects. BU treatment is now moving toward a full orally available treatment of clarithromycin-rifampicin. Although effective and mostly well tolerated, this new treatment is still associated with side effects and only moxifloxacin is additionally recommended by WHO for BU therapy. New drugs are thus needed to increase the number of available treatments, reduce side effects, and improve efficacy with treatments shorter than 8 weeks.

The potential use of clinically approved beta-lactams for BU treatment was investigated *in vitro* against *Mycobacterium ulcerans* clinical isolates. Beta-lactams tested were effective alone and also displayed a strong synergistic profile in combination with antibiotics currently used to treat BU, i.e. rifampicin and clarithromycin; this activity was further potentiated in the presence of the beta-lactamase inhibitor clavulanate. In addition, quadruple combinations of rifampicin, clarithromycin, clavulanate and beta-lactams resulted in multiplicative reductions in their minimal inhibitory concentration (MIC) values; the MIC of amoxicillin against a panel of clinical isolates decreased more than 200-fold within this quadruple combination, and between 32 to 64-fold in the case of rifampicin and clarithromycin.

Here **we describe for the first time the potential inclusion of beta-lactams in BU therapy.** Using a repurposing approach and technology already developed in TB R&D programs, we have identified amoxicillin/clavulanate as a new potential anti-BU drug to be used in combination therapy with rifampicin and clarithromycin, current first-line anti-BU drugs. Amoxicillin/clavulanate is oral, suitable for the treatment of children, and readily available with a long track record of clinical pedigree. The inclusion of amoxicillin/clavulanate in a triple oral therapy would quickly reduce the initial bacterial burden (which is associated with healing time) and would increase of the sterilization activity of rifampicin (which is associated with cure rates and treatment shortening).

In summary, the inclusion of amoxicillin/clavulanate in current anti-BU therapy has the potential to improve healing outcomes and shorten BU treatment. **We propose that the use of high-dose extended release formulations of amoxicillin/clavulanate during the first two weeks of BU therapy might reduce treatment to just 4 weeks**, although this hypothesis needs to be validated in clinical trials.

High-dose rifampin for Buruli ulcer: pre-clinical studies and recommendations for clinical testing

Presented by Till F. Omansen

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Buruli ulcer (BU), a neglected tropical disease continues to cause skin lesions and related sequelae such as wounds, scars that results in disability and stigma. With no vaccine available and an unknown transmission cycle, quick diagnosis and highly efficient, short-course therapy is the main strategy for BU disease control. BU treatment has come a long way from surgery, to 8 weeks Rifampin (RIF) and Streptomycin (STR) and now to the replacement of Streptomycin (STR) with Clarithromycin (CLR) for still 8 weeks. Here, we conducted two pre-clinical studies to evaluate the ability of high-dose RIF. First, we conducted a dose-ranging study. BALB/c (n=110) were infected with *M. ulcerans* in the footpad and daily, oral treatment was initiated after 6 weeks' incubation time. We tested RIF 5, 10, 20, 40 mg/kg as well as rifapentine (RPT) 5, 10 and 20 mg/kg, both in combination with CLR. We observed dose-dependent efficacy of both rifamycin; 40 mg/kg RIF and all RPT regimens delivered culture-free lesions after 4 weeks of treatment. Secondly, we conducted a confirmatory study with both microbiological outcome and also relapse assessment. In the second study, BALB/c mice (n=176) were infected as described above and treated with 10-30 mg/kg of RIF in combination with CLR, or with azithromycin (AZI). AZI has less drug-drug interactions with RIF and is therefore hypothesized to be more efficacious in this combination regimen. We analyzed a) the pharmacokinetic profile, comparing CLR with AZI, b) the microbiological (CFU) outcome and c) the rate of relapse after each treatment. While the 4 week 30 mg/kg RIF+CLR regimen was highly efficient, AZI appeared to be even more favorable than CLR. There are several new therapeutic options to treat BU, such as diarylquinolines or Q203. Here, we provide extended evidence on the use of high-dose RIF for the treatment of BU, which can either be combined with CLR or AZI, with clofazimine as we previously showed, or with one of the newer compounds like BDQ or Q203. High-dose RIF is a cost-effective, highly efficient, easily implementable solution to shorten BU treatment duration; further recommendations on clinical studies that should follow these in-vivo results are provided in the presentation.

Repurposing of tuberculosis drug candidates for the treatment of Buruli ulcer

Presented by Gerd Pluschke

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Mycobacterium ulcerans shows only limited sensitivity to most established antibiotics and current Buruli ulcer treatment is therefore highly dependent on one drug, rifampicin. In view of the reported severe negative side effects of the currently recommended combination therapies in some of the patients, it would be desirable to have alternative treatment options. Repurposing of new tuberculosis drug candidates is one attractive approach to search for new compounds active against *M. ulcerans*. However, most tuberculosis-active scaffolds that we have tested, showed no, or only limited activity (1). Remarkable exceptions are imidazopyridine carboxamide (IPA) compounds, such as the clinical-stage tuberculosis drug candidate Q203 (2). In contrast to all other scaffolds we have tested, the IPA compounds targeting the respiratory cytochrome bc_1:aa_3 (cyt-bc_1:aa_3) are more active against *M. ulcerans* than against *M. tuberculosis.* This increased susceptibility is related to reductive evolution in *M. ulcerans*: while cyt-bc_1:aa_3 is the primary terminal oxidase in *M. tuberculosis*, the presence of an alternate *bd*-type terminal oxidase limits the bactericidal and sterilizing potency of IPA compounds in this bacterium. *M. ulcerans* strains belonging to the classical lineage from Africa and Australia, lost all alternate terminal electron acceptors, and rely exclusively on the cytochrome bc_1:aa_3 to respire oxygen. As a result, IPA compounds are bactericidal at very low dose against *M. ulcerans* replicating *in vitro* and in experimentally infected mice. The natural loss of cyt-*bd* function argues that Q203 may have a much higher efficacy and safety margin for Buruli ulcer than for tuberculosis treatment. This should be tested in human clinical trials.

Related publication:

1. Scherr N, Bieri R, Thomas SS, Chauffour A, Kalia NP, Schneide P, Ruf MT, Lamelas A, Manimekalai MSS, Grüber G, Ishii N, Suzuki; K, Tanner M, Moraski GC, Miller MJ, Witschel M, Jarlier V, Pluschke G, Pethe K. Targeting the *Mycobacterium ulcerans* cytochrome bc1:aa3 for the treatment of Buruli ulcer. *Nat Commun*. 2018;9:5370.

2. Scherr N, Pluschke G, Panda M. A comparative study of activities of a diverse set of anti-mycobacterial agents against *Mycobacterium tuberculosis* and *Mycobacterium ulcerans*. *Antimicrob Agents Chemother*. 2016;60(5):3132-3137.

Further shortening of Buruli ulcer treatment: targeting the respiratory chain and exploiting *M. ulcerans* gene decay

Presented by Paul J. Converse

Paul J. Converse[*1], Deepak V. Almeida[1], Sandeep Tyagi[1], Jian Xu[1], Eric L. Nuermberger[1]

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Buruli ulcer is treatable with antibiotics. An 8-week course of rifampin (RIF) and either streptomycin (STR) or clarithromycin (CLR) cures over 90% of patients. However, STR may be toxic and CLR shares an adverse drug-drug interaction with RIF and may be poorly tolerated. Studies in a mouse footpad infection model showed that increasing the dose of RIF or using the long-acting rifamycin, rifapentine (RPT), in combination with clofazimine, CFZ, a relatively well-tolerated antibiotic, can shorten treatment to 4 weeks. CFZ is reduced by a component of the electron transport chain (ETC) to produce reactive oxygen species toxic to bacteria. Synergistic activity of CFZ with other ETC-targeting drugs, the ATP synthase inhibitor bedaquiline (BDQ) and the $cc_3{:}bc_1$ oxidase inhibitor Q203, was recently described against *Mycobacterium tuberculosis*. Recognizing that *M. tuberculosis* mutants lacking the alternative *bd* oxidase are hypersusceptible to Q203 and that *Mycobacterium ulcerans* is a natural *bd* oxidase-deficient mutant, we tested the *in vitro* susceptibility of *M. ulcerans* to Q203 and evaluated the treatment-shortening potential of novel 3- and 4-drug regimens combining RPT, CFZ, Q203 and BDQ in a mouse footpad model. The MIC of Q203 was extremely low between 0.00015 - 0.000075 μg/ml. Footpad swelling decreased more rapidly in mice treated with Q203-containing regimens compared to RIF+STR and RPT+CFZ. Nearly all footpads were culture-negative after only 2 weeks of treatment with regimens containing RPT, CFZ, and Q203. No relapse was detected after only 2 weeks of treatment in mice treated with any of the Q203-containing regimens. In contrast, 15% of mice receiving RIF+STR for 4 weeks relapsed. We conclude that it may be possible to cure patients with Buruli ulcer in 14 days or less using Q203-containing regimens rather than currently recommended 56-day regimens.

High-dose rifampicin and Q203 for ultra-short treatment of Buruli ulcer

Presented by Deepak V. Almeida

Deepak V. Almeida[1], Paul J. Converse[1], Till F. Omansen[1,2], Sandeep Tyagi[1] and Eric L. Nuermberger[1]

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Introduction

Although the combination of rifampicin (RIF) and clarithromycin (CLR) now provides a fully oral treatment regimen for Buruli ulcer, the 8-week duration of treatment required for cure remains an obstacle. Shorter treatment durations will improve treatment completion rates and reduce the burden on patients and providers. Q203 is a new anti-tubercular drug candidate targeting the respiratory cytochrome bc_1:aa_3 complex [1]. Because *M. tuberculosis* mutants without a functional alternative cytochrome *bd* oxidase are hyper-susceptible to [2] Q203 and the classical sequenced strains of *Mycobacterium ulcerans* the *cydA* gene of the *bd* oxidase appears to be [3] mutated, we hypothesized that *M. ulcerans* is exquisitely susceptible to Q203. Indeed, Q203 has extremely low MICs against the strains used in our murine models of Buruli ulcer [4]. We previously reported that high-dose RIF improves the bactericidal activity of *M. ulcerans* treatment regimens in the murine model [5]. In the present experiment, we tested the efficacy of novel regimens combining Q203 with RIF at normal and high doses to determine their potential as ultra-short treatment regimens of 4 weeks or less for Buruli ulcer.

Methods

BALB/c mice (n = 135) were infected in both footpads [4] with *M. ulcerans* 1059, a Ghanaian strain. Treatment began seven weeks later when all mice had an average lesion index (ALI) of 2-3. Mice were randomized to the following treatment groups: $Q203_{\mathbf{5}}$, $Q203_{\mathbf{10}}$, $RIF_{\mathbf{10}}$ + clarithromycin $(CLR)_{\mathbf{100}}$, $RIF_{\mathbf{10}}$+$Q203_{\mathbf{5}}$, $RIF_{\mathbf{20}}$+$Q203_{\mathbf{5}}$, $RIF_{\mathbf{10}}$+$Q203_{\mathbf{10}}$ and $RIF_{\mathbf{20}}$+$Q203_{\mathbf{10}}$, with the drug dose (in mg/kg) represented by the number in subscript. Response to treatment was determined by (a) decrease in swelling in the footpads, (b) reduction in footpad CFU counts and (c) culture-positive relapse in the footpads after stopping treatment. Swelling assessments were done weekly for the first 4 weeks of treatment and then done bi–weekly. CFU counts were determined after 1, 2 and 4 weeks of treatment except in mice treated with $Q203_{\mathbf{5}}$ alone or $Q203_{\mathbf{10}}$ alone which were assessed only after 2 weeks or after 1 and 2 weeks, respectively, of treatment. Mice were held for relapse after 2 and 4 weeks of treatment for all RIF + Q203 containing regimens, mice treated with $RIF_{\mathbf{10}}$ + $CLR_{\mathbf{100}}$ were only assessed for relapse after 4 weeks of treatment.

Results

Footpad swelling: A rapid decrease in footpad swelling was observed in all Q203-treated groups. After 1 week, mice treated with any RIF + Q203 regimen or $Q203_{\mathbf{10}}$ alone had ALI ≤ 1, and those treated with $Q203_{\mathbf{5}}$ alone had an ALI = 1.5. By comparison, the swelling in $RIF_{\mathbf{10}}$ + $CLR_{\mathbf{100}}$ treated mice was unchanged from the Day 0 ALI of 2.5. After 2 weeks of treatment, the footpads of all mice treated with any Q203 containing regimen showed almost no swelling, while those treated with RIF+CLR still had an ALI = 1.5. After 3 weeks of treatment mice in all treatment regimens had near normal footpads.

CFU counts: The mean $\log_{10}$ CFU/footpad (±SD) at the start of treatment (D0) was 5.42 ± 0.56. After 1 week of treatment the mean CFU counts had decreased in all treatment groups except $RIF_{\mathbf{10}}$ + $CLR_{\mathbf{100}}$, which harbored 5.51±0.41. CFU counts in Q203-containing groups were as follows: $Q203_{10}$, 4.77 ± 0.54; RIF_{10}+$Q203_{\mathbf{5}}$, 4.00 ± 1.15; RIF_{20}+$Q203_{5}$, 3.67 ± 0.72; RIF_{10}+$Q203_{10}$, 2.18 ± 1.30; RIF_{20}+$Q203_{10}$, 2.98 ±1.13. After 2 weeks of treatment the $RIF_{\mathbf{10}}$ + $CLR_{\mathbf{100}}$ CFU counts were 2.63 ± 0.37, while no CFU could be detected in any Q203-treated mouse with the exception of one positive footpad (among 6) in each group other than $RIF_{\mathbf{20}}$+$Q203_{\mathbf{10}}$. The CFU counts were as follows: $Q203_{\mathbf{5}}$, 0.14 ± 0.35; $Q203_{\mathbf{10}}$, 0.33 ± 0.80;

RIF_{10}+$Q203_5$, 0.33 ± 0.80; RIF_{20}+$Q203_5$, 0.53 ± 0.85; RIF_{10}+$Q203_{10}$, 0.89 ± 1.49; RIF_{20}+$Q203_{10}$, 0. After 4 weeks of treatment no CFU could be detected in any treatment group.
Relapse assessment: In mice held for relapse after 2 and 4 weeks of treatment no re-swelling has been observed despite 2 months of follow-up without treatment. We will have the results of follow-up for 4 months after treatment at the time of the meeting presentation.

Conclusion

As recently reported by Scherr et al [6], we found *M. ulcerans* to be exquisitely susceptible to Q203. We extend their findings to show that Q203 has strong, but dose-dependent, activity in mice and that the regimens combining RIF with Q203 containing regimens resulted in rapid reduction of footpad swelling and CFU counts indicating that it may be a promising candidate to combine with rifampicin and has potential for developing ultra-short regimen in treatment of Buruli Ulcer.

Acknowledgments

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References

[1] Pethe, K. et al. **2013.** Discovery of Q203, a potent clinical candidate for the treatment of tuberculosis. *Nat. Med.* 19, 1157–1160.
[2] Kalia, NP et al. **2017**. Exploiting the synthetic lethality between terminal respiratory oxidases to kill Mycobacterium tuberculosis and clear host infection. Proc Natl Acad Sci USA. 114: 7426-7431.
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[5] Omansen, TF et al. **2018.** High-dose rifamycins enable shorter oral treatment in a murine model of Mycobacterium ulcerans disease. Antimicrob Agents Chemother Nov 2018, AAC.01478-18; DOI: 10.1128/AAC.01478-18. [Epub ahead of print]
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A pilot study of nitric oxide generating dressing (EDX) in the management of Buruli ulcer disease

Presented by Richard Phillips

Bernadette Agbavor[1], Michael Frimpong[1], Francisca Sarpong[1], Abigail Agbanyo[1], Abass K. Mohammed[2], Solomon Gyabaah[1], Mark Wansbrough-Jones[3], Richard Phillips[1*]

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Background

The introduction of antibiotic treatment over the past ten years has transformed the outcomes of Buruli ulcer disease. The current recommended regimen of a combination of oral rifampicin combined with clarithromycin daily for 8 weeks (RC8) is rather demanding. Healing rates are highly variable in patients with seemingly similar lesions though the disease is cured in patients who adhere to the regimen. From previous studies the baseline bacterial load and the development of paradoxical reactions contribute significantly to this. An alternative treatment approach proposed is the concurrent application of novel nitric oxide (NO) generating wound dressing (EDX dressing) that are known to exhibit broad spectrum antimicrobial activity including activity against *M. ulcerans.* We present here pilot results determining the ability of the EDX dressing combined with the antibiotics regimen to improve healing outcomes in Buruli lesions in comparison with the current standard treatment and standard dressings.

Methods

Using an open-label study design, 23 BU confirmed cases were randomized into two wound dressing arms; Eleven patients with Buruli ulcer were successively offered NO dressings on compassionate grounds to enhance their wound healing. Their healing outcomes were compared with healing of 12 randomly selected similar sized lesions that received standard routine gauze dressings. Swab / FNA samples were collected from patients after informed consent at baseline and during treatment (2,4,8 weeks) and after treatment (12 and 16 weeks) when the lesion persisted for the combined 16SrRNA /IS*2404* assays and Mu culture. On review lesion measurements were done and time to healing noted. Demographic data from standard BU01 forms and photographs was documented. Healing outcome and killing of bacteria were noted.

Principal Findings

The median (range) age of participants who received the NO dressings was 11 (3-50) comparable to those who received standard dressings 12 (5-51). The participants in both arms had similar lesion characteristics; same proportion of nodules, plaques and ulcers and category of lesions. There were 6 (50%) category I and 6 (50%) category II lesions. The median time to healing for the NO patients was 4 weeks in comparison to 24 for the standard patients (log-rank test, p=0.0002). Clearance rate of viable organisms was faster in NO group compared to the standard dressings (8 weeks vrs 16 weeks) with a significance difference in the proportion of patients with detectable viable organisms and copies of IS*2404* at weeks 4 and 8.

Discussion/Conclusion

The results suggest more rapid killing and healing of lesions in patients that received NO releasing dressings in addition to RC8. There is the need for a larger study to confirm these findings. Success would have a major impact on the management of Buruli ulcer, with faster healing leading to shorter treatment duration for many patients and further economic and social benefits.

Agenda

WHO Meeting on Buruli ulcer
and other skin neglected tropical diseases

25–27 March 2019

WHO Headquarters, Geneva, Switzerland

THEME:

"ENHANCING DETECTION OF SKIN-NTDS THROUGH INTEGRATION"

PLENARY SESSIONS

Monday 25 March 2019

Executive Board Room

The objectives of this meeting are:

- To review the epidemiological situation of Buruli ulcer from endemic countries (2017–2018);
- To share information on activities carried out on Buruli ulcer control and research and achievements made;
- To share experiences on the integrated strategy to control skin NTDs;
- To agree on control and research priorities for the next 2 years and coordinate their implementation; and
- To discuss the post-2020 NTD agenda and targets.

Monday 25 March 2019 **09:00 – 12:00** **Chair: Mark Wansbrough-Jones**		
Time	**Subject**	**Presenters**
08:00 – 09:00	Registration and welcome coffee	
09:00 – 09:30	Welcome remarks and updates on Neglected Tropical Diseases Short remarks Rationale and objectives of the meeting	Mwelecele Ntuli Malecela Daniel Argaw Dagne Kingsley Asiedu
09:30 – 10:00	Tribute to the contributions of the late Dr Wayne Meyers towards Buruli ulcer and leprosy	Françoise Portaels
10:00 – 10:20	Buruli ulcer in Australia – 2017–2018 and plans for 2019 • Victoria • Queensland	Paul Johnson Christina Steffen
10:20 – 10:40	Buruli ulcer in Australian Children	N. Deborah Friedman
10:40 – 11:00	Buruli ulcer and other skin-NTDs activities in Côte d'Ivoire – 2017–2018 and plans for 2019	Henri Assé
11:00 – 11:20	Buruli ulcer and other skin-NTDs activities in Benin – 2017–2018 and plans for 2019	Jean Gabin Houézo
11:20 – 11:40	A randomized controlled trial comparing efficacy of 8 weeks treatment with clarithromycin and rifampicin (RC8) versus streptomycin and rifampicin (RS8) for Buruli ulcer in Ghana and Benin – Update	Tjip van der Werf Richard Phillips
11:40 – 12:00	Six versus eight weeks of antibiotics for small *Mycobacterium ulcerans* lesions in Australian patients	Daniel O'Brien

Monday 25 March 2019

14:00 – 17:00

Chair: Françoise Portaels

Time	Subject	Presenters
14:00 – 14:20	Fourth round of External Quality Assessment Program (EQAP) of molecular detection of *Mycobacterium ulcerans* in clinical specimens – results and way forward	Miriam Eddyani
14:20 – 14:40	Rationale approach for effective wound care in Benin and Côte d'Ivoire: method and results	Christian Johnson Anita Wadagni
14:40 – 15:00	Skin NTDs – new initiatives	Roderick Hay
15:00 – 15:20	Update on AFRO Integrated Strategy for Case Management of five Neglected Tropical Diseases (Buruli ulcer, Human African Trypanosomiasis, Leishmaniasis, Leprosy and Yaws) in the WHO African Region	Alexandre Tiendrebeogo
15:20 – 15:40	Skin diseases prevalence survey as a part of integrated activities for skin NTDs in Côte d'Ivoire: results from the Adzopé and Gagnoa health districts and implications for future implementation	Rie Yotsu
15:40 – 16:00	Buruli ulcer – where are we now? 2014 WHO programmatic targets and global epidemiology Summary of the 2017 global survey on yaws and mycetoma	Till Omansen
16:00 – 16:20	Post-2020 targets for Buruli ulcer control	Kingsley Asiedu
16:20 – 17:00	Data management tools for Buruli ulcer and yaws and DHIS2	Lise Grout
17:00 – 17:30	***Coffee-break***	

CONTROL SESSIONS

Tuesday 26 March 2019

Salle B

EACH SPEAKER HAS 15 MINUTES FOR PRESENTATION
PLUS 5 MINUTES FOR QUESTIONS

Tuesday 26 March 2019

Control Session 1 – Integration

09:00 – 12:00

Chair: Emmanuel Agumah

08:30 – 09:00	***Welcome coffee***

Time	Subject	Presenters
09:00 – 09:20	Brief updates: • International conference on mycetoma, Khartoum, Sudan 15-17 February 2019 • WHO Informal Consultation on a Framework for Scabies Control, Manilla, Philippines, 19-21 February 2019	Roderick Hay Michael Marks
09:20 – 09:40	Review of Buruli ulcer surveillance data in Victoria, Australia, 2004 to 2018	Ee Laine Tay
09:40 – 10:00	Buruli ulcer and other skin-NTDs in French-Guiana: 2017-2018 and plans for 2019	Pierre Couppié
10:00 – 10:20	Buruli ulcer and other skin-NTDs in Japan: 2017-2018 and plans for 2019	Murase Chiaki Mariko Sugawara-Mikami
10:20 – 10:40	Buruli ulcer in Gabon: 2017-2018 and plans for 2019	Annick Mondjo
10:40 – 11:00	Buruli ulcer and other skin-NTDs in Ghana: 2017-2018 and plans for 2019	Nana Konama Kotey
11:00 – 11:20	Evidence of the high endemicity of leprosy and yaws in Bale Loko commune, Central African Republic	Alphonse Um Boock
11:20 – 11:40	Integrated approach to the control of skin neglected tropical diseases in Benin	Yves Barogui
11:40 – 12:00	Pilot study on integration in the control of against skin neglected tropical diseases in Togo's Maritime region	Charlotte Amedifou
12:00 – 14:00	***Lunch break***	

Control Session 2 – Integration

14:00 – 17:00

Chair: Alexandre Tiendrebeogo

Time	Subject	Presenters
14:00 – 14:20	Epidemiological facies of leprosy in Benin between 2006 and 2018	Ronald Gnimavo
14:20 – 14:40	Developments in the epidemiological situation of Buruli ulcer in Benin between 2008 and 2018	Anita Wadagni
14:40 – 15:00	Disease burden and epidemiology of skin-presenting NTDs in Maryland County, Liberia: results from an integrated cluster-randomised active case search	Emerson Rogers
15:00 – 15:20	Integrating mobile phone and social media interventions into health research: A case for improving early case detection of Buruli ulcer in Ghana and Cote d'Ivoire	Charles Quaye
15:20 – 15:40	Using medical illustrations to aid diagnosis of neglected tropical diseases	Joanna Butler
15:40 – 16:00	Interactive mapping as a tool to investigate for lesion distribution patterns among patients with Buruli ulcer	Arvind Yerramilli
16:00 – 16:20	Update on the further development of the SkinApp	Benita Jansen
16:20 – 16:40	Capacity building practical dermatology skills for NTD and other global health programmes	Claire Fuller
16:40 – 17:00	WHO-UOC Skin NTDs on-line training program: Lessons learnt from former editions	Carme Carrion Ribas

17:00 – 18:00	**Informal consultation on medical illustrations of NTDs (optional):** During this session, Joanna Butler will present medical illustrations to interested participants and invite their comments	Joanna Butler

RESEARCH SESSIONS

Tuesday 26 March 2019

Executive Board Room

Tuesday 26 March 2019

Research session 1 – Poster session

08:30 – 10:00

Chairs: Richard Phillips and Bouke De Jong

Each presenter of this poster session is given the option to introduce their work to the group with a 3-minute slot and a maximum of 3 slides

Poster Presenters

Diagnostics	
1. Stand Chudy	E-nose detection of Buruli ulcer in the DRC
2. Michael Marks	Molecular tools to improve the understanding of yaws in Ghana
Transmission	
3. Yaw Amoako	Buruli ulcer in two neonates: providing insight into incubation period of *M. ulcerans* disease in this age group
4. Fosu Samuel Gyasi	The influence of climatic variations patterns to the development of *M. ulcerans* infections in the Brong Ahafo Region of Ghana.
5. David Coulibaly N'golo	Molecular evidence of the implication of non-*M. ulcerans* pathogens in skin diseases liked Buruli ulcer using PCR targeting the insertion sequences and the ketoreductase gene
6. Daniel Sanhueza	Towards an index of biotic integrity for use in Buruli ulcer endemic and non-endemic tropical regions
7. Bouke De Jong/Tim Stinear	Introduction of Buruli ulcer in the Bankim HD of Cameroon follows damming the Mapé River

Treatment	
8. Maria Letizia Iabichella	Skin microcirculation assessment in Buruli ulcer
9. Daniel O'Brien	Spontaneous healing of *Mycobacterium ulcerans* disease in Australian patients
10. Kurt-Wilhelm Stahl	LeiProtect®, a specially approved, economic filmogenic gel, for NTD skin lesion management
11. Antonio Carlo Galoforo	Implementation of a nursing protocol for the use of ozonotherapy in the treatment of Buruli ulcer
Vaccines	
12. Justice Boakye-Appiah	Buruli ulcer disease: the search for mycolactone-based vaccine
13. Mélanie Foulon	Local humoral response during *M. ulcerans* infection: production of mycolactone-recognizing and neutralizing antibodies
14. Tim Stinear	Identifying correlates of protection for a vaccine against *Mycobacterium ulcerans* infection in a low-dose murine challenge model
Other skin NTDs	
15. Ymkje Stienstra	Efficacy of ivermectin mass-drug administration to control scabies in asylum seekers in the Netherlands: A retrospective cohort study between January 2014 - March 2016
16. Leila Zaki	Preventive and therapeutic effects of morphine on ulcers caused by *Leishmania major* in BALB/c mice
10:00 – 11:00	***Electronic poster session and coffee***

ORAL PRESENTATIONS

EACH SPEAKER HAS 10 MINUTES PLUS 5 MINUTES FOR QUESTIONS

Research session 2 – Pathogenesis

11:00 – 12:00

Chairs: Rachel Simmonds and Laure Guenin-Macé

Time	Subject	Presenter
Pathogenesis		
11:00 – 11:15	Sec61 blockade by mycolactone: a central mechanism in Buruli ulcer disease	Caroline Demangel
11:15 – 11:30	Proteomic analysis of the endothelial cell response to mycolactone	Belinda Hall
11:30 – 11:45	Local coagulopathy in the skin lesions of Buruli ulcer patients	Louise Tzung-Harn Hsieh
11:45 – 12:00	Understanding host interactions of mycolactone in order to improve storage and measurement, facilitating diagnostics	Harshini Mukundan
12:00 – 14:00	***Lunch break***	

Research session 3 – Diagnostics and non-antibiotic treatments 14:00 – 16:00 Chair: Tjip van der Werf and Marie-Thérèse Ruf		
Time	**Subject**	**Presenter**
Diagnostics and non-antibiotic treatments		
14:00 – 14:15	Initial serological screening test for *Mycobacterium ulcerans* exposure in Victoria, Australia	Michael Selorm Avumegah
14:15 – 14:30	Joint efforts to develop rapid diagnostic tests for the early diagnosis of Buruli ulcer	Israel Cruz
14:30 – 14:45	A field-deployable recombinase polymerase amplification assay for rapid detection of *Mycobacterium ulcerans*	Michael Frimpong
14:45 – 15:00	Assessment of a field-deployable LAMP assay for rapid detection of *Mycobacterium ulcerans*	Tim Stinear
15:00 – 15:15	Potential therapeutic application of autologous leukocyte and platelet rich fibrin (L-PRF) as an alternative intervention for wound healing in Buruli ulcer	Indra Bahadur Napit
15:15 – 15:30	Acute changes of skin microcirculation in Buruli ulcers after local ozone therapy	Maria Letizia Iabichella
15:30 – 16:00	***Coffee break***	

Research session 4 – Transmission 16:00– 17:15 Chairs: Estelle Marion and Michael Frimpong		
16:00 – 16:15	Controlling Buruli ulcer in Victoria: case-control study	Eugene Athan
16:15 – 16:30	A multifactorial mosquito control intervention versus standard community information for the reduction of Buruli ulcer in Victoria, Australia: a cluster randomised controlled trial	Jane Oliver Simon Crouch
16:30 – 16:45	Environmental control of diseases: quantitative survey of the impact of well-drilling on Buruli ulcer	Horace Degnonvi
16:45 – 17:00	The association of Buruli ulcer disease endemicity with major climatic, epidemiological and socio-environmental factors: a geospatial analysis from southern Nigeria	Saskia Kreibich

PLENARY SESSIONS

Wednesday 27 March 2019

Executive Board Room

Control Session – General topics 09:00 – 12:00 Chair: Ghislain Sopoh		
08:30 – 09:00	***Welcome coffee***	
Time	**Subject**	**Presenters**
09:00 – 09:20	The search for Buruli ulcer in Sierra Leone	Helen Please
09:20 – 09:40	Buruli ulcer treatment: antimicrobial therapy is the mainstay of treatment, but the rate of surgical intervention differs highly between treatment centres	Anita Wadagni
09:40 – 10:00	The integrated control of skin NTDs in Cameroon	Earnest Njih Tabah
10:00 – 10:20	Implementation of an integrated management of skin NTDs in Ghana: Experiences from the laboratory	Bernadette Agbavor
10:20 – 10:40	Prevalence and profile of HIV in patients with *Mycobacterium ulcerans* infection in Nigeria	Anthony Meka
10:40 – 11:00	Assessment of community understanding of the aetiology, transmission, presentation, treatment and prevention of Buruli ulcer disease (*Mycobacterium ulcerans* infection) in Southern Nigeria	Ngozi Ekeke
11:00 – 11:20	Health seeking behaviour for Buruli ulcer disease in the Obom sub-district of the Ga south Municipality of Ghana	Eric Koka
11:20 – 11:40	Integrated approach to tropical lymphoedemas: simple interventions reduce acute episodes in all tropical lymphoedemas and improve quality of life.	Claire Fuller
11:40 – 12:00	The ENDPoINT Consortium – integrating limb care and wellbeing support across skin-NTDs	Gail Davey
12:00 – 14:00	***Lunch break***	

Research session – Treatment

Wednesday 14:00 – 15:30

Chair: Ymkje Stienstra

Time	Subject	Presenter
Treatment		
14:00 – 14:15	Triple oral beta-lactam containing therapy for Buruli ulcer treatment shortening	Santiago Ramon-Garcia
14:15 – 14:30	High-dose rifampin for Buruli ulcer: pre-clinical studies and recommendations for clinical testing	Till Omansen
14:30 – 14:45	Repurposing of tuberculosis drug candidates for the treatment of Buruli ulcer	Gerd Pluschke
14:45 – 15:00	Further shortening of Buruli ulcer treatment: targeting the respiratory chain and exploiting *M. ulcerans* gene decay	Paul Converse
15:00 - 15:15	High-dose rifampicin and Q203 for ultra-short treatment of Buruli ulcer	Deepak Almeida
15:15 – 15:30	A pilot study of nitric oxide generating dressing (EDX) in the management of Buruli ulcer disease	Richard Phillips
15:30 – 16:00	***Coffee break***	

Conclusions and recommendations

16:00 – 17:00

Executive Board Room

List of participants

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