Report of a WHO–FIND meeting on diagnostics for Buruli ulcer

Geneva, 26–27 March 2018

World Health Organization

FIND
Because diagnosis matters

Suggested citation. Report of a WHO–FIND meeting on diagnostics for Buruli ulcer, Geneva, 26–27 March 2018. Geneva: World Health Organization; 2018. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at http://apps.who.int/iris.

WHO/CDS/NTD/IDM/2018.09

Contents

Abbreviations

BU	Buruli ulcer
ELISA	enzyme-linked immunosorbent assay
EQA	external quality assurance
FIND	Foundation for Innovative New Diagnostics
fTLC	fluorescent thin-layer chromatography
LAMP	loop-mediated isothermal amplification
mAbs	monoclonal antibodies
PCR	polymerase chain reaction
RDT	rapid diagnostic test
RPA	recombinase polymerase amplification
TPP	target product profile
WHO	World Health Organization

1. Background

The target of the World Health Organization (WHO) roadmap on neglected tropical diseases[1] for Buruli ulcer (BU) is that by 2020, 70% of all cases are detected at an early stage and cured with antibiotics in all countries where the disease is endemic. The Foundation for Innovative New Diagnostics (FIND) is collaborating with WHO to achieve this target for control of the disease. FIND's main focus is on promoting and supporting the development of new diagnostic tools to improve early detection of BU. The current FIND strategy on BU diagnostics was developed after a meeting of experts convened by WHO and FIND in 2013. Since then, FIND has been working with partners in academia and industry to develop a rapid test for screening and diagnosis at the community level, and to develop a molecular test for confirmatory diagnosis at the microscopy laboratory or district hospital level; and is supporting WHO in the evaluation and implementation of fluorescent thin-layer chromatography (fTLC) to detect mycolactone in lesions from BU suspected cases.

During a meeting of the WHO Technical Advisory Group (TAG) on Buruli ulcer (Geneva, 21 March 2017), a number of problems with laboratory confirmation of BU were identified: (i) low rate of polymerase chain reaction (PCR) confirmation in a number of endemic countries; (ii) long delays in getting results from laboratories; (iii) low participation in external quality assurance (EQA) programme by national reference laboratories; and (iv) lack of funding for sustaining the EQA programme. The TAG noted with satisfaction the progress made to develop diagnostic tests for BU by many research groups; however, considerable time is still needed to optimize methods and to progress them to field testing.

To accelerate progress, WHO and FIND convened a second global meeting at WHO headquarters in Geneva, Switzerland with the aim of establishing an action plan to develop new diagnostic solutions for BU and to create a framework of collaboration to address unmet needs in BU diagnostics.

[1] Accelerating work to overcome the global impact of neglected tropical diseases: a roadmap for implementation. Geneva: World Health Organization; 2012 (http://www.who.int/neglected_diseases/NTD_RoadMap_2012_Fullversion.pdf).

2. Meeting summary

The meeting was held from 26 to 27 March 2018 to review and discuss the following topics:

- Advances and challenges in the use of fTLC, and new approaches to detecting mycolactone using monoclonal antibodies (mAbs).
- The status of development of rapid diagnostic tests (RDTs) targeting the MUL_3720 protein.
- The role of PCR as a reference test, and hurdles in providing a confirmatory diagnosis and in establishing a quality assurance programme.
- New molecular tools with potential for implementation at a level lower than in the national or regional reference laboratory, such as loop-mediated isothermal amplification (LAMP) and recombinase polymerase amplification (RPA).
- The need to harmonize and standardize methods for collection and preparation of specimens, so samples can be referred for diagnosis and stored for evaluation of new diagnostic tests in optimal conditions.
- Barriers to accessing early diagnosis and treatment, including coordination at the programme level, and lack of adequate diagnostic tools.
- Defining target product profiles (TPPs) to guide the development of new diagnostic tools that can be applied at different levels of the health system. Participants agreed that two TPPs would be developed to address the current gaps: (i) a rapid test for BU diagnosis at the primary health-care level; and (ii) a test for diagnosis of BU that can also assist in treatment monitoring and differential diagnosis at the district hospital or reference centre.

3. Key discussion points

3.1. Targeting mycolactone for the diagnosis of Buruli ulcer

- Preliminary results show that mycolactone or its metabolites may be present in the urine of mice infected with *Mycobacterium ulcerans* and in cases of BU, but further research is needed. Levels of mycolactone in ulcerative lesions decrease with treatment, highlighting its potential as a test of cure. Studies by Johns Hopkins University on liquid chromatography-mass spectrometry using experimental infections in mice and guinea-pigs show that the concentration of mycolactone is highest in the centre of the lesion, which may have implications for collection of samples for mycolactone detection tests.

- The stability of mycolactone for testing requires collection of samples in absolute ethanol and protection from light; the use of plastic tubes is not advised as mycolactone adheres to this material. The use of siliconized or glass tubes is encouraged.
- Data from the *mycostudy*, presented by the University of Ghana, show variable sensitivity (25–80%) and specificity (35–75%) of fTLC across sites. The method is standardized and appears straightforward, but the interpretation of results can be challenging, especially when swab samples are analysed. The accuracy of the PCR methods from the different national laboratories (with different protocols) used as a reference test in this study might not be ideal and could compromise the results of the evaluation.
- Different mAbs against mycolactone or mycolactone analogues have been developed using a library of either recombinant mAbs and selection with phage and yeast display (Specifica) or mouse hybridoma cells (Swiss Tropical and Public Health Institute). Assemblies of clones producing scFv and full antibodies have been generated by Specifica and the Swiss Tropical and Public Health Institute respectively. These present high affinity, in the range of the mycolactone concentration found in lesions from infected mice and BU cases (1–1000 nM). Preliminary testing has been conducted using competition enzyme-linked immunosorbent assays (ELISAs). With the availability of more synthetic mycolactone, it was proposed that open Fv ELISA and open sandwich assays could be developed, in which antibodies recognizing antibody-mycolactone complexes can be used. Both groups would join forces to work on the development of an RDT using mAbs to detect mycolactone in clinical samples. mAbs for use in the development of a prototype RDT may be ready in less than one year. Studies to assess the stability of mycolactone in stored samples will be needed.
- Access to synthetic mycolactone is an important aspect in the development of mycolactone detecting tests in order to conduct feasibility studies and as a control in the fTLC test. Professor Kishi (Harvard University) has produced large quantities of synthetic mycolactone; some are stored in his laboratory and some at WHO.

3.2. Protein (MUL_3720) capture assay in the diagnosis of Buruli ulcer

- The Swiss Tropical and Public Health Institute has developed 19 mAbs against the *M. ulcerans* surface protein MUL_3720. With PCR as reference, a pair of mAbs used in a capture ELISA shows very high specificity, but moderate sensitivity (*c*60%).

- Abbott/Standard Diagnostics has produced two prototype RDTs based on selected anti-MUL_3720 mAbs and an avidin-biotin system, which have a sensitivity in the range of 3–6 ng/mL when *M. ulcerans* protein lysates are tested. Prototypes are being produced to test clinical samples.

3.3. Molecular diagnosis of Buruli ulcer

- Evaluation of the performance of PCR/quantitative PCR (qPCR) in multiple centres by an EQA programme led by the Institute of Tropical Medicine, Antwerp has shown improvement by the participating laboratories (during 2009–2014), but some limitations remain: approximately 20% of the laboratories reported false–positive results and 30% were unable to detect weak positive samples; and the participation rate is decreasing. Participation in EQA may depend on the availability of funds for PCR/qPCR reagents, which may also affect confirmation of referred samples. Around 50% of the laboratories use home-brewed DNA extraction methods and the PCR/qPCR methodology used varies among laboratories; thus a quality assurance programme targeting harmonization rather than standardization is preferred.
- A recent study conducted by the Institute of Tropical Medicine, Antwerp and partners in Benin revealed that although clinical diagnosis has higher sensitivity than laboratory tests, it may miss BU cases, especially in the early stages (nodular forms). With declining BU incidence, the accuracy of clinical diagnosis will also decrease. Awareness of BU must therefore be sustained while rapid and cost–effective diagnostic tests are developed, as PCR should be reserved for microscopy-negative BU suspects. However, microscopy for BU is not done in many hospitals.
- Studies on the evaluation of simpler approaches to the molecular diagnosis of BU using stored clinical samples were presented, showing promising results. An evaluation of RPA using stored samples from Ghana, presented by the Kumasi Centre for Collaborative Research in Tropical Medicine, showed 86% sensitivity and 100% specificity in a set of 55 clinical samples from BU suspects. An evaluation of LAMP conducted by the Department of Infectious and Tropical Medicine/KUM, Munich and the Noguchi Memorial Institute for Medical Research on a set of 75 clinical samples from suspected cases of BU in Togo returned 100% sensitivity and specificity. In both studies IS*2404* qPCR was used as the reference. A prospective evaluation of these tests will be conducted and, if successful, may be considered to replace PCR and implemented at a level lower than the regional or national reference laboratory, as they present a number of advantages over PCR, namely: (i) their presentation in a dry reagents-based ready-to-use format

that minimizes preparation steps and avoids a cold chain; and (ii) amplification and detection are conducted in a robust, portable and automated platform. Simple methods for DNA preparation to be used with these two methods are available but need to be evaluated.

3.4. Histopathology of Buruli ulcer and sample collection

- Studies by the Swiss Tropical and Public Health Institute analysing histopathology sections from experimental infection in animals and BU cases show that *M. ulcerans* penetrates the subcutaneous tissue and is unevenly distributed, while mycolactone diffuses beyond the bacterial clumps and is widespread. This finding may have implications for sample collection and diagnosis, making mycolactone a preferred target. Levels of mycolactone decrease with treatment, whereas DNA and bacterial cells remain for some time after treatment; this finding points also to the suitability of mycolactone detection in monitoring of treatment. Microscopy may also assist by identification of a beading pattern, i.e. the loss of solid staining, of acid fast bacilli.
- Adequate collection of test samples is critical to maximize the likelihood of detecting *M. ulcerans* in a lesion from a suspected case. Current methods are based on the use of fine-needle aspirates, mainly for non-ulcerative lesions (nodules, plaques and oedema), and cotton swabs, for ulcers. The Swiss Tropical and Public Health Institute has been evaluating the use of FLOQ® swabs, which are composed of a flocking of nylon fibres that allows 10 times more material to be collected than traditional cotton swabs.
- Samples from suspected BU cases can now be analysed by different methods, and can be stored in collections to be used in feasibility studies of new diagnostic tests. Thus it is important to identify collection formats that are compatible with different downstream applications. As an example, when diagnosis by culture is not the recommended routine method of confirming cases for treatment, it is unnecessary and costly to use culture media to collect and store samples from treatment centres. Storing samples in absolute ethanol is compatible with both mycolactone and DNA detection systems, and while long-term thermal stability of mycolactone is assessed, it is recommended to store samples in glass or siliconized tubes protected from light and at −20°C. This will allow generation of results on mycolactone detection tests that are comparable to DNA detection on the same sample.

3.5. Challenges in laboratory confirmation of Buruli ulcer

- Current challenges in laboratory confirmation were presented from the perspective of the Centre de dépistage et de traitement de l'ulcère de Buruli d'Allada (Benin) and the Institut Pasteur (Côte d'Ivoire). The rate of biological confirmation of BU cases is still low (< 70%) in many countries due to gaps in many links of the referral chain, including sample collection, transport, analysis and reporting of results, namely: (i) poor quality, integrity and information on samples collected; (ii) lack of clarity about when to refer samples for biological confirmation; (iii) delay in transport of samples to the reference laboratory; (iv) poor coordination between national programmes or health centres and reference laboratories; (v) long time to receive the results, (vi) decreased motivation and technical and clinical capacity; and (vii) lower sensitivity than previously believed.
- It is generally understood that the availability of a point-of-care confirmatory test and oral antibiotic therapy would improve case management.

3.6. Target product profiles

- Participants discussed the four use cases describing the application of potential new tests:
  - screening for BU at community level;
  - diagnosis (and confirmation) of BU at community or primary health-care level;
  - diagnosis and confirmation of BU in equipped district-level laboratories and national or regional reference laboratories; and
  - test of cure for BU.

  It was agreed that screening at the community level was not a priority given that clinical assessment has an acceptable positive predictive value, and that new tests should fulfil the criteria defined in two different draft TPPs: (i) a rapid test for BU diagnosis at the primary health-care level; and (ii) a test for diagnosis of BU that can optimally assist in treatment monitoring and differential diagnosis at district hospital or reference centre. The preliminary priority features for these two TPPs are described below and will be further refined in consultation with experts in BU diagnostics.

Target product profile 1 (draft) Rapid test for diagnosis of Buruli ulcer at the primary health-care level		
Scope		
Characteristic	Optimal	Minimal
Intended use	Confirmation of Buruli ulcer	Confirmation of Buruli ulcer
Target population	Suspected cases, early stages	Suspected cases, ulcerated lesions
Target operator of the test	Nurse, laboratory technician	Nurse, laboratory technician
Lowest setting for implementation	Community, but as part of active case-finding activities	Health centre
Target analyte	Mycolactone	Protein, DNA
Performance characteristics		
Clinical sensitivity (assessed in a latent class analysis)	Polymerase chain reaction	Ziehl–Neelsen microscopy
Clinical specificity (assessed in a latent class analysis)	Polymerase chain reaction	Ziehl–Neelsen microscopy
Strain specificity	Global	African strains
Type of analysis, quantitation	Qualitative	Qualitative
Test procedure		
Training needs, time (including sample collection)	1 day	2 days
Sample type	Lesion swab, fine-needle aspirate	Lesion swab, fine-needle aspirate
Sample preparation, steps	Direct testing on sample	3–5 steps
N° of steps to be performed by operator	< 3	< 10
Need to transfer precise volumes	No	Acceptable with a disposable transfer device
Time to result	< 20 min	Same day
Reading system	Visual (naked eye)	Simple reading device
Power requirements	None	Battery operated
Operational characteristics		
Operating conditions	5–50 °C, 90% relative humidity	5–40 °C, 80% relative humidity
Kit transport	No cold chain required; tolerance of transport stress for a minimum of 1 week at −15 °C to + 50 °C	No cold chain required; tolerance of transport stress for a minimum of 72 h at −15 °C to + 50 °C
Kit storage/stability	No cold chain required; 24 months at 50 °C, 90% humidity	No cold chain required; > 12 months at 40 °C, 70% humidity
Reagents reconstitution	All reagents ready to use	Minor preparation steps, e.g. mixing reagents
In use stability	> 1 h for single use test after opening the pouch	> 2 h for single use test after opening the pouch

Target product profile 2 (draft) Test for diagnosis of Buruli ulcer, to assist in treatment monitoring and differential diagnosis at the district hospital or reference centre		
Scope		
Characteristic	Optimal	Minimal
Intended use	Treatment monitoring and differential diagnosis	Confirmation of Buruli ulcer
Target population	Suspected cases, early stages	Suspected cases, ulcerated lesions
Target operator of the test	Laboratory technician	Laboratory technologist
Lowest setting for implementation	District hospital	Regional or national reference laboratory
Target analyte	DNA	DNA
Performance characteristics		
Clinical sensitivity (assessed in a latent class analysis)	Polymerase chain reaction	Ziehl–Neelsen microscopy
Clinical specificity (assessed in a latent class analysis)	Polymerase chain reaction	Ziehl–Neelsen microscopy
Strain specificity	Global	African strains
Type of analysis, quantitation	Quantitative	Qualitative
Multiplexing	Yes (other pathogens, drug resistance profile)	Not necessary
Test procedure		
Training needs, time	1 day	5 days
Sample type	Lesion swab, fine-needle aspirate	Lesion swab, fine-needle aspirate
Sample preparation, steps	< 10	< 15
Number of steps to be performed by operator	< 10	< 15
Need to transfer precise volumes	Accepted	Accepted
Time to result	< 1 h	< 2 days
Reading system	Accepted	Accepted
Power requirements	Accepted	Accepted
Operational characteristics		
Operating conditions	5–30 °C, 80% relative humidity	5–25 °C, 60% relative humidity
Kit transport	No cold chain required; tolerance of transport stress for a minimum of 1 week at −15 °C to + 50 °C	Cold chain required; ideally refrigerated
Kit storage/stability	No cold chain required< 24 months at 50 °C, 90% humidity	Cold chain required, refrigeration; > 12 months at < 10 °C
Reagent reconstitution	Minor preparation steps, e.g. mixing reagents	Major preparation steps, e.g. mixing reagents
In-use stability	> 1 h for single use test after opening the reagent bottle	> 2 h for single use test after opening the reagent bottle

4. Discussion

- Many challenges remain in BU diagnosis, from sample collection and referral to the availability of needed tests. Effective coordination and collaboration among all actors must be ensured to accelerate progress and define a stepwise approach for laboratory diagnosis of BU.
- National and international referral laboratories[2] should work towards the harmonization of PCR processes, and quality assurance programmes (internal and external) should be put in place. A landscape analysis of PCR methods and processes, as well as gaps in the referral and reporting chain, should be conducted.
- PCR tests must perform adequately for both confirmation and as a reference test in the evaluation of new diagnostics. Results from available studies should be reviewed to better understand the diagnostic performance of PCR.
- Results from prospective evaluations of RPA and LAMP will inform the opportuneness of these methods for molecular diagnosis, but would need to be independently assessed by other laboratories.
- fTLC is still under evaluation and funds need to be secured. Reliable PCR protocols must be in place to ensure that the evaluation of fTLC includes a qualified reference test. Pooling samples from the same patient and storage in absolute ethanol solution will aid in the comparison of fTLC and PCR results.
- Teams working on detection of mycolactone with mAbs are ready to collaborate and it is anticipated that testing on stored samples will soon be possible using platforms based on capture ELISA and waveguide-based optical biosensor.
- Mycolactone appears to be a suitable target for treatment monitoring or test of cure.
- Synthetic mycolactone must be made available for studies on mycolactone detection. Professor Kishi has produced some quantities of synthetic mycolactone that can be made available to researchers. However, long-term production should be pursued.
- Evaluation of prototype RDTs detecting MUL_3720 in stored clinical samples is expected in 2018 and will inform the opportuneness of conducting a prospective evaluation.

[2] Global network of laboratories for confirming *Mycobacterium ulcerans* infection (Buruli ulcer). Geneva: World Health Organization; 2017 (http://www.who.int/buruli/Global_network_laboratories_PCR.pdf).

5. Next steps

- Conduct a landscape analysis of gaps in PCR methods and referral chain for confirmation.
- Develop a quality assurance plan for PCR.
- Harmonize protocols for sample collection, storage and preparation; and develop guidance and training packages if needed.
- Define repositories for clinical samples that can assist in quality assurance activities and evaluation of new diagnostic tests.
- Coordinate groups working on detection of mycolactone with mAbs to accelerate the development of a point-of-care test; ensure availability of synthetic mycolactone.
- Continue evaluation of fTLC and conduct further studies to address the background problems with swabs; ensure that evaluation includes blinded reading of results.
- Monitor progress in the development of LAMP and RPA methods for implementation at a level lower than the national or regional reference laboratory.
- Provide support to national programmes to strengthen laboratory capacity and referral systems.

6. Key priority activities for the next 5 years and timeline for implementation

Activity	2018	2019	2020	2021	2022
Conduct gap analysis of confirmation by PCR and develop a sustainable quality assurance plan.					
Analyse need for support to national programmes for strengthening laboratories, capacity and referral systems.					
Develop harmonized protocols for sample collection, storage and processing, and build capacity for collection of clinical samples.					
Complete evaluation and troubleshooting for fTLC. Ensure evaluation includes blinded reading of results.					
Monitor progress in evaluation of LAMP and RPA methods for implementation at a level lower than the national or regional reference laboratory.					
Carry out collaborative work to develop and evaluate an RDT for mycolactone detection.					

Annex. List of participants

Anthony Ablordey
Bacteriology Department
Noguchi Memorial Institute for Medical Research
College of Health Sciences
University of Ghana
P.O. Box LG 581
Legon, Accra
Ghana
Tel: +233 275 652 022; +233 268 564 661
Email: aablordey@hotmail.com
AAblordey@noguchi.mimcom.org

Richard Kwamla Amewu
Department of Chemistry
University of Ghana
P.O. Box LG56
Legon, Accra
Ghana
Tel: +233 543 823 483
Email: amewu@ug.edu.gh
ramewu@staff.ug.edu.gh

Mercè Bosch
Project Manager
Fundación Probitas
Av. de la Generalitat, 152–158
Sant Cugat del Vallès
08174 Barcelona
Spain
Tel: +34938008525
Email: mercedes.bosch@grifols.com

Andrew Bradbury
Specifica
NMC Biological Laboratory
100 Entrada Drive
Los Alamos, NM 87544
United States of America
Tel: +1 505 665 0281
Email: abradbury@specifica.bio

Paul Converse
Department of Medicine
Johns Hopkins University
1551 East Jefferson Street
Center for TB Research, CRB-II #103
Baltimore, MD 21287
United States of America
Tel: +1 410 502 8236
Email: pconver1@jhmi.edu

David Coulibaly N'golo
Plateforme de Biologie Moléculaire/Département Technique et Technologique
Institut Pasteur de Côte d'Ivoire
Route de Dabou, Km 17 Adiopodoumé
01 BP 490 Abidjan
Côte d'Ivoire
Tel: +225 08 43 63 61
Email: david79tr@yahoo.fr

Isra Cruz
Neglected Tropical Diseases Programme
Foundation for Innovative New Diagnostics (FIND)
Campus Biotech
9 Chemin des Mines
1202 Geneva
Switzerland
Tel: +41 22 710 0954
Email: isra.cruz@finddx.org

Dziedzom De Souza
Foundation for Innovative New Diagnostics (FIND)
Campus Biotech
9 Chemin des Mines
1202 Geneva
Switzerland
Tel: +41 76 634 6664
Email: dziedzom.desouza@finddx.org

Miriam Eddyani
Department of Biomedical Sciences
Institute of Tropical Medicine
Nationalestraat 155
2000 Antwerpen
Belgium
Tel: +32 3 34 55 548
Email: meddyani@itg.be

Michael Frimpong
Buruli ulcer research/control group
Kumasi Centre for Collaborative Research in Tropical Medicine (KCCR)
Asuogya road, KNUST/KCCR
Kumasi
Ghana
Tel: +233 26 594 0908
Email: mfrimpong28@gmail.com

Hanako Fukano
Department of Mycobacteriology, Leprosy Research Center
National Institute of Infectious Diseases (NIID)
4-2-1 Aoba-cho
Higashimurayama-shi
Tokyo 189–0002
Japan
Email: hfukano@nih.go.jp

E. Solange Kakou-Ngazoa
Département de Bacteriologie-Virologie
Institut Pasteur de Côte d'Ivoire
Abidjan 01
Côte d'Ivoire
Tel: +225 08 24 04 53
Email: ngazoa_solange@yahoo.fr

Jessica Kubicek-Sutherland
Chemistry Division
Los Alamos National Laboratory
PO Box 1663, MS J567
Los Alamos, NM 87545
United States of America
Tel: +1 505 665 6267
Email: jzk@lanl.gov

Joseph Ndung'u
Neglected Tropical Diseases Programme
Foundation for Innovative New Diagnostics (FIND)
Campus Biotech
Chemin des Mines 9
1202 Geneva
Switzerland
Tel: +41 22 710 05 90
Email: joseph.ndungu@finddx.org

Gerd Pluschke
Department of Molecular Immunology
Swiss Tropical and Public Health Institute
Socinstrasse 57
Basel 4002
Switzerland
Tel: +41 61 284 8235
Fax: +41 61 271 8654
Email: Gerd.Pluschke@swisstph.ch

Ghislain Sopoh
Progarmme national de lutte contre la lèpre et l'ulcère de Buruli
Ministère de la Santé
01 BP 875 RP
Cotonou
Benin
Tel: +229 95 79 61 22
Email: ghislainsop@yahoo.fr

Koichi Suzuki
Department of Clinical Laboratory Science, Faculty of Medical Technology
Teikyo University
2-11-1 Kaga, Itabashi
Tokyo 173–8605
Japan
Tel: +81 3 5376 9765
Email: koichis0923@med.teikyo-u.ac.jp

Mark Wansbrough-Jones
Infection and Immunity Institute
St George's, University of London
Cranmer Terrace
London SW17 0RE
United Kingdom of Great Britain and Northern Ireland

Tel: +44 208 653 7968
Email: wansbrou@sgul.ac.uk

Rie Roselyne Yotsu
Department of Dermatology
National Suruga Sanatorium / National Center for Global Health and Medicine
1915 Kouyama
Gotemba-shi
Shizuoka 412-8512
Japan

Tel: +81 90 4065 2458
Email: yotsurie@hotmail.com

WHO Secretariat

Daniel Argaw Dagne
Innovative & Intensified Disease Management unit
Department of Control of Neglected Tropical Diseases
Communicable Diseases
World Health Organization
Avenue Appia 20
1211 Geneva 27
Switzerland

Tel: +41 22 791 4532
Email: biswasg@who.int

Stéphanie Jourdan
Global Yaws Eradication Programme
Innovative & Intensified Disease Management unit
Department of Control of Neglected Tropical Diseases
Communicable Diseases
World Health Organization
Avenue Appia 20
1211 Geneva 27
Switzerland

Tel: +41 22 791 2498
Email: jourdans@who.int