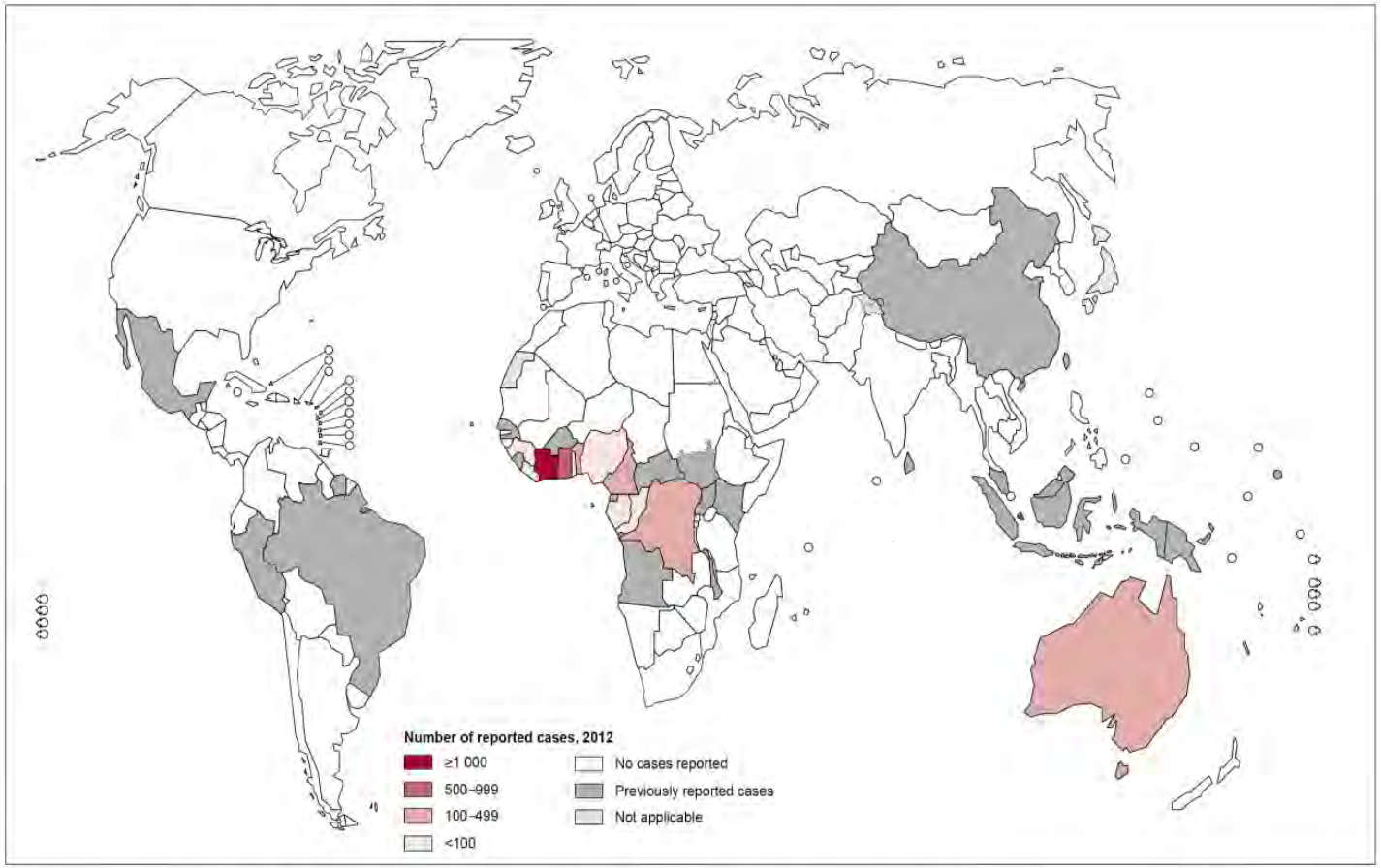
Buruli ulcer

Bairnsdale ulcer

Mycobacterium ulcerans disease

Distribution of Buruli ulcer, worldwide, 2012



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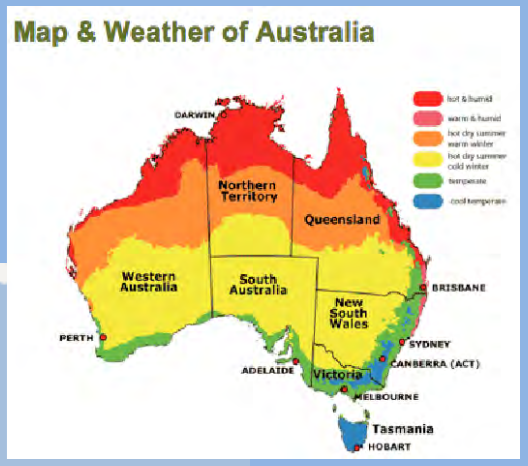
Data Source: World Health Organization
Map Production: Control of Neglected Tropical Diseases (NTD)
World Health Organization

World Health Organization

Buruli in Australia since 1939

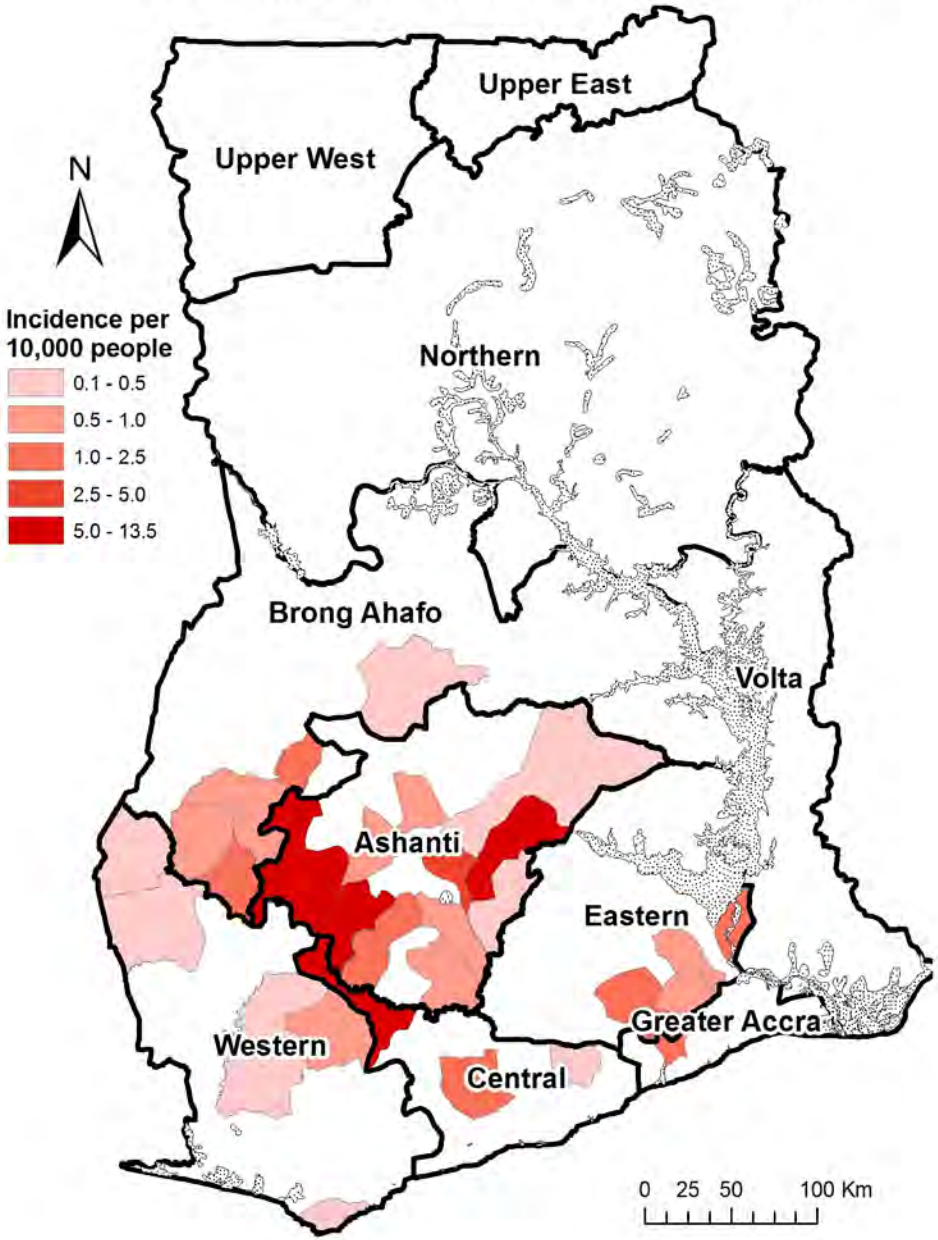


Tropic of Capricorn 23° S

Timor Sea
Darwin
Northern Territory
Coral Sea
Queensland
Australia
Western Australia
Brisbane
South Australia
Perth
New South Wales
Sydney
Adelaide
Canberra
Australian Capital Territory
Great Australian Bight
Tasmania
Hobart

Documented cases of BU since 1939 (scale approximate)

Buruli Ulcer Incidence in Ghana: 2008



Mycobacterium ulcerans disease - Buruli ulcer

Research priorities:

- Development of a low toxicity oral antibiotic regimen
  - optimal duration to reduce time to complete healing
- Improved point of care diagnosis
- Capacity strengthening
- Prevention: Transmission
  Vaccine

Diagnosis

- Microscopy for AFB: Sensitivity 40-60%
- Culture for *M. ulcerans*:
  - Delay
  - Sensitivity 40-60%
- PCR for *IS 2404*
  - Sensitivity on FNA / swabs 86%
  - Cost
  - Training / quality control

Diagnostic tests

- Current gold standard is PCR on swab/FNA sample
- Possible alternatives:
  - Mycolactone detection in swabs / FNA by TLC
  - Antigen capture approach likely to lead to a test that could be used in the field
  - Loop-mediated isothermal amplification (LAMP)

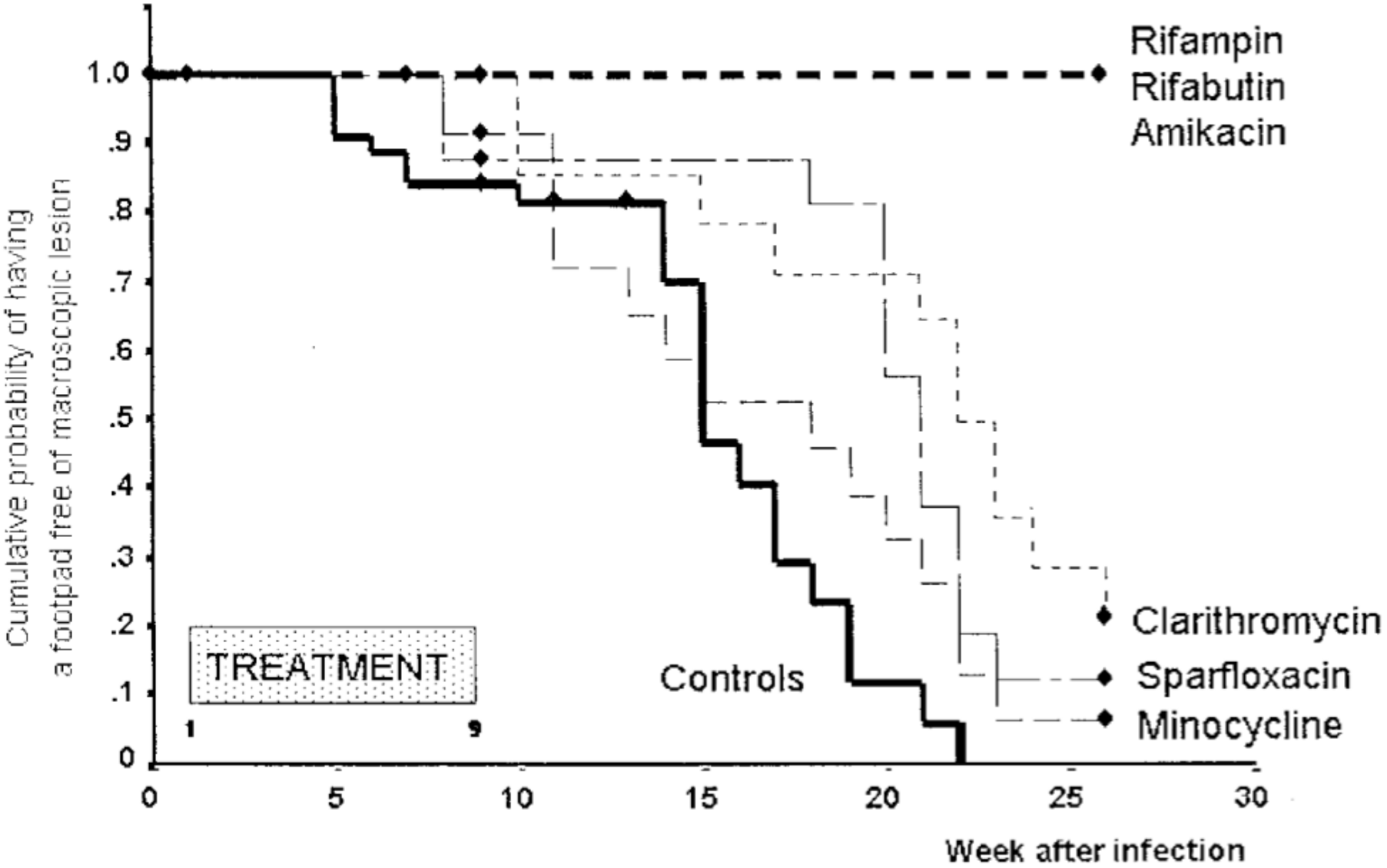
Antibiotics in vitro

Bactericidal:

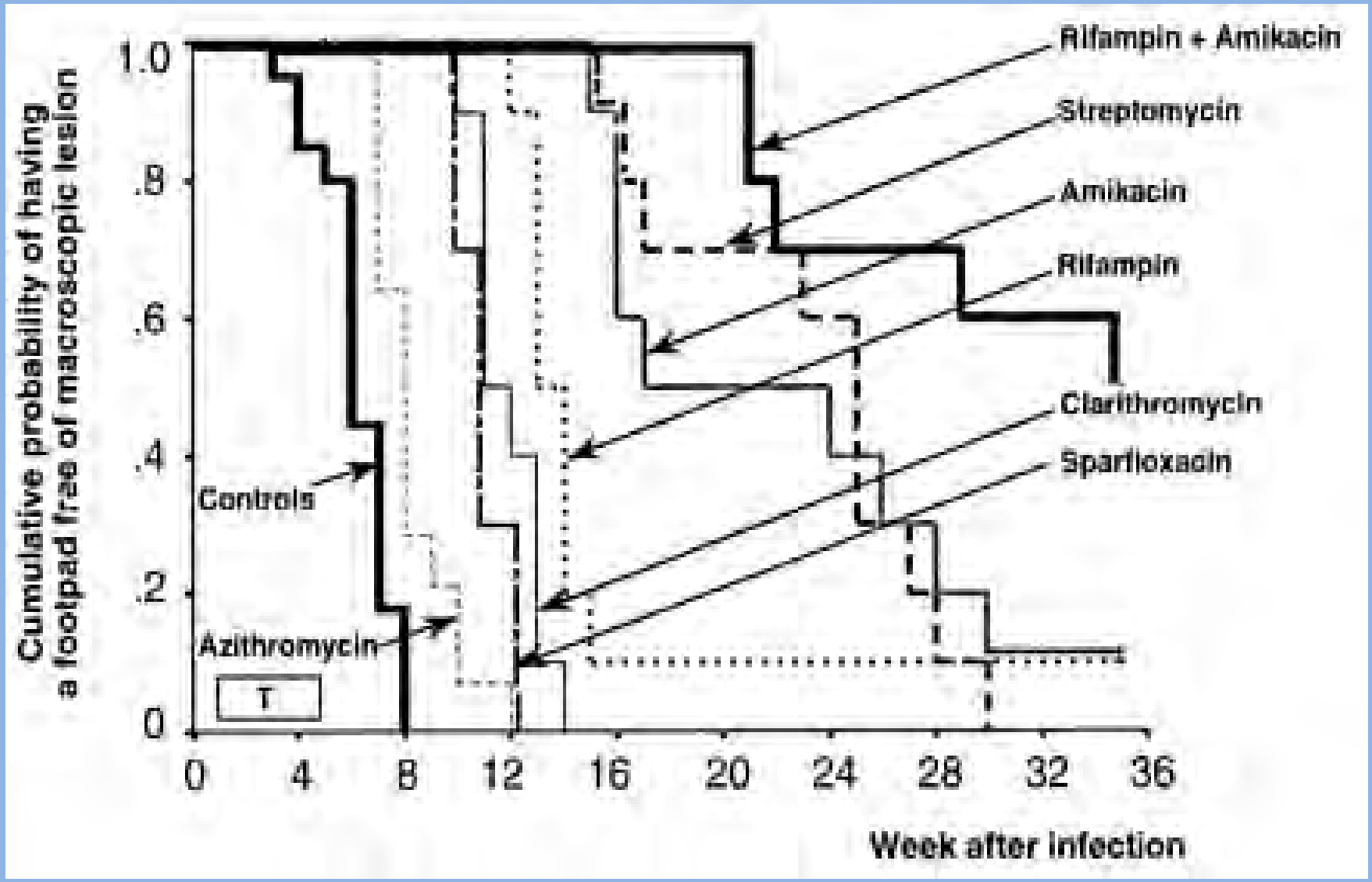
- Aminoglycosides
- Rifamycins

Bacteriostatic:

- Quinolones
- Macrolides



Degas et al. Antimicrobial Agents& Chemotherapy 2000. 44: 2367–2372



Bentoucha et al 2001. AAC 45(11);3109

Table 1: Mean number (log_{10}) of CFU per footpad in various groups of mice (9th experiment of *M.ulcerans*)

Regimen	Results at: D0[a]	2 wk			4 wk			8 wk		
	Mean (±SD) CFU per footpad for the group	No. mice culture (+)/ total no. of mice	Mean (±SD) CFU per culture (+) footpad	Mean (±SD) CFU per footpad for the group	No. mice culture (+)/ total no. of mice	Mean (±SD) CFU per culture (+) footpad	Mean (±SD) CFU per footpad for the group	No. mice culture (+)/ total no. of mice	Mean (±SD) CFU per culture (+) footpad	Mean (±SD) CFU per footpad for the group
1) Untreated control	6.24±0.45	10/10	5.94±0.51	5.94±0.51	7/7[b]	6.03/0.76	6.03±0.76			
2) RIF alone					3/10	1.52±1.01	0.46±0.87	0/10		All 10 pads (-)
3) MXF alone					9/10	3.23±0.87	2.99±1.12	7/10	1.72±0.95	1.25±1.08
4) CLR alone					5/10	3.43±1.03	2.53±1.21	0/10[c]		<1.82[d]
5) RIF-STR					5/10	1.05±0.73	0.53±0.74	0/10		All 10 pads (-)
6) (RIF-STR 4 wk) followed by (RIF-MXF 4 wk)					2/10	0.50±0.71	0.10±0.32	0/20		All 20 pads (-)
7) (RIF-STR 2 wk) followed by (RIF-MXF 6 wk)		7/10	2.50±1.23	1.88±1.43				0/20		All 20 pads (-)
8) RIF-MXF					4/10	1.07±0.65	0.43±0.67	0/10		All 10 pads (-)
9) RIF-CLR					0/10		All 10 pads (-)	0/10		All 10 pads (-)
10) MXF-CLR					8/10	1.07±0.83	0.86±0.86	1/10[e]	0[e]	0[e]

[a]: Mice were inoculated with $1.2X10^4$ CFU of *M.ulcerans* CU001 per footpad; the next day after inoculation, the mean number (log_{10}) of CFU per inoculated footpad was 3.34 ±0.38. Treatment was begun 7 weeks after inoculation, when all mice developed a 'lesion index' of 2 or 3. All drugs were administered by gavage, except STR was injected subcutaneously, 5 days per week. The dosages for each treatment were RIF 10 mg/kg, STR 150 mg/kg, MXF 100 mg/kg, and CLR 100 mg/kg.

[b] : Among untreated control mice, 1 died, 2 of the remaining 9 footpads were contaminated during enumeration of CFUs.

[c] : Although all 10 pads were culture negative, only 0.1 ml of 1:10, 1:100 or 1:1000 diluted suspensions of the inoculated footpad were plated, in triplicate, on Löwenstein-Jensen medium.

[d] : If a single colony was detected in the 3 tubes plated with 0.1 ml each of the 1:10 diluted suspension, the number (log_{10}) of CFU per footpad was 1.82.

[e] : Only one of the 10 footpads was culture positive: a single colony was detected in the entire volume of the undiluted tissue suspension (2 ml) which had been plated onto 10 tubes of Löwenstein-Jensen medium. Consequently, both the number (log_{10}) of CFU of the positive footpad and the mean number (log_{10}) of CFU per footpad for the group were 0.

WHO trial of antibiotic treatment for early nodular *Mu* lesions

Group	No. of patients	No. with positive result				Typical necrosis
		Culture	Mice	PCR	AFB	
I	5	5	5	5	4	4
II	5	5	5	5	5	5
III	3	0	0	3	3	2
IV	5	0	0	5	5	5
V	3	0	0	3	3	1

Group I No antibiotic

Group II RS for 2 weeks

Group III RS for 4 weeks

Group IV RS for 8 weeks

Group V RS for 12 weeks

Etuaful et al. 2005 AAC 49(8);3182

WHO recommended treatment

Rifampicin 10 mg/kg po

\+ Streptomycin 15 mg/kg I/M

Administered daily for 8 weeks to ambulant patients

Recurrence rate

Surgery (no antibiotics): 6-47%

Phillips et al.: 0/144 (0%)

Chauty et al.: 3/208 (1.4%)

- 2/122 (1.6%) antibiotics alone
- 1/107 (0.9%) after antibiotics + surgery

Aim: Development of a low toxicity oral antibiotic regimen

First step:

Controlled trial of RS8 vs RS4 followed by rifampicin + clarithromycin for 4 weeks (RC4)

Two sites in Ashanti Region, Ghana
Team led by Tjip van der Werf and colleagues, Groningen University, Netherlands
Funded as part of EU FP7 consortium – 'Burulico'

Outcome: No evidence of inferiority

Lancet 2010 375(9715):664-72

Next step

Current trial:

Comparison of RS8 with rifampicin + clarithromycin for 8 weeks (RC8)

- 332 PCR confirmed patients with small (<10cm) lesions in 3 years (before December 2015) from 2 endemic countries

PI:	Tjip van der Werf, University Medical Centre, Groningen
Study chair:	Kingsley Asiedu, WHO
Benin (Pobe):	Study director Dr Annique Chauty - recruiting in 1 site
Ghana (Kumasi):	Study director Dr Richard Phillips - recruiting in 4 sites

Currently recruited:	Benin	8
	Ghana	47
Funding:	Benin	Raoul Follereaux
	Ghana	American Leprosy Missions

Further work:

- Choice / dose of antibiotics
- Duration of treatment
- Optimal time for grafting
- Adjunctive treatment to improve wound healing
  - Dressings
  - Absorption / neutralisation of mycolactone