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Delayed versus standard assessment for excision surgery in patients with Buruli ulcer in Benin: a randomised controlled trial

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Summary

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Background Surgical intervention was once the mainstay of treatment for Buruli ulcer disease, a neglected tropical disease caused by *Mycobacterium ulcerans*. Since the introduction of streptomycin and rifampicin for 8 weeks as standard care, surgery has persisted as an adjunct therapy, but its role is uncertain. We investigated the effect of delaying the decision to operate to 14 weeks on rates of healing without surgery.

Methods In this randomised controlled trial, we enrolled patients aged 3 years or older with confirmed disease at one hospital in Lalo, Benin. Patients were randomly assigned (1:1) to groups assessing the need for excision surgery 8 weeks (standard care) or 14 weeks after initiation of antimicrobial treatment. The primary endpoint was the number of patients healed without the need for surgery (not including skin grafting), assessed in all patients in follow-up at 50 weeks (or last observation for those healed for >10 weeks). A doctor masked to treatment assignment checked the indications for surgery according to predefined criteria. This study is registered with ClinicalTrials.gov, number NCT01432925.

Findings Between July 1, 2011, and Jan 15, 2015, 119 patients were enrolled, with two patients per group lost to follow-up. 55 (96%) of 57 participants in the delayed-decision group and 52 (90%) of 58 participants in the standard-care group had healed lesions 1 year after start of antimicrobial treatment (relative risk [RR] 1·08, 95% CI 0·97–1·19). 37 (67%) of 55 patients in the delayed-decision group had their lesions healed without surgical intervention, as did 25 (48%) of 52 in the standard-care group (RR 1·40, 95% CI 1·00–1·96). The time to heal and residual functional limitations did not differ between the two groups (median time to heal 21 weeks [IQR 10–27] in the delayed-decision group and 21 weeks [10–39] in the standard-care group; functional limitations in six [11%] of 57 and three [5%] of 58 patients; p=0·32). Postponing the decision to operate resulted in reduced median duration of hospitalisation (5 days [IQR 0–187] *vs* 131 days [0–224]; p=0·024) and wound care (153 days [IQR 56–224] *vs* 182 days [94–307]; p=0·036).

Interpretation In our study, patients treated for Buruli ulcer benefited from delaying the decision to operate. Even large ulcers can heal with antibiotics alone, without delaying healing rate and without an increase in residual functional limitations.

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Introduction

Buruli ulcer, caused by *Mycobacterium ulcerans*, is a neglected tropical disease reported in about 33 countries; the highest prevalence is in west Africa.[1] It can manifest as a nodule, a plaque, or an oedema that can progress to a large ulcer in the absence of treatment. Late presentation with large ulcers and subsequent contractures contribute to both permanent functional limitations and community participation restrictions.[2,3] The current treatment consists of 8 weeks of antimicrobial therapy (oral rifampicin combined with intramuscular streptomycin), wound care, surgery, and disability prevention by functional rehabilitation.[4–6]

In terms of severity, Buruli ulcer has been classified into three categories. Category I lesions are single small lesions, such as nodules, papules, plaques, and ulcers that are less than 5 cm in diameter. Category II lesions consist of non-ulcerative or ulcerative plaques, oedematous forms, and single large ulcerative lesions of 5–15 cm in

cross-sectional diameter. Lesions in the head, neck, and face region, disseminated and mixed forms including osteomyelitis, and extensive lesions of more than 15 cm in diameter are considered category III lesions.[7]

Antibiotic therapy was introduced in 2004. Before 2004, extensive surgical excision to remove infected tissue followed by skin grafting was considered the most effective treatment. This treatment involved multiple operations, an average hospitalisation period of about 3 months, and high costs.[8] With the introduction of antibiotic therapy, early lesions (cross-sectional diameter <10 cm) were proved to heal without surgical intervention.[5] However, surgical intervention is still thought to be required in patients with larger lesions (category II and III). WHO recommends that antibiotic treatment should precede surgery by a minimum of 4 weeks.[7,9] Common practice among clinicians in endemic areas is to wait until the end of 8 weeks of antimicrobial therapy to decide on the need for surgical intervention.

Research in context

Evidence before this study
Before beginning this study, we searched PubMed and the WHO website, without date or language restrictions, with the terms "Buruli ulcer or *Mycobacterium ulcerans*" and "treatment or surgery". Buruli ulcer, caused by *M ulcerans*, is a neglected tropical disease that leads to necrotising infection of subcutaneous tissue. Before introduction of antimicrobials in the treatment of Buruli ulcer in 2004, the treatment strategy was solely based on surgery for all patients. A standard recommendation was that all necrotic tissue should be excised, until normal skin and subcutaneous tissue were reached. For larger ulcers, this guideline implied extensive surgical procedures and prolonged hospitalisation, and scarring, disfigurement, and contractures frequently developed. Since the introduction of antimicrobial therapy, evidence on the role of surgery is lacking. The standard practice of surgery varies per centre and is based on expert opinion. WHO recommends that antibiotic treatment should precede surgery by a minimum of 4 weeks. Common practice among clinicians in endemic areas is to wait until the end of 8 weeks of antimicrobial therapy to decide on the need for surgical intervention.

Added value of this study
This report describes the first randomised clinical trial on the role of surgical intervention in the treatment of Buruli ulcer.

Patients with confirmed disease were randomly assigned to groups to assess the need for excision surgery 8 weeks (standard care) or 14 weeks (delayed decision) after start of antimicrobial treatment. Among the participants in the delayed-decision group, lesions healed without surgical intervention in 37 (67%) of 55 patients, whereas in the standard-care group 25 (48%) of 52 lesions healed without surgery. The time to heal and residual functional limitations did not differ between the two groups. Postponing the decision to operate resulted in reduced duration of hospitalisation and wound care.

Implications of all the available evidence
Delaying the decision to operate seems to be beneficial. Even large ulcers can heal solely with antibiotics, without negative effects on healing rate and occurrence of functional limitation. Reducing surgical intervention might affect health-care-seeking behaviour; fear of surgery might be one of the risk factors for patients' delay in seeking treatment. Furthermore, because most countries where Buruli ulcer is a burden are low-income countries, this finding will save resources and therefore have immediate implications for Buruli ulcer treatment guidelines.

During antibiotic therapy, the number and size of lesions can increase as a result of a paradoxical reaction, an inflammatory response caused by treatment-induced recovery of the immune system. These paradoxical reactions often occur after around 8 weeks of antimicrobial therapy and can be misinterpreted as failure to respond to treatment, which leads to surgery.[5,10,11] A delay in the decision on the necessity of surgery could reduce the percentage of patients needing surgical interventions. We postulated that by postponing the decision of surgery, the number of surgical interventions would decrease, enabling antimicrobial treatment and wound care to show their effectiveness even in large ulcers. Week 14 was chosen as the timepoint for deciding on surgery, since in another trial,[12] most paradoxical reactions occurred between week 8 and week 14.

Methods

Study design
The study was a single-centre, randomised controlled trial done in a hospital in Benin between July 1, 2011, and Dec 31, 2015 (including 1 year of follow-up). The study adhered to the CONSORT guidelines.[13,14] The study was started as a multicentre clinical trial including two hospitals in Benin. Unfortunately, after 67 patients had been enrolled, we detected data fabrication during one of the internal audits at the site in Allada (Centre de Dépistage et de Traitement de l'Ulcère de Buruli d'Allada) in September, 2014. Subsequently, we excluded all data

obtained from this hospital after consulting the data safety monitoring board and informing the Beninois Medical Ethical Committee of the findings.

Participants
Patients were recruited at one hospital in Benin (Centre de Dépistage et de Traitement de l'Ulcère de Buruli de Lalo). Patients clinically diagnosed with Buruli ulcer disease were eligible for enrolment if they were aged 3 years or older and if they lived in a district covered by the hospital. Only patients with disease confirmed by direct microscopy following acid-fast bacilli staining or PCR were included for further analysis. Exclusion criteria were pregnancy, rifampicin and streptomycin intolerance or anticipated non-compliance, a positive HIV test, osteomyelitis, contraindications to anaesthesia, treatment for tuberculosis in the previous month, and a Buruli ulcer lesion close to the eye (as for such lesions, the preferred strategy has been to delay surgical intervention at all times). The study was approved by the Benin Research Ethics Committee under ethics clearance IRB00006860, according to the principles of the Declaration of Helsinki, the Dutch Medical Research Involving Human Subjects Act, and Good Clinical Practice. The Medical Ethics Review Committee of the University Medical Centre Groningen, Netherlands, reviewed the protocol before ethics clearance in Benin. Written and verbal informed consent or assent was obtained from all participants aged 12 years or older, and

from parents, guardians, or legal representatives of participants aged 18 years or younger.

Randomisation and masking

Participants were randomly allocated to study groups (1:1), independent of stage of disease, at start of antibiotic treatment to an assessment for the need for surgical intervention at 8 weeks (standard care) or at 14 weeks (delayed decision) after start of treatment. The attending doctor sent information (age, study code number, and date of inclusion in the study) by mobile-phone text messaging or email to University Medical Centre Groningen. Computer-generated block randomisation (block size of six) was used, and the randomly assigned allocation was sent back by text message. At either week 8 or week 14, the attending doctor presented the clinical data (lesion size measurements), digital images, and information on the predefined criteria for surgical intervention to a doctor masked for the duration of treatment, who supported the decision to operate or not to operate. In case the attending doctor considered surgical intervention at any other timepoint other than week 8 or week 14 after start of treatment, he informed the doctor masked for the duration of treatment.

Procedures

After participants had given informed consent, we obtained demographic and clinical information. The lesion was assessed by digital photography, tracing of the lesion onto an acetate sheet, and measurement of the maximum diameter and the diameter at right angles to the maximum diameter line. Liver and kidney function tests, a pregnancy test (in female patients older than 10 years), and an HIV test were done as standard care before start of antimicrobial treatment. Two swabs from the ulcer or two fine-needle aspiration samples from non-ulcerated lesions were sent for PCR to the National Reference Laboratory for Mycobacteria (Cotonou, Benin; which is participating in the external quality assessment programme for PCR detection of *M ulcerans*) and for acid-fast bacilli staining in both the participating hospital in Lalo and the National Reference Laboratory for Mycobacteria.[15,16] In patients with negative PCR results, diagnostic swabs were repeated after 2 weeks and were submitted for PCR to the National Reference Laboratory for Mycobacteria. Participants started streptomycin (15 mg/kg once-daily) and rifampicin (10 mg/kg once-daily) for 8 weeks under the directly observed treatment protocol. Patients were then randomly assigned to groups for assessment for the need for surgical intervention either at 8 weeks or at 14 weeks after start of treatment. The criteria for surgical intervention were predefined as a less than 50% reduction of the lesion surface area, no tendency towards healing (ie, no scar formation), persistence of necrotic tissue, or persistence of undermining edges. Criteria for surgical intervention at timepoints other than week 8 or week 14 were predefined

in expert opinion meetings as a lesion with visible functional limitation at admission, refusal by a patient to continue treatment without surgical intervention, a lesion with delicate localisation, extensive oedema, or a lesion that failed to reduce in size after week 8 or week 14. Skin grafting or removal of necrotic tissue during wound care was not counted as excision surgery.

Patients receiving antimicrobial treatment in their community were seen by the Buruli ulcer team at least once a week until 8 weeks or 14 weeks according to their allocation group. At the weekly assessment, lesion size was measured and a photo was taken. Laboratory investigations were done if they were considered necessary by the treating doctor. Admitted patients were assessed daily. At the end of the antibiotic treatment or after the patient was discharged, the patient was followed monthly, until 4 months after treatment. The final follow-up was done 1 year after the start of antibiotic treatment.

Outcomes

The primary outcome of the study was the number of patients whose lesions healed without surgery 1 year after start of initial treatment. Secondary outcome measures were recurrences within 4 months after healing, time to heal, duration of hospitalisation, and functional limitations as measured by the Buruli ulcer functional limitation score (BUFLS) 1 year after the start of treatment. The BUFLS is a validated tool to measure functional limitations in patients with Buruli ulcer who have been treated.[17] The total number of days that patients needed dressing for wound care was reported.

Statistical analysis

In 2009, around 50% of the 315 patients on antimicrobial therapy had a surgical intervention in the two hospitals in Benin originally involved in the trial. A 20% difference in the number of surgeries needed was considered as a relevant difference to be detected, and 94 patients in each treatment arm were estimated to be sufficient to detect this difference with a power of 80% and a two-sided α level of 5%. Assuming about 80% of the cases could be confirmed and accounting for some patients who might be lost to follow-up, 130 patients per treatment arm had to be included in the two study sites (260 patients overall).

We report descriptive characteristics as n (%), mean (SD), or median (IQR) as appropriate. For the primary outcome, we reported percentage of patients who healed without surgery and relative risks (RRs, 95% CI). We used logistic regression to check for confounders (age, sex, or category of lesion) that might be unequally divided between treatment arms. Odds ratios (ORs) resulting from this logistic regression did not replace the primary outcome measure (RR) considering the commonness of the endpoint surgery. We analysed time to healing with the Kaplan-Meier method and Cox regression (after testing the proportional hazards assumption). The BUFLS score was expressed

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dichotomously (BUFLS score >0 indicating a functional limitation) and compared with the χ² test. We compared severity of functional limitations between arms for those patients with a positive score with the Mann-Whitney U test.

For patients with a missing follow-up visit at week 50 but with a lesion observed as healed for at least 10 weeks, the observation of the latest follow-up visit was carried forward to the week-50 visit. All patients who entered randomisation and completed follow-up visits for more than 3 months were included for further analysis and were evaluated for being healed 1 year after start of the treatment for the primary analysis.

The data safety monitoring board received a report after including 100 patients who completed follow-up for 6 months. The interim analysis was focused on the stopping rule (difference of >30% in need for surgical intervention or >10% difference in frequency of functional limitations). Monitoring visits and internal audits were included.

This trial is registered with ClinicalTrials.gov, number NCT01432925.

Role of the funding source
The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
In 2009, 674 patients had newly reported Buruli ulcer recorded at the national programme compared with 312 in 2016. Decreases in patient numbers at the study site in Lalo were steep (205 in 2009 to 22 in 2016) compared with Pobè (156 in 2009, and 128 in 2016; table 1). Active case-finding activities in Lalo were similar in 2009–16.

119 (80%) of 149 patients with Buruli ulcer visiting the hospital between July 1, 2011, and Jan 15, 2015, were enrolled in the trial and underwent randomisation (figure 1). The most common reason for non-enrolment was living in an area not covered by the hospital (14 [47%] of 30 excluded patients). After randomisation, one patient died of a cause deemed unrelated to Buruli ulcer and three patients were lost to follow-up. These three patients had active lesions at the last follow-up visit available. Three other patients missed week 50 follow-up, but were included in the analysis because they had a lesion observed as healed for at least 10 weeks. 115 patients were included in the primary analysis of number of patients healed without surgery (figure 1). All patients were confirmed to have Buruli ulcer by PCR (n=41), acid-fast bacilli staining (n=3), or both (n=71). In 19 (17%) of the 115 participants, the initial diagnostic tests were negative but proved positive when tests were repeated after 2 weeks of antibiotic treatment.

	2009	2010	2011	2012	2013	2014	2015	2016
Allada	110	95	80	57	62	44	32	40
Lalo	205	183	120	52	40	28	32	22
Pobè	156	140	150	140	140	151	150	128
Zagnanado	203	154	142	116	136	107	97	122
Overall	674	572	492	365	378	330	311	312

The number of patients in Lalo, Benin, differs from the number of patients evaluated for trial participation in figure 1. Patients were included in the trial between July 1, 2011, and Jan 15, 2015.

Table 1: Patients with newly diagnosed Buruli ulcer reported in Benin, by town or city, including the study site in Lalo (2009–16)
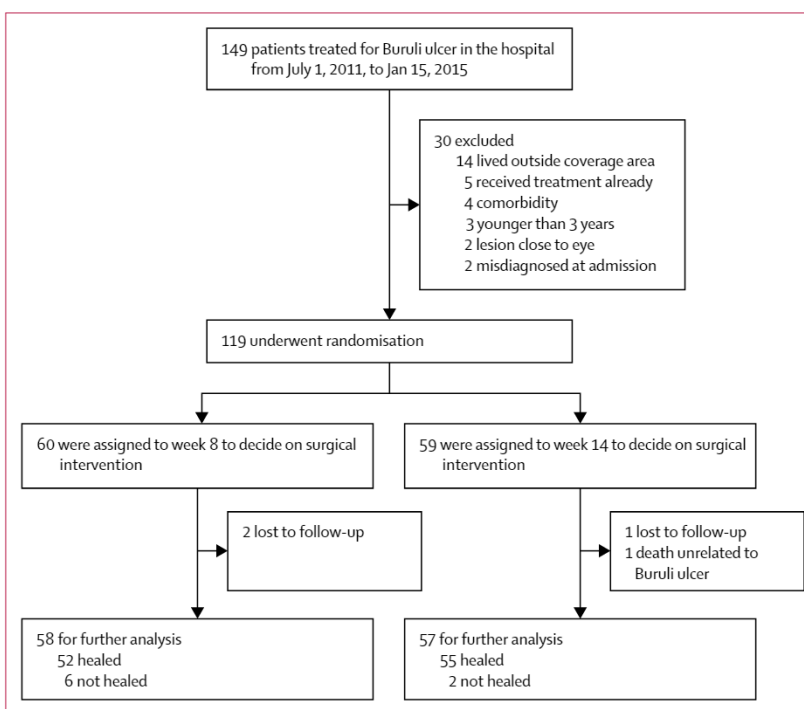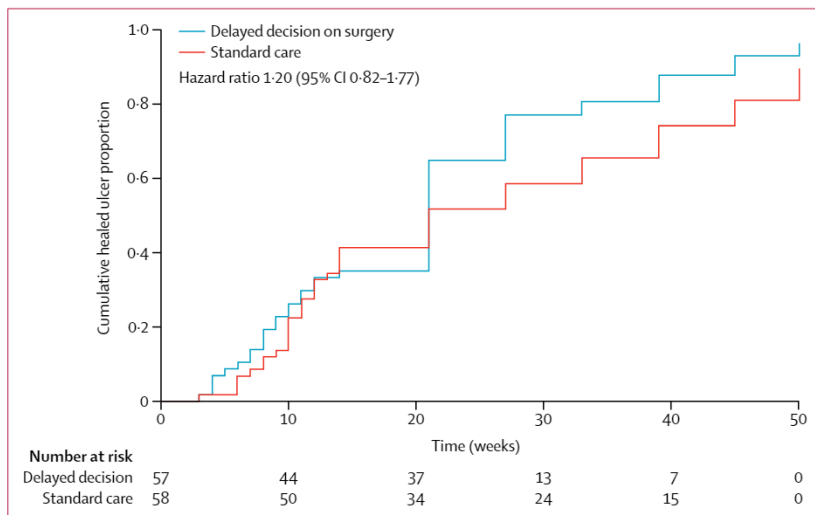

Figure 1: Trial profile

Baseline characteristics were similar in the two groups (table 2), but the category of disease (indicating disease severity) differed slightly between the two study arms despite randomisation. 107 patients (93%) were healed after 1 year of follow-up. One patient received 86% of the antibiotic treatment under the directly observed treatment protocol, whereas all other patients received 100% of the prescribed antibiotic treatment.

Among participants who had healed lesions, 37 (67%) of 55 patients in the delayed-decision group healed without surgical intervention compared with 25 (48%) of 52 patients in the standard-care group (RR 1·40, 95% CI 1·00–1·96). In a logistic regression, no confounding by category of lesion was found: OR 2·22 (1·02–4·86) and adjusted OR 2·04 (0·89–4·65). One patient in the delayed-decision group needed urgent surgery before week 14 because of the perceived risk of functional limitation due to a lesion close to a

	Standard-care group (n=58)	Delayed-decision group (n=57)
Median (IQR) age, years	11 (6–15)	12 (7·5–27·5)
Sex		
Male	32 (55%)	22 (39%)
Female	26 (45%)	35 (61%)
Median (IQR) patient delay, weeks	8 (4–12)	8 (4–12)
Location of lesion		
Upper limb	19 (33%)	16 (28%)
Lower limb	31 (53%)	34 (60%)
Trunk	8 (14%)	7 (12%)
Category of lesion		
Category I*	4 (7%)	7 (12%)
Category II†	27 (47%)	32 (56%)
Category III‡	27 (47%)	18 (32%)
Stage of lesion		
Ulcer	52 (90%)	54 (95%)
Healed after 1 year of follow-up	52 (90%)	55 (96%)

Data are median (IQR) or n (%). *Single small lesions <5 cm in diameter. †Non-ulcerative or ulcerative plaques, oedematous forms, or single large ulcers of 5–15 cm in diameter. ‡Lesions in the head, neck, and face region, disseminated and mixed forms including osteomyelitis, and extensive lesions >15 cm in diameter.

Table 2: Patient characteristics

Figure 2: Kaplan-Meier plot of the cumulative proportion of patients with Buruli ulcer whose lesions healed over time

See **Online** for appendix

necrotic tissue. Both interventions were not counted as surgical intervention in this trial.

The median time to heal was 21 weeks (IQR 10–27) in the delayed-decision group and 21 weeks (10–39) in the standard-care group, which did not differ on Cox regression analysis (hazard ratio [HR] 1·20, 95% CI 0·82–1·77; figure 2).

Fewer patients in the delayed-decision group needed to be admitted to the hospital than did those in the standard-care group (30 [53%] vs 41 [71%]; p=0·047). The median number of days patients were admitted was 5 (IQR 0–187) in the delayed-decision group and 131 (0–224) in the standard-care group (p=0·024).

One (2%) of 57 patients in the delayed-decison group and two (3%) of 58 patients in the standard-care group received wound care. Wound care was needed for a median of 153 days (IQR 56–224) in the delayed-decision group and a median of 182 days (94–307) in the standard-care group (p=0·036).

One patient (female, aged 15 years) in the standard-care group had a new ulcer at the follow-up visit 50 weeks after start of initial treatment. At inclusion, she had a unique initial lesion (300 mm×140 mm×110 mm) on the right knee. She had a surgical intervention at week 8 for a category III lesion that healed at week 13. The new ulcer was on the lower leg, distal from the original lesion. The measurement of the new lesion at week 50 was 35 mm×30 mm×16·25 mm. This patient is among the eight patients reported as not healed 1 year after start of treatment.

We noted no significant differences in functional limitation between the two groups at final follow-up. Functional limitation was observed in six patients (11%) in the delayed-decision group and in three patients (5%) in the standard-care group (p=0·32). Scores did not differ by group for the nine patients with functional limitations (BUFLS >0): delayed-decision group median score of 5·4 (IQR 4·6–10·5) vs standard-care group median of 7·9 (5·6–10·53; p=0·39).

Eight patients were not healed 1 year after start of treatment (five female patients and three male patients, mean age 23 years of male and female patients; appendix). Seven of the eight patients had category III lesions at start of treatment. One of these patients had sickle cell disease and another patient had the previously described recurrence. None of these patients received prolonged antimicrobial treatment (ie, >8 weeks).

Discussion

In our study, patients with Buruli ulcer lesions treated with standard antimicrobial treatment benefited from delaying decisions about surgery to week 14, instead of week 8 at the end of antimicrobial treatment. Even large ulcers healed without surgery if the decision to operate was delayed. Delaying the decision of surgery until week 14 after start of antimicrobial treatment, instead of

joint. No patients received their first surgical intervention later than the scheduled timepoint according to the randomisation.

55 participants (96%) in the delayed-decision group and 52 (90%) in the standard-care group were healed at the final follow-up visit 1 year after start of the treatment (RR 1·08, 95% CI 0·97–1·19).

36 patients (31%) received a skin graft at least once during their treatment and the number of patients who needed a skin graft did not differ between the intervention arms. No patients received a bedside debridement of

week 4 as recommended by WHO or week 8 in clinicians' daily practice did not have negative effects on healing rate and functional limitations. Postponing the decision of surgery increased the probability of patients with Buruli ulcer healing without surgery. It also reduced median time of hospitalisation and wound care.

Before introduction of antimicrobial therapy for Buruli ulcer, the treatment strategy was solely based on surgery for all patients. Pre-ulcerative lesions were managed by simple surgical excision and suturing, whereas late cases were managed by extensive surgery despite poor acceptability, high costs, and failure to prevent recurrence. Since the introduction of antimicrobial treatment, surgery was reserved only for lesions with a reduction in size of less than 50% after the first 4 weeks of antibiotic treatment.[18] The standard practice of surgery varies per centre and is probably based on severity of the lesion and expert opinion. In 2006, a study done in Lalo found that among 179 patients with Buruli ulcer, 110 (61%) had surgery only and 69 (39%) were treated with antimicrobial drugs. Among those 69 patients treated with antimicrobials, 58 (84%) still needed surgery.[2] In another study of 224 patients treated with 8 weeks of antimicrobial therapy, about 50% still needed surgery in addition to their antibiotic treatment.[19] In our study, the need for surgery was reduced to a third of the participants in the delayed-decision group.

The median time to heal in our study was 21 weeks irrespective of study group, which is comparable to a median time to heal of 18 weeks (category I lesions) and 30 weeks (category III lesions) in a clinical trial in Ghana.[5]

Recurrences of Buruli ulcer occur frequently in patients with surgical treatment alone.[20] Reported recurrence rates vary from 6% to 21·5%.[21–23] In our study, we observed only one recurrence (<1%). This recurrence rate is similar to those found in recent literature such as the randomised clinical trial[5] on antimicrobials in category I lesions, which found no recurrence at 1-year follow-up, and a cohort study[24] that showed no recurrences when treated with both surgery and antimicrobial treatment. Previous studies[25,26] have shown that functional limitation occurs in up to 57% of patients with Buruli ulcer. In our study, only nine patients (8%) had a functional limitation. Postponing the decision of surgery had no negative effect on occurrence of functional limitation.

The main weakness of our study was the fact that the expected sample size could not be reached. The prevalence of Buruli ulcer is decreasing in countries in west Africa. The cause of this decline is unknown. This study was planned to be a multicentre trial, but we were forced to modify it into a single-site study because of data fabrication observed in the other hospital. Combined with the decreasing incidence since 2009, the recruitment period was extended from 2 years to 4·5 years and was stopped to prevent lower quality of data due to trial fatigue and restrained financial resources.

Our study emphasises the need for proper auditing and monitoring. The lack of resources for clinical trials on neglected tropical diseases should not jeopardise their quality. Several studies have shown the necessity for researchers in neglected tropical diseases to combine their efforts.[27,28] Quality of research in neglected tropical diseases could benefit from including quality management systems in a neglected tropical diseases network.

The major strength of our study is that Buruli ulcer disease has been confirmed in all participants included in the study. At the WHO Technical Advisory Group meeting on Buruli ulcer, in March, 2017, in Geneva (Switzerland), the standard antimicrobial treatment of Buruli ulcer was changed into the completely oral regimen with rifampicin and clarithromycin. This switch does not affect the findings of our study since the clinical response to these two different regimens, such as time to healing, is similar.

The findings of our study are especially important for patients with large ulcers since evidence on the role of surgery in these patients is scarce. Reducing surgical intervention might affect health-care-seeking behaviour; fear of surgery might be one of the risk factors for patients' delay in seeking treatment.[2] Furthermore, because most countries where Buruli ulcer is a burden are low-income countries, this finding will save resources.

References
1 WHO. *Mycobacterium ulcerans* (Buruli ulcer). http://who.int/topics/mycobacterium_ulcerans/en/ (accessed July 11, 2016).
2 Barogui Y, Johnson RC, van der Werf TS, et al. Functional limitations after surgical or antibiotic treatment for Buruli ulcer in Benin. *Am J Trop Med Hyg* 2009; 81: 82–87.
3 de Zeeuw J, Omansen TF, Douwstra M, et al. Persisting social participation restrictions among former Buruli ulcer patients in Ghana and Benin. *PLoS Negl Trop Dis* 2014; 8: e3303.
4 Converse PJ, Nuermberger EL, Almeida DV, Grosset JH. Treating *Mycobacterium ulcerans* disease (Buruli ulcer): from surgery to antibiotics, is the pill mightier than the knife? *Future Microbiol* 2011; 6: 1185–98.
5 Nienhuis WA, Stienstra Y, Thompson WA, et al. Antimicrobial treatment for early, limited *Mycobacterium ulcerans* infection: a randomised controlled trial. *Lancet* 2010; 375: 664–72.
6 Velding K, Klis SA, Abass KM, Tuah W, Stienstra Y, van der Werf T. Wound care in Buruli ulcer disease in Ghana and Benin. *Am J Trop Med Hyg* 2014; 91: 313–18.

7   WHO. Treatment of *Mycobacterium ulcerans* disease (Buruli ulcer). http://apps.who.int/iris/bitstream/10665/77771/1/9789241503402_eng.pdf (accessed July 11, 2016).

8   Asiedu K, Etuaful S. Socioeconomic implications of Buruli ulcer in Ghana: a three-year review. *Am J Trop Med Hyg* 1998; **59:** 1015–22.

9   Adu E, Ampadu E, Acheampong D. Surgical management of Buruli ulcer disease: a four-year experience from four endemic districts in Ghana. *Ghana Med J* 2011; **45:** 4–9.

10   Ruf MT, Sopoh GE, Brun LV, et al. Histopathological changes and clinical responses of Buruli ulcer plaque lesions during chemotherapy: a role for surgical removal of necrotic tissue? *PLoS Negl Trop Dis* 2011; **5:** e1334.

11   O'Brien DP, Robson ME, Callan PP, McDonald AH. "Paradoxical" immune-mediated reactions to *Mycobacterium ulcerans* during antibiotic treatment: a result of treatment success, not failure. *Med J Aust* 2009; **191:** 564–66.

12   Nienhuis WA, Stienstra Y, Abass KM, et al. Paradoxical responses after start of antimicrobial treatment in *Mycobacterium ulcerans* infection. *Clin Infect Dis* 2012; **54:** 519–26.

13   Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *PLoS Med* 2010; **7:** e1000251.

14   Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 Explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *J Clin Epidemiol* 2010; **63:** e1–37.

15   Eddyani M, Lavender C, de Rijk WB, et al. Multicenter external quality assessment program for PCR detection of *Mycobacterium ulcerans* in clinical and environmental specimens. *PLoS One* 2014; **9:** e89407.

16   Beissner M, Herbinger KH, Bretzel G. Laboratory diagnosis of Buruli ulcer disease. *Future Microbiol* 2010; **5:** 363–70.

17   Stienstra Y, Dijkstra PU, Van Wezel MJ, et al. Reliability and validity of the Buruli ulcer functional limitation score questionnaire. *Am J Trop Med Hyg* 2005; **72:** 449–52.

18   WHO, Global Buruli Ulcer Initiative. Provisional guidance on the role of specific antibiotics in the management of *Mycobacterium ulcerans* disease (Buruli ulcer). http://www.who.int/iris/handle/10665/68839 5 (accessed July 11, 2016).

19   Chauty A, Ardant MF, Adeye A, et al. Promising clinical efficacy of streptomycin-rifampin combination for treatment of Buruli ulcer (*Mycobacterium ulcerans* disease). *Antimicrob Agents Chemother* 2007; **51:** 4029–35.

20   O'Brien DP, Walton A, Hughes AJ, et al. Risk factors for recurrent *Mycobacterium ulcerans* disease after exclusive surgical treatment in an Australian cohort. *Med J Aust* 2013; **198:** 436–39.

21   Kanga JM, Kacou DE, Sangare A, Dabila Y, Asse NH, Djakeaux S. Recurrence after surgical treatment of Buruli ulcer in Cote d'Ivoire. *Bull Soc Pathol Exot* 2003; **96:** 406–09 (in French).

22   Debacker M, Aguiar J, Steunou C, Zinsou C, Meyers WM, Portaels F. Buruli ulcer recurrence, Benin. *Emerg Infect Dis* 2005; **11:** 584–89.

23   Kibadi K, Mputu-Yamba JB, Mokassa B, Panda M, Muyembe-Tamfum JJ. Relapse after surgical treatment of *Mycobacterium ulcerans* infection (Buruli ulcer): study of risk factors in 84 patients in the Democratic Republic of the Congo. *Med Trop (Mars)* 2009; **69:** 471–74.

24   O'Brien DP, McDonald A, Callan P, et al. Successful outcomes with oral fluoroquinolones combined with rifampicin in the treatment of *Mycobacterium ulcerans*: an observational cohort study. *PLoS Negl Trop Dis* 2012; **6:** e1473.

25   Stienstra Y, van Roest MH, van Wezel MJ, et al. Factors associated with functional limitations and subsequent employment or schooling in Buruli ulcer patients. *Trop Med Int Health* 2005; **10:** 1251–57.

26   Ellen DE, Stienstra Y, Teelken MA, Dijkstra PU, van der Graaf WT, van der Werf TS. Assessment of functional limitations caused by *Mycobacterium ulcerans* infection: towards a Buruli ulcer functional limitation score. *Trop Med Int Health* 2003; **8:** 90–96.

27   Phillips K, Kohler JC, Pennefather P, Thorsteinsdottir H, Wong J. Canada's neglected tropical disease research network: who's in the core-who's on the periphery? *PLoS Negl Trop Dis* 2013; **7:** e2568.

28   Pollastri MP. Finding new collaboration models for enabling neglected tropical disease drug discovery. *PLoS Negl Trop Dis* 2014; **8:** e2866.