# Vingt-cinquième Journée Scientifique
# Twenty-fifth Scientific Day

## 4 juin 2015 - 4 June 2015

## Résumés des communications
## Presentation abstracts

epicentre
ÉPIDÉMIOLOGIE • EPIDEMIOLOGY

MEDECINS SANS FRONTIERES

Paris, 4 juin 2015

Bonjour à tous,

L'activité d'Epicentre auprès des équipes de MSF ne se réduit pas à décrire des actions et des contraintes dans l'exercice des soins. Elle veut contribuer à concevoir de nouvelles solutions opérationnelles, à les tester et à en rendre compte. Epicentre a construit sa réputation sur cette capacité à conduire des études compliquées, qui ont du sens pour MSF, dans des environnements complexes.

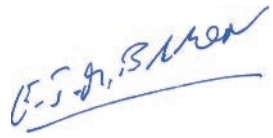
Pour débuter la journée, deux sessions thématiques seront consacrées à deux maladies bien connues et toujours présentes : la tuberculose, où le diagnostic chez l'enfant demeure un défi, mais où renaît l'espoir de traiter plus efficacement les formes résistantes ; puis le paludisme, toujours responsable d'une importante morbidité et mortalité infantiles mais pour lequel des stratégies thérapeutiques, en consultation, à l'hôpital ou en population, se développent.

Le travail d'Epicentre consiste aussi à étudier des situations singulières tout en conservant une diversité des méthodes et des sujets. Ainsi en fin de matinée nous présenterons successivement une revue des méthodes d'enquête de couverture des programmes nutritionnels, une étude sur un algorithme diagnostique de l'ulcère de Buruli ainsi qu'une présentation « late breaker ».

Après la session de posters nous reviendrons sur les deux axes de notre action au cours de l''épidémie de fièvre Ebola. D'une part comme acteur dans la réponse opérationnelle de MSF, avec nos travaux sur l'impact de l'épidémie sur l'offre de soins et sur la mortalité générale, sur le monitoring des patients admis dans les centres de prise en charge et sur le suivi après la sortie ; d'autre part dans la réflexion et la proposition sur la conception d'études cliniques dans ce contexte où exigences éthiques et contraintes opérationnelles sont fortes.

Une table ronde réunissant des scientifiques reconnus dans les domaines de l'épidémiologie, la recherche et le développement permettra d'approfondir la réflexion sur les contraintes et les méthodes de l'exploration de nouvelles solutions lors d'épidémies. Elle sera introduite par l'étude de l'effet de l'amodiaquine sur l'évolution de la maladie puis par la présentation de l'étude vaccinale conduite parmi les travailleurs de santé en première ligne en Guinée.

Je vous souhaite une très bonne journée,



Emmanuel Baron
Directeur Général, Epicentre

Paris, 4 June 2015

Good morning,

Epicentre's activity is not restricted solely to describing the MSF's actions and constraints in providing healthcare, but we also aim to help develop new operational solutions and test and report on them. Epicentre has built its reputation on our ability to conduct complicated studies, which are meaningful for MSF, in complex environments.

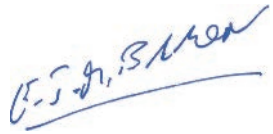
To start the day, two thematic sessions are devoted to two well-known and still present diseases: tuberculosis, where diagnosis in children remains a challenge, but where hope is on the horizon for more effective treatment of resistant forms; and malaria, still responsible for significant infant morbidity and mortality, but where treatment strategies in clinics, in hospitals and in community clinics are being actively developed.

The work of Epicentre also involves studying special situations while continuing to explore a diverse range of methodologies and topics. At the end of the morning, we will present a review of nutritional programme coverage survey methods, followed by a study on an algorithm for diagnosing Buruli ulcer, and finally a "late breaker" presentation.

After the poster session, we will report on the two directions of our activities during the Ebola epidemic. First, as part of MSF's operational response, with our work on the impact of the epidemic on healthcare and on all-cause mortality, on the monitoring of patients admitted to treatment centres and on their post-discharge follow-up; and second, contributing and participating to the conception of clinical studies in a context marked by significant ethical imperatives and operational constraints.

A panel discussion featuring renowned scientists in the areas of epidemiology and research and development will allow us to explore further the limitations and methods for exploring new solutions during epidemics. It will be introduced by a study on the effect of amodiaquine on development of the disease, followed by a presentation on the vaccine study conducted among Front-line workers in Guinea.

I wish you all an excellent day.



Emmanuel Baron
Executive Director, Epicentre

# Journée Scientifique Epicentre/Médecins Sans Frontières - Jeudi 4 juin 2015

**8h45 – Accueil et café**

**9h15 – Introduction générale - Emmanuel Baron**

**9h25 – Session 1 : Tuberculose**

Modérateur : Sara Eyangoh, Institut Pasteur, Cameroun

- Prévalence des mycobactéries atypiques chez des patients avec suspicion clinique de tuberculose au Cambodge. (Maryline Bonnet)
- Randomisation innovante pour l'essai endTB : évaluation de différentes combinaisons pour le traitement de la tuberculose multirésistante. (Elisabeth Baudin)
- Faisabilité et performance du dépistage des enfants contacts d'adultes diagnostiqués avec une tuberculose à l'hôpital de Mbarara, Ouganda. (Julius Kiwanuka)

**10h25 – Session 2 : Malaria**

Modérateur : Ali Djibo, Hôpital National, Niger

- Efficacité et innocuité de l'inhalation d'oxyde nitrique comme traitement adjuvant du paludisme cérébral chez les enfants, Mbarara, Ouganda. (Juliet Mwanga-Amumpaire)
- Point sur la chimioprophylaxie antipaludéenne intermittente dans le Sahel. (Francesco Grandesso)

**11h05 – Pause café**

**11h30 – Session 2 : suite**

- Efficacité de trois combinaisons thérapeutiques pour le traitement du paludisme non compliqué chez les enfants au Niger. (Ousmane Guindo)
- Efficacité et pharmacocinétique de l'artémether-luméfantrine chez l'enfant présentant une malnutrition aiguë sévère, Mali et Niger. (Lise Denoeud)

**12h10 – Session 3 : Générale**

Modérateur : Sani Sayadi, BEFEN, Niger

- Revue et questions ouvertes sur l'évaluation de la couverture des programmes nutritionnels. (Sheila Isanaka)
- Développement d'un score clinique pour le diagnostic de l'ulcère de Buruli au Cameroun. (Yolanda Müller)
- Late breaker

**13h10 – Buffet sur place**

**14h10 – Session posters**

**14h55 – Session 4 : Ebola**

Modérateur : Micaela Serafini, MSF-Suisse

- Fonctionnement des structures de santé et mortalité au cours de l'épidémie Ebola à Freetown et Monrovia. (Etienne Gignoux)
- Caractéristiques et risque de mortalité des patients dans les centres de prise en charge Ebola de Médecins Sans Frontières pendant l'épidémie Ebola en Afrique de l'Ouest - Analyses préliminaires. (Sophie Masson)
- Description clinique des patients Ebola à N'Zérékoré, Guinée. (Romain Palich)
- Suivi des personnes ayant survécu à une fièvre Ebola. (Amanda Tiffany)

**16h15 – Table ronde :**
**Rôle de la Recherche et Développement dans la réponse aux épidémies**

Modérateur : Thomas Nierle, MSF-Suisse

- Effet de l'Artesunate/Amodiaquine sur la mortalité des patients avec une fièvre Ebola confirmée, Lofa, Libéria. (Iza Ciglenecki)
- Evaluation d'un vaccin expérimental contre le virus Ebola en Guinée. (Aboubacar Soumah)

Participants externes :

- Graeme Bilbe – DNDi, Genève
- Marc Lipsitch – Harvard School of Public Health, Boston
- Martin Friede – OMS, Genève

**17h30 – Pot de clôture sur place, 9ème étage, Terrasse - Institut du Monde Arabe**

# Epicentre/Médecins Sans Frontières Scientific Day - Thursday 4 June 2015

**8.45 – Welcome and coffee**

**9.15 – General introduction – Emmanuel Baron**

**9.25 – Session 1: Tuberculosis**

Chairman: Sara Eyangoh, Institut Pasteur, Cameroon

- Prevalence of non-tuberculosis mycobacteria in patients with clinical suspicion of tuberculosis in Cambodia. (Maryline Bonnet)
- Innovative randomization in the endTB Trial: evaluating multiple regimens for MDR-TB treatment. (Elisabeth Baudin)
- Feasibility and performance of hospital-based screening of household child contacts of newly diagnosed adult tuberculosis patients in Mbarara, Uganda. (Julius Kiwanuka)

**10.25 – Session 2: Malaria**

Chairman: Ali Djibo, Hôpital National, Niger

- Efficacy and safety of inhaled nitric oxide as adjunctive treatment for cerebral malaria in children, Mbarara, Uganda. (Juliet Mwanga-Amumpaire)
- Taking stock of seasonal malaria chemoprophylaxis in the Sahel. (Francesco Grandesso)

**11.05 – Coffee break**

**11.30 – Session 2: cont'd**

- Efficacy of three simple malaria treatment combinations in children in Niger. (Ousmane Guindo)
- Efficacy and pharmokinetics of artemether-lumefantrine in children with severe acute malnutrition, Mali and Niger. (Lise Denoeud)

**12.10 – Session 3: General**

Chairman: Sani Sayadi, BEFEN, Niger

- Review and open questions in nutritional program coverage evaluations. (Sheila Isanaka)
- Developing a clinical score for the diagnosis of Buruli ulcer in Cameroon. (Yolanda Müller)
- Late breaker

**13.10 – Lunch on site**

**14.10 – Poster sessions**

**14.55 – Session 4: Ebola**

Chairman: Micaela Serafini, MSF-Switzerland

- Operation of health structures and mortality during the Ebola epidemic in Freetown and Monrovia. (Etienne Gignoux)
- Patient characteristics and risk of mortality in the Médecins Sans Frontières Ebola Management Centres during the West African Ebola outbreak-Preliminary analysis. (Sophie Masson)
- Clinical description of Ebola cases in N'Zérékoré, Guinea. (Romain Palich)
- Follow-up of Ebola survivors. (Amanda Tiffany)

**16.15 – Round table:**
**Role of Research and Development in responding to epidemics**

Chairman: Thomas Nierle, MSF-Switzerland

- Effect of Artesunate/Amodiaquine on mortality in patients with confirmed Ebola virus disease, Lofa, Liberia. (Iza Ciglenecki)
- Evaluating an experimental Ebola vaccine in Guinea. (Aboubacar Soumah)

External participants:

- Graeme Bilbe – DNDi, Geneva
- Marc Lipsitch – Harvard School of Public Health, Boston
- Martin Friede – WHO, Geneva

**17.30 – Farewell drinks on site, on 9th floor Terrace - Institut du Monde Arabe**

# Posters

1. Capture-recapture method to estimate total Ebola cases In Montserrado County Liberia in the midst of the West African Outbreak. Etienne **Gignoux**

2. A cell phone survey to assess morbidity. Access to health care and mortality in the city of Monrovia, during the Ebola Epidemic. Etienne **Gignoux**

3. Who is at risk of being untested and unaware of HIV-positive status in KwaZulu-Natal? Helena **Huerga**

4. Self-reported versus blood-tested ART intake to estimate ART coverage in South Africa. Helena **Huerga**

5. Starting ART at 500 CD4 in Southern Africa: what is the impact on ART eligibility? Helena **Huerga**

6. Differentiating high and low suspect Ebola cases based on clinical presentation and history of contact. Anna **Kuehne**

7. Retrospective assessment of Vikia® Rota-Adeno and Premier Rotaclone® tests compared to reverse transcription polymerase chain reaction for detection of group A rotavirus. Adamou **Lagare**

8. Cholera epidemic in Kenya, 2015. Support and challenges. Christelle **Lécossais**

9. Access to health care in a crisis context, Rome, Italy. 2014-2015. Silvia **Mancini**

10. Linkage to HIV care following home-based testing and CD4 in rural Malawi. Sophie **Masson**

11. Effect of point-of-care CD4 testing on time to ART-initiation and Pre-ART attrition in rural decentralised health centres in Chiradzulu District, Malawi. Sarala **Nicholas**

12. Digital pen for Ebola: a pilot project in Freetown to collect and transmit patient data from isolated high risk zone. Ludovic **Rossel**

13. Evaluation of HIV PIMA™ CD4 point-of-care test-operation by trained non-health workers in rural health centers in Chiradzulu District, Malawi. Birgit **Schramm**

14. Surveillance communautaire Ebola dans la région sanitaire du Tonkpi, Côte d'Ivoire, par SMS. Brahima **Touré**

# Session 1: Tuberculosis

# Prevalence of non-tuberculosis mycobacteria in patients with clinical suspicion of tuberculosis in Cambodia

Maryline Bonnet, Epicentre, on behalf of IRD UMI 233 TransVIHMI - UM – INSERM U1175, France


## Background

Prevalence and case management of *Non-Tuberculosis Mycobacteria* (NTM) are poorly documented in high tuberculosis (TB) burden countries. We present the prevalence, risk factors and clinical implications of NTM in the district of Kampong-Cham, Cambodia.

## Methods

Consecutive adult TB suspects were enrolled in a prospective cohort with baseline epidemiological, clinical, radiological and sputum mycobacterial investigations, and 12 months follow-up of patients with NTM isolates. An advisory committee classified patients as NTM lung disease or colonisation using the 2007 American Thoracic Society guidelines and advised on NTM treatment.

## Results

Of 1188 patients (51.4% female, 54 years median age), 218 (18.3%) were diagnosed with *Mycobacterium tuberculosis* and 124 had NTM isolates (10.4%). Among them, 11 were classified as NTM lung disease (8.6%) and 113 as colonisation (87.8%). Amongst smear positive patient, 10/196 (5.1%) grew only NTM. Most common NTM were *M fortuitum* (23.4%), *M intracelluare* (16.1%), *M abscessus* (11.3%), *M scrofulaceum* (10.5%) and *M gordonae* (10.5%). HIV-infection (aOR 3.4, 95%CI [1.2-9.8]) and past TB history (aOR 1.6, 95%CI [1.1-2.7] were associated with isolation of NTM.

Patients with NTM lung disease were more likely to have past TB history (63.4% vs 6.0%), HIV infection (27.3% vs 1.1%), low body mass index (median 14.8 vs 18.1 Kg/m2) and bronchiectasis (60.0% vs 13.4%) on chest X-ray compared to TB patients. Eight patients were started on NTM treatment (5 cured, 1 death and 2 still on treatment) and 8/116 (6.9%) non-treated patients died during follow-up.

## Conclusions

NTM represent more than 1/3 of sputum mycobacterial growth from TB suspects. The 5% of smear-positive patients due to NTM are at risk of being over treated for TB. Decision to start NTM treatment should be rapid and systematic in advanced HIV-infected patients. However, in HIV-negative patients, it should also depend on the NTM species and host co-morbidity, especially bronchiectasis.


The burden of *Non-Tuberculosis* Mycobacteria in specimen of patients with tuberculosis suspicion is high in Cambodia, especially in HIV-infected patients and patients with post-tuberculosis sequelae but only 10% require treatment.

# Innovative randomization in the endTB Trial: evaluating multiple regimens for MDR-TB treatment

Elisabeth Baudin, Epicentre, Paris, on behalf of the endTB clinical trial team

## Background

Current multi-drug resistant tuberculosis (MDR-TB) treatment is long, toxic and the outcome is poor: less than 50% of treated patients are cured. Two new drugs, Bedaquiline and Delamanid, hold promise to provide effective and better tolerated regimens using oral drugs only with shortened treatment duration. Bayesian adaptive randomization (BAR) could accelerate the evaluation of new regimens for MDR-TB, thereby bringing about change in treatment regimens faster.

## Methods

The endTB clinical trial compares the efficacy of 5 new experimental regimens. Each experimental arm contains one of the two new drugs. The primary endpoint is treatment success at 65 weeks. Randomization is based on response to preliminary outcomes measured at 8 and 39 weeks: good preliminary outcomes in a regimen increase the probability of randomization to that regimen. We present a comparison of the adaptive randomization and non-adaptive randomization and discuss their relative benefits and weaknesses.

## Results

The total number of patients needed to achieve the same statistical power is 20% less using Bayesian randomization compared to non-adaptive methods. The gains are still present with changes in the parameter assumptions.

## Discussion

Bayesian adaptive randomization allows for multiple regimens to be evaluated in one clinical trial, reduces sample size compared to the non-adaptive methods, and treats more patients with the most effective regimen(s). Adaptive designs have shown their advantages in some other therapeutic areas and could now benefit the MDR TB.

Clinical trials using Bayesian adaptive randomization treat more patients with the most effective drugs. This approach to drug evaluation accelerates the introduction of new regimens for MDR- TB.

# Feasibility and performance of hospital-based screening of household child contacts of newly diagnosed adult tuberculosis patients in Mbarara, Uganda

Julius Kiwanuka, Mbarara University of Science and Technology and Mbarara Regional Referral Hospital, Mbarara, Uganda


## Background

TB contact investigations can be an efficient method of finding child TB cases and children for isoniazid preventive therapy (IPT). However, this is rarely practiced in most low-resource countries. One reason is the difficulty in excluding active TB. We assessed the feasibility and performance of hospital-based investigation, and evaluated the accuracy of symptom-based screening for active TB among household child contacts of adult TB cases.

## Methods

Children <5 years in households of confirmed pulmonary TB adult cases were assessed for active TB or latent TB infection (LTBI) using a symptom screen, tuberculin skin test (TST) and chest radiography. The accuracy of symptom-based screening was estimated against a chest x-ray-based reference definition of active TB. Children with suspected active TB were referred for further evaluation and treatment. The rest were prescribed 6 months of IPT and followed for 9 months.

## Results

Out of 339 eligible children 281 (82.4%) were assessed; median age 33 months, 4.5% HIV infected. Forty three children (15.3%) were referred for TB treatment, 3 did not return for TST reading, 102 (36.3%) were classified as LTBI and 133 (47.3%) as uninfected.

Of 235 LTBI or uninfected children 227 (96.6%) started IPT and 185 (81.5 %) of these completed 6 months. After adjustment on age, HIV and sex, cough (aOR 3.2, 95%CI 1.4-7.6), reduced playfulness (aOR 9.7, 95%CI 2.5-37.7) and moderate-to-severe malnutrition (aOR 13.0, 95%CI 1.8-91.9) were associated with active TB. Screening based on the presence of one of these 3 signs showed 71.4% (25/35) sensitivity, 63.1% (154/244) specificity and 93.9% (154/164) negative predictive value.

## Conclusions

Hospital-based contact investigation was feasible and yielded a high number of child cases of active TB and LTBI. Symptom-based screening could be effective in excluding active TB among child contacts. Home-based follow-up could help to optimize uptake and completion of investigation and IPT.


Hospital-based investigations of child contacts of adult TB cases yielded a significant number of children with active and latent TB, and demonstrated good utility of symptom-based screening for active TB.

# Session 2: Malaria

# Efficacy and safety of inhaled nitric oxide as adjunctive treatment for cerebral malaria in children, Mbarara, Uganda

Juliet Mwanga-Amumpaire, Epicentre, Uganda on behalf of University of Science and Technology, Uganda - Massachusetts, General Hospital, United States - University of Southampton, UK - Ikaria, United States

## Background

Despite advances in antimalarial treatment, mortality from cerebral malaria remains high. Current treatments primarily target the parasite yet many complications result from the host immune response.

## Methods

We conducted a phase II randomized open-label control trial on the safety and efficacy of 80 parts per million (ppm) of inhaled nitric oxide (NO) as an adjunctive therapy in pediatric patients with cerebral malaria, in Mbarara Regional Referral Hospital, Uganda. We enrolled children aged 2 months -12 years, weighing 5 – 20 kg, with *Plasmodium falciparum* infection and coma. Patients received intravenous artesunate and either 80 ppm of NO in nitrogen or pure nitrogen (N2) for 48 to 120 hours, via nasal cannula by an INOPulse™ delivery device. The primary endpoint was increase in plasma angiopoietin-1 (Ang-1) levels at 48 hours. Other endpoints included reduction of plasma angiopoietin-2 (Ang-2), the Ang-2/Ang-1 ratio, selected plasma cytokine levels, mortality during hospitalization, time to recover from coma, and neurological sequelae. We monitored blood methemoglobin (metHb%) and NO metabolites.

## Results

Ninety-two children were randomized to receive either gas mixture. Plasma Ang-1 levels increased in both treatment groups, with no difference between the groups at 48 hours. Plasma Ang-2 and cytokine levels (TNF-α, IFN-γ, IL-1β, IL-6, IL-10, and MCP-1) decreased between the time of commencing study and 48 hours in both treatment groups, but there was no difference between the groups. After 48 hours of therapy, blood NO metabolite and metHb% levels were elevated in patients treated with NO ($P<0.05$). Seven patients in the placebo group and 4 patients in the NO arm died. Five patients in the placebo group and 6 in the NO group had neurological sequelae at hospital discharge.

## Conclusions

It was safe to breathe 80 ppm NO as an adjunctive treatment for cerebral malaria however, there was no greater increase of plasma Ang-1 levels at 48 hours.

To reduce cerebral malaria related mortality the treatment should be more than antimalarial drugs. As adjunctive therapy, INO can be delivered safely but additional efficacy studies are needed.

# Taking stock of seasonal malaria chemoprevention in the Sahel

Francesco Grandesso, Epicentre, Paris

## Background

Since 2012 Médecins Sans Frontières has implemented seasonal malaria chemoprevention (SMC) in Chad, Mali and Niger. A loose combination of sulfadoxine-pyrimethamine (SP) and amodiaquine (AQ) is administered monthly during the peak malaria season. Concerns have been raised about the risk of increasing parasite resistance, in particular to amodiaquine, which is used in fixed-dose combination with artesunate for the treatment of uncomplicated malaria.

## Objective

The frequency of molecular markers indicating genetic mutations associated with resistance to SP and AQ was described over time in Moïssala (Chad) and Madarounfa (Niger).

## Methods

In Moïssala, proportions of malaria patients with mutated parasites in 2014 were compared to baseline data prior to the implementation of SMC in 2012.

In Madarounfa, a prospective cohort consisting of all children in two villages provided samples during six study visits in 2013-2014, and the same proportions were described over time.

## Results

In Moïssala, the quintuple mutation (triple *dhfr* and double *dhps*), which is highly associated with resistance to SP, was present in 0.5% of cases prior to SMC implementation; in 2014, it was present in 8.0% and 2.5% of cases in areas where SMC had been implemented for one and two years, respectively. Mutations in *pfcrt* gene, associated with AQ resistance, were present in 23.3% of cases prior to SMC; in 2014, they were present in 45.9% and 41.4% in areas with one and two years of SMC, respectively. Mutations in *pfmdr1*, also associated with AQ resistance, were present in 9.0% of cases prior to SMC; in 2014, they were present in 10.1% and 8.4% in areas with one and two years of SMC, respectively. Preliminary analysis of data from Madarounfa suggests similar trends.

## Discussion

The prevalence of molecular markers of resistance to SP and AQ has increased since the introduction of SMC. Future investigation is warranted to evaluate the effects of these molecular mutations on the effectiveness of SP-AQ when used for SMC, and also of AQ when it is used in combination with other drugs for the treatment of clinical malaria.

Molecular markers indicating genetic mutations associated with resistance to sulfadoxine-pyrimethamine and amodiaquine have increased considerably in areas where one or two years of seasonal malaria chemoprevention has been implemented.

# Efficacy of three artemisinin combinations for the treatment of uncomplicated malaria in Niger

Ousmane Guindo, Epicentre, Niger for the 3ACT study group


## Background

First-line antimalarial treatments in Niger are artemether-lumefantrine (AM-LM) and artesunate-amodiaquine (AS-AQ). We evaluated in vivo efficacy of these two artemisinin-combination therapies (ACTs) as well as dihydroartemisinin-piperaquine (DHA-PQP) for the treatment of uncomplicated malaria in children less than 5 years of age in Maradi, Niger. We measured the clinical and parasitological efficacy of the three artemisinin combination therapies over a period of 42 days from the start of treatment and with PCR adjustment. We also estimated parasite clearance as an early indicator of the emergence of resistance to artemisinin as well as blood concentration of the non-artemisinin component 7 days after treatment initiation.

## Methods

We used the WHO standardised protocol for the surveillance of antimalarial drug efficacy with additional components for parasite clearance as estimated by the WWARN parasite clearance estimator module and for blood concentration of the non-artemisinin partner treatment. A total of 221 were enrolled in each treatment arm and followed up to 42 days. PCR was used to distinguish between recrudescences and reinfections.

## Results

The day-42 PCR adjusted efficacy was 88.3% [95% CI, 82.8–92.1] for AL-LM, 95.6% [95% CI, 91.7–97.7] for AS-AQ and 95.4% [95% CI, 91.3–97.6] for DHA-PQP. Parasite clearance half-life was 2.77 hours (2.29–3.42) for AL-LM, 2.61 hours (IQR 2.15–3.18) for AS-AQ, 2.68 hours (2.23–3.23) and for DHA-PQP. Blood concentration data on partner treatment are in process.

## Discussion

Efficacies of AS-AQ and DHA-PQP were as expected and satisfactory. The efficacy of AL-LM was below the WHO threshold of 90%. No difference on parasite clearance was observed between the three treatments, leading to the hypothesis that the lower efficacy of AL-LM is due to the loss of efficacy on lumefantrine rather than to the artemisinin derivative. Data on blood concentration may provide additional explanation for the lower efficacy of AL-LM reported here.


Efficacy of artemether-lumefantrine was lower than the efficacies of artesunate-amodiaquine and dihydroartemisinin-piperaquine for the treatment of uncomplicated malaria in Niger.

# Efficacy and pharmacokinetics of Artemether-Lumefantrine in children with severe acute malnutrition in Mali and Niger

Lise Denoeud-Ndam, Epicentre, Paris, on behalf of the Mal-Nut study team


## Background

Efficacy of antimalarial treatments, including artemisin-based combination therapies could be reduced in children with severe acute malnutrition (SAM) due to specific pharmacokinetic (PK) profiles and lower drug concentrations. We aimed to assess whether the efficacy of Artemether-Lumefantrine (AL) is altered in children suffering from SAM compared to non-SAM children, and to what extent this could be attributed to a sub-optimal pharmacokinetic profile in children under 5 with uncomplicated microscopically-confirmed *P. falciparum* malaria.

## Methods

Children were enrolled between November 2013 and December 2014 in Mali and between October 2014 and January 2015 in Niger. For each case of SAM, two unmatched non-SAM controls were enrolled. The 3-day AL treatment was directly observed and the primary efficacy endpoint was assessed at Day 28. Polymerase Chain Reaction (PCR) genotyping was used to distinguish between recrudescence and re-infection. The pharmacokinetic profile of lumefantrine was assessed using a sparse sampling approach, with 5 capillary blood samplings per child.

## Results

A total of 399 children (360 in Mali and 39 in Niger) were enrolled. In both countries, SAM children were younger than non-SAM children (17 versus 28 months, p<0.001). During follow-up, 103 *P. falciparum* infections were observed. Without PCR correction, the crude failure rate at day 28 was similar (19% in SAM, and 17% in non-SAM, P=0.61). PCR results indicated that most infections were new (only 5 recrudescences), and the corrected adequate clinical and parasitological response at day 28 was greater than 96% in both groups.

No early failure was observed and the parasite clearance slopes were comparable in SAM and non-SAM children. Preliminary results regarding lumefantrine PK profiles showed lower concentrations in SAM children.

## Conclusion

This study shows comparable, adequate therapeutic efficacy of AL in SAM and non-SAM children, though a lower concentration of lumefantrine in SAM children could have an impact on the post-treatment prophylactic effect of AL.


This study shows comparable, adequate therapeutic efficacy of AL in children with and without severe acute malnutrition, though a lower concentration of lumefantrine was observed in SAM children.

# Session 3: General

# Review and open questions in nutritional program coverage evaluations

Sheila Isanaka, Epicentre, Paris

Over the last 10+ years, there has been a dramatic shift in the management of childhood acute malnutrition, with a move from the previous inpatient model of care to community-based management. In the community-based model, good clinical outcomes are largely insured through the promotion of early access to treatment and use of simple but robust medical and nutritional protocols. In this context, program impact is often evaluated not only through measures of clinical outcomes but also program coverage.

Reliable coverage information is essential to design nutritional programs and ensure equitable access to treatment, but currently available methods for coverage assessment have important limitations. Here, we present a review of indirect and direct methods of coverage assessment. We discuss the limitations of these and suggest possible ways forward with the aim to improve the quality of future coverage assessment of nutritional programs.

This presentation reviews currently available methods for coverage assessment and suggests areas for possible ways forward to improve nutritional program coverage evaluation.

# Developing a clinical score for the diagnosis of Buruli Ulcer, Cameroon

Yolanda Müller, Epicentre, Geneva


## Introduction

Access to laboratory diagnosis can be a challenge for individuals suspected of Buruli Ulcer (BU). Our objective was to establish a clinical score to assist clinicians working in resource-limited settings for BU diagnosis.

## Methods

Between 2011 and 2013, individuals presenting at Akonolinga District Hospital, Cameroon, with a skin lesion suspect of new BU and providing informed consent were enrolled consecutively. Clinical and laboratory data were collected prospectively. Results of the laboratory tests (ZN, PCR, culture) were included in a latent class model. Based on this model, patients were categorized into high or low BU probability. Variables associated with a high BU probability in a multivariate model were included in the Buruli score. Score cut-offs were chosen based on calculated predictive values.

## Results

Of 325 patients with an ulcerative lesion, 51 (15.7%) had a high BU probability. The following variables were included in the Buruli score: characteristic smell (+3 points), yellow color (+3), female sex (+2), lesion hyposensitivity (+2), neurological anomalies (-10), age above 20 and below 40 years (-3), age above 40 (-5), and locoregional adenopathy (-2).

This score had an area under the ROC of 0.87 (95CI 0.82 – 0.90) compared to the latent class standard indicating good discrimination between infected and non-infected individuals. The cut-off to reasonably exclude BU was set at scores of 0 and below (NPV 95.7%; 95CI 92.0–98.0). The treatment threshold was set at a cut-off of 5 and above (PPV 69.0%; 95CI 49.2–84.7). Patients with intermediate BU probability (scores between 1 and 4) needed to be tested by PCR.

## Conclusion

We developed a decisional algorithm based on a clinical score assessing BU probability, reducing the number of patients requiring a PCR for diagnosis. The score still requires further validation and standardization before it can be recommended for wide use.


We developed a clinical score to assess the probability that patients with skin ulcers in endemic areas are suffering from Buruli Ulcer. This reduces the need for expensive laboratory testing.

# Session 4: Ebola

# Functioning of health structures and mortality during the Ebola epidemic in Freetown and Monrovia

Etienne Gignoux, Epicentre, Geneva

## Rational and objective

Among the 479 cases of Ebola reported in Monrovia by the end of August 2014, 62 were healthcare workers. By late summer of 2014 fear of Ebola had led to the closure of many healthcare facilities, an increase in absenteeism of healthcare workers at facilities remaining open and a decrease in attendance by the general population. To assess disruption of healthcare access and its impact on mortality in the general population, we conducted a cross sectional survey among healthcare facilities in Monrovia and retrospective mortality surveys of the populations of Monrovia, Liberia and Freetown, Sierra Leone.

## Methods

Three separate surveys were conducted:

- An exhaustive, cross-sectional telephone survey of health facilities in Monrovia between 21 and 25 August 2014.
- A cellphone survey of the population of Monrovia to estimate the retrospective mortality from May 15th, 2014 to January 2015.
- A cluster survey of the population of Freetown to estimate the retrospective mortality from May 25th, 2014 to February 2015.

## Results

In Monrovia, in comparison to August 2013, the number of available hospital beds had decreased by 47%, and overall number of consultations had decreased by 60%. At the time of the survey, only 10% of facilities made use of a standardized case definition, and only 13% of facilities made use of a patient triage system. Retrospective mortality rate in Monrovia was estimated at 0.32 (CI 95%: 0.22-0.44) and 0.52 (95% CI: 0.29- 0.76) in Freetown. Ebola represented 22% of total mortality in Monrovia and 40% of total mortality in Freetown.

## Discussion

The availability and utilization of healthcare services in Monrovia decreased during the Ebola outbreak. Others studies found similar findings in Freetown. Ebola represented an important proportion of mortality in both cities, however overall crude mortality rate was two times below the emergency threshold. This suggests excess mortality in the population directly resulting from Ebola. Reduced access to health facilities did not increase non Ebola mortality to the extent originally thought. Our survey had several limitations. The non-response rate in the cell phone surveys in Monrovia may have led to under reporting of mortality artificially decreasing estimates. Ebola attack rate is tightly clustered, and therefore the cluster survey design as was done in Freetown may have influenced the precision of the Ebola mortality estimate.

During the Ebola outbreak, health care access decreased by two fold in Monrovia. Crude mortality rate was twice below the emergency threshold. Excess mortality in the population resulted directly from Ebola.

# Patient characteristics and risk of mortality in the Médecins sans frontières Ebola Management Centres during the West African Ebola outbreak-Preliminary analysis

Sophie Masson, Epicentre, Paris, on behalf of MSF Ebola collaborators

## Introduction

The Ebola virus disease (EVD) outbreak, ongoing in West Africa since March 2014, is the largest in history. A major activity of MSF has been providing patient care in Ebola Management Centres (EMCs). We present a retrospective analysis of the main characteristics of patients admitted to nine MSF EMCs operational between March 2014 and May 2015 in Guinea, Sierra Leone and Liberia.

## Methods

Retrospective descriptive analysis was performed on a pooled line list on common variables collected. Poisson regression analysis, adjusted for centres variation, was used to explore factors associated with the risk of dying (age, sex, time to admission, cycle threshold (CT) value as a proxy of viral load).

## Results

By May 10th, 2015, 8667 people with EVD suspicion had been admitted to an MSF EMC. 5040 (68%) were confirmed with EVD. Among confirmed cases, 3569 (72%) were aged 15-54 years, 437 (9%) were ≥55 years, and 974 (28%) were <15 years. Median time to admission was 5 days (IQR 3-7). The overall case fatality rate (CFR) was 52%. CFR varied significantly between centres. In multivariate analysis, younger and older age had an increased risk of death (IRR 1.8, 95%CI 1.4-2.3 for children <5 years, IRR 1.37, 95%CI 1.2-1.6 for patients aged 15-54 years, IRR 2.1, 95%CI 1.7-2.5 for patients 55 years old and older, patients aged 5-14:REF). Lower CT value at admission was highly associated with risk of death, (IRR 7.28, 95%CI 6.2-8.5 for CT<18, IRR 2.5, 95%CI 2.2-2.8, for CT between 18 and 22, CT value >22:REF). Case fatality decreased significantly over time.

## Conclusion

This Ebola outbreak is unprecedented, leading to an unprecedented response from MSF. Harmonization and completeness of inpatient information consequently remain a challenge. Symptoms at admission, treatment provided during the course of hospitalisation, workload in the EMC, as well as factors associated with higher viral load should be further investigated.

The retrospective analysis of the pool main characteristics of patient admitted to MSF EMCs showed that age, and CT value were the main predictors of death. Specificity of each EMC context should be investigated.

# Clinical features of 69 patients with Ebola virus infection in N'zérékoré, Guinée

Romain Palich, ALIMA, Sénégal

## Introduction

On December 2, 2014 ALIMA opened a 40 bed Ebola treatment unit in N'zérékoré, Guinée. Through February 20, 2015 the program admitted 76 patients infected with Ebola virus [EBOV] including 7 children under 5 years of age. Of these 76 patients, 43 participated in the Favipiravir clinical trial.

In an effort to contribute to describing EBOV disease course and improving medical management, ALIMA used real-time data entry from patient files to create a database.

## Methods

This analysis includes 69 patients over 5 years of age. The database was built from 300 variables covering demographic, epidemiologic, clinical, laboratory and therapeutic features of patients' clinical history.

## Results

Overall, 30 patients (43.3%) survived and 39 (56.5%) died. Of patients classified as having a high viral load, that is, a Real-time PCR cycle threshold (Ct) less than 20, 31/33 died whereas 26/34 patients (76.4%) with Ct ≥20 survived. Normal serum creatinine levels range between 53-106 µmol/L ,for the 37 patients with data available, median creatinine value upon admission was 191 µmol/L among those who died (n=22) and 81 µmol/L among survivors (n=15).

60/69 patients received fluid resuscitation with Ringers Lactate plus or minus normal saline: 27/28 survivors and 31/39 who died.

50/69 patients (72.5%) had one or more electrolyte panel measurements, 27 who died and 23 survivors. 27/50 patients (54%) were hypokalemic (serum potassium < 3;5 mmol/L) of whom 11 died and 16 survived.

13/23 (56.5%) of survivors with electrolyte data received at least one potassium correction either intravenously and/or orally.

## Conclusion

As shown in other EBOV cohorts, the two main prognostic factors upon admission are viral load and serum creatinine. In this cohort, 72.5% of patients had at least one electrolyte panel drawn. Hypokalemia during the phase of significant digestive losses is common among patients with lesser viral loads (≥ 20 Ct upon admission), in spite of administration of potassium containing intravenous fluids.

Electrolyte monitoring of patients infected with Ebola virus is possible in an ETU and leads to modifications in treatment. Hypokalemia is common during the phase of illness marked by significant digestive losses in spite of volume resuscitation with potassium containing fluids.

# Follow-up of Ebola survivors

Amanda Tiffany, Epicentre, Geneva

## Introduction

An outbreak of Ebola virus disease (EVD) of unprecedented scale has affected the West African countries of Guinea, Liberia, and Sierra Leone since March 2014. In Sierra Leone, over 12,250 cases and 3,850 deaths due to EVD have been reported. Conversely, several thousand EVD patients have survived and little is known about the long term consequences of the disease. The magnitude of the outbreak has resulted in thousands of EVD survivors. On December 10, 2014, MSF Switzerland opened an Ebola Treatment Centre (ETC) in Freetown, Sierra Leone. While it was open 172 EVD confirmed patients were admitted and 83 discharged as recovered. A follow-up programme for survivors began in early February with the aim of addressing the long-term consequences of Ebola and providing early diagnosis and treatment.

## Methods

Survivors from MSF ETCs were invited to participate in the follow-up program as well as their family members if their family member was also an EVD survivor. Follow-up visits included clinical assessment by a physician, psychological evaluation, and a discussion with the health promotion team. For vision-related problems survivors were referred to an eye clinic for further diagnosis, treatment, and follow-up.

## Results

A total of 162 survivors have been enrolled in the survivor follow-up program and have made at least 1 visit.

The median time between discharge from an ETC and first follow-up visit is 36 days (IQR 18-82.5). Frequent diagnoses made by the MSF physician at the first follow-up visit were; polyarthralgia (43.8%, n=71), anemia (24.6%, n=40), skin problems (16%, n=26) and hair loss (8.6%, n=14). Additionally 86 EVD survivors (53%) were referred to and attended the eye clinic. Eighty-two (95.3%) were diagnosed with an eye condition. The most frequent diagnosis for survivors attending the eye clinic was uveitis (55%, n=48).

## Conclusion

Information gathered from this follow-up programme will help improve clinical management of survivors and allow health-care workers to presumptively treat, diagnose, and manage conditions. Data from these initial analyses suggest that post discharge complications in EVD survivors continue well beyond the first few weeks of recovery and can lead to lifelong disabilities such as blindness if not treated early.

The long-term consequences of EVD infection for survivors are currently unknown. A cohort of 162 survivors of Ebola Virus Disease in Sierra Leone are being followed up with early data suggesting that post discharge complications continue well beyond the first few weeks of recovery.

# Round table

**Role of Research and Development in responding to epidemics**

**Chairman:** Thomas Nierle, MSF-Switzerland

**External participants:**
- Graeme Bilbe, Geneva
- Marc Lipsitch, Harvard School of Public Health, Boston
- Martin Friede, WHO Geneva

# Notes


Epicentre, 8 rue Saint Sabin, 75011 Paris, France
Tél : 01 40 21 55 55 - Fax : 01 40 21 55 00 - epimail@epicentre.msf.org
www.epicentre.msf.org