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Dix-huitième Journée Scientifique **Eighteenth Scientific Day**

30 mai 2008 - 30th May 2008



Résumés des communications

Abstracts of the presentations

Paris, le 30 mai 2008

Chers collègues et amis,

Sida, paludisme et tuberculose demeurent des fléaux contre lesquels la mobilisation internationale doit être renforcée. En marge d'initiatives telles que la création du Fonds Mondial, la réalité du quotidien oblige les équipes médicales sur le terrain à chercher de nouveaux modes de prise en charge. Les travaux présentés dans cette première session mettent en évidence ces difficultés et apportent des éléments pour faciliter le diagnostic et le suivi de patients atteints par le VIH, le paludisme ou la tuberculose, trois défis encore d'actualité.

Des difficultés de prise en charge des patients persistent dans les institutions hospitalières, notamment en pédiatrie, où les capacités diagnostiques sont encore faibles et le traitement trop aléatoire, comme le rapporte l'enquête menée à Bunia en République Démocratique du Congo. Dans d'autres cas, tels que dans la trypanosomiase africaine, c'est la simplification du traitement qui est l'enjeu : les premières données de tolérance d'une nouvelle association thérapeutique sont présentées ici.

Les stratégies de prise en charge des enfants atteints de malnutrition ont été revues grâce aux produits prêts à l'emploi qui permettent d'envisager des interventions à des stades plus précoces de l'évolution de la maladie. Ces stratégies s'appuient également sur l'utilisation des nouvelles normes de croissance de l'Organisation Mondiale de la Santé.

Paris, May 30, 2008

Dear Friends and colleagues,

AIDS, malaria and tuberculosis continue to plague and reinforced international mobilisation is needed. Working on the sidelines of initiatives such as The Global Fund, the realities of daily life have forced medical teams in the field to seek new ways of dealing with these epidemics. The papers presented in this first session highlight the difficulties and offer assistance in the diagnosis and monitoring of HIV/AIDS, malaria or tuberculosis patients, three contemporary challenges.

Difficulties in treating patients in hospital settings remain, especially in paediatrics, where diagnosis is still underdeveloped and the treatment continues to be far too hit-and-miss. This can be seen from the research conducted in Bunia in the Democratic Republic of Congo. In other cases, such as African trypanosomiasis, simplification of the treatment is the challenge. The first tolerance data for a new combination treatment is presented.

Ready-to-use foods have revolutionized strategies for treating children suffering from malnutrition, making it possible to consider intervening at earlier stages in the development of the disease. These strategies are also based on the use of the new World Health Organization growth standards. The impact of using these new standards and the results of various strategies are presented.

L'impact de l'utilisation de ces courbes est abordé et les résultats de différentes stratégies de prise en charge présentés.

Dans les urgences, le recueil et l'analyse des données permettent d'éclairer les décisions opérationnelles. Cette session aborde la question de l'interprétation dans différentes situations (épidémies, conflit) où le lien entre information et action est décisif. La question de la validité des indicateurs de mortalité est aussi posée ici.

Outre le recueil et l'analyse des données, de nouveaux outils diagnostiques et de traitement permettent d'élargir nos champs d'intervention. Après la description de la mise en place d'un laboratoire dans le cadre d'une étude sur les infections en pédiatrie, des modèles de développement de ces outils sont présentés dans les deux dernières interventions.

Ces différents thèmes vous seront présentés par des collaborateurs externes, des membres de Médecins Sans Frontières et d'Epicentre. Un espace de débat est prévu à l'issue de chaque session. Une traduction simultanée français/anglais sera assurée en permanence.

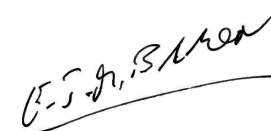
Nous comptons sur votre participation active au cours des discussions et vous souhaitons une journée scientifique agréable et enrichissante.

In emergencies, the collection and analysis of data helps clarify operational decisions. The first presentation tackles the question of the interpretation in various situations (epidemics, conflict, etc.) in which the link between information and action is decisive. Another presentation addresses questions about the validity of mortality indicators in emergencies.

Besides the collection and analysis of data, new tools for diagnosis and treatment increase the scope of interventions. After a description of setting up a laboratory in the context of a study of paediatric infections, two different models for the development of these tools are presented in the last two presentations.

These presentations are given by various external partners, Médecins Sans Frontières and Epicentre members. There will be time for discussion at the end of each session. A simultaneous French-English interpretation will be available throughout the day.

We look forward to your participation in the discussions and sincerely hope you will enjoy this Scientific Day.



Emmanuel Baron
General Director, Epicentre

Journée Scientifique Épicentre/Médecins Sans Frontières - 30 mai 2008

8h45 Accueil et café

9h30 Introduction générale

9.45 Session 1

Sur les traces du Global Fund : diagnostic, traitement et suivi

Modérateur : Pr. Matthias Egger, Institute of Social and Preventive Medicine (ISPM), Université de Berne, Suisse

- Le gain de poids est un indicateur utile pour le suivi des adultes infectés par le VIH et sous traitement antirétroviral : analyses de deux cohortes africaines. *Yoann Madec*
- Comparaison de deux méthodes indirectes d'évaluation de l'observance au traitement anti-rétroviral. *Elisabeth Poulet*
- Evaluation de 3 tests diagnostiques rapides pour le diagnostic du paludisme à *P. vivax* et à *P. falciparum* au Myanmar. *Elizabeth Ashley*
- Résultats de traitement et amplification de la résistance aux antituberculeux dans une région à haute prévalence de tuberculose multirésistante. *Maryline Bonnet*

11.00 Pause café

11.30 Session 2

Complexité des problèmes dans des contextes difficiles

Modérateur : Dr. François Chappuis, Hôpitaux Universitaires de Genève, MSF - Suisse

- Causes et caractéristiques des décès dans le service de pédiatrie de l'Hôpital Bon Marché, Bunia, République Démocratique du Congo. *Marie-Claude Bottineau*
- Essai clinique multicentrique sur l'association nifurtimox-eflornithine pour le traitement de la maladie du sommeil au deuxième stade. Résultats sur la tolérance. *Gerardo Priotto*

12.15 Session 3

La réhabilitation nutritionnelle à la croisée des chemins

Modérateur : Dr. Martin Bloem, Programme Alimentaire Mondial (PAM), Rome, Italie

- Mise en place des courbes OMS de mesure de la croissance : impact sur le programme de traitement de la malnutrition à Maradi, Niger. *Naël Lapidus*

- Comparaison de l'efficacité d'un aliment thérapeutique prêt à l'emploi et d'une préparation de farines de soja et de maïs, huile et sucre, pour le traitement de la malnutrition infantile aiguë modérée : essai contrôlé randomisé à Magaria, Niger. *Fabienne Nackers*
- Effet de la supplémentation à l'aide d'aliments prêts à l'emploi sur le statut nutritionnel, la mortalité et la morbidité d'enfants de 6 à 59 mois au Niger : un essai randomisé en grappes. *Rebecca Grais*

13.00-14.15 Déjeuner - Buffet sur place

14.15 Session 4

Repenser le b.a-ba dans les urgences

Modérateur : Dr. Dominique Legros, Organisation Mondiale de la Santé (OMS), Genève Suisse

- De l'alerte épidémiologique à la réponse opérationnelle : épidémie d'Ebola, RDC, 2007. *Armand Sprecher*
- Mise en place d'un système de surveillance de la mortalité dans un contexte d'urgence, Tchad, 2007. *Biagio Pedalino*
- Le taux brut de mortalité est-il un bon indicateur dans les situations d'urgence ? Analyse préliminaire de la validité et de la précision des estimations. *Francisco Luquero*
- Lutte contre le choléra : adaptation des approches et rôle de MSF. *Kathryn Alberti*

16.00 Pause café

16.15 Session 5

Techniques pour interventions humanitaires

Modérateur : Pr. Philippe, J. Sansonetti, Institut Pasteur, Paris

- Conception et expérience d'un laboratoire de bactériologie dans un contexte de ressources précaires : qu'avons-nous appris ? *Ann-Carole Janssens*
- Vers de nouveaux outils diagnostiques adaptés au terrain. *Anne-Laure Page*
- Un incubateur à partir de pièces détachées de voiture : une solution innovante. *Kristian R. Olson*

17.30 Pot de clôture à MSF France, 8 rue Saint Sabin - 75011 Paris (métro Bastille)

Epicentre/Médecins Sans Frontières Scientific Day - 30th May 2008

8.45 Welcome and coffee

9.30 General introduction

9.45 Session 1

In the wake of the Global Fund: diagnosis, treatment and follow-up

Chairman: Pr. Matthias Egger, Institute of Social and Preventive Medicine (ISPM), University of Bern, Switzerland

- Prognostic value of weight gain on mortality under antiretroviral treatment: results from Cambodia and Kenya. *Yoann Madec*
- Assessing ART adherence: comparison of three indirect methods. *Elisabeth Poulet*
- Evaluation of 3 rapid diagnostic tests for the detection of *P. vivax* and *P. falciparum* malaria in Myanmar. *Elizabeth Ashley*
- Tuberculosis treatment outcomes and resistance amplification in a high-prevalence multi drug-resistance region. *Maryline Bonnet*

11.00 Coffee break

11.30 Session 2

Difficult problems in difficult contexts

Chairman: Dr. François Chappuis, Hôpital Cantonale de Genève, Switzerland

- Causes and patterns of mortality in the paediatric inpatient department of the Bon Marché Hospital. Bunia, Democratic Republic of Congo. *Marie-Claude Bottineau*
- Multicentre clinical trial of nifurtimox-eflornithine combination treatment for second-stage sleeping sickness. Safety results. *Gerardo Priotto*

12.15 Session 3

Nutrition at a crossroads, how to move forward?

Chairman: Dr. Martin Bloem, World Food Programme (WFP), Roma, Italy

- Introduction of the WHO Growth Standards: impact on the nutritional program in Maradi, Niger. *Naël Lapidus*

- Efficacy of ready-to-use therapeutic food compared to a premix (Corn Soya Blend, oil and sugar) for the treatment of moderate acute malnutrition in children: a randomised controlled trial in Magaria, Niger. *Fabienne Nackers*
- Effect of ready-to-use-food supplementation on the nutritional status, mortality and morbidity of children 6 to 59 months in Niger: a cluster randomized trial. *Rebecca Grais*

13.00-14.15 Buffet lunch on site

14.15 Session 4

Rethinking the fundamentals in emergencies

Chairman: Dr. Dominique Legros, World Health Organisation (WHO), Geneva Switzerland

- From epidemiological alert to operational response: ebola outbreak, DRC 2007. *Armand Sprecher*
- Implementation of a mortality surveillance system in emergency situation, Chad 2007. *Biagio Pedalino*
- Is crude mortality a good indicator in emergencies? A preliminary analysis of validity and precision. *Francisco Luquero*
- Managing cholera: adapting approaches and MSF's role. *Kathryn Alberti*

16.00 Coffee break

16.15 Session 5

Technology for humanitarian intervention

Chairman: Pr. Philippe J. Sansonetti, Institut Pasteur, Paris

- Conception and experience of a bacteriology laboratory in a resource limited context: what did we learn? *Ann-Carole Janssens*
- Towards new diagnostic tools for the field. *Anne-Laure Page*
- From car parts to incubator: an innovative solution. *Kristian R. Olson*

17.30 Farewell drinks in MSF France, 8 rue Saint Sabin 75011 Paris (Métro Bastille)

First Session

**In the wake of the Global Fund:
diagnosis, treatment and follow-up**

Weight gain is an effective tool to monitor HIV+ adults on ART: evidence from two developing countries

Y. Madec¹, E. Szumilin², C. Genevier³, L. Ferradini⁴, S. Balkan², M. Pujades⁵, A. Fontanet¹

¹ Institut Pasteur, France - ² MSF France, France - ³ MSF Homabay, Kenya - ⁴ MSF Phnom Penh, Cambodia - ⁵ Epicentre, France

Background

In developing countries, access to biological measurements remains limited, and identifying simple monitoring tools is essential. We investigated the use of weight gain as an easy and costless tool to predict death in HIV-infected adults.

Methods

Adults (>18 yr) who initiated ART and were followed for more than 3 months in two Médecins Sans Frontières (MSF) programmes in Cambodia and Kenya were included. Factors associated with weight gain at 6 months were identified using multiple linear regression. The prognostic value on short-term mortality of weight gain at 3 and 6 months of ART was estimated using a Poisson regression model.

Results

2 451 patients from Cambodia and 2 618 patients from Kenya were included in the analyses. Median weight gain 6 months after ART initiation was 5.8% (IQR: 0.0% to 13.4%). Weight gain was greater in patients of low body mass index (BMI) and in those at WHO stage IV or with CD4 count ≤ 50 cells/mm³ at ART initiation. In patients with BMI <20 kg/m² at ART initiation, weight gain of less than 5% and between 5 and 10% at 3 months were associated with a higher mortality within the following 3 months, when compared to a weight gain $\geq 10\%$ (Incidence rate ratio (IRR): 6.3 (95% CI: 3.0-17.2) and 3.0 (1.2-7.3), respectively). The IRR remained unchanged after adjustment for other baseline cofactors.

Conclusion

A weight gain of less than 10% at 3 months was associated with increased short-term mortality in patients with BMI <20 kg/m² at ART initiation. Low weight gain at 3 months can be used to identify high-risk patients and to address potential problems of poor adherence and/or underlying opportunistic infection.

Assessing ART adherence : comparison of two indirect methods

E. Poulet¹, L. Ahoua¹, L. Ciaffi², S. Balkan³, M. Pujades¹

¹ Epicentre - ² Médecins Sans Frontières, Switzerland - ³ Médecins Sans Frontières, France

Background

Optimal adherence to antiretroviral therapy (ART) is essential to ensure the effectiveness of therapy. In resource-limited settings where access to viral load (VL) testing is limited, indirect methods, such as patient recall of missed pills or the visual analogue scale (VAS), could routinely be used to identify patients with suboptimal adherence. The performance of these methods needs to be evaluated in those settings.

Methods

We analysed adherence and VL data collected from adult patients on ART for 24 months during two cross-sectional surveys: Arua, Uganda (Nov 2005-Apr 2006) and Yaoundé, Cameroon (Sep 2006-May 2007). Two indirect methods, patient recall of missed pills in the last four days and a 6-point VAS over the last month, were validated against VL measurements. We calculated sensitivity, specificity and the proportion of patients correctly classified by using different thresholds.

Results

Patients' median age (N=508) was 38 years and 99% were ARV-naïve at ART start. The level of education was higher in Yaoundé than in Arua. 85% of the patients received d4T/3TC/NVP and 15% >2 pills/day. At 24 months, median BMI (20.8 vs. 24.2 kg/m²) and CD4 values (238 vs. 339 cells/μl) were lower in Arua than in Yaoundé patients; and detectable VL was more common in Arua (29% vs. 20%). Compared to VL testing, the use of a threshold of 25% of pills taken correctly classified 75% of patients and showed 98% sensitivity and 6% specificity. A VAS threshold of 3 correctly classified 77% of patients and revealed 100% sensitivity and 5% specificity. The numbers of observed false positive (95%) and of virological failures not predicted by either method (25%) were high.

Discussion

After 24 months of ART, more than 75% of patients were correctly classified as having detectable or undetectable VL by the two methods evaluated. Sensitivities were high but one in four patients categorised as adherent to ART actually had detectable VL. Because patients treated with ART for 24 months may have already developed drug-resistance mutations despite current optimal adherence to ART, applying the same methods to patients at earlier stages of treatment might be more appropriate (e.g. at 12 months of ART).

Evaluation of 3 rapid diagnostic tests (CareStart™ Malaria 3 line pLDH (Pan, Pf), OptiMAL-IT® pLDH (Pan, Pf) and CareStart™ 2 line pLDH (Pan) for the diagnosis of malaria in Myanmar.

E. A. Ashley¹, M. Touabi^{1,2}, M. Ahrer², R. Hutagalung¹, K. Htun², M. Min Lwin², A. Koscalova², E. Comte², P. Hamade³, A-L. Page¹, J. Luchavez⁴, S. Proux⁵, F. Nosten⁵, P.J. Guerin¹.

¹ Epicentre, Paris - ² Médecins sans Frontières, Switzerland - ³ Médecins sans Frontières Malaria Working Group, United Kingdom - ⁴ Research Institute for Tropical Medicine, Philippines - ⁵ Shoklo Malaria Research Unit, Thailand

Background

Obtaining biological confirmation of the diagnosis is considered an essential element of the detection and treatment of malaria in MSF programmes. Several Rapid Diagnosis Tests (RDTs) using monoclonal antibodies against histidine-rich protein 2 (HRP-2) produced by *Plasmodium falciparum*, have shown reliable results when evaluated. A second type of RDT, targeting parasite lactate dehydrogenase (pLDH), produced by all *Plasmodia* species, is appearing on the market increasingly, but few studies support the use of these new tests.

Methods

In an MSF-Switzerland programme in Dawei, Myanmar, 3 pLDH based RDTs were evaluated in patients presenting with clinically suspected malaria. A subset of patients with microscopically confirmed malaria had their RDTs repeated on days 2, 7 and then weekly until negative. Each RDT was read twice. At the end of the study samples of study RDTs were sent for temperature stability and quality control testing.

Results

Between August and November 2007, 1 004 patients aged between 1 and 93 years were enrolled in the study. Slide microscopy (the reference standard) diagnosed 213 *Plasmodium vivax* (PV) monoinfections, 98 *Plasmodium falciparum* (PF) monoinfections and no malaria in 650 cases.

The sensitivities (sens) and specificities (spec), of the RDTs for the detection of malaria were :

OptiMal-IT®: PF+/- other: sens 95.2% [CI⁹⁵ 87.5-98.2], spec 94.7%; [92.8-96.2], PPV 65.2% [55.7-73.6], NPV 99.5% [98.6-99.8]; non-PF: sens 89.6% [83.6-93.6], spec 96.5% [94.8-97.7], PPV 85.9% [79.4-90.5], NPV 97.5% [96.0-98.5]; PV alone: sens 91.4% [85.3-95.2]

CareStart Malaria™ 3 line: PF+/- other: sens 93.5% [CI⁹⁵ 85.4-97.3], spec 97.4% [95.9-98.3], PPV 78.9% [69.1-86.2], NPV 99.3% [98.4-99.7]; non-PF: sens 78.5% [71.1-84.4], spec 97.8% [96.3-98.7], PPV 89.5% [83.0-93.8], NPV 95.0% [93.1-96.5]; PV alone: sens 80.6% [72.9-86.5].

CareStart Malaria™ 2 line: PF/other: sens 89.1% [CI⁹⁵ 84.2-92.6], spec 94.7% [92.5-96.3], PPV 87.0% [81.9-90.8], NPV 95.6% [93.5-97.0]; PF alone: sens 95.6% [87.7-98.5]; PV alone: sens 91.0% [92.5-96.3].

Inter-observer agreement was excellent for all tests (kappa > 0.9; p<0.001). The median time for the RDTs to become negative was 2 days for the CareStart™ tests and 7 days for OptiMAL-IT®. Tests were heat stable up to 90 days except for OptiMAL-IT® (Pf specific pLDH stable to day 20 at 35°C only).

Conclusion

In this study OptiMAL-IT® RDT and the CareStart™ 2 line pLDH (Pan) test met the 95% threshold of sensitivity for detection of falciparum malaria set by the World Health Organisation. The sensitivity of both tests to detect vivax malaria exceeded 90%. However any decision to implement one of these tests should take into account the heat stability results, positive predictive value in the context in which it would be deployed and cost-effectiveness.

Tuberculosis treatment outcomes and resistance amplification in a high-prevalence multidrug-resistance region

M. Bonnet¹, M. Pardini², P. W. Andrew³, H. Yesilkaya³, H. Rinder⁴, G. Orrù⁵, F. Meacci⁶, M. Oggioni⁶, L. Fattorini², T. Jarosz⁷, S. Niemann⁸, F. Varaine⁹

¹ Epicentre, Switzerland - ² Laboratory of Bacteriology and Medical mycology Istituto Superiore di Sanita, Italy - ³ Department of Infection, Immunity and Inflammation, University of Leicester, United Kingdom - ⁴ Department of Infectious Diseases and Tropical Medicine Universität München, Germany - ⁵ Oral Biotechnology Laboratory, Università di Cagliari, Italy - ⁶ Laboratorio di Microbiologia Molecolare e Biotecnologia, Università di Siena, Italy - ⁷ Société 3 ES, Paris, France - ⁸ National Reference Center for Mycobacteria, Forschungszentrum, Borstel, Germany - ⁹ Médecins Sans Frontières, France

Background

In high-prevalence areas of multidrug-resistant tuberculosis (MDR-TB), WHO recommends starting patients on standard regimens and adapting treatment according to individual drug susceptibility testing (DST). We evaluated treatment outcomes using this strategy in a 3-year prospective cohort study in Abkhazia (Georgia) between 2003 and 2005, where 21% of patients have MDR-TB.

Methods

M. tuberculosis culture, DST, IS6110 DNA fingerprinting, and spoligotyping were performed in all consecutive smear-positive TB patients before and during treatment. Treatment outcomes were defined per WHO recommendations and grouped as favourable (cured or treatment completed) or unfavourable (death or failure). Resistance amplification was defined as resistance increase from baseline to follow-up in strains of identical genotype, and re-infection as infection by a different strain.

Results

Overall treatment success was 72.1% (233/323). Beijing genotype infection, past TB treatment, prisoner history, number of baseline resistant drugs, and MDR were significantly associated with unfavourable outcomes. MDR was the only risk factor after multivariate analysis (OR 12.7, 95% CI [5.5-29.0]). Two of the 258 non-MDR-TB patients had MDR amplification (0.8%), and 3 were re-infected (1.2%) by a MDR strain. Of the 66 MDR-TB patients, 5 (7.6%) amplified resistance to ofloxacin and became extensively drug-resistant (XDR), 3 (4.5%) to ethionamide, and 1 (1.5%) to kanamycin. Amplification of resistance to ofloxacin was associated with unfavourable outcomes (P=0.04).

Conclusion

Despite individualised treatment of drug-resistant cases, MDR remains a strong risk factor of unfavourable outcomes, with quinolone resistance amplification difficult to prevent.

Second Session

Difficult problems in difficult contexts

Causes and patterns of mortality in the paediatric ward of the Bon Marché Hospital. Bunia, Democratic Republic of Congo.

F. Nackers¹, M-C. Bottineau², F. Broillet², K. Porten¹, D. Sapo³, P.J. Guérin¹.

¹ Epicentre, France - ² MSF-CH, Geneva - ³ Bon Marché Hospital, Democratic Republic of Congo.

Background

The “Bon Marché” Hospital (BMH) provides secondary level care in Bunia (DRC). In 2006 - 2007, over 350 children were admitted monthly in its paediatric ward, reporting worrying mortality rates. We investigated the reasons for this mortality.

Methods

Nurses prospectively collected socio-demographic and clinical data regarding all children admitted in the BMH paediatric ward from 9th of May to 31st of July 2007. Physicians reviewed the data concerning children who died and they were asked whether they could identify failures in the health system or in quality of care (modifiable factors) which might have contributed to their deaths. Data were analysed using descriptive statistics.

Results

Among 1 372 children, 114 (8.3%) died. Neonates accounted for 19 (17%) deaths. 47 deaths (41%) occurred during the first 24 hours. Mortality increased with distance between home and BMH and a delay in seeking care. Severe malaria and anaemia were frequent diagnoses at entry (52% and 40% of all admissions). Case fatality rate (CFR) was 7% (47/708) for severe malaria, 6% (34/545) for severe anaemia and 5% (25/494) when they occurred together.

Other severe infections presented high CFR: 38% (13/34) for septicaemia, 20% (10/49) for meningitis, 15% (13/88) for neonatal infections and 18% (20/114) for lower respiratory tract infections (LRTI). Dehydration, malnutrition, non-malaria anaemia, hypoglycaemia and low birth weight also predicted a poor outcome.

Medical doctors identified 214 modifiable factors (55% occurring at home, 9% at the primary health care level and 36% at BMH). They classified 41% of causes of death as uncertain.

Discussion

Limited access to care contributed greatly to the observed early mortality. Severe malaria and severe anaemia were not causes of over-mortality as were other infectious diseases. Absence of a clear diagnosis appeared to be a direct cause of death since it leads to inefficient care. There is an urgent need to provide guidelines and training in neonatal care.

This survey, although using mainly basic descriptive data, was a positive field experience that allowed evaluation of program quality and redirection of priorities.

Multicenter clinical trial of nifurtimox-eflornithine combination treatment for second-stage sleeping sickness. Safety results

G. Priotto¹, S. Kasparian², D. Ngouama⁴, S. Ghorashian², U. Arnold², S. Ghabri¹, E. Baudin¹, V. Buard³, S. Kazadi-Kyanza³, V. Kande⁵, W. Mutombo⁵, M. Ilunga⁵, W. Mutangala⁴ ⁵, C. Schmid⁶, E. Torrele⁷, U. Karunakara²

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⁵ PNLTHA, Ministry of Health, Democratic Republic of Congo - ⁶ Swiss Tropical Institute - ⁷ Drugs for Neglected Diseases initiative

Background

Current treatment options for second-stage gambiense human African trypanosomiasis (sleeping sickness) are either toxic or impracticable in field conditions. Most patients are still treated with highly toxic melarsoprol, with failure rates increasing in several foci. Eflornithine, the only alternative, is difficult to implement, and is used in first-line only in a few resource-intensive treatment centers.

Methods

We compared the efficacy and safety of a simplified nifurtimox-eflornithine drug combination (i.e. 14 intravenous infusions) to the standard eflornithine regimen (i.e. 56 intravenous infusions) in a randomized, non-inferiority, multicenter trial. Participants were parasitologically confirmed, had more than 20 leukocytes/ μ L of cerebrospinal fluid and were \geq 15 years old. The investigational treatment was nifurtimox: 15 mg/kg/day, 8-hourly, for 10 days, plus eflornithine: 400 mg/kg/day, 12-hourly for 7 days (N+E). The active comparator was standard eflornithine: 400 mg/kg/day, 6-hourly for 14 days. Safety assessments included clinical adverse events, hematology and biochemistry monitoring of hepatic and renal functions. Patients are followed-up for 18 months for efficacy assessment.

Results

Between 2003 and 2006, 287 patients were enrolled in 4 sites (Nkayi, Congo; Isangi, Dipumba and Katanda, Democratic Republic of Congo). There were three deaths with eflornithine and one with N+E. Patients suffering severe adverse events were fewer with N+E (14.0% vs. 28.7%; $p=0.002$). Outstanding adverse events with N+E were nausea/vomiting and with eflornithine neutropenia, infections, fever, diarrhea, hypertension.

Discussion

From a first comparison of safety indicators, the nifurtimox-eflornithine combination shows better tolerability than eflornithine monotherapy. A more in-depth analysis of the safety data is underway to confirm its clinical significance. For efficacy, the results will be available in Q3-2008, when the 18-months follow up of all patients will be completed.

Third Session

Nutrition at a crossroads, how to move forward?

Introduction of the WHO Growth Standards: impact on the nutritional program in Maradi, Niger

N. Lapidus¹, S. Isanaka², E. Villamor², F. Luquero¹, V. Gaboulaud¹, S. Shepherd³, R.F. Grais¹

¹ Epicentre, France - ² Departments of Epidemiology and Nutrition, Harvard School of Public Health, USA - ³ Médecins Sans Frontières, France

Background

Important differences exist in the diagnosis of malnutrition between the 2006 World Health Organization Child Growth Standards (WHO reference) and the 1977 National Center for Health Statistics reference (NCHS reference). We compared the two standards regarding response to treatment. We also assessed their accuracy at admission, along with the mid-upper arm circumference (MUAC), to predict the risk of death.

Methods

We analyzed data from children aged 6-59 months admitted to the MSF program in Maradi, Niger in 2006. Outcome measures included weight gain, treatment duration, recovery, death, defaulting, and need for inpatient care. Both weight-for-height in Z-score (WHZ) and percentage of the median (WH%) were examined. The receiver operating characteristic (ROC) and area under curve (AUC) were estimated for WHZ, WH% and MUAC to predict the risk of death.

Results

Children included according to the WHO reference (WHZ) had shorter treatment durations, greater recovery and less death, defaulting and need for inpatient care than those admitted according to the NCHS reference (WH%). These children were younger and admitted with higher WHZ scores than those included under NCHS. Patterns remained after adjustment for differences in age and sex. No child included by the NCHS reference (WH%) was excluded by the WHO standards (WHZ). In predicting mortality, AUC values for the WHO standards provided higher accuracy (WHZ:0.76 [95%CI:0.75-0.80] and WH%:0.77 [0.75-0.80]) than the NCHS references (WHZ:0.63 [0.60-0.66] and WH%:0.71 [0.68-0.74]). The relationship between MUAC and mortality risk appeared weaker, with AUC=0.63 [0.60-0.67]. Analyses stratified by sex and age yielded similar results.

Conclusion

The WHO reference and the Z score criterion expand programs to include children who are younger but less severely wasted. Identified at earlier stages, these children have fewer medical complications requiring inpatient care and were more likely to experience favorable discharge outcomes.

Efficacy of ready-to-use therapeutic food compared to a premix (corn soy blend, oil and sugar) for the treatment of moderate acute malnutrition in children: a randomised controlled trial in Magaria, Niger.

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Background

In Niger, the national protocol recommends the use of fortified blended flours to treat moderate acute malnutrition. In 2006, MSF implemented a protocol using a Ready to Use Therapeutic Food (RUTF) in its home-based Supplementary Feeding Program (SFP) in South-east Niger. We conducted an open randomized trial to compare RUTF and fortified blend flours for the treatment of moderately malnourished children.

Methods

The study took place in 2 MSF supplementary feeding centres in Magaria, a department in the Zinder region. Moderate malnutrition was defined as a weight-for-height (WFH) between 70% and 80% of the median (NCHS reference), without oedema and with a mid-upper arm circumference ≥ 110 mm. All children aged 6 to 59 months newly admitted to the SFP with moderate malnutrition were eligible for inclusion. Children were randomly allocated to the intervention group receiving RUTF (Plumpy'nut®) or to the control group, which received a premix of Corn Soy Blend, oil, sugar and iron supplementation. Other interventions were similar in both groups (e.g. weekly family ration and exit ration). Children were followed on a weekly basis until their discharge, which occurred when they reached a WFH $\geq 85\%$ of the median (NCHS reference) for two consecutive weeks. They were seen again at 1, 3 and 6 months after their discharge. Primary measured outcomes were cure rate and weight gain (g/Kg/day).

Results

The study took place between August 2007 and January 2008. Preliminary analysis was conducted on 197 children receiving RUTF and 204 children receiving premix. Group characteristics were balanced at baseline. In a Kaplan-Meier survival analysis, cure rate at four weeks was 52% in the RUTF arm [95%CI: 45-59%] and 30% in the premix arm [95%CI: 24 - 37%]. Mean weight gain up to discharge was higher in the RUTF arm (5.7 ± 2.6 g/Kg/day) compared to the premix arm (4.7 ± 2.4 g/Kg/day). The length of stay was shorter in the children receiving RUTF. However, more transfers to the inpatient feeding centre were observed in the premix arm compared to the RUTF arm. This might be a potential confounder of our results.

Discussion

Preliminary analyses suggest that RUTF may present some advantages over premix in treating childhood moderate malnutrition. Follow-up data will be collected up to 6 months after discharge. This will allow to compare the longer-term efficacy of both products and will help to identify the most appropriate food regimen with which to treat moderate malnutrition in Niger.

Effect of preventive ready-to-use-food supplementation on the nutritional status of children 6 to 36 months in Niger: an observational cohort

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Background

In 2007, MSF implemented a new strategy for the prevention of malnutrition in children 6-36 months old using a ready-to-use-food in Maradi, Niger. Previous evidence suggests that preventive distribution of Plumpy'nut® leads to a reduction in the incidence of wasting in children under 5 years. A new product, Plumpy'doz® related to Plumpy'nut®, was developed with the aim of providing essential micro-nutrients in an easily administered formulation. Here, we examine the effect of two strategies for the prevention of malnutrition in children 6-36 months old in Maradi, Niger.

Methods

An observational cohort of all children aged 6-36 months living in 6 villages was visited monthly from March 2007 to March 2008. In three villages, all children (n=520) received monthly distributions of one Plumpy'nut®/day (500kcal/day/child) during four months (July-October 2007). In the other three villages, all children (n=393) received monthly distributions of Plumpy'doz® (250 kcal/day/child) for six months (May-October 2007). At the monthly visits, children were referred for nutritional treatment with oedema or a weight-for-height Z-score (WHZ) of < -3 according to the WHO growth standards. Primary outcome measures were incidence of wasting (WHZ < -2), severe wasting (WHZ < -3), stunting, and mortality over 11 months of follow-up. We analysed the incidence rate of the different outcomes adjusted by age, sex and nutritional status at baseline to obtain the adjusted hazard ratio (AHR).

Results

Considering only non-malnourished children at baseline (March 2007), a lower incidence of severe wasting was observed in children receiving a four month distribution of Plumpy'nut® (1.9/10,000/day), compared to those children receiving a six month distribution of Plumpy'doz® (4.2/10,000/day) with an AHR of 2.14 (95%CI=1.02-4.49). There was no evidence of a difference between the two interventions in reduction of global wasting (AHR: 1.09; 95%CI: 0.78-1.54). Although a reduction was seen for stunting in the children receiving the Plumpy'doz® distribution (AHR: 0.8; 95%CI=0.59-1.25) as compared to those receiving the Plumpy'nut® distribution, this was not statistically significant. No difference in mortality was seen between the two interventions with 20 deaths reported in total.

Discussion

These results suggest that the four month distribution of Plumpy'nut® reduced the risk of severe wasting in children 6-36 months compared to the six month distribution of Plumpy'doz® in Niger. This research highlights the importance of products and strategies adapted to the nutritional context and target population and the need for future research evaluating different strategies.

Fourth Session

Rethinking the fundamentals in emergencies

From epidemiological alert to operational response: Ebola outbreak, DRC 2007

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Background

Ebola viruses are responsible for outbreaks of severe hemorrhagic fever in humans, with case fatality ratios (CFR) up to 88%, as it was in 1976 in Yambuku, formerly Zaire and now the Democratic Republic of Congo (DRC). On August 18, 2007, a nurse working near Kampungu in the DRC informed his supervisors of a large number of deaths in this area since that June. An MSF-OCB emergency pool team arrived in Kampungu on September 2nd and isolation for presumed dysentery was initiated on September 4th. The causal agent was determined to be Ebola-Zaire on September 10th.

Methods

The international response, coordinated by the DRC Ministry of Health (MoH) and WHO, included MSF, Epicentre, the US CDC, and the Public Health Agency of Canada. The strategies used were: 1) Case detection through active surveillance and contact tracing; 2) medical management in isolation of suspect cases with subsequent laboratory confirmation; and 3) community infection control, emphasizing health promotion, safe burials, and household disinfection.

Results

During our surveillance a total of 205 patients were either laboratory confirmed and/or linked to another case. A few other suspects were identified by the MoH. The outbreak stemmed from a single introduction, had no nosocomial amplification, and had limited geographic spread. The attack rate was 4.6 times higher in adults than in children roughly equal between males and females, and especially high in six villages (~1%-5%), especially in one specific religious sub-group. Forty-six patients were cared for in the isolation unit, of whom 18 were laboratory confirmed - these having a CFR of 72.2%, compared to 88.2% in non-isolated cases. Community-based measures facilitated control, especially an early self-imposed suspension of unhygienic burial practices, and created a strong working relationship between the population and the international team.

Conclusion

Confronted by an outbreak of ebola virus, in which dysentery was expected, the need for good application of standard precautions is reinforced. Good acceptance of outbreak management by the affected population facilitated disease control.

We showed that it is possible to set up a comprehensive outbreak control program rapidly, in an isolated rural setting, which includes an isolation unit that provides medical care that can reduce mortality.

Implementation of a mortality surveillance system in emergency situation, Chad 2007

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Background

A cross-sectional survey conducted by Epicentre in May 2007 among Internal Displaced Populations (IDPs) living in Gozbeida (Eastern Chad) showed that mortality rates (both crude (CMR) and under five (U5MR)) were higher than the emergency thresholds (CMR > 1death/10 000/day; U5MR > 2deaths/10 000/day). A number of interventions, e.g. medical consultations, water and sanitation programs were consequently established by MSF-F. MSF-F projects targeting IDPs were opened in two other sites (Koukou and Dogdoré) in the same Eastern Chad Department. In order to monitor the health status of the IDPs (approximately 100 000 inhabitants), a surveillance system was implemented.

Methods

Simple, active and prospective surveillance systems were implemented in three of the major IDPs camps (GozBeida, Koukou and Dogdoré) in the Dar Sila Department, Eastern Chad. Mortality and morbidity (severe cases only) data were collected as were the demographic characteristics of the population (departures /arrivals/births). The system was implemented during week 21/08. Data were collected daily by home visitors and reported weekly to the MSF-F person in charge. Weekly data summaries were compiled and sent to Paris.

Results

92 home visitors were deployed to collect the data. Both CMR and U5MR were 1.2 times the emergency thresholds during week 25/08. The main reported disease was diarrhoea with an average of 200 cases per week.

Discussion

Despite the difficulties in implementing an active surveillance system during emergency situations, it provides an important way to be in continuing contact with the target population. In Chad it enabled the investigators to 1) monitor the demography of the population, 2) to observe a decrease in the mortality rates (both CMR and U5MR) and 3) to observe disease trends. The activities implemented by MSF-F dramatically contributed to the improvement of the health status of the IDPs population in the Department of Dar Sila.

Retrospective mortality surveys: Interpreting and improving estimates of the CMR

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Introduction

The crude mortality rate (CMR) is used internationally to benchmark the severity of crises. Although a prospective surveillance system is ideal; retrospective mortality surveys, often using cluster-based sampling, are frequently the only reasonable alternative to obtaining a CMR in complex emergencies. Despite their widespread use and policy implications, these surveys have been validated only in specific contexts. Here, we examine the interest of the CMR as an indicator in CE and explore its robustness using a cluster sampling design.

Methods

Using the Delphi method, first, we surveyed a panel of international experts on their interpretation of the CMR in evaluating the severity of a crisis. Second, we developed a Monte Carlo simulation tool to explore the precision of different sampling strategies. Using sampling frames reflecting different contexts and spatial distributions of deaths, we performed cluster sampling to explore the variation of the design effect selecting different combinations of clusters and household in each cluster.

Results

Expert participants considered the CMR as one of the most useful indicators defining complex emergencies; but no consensus was obtained on their interpretation. The internationally accepted emergency threshold of 1/10,000 deaths per day provides only partial information. The simulation study confirmed that when mortality is clustered, the use of cluster-based sampling leads to a high loss of precision and increased design effect. Increasing the number of clusters, decreases the design effect, but non-linearly. The 30 by 30 design classically used to ensure the desired level of precision assuming a design effect of two, appears insufficient to provide quality estimates of the CMR in heterogeneous contexts where deaths are cluster distributed.

Conclusion

Even when a good level of precision is obtained in retrospective mortality surveys using cluster sampling, selection bias can invalidate the results. Heterogeneity in the distribution of deaths is common in complex emergencies, and is not easily captured by cluster sampling estimates. As clustering in the distribution of deaths determines the magnitude of the design effect, increasing the number of clusters sampled may partially improve the robustness. This research highlights the importance of considering the uniqueness of each situation and the need to explore alternative ways to measure CMR in complex emergencies.

Managing cholera : adapting approaches and MSFs role

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Background

In early 2006, after 10 years of no reported cases of cholera, Angola experienced a major epidemic with 49 620 cases reported nationally. All 5 operational sections of Médecins Sans Frontières (MSF) provided assistance to victims of the disease in 10 of the 15 provinces affected by the epidemic. One year after the intervention, a review of the interventions was carried out.

Methods

Interviews were carried out with key headquarters and field staff of all 5 sections and with partners in Angola. Documents and data bases were also reviewed.

Results

Inland regions, historically not affected by cholera were touched by the disease in 2006. In the capital Luanda, the attack rate of 0.5 was similar to those seen in the past, but in absolute numbers represented more than double the number of cases reported during previous epidemics.

Overall, 79.9% (39 646/49 620) of the total cases reported in Angola during the 2006 epidemic were treated in cholera treatment structures supported by MSF. In Luanda 80.2 % (18 647/23 252) were treated in MSF supported structures.

Despite requests to other organizations and institutions, no partners took on a significant role in managing this epidemic, neither in case management nor in preventive activities.

Conclusion

Nationally, the change in geographic spread of cholera during the 2006 epidemic, as compared to previous epidemics, is likely due to changing patterns of population movement since the civil war ended in 2002. In Luanda, the zones most affected did not differ from those seen in the past. However, with increased population density and difficulties of transport, the need for adapted approaches, including the decentralization of cholera treatment centers was highlighted.

The absence of major partners during this epidemic is flagrant in the proportion of cases treated in MSF centers and suggests a regrettable lack of actors in this domaine.

Fifth Session

Technology for humanitarian interventions

Conception and Experience of a Microbiology Laboratory in a Resource-Limited Context: What did we learn?

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Infectious diseases are the main causes of mortality in children under 5 years of age, especially when associated with an underlying pathology e.g. malnutrition, sickle cell disease, HIV. Investigations of the ecology of infectious disease in sub-Saharan African children are necessary to improve our treatment protocols and decrease mortality in this population.

We have therefore established a study to estimate the prevalence of infectious diseases and identify the types of microbial agents among severely malnourished children hospitalized in the acute care unit of the Rehabilitation and Intensive Nutritional Education Center of Maradi, Niger.

We identified the storage room of the pharmacy within the regional hospital of Maradi as the most appropriate setting for our microbiology laboratory. In a short period of time and using locally available resources, we rehabilitated this room, transforming it into a functional laboratory. During the rehabilitation, we faced numerous challenges regarding construction, installations, electrical security, logistics (supplies, cold chain,...), as well as in our relations with authorities, our integration into the host structure, and the qualifications and training of staff.

Since October 2007, we have been performing standard bacterial cultures e.g. blood cultures, cytobacteriological urine examination, stool and other liquids culture. We have also performed rapid bacteriological tests, e.g. the detection of pneumococcal antigen in urine and meningococcal antigen (CSF). Our study also includes parasitology (thin and thick smears for malaria diagnosis); virology (HIV rapid tests in blood, and rotavirus/adenovirus in stools) and biochemical (CRP and procalcitonin rapid tests) as well as hematological analyses (hemogram and hemoglobin electrophoresis). High quality results rely on continuous and sustained supervision and the effective management of a complex organization.

Establishing a microbiology laboratory is relatively easy in France but quite complicated in a resource-limited setting. It requires constant attention and timely reaction in order to respond to the unpredictable difficulties during all phases of the project, from the time of its initiation to the current daily routine work. Lessons learned from this experience should help future implementation of laboratories for clinical studies in resource-limited contexts and also stimulate discussion of the use of diagnostic laboratories in MSF or similar programs.

Towards new diagnostic tools for the field

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“My vision as a clinician is that I send a sample to the laboratory and I receive a result 3 hours later”. For many clinicians in rich countries, laboratory diagnostics are a black box. The clinician may not be not aware of any difficulties that have occurred in obtaining biological results. In contrast, in resource-limited countries, laboratory diagnosis is so inaccessible that it is underused even when available. Nevertheless, the need for diagnostic tests to improve case management is widely recognized.

In the settings in which MSF works, a good diagnostic test needs to meet many restrictive specifications: ease of use even for non laboratory-trained staff, stability at high temperatures, no need for electricity or additional material, etc. For a high impact on MSF programs and more generally on public health, it is important to focus on diagnostic tests which will answer questions encountered by the field medical staff, e.g. is an infection bacterial or viral, which treatment will be appropriate, etc. These criteria need to be borne in mind during the early phases of the development of the tests, to avoid developing tests that are appealing but inappropriate for field use. In the absence of an early collaboration between clinicians and research organizations regarding the need and use of diagnostic tests, many commercial tests are underused or developed inappropriately.

Based on the needs expressed by MSF medical staff, as well as the theoretical feasibility of the projects, several high-priority axes have been identified. Syndromic tests distinguishing bacterial, viral and parasitic infections are needed for the diagnosis of infections of the central nervous system and diarrheal diseases. In addition, there is a crucial need for reliable and simple diagnostic tools for tuberculosis and typhoid fever. A collaboration is being developed, bringing together MSF/Epicentre field experiences and the Institut Pasteur biological expertise to facilitate research on these field priorities.

Local Car-Parts Neonatal Isolette

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Background

Four million infants die within a month of birth every year. Ninety-eight percent of these occur in developing countries. Neonatal deaths account for 37% of mortality among children less than five. Best estimates indicate that enhanced clinical care is needed to realize greater than 50% of mortality reduction in neonates and needs to be complementary to community based efforts. Our project aim is to reduce neonatal mortality by developing a higher performing, low-cost neonatal isolette (otherwise known as a 'newborn incubator') with key components from automotive and other locally available parts.

Current neonatal isolettes in developing countries are of limited utility and longevity due to lack of replacement parts, maintenance and training of personnel.

Methods

A multidisciplinary team of clinicians, designers, and engineers was assembled to explore the feasibility of using the car-part opportunity with respect to building an effective isolette.

We utilized feedback from health providers in Indonesia, Nepal, and Zambia as well as interactive design reviews and focus groups with domain experts. Engineers and designers interacted with clinical teams in a rapid-feedback cyclical design to develop prototypes over a four month period.

Results

We conclude that automotive and off-the-shelf parts are capable of being repurposed to produce heat, light, air convection and filtration, a power reservoir, and well as auditory and visual alarms as principal components of a higher performing neonatal isolette for the developing world.

Discussion

Coupled to stimulate adoption and training, this approach can serve to enable a culture of innovation. Building on existing local resources can be a model for decreased reliance on medical product importation and stimulate greater focus on developing local infrastructure, economy and clinical skills to maintain sustainable health care. Approaches to measuring the effects of device dissemination need to be explored prior to implementation.

