COMPTES-RENDUS DE SÉANCES

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The contribution of Médecins Sans Frontières to the assessment of efficacy of antimalarial treatment, 1996-2004.

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At the turn of the century, most countries in which Médecins Sans Frontières (MSF) was operating were affected by the emergence of resistance to antimalarial treatment, but evidence of this phenomenon was often lacking. A review was conducted of 43 in vivo antimalarial efficacy studies performed by MSF in Africa and Asia from 1996 to 2004.

We identified all MSF *Plasmodium falciparum* (Pf) efficacy studies conducted during this period. Characteristics of each study were summarized. We calculated the proportion of MSF studies among the total Pf efficacy studies conducted in a given country during the same period. We used this proportion (combined with two other criteria) to classify MSF studies as having made a definitive, probable or low or negligible contribution to the changes in antimalarial treatment policies in a given country. We also calculated the proportion of MSF/Epicentre articles among all published articles overall and separately for countries where MSF's contribution was considered definite, probable, or low or negligible.

Overall, 12,145 patients were enrolled in 43 efficacy studies or clinical trials conducted in 18 countries. Eight (17%) took place in Asia and 35 (83%) in Africa. Most MSF studies (88%) were conducted between 2001 and 2004 and had a post-treatment follow-up of 28 days or more (n=34, 79%). These studies represented 24% of the total studies conducted in these countries. MSF's contribution to the drug policy change was considered definite or probable in ten (55%) countries and low or negligible in eight. MSF studies accounted for 58% (11/19) of the total articles published in the six countries where its role in policy change was considered definite. This proportion was lower in the four (26%, 12/45) and in the eight (11%, 8/73) countries where its role was considered probable or low or negligible, respectively.

MSF's work has had a considerable impact on antimalarial treatment policy change, although the change was implemented usually with delay. Had some national and international institutions stimulated a systematic process of monitoring antimalarial efficacy from the very onset of reports of drug resistance, changes might have occurred much earlier.

Immunogenicity of fractional doses of Tetravalent A/C/Y/W135 Meningococcal polysaccharide vaccine: results from a randomised non-inferiority controlled trial in Uganda.

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Neisseria meningitidis serogroup A and W135 are the main causative pathogens of meningitis epidemics in sub-Saharan Africa. Mass vaccination campaigns with polysaccharide vaccines are a key element to control these epidemics. Facing a global vaccine shortage, we explored the use of fractional doses of a licensed A/C/Y/W135 polysaccharide meningococcal vaccine.

We conducted a randomized, non-inferiority trial in 750 healthy volunteers 2-19 years old in Mbarara, Uganda, to compare the immune response of the full dose of the vaccine versus fractional doses (1/5 or 1/10). Pre- and post-vaccination sera were analyzed by measuring serum bactericidal activity (SBA). A responder was defined as a subject with a ≥4-fold increase in SBA against a target strain from each serogroup and SBA titer >128.

For serogroup W135, 94 and 97% of the vaccinees in the 1/5- and 1/10-dose arms, respectively, were responders, *versus* 94% in the full-dose arm; for serogroup A, 92 and 88% were responders, respectively, *versus* 95%. Non-inferiority was demonstrated between the full dose and both fractional doses in SBA seroresponse against serogroups W135 and Y, in total population analysis. Non-inferiority was documented between the full and 1/5 doses for serogroup A in the pre-vaccination, non-immune population. For the 1/10-dose arm,

non-inferiority was also shown for serogroups W135 and Y in this population.

These results suggest that 1/5 dose of the licensed A/C/Y/W135 polysaccharide meningococcal vaccine can confer a similar functional immune response as a full dose.

Nifurtimox-Eflornithine combination therapy for late-stage Gambiense sleeping sickness: randomised clinical trial in Congo.

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Human African trypanosomiasis caused by *Trypanosoma brucei Gambiense* is a fatal disease. Current treatment options for late-stage patients are either highly toxic or impracticable in field conditions. We compared the efficacy and safety of the Nifurtimox-Eflornithine drug combination to the standard Eflornithine regimen for the treatment of the late-stage.

A randomised, open-label, active control, phase III clinical trial comparing two arms, was conducted at the Sleeping Sickness Treatment Center run by Médecins Sans Frontières in Nkayi, Bouenza Province, Republic of Congo. Patients were screened for inclusion and randomly assigned to receive IV eflornithine 400 mg/kg/d, every 6 h for 14 d (E); or IV eflornithine 400 mg/kg/d, every 12 h for 7 d + oral nifurtimox 15 mg/kg/d, every 8 h for 10 d (N+E). Patients were followed up for 18 mo. Outcomes were cure rates and adverse events attributable to treatment.

A total of 103 stage 2 patients were enrolled. Cure rates were E= 94·1% and N+E= 96·2%. Drug reactions were frequent in both arms and severe ones affected 25·5% of patients in the E group and 9·6% in the N+E group, resulting in 2 and 1 treatment suspensions respectively. One patient died who was taking E and none in the N+E arm.

The N+E combination appears to be a promising first-line therapy for second stage sleeping sickness. If our data is corroborated by additional studies, the new N+E combination therapy will mark a major and multifaceted advance over current therapies.

Detection of tuberculosis using "Bleach microscopy method": field evaluation in a high HIV prevalence setting.

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Setting: Urban health clinic, Nairobi, Kenya (50% HIV/TB co-infection).

Objective: To evaluate the smear positive detection yield and feasibility of the microscopy after overnight bleach sedimentation (BS) compared to direct smear (DS) method in high HIV prevalence setting.

Design: Prospective, blinded field evaluation. Three sputa collected over 2 days from consecutive pulmonary TB suspects were examined. Ziehl-Neelsen stained was performed on fresh specimens and specimens after processing by 3.5% household bleach and overnight sedimentation. Two acid-fast bacilli (AFB) cut-offs were used to define a positive smear (PS) (>10 AFB/100 high power fields (HPF) and >1 AFB).

Results: Out of 1879 specimens from 644 pulmonary TB suspects, 363 (19.3%) and 460 (24.5%) were positive with BS method compared to 301 (16%) and 374 (19.9%) with DS method when using 10 AFB/100HPF cut-off ($p<0.001$) and 1 AFB cut-off ($p<0.001$), respectively. Based on WHO/IUATLD smear positive case definition, 136 (21.9%) suspects were detected positive with BS method compared to 116 (18.7%) with DS method ($p<0.001$). Inter-reader and intra-reader reproducibility was very good with 0.83 and 0.91 kappa coefficient, respectively. There were significantly more invalid results (1.9% versus 0.2%) and smears were more fragile with BS compared to DS. BS method was cheap and not time consuming.

Conclusion: Overnight BS microscopy is an effective and simple method to improve smear microscopy in high HIV prevalence setting. More field evaluations using the same simple processing method are required before using it in routine program conditions.

Arbovirus et grossesse : conséquences pour la mère et l'enfant

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Depuis qu'en 1941, l'ophtalmologiste australien Gregg McAlister a établi pour la première fois un lien entre une rubéole acquise durant la grossesse et une cataracte congénitale, on s'est rendu compte que de nombreux autres virus pouvaient entraîner des manifestations pathologiques graves au cours de la grossesse, tant chez la mère que chez l'enfant à naître. Parmi ces virus, un nombre relativement restreint d'arbovirus semblait capable de provoquer des infections materno-fœtales : les *flavivirus* de la dengue, les *alphavirus* des encéphalites équines américaines de l'Ouest et du Venezuela, le *phlebovirus* de la fièvre de la Vallée du Rift, le *nairovirus* de la fièvre hémorragique Congo-Crimée et le *coltivirus* de la fièvre à tiques du Colorado (Chastel, 1999). Mais depuis peu, de nouvelles observations de transmission materno-fœtale ont été rapportées de différentes régions du monde. Elles concernent la dengue et l'encéphalite japonaise en Asie du Sud-Est, les infections à virus West Nile aux États-Unis et, surtout, les infections à virus Chikungunya sur l'île de la Réunion (2005-2006). Pour les virus West Nile et Chikungunya, ces observations ont été faites dans des régions où ces virus avaient été récemment importés et dans des populations immunologiquement totalement vierges.

Prevalence of Buruli Ulcer cases in the health district of Akonolinga, Cameroon. A cross sectional survey using centric systematic area sampling.

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Buruli ulcer (BU) is a chronic, indolent necrotizing disease of the skin and underlying tissues caused by Mycobacterium ulcerans (1), which may result in functional incapacity. In 2002, MSF opened a Buruli programme in Akonolinga hospital, Cameroon, offering antibiotic treatment, surgery and general medical care. Five hundred patients have been treated in the project to date. The objective of this survey was to estimate the prevalence of BU in the health district of Akonolinga describe the geographic extension of the highly endemic area within the health district and determine the programme coverage its geographical distribution.

A cross-sectional population survey was conducted, using centric systematic area sampling (CSAS). A 15 x 15 km grid (quadrats of 225 km2) was overlaid on to a map of Akonolinga district with its position chosen to maximize the area covered by the survey. Quadrats were selected if more than 50% of the quadrat was inside of the health district. The chiefdom located closest to the centre of each quadrat were selected and Buruli cases were identified using an active case finding strategy (the sensitivity of the strategy was estimated by capture-recapture).WHO-case definitions were used for nodules, plaque, ulcer, oedema and sequellae.

Out a total population of 103,000 inhabitants, 26,679 were surveyed within the twenty selected quadrats. Sensitivity of case finding strategy was estimated to be 84% (95%CI 54% - 97%) by capture recapture. The overall prevalence was 0.47% (n=105) for all cases including sequellae and 0.25% (n=56) for active stages of the disease. Five quadrats presented with high prevalence, >0.6% to 0.9%, 5 with prevalence >0.3% to 0.6%. and 10 <0.3%. The quadrats with the higher prevalence were situated along the river Nyong and Mfoumou. Overall coverage of the project was 18% (12-27%) for all cases and 16% (9-18%) for active cases, but was limited to the quadrates neighbouring Akonolinga hospital.

Prevalence was highest in the area neighbouring the river Nyong. Coverage was limited to the area close to the hospital and efforts have to be made to increase access to care in the high prevalence areas. This method was particularly interesting for project planning and to identify priority areas of intervention.

Démodécie : ectoparasitose opportuniste lors de l'infection par le VIH.

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La démodécie est une entité bien connue chez l'animal. Chez l'homme, elle est due à *Demodex folliculorum*. Plusieurs tableaux cliniques ont été individualisé chez l'homme : folliculite, rosacée-*like*, blépharite. Une vingtaine d'observation ont été décrite chez le sujet infecté par le VIH. Nous présentons les caractéristiques de 7 observations de cette co-infection.

De janvier 1998 à décembre 2005, nous avons répertorié les observations de patients infectés par le VIH présentant une démodécie. Le diagnostic de démodécie était effectué sur un faisceau d'arguments: tableau clinique suggestif, présence de nombreux *Demodex* à l'examen direct et/ou examen l'histopathologique, enfin guérison sous acaricide. Le traitement faisait appel à une cure unique d'ivermectine (200 µg/kg), répétée en cas de résurgence.

Nous avons colligé 7 observations de démodécie chez des patients infectés par le VIH. Il s'agissait de 5 femmes et 2 hommes. L'âge moyen était de 41 ans. Tous les patients étaient déjà connus infectés par le VIH. Les présentations cliniques étaient les suivantes : aspect de folliculite, 6 cas ; rosacée-*like*, 1 cas. La guérison était obtenue après 1 cure (3 cas), 2 cures (2 cas), 3 cures (1 cas).

De 1989 à 2004, 12 observations de démodécie chez des patients infectés par le VIH sont répertoriées dans la littérature. Les patients sont au stade sida ou ont des lymphocytes CD4 inférieurs à 200/mm^3. De plus, l'ectoparasitose peut être symptomatique d'un syndrome de restauration immunitaire. La présentation clinique est celle d'une dermatose papulo-pustuleuse prurigineuse du visage. Le traitement, mal codifié, faisait appel à des molécules diverses (perméthrine, crotamiton, lindane, benzyl benzoate) avec une efficacité variable. Les résultats de notre étude concordent avec ceux de la littérature: survenue de la démodécie à un stade d'immunodépression profonde, aspect monomorphe de la présentation clinique sous forme de folliculite du visage. L'ivernectine paraît être efficace pour cette parasitose, la cure unique pouvant être répétée lors de récidive. Par ailleurs, l'ivermectine est dépourvue d'effets secondaires à type d'irritation comme les autres molécules acaricides de contact.

La démodécie semble être une ectoparasitose opportuniste lors de l'infection par le VIH. La présentation clinique est stéréotypée et assez caractéristique. L'ivermectine paraît être une bonne alternative aux autres traitements acaricides locaux.

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Traitement minute de la donovanose par azithromycine.

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De nombreuses molécules sont efficaces dans le traitement de la donovanose (1). La durée de traitement habituel est de 3 semaines. Récemment, l'utilisation de l'azithromycine a permis de raccourcir la durée du traitement à une semaine (2). Nous rapportons 7 observations de donovanose guérie par cure unique de 1 gramme d'azithromycine.

De janvier 2000 à mars 2004, nous avons pu proposer un traitement minute par azithromycine aux patients atteints de donovanose. Le diagnostic était confirmé par examen direct d'un frottis coloré au RAL 555 mettant en évidence les corps de Donovan. L'âge, le sexe et l'origine ethnique des patients étaient notifiés.

7 patients ont pu bénéficié du traitement minute par azithromycine. Tous les patients étaient des hommes d'une moyenne d'age de 34 ans. Il y avait 4 Noirs Marrons et 3 Créoles. Deux des patients étaient infectés par le VIH. Le traitement minute a entraîné la guérison de tous les patients dans un délai de 15 jours à 1 mois.

De nombreux antibiotiques se sont montrés efficaces dans le traitement de la donovanose. Les molécules recommandées en première intention sont : cotrimoxazole, doxycycline, érythromycine pendant une durée de trois semaines, ainsi

que l'azithromycine pendant 1 semaine (3). Dans la dernière décennie, les fluoroquinolones et les céphalosporine ont été utilisées. La ciprofloxacine semble constituer une alternative intéressante. L'azithromycine est le dernier venu dans cet arsenal. Il s'agit d'un macrolide semi synthétique aux propriétés pharmacologiques originales (longue demi-vie, forte pénétration intra-cellulaire). Ces propriétés ont permis de raccourcir les traitements de plusieurs infections (angine et pneumopathies communautaires). De même, dans les infections sexuellement transmissibles, un traitement monodose par azithromycine s'est montré aussi efficace que des traitements de référence de 7 jours dans les infections dues à *Chlamydia trachomatis*, à gonocoques et à *Haemophilus ducreyi*. En 1996, BOWDEN *et al.* ont documenté l'efficacité de l'azithromycine dans la donovanose à la dose de 500 mg/j pendant 7 jours. Le succès du traitement minute est à notre connaissance inédit. Il pourrait, par sa simplicité, constituer une innovation thérapeutique dans la prise en charge de la donovanose.

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