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Examples of tropical disease control in the humanitarian medical programmes of MSF and Merlin [☆]

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Summary Humanitarian medical programmes in the tropics have the opportunity to provide beacons of good practice. The use of modern drugs and diagnostics, a lack of bureaucracy, adequate budgets, motivated staff and well-functioning supply lines all contribute to the success of this approach. At a joint meeting of the Royal Society of Tropical Medicine, the London School of Hygiene and Tropical Medicine, Médecins Sans Frontières and Merlin, new data were presented on the outcomes of recent humanitarian programmes to control malaria (Ethiopia), human African trypanosomiasis (south Sudan), Lassa fever (Sierra Leone) and tuberculosis (Tomsk, former USSR).
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1. Introduction

A meeting was convened to present examples of tropical infectious diseases control during humanitarian medical work. We hoped to show how, even in humanitarian crises and remote areas, patients can receive modern treatment with excellent outcomes.

2. Implementation of artemether—lumefantrine (Coartem®) combination treatment for falciparum malaria in Ethiopia

Manica Balasegaram
In Ethiopia in 2003, malaria accounted for 15% of outpatient consultations, 20% of hospital

admissions and 27% of inpatient deaths. Forty per-cent of Ethiopia is malaria-endemic; 60% of attacks are due to *Plasmodium falciparum* and 40% to *P. vivax* (WHO/UNICEF, 2003; WHO AFRO, 2003).

Within a few years of the introduction in 1999 of a national protocol using a combination of chloroquine (CQ) and sulfadoxine–pyrimethamine (SP), there were concerns over SP resistance. Dur-ing 2003, several outbreaks of malaria occurred, and Médecins Sans Frontières (MSF) strongly advo-cated the use of artemisinin combination treatment (ACT). By the end of 2003, the Ethiopian Federal Ministry of Health began conducting efficacy stud-ies on artemether–lumefantrine (Coartem®) and SP in several sentinel sites. These showed a 71.8% failure rate to SP after 28 days with no failures to artemether–lumefantrine (Federal Ministry of Health, Ethiopia, 2004a). This prompted a national workshop in May 2004 that led to a protocol change to the use of artemether–lumefantrine for the first-line treatment of *P. falciparum*, CQ for *P. vivax*, with quinine reserved for second-line use as well as all cases of *P. falciparum* during pregnancy (Federal Ministry of Health, Ethiopia, 2004b).

At the end of 2003, MSF implemented a malaria pilot programme, composed of four mobile teams consisting of two nurses and a health educator, each covering all 18 of the state health posts and clinics in Kafta Humera Woreda (Tigray), and two health facilities in the neighbouring Tach Amarcho Woreda (Amhara), as well as health posts on state and private farms. On our initial assessment, several problems were seen in the traditional diagnosis and treatment of cases. Foremost was lack of an effica-cious first-line treatment resulting in high levels of treatment failure (Figure 1). Cases were also mainly diagnosed by clinical features alone, resulting in gross over-diagnosis of malaria and inappropriate treatment. Finally, there was little patient infor-mation, or education on treatment and adherence. We therefore set up a programme to systematically meet each challenge. We began with health educa-tion (February 2004), training of staff (March 2004), data collection and monitoring (March 2004), imple-mentation of the Paracheck® rapid diagnostic test (RDT) (April 2004) and culminating in the introduc-tion of artemether–lumefantrine as first-line treat-ment for *P. falciparum* (September 2004). Data and performance was evaluated monthly. Over-all, malaria accounted for 38% of all consultations (Table 1).

There was a sharp rise in cases during the rainy season. Unusually, a large proportion of cases and a high percentage of positive RDTs were in peo-ple ≥5 years old. This reflects the high proportion of non-immune adult migrant workers, who often
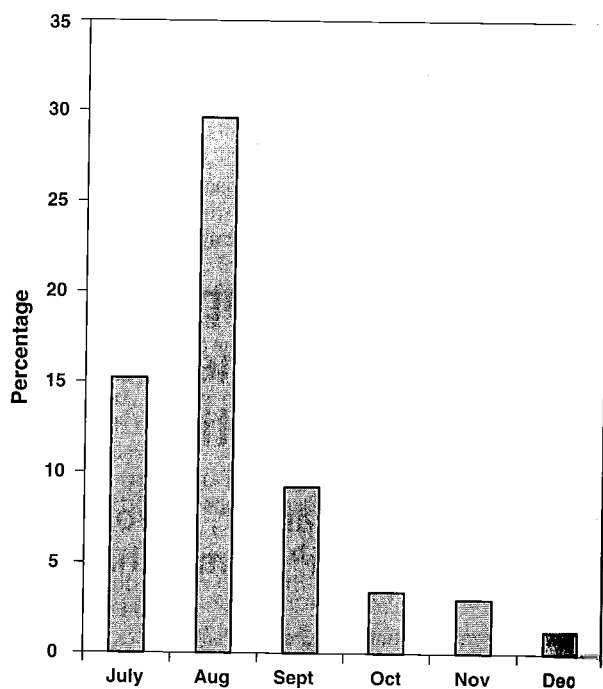

Figure 1 Percentage of *Plasmodium falciparum* cases requiring second-line or re-treatment in 2004.

sleep exposed to mosquitoes in the fields at night. Most cases treated for *P. falciparum* were con-firmed by a Paracheck® RDT. The choice to use this test was based on its low cost and its high sensi-tivity in detecting *P. falciparum*. It is our intention to change, when feasible, to a test that detects both *P. vivax* and *P. falciparum* (Guthmann et al., 2002; Mason et al., 2002). With the introduction of artemether–lumefantrine in September 2004, sus-tained effort was applied to minimize unsupported clinical diagnosis.

After the introduction of artemether–lume-fantrine, the numbers requiring second-line or re-treatment decreased substantially (Figure 1). This probably reflects the improved efficacy of artemether–lumefantrine, although further mon-itoring is needed to ensure continuation of this trend.

We estimate that by relying on RDT instead of clinical diagnosis for *P. falciparum*, ~19 000 treatments were avoided in September–December 2004. These were all patients that were clini-cally suspected of malaria but were RDT nega-tive. At a cost of US$2.40 per adult treatment of artemether–lumefantrine, this represented a sav-ing of around US$45 600 in drug costs. Given that 41 450 RDTs (at US$0.60 per test) were used over this same 4-month period, we estimate an over-all saving of around US$20 730 for this period (total saving = (2.40 × 19 000) − (41 450 × 0.60) = 20 730).

Table 1   Overall malaria primary health care data from Kafta Humera Woreda (all health facilities) and Tach Armacho Woreda (one health post and one clinic only), March—December 2004

	Age <5 years	Age ≥5 years	Total
Outpatient consultations	18 188	102 641	120 829
Paracheck® performed	4 939	42 230	47 169
Paracheck® positive (P. falciparum only)	1 361	18 111	19 472
% positive	28%	43%	41%
No. of blood films	813	3 251	4 064
Blood films positive for P. falciparum	175	732	907
Blood films positive for P. vivax	140	459	599
Diagnosed clinically with P. falciparum	434	2 948	3 382
Diagnosed clinically with P. vivax	2 757	19 796	22 553
Treated for P. falciparum with SP (first-line until September 2004)	421	3 982	4 403
Treated for P. falciparum with artemether—lumefantrine	1 211	15 363	16 574
Treated for P. falciparum with quinine	142	1 444	1 586
Pregnant women treated for P. falciparum with quinine	0	202	202
<5 kg babies treated for P. falciparum with quinine	58	0	58
Treated for P. falciparum with iv quinine	16	225	241
Treated for P. vivax with first-line chloroquine	2 995	20 456	23 451
Total number of malaria cases treated	4 843	41 672	46 515
Suspected malaria deaths in outpatients	0	16	16

The clinical diagnosis of P. vivax cases led to inevitable over-diagnosis. These cases were all treated with chloroquine.

Adherence was emphasized by health education on the need for adherence: the use of posters, flip charts and pamphlets in the local language; training of health workers including dispensers; direct observation of the first dose at the health post; and the use of blister packs for dosing patients according to weight group.

In November 2004, a survey of 175 patients randomly chosen from two health posts revealed that 98% of patients knew the cause of their initial illness as malaria and 99% received their first dose in the clinic. However, only 39% took their medication with food or milk; the remaining took their medication with water or tea. Ninety-five percent of patients were adherent or probably adherent. Only 5% were classed as definitely not adherent (tablets were seen remaining at pill count) (Dejene, 2004). The results of the survey reinforced the strategy undertaken as well as the need for continued health education to maximize adherence to treatment.

In conclusion, we found that artemether—lumefantrine was well accepted by health staff and efficiently implemented at Woreda level. Rapid diagnostic tests were also well accepted and proved to be of considerable value when used in conjunction with this treatment. MSF plans to continue RDT and artemether—lumefantrine supply in 2005.

Supervision will gradually be diminished over the year with the aim of eventual handover of the programme to the state Ministry of Health in 2006. We consider that a combined strategy of confirmed malaria diagnosis, effective treatment and patient education (especially on adherence) is essential to the successful implementation of ACT in the field.

3. Eflornithine treatment for sleeping sickness in southern Sudan

Manica Balasegaram, Peter Tinnemann

Trypanosoma brucei gambiense causes around 30 000 cases of human disease in foci in sub-Saharan Africa (TDR, 2003). Human African trypanosomiasis (HAT, sleeping sickness) has re-emerged as a serious health problem because of war-related constraints, which have prevented disease control. Angola, the Democratic Republic of Congo and south Sudan have suffered epidemic levels of the disease. Control of HAT relies primarily on active case finding followed by chemotherapy and is threatened by problems of drug resistance. MSF has been treating cases of HAT in northern Uganda and southern Sudan since 1986. Until recently, the treatment of the second (neurological) stage was melarsoprol. This drug has unacceptable side effects causing an acute reactive encephalopathy in 5—10% with a case fatality

rate of 10–70% (Cook and Zumla, 2003). From 1998, MSF clinicians faced a further therapeutic dilemma when treatment failure rates reached 20–30% in northern Uganda and southern Sudan (Matovu et al., 2001). Alternative regimens were limited because eflornithine, the only other drug used for the second stage of HAT, was withdrawn from production in the mid-1990s. Following strong advocacy by MSF and others, eflornithine production was restarted and made available for field use.

MSF implemented a new protocol for newly diagnosed second-stage HAT cases using eflornithine in November 2001 in Ibba, Western Equatoria, southern Sudan. Eflornithine 100 mg/kg i.v. four times a day (and 150 mg/kg four times a day in children <12 years) was administered for 14 days (Milord et al., 1992). Eflornithine was diluted in normal saline and infused over 2 h.

From January to June 2002, we treated 524 second-stage HAT patients with eflornithine. We could not maintain vigilance for leucopenia, a known hazard of eflornithine, because of our very limited laboratory facilities. We found eflornithine to be extremely well tolerated, with few significant clinical adverse events and treatment interruptions noted (Table 2). There were no significant differences between the two eflornithine dosages. High fever and convulsions were observed to be self-limiting, but did result in some deaths. Not all deaths occurred at the time of these events; in some cases these were attributable to advanced disease.

We noted the unexpected and frequent occurrence of pyomyositis. This infection occurred in eight patients, two of whom died. The initial sign was typically fever, followed by localized pain within a few days. Heat and swelling would then develop over the site, which could be anywhere in the limbs and trunk, and sometimes in multiple sites. It was rarely associated with localised phlebitis at the i.v. cannula sites, but we felt these to be the source of the infection. It was unknown whether an intrinsic property of the drug was a contributory factor, though peripheral white cell counts done on two affected patients were moderately raised. Patients generally responded well to i.v. cloxacillin, though some abscesses required surgical drainage. We introduced regular cannula monitoring and dressing, and changed cannulas every 48 h. In addition patient education on cannula care needed to be rigorously enforced. Lack of venous access proved to be a problem, particularly in children where it was the major cause of treatment interruption.

Our experience highlights some of the limitations of the use of eflornithine in field conditions. The drug is labour-intensive and complicated to administer. It also requires i.v. fluids, drip sets and cannulas, which results in additional logistic requirements and hidden costs. Furthermore, its efficacy in HIV co-infected patients remains in question. Also uncertain is its continued production after 2006. These drawbacks are set against the greatly reduced case fatality rate (1.5%). In addition, eflornithine used over 2 years was followed by a relapse

Table 2 Clinical adverse event profile of eflornithine (all adverse events are included), Ibba sleeping sickness project, southern Sudan, January–June 2002

Adverse event	Eflornithine 400 mg/kg (n = 456)			Eflornithine 600 mg/kg (n = 68)			Total (n = 524)
	No. affected	Treatment interrupted	Died	No. affected	Treatment interrupted	Died	
Fever	68 (15%)	2	1	10 (15%)	2	0	78
Tremor	32 (7%)	0	0	2 (3%)	0	0	34
Convulsion	18 (2%)	11	2	3 (4%)	2	1	21
Bleeding	5 (1%)	2	0	2 (3%)	0	0	7
Pyomyositis	7 (2%)	4	2	1 (1%)	0	0	8
Chest pain	16 (4%)	0	1	8 (12%)	0	0	24
Abdominal pain	81 (18%)	0	0	11 (16%)	0	0	92
Vomiting	56 (12%)	1	0	9 (13%)	0	0	65
Diarrhoea	107 (23%)	1	0	17 (25%)	1	1	124
Dizziness	6 (1%)	0	0	0 (0%)	0	0	6
Mouth ulcers	6 (1%)	0	0	2 (3%)	0	0	8
No i.v. access	2 (<1%)	2	0	4 (6%)	4	0	6
Wheeze	1 (<1%)	0	0	0 (0%)	0	0	1
Confusion	1 (<1%)	0	0	0 (0%)	0	0	1
Total (%)	406	23 (5%)	6 (1.3%)	69	9 (13%)	2 (2.9%)	475

rate of ~6.8%, far lower than the rate of 30% previously seen with melarsoprol (G. Priotto, personal communication, 2005).

4. Lassa fever control in Sierra Leone

Peter Tinnemann

Highly contagious diseases with high mortality are a constant major threat to public health. When no specific treatments are available, priority must be given to education of medical staff and to prevention of nosocomial transmission by using meticulous barrier nursing techniques. Lassa fever is a viral haemorrhagic fever (VHF) transmitted by the infected rodent *Mastomys natelensis*, but human-to-human transmission does occur. Outbreaks have been reported from Nigeria, Sierra Leone, Liberia and Guinea, and serological evidence has been found in the Democratic Republic of Congo, Central African Republic, Mali and Senegal. An estimated 5000–300 000 people die annually of Lassa fever and ~2 million people are at risk of infection. Over the course of the disease patients display a diverse clinical picture, and the differential diagnosis includes severe malaria, sepsis and other VHFs (Richmond and Baglole, 2003).

Special high-containment facilities and laboratories are needed for Lassa fever patients, since the virus requires the highest level of biosafety. Infected patients are treated with ribavirin i.v. for 10 days (loading dose: 30 mg/kg; days 1–4: 15 mg/kg four times/day; days 5–10: 7.5 mg/kg three times/day). Supportive measures include antipyretics/analgesics, nasal oxygen, generous fluid replacement, frequently blood transfusions — anaemia is caused by bleeding and haemolysis due to ribavirin treatment. Aspirin and i.m. injections should be avoided to prevent bleeding.

Strict barrier isolation of cases is essential to prevent transmission of the virus to others. Most human-to-human transmission occurs in hospital settings. In the absence of an effective vaccine, individuals exposed to Lassa fever patients should be considered for prophylactic treatment with ribavirin.

Our Lassa fever treatment and control activities began in 1996 when a CDC (Center for Disease Control, Atlanta, USA) research and treatment facility was handed over to Merlin, who provided medical supplies and staff. A high standard of clinical care on the Lassa fever ward, backed up by a laboratory service, was provided in Kenema
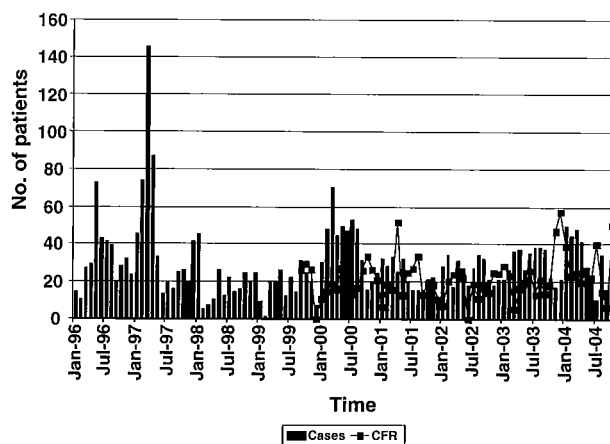

Figure 2 Number of Lassa fever cases (*n* = 3054) admitted to Kenema Lassa Fever ward (January 1996–October 2004). CFR: case fatality ratio.

town, Sierra Leone. In the district, our activities were health education, surveillance and contact tracing.

Running a VHF treatment unit in an isolated rural African setting requires intensive staff support (including training and supervision) and logistics. Doctors and nurses in the endemic areas are at high risk of acquiring Lassa fever through patient contact, as are midwives treating cases of spontaneous abortion. Moreover, fears and cultural attitudes of patients, their relatives and medical staff stigmatize everybody involved with the Lassa fever project and create issues impacting on the project.

A senior medical doctor who had been involved for years with the Lassa fever project died after a needle stick injury infected him with the Lassa fever virus. He did not consider it necessary to treat himself with ribavirin believing that he had acquired sufficient immunity against the disease. Senior nursing staff caring for him did not apply strict barrier nursing procedures since they did not want to suggest to him that he was seriously ill. The senior nurse caring for the doctor also became infected, but did survive.

From January 2000 to September 2004, 1700 patients were admitted, of whom 348 (20.4%) died (Figure 2). Fewer patients were admitted to the ward when the political or military situation in Sierra Leone deteriorated, e.g. a coup in Freetown (May 1997), heavy fighting in Freetown (February 1998) and rebel capture of Freetown (January 1999). Conversely, higher numbers of patients were recorded immediately after the medical team could resume their work. Patients infected with Lassa fever in Sierra Leone had great difficulty accessing treatment during times of political or

military turmoil. Additionally, during these times active case tracing, surveillance activities and rodent control efforts broke down, increasing the risk of infection for residents. From January 2001 onwards, the political situation in Sierra Leone stabilized and so did the number of patients admitted monthly to the ward.

During the 8 years when Merlin implemented Lassa fever control, major outbreaks were averted and, importantly, 3054 of patients with Lassa fever were treated on the Lassa fever ward. Additionally, local and international expertise was combined and enhanced.

Merlin's funding for Lassa fever control from international donor agencies ended in December 2004 and all activities of the organization were handed over to the Sierra Leonean Ministry of Health. A lack of interest and expertise within the Sierra Leonean medical community, and lack of funding within the Ministry of Health for the continuation of Lassa fever control efforts, make the maintenance of the programme uncertain. Further research should be conducted to compare cost-effectiveness of ongoing Lassa fever control efforts in an endemic area versus high profile intervention during epidemic outbreaks.

5. Tuberculosis control in Tomsk

Samantha Perkins

Humanitarian relief contexts by their nature are characterized by displacement, stress (emotional and physical), chaos and insecurity. There has been much debate within MSF and Merlin as to whether tuberculosis (TB) treatment programmes should be a priority in such settings, given the need for a stable environment for both patient and health services for successful treatment and control. Both MSF and Merlin have embarked on TB programmes, including some in areas of chronic instability, and the results are, so far, very encouraging.

Incidence rates of TB in Russia continued to decline from the 1970s until the early 1990s (approximately 35 per 100 000 in 1992). Separately funded vertical TB services undertook active case finding through annual mass miniature chest X-ray screening of the whole population, and BCG vaccination of all children at birth. Treatment involved prolonged periods of hospitalization (up to 2 years) and individualized treatment regimens for identified cases.

Following the collapse of the Soviet Union and the subsequent breakdown in infrastructure and deterioration in socio-economic conditions, TB notification rates have begun to increase, and incidence rates in Tomsk (excluding the penitentiary system) were estimated to be ~80 per 100 000 population by 1997, vs. ~73 per 100 000 throughout Russia. Latest WHO estimates indicate an incidence rate for all cases in Russia (new and re-treatment) of 126 per 100 000 population (WHO, 1998, 2004).

Tuberculosis rates in prisons can be up to 70 times higher than in the community, although direct comparisons are not always possible due to differences in data collection and analysis. Significantly higher numbers of cases in the prisons do, however, reflect the size of the incarcerated population, large flows of inmates in and out of the system and the resultant lack of continuity of TB treatment in the community, and problems with overcrowding and poor nutrition in this setting.

Merlin, together with national and international partners began a TB control project in Tomsk Oblast, western Siberia, in 1996, based on the WHO DOTS (directly observed therapy, short-course) strategy. At the beginning of the project, clinical trials were undertaken to identify whether there were advantages to a DOTS based approach over traditional Russian methods. Interestingly, this study (Mawer et al., 2001) found no significant difference between the two approaches in cure rate, treatment rates or smear conversion rates at 6 months, although it did demonstrate that DOTS based programmes were applicable in this setting. A further cost-effectiveness study (Jacobs et al., 2002), indicated that a DOTS based approach could be up to 2.8 times cheaper to implement. As a result of these findings a modified DOTS programme, incorporating some of the Russian methods, was introduced throughout the region.

Key project activities included:

- passive case finding, with the exception of identified risk groups
- sputum smear microscopy and culture of all specimens
- standardized short-course chemotherapy based on WHO treatment regimens, delivered entirely on an outpatient basis in over 50% of cases by 2002
- fully integrated programme between community and penitentiary TB services
- incentives and social support for the most vulnerable patients
- development of the DOTS-Plus programme for the treatment of multidrug-resistant TB (MDR TB — i.e. resistance to at least isoniazid and rifampicin).

Following the implementation of the modified DOTS programme in Tomsk in 1997/1998 and the

Table 3 Outcomes of tuberculosis treatment in the Merlin/Tomsk Oblast TB Services

	Cure rates — all cases (%)	Treatment failure (%)	Mortality (%)	Default (%)
1997	68	6	11	6.2
1998	69	6.5	9	5
1999	78	7	5	2

introduction of standardized treatment regimens, cure rates for all cases including those with initial drug resistance, showed a gradual increase to 1999 to 78%. The cure rate of fully sensitive TB cases was 82% in 1999. Treatment failure in new cases showed a slight increase between 1997 to 1999, indicating ongoing transmission of primary drug resistance, and probable amplification of primary resistance (i.e. as a result of the use of standard regimens to which the patient was already partially resistant) (Table 3). Mortality and default rates continued to decline in new patients during this period, through a combination of improved case finding, case management and patient compliance (including through the use of patient incentives, and the provision of more patient-centred services).

Resistance to all four first-line drugs decreased from 48% to 35% in new patients from 1999 to 2000, with MDR TB rates decreasing from 12% to 10% in the same time period (which while not statistically validated indicates an encouraging trend in this cohort). Almost all rifampicin resistance was found to be in combination with resistance to isoniazid amongst new patients (i.e. as MDR TB), while resistance to streptomycin, either alone or in combination with isoniazid was common. If streptomycin resistance was discounted in 2000, total resistance would have been below 20%.

Meanwhile, MDR TB in all cases (new, relapsed and re-treatment) rose steadily from 6 to 12% between 1997 and 2000; this is attributed in part to a significant number of patients being 'transferred in' from the penitentiary system, along with an ongoing amplification of resistance in relapsed and previously treated patients.

These findings highlight the importance of rapid case finding, standardized treatment (backed up by timely drug sensitivity testing, to allow for appropriate changes in treatment regimens in patients found to have primary drug resistance) and good patient compliance in any setting if TB is to be controlled. Given the complexity and constraints found in humanitarian relief settings, the ability to provide full and consistent treatment and patient-centred support throughout must be assured if TB control is to be effectively achieved.

6. Conclusions

Our experience shows that treating tropical diseases in remote settings and during political or military insecurity does not mean that simple, failing or old-fashioned regimens should be used. On the contrary, excellent results are obtained when modern approaches are used in a motivated and well-supported programme.

Conflicts of interest statement
None of the authors have any financial or other conflict of interests concerning the work reported in this paper.

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