Articles

# Public health impact of Rwandan refugee crisis: what happened in Goma, Zaire, in July, 1994?

*Goma Epidemiology Group**


## Summary

The flight of 500 000–800 000 Rwandan refugees into the North Kivu region of Zaire in July, 1994, overwhelmed the world's response capacity.

During the first month after the influx, almost 50 000 refugees died, an average crude mortality rate of 20–35 per 10 000 per day. This death rate was associated with explosive epidemics of diarrhoeal disease caused by *Vibrio cholerae* O1 and *Shigella dysenteriae* type 1. 3–4 weeks after the influx of refugees, acute malnutrition rates among children under 5 years old ranged between 18 and 23%. Children with a recent history of dysentery and those in households headed by women were at higher risk of malnutrition. A well-coordinated relief programme, based on rapidly acquired health data and effective interventions, was associated with a steep decline in death rates to 5 to 8 per 10 000 per day by the second month of the crisis.

The prevention of high mortality due to diarrhoeal disease epidemics in displaced populations relies primarily on the prompt provision of adequate quantities of disinfected water, basic sanitation, community outreach, and effective case management of ill patients. In the emergency phase, effective, low-technology measures include bucket chlorination at untreated water sources, designated defaecation areas, active case-finding through community outreach, and oral rehydration. Relief agencies must place increased emphasis on training personnel in relevant skills to address major public health emergencies caused by population displacement.


*Lancet* 1995; **345:** 339–44

## Introduction

In April, 1994, the presidents of Burundi and Rwanda were killed in an airplane crash near the Rwandan capital, Kigali. Civil disturbance throughout Rwanda followed, resulting in the deaths of between 500 000 and 1000 000 civilians, mostly ethnic Tutsis. In July, the Tutsi-dominated Rwandan Patriotic Front defeated government forces and established a new national government. Between July 14 and 17, large numbers of ethnic Hutus fled Rwanda and sought refuge in the North Kivu region of neighbouring Zaire; initial estimates were as high as 1·2 million. Many refugees entered through the town of Goma, at the northern end of Lake Kivu, and others crossed the border and settled in the vicinity of Kibumba camp (figure 1). During subsequent weeks, thousands of refugees died in the streets of Goma. Most of those who survived moved out of the town to camps at Munigi, Kibumba, Katale, and Mugunga. In early August, Munigi was closed and its residents relocated in the other three camps. Unknown numbers of refugees settled in smaller groups to the north of Katale, to the west of Mugunga, and in the town of Goma.

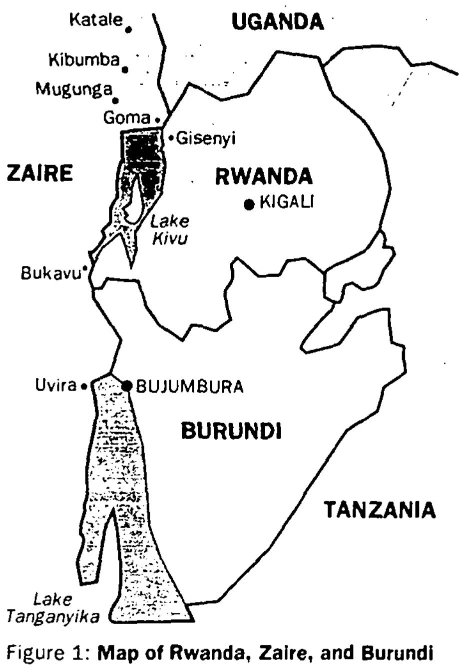


Figure 1: **Map of Rwanda, Zaire, and Burundi**

Refugee assistance was provided by several United Nations agencies, non-governmental relief organisations, and military forces, and was coordinated by the Office of the United Nations High Commissioner for Refugees (UNHCR). The arrival of such an enormous number of dependent refugees during a short period overwhelmed the capacity of the host government and relief organisations already present. We summarise the public

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health consequences of this influx of refugees during the month after their arrival.

## Methods

### *Mortality surveillance*

Mortality rates were calculated from daily counts of the number of bodies collected and estimates of the refugee population. Because the ground in the area where most refugees were located is hard volcanic rock, graves cannot readily be dug and most bodies were left beside roads and in other public places, to be picked up later by trucks for burial in mass graves. Information on mortality was based on records maintained by the agencies that supplied the trucks; body tallies were reported to UNHCR daily. During the week of July 18–25, when the truck collection system was first established, several agencies reported that their workers may have been exaggerating the body counts because of the misconception that payment was related to the number of bodies collected. Body counts from this period have been adjusted downward by as much as 40% by comparing truck collection figures on certain days with burial figures collected by the French army on the same days. The problem of over-reporting was resolved by UNHCR on July 26, and figures after this date are thought to be reliable. Where possible, mortality data were also collected from health facilities and centres caring for unaccompanied children.

### *Morbidity surveillance*

After the onset of the cholera outbreak in Goma, a surveillance system was established in which cases and deaths associated with diarrhoeal disease were reported daily from most clinics and hospitals in Goma and the camps. Initially, the reporting system did not differentiate between cholera, dysentery, and non-specific dehydration. Laboratory support was provided locally by French (Bioforce) and Israeli military forces, and by reference laboratories in France and the Netherlands. From July 31, cases of watery diarrhoea and bloody diarrhoea were reported separately.

In early August, a more comprehensive morbidity surveillance system was established, covering all health facilities in the three main camps and in the town of Goma. Cases of watery diarrhoea, bloody diarrhoea, measles, meningitis, acute respiratory infections, malaria (or unexplained fever), and other conditions were recorded daily on a standard data form. Illness was classified according to clinical case definitions supplied by UNHCR. Surveillance data were reported weekly to UNHCR, which compiled, analysed, and disseminated the information in a bulletin. Any suspected case of meningitis was reported immediately to UNHCR and cerebrospinal fluid samples were sent to the military laboratories in Goma for bacterial culture and antigen detection tests.

### *Population surveys*

Between Aug 4 and 14, three cluster-sample surveys were done, in the Katale, Kibumba, and Mugunga camps. Each camp was mapped and divided into segments based on size and population density. Thirty clusters were allocated to each camp; the proportion assigned to each segment was based on the estimated population. In each cluster, twenty households were sampled randomly to ascertain how many members had died since arrival in Zaire. Household members who were missing and unaccounted for were not counted as deaths. In addition, 20 children aged between 6 and 59 months (or <110 cm tall) were sampled randomly in each cluster, weighed on Salter scales, and measured on standard height-measuring boards. Children smaller than 85 cm were measured while supine; taller children were measured standing. The weight-for-height index of each child was compared with a standard reference population.[1]

Additional information gathered by some or all surveys included probable cause of death, adequacy of shelter, presence or absence of adult men in the household, access to distributed food rations and local markets, size of household food reserves, history of diarrhoeal disease, and access to health care. Survey data from each of the three camps were analysed separately.

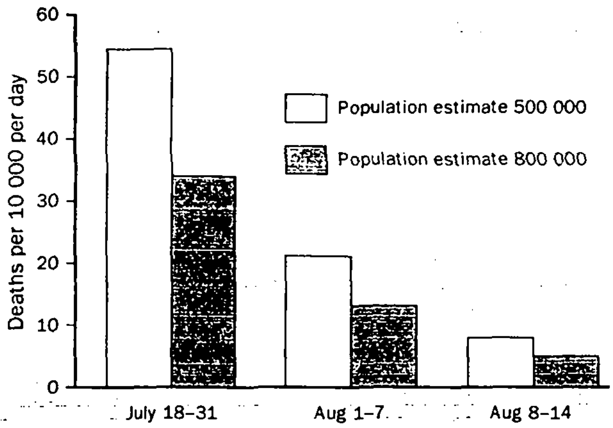


Figure 2: **CMR estimates for Rwandan refugee population**

## Results

### *Mortality*

48 347 bodies were collected by the trucks between July 14 and Aug 14. This figure represents a minimum estimate for mortality in this population because an unknown, though probably small, number of refugees who died during the first few weeks were buried privately and, therefore, were not counted by the body collection system. The estimation of mortality rates was complicated by the lack of a reliable total population figure for refugees in the Goma area, since no census or registration procedure was done. Although early estimates put the total number of refugees at more than a million, later population estimates ranged between 500 000 and 800 000, based on water and food ration distribution figures and on mapping exercises by relief agencies.

The average crude mortality rate (CMR) from July 14 to Aug 14 was between 19·5 and 31·2 per 10 000 per day, based on population estimates of 800 000 and 500 000, respectively. Even if the population estimate of 1·2 million were used, the average CMR would have been 13·0 per 10 000. By comparison, the baseline, pre-war CMR in Rwanda was about 0·6 per 10 000 per day.[2] An overall mortality rate was calculated for the period July 14–31 because many bodies were left uncollected during the early days of the emergency and not counted until later. During this period, the average CMR was between 28·1 and 44·9 per 10 000 per day; by the week of Aug 8–14, it had fallen to less than 10·0 per 10 000 per day (figure 2).

Mortality reporting systems were unable to distinguish between age groups. However, unaccompanied children, a particularly high-risk group of more than 10 000, had extremely high death rates. Between July 23 and Aug 12, for example, the CMR in some centres for unaccompanied children ranged between 20 and 120 per

| | Survey period (July 14 to:) | Estimated population (×10³) | CMR (per 10 000 per day) | % population dying during period (95% CI) |
|---|---|---|---|---|
| Katale survey | Aug 4 | 80 | 41·3 | 8·3 (7·1–9·5) |
| Kibumba survey | Aug 9 | 180 | 28·1 | 7·3 (6·2–8·4) |
| Mugunga survey | Aug 13 | 150 | 29·4 | 9·1 (7·9–10·3) |
| Body count (all areas) | Aug 14 | 500/800 | 31·2/19·5 | 9·7/6·0 |

Table 1: **Comparison of CMR estimates derived from body count and from population surveys**

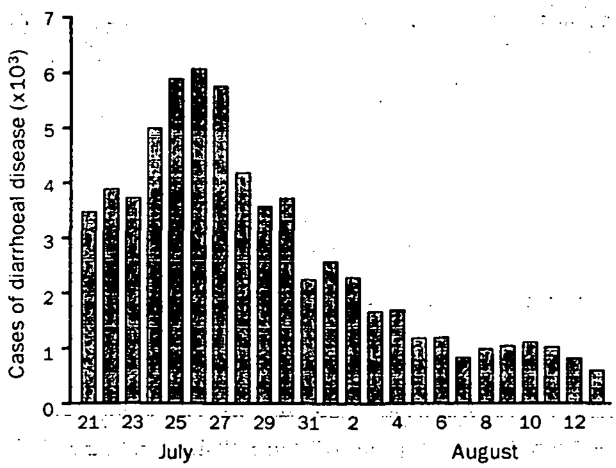


Figure 3: **Reported cases of diarrhoeal disease (cholera, dysentery, and dehydration)**

10 000 per day. Among unaccompanied infants, average daily death rates ranged from 100 to 800 per 10 000.

Population surveys in Katale, Kibumba, and Mugunga allowed us to estimate the proportion of the population who died between the time of the influx and the date of the surveys (table 1). The estimates correspond to average daily CMRs consistent with those derived from body counts (table 1). According to the surveys, 85–90% of deaths reported by household respondents were associated with diarrhoeal disease. In most refugee emergencies, death rates are several times higher among children under 5 years old than in older age groups.[3] However, the Katale survey reported that 8·0% (5·2–10·8) of children under 5 years died during the 20-day recall period, compared with 8·4% (7·1–9·7) of people over 5 years, which suggests that diarrhoeal diseases equally affected all age groups.[4]

*Morbidity*

Following the diagnosis of the first case of cholera on July 20, there was a massive increase in diarrhoeal disease, reaching a peak of more than 6000 cases reported on July 26 (figure 3). Laboratories isolated *Vibrio cholerae* O1, biotype El Tor, serotype Ogawa, which was resistant to tetracycline and doxycycline but sensitive to furazolidone and ciprofloxacin.

The total number of cases of cholera, including those who did not present to clinics, was approximated so that the overall cholera attack rate could be calculated. Between July 14 and Aug 12, more than 62 000 cases of diarrhoeal disease were reported from health facilities. If we assume that 57% of these cases were cholera (the Mugunga survey found that 57% of diarrhoeal deaths were due to watery diarrhoea), about 35 500 (57% of 62 000) patients with cholera presented to health facilities (assuming that the case-fatality rates for cholera and dysentery were approximately equal). Estimation of the number of cholera cases never seen at health facilities is more difficult. According to the Mugunga survey, about 88% (41 800) of the 47 500 deaths during this period were associated with diarrhoeal disease, and 57% of diarrhoeal deaths (23 800) were due to cholera. Of the 23 800 people who died of cholera, 47% (11 200) had never sought health care. If we assume, from anecdotal information, that the cholera case-fatality rate among people who never received medical attention was between 25% and 50%, a further 22 400 to 44 800 cases of cholera could have occurred among patients who never presented at health facilities. Overall, therefore, we estimate that between 58 000 and 80 000 cases of cholera occurred in the first month after the influx, giving an attack rate between 7·3% (58 000 cases in 800 000 refugees) and 16·0% (80 000 cases in 500 000 refugees).

The centre of the cholera outbreak was probably Goma town. 57% of all cases of diarrhoeal disease between July 21 and 27 were reported in health facilities in Goma, and a further 21% were reported from Munigi camp, only 10 km away. Nevertheless, the lack of geographically precise population figures during this period precludes any comparison of incidence rates in different locations. According to surveillance reports, the case-fatality rate among patients with diarrhoea seen in clinics reached as high as 22% on July 23 (when most cases were probably cholera), decreasing to 3–5% between July 27 and Aug 12. The case-fatality rate for treated diarrhoea and dysentery was 6·7% between July 21 and Aug 12. WHO suggests that the cholera case-fatality rate should be as low as 1%; however, in most cholera epidemics in refugee camps during the past 10 years, case-fatality rates have been between 2 and 3%.[3,5] Since the early surveillance system did not differentiate between bloody and non-bloody diarrhoea and since most deaths occurred outside health facilities, it is not possible to estimate the overall cholera-specific case-fatality rate in this epidemic.

Bloody diarrhoea surpassed watery diarrhoea in terms of number of reported cases by July 31 in Mugunga, Aug 2 in Kibumba, and Aug 4 in Goma and Katale. Laboratories identified *Shigella dysenteriae* type 1 as the causative organism; the strain was resistant to most commonly used antibiotics, including nalidixic acid, but sensitive to ciprofloxacin. The UNHCR morbidity surveillance system reported 15 543 cases of dysentery between Aug 8 and 14, a weekly incidence rate of 2–3%, twice the rate of watery diarrhoea reported during the same period. The case definition for dysentery was clinical; since blood in the stool may not have been verified for all patients, there may have been over-reporting of this disorder. According to the Mugunga survey, almost 40% of all deaths during the first month after the influx were associated with bloody diarrhoea.

Between Aug 1 and 16, 162 patients with suspected meningitis were detected by the surveillance system; 83 (52%) were confirmed as having meningitis caused by *Neisseria meningitidis*, group A, sensitive to penicillin and chloramphenicol. To decide whether to proceed with mass immunisation, a threshold incidence rate of 15 cases per 100 000 per week in a camp was established as predictive of a meningitis outbreak.[6] In Kibumba camp, 4 cases were reported during the first week of surveillance, followed by 34 cases during the second week (weekly incidence rate 19 per 100 000). Consequently, mass immunisation against meningococcal meningitis was instituted in this camp.

*Nutritional status*

The three population surveys between Aug 4 and 14 showed that 18–23% of children aged 6–59 months had acute protein-energy malnutrition (table 2). The prevalence in non-refugee populations in Africa is normally between 5 and 8%.[3] Both of the surveys that carried out the analysis found a significantly higher prevalence of acute malnutrition among children in

| Camp | Date | Sample size | Percentage of children | | Overall percent with malnutrition (95% CI) |
|---|---|---|---|---|---|
| | | | Moderate malnutrition | Severe malnutrition | |
| Katale | Aug 4 | 567 | 16·6 | 6·5 | 23·1 (18·3–28·7) |
| Kibumba | Aug 9 | 694 | 17·1 | 3·0 | 20·1 (16·1–25·0) |
| Mugunga | Aug 13 | 723 | 14·4 | 3·3 | 17·7 (15·0–21·0) |

Moderate malnutrition=weight-for-height *z* score less than −2 but more than −3 (between 2 and 3 standard deviations below reference population mean); severe malnutrition=weight-for-height *z* score less than −3 or oedema.

Table 2: **Frequency of acute malnutrition according to population surveys in children 6–59 months**

female-headed households (without at least one man 18 years or older). In Mugunga, the only survey that asked about a history of diarrhoeal disease, 36% of children who had had dysentery during the 3 days preceding the survey were acutely malnourished, compared with 12% of children with no recent history of dysentery (relative risk 2·89 [95% CI 2·16–3·86]). All three surveys found that more than 25% of households did not have adequate water-resistant shelter. The Mugunga survey found that significantly fewer female-headed households than households headed by men reported having received food rations.

## Discussion

The data gathered during the month after the influx of Rwandan refugees into Zaire describe a public health disaster of major proportions. Although early surveillance data on diarrhoeal cases and deaths varied in quality and how representative they were, three rapid population surveys collected comparable data by similar methods and provided consistent information on mortality, nutrition, and programme indicators. By early August, a standardised surveillance system was established, allowing relief agencies to monitor disease trends, reassess priorities, and evaluate the effectiveness of interventions. This combination of rapid surveys and standardised surveillance needs to be a routine element of emergency relief programmes.

Between 6 and 10% of the refugee population died during the month after arrival in Zaire, a death rate two to three times the highest previously reported rates among refugees in Thailand (1979), Somalia (1980), and Sudan (1985).[3] This high mortality was due almost entirely to the epidemic of diarrhoeal diseases. Epidemics of diarrhoea and dysentery have caused high rates of morbidity and mortality in several refugee and displaced populations lately—among Kurdish refugees in 1991,[7] displaced Somalis in 1992,[8] and Burundian refugees in Rwanda in 1993.[9] Long-term solutions require time and resources, but the excess mortality associated with diarrhoeal disease outbreaks may be mitigated by prompt implementation of several effective measures that depend more on human than technological resources. These measures include the organisation of chlorination brigades at untreated water sources, the designation of physically isolated defaecation fields, community outreach to identify and treat patients outside of clinics, and oral rehydration therapy. In addition, greater emphasis needs to be placed on education about personal hygiene and the provision of soap.

After the July 14 influx into Goma, many of the refugees were located near a large body of water, Lake Kivu; however, at the time there was no available way to purify and transport sufficient quantities of water. Efforts were made by some agencies to chlorinate water in containers as refugees removed it from the lake, but coverage was inadequate and most refugees consumed untreated water. The diarrhoea epidemic had already peaked before July 29, when the relief operation was able to provide an average of only 1 L purified water per person per day. UNHCR recommends a minimum of 15–20 L water per person per day.[10]

At least 58 000 cases of symptomatic cholera occurred in this population. Given the usual high ratio of symptomless to symptomatic infections (up to 10 to 1), it is likely that most refugees in the Goma area were infected with *V cholerae* O1, and that few infections were prevented.[11] The speed of transmission and the high clinical attack rate of cholera in Goma were related to the common practice of drinking untreated lake water (the likely common source of infection), crowding, poor personal hygiene, and the debilitation of this refugee population. Once significant numbers of refugees had been infected by drinking lake water, it is likely that there was substantial secondary contamination of other water sources and storage containers in the area. This situation was exacerbated by inadequate sanitation, due in part to the rocky, volcanic nature of the soil in the Goma area, which made digging latrines almost impossible.

Mass vaccination would not have altered the course of this cholera epidemic.[12] Of the two newer and potentially effective vaccines available, one requires two doses and does not induce immunity until 7–10 days after the second dose. The other, a single-dose, oral, live vaccine, has not been subjected to testing under field conditions and its use in refugee populations would be questionable. In any event, it is unlikely that the vaccine could have been given rapidly enough to affect the progression of the epidemic. Vaccination teams of 8–10 people managed to immunise up to 5000 refugees per day with oral poliomyelitis vaccine in Kibumba camp. Therefore, to vaccinate the whole population of between 500 000 and 800 000 refugees with a single-dose oral cholera vaccine would have taken 80–100 health-care workers 10–16 days. Clearly, by the time vaccine could have been obtained, administered, and provided immunity, the epidemic would have already run its course.

The diarrhoeal disease case-fatality rate early in the epidemic was extremely high, reaching 22% on July 23. The relatively few health-workers on the scene early in the epidemic were overwhelmed by the patient load and had inadequate therapeutic resources. However, by the 6th day of the epidemic (July 26), the efforts of medical workers had had a pronounced impact and the case-fatality rate among patients treated in clinics had decreased to 4%. It seems that the high death rate during this epidemic was due largely to the inability of many refugees to reach health facilities. Outreach programmes to identify sick patients promptly and to initiate early treatment were not launched until the second week of the epidemic.

Even when the number of agencies and relief workers increased substantially at the end of July, there was substantial variation among health-workers in the level of expertise in rehydration. Skills in effective oral rehydration are still rare among physicians and nurses trained in western-style medical practice. There is an urgent need for more intensive and focused training of relief workers to develop relevant expertise in the prevention and management of diarrhoeal diseases, as well as other essential elements of relief programmes, such as measles immunisation, public-health surveillance, community outreach, and nutritional rehabilitation.

The cholera outbreak was quickly followed by a lethal outbreak of bacillary dysentery. Earlier studies in Burundi, Rwanda, and Tanzania showed that epidemic dysentery in that region is predominantly caused by *S dysenteriae* type 1.[9,13] In addition, these studies had alerted the public-health community to a trend of rapidly increasing antibiotic resistance. In Goma, after laboratory confirmation of shigella resistance to nalidixic acid, an expert committee was formed to consider treatment options. After comparing the risks of untreated shigellosis and the risks of treating large numbers of patients (including young children, for whom there are theoretical risks from fluoroquinolones), the committee decided to advocate a policy of carefully monitored treatment with ciprofloxacin for certain high-risk groups, including children under 5 years, pregnant women, people older than 55 years, and patients with severe illness. There is a need for operational research to develop more effective prevention and case-management strategies for this disorder.

By the third week of the influx, the international community's response began to have a significant impact. Routine refugee relief measures such as measles immunisation, vitamin A supplementation, standard disease treatment protocols, and community outreach programmes were established in each camp, and the water distribution system provided an average of 5–10 L per person per day. A consensus was quickly reached on standard information gathering, and a high level of cooperation and coordination of public health programmes was achieved, under the leadership of UNHCR.

The prevalence of acute malnutrition among children was probably related to the high incidence of diarrhoeal diseases and to the food distribution system, which was controlled by Rwandan political leaders and was unable to distribute food rations directly to refugee families. Children in households headed by women were at high risk of malnutrition. The survey findings led to recommendations for supplementary and therapeutic feeding programmmes, systematic registration of refugees, and changes in distribution procedures to allow for more equitable access to relief food. However, changes in the food distribution procedure were dificult to implement because of the insecure situation in the camps and resistance by former Rwandan political and military leaders who exercised stringent control over the refugee population. Lack of security has been a feature of several recent refugee operations; therefore, effective means of preventing the misuse of relief items need to be developed by the international community.

The high mortality rates experienced by Rwandan refugees in eastern Zaire were almost unprecedented in refugee populations, and the world must take note of the lessons from this disaster. The immediate, medical cause of most deaths was diarrhoeal disease, but the underlying causes were the historical, ethnic, demographic, socioeconomic, and political factors that led to the collapse of Rwandan society and to this mass population migration.[14] Correspondents to *The Lancet* have pointed out that extensive information on the deteriorating conditions in Rwanda had been published during the past 20 years.[15] However, the international community has been unable to develop effective strategies to prevent the collapse of small, vulnerable countries such as Rwanda, Liberia, and Somalia. The observations of early warning information systems, where they exist, are often ignored, especially if the immediate political interests of wealthy nations are not threatened.

Although generally proven interventions against diarrhoeal disease were eventually implemented in Goma, they were insufficient in relation to the scale of the disaster. The world was simply not prepared for an emergency of this magnitude. The leaders of wealthy nations tend to wait until public opinion forces them to respond to disasters with enormous resource infusions. Although this delayed response has included the deployment of military forces with their formidable logistic capability, the mobilisation of military resources is very expensive. Because military deployment depends on political decisions, it cannot always be integrated into disaster preparedness planning. Therefore, while continuing to explore ways of improving the efficiency and cost-effectiveness of the military role in emergency relief, donor nations would be wise to invest funds in strengthening the existing network of relief organisations. These agencies need resources to implement early warning systems, maintain technical expertise, train staff, build reserves of relief supplies, and develop their logistic capacity. Unless global action is taken urgently to improve the state of emergency preparedness, there will be more public health disasters like the one we have described in Goma.

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*Acknowledgments*
We thank all those who helped in the collection of the data on which this article was based, including Zaire Ministry of Health officials, non-governmental organisation staff, and refugees, and the staff of the Goma office of UNHCR, especially Claire Bourgeois and Patricia Kormoss, the medical and nutrition coordinators.

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# Effects of pulsed β-stimulant therapy on β-adrenoceptors and chronotropic responsiveness in chronic heart failure

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## Summary

In animals, intermittent sympathomimetic stimulation with dobutamine produces benefits analogous to those of physical conditioning. Longer intermittent or continuous β-stimulant therapies have not, however, been successful in managing patients with chronic heart failure. We have investigated the role of β-receptor stimulants in patients with severe chronic heart failure by changing the method of administration to intermittent, very short-duration pulsed intrope therapy (PIT).

We studied 10 patients (mean age 64 [SE 2] years) with stable moderate to severe chronic heart failure (ejection fraction 23 [3]%) who received PIT, and 10 control patients matched for age and severity. We infused sufficient dobutamine to raise heart rate to 70–80% maximum for 30 min per day, 4 days per week for 3 weeks. PIT increased exercise tolerance (from 10·4 [1·2] min at baseline to 13·0 [1·5] min at 3 weeks; $p<0{\cdot}001$, 95% CI for difference 1·6 to 3·9) and lowered peripheral vascular resistance (19·8 [3·1] to 17·7 [2·4] mm Hg.min.L$^{-1}$; $p<0{\cdot}05$, −4·1 to −0·1). PIT produced significant increases in lymphocyte β-receptor density (502 [110] to 1200 [219] per cell, $p<0{\cdot}02$, 258 to 1138) and chronotropic responsiveness to exercise (change in heart rest to peak exercise 51·0 [3·2] to 57·5 [3·9] beats per min; $p<0{\cdot}01$, 2·9–10·1). Plasma noradrenaline concentrations (2·39 [0·28] to 1·65 [0·19] nmol/L, $p<0{\cdot}05$) were reduced. The patients' symptoms were also improved. By contrast, no change in autonomic function or exercise capacity was seen in the control group.

Short-duration PIT induces pharmacological conditioning with improved symptoms, autonomic balance, exercise tolerance, β-receptor up-regulation, and enhanced chronotropic responsiveness in chronic heart failure.

*Lancet* 1995; **345:** 344–49

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## Introduction

Chronic heart failure is a complex syndrome with many non-cardiac abnormalities, which may contribute to the associated symptoms, exercise tolerance, and high mortality rate. Specific strategies to reverse these abnormalities have not yet been discovered. One important abnormality that contributes to exercise intolerance in chronic heart failure is β-receptor down-regulation[1] and, as a consequence, a reduced ability to mount an adequate heart-rate response to exercise (chronotropic incompetence).[2]

Long-term inhibition of angiotensin-converting enzyme (ACE)[3] and β-blocker therapy[4] have been reported to up-regulate β-receptors. Although sympathetic withdrawal cannot be excluded, this up-regulation may be secondary to a general improvement in condition with ACE inhibition, and may be possible in only a minority of the affected patients in the case of β-blockade. No specific treatment to up-regulate β-receptors is available.

The mechanism of β-receptor down-regulation is thought to be persistent β-stimulation by the sympathetic hyperactivation known to occur in chronic heart failure. It is not known whether pulsatile rather than continuous chronic β-receptor stimulation would cause less down-regulation but evidence from receptor-agonist systems suggests the possibility.

Experiments in animals have shown that intermittent sympathomimetic stimulation with dobutamine can produce beneficial changes analogous to the effects of physical training.[5] As did physical training,[6] dobutamine infusions improved exercise performance and reduced resting heart rate, exercise-provoked increases in heart rate, arterial blood lactate, plasma renin activity, and plasma noradrenaline concentration.[7] These encouraging results led to studies in patients with severe chronic heart failure; the treatment produced significant improvements in resting haemodynamics, exercise tolerance, and symptoms that persisted for weeks.[8] Long-term β-stimulant or other inotrope therapy has not, however, been successful in management of chronic heart failure for two main reasons—tolerance to the inotropic stimulation, which for β-stimulants is substantially related to β-receptor down-regulation,[9] and an increased frequency of ventricular arrhythmias, which may increase mortality.[10,11]

There was an important difference, however, between the animal and human studies. The short infusions