



UPDATE

Fighting back against Lassa Fever

A disease that affects tens of thousands of people each year, kills hundreds or possibly thousands, causes vast numbers of miscarriages and leaves huge numbers of people incapacitated by deafness. Headline news? The target of massive research funding? Curiously not. On the other hand, Ebola, albeit an even more serious and usually fatal disease, but which occurs far less frequently, receives global attention and has become a popular choice for microbiology researchers all over the world. Somehow, the priorities seem to be misplaced.

Establishing more active links is the only way to help maintain the momentum of international research into Lassa Fever, and help ensure that it is focused on benefiting those most at risk from the disease.

So what is this disease and where does it come from? Lassa Fever is a zoonotic viral haemorrhagic fever caused by an arenavirus (so called because it resembles a grain of sand). It is endemic in Sierra Leone, Liberia, Guinea and some parts of Nigeria. The natural hosts for the virus are Multimammate rats (*Mastomys* spp.). Rats of this genus are widely distributed throughout sub-Saharan Africa and are probably the most common rodents in tropical Africa. The taxonomy of this genus is not clear and our understanding of the epizootiology of Lassa in the rodent host is only fragmentary. What is known is that certain members of the genus (*M.natalensis*) are persistently infected and shed the virus in their excreta. Humans are infected by contact with rat excreta, often in contaminated food, or by unprotected contact with an infected human. In Sierra Leone, the main focus of infection is in the east of the country and is centred upon the region immediately to the north of Kenema and around the diamond mining towns of Segbwema, Panguma and Tongo.

No one would deny the seriousness of Ebola, the need to combat it effectively or to understand the virus, but Lassa fever is a far bigger problem for West Africans yet it is virtually unknown.

However, the picture is not entirely bleak: a few dedicated individuals are struggling to combat the disease in the field and in a number of international research laboratories). The centre of activity in the field is Kenema in the Eastern Region of Sierra Leone, where Dr Aniru Conteh, the world's leading clinical expert on the treatment of Lassa and his team are based.

Nevertheless, Lassa Fever is much more than just a Sierra Leonean problem: it is found in a number of countries in West Africa that form a 'Lassa Fever belt'. Furthermore, the international response to the crisis in Sierra Leone has meant that more and more people working for international organisations have become exposed to the threat of the disease. Lassa Fever has already killed a member of the UK Department

for International Development and a member of the International Committee of the Red Cross. It infected four military members of the United Nations Mission in Sierra Leone (UNAMSIL), one of whom subsequently died.

Although interest of the international research community in haemorrhagic fevers remains high, and research on Lassa is occurring in a number of centres, there are no ongoing research links between the main treatment centre in Kenema and any of the current research programmes. Establishing more active links is the only way to help maintain the momentum of international research into Lassa Fever, and help ensure that it is focused on benefiting those most at risk from the disease.



Lassa patient on Lassa Ward, Kenema, showing the typical signs of red eyes and a swollen neck. The patient survived.

Clinician Dr Conteh. Photo: Simon Mardel 1997

A major challenge is the very real threat of an epidemic of Lassa Fever once the dry season begins in November 2002. Exacerbating this risk is the unprecedented movement and displacement of people within the Lassa belt. Returning refugees from Liberia and IDPs from camps around Bo and Kenema are being resettled in the Lassa endemic areas. Moreover, the flow of refugees fleeing escalating fighting in Liberia is increasing, with two new refugee camps built in Southern Province this month.

The aim of this newsletter is to give an update to all those who have contributed to the fight against Lassa Fever, and to ask for your support and suggestions as to how we can build on the foundations that you have helped to establish.

Thank you for your support.

Nicholas Mellor

Twenty Five years of Lassa Fever research in Sierra Leone

In 1969 there was a mysterious outbreak of a fever in a mission hospital in Nigeria, the fever quickly infected three of the missionary nurses. Two died, but the third survived having been evacuated to the Colombia Presbyterian Hospital in New York. Blood from this patient was sent to the Arbovirus Research Unit at Yale University. Drs Wilbur Downs, Jordi Casals and Sonja Buckley worked on the project. A virus was isolated and named Lassa after the village near which the first case came from. Soon after the isolation of the virus, the death of one of the laboratory workers who had had no known direct contact with the blood specimen, highlighted the danger of this virus.

The same Arbovirus Research Unit with support from the Rockefeller Foundation was also responsible for the isolation of the antigen used to develop the Yellow Fever vaccine which earned them a Nobel Prize.

Following another outbreak in the Catholic Missionary Hospital in Panguma, in 1976, Joe McCormick led a team from CDC Atlanta to set up a research programme working with Karl Johnson in Atlanta. The research was carried out at the Nixon Memorial Hospital in Segbwema, also in Kenema and Panguma. Tom Monath had visited the area several years earlier in 1972 with David Fraser from CDC, looking at the vector for the disease.

The CDC research programme had four objectives:

1. Identify the clinical and epidemiological importance of the disease, and assess the size of the virus reservoir, the *Mastomys* rat.
2. Describe the clinical manifestations and explore treatment possibilities.
3. Develop the scientific basis for a vaccine.
4. Train counterparts in Sierra Leone

A known reservoir from Tom Monath's work was the multimammate rat, *Mastomys natalensis*, and it was shown in the first two years of work that it was the only significant reservoir, and that this rodent was widespread, and could live in close contact with humans.

“An extensive programme of prevention was developed by the Lassa Fever research initiative”

Joe McCormick identified Ribavirin as an effective therapy when commenced in the first week following the onset of symptoms. Ribavirin was a new drug and not available in any commercial market. The side effects are mostly minor, for example, mild anaemia. The drug is more widely available today, being manufactured in a number of different countries, and is also used for treating hepatitis C infection.

Joe McCormick's study of adults admitted to medical wards over a 2 year period in the Eastern Province of Sierra Leone showed that 13% of these had Lassa Fever, indicating the extent to which the disease is endemic and the toll it takes on the community.

Another of his studies found that about a third of the hospitalised cases develop acute deafness, which becomes permanent in two thirds of the cases. Consequently, Lassa Fever may well be

the most important cause of sudden onset deafness in West Africa. Sudden onset deafness could prove to be valuable as a marker for determining the prevalence of the disease in the region, in the absence of a spot test for quickly and cost effectively determining exposure to the disease through Lassa Fever antigens in the blood.

An extensive programme of prevention was developed by the Lassa Fever research initiative, including music tapes, plays, school interventions and meetings with villages to raise the awareness and understanding of Lassa fever in order to reduce contact with rodents and to encourage people to get to the hospital early when ill. In addition, all of the immunological information to develop a vaccine strategy was obtained over the years, and a vaccine was produced which protects non-human primates from a larger dose of Lassa virus than one would expect under natural conditions. The lack of financial interest on the part of vaccine companies has hindered its development to the point of being able to conduct clinical trials.

“Lassa Fever may well be the most important cause of sudden onset deafness in West Africa.”

The program had to be closed down in 1993 due to the war. Three years later, MERLIN which had established a base in Sierra Leone to run a variety of emergency medical programmes, set up a Lassa Fever unit at Kenema, when it was safe enough to do so, with some of the members of the original team. Dr. Aniru Conteh led the Merlin clinical team. Dr. Conteh had worked with the CDC team and Dr. Austin Demby, the Sierra Leonean deputy director of the Lassa Fever research Program at the Nixon Memorial Hospital.

Merlin focussed on both clinical and preventive work. Since that time intensive health education and community sensitisation programmes through radio discussion have been carried out by the outreach team supported by Merlin. Merlin also began providing drugs, medical equipment and supplies including barrier-nursing equipment to the Lassa ward for the direct case management of all suspected cases of Lassa fever.

At present the annual governmental expenditure on health is about 4300 Leones (\$2) per capita. Since the government is currently faced with major problems due to malaria, an increasing burden of TB and of AIDS/HIV as well as Lassa fever, its ability to support the Lassa programme is severely limited. In addition, much of the Lassa fever problem is in the Eastern region, remote from the capital Freetown.

CDC's original goal of a locally run Sierra Leone Lassa research programme has had many set backs over the last decade. However, the current peace and commitment of the remaining staff to the Lassa programme make it attainable with a sufficient level of support.

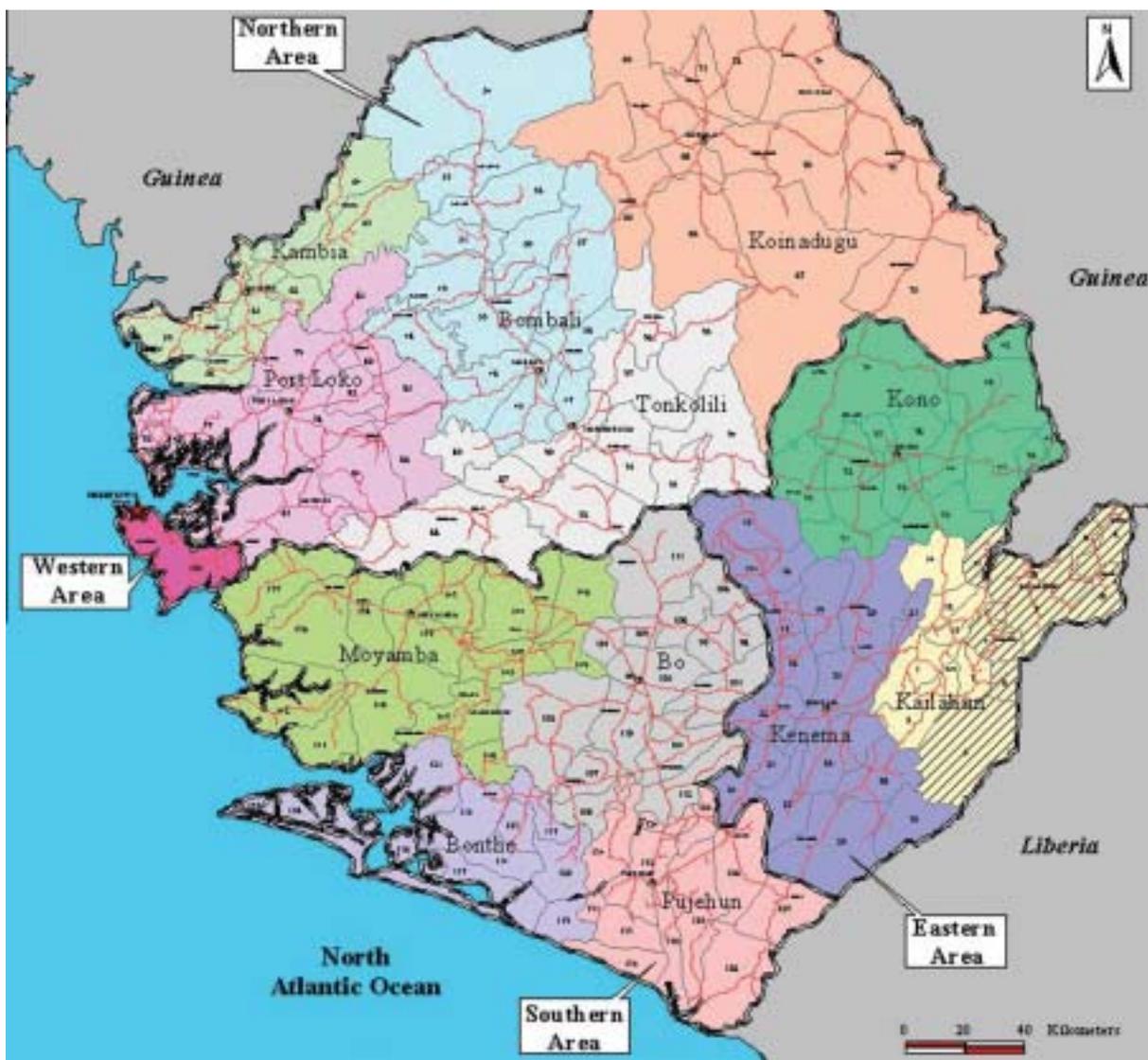
The Longer Term Vision

According to Dr Wurie, Disease Prevention and Control Adviser, WHO Sierra Leone, WHO sees scope for building joint Merlin/WHO/CDC work in Kenema to create a West African regional centre for treatment, control, training, emergency preparedness and research into Lassa Fever and potentially other haemorrhagic fevers. For example, Ebola has been found in the Cote d'Ivoire and Liberia. Lassa Fever is endemic in Guinea, Sierra Leone, Liberia and Nigeria. The Lassa ward at Kenema is the only facility in West Africa where large numbers of patients with haemorrhagic fevers are treated routinely throughout the year. The skills developed by that team are also relevant to other communicable diseases where barrier nursing is important, such as TB and HIV AIDS.

The building of the new laboratory and the means for the secure transport of Lassa Fever material internationally should open up scope for collaboration with international research initiatives. In addition, as more staff become trained, a team could be on standby for responding to outbreaks in the region.



Right - Children in the Lassa epidemic region of Tongo © Merlin



Report from Kenema

Kenema Government Hospital (KGH) in Kenema, the capital of the Eastern region of Sierra Leone, is the main functioning district general hospital for the Lassa fever endemic region and is the only hospital in Sierra Leone providing care for Lassa fever patients on a routine basis.

The hospital which has 400 beds is in a poor state of repair, though recently supported by international aid efforts.

Merlin has supported the Lassa fever ward in Kenema hospital since 1995. It has bed spaces for 20 patients, and is still run by Dr Aniru Conteh, who is now the most experienced physician in the diagnosis and treatment of Lassa fever.

The case load remains high. In the year 2001, 268 individuals were admitted to the Lassa ward with suspected Lassa fever whom 54 or 20.2% died. The average length of stay in the ward was 10 days. So far this year 137 patients have been treated.

The pattern of cases is conforming broadly to that seen in the past with a decrease in numbers during the rainy season (Fig 1).

The expertise and standard operating practices developed in the Lassa ward are proving to be a valuable resource for demonstrating barrier nursing and contact tracing - increasingly important in other programmes such as TB and HIV. In addition, those clinicians and scientists who have had the privilege of working alongside the Lassa team at Kenema have often gone on to take part in global outbreak response missions where their field experience of responding to a Class Four Pathogen outbreak has made a major difference to operational effectiveness.



Dr Conteh has been running regular seminars on case definition and diagnosis for health care workers new to the region. © Merlin

STOP PRESS: THE DANGER OF AN EPIDEMIC.

Five years ago during the last major resettlement of IDPs and refugees there was a major increase in the incidence of Lassa Fever. People returned to derelict and dilapidated houses where vegetation had grown close to houses, thus providing ideal conditions for rats to live and breed in close proximity to inhabitants. This risk factor was compounded by the distribution of three months supply of grain and seeds to returning families in sacks that proved only too easy for rats to break into. The breakdown in the control of diamond mining in the Tongo diamond fields - a region with one of the highest incidences of Lassa infection - has brought thousands of miners flocking into the area. The highest incidence of Lassa infection is in the dry season. With clinical resources already overstretched, and outreach activities reduced to a single person, the local team fears that this November could see an overwhelming epidemic.

Update from the Outreach Team

Merlin is the leading NGO involved in the control of Lassa Fever infection in the region. In addition to funding the Lassa fever ward it has been involved with public education programmes. In the past these have included passive education via billboards and an active population-based education programme run by its Lassa outreach teams in Kenema town, the surrounding countryside and in the IDP camps. In addition, one team has undertaken contact tracing and education in areas where known cases have occurred. By the criteria of general population awareness this programme has been highly effective.



Richard Fonnio who leads the outreach programme and Nicholas Mellor visiting a family where three people had been infected with Lassa Fever.

Richard Fonnio, from Merlin, is leading the outreach activities, using video, posters, music, drama and training of healthcare workers. Over the past five years these have been a major part of MERLIN's activities, helping to ensure cases of Lassa Fever are recognised and referred to hospital early on. This had a significant impact in reducing the mortality among hospitalised cases. These outreach activities have formed the basis for vector control, and reducing the danger of panic that has led to medical facilities being abandoned when a Lassa Fever case has been brought in.

The numbers of cases presenting at the Lassa ward at Kenema hospital by no means represents the true number of Lassa cases in the region. Mapping of the homes of the cases has shown a strong link to areas where Merlin (and formerly CDC) have undertaken outreach work. In addition, most of the cases lived along main roads suggesting that ability to travel to the hospital may be an important factor in the decision of patients to seek treatment.

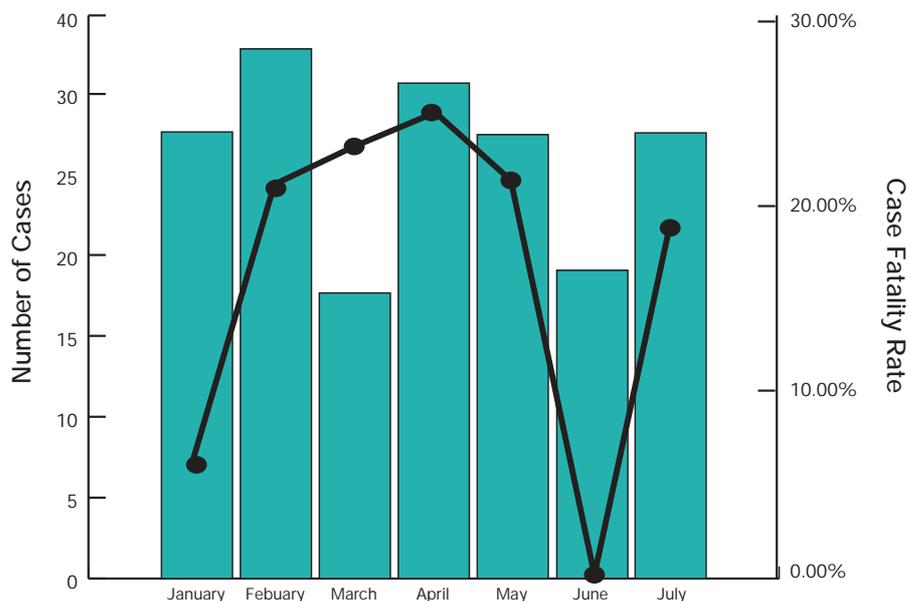
Sadly, a direct result of the improved political stability in the country has been a withdrawal by emergency funding. This,



Publicity boards have been crucial in raising public awareness of Lassa Fever.

and the inability of the government to provide replacement funds has left a funding gap and the capacity of the hospital to treat Lassa fever has suffered as a result. In addition, the outreach programme has been seriously affected and is now reduced to the contact tracing team alone. In the absence of continued widespread community sensitisation to the problem a progressive deterioration in effective control and a concomitant increase in cases and deaths may be expected. This is especially serious at a time when large numbers of people are returning to areas that have been neglected for many years and very large numbers of refugees are entering the country from Liberia.

Evolution of Cases and Case Fatality Rate (CFR) in Lassa Ward by Month - 2002



Epidemiological Review

The last serological survey dates back to the 1980s, which showed sero-prevalences varying between 60% in some parts of Sierra Leone, 15-20% in Nigeria and 4-6% in Guinea. An analysis of the geographical distribution of the homes of the cases treated in the Lassa ward in 2001 has shown that the majority came from Kenema and Tongo. Almost all the other cases lived close to main roads. However, this distribution is unlikely to be an accurate reflection of the actual distribution of Lassa cases in the area. It has probably been affected by the

extensive outreach work that has raised awareness of Lassa in these areas and probably also reflects the ability of the patients to reach transport that can get them to hospital.

The Lassa belt appears to be widening and so education is being disseminated to areas where cases have not previously presented. There are also an unusually high number of cases being seen outside the traditional Lassa season (November-May) - probably a result of overcrowded conditions.

The Colindale Meeting 2001

In 2001, Merlin with the support of the World Health Organisation (WHO) and the Central Public Health Laboratory in Colindale, UK, arranged a one-day conference to bring together all the organisations working with the Lassa team at Kenema.

Participants included:

- Center for Disease Control, Atlanta, Georgia;
- ICRC, Switzerland;
- MERLIN Sierra Leone and UK;
- Ministry of Health and Sanitation, Sierra Leone;
- Public Health Laboratory Service, UK;
- National Health Service, UK;
- World Health Organisation; and
- Royal Army Medical Corps, UK

Following on from the conference, new initiatives to improve the diagnosis, treatment and control of the disease are being considered. As a part of that process, MERLIN has started a new initiative to improve the laboratory facilities at Kenema hospital in association with the Central Public Health Laboratory of the Public Health Laboratory Service of England and Wales.



Villagers in Tongo listening to the Outreach Team © Merlin

Advances in vaccines research

Professor CJ Peters established a basis for the vaccine research programme through successfully developing a vaccine for South American Haemorrhagic fever. This was the first arenavirus vaccine developed and used on humans.

A number of vaccine models for Lassa Fever have now been developed, but they remain a long way from clinical trials. In an area as poor and unstable as the Mano River Belt has proved to be over the past decade, questions have been raised as to the viability of a long term Lassa vaccination programme. The success of the Yellow Fever vaccination programme proposed for Sierra Leone (to be supported by the Global Health Fund) will be an indicator as to whether a Lassa vaccination programme might be possible to implement successfully in the future. Nevertheless, research is continuing in a number of centres into the development of a Lassa vaccine.

Establishing a new laboratory facility

The report of a recent joint assessment of laboratory facilities in Kenema by Merlin and the Public Health Laboratory Service, Central Public Health Laboratory (CPHL) set out proposals for the rehabilitation of the Kenema hospital laboratory.

The draft plans for this laboratory have been provisionally approved by senior officials at the MoHS in Freetown, the Superintendents of the Kenema hospital and laboratory, and the Hospital Board. Funding has been obtained by Merlin for the construction from JOA (Jersey Overseas Aid), and it is hoped

- Support studies of the epizootiology of the disease
- Support epidemiological studies

Funds are still being sought for new equipment and for staff training.

The ICRC has recently sent a microbiologist to Kenema who has provided essential training in basic diagnostic techniques to the laboratory staff. Merlin is supporting the intent of the MoHS to build on this foundation and the new laboratory will open up new ways in which the team in Kenema can improve the treatment of patients and host visiting researchers.

The Lassa Fever isolation ward at Kenema has a small amount of mostly non-functioning equipment remaining from the previous CDC studies. All work is done on a table in a room approximately three metres square. The table is below a window that houses an air conditioning unit. There is no conventional laboratory benching in this room and no services other than intermittent electricity. There is no running water in the unit and only basic facilities for hand washing.



Tim Healing explaining the design of the new laboratory

that the structure will be complete by the end of the year.

The proposed Category I facility has the potential to:

- Provide facilities for accurate diagnosis of common infections that may be co-existing with Lassa fever or may be the main cause of the patient's illness.
- Be modified to provide a Category III facility where diagnosis of Lassa can be performed.
- Provide material for the development of new and rapid tests for Lassa



Close consultation has been the key to planning the new laboratory

The people behind international Lassa Fever Research

None of the work over the last 25 years would have been possible without the support of CJ Peters of CDC, who initiated the original research programme, and the clinical directors and medical co-ordinators who worked in Sierra Leone. They helped to lay the foundation upon which we are now seeking to build.

Clinical Directors of the Lassa Fever Research Project, Sierra Leone.

1976-79	Joseph McCormick, M.D.
1979-81	Patricia Webb, M.D.
1979--80	David Morens, M.D.
1980-81	Sally Tripple, M.D.
1981-83	Curtis Scribner, M.D.
1983-86	Robert Craven, M.D.
1986-89	Dianne Bennett, M.D.
1989-90	Mary Lou Solbrig, M.D.

Since 1996 MERLIN Medical Co-ordinators have supported the work in Kenema.

1996	Rachel Tapsell
1997	Rob Bennett
1997	Kathleen Skinner
1997	Simon Mardel
1997	James Bunn
1997-2001	Nzenge Mutota
1998	Monica Norlan
1999	Susan Lillicrap
2000	Jane Moore
2001	Nicola Cadge
2001	Akeem Ali
2001	Emmanuel Owoso and Kazuko Kumon
2002	Kay Richmond
2002	Valerie Bemo

Research Supporters

A number of organisations have supported Lassa research in Sierra Leone including:

- BUZA
- Center for Disease Control (CDC), US
- Division of Viral and Rickettsial Diseases (DVRD), US
- Government of Italy
- MERLIN, UK
- Ministry of Health and Sanitation, Sierra Leone
- National Centre for Infectious Diseases (NCID), US
- OFDA
- Public Health Program Planning Office (PHPPPO), US
- Rockefeller Foundation, US
- Special Pathogens Branch, US

Thanks to current donors

Merlin's work on Lassa fever over the last few years has been made possible by contributions from OFDA, BUZA, Jersey Overseas Aid and the Rockefeller Foundation. OFDA supports the Lassa Fever outreach teams enabling them to remain proactive in case finding, disease surveillance, and contact tracing activities in Kenema Township and IDP (Internally Displaced Persons) camps. BUZA are funding provision of essential drugs and supplies, training and staff support at the Lassa ward. JOA are funding the construction of the Lassa Fever diagnostic laboratory.

The Rockefeller Foundation is sponsoring a study to assess the socio-economic impact of Lassa Fever. We are looking at the burden of disease and evaluating the cost effectiveness of different interventions for the control of Lassa Fever. This will provide a foundation for a longer term Lassa Fever research strategy.

'Thank you for all the support over the last 25 years in the fight against Lassa Fever. The struggle continues and we need all your support.'

Dr. Noah Conteh, Director General Medical Services,
Ministry of Health and Sanitation, Sierra Leone.



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