LASSA FEVER UPDATE
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Health Care In Crises

Fighting back against Lassa Fever

In the first edition we looked at the background to research into Lassa Fever and the operational activities in the field. This second edition focuses on case recognition, treatment, diagnosis and vaccine development.

Early and accurate diagnosis is one of the most important factors in reducing the mortality rate, however accurate diagnosis is limited by the lack of both laboratory facilities capable of carrying out diagnosis and a diagnostic tool that could be used more widely in the field. In this issue we review the different approaches to diagnosis and the research challenges.

We look at the clinical picture presented by Lassa fever and the current approach to case management. Simon Mardel looks at importance of universal precautions in the management of Lassa patients and in dealing with outbreaks of other types of haemorrhagic fevers.

We summarise the work being done to look at the cost effectiveness of the various interventions potentially available for the control of Lassa fever and also look at the current approaches to the development of a vaccine.

The map provides an overview of the various centres of expertise or research around the world. One of the themes of this project has been to see how stronger links between the field and the various international centres of expertise could be built, and this will be explored in the next edition. A key factor in outbreak control is social mobilisation and this will be reviewed in greater detail in the next edition as well.

Many thanks to those who sent us their comments in our first edition - they were all very constructive and helpful. We are very grateful for everyone's support to this newsletter and encourage you to continue to give us feedback and comments on this and future editions.

Wishing you all our best wishes for the New Year.

Nicholas Mellor

Building of the new laboratory well underway Photo © Merlin

Dr Kabba Koeta the Hospital Superintendent in Kenema laying the foundation stone for the new laboratory in Kenema (see Lassa Fever Update August 2002) Photo © Merlin

Diagnosis and Case Recognition

Tim Healing

Lassa Fever is endemic in several tropical West African countries. Although it is limited in geographical distribution, hundreds of thousands of people are at continual risk of acquiring this infection and developing life-threatening haemorrhagic fever. However, the true burden of infection remains unknown since there are few centres in the region that are capable of diagnosing and treating the disease.

Mortality from Lassa infection can be reduced if the patient is given a suitable antiviral drug (Ribavarin) during the first few days of infection. Unfortunately, clinical diagnosis is complicated by the fact that the initial symptoms of the disease are indistinguishable from a number of other infections endemic in the area including malaria, typhoid septicaemia and yellow fever. Rapid laboratory confirmation of infection is therefore most important both to increase patient survival and to reduce unnecessary use of costly antivirals. However, most of the tests currently available for the laboratory diagnosis of Lassa Fever require a well-equipped laboratory, well trained staff and the use of expensive reagents, media and equipment. The specimens are likely to be hazardous and any laboratory handling such material should be equipped with appropriate biosafety measures. The under-funded and ill-equipped laboratories that are common in areas where Lassa Fever is endemic are rarely able to undertake the diagnosis of the disease without substantial external support.

The 'gold standard' for the diagnosis of acute Lassa infection is isolation of the virus from the patient. This procedure is quite slow (culture of the virus may take 7-10 days) and is not to be undertaken lightly. Lassa Fever virus (LFV) is internationally categorised as a hazard Group 4 pathogen, the group of infectious agents considered to pose the greatest risk to life for an individual and the community. Propagation of the LFV is routinely undertaken in Biosafety Level 4 laboratories, the most sophisticated but also the most expensive of all biological laboratories. Those who work in these laboratories are highly trained specialists in handling 'high risk' viruses. The lack of appropriately 'biosafe' laboratories and specialist staff makes virus isolation in endemic areas currently impossible.

As a surrogate for virus isolation, rapid and sensitive RT-PCR assays have recently been developed. These techniques have already proved of considerable value in the rapid diagnosis and molecular characterisation of Lassa Fever virus strains[1,2]. However, the expense and the lack of suitable laboratories with trained staff pose practical problems for implementing such methods at present in the countries making up the Lassa Fever belt.

Laboratory diagnosis has traditionally been by the indirect fluorescent-antibody (IFA) test and this still remains the standard method. A particular advantage of this methodology for use in laboratories in the developing world is that it requires relatively unsophisticated equipment and reagents that are reasonably heat stable. IFA as a tool to diagnose acute clinical infections has been criticised on the grounds that it is affected by the presence of the relevant antibodies during both acute and convalescent stages of infection and by the subjective nature of the assay. The appearance of IFA antibody early in the course of Lassa infection may be useful in identifying patients with poor prognoses and a recent study showed that the presence of antibodies detectable by this method early in the course of illness correlated with death[3].

Enzyme-linked immunosorbent assays (ELISAs) for Lassa virus antigen and immunoglobulins M and G (IgM & IgG) antibodies are currently the most sensitive and specific serological tests for acute Lassa virus infection. In a recent study antigen detection was shown to be particularly useful in providing both early diagnosis and prognostic information[3]. Levels of antigenaemia varied inversely with survival. Detection by ELISA of IgG antibody early in the course of illness helped rule out acute Lassa virus infection. However, use of this technology in Lassa Fever endemic areas is again limited by the availability and maintenance of equipment. Additionally, the various sera and reagents required for this assay are heat sensitive and require a good cold chain and proper storage in the laboratory if they are to work properly. An advantage of the provision of ELISA equipment and training of staff in the methods is that the techniques can be used for the diagnosis of other diseases. ELISA-based methods have been developed for the diagnosis of a number of diseases that are prevalent in developing countries (e.g. HIV/AIDS, the hepatitis viruses, typhoid fever). The provision of ELISA equipment and appropriate staff training can, therefore, greatly expand the diagnostic capabilities of suitable local laboratories.

There remains a need for a sensitive and specific rapid (bedside) test for Lassa Fever. A rapid diagnostic immunoblot assay for Lassa Fever has been developed for field use[4], but its usefulness is limited by its low sensitivity and it is unable to provide the prognostic information available from the antigen. However, it appears probable that further development of this technology may allow rapid, specific confirmation of infection. Such a test could also be of great value for epidemiological work on the disease. Merlin and the PHLS Central Public Health Laboratory are beginning collaborative work aimed at producing such a test.

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Lassa Fever Diagnosis

Lassa Fever is most often diagnosed using enzyme-linked immunosorbent serological assays (ELISA), which detect IgM and IgG antibodies as well as Lassa antigen. However this is not available in Sierra Leone at the present time. As such, treatment is commenced as early as possible in response to reasonable suspicion based on clinical manifestations and history.

CASE DEFINITION

Patient with fever (100.4°F / 38°C or more) not responding adequately to antimalarial and antibiotic drugs.

SIGNS & SYMPTOMS

The onset is gradual and at the beginning the symptoms are similar to those of many other conditions such as flu and malaria.

No one clnical picture will tell you that a person has Lassa Fever.

Approximately 20% of patients will progress on to stage 4. However, many patients will recover before reaching stage 3 because they have a low initial virus dose, they have a competent immune system to fight off the virus, or they have received early treatment. Please note that any patient who has died after having any of the above signs and symptoms should be considered a case and precautions taken accordingly.

Stage 1

Starts with high fever, >39 °C, constant with peaks 40-41° C, general weakness and malaise.

Stage 2 after 4-7 days

- **sore throat (with white exudative patches) - very common;**
- **headache;**
- **back/chest/side/abdominal pain;**
- **conjunctivitis;**
- **nausea and vomiting;**
- **diarrhoea;**
- **proteinuria;**
- **low blood pressure (systolic BP <100 Hg);**
- **anaemia; and/or**
- **productive cough.**

Stage 3 after 7 days

- **facial oedema;**
- **convulsions;**
- **confusion/disorientation;**
- **mucosal bleeding (mouth, nose, eyes); and/or**
- **internal bleeding.**

Stage 3 after 14 days

- coma; and
- death.

Signs associated with poor prognosis are:

- convulsions;
- bleeding (usually oozing, not frank bleeding, from the gums, vagina, rectum and haemoptysis); and
- pregnancy (Lassa Fever is particularly serious in pregnant women, with an 85% mortality rate even with treatment).

COMPLICATIONS:

- Temporary or permanent hearing loss - 30% of survivors of hospital admission; there are many more cases within the general population, in people who have not required hospital admission or have had subclinical infections. In 1990, Cummins et al. demonstrated a sensorineural hearing deficit (SNHD) in 29% of confirmed cases of Lassa Fever and in none of the febrile controls in hospital in-patients. SNHD was present in 17.6% of people who had evidence of previous Lassa virus infection. Amongst local residents who had previously sustained a sudden deafness 81.3% had antibody titres to Lassa virus, compared with 18.8% of matched controls. This degree of viral-related hearing impairment appears to be greater than that reported from anywhere else in the world.
- Lassa Fever accounted for 25% of maternal deaths, most occurring in the first trimester, in a prospective study in Sierra Leone. The death rate was highest in the third trimester (30% versus 7.1% for the other two trimesters). The condition of the mother improved rapidly after evacuation of the uterus, whether by spontaneous abortion, surgical evacuation of retained products of conception, or normal delivery; 10 out of 26 (38.5%) women without uterine evacuation died, but only four out of 39 (10.3%) women with evacuation. Foetal and neonatal loss was 87%.

TREATMENT:

As prompt treatment significantly reduces the risk of mortality, ideally it should be started immediately there is reasonable suspicion of the disease. Untreated, the patient who survives will improve after the second week, and will be considerably better by about 4 weeks. Treatment should be undertaken in an appropriate setting. Currently, in Sierra Leone, this is the Lassa Fever ward at Kenema Government Hospital and is the only one if its kind in Sierra Leone. Due to the virulence of Lassa fever, the need to adhere to strict barrier nursing techniques and the specialised treatment and observation required, it is not foreseen nor recommended that other centres should be developed as a response to the current situation, in Sierre Leone.

Treatment Includes:

- Intravenous ribavirin for ten days with supportive and symptomatic therapy.
- Transfer of suspected cases should be done only following consultation with the relevant authorities and using strict barrier nursing techniques to avoid exposure to the non-infected.

Universal Precautions - Universal Rights

Lessons from Haemorrhagic Fever Epidemics

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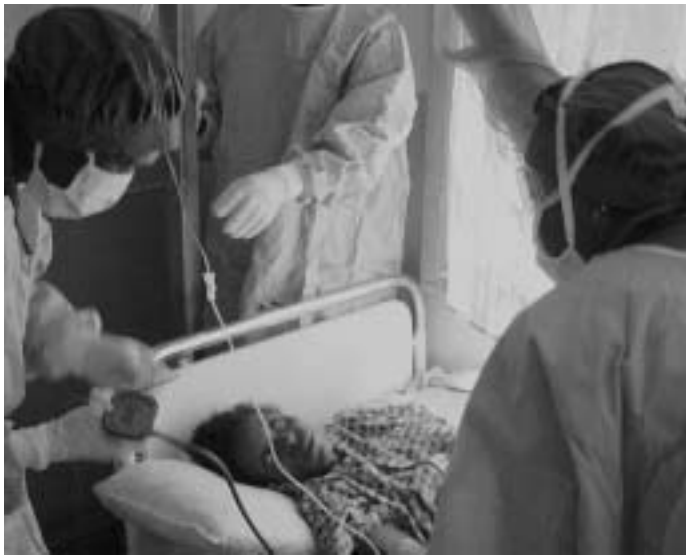
Experience of Haemorrhagic fevers in Sierra Leone (Lassa), DRCongo (Marburg), Uganda and Gabon (Ebola)

Included among the many Haemorrhagic Fevers are such diseases as Marburg, Lassa and Ebola. Such diagnoses often strike fear into health workers, patients and communities but once a patient is suspected of having a viral haemorrhagic fever (VHF) then a system of measures are put into place to prevent spread of the disease to health workers, relatives and other patients. These measures are well described in a manual produced jointly by WHO and CDC : "Infection Control for Viral Haemorrhagic Fevers in the African Health Care Setting" WHO/EMC/ESR/98.2 and their implementation has helped control recent epidemics including Ebola in Uganda and Gabon, and Marburg in DRCongo



Effective barrier nursing is critical to prevent nosocomial amplification in outbreaks Photo © Merlin

Isolation and treatment of suspected and confirmed cases requires intense support to staff in training, supervision and logistics. Health professionals, cleaners, burial teams, laundry and ambulance staff who come into direct contact with suspected or confirmed cases or their body fluids are protected by work clothes, coveralls or theatre style gowns together with double gloves, waterproof aprons, gum boots, masks, hats and goggles. Further protection is given by constantly reducing viral contamination on the isolation unit using copious amounts of bleach (hypochlorite) solutions to which these viruses are sensitive. Two of these simple commodities exemplify the logistical and financial burden of running a busy isolation unit: the daily provision of about 500 litres of diluted bleach solutions and the daily use of several hundred pairs of disposable gloves. Even with such massive logistic support several isolation units have temporarily failed in their tasks due to difficulties of a more human kind, such as failure to remove and bury corpses from the wards, desertion of medical and nursing staff or refusal by patients (or their relatives) to be isolated.

Less obvious are the risks posed by cases presenting to or remaining in health structures outside of these well equipped and generally well supported isolation units. Such cases may arise through several mechanisms acting singly or in combination:

Failure to find a history of possible contact:

Failures in contact tracing and follow up

New epidemics where health services are unprepared for or unfamiliar with the disease

New or unidentified chains of transmission during an epidemic

Endemic disease (such as Lassa fever in Sierra Leone)

Failure to question the patient about contact and travel history

Concealment of a history of contact in a patient developing VHF (as part of a process of denial or deliberate avoidance of isolation)

Failure to suspect the illness on clinical grounds

In most cases there is a lack of specific signs such as haemorrhagic features or conjunctival injection (red eyes) particularly early in the disease

The preponderance of non-specific or gastro-intestinal symptoms that may mimic malaria or dysentery

Failure to review cases on wards as the clinical picture of VHF evolves

Undertaking investigations or therapy while symptoms are attributed to another cause

(these merit special consideration because they carry a high risk of direct contact with blood and other body fluids)

Midwives treating cases of spontaneous abortion (VHF in pregnant women frequently causes this and the clinical picture may be confused with malaria or sepsis)

Nurses and doctors treating sick children where VHF is endemic such as Lassa fever in Sierra Leone

Laboratory technicians obtaining or examining specimens from VHF patients undergoing investigation

Continuing investigations after suspecting VHF

Placement of intravenous lines for severe dehydration and shock

Surgeons performing laparotomy on cases failing to recognize the clinical picture of right upper quadrant peritonism and shock that can occur in Marburg and Ebola

Packing the nose to treat epistaxis (for example in Crimean Congo HF)

Delays in establishing effective isolation for a suspected case

Reluctance of clinicians to institute isolation measures

Waiting for results of laboratory testing

Fear of isolation unit by patient or relatives

Reliance on inappropriate isolation measures (such as dysentery or TB units)

Nursing and midwifery staff not empowered to refer suspect cases to isolation unit

Failure of authorities to react to reports of suspected cases

Lack of prepared vehicle and attendants to implement transfer to isolation unit

Lack of prepared and staffed isolation unit

As well as potentially infecting many other individuals in a hospital at the same time (a process known as nosocomial amplification) such new chains of transmission are by their very nature unexpected and the response of the epidemic control team may only occur when several unexpected deaths have already occurred for example among health care workers. Some of these risks are due to errors or failings that could be prevented by better preparedness including health worker education, but many of these risks can only be minimized by the widespread use of standard or universal precautions which are outlined in Table 1. These measures apply to blood and most body fluids, broken skin and mucous membranes and are simple in comparison to the measures on an isolation unit but have less efficacy in preventing transmission of VHF. However because they are feasible to implement throughout all health care settings, they may be effective in reducing transmission from unrecognized cases. Most importantly they also reduce the risk of transmitting human immunodeficiency virus (HIV) and hepatitis viruses in the health care setting and are widely accepted for use with all patients.

Table 1 - Some of the Universal or Standard Precautions for Infection Control in Health care settings

1. Wash hands immediately with soap and water before and after examining patients and after any contact with blood, body fluids and contaminated items
2. Wear clean, ordinary thin gloves anytime there is contact with blood, body fluids, mucous membrane, and broken skin. Change gloves between tasks or procedures on the same patient. Before going to another patient, remove gloves promptly and wash hands immediately, and then put on new gloves.
3. Wear a mask, protective eyewear and gown during any patient-care activity when splashes or sprays of body fluids are likely. Remove the soiled gown as soon as possible and wash hands.
4. Handle needles and other sharp instruments safely. Do not recap needles. Make sure contaminated equipment is not reused with another patient until it has been cleaned, disinfected, and sterilized properly. Dispose of non-reusable needles, syringes, and other sharp patient-care instruments in puncture-resistant containers.
5. Routinely clean and disinfect frequently touched surfaces including beds, bed rails, patient examination tables and bedside tables.
6. Clean and disinfect soiled linens and launder them safely. Avoid direct contact with items soiled with blood and body fluids.
7. Place a patient whose blood or body fluids are likely to contaminate surfaces or other patients in an isolation room or area.
8. Minimize the use of invasive procedures to avoid the potential for injury and accidental exposure. Use oral rather than injectable medications whenever possible.

Anyone working in developing countries will appreciate that most of the above are seldom achieved, particularly (but by no means exclusively), in those areas affected by poverty, civil or political disruption. Some of the obstructions to implementation are listed under the main headings of economic issues, health worker training and supervision and patient expectation issues:

Economic and logistic issues

In local pharmacies a pair of surgical gloves can cost 1USD, a pair of disposable gloves 0.5 USD. Domestic rubber gloves (not suitable for fine tasks) are more easily reusable than surgical gloves but are more expensive or not widely available. Plastic gloves and plastic bags may also be used where appropriate.

Where cost recovery schemes operate the costs of gloves for midwifery or surgical intervention are sometimes passed directly to the patient who may even be instructed to purchase them from pharmacies. Similarly some patients purchasing their drugs are sometimes asked to purchase new disposable needles and syringes. This can inflate prices due to lack of bulk purchasing by health structures, and further disadvantage the poor.

High prices of disposables in some areas suggest lack of a free market or reliance on expensive imports.

Plastic sharps boxes (for disposing of needles) are often either imported and unsustainable, while even plastic cooking oil cans that can be adapted, have a significant second hand value and are unlikely to be burned. Cardboard versions can be difficult to construct.

Running water may not be available due to lack of infrastructure, maintenance or energy source.

Cost recovery and private medical schemes may encourage interventions.

Health worker training and supervision.

Lack of accountability or inspection to counter unsafe working conditions or practices.

Sharp instruments often not handled safely, surgical instruments blunt, faulty or inappropriate.

Poor techniques or instruments such as oral pipetting, broken microscope slides and blunt needles may put laboratory technicians, midwives, surgeons or their assistants at risk.

Lack of effective reporting system for monitoring (and reducing) inoculation injuries

Waste disposal insufficient to separate combustible from liquid waste increasing costs of fuel for incineration.

Storage, incineration or burial of infected waste inadequately supervised.

Failure of staff involved with cleaning reusable instruments to appreciate concepts of microbial basis for infection and prevention by cleaning, disinfection and sterilization

Training and provision of protective materials inconsistent or unsustainable

Nurses, midwives, technicians and cleaners may not be empowered to improve working practices

Habituation to established customs.

Patient expectation issues

Invasive procedures such as IV infusions, injections, blood tests and suturing may be expected by patients and relatives even where their use is clinically inappropriate.

Patients may accept use of reused needles and syringes or drugs from multiuse vials

Failure to appreciate concepts of microbes and sterilization

Hand washing by health workers may not be recognized as quality of care issue

Where running water is not available the need for large quantities to be carried to health structures is not appreciated by the community or patients' relatives.

Infrastructure of health facility such as water supply, waste disposal not seen as part of local community or wider political agenda

The solutions to these problems may also lie within the three main areas.

Some of the logistical problems require innovative practice such as the supply of disposables within packaging that then serves as disposal devices. Reducing costs and increasing availability of disposables such as gloves require reinforcement of National essential drugs and equipment purchasing policies, but may also respond to consistent increase in demands for their use. Providing or refurbishing water supplies can be associated with heavy capital and recurrent costs, and central programmes or widespread aid packages are unlikely to improve water supplies to health structures in a way which is truly equitable, accessible and sustainable unless this is underpinned by widespread local support.

Issues involving health workers and patients maybe improved by recent paradigm shifts in public health that focus less on epidemiological causes of disease but combine epidemiology with evaluation of health services. Most effective of all might be a concerted effort to raise the expectations of patients and health workers (Table 2 & 3), this was proposed in November 2001 during the Ebola epidemic in Uganda and was widely accepted by National and International staff engaged in control of the epidemic.

Table 2. - PATIENTS RIGHTS

- **Your health worker must wash their hands before and after touching each patient.**
- **You must have no contact with blood, vomit, stool, urine or sweat from other patients.**
- **Ask if any injection treatment or blood test is really necessary.**
- **For any blood test or injection a new syringe and needle must be used.**
- **Immunization programs must continue as usual.**

Table 3. HEALTH WORKERS RIGHTS

Midwives, laboratory staff, doctors, cleaners, clinical officers, nurses and patient attendants should expect:

- **Adequate hand washing facilities to allow hand washing between every patient contact.**
- **Adequate cleaning facilities to keep the work environment clean.**
- **Adequate gloves to protect you from contact with blood or other body fluids.**
- **Adequate supplies of new syringes or needles for each new patient**
- **Adequate facilities for quick and safe disposal of sharps and other waste.**
- **A system for reporting suspected Ebola cases.**

Such rights should exist outside of epidemics of VHF but will require continual emphasis and support by individuals, communities, NGOs and Governments if they are to be achieved.

Frequent hand washing in a solution of bleach greatly reduces the risk of spreading the disease. *Photo © Simon Mardel*

Predicting the cost-effectiveness for interventions for the control of Lassa Fever in Sierra Leone

Kay Richmond

Objective

To predict the cost-effectiveness of treatment, social mobilisation/health promotion, laboratory and diagnostics and the development and introduction of a vaccine.

Setting

The setting of the study was Sierra Leone, West Africa. The treatment available is Ribavirin given as a 10 day course to inpatients at Kenema Government hospital, together with appropriate supportive medication. It is considered to be the gold standard for the treatment of Lassa Fever. An outreach team provides public health education and contact tracing. However, it is limited in geographical and population coverage as a consequence of resource constraints and the unstable security situation.

The proposed interventions are:

- Social mobilisation/public health campaigns. These would seek to decrease incidence and prevalence of the disease by educating the population about the risks and ways of preventing the disease e.g. through the safe storage of food and improved hygiene. Increased knowledge about the disease and symptoms enables people, together with appropriate changes in practice, to seek medical treatment at an early stage before it is too late for effective treatment.
- A new laboratory with the ability to confirm the differential diagnosis of Lassa Fever is being provided. This aims to increase the chance of survival through earlier, accurate diagnosis. Currently, confirmation of the diagnosis of Lassa Fever is not available locally, with the possibility of wrong diagnosis. The aim would be to facilitate speedier diagnosis and institution of earlier treatment, thus increasing the chance of survival.
- The development and introduction of a new vaccine. This would prevent people from contracting the disease, therefore reducing the incidence and prevalence of the disease.

In addition, as the current treatment is expensive, the option of do-nothing/supportive treatment only was considered.

Methodology

This was a desk bound study, and in the absence of appropriate laboratory facilities and a vaccine, a number of methods were used to give an estimate of the costs and effects of the interventions.

The perspective of the study was that of the funder and/or provider of services. Social/indirect costs were excluded. The base year for the study is 2002. Costs were calculated and reported in US dollars (2002 prices).

First a systematic literature search was undertaken to find any literature pertaining to the costs of the disease in Sierra Leone. A second literature search was made to find information on the pathology and epidemiology of the disease, and the estimated effects of proposed interventions. Primary data was collected from Kenema Government Hospital and Sierra Leone for the cost of providing care and treatment. Grey literature and experts were used for estimates of the costs and effects of the programmes, as well as the design of the model.

Second, a decision analytic model was designed using the course of events with the different interventions as a guide. DATA 3.5 (Treeage) was used to design the tree.

Findings

The initial results of the costs and effects, and the cost-effectiveness of each of the interventions, when compared with the Do-nothing approach are shown in Tables 4 & 5.

Strategy	Average Cost per person/dose	Effect/ DALYs	DALYs Averted	US$ per DALY Averted
Base Case	6.1	6.31	-	-
Social Mobilisation	22.3	2.13	4.18	5.33
Laboratory	23.9	3.01	3.297	7.23
Treatment	55.9	1.49	4.82	11.69
Vaccine	138,157	0.24	6.08	22723.19

Table 4 - The average cost, effect in DALYs, and cost per DALY averted.

Intervention	Cost US$
Do-Nothing (per patient)	4.3
Treatment (per patient)	28.81
Laboratory (for Lassa fever per patient)	182.67
Health Promotion/Social Mobilisation *(For population – 594,451)*	20,000
Vaccine (Per person)	127,471

Table 5 - The total cost of the interventions.

Social mobilisation/health promotion is the most cost-effective option, while the vaccine is the least cost-effective. The interventions of social mobilisation, laboratory and diagnostics and treatment are all cost-effective when considering the World Bank threshold of 50 US dollars per DALY averted.

Sensitivity analysis was performed on some of the key variables. The cost of Ribavrin was sensitive; if it increases in price, the cost-effectiveness of the treatment is reduced. For the laboratory, the cost-effectiveness will be dependent upon the throughput and quality of the laboratory, for which data was not available at the time of analysis. A best case analysis was performed for the vaccine, which reduced the US dollars per DALY averted to 10,480 per person.

Social mobilisation/public health campaigns have proved to be the most cost-effective means of preventing Lassa Fever.

KNOWLEDGE + PRACTICE = PREVENTION

Photographs © Merlin

Commentary

An economic model will always produce numeric results - in this case the cost effectiveness ratios for alternative interventions for the control of Lassa Fever - but the validity of the results can only be as good as the quality of the data used to populate the model. The data used in this study are based largely on the views of experts, since little hard data is available, particularly on costs.

The sensitivity analyses undertaken considered the discount rate of capital costs but incidence and prevalence rates would have had greater relevance and, probably, greater effects - they were not available at the time of the study. Thus, conclusions with regard to the laboratory and vaccine are unreliable.

The main conclusion that can be drawn from this study is that the health promotion intervention is probably the most cost effective of the three alternatives. There would be many benefits from improved hygiene in addition to those from a reduced incidence of Lassa Fever - such as a reduced incidence of diarrhoeal diseases. These conclusions make it even better value for money than the vaccine or laboratory alternative. However, given the possibility of the Lassa virus being used as a biological warfare agent and the consequent need for a vaccine to counteract this threat, the development of an effective vaccine remains high on the international agenda.

Vaccination against Lassa Fever?

"Towards a human Lassa Fever Vaccine"

S.P. Fisher-Hoch and J.B. McCormick Reviews in Medical Virology 2001: 11:331-341 **Reviewed by Tim Healing**

In this article Drs Fisher-Hoch and McCormick reviewed the current situation as regards the need for and development of a vaccine for Lassa Fever. This is a very detailed and valuable article which we are summarising here as a contribution to the discussions on Lassa control activities that we hope will be stimulated by these newsletters.

The authors point out that Lassa is potentially a major threat to the health of between 160 million and 200 million people in the Lassa Fever belt of West Africa. It has been estimated that there are 300,000 cases a year in that region, with death rates varying from 4-6% in Guinea to 15% - 20% in Nigeria. Lassa Fever may account for up to 16% of adult medical admissions and about 30% of adult deaths in endemic areas. The population explosion in the Lassa belt over the last fifty years and the movements of people that have resulted from the wars in the region have led to increases in the incidence of Lassa.

Lassa is a disease that is potentially preventable by good public health practices. The infection is acquired in the community from infected *Mastomys* rodents and from infected people. Spread from rodents mainly occurs due to poor food storage and hygiene practices and from the practice of using the rodents as food. Person to person spread occurs due to direct contact - often when nursing a patient. Proper rodent control measures and appropriate hygiene and food storage practices would largely eliminate primary infections and hence person to person spread. However, the measures necessary to control rodents and prevent the spread of disease are difficult to sustain. The authors consider that a vaccine is an attractive and rational solution to the problem.

Immunity to Lassa infection appears to depend mainly on cytotoxic T-cell responses. There is a vigorous B-cell response with IgM and IgG antibodies being produced, but high levels of neutralising antibody in the blood are not correlated with virus clearance and indeed, there is some correlation between death from Lassa Fever and early detection of IgM antibody. Several different potential vaccines have been tried in laboratory conditions:

1. A virus closely related to Lassa Fever virus (Mopeia virus) which seems to be only mildly pathogenic to humans, has shown cross protection in animal models but relatively little is known about the infection in humans and there are concerns about safety.
2. Killed whole virus vaccines have been shown to trigger the production of antibodies but provided no protection in animals because of their failure to trigger a T cell response.
3. Recombinant vaccines using vaccinia virus and bearing a particular Lassa glycoprotein have shown considerable promise, but the high prevalence of HIV in the Lassa Fever belt means that such a delivery system is not feasible.

New approaches are therefore necessary, and the authors put forward the attractive idea of using the 17D strain of Yellow Fever virus as a vehicle, and producing a Yellow Fever/Lassa chimera able to vaccinate the recipients effectively against both diseases with a single dose. Such vaccines are already undergoing trials for Dengue and Japanese Encephalitis but these viruses, like Yellow Fever, are flaviviruses. To combine a flavivirus and an arenavirus will require a different approach involving gene insertion. Immunity to Lassa seems to endure for a considerable period after infection and may even be life long. A single vaccination with an effective vaccine may therefore provide excellent cover for a long period. There are many advantages to a 'single shot' vaccine in areas where the population may be transient or access intermittent or difficult. A problem would be that a cold chain would be necessary.

The major obstacles at present preventing the development of such a vaccine are financial and political. A Lassa vaccine is not currently considered to be a marketable item by pharmaceutical companies and the costs of producing vaccines and of clinical trials are rising very rapidly. The clinical trials of a Lassa vaccine will require political support both by national governments and international bodies. Innovative approaches to such a project are required if these obstacles are to be overcome.

Relevant expertise and research intersts in Lassa Fever are found in a number of centres around the world

Pasteur Insitutue	Cote d'Ivoire
Laboratoire P4 Jean Merieux	France
Bernard Nocht Institute	Germany
University of Marburg	Germany
CHU Donka	Guinea
University of Ibadan	Nigeria
Merlin	Sierra Leone
National Institute of Virology	South Africa
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