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Presentation

Challenges to Clinical Research in a Rural African Hospital; a Personal Perspective from Tanzania

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Abstract: This article is based on a talk given at the Japanese Society for Tropical medicine Annual Meeting in 2014.
The severe febrile illness study was established in 2005. The aim of the project was to define the aetiology of febrile disease in children admitted to a hospital in Tanzania. Challenges arose in many areas:
Study design: An initial plan to recruit only the severely ill was revised to enroll all febrile admissions leading to a more comprehensive dataset but much increased costs. Operationally a decision was made to set up a paediatric acute admissions unit (PAAU) in the hospital to facilitate recruitment and to provide appropriate initial care in line with perceived ethical obligations. This had knock on effects relating to the responsibilities that were taken on but also some unexpected positive outcomes.
Study personnel: Local research staff were sometimes called upon to make up temporary shortfalls in the hospital staffing. Lack of staff made it impossible to recruit patients around the clock, seven days a week creating the challenge of ensuring representative sampling.
Quality control: Studies based on clinical examination create unique quality control challenges—how to ensure that clinical staff are examining in a systematic and reproducible way. We designed a sub-study to both explore this and improve quality.
Summary: Setting up clinical research projects is severely resource poor settings creates many challenges including those of an operational, technical and ethical nature. Whilst there are no 'right answers' an awareness of these problems can help overcome them.
Key words: Plasmodium falciparum, salmonella, Tanzania, child, research design

Introduction

The work I'm going to discuss is work that I did when I was working with the London School of Hygiene and Tropical Medicine in Tanzania. The study I'm going to discuss was called the severe febrile illness (SFI) study and I'll discuss its study design, going behind the data to explore the challenges of implementing that study design; looking in particular at infrastructure challenges, challenges relating to personnel, and quality control, to illustrate some of these difficulties. Then to discuss some of the outcomes of the study and some of the research that we did.

The aim of the severe febrile illness study was to determine the treatable causes of severe febrile illness amongst children admitted to an African rural district hospital in an area where there was high malaria transmission. Where is this study? Muheza, Tanzania, in East Africa, near the Indian Ocean coast. It's a lowland area with high malaria transmission at the time of the study.

Study Design

The design was a prospective observational study that would run over 1 calendar year. The original plan was to include severely ill admissions to the pediatric ward aged between 2 months and 13 years who had a fever or a history of fever. As we began to plan the study more carefully, it became clear that defining severe febrile illness was not so straightforward. Whilst there are good criteria to define severe malaria [1, 2], for non-malarial febrile illness, it's not so easy. We decided instead to enroll all admissions with a fever or a history of fever regardless of their severity, so that we could determine severity criteria

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ourselves. This of course had important implications in that we went from anticipating recruitment of perhaps 500 or 600 to anticipating recruitment of several thousand patients.

Challenges with Infrastructure

The hospital we were working in was a district hospital, rather than a university or teaching hospital. This brought with it some challenges. In terms of the infrastructure in the hospital, children were admitted to two wards at the time that we began the study. Clearly, if you're aiming to capture every admission, then having to be in two places creates a fairly simple problem. Bed occupancy was very high, often two or three children per bed, particularly after the rainy season. This meant that the clinical staff were very, very busy doing their own work. With such high admission numbers, there were often stock-outs of essential medicines including quinine, which was the first-line treatment for severe malaria at that time. There was also very little oxygen available, indeed often there was no oxygen available on the pediatric ward for weeks at a time.

Why is this relevant to doing research? Well, when we were trying to see how the hospital worked in order to build the study, we would often see children who were severely ill being admitted and it was not uncommon that because of lack of resources, because of lack of stocks, children were dying from preventable causes. To take data from these children without addressing their health needs would not have been right. This was a problem that we needed to address.

In terms of research infrastructure, this was the largest piece of inpatient research that had been attempted at this hospital. There had been some important outpatient research in malaria treatments, but nothing of this scale addressing inpatients. The hospital had a limited microbiology service, and our aim was to be doing blood cultures on all of these children. In common with most district hospitals, there was little quality control of malaria microscopy, so this also needed to be improved.

Infrastructure Solutions

How did we propose to solve these problems? We set up and built a pediatric admissions unit for the hospital. Outside one of the paediatric wards we built a concreted seating area with a roof, so that we had somewhere the mothers could wait with their children before they were seen by one of the clinical assistants.

Inside the ward, we sectioned off one end with a wooden partition. On one side of the partition we had two beds in which we could systematically record the examination findings in the consenting children and do a set of simple tests (Fig. 1). All of the consenting children had rapid tests for malaria, they were tested for HIV if their parents gave consent, they had a blood culture performed and had bedside tests for hemoglobin, blood lactate, and blood glucose. Based on the clinical examination and results of these tests, we gave them an admission diagnosis and provided them with initial treatments, including resuscitation where necessary.

Fig. 1. The paediatric assessment unit with the ward in the background.

To support the unit, we procured our own essential medications, our own fluids and giving sets and we even set up our own avenue for getting an oxygen supply for the children. The laboratory also required improvement; we procured a BacT-ALERT automated culture system for blood cultures, a Coulter counter for full blood counts and some other fairly simple machines that weren't available previously. Culture media and some reagents had to be imported to ensure results were of the highest quality, since previously homemade culture media had been used.

Human Resources Challenges

Of course, a new admissions unit is no good without staff. At the time that we started, the only paediatrician was heavily involved in hospital management, and there was no qualified physician on the pediatric wards. The pediatric ward was staffed by clinical officers, a grade of non-physician clinicians who have 2–3 years of training before they are deployed. They are the backbone of staff in district hospitals. There was one clinical officer for the ward, though they were often redeployed after their morning ward round. Things were little better from the nursing perspective, with a shortage of trained nurses on the wards. The solution was that we had to provide research staff. On

site we had a UK-trained clinician in me and a UK-trained microbiologist. We recruited four clinical officers, four nurses, two assistants, and four lab staff in Tanzania. About halfway through the study, we also recruited a Tanzanian counterpart to me—another physician. Of course, the staff had to be trained in certain clinical skills and in research methods and Good Clinical Practice. Skills in resuscitation, when you're not able to practice it are soon forgotten. For most of our clinical officers, deprived of the resources and support to exercise these skills, the knowledge and skills in resuscitation had lapsed. We had to retrain them using roleplay and close supervision. This included a systematic approach to recording clinical signs. One of the most rewarding things of my time in Tanzania was that by the time I left the staff were able to run resuscitation of children themselves without any supervision. I can remember towards the end of the time I was there receiving a phone call in the office, at the hospital, saying that I was needed on the ward. I went down to the ward quickly expecting that they were having some difficulty resuscitating a child that needed an intra-osseous infusion or some such. However when I got there, there was no child in distress, it was simply that the printer wasn't working! This was how they had evolved over the time.

Another issue that we had to face, because of a temporary staffing crisis in the hospital itself, was that the hospital came to us asking if they could borrow our staff for clinical duties within the hospital. At this point we had more clinical officers working in the research project than the whole hospital had for other care. The difficulty was that to some extent we would be compromising our research by lending our staff to the hospital. However the hospital and the patients certainly needed our help, so we reduced our recruiting times a little for a period and deployed staff to the hospital.

Quality Control

Quality control in this environment is obviously important and a lot of this was achieved through supervision. We also organized a system of performing replicate measurements; one clinical officer would look at child and describe their status, respiratory rate, chest in-drawing, and so forth. Then another clinical officer or nurse would look at the same child and describe the same factors. We would analyse the concordance and we were later able to publish our findings [3]. We did the same duplication with height and weight, ensuring that our repeat measurements were within acceptable margins.

In the lab, supervision of microbiology was necessary and we had two collaborators that helped to make sure that we were identifying bacteria correctly. One was a surveillance group working in East Africa to whom we sent all of our pneumococci and Haemophilus (NETSPEAR). The other one was the University of Queensland in Australia who received Gram negatives.

In microscopy again supervision was important for quality control. Here we used a system suggested to me by one of my Professors—a lighthearted wager with the microscopist. I would meet the microscopist to challenge him that I could find a malaria parasite on a film that he had reported as negative. If a parasite was found, he had to buy the sodas, if I failed, I had to buy them. This way, he knew that there was going to be somebody double checking his results all the time. He also learnt that he could get a lot of sodas out of me! Of course, in any case all of the blood slides were double read with discordant slides read for a third time.

Results and Research Output

What did all of this achieve? Well, in terms of the etiology of disease, we recruited just over 3500 children over the course of 1 year. This was out of an estimated 6500 children that we think were hospitalized over that period—around two-thirds. Unsurprisingly, about two-thirds of the patients had falciparum malaria on a blood slide. About 9% had invasive bacterial disease (IBD)—either a positive blood culture or a positive CSF sample. HIV prevalence was low, around 4%. We had very high rates of acceptance for HIV testing, with very few mothers who refused to have their child tested. There was a group of about 20% or 30% where we could not find any pathogen at all [4] (Fig. 2).

In terms of the bacteria that were isolated from blood, the headline was high rates of Non-typhoid Salmonella septicaemia. Almost half of the bacterial isolates that we found were Salmonella typhimurium or Salmonella enteritidis. This is in keeping with data from other centers where there are high levels of malaria transmission [5]. The next most common was *Streptococcus pneumonia*e and *Haemophilus influenzae* B. At the time of the study, there was no vaccination program for *Haemophilus influenzae* B in Tanzania. Since then the Ministry of Health has gone on to institute a vaccination program, which is now well underway. The key to making the most of this microbiological data was tying the microbiology and the clinical data together and putting it in a context that was clinically relevant. At the time the Pocket Book of Hospital Care for Children was produced by the WHO [6]. The aim was that this would be a reference book that could fit in the pocket of a doctor or clinical officer working in a district hospital,

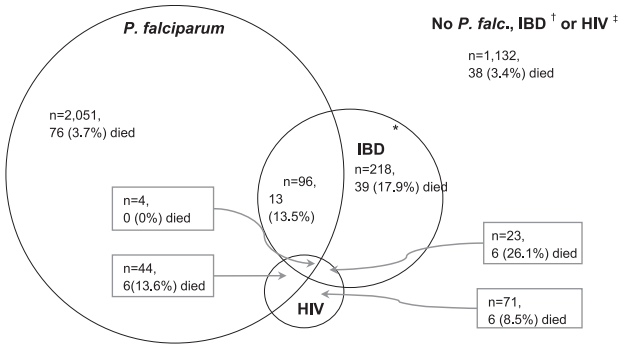

Fig. 2. Numbers and deaths (CFR) of children infected with *P. falciparum*, IBD or HIV.
Venn diagram approximately to scale.
* IBD consisted of 336 children with a positive blood culture, of whom 20 also had a positive CSF culture and an additional 5 with a pathogenic organism isolated from CSF and a negative or contaminated blood culture.
† Blood cultures classified as negative included 251 (6.9%) from which contaminant organisms only were cultured.
Three negative HIV results were based on Capillus-testing only (negative predictive value 99.5%, detail not shown); all other HIV results based on at least 2 concordant test results.

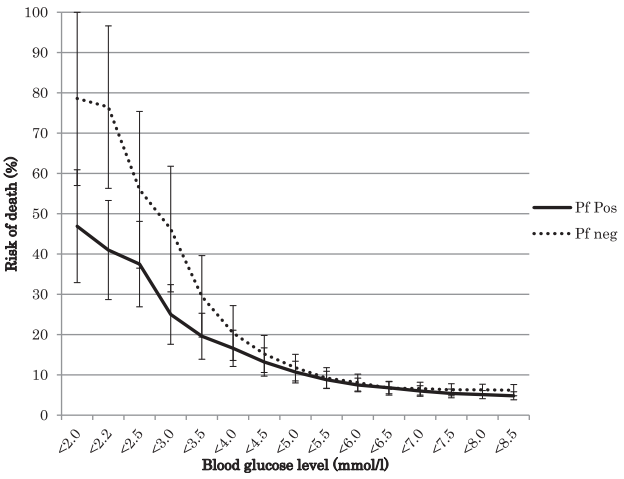

Fig. 3. Mortality risk by admission blood glucose and results of admission blood slide for *Plasmodium falciparum*. Bars represent 95% confidence intervals.

providing them with guidance on how to treat common conditions. The guidance provided a clinical diagnosis based on few tests and the management plan including antibiotic therapy. We found that in our setting, one-third of the patients who were shown to have invasive bacterial disease by blood culture or CSF were missed by these guidelines. This was improved a little by the addition of several other factors as indications for bacterial disease. But in terms of the choice of antibiotic, the guidelines performed poorly; in over half of the cases the bacteria isolated were resistant to the recommended antibiotics. We found the guidelines did not function as well as they should have done in this setting with a lot of malaria transmission [4].

Some other outputs from the study; we explored the relationship between point-of-care blood lactate and mortality. In both malaria slide-positive and slide-negative children, high blood lactate, measured with a point of care device, was associated with a raised case fatality and clinical signs had poor sensitivity to predict hyperlactatemia [7].

We also described the relationship between mortality and admission blood glucose, also measured in all children at admission. Whilst the normal cutoff for hypoglycemia is 2.5 mmol/L, there was greater mortality at levels of blood glucose that were low, but above this threshold for hypoglycemia compared with children with higher blood glucose levels [8] (Fig. 3). Paediatric admissions with blood glucose in this range need to be studied to see if there is anything that could be done to prevent this excess mortality.

Because we were at this site for several years, we were able to look at malaria and non-typhoidal Salmonella over the course of time. In a similar fashion to the studies published from Kilifi in Kenya and also from The Gambia [9, 10], we showed that malaria declined over the course of these years [11]. With this decline came a big drop in non-typhoidal Salmonella bacteraemia and hence all-cause bacteraemia.

Many papers have now been published involving data from the pediatric assessment unit that we set up in 2005 for the SFI study. The unit was then involved in further research and currently the Muheza unit has been involved in over 25 publications relating to the management of child health in African hospitals. The site was involved in two of the most important recent studies. Firstly the AQUAMAT study comparing artesunate and quinine in severe malaria, the Muheza site provided a large number of children to the study [12]. Then, the Fluid Expansion As Supportive Therapy (FEAST) trial for treating impaired perfusion in African children [13]. I think had we not set up the paediatric assessment unit at the beginning, some of this work would not have happened in that setting.

Failings; I think we have been a little bit show in publishing. I think publishing in 2013 research that was completed in 2007 is a bit slow. Also we collected a large number of convalescent plasma samples from patients and we have published little with that, which is a shame. We have published little concerning HIV and severe acute

malnutrition, though some publications may yet come from these data.

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