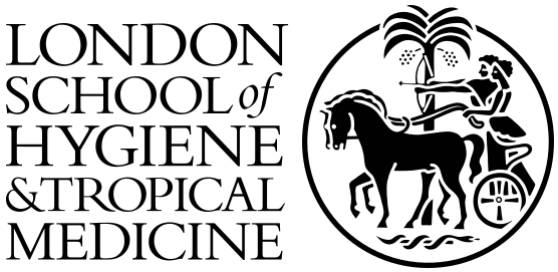

Hospital-acquired infections in two District Hospitals in Kenya

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for Charlotte

Abstract

Introduction: Little is known about hospital-acquired infections (HAI) in developing countries although surgical site infections (SSI) are thought to be a particular problem. The aim of the work in this thesis was to describe three different forms of HAI (SSI, hospital-acquired bacteraemia in children, transmission of MRSA in hospital inpatients) in hospitals in sub-Saharan Africa and to make changes, where possible, to prevent their occurrence.

Methods: A literature review on the subject of SSI in sub-Saharan Africa was conducted as part of the preliminary investigation. To study the occurrence of SSI in Thika Hospital in Kenya, SSI surveillance was established at this site and we subsequently implemented a change in the use of surgical antibiotic prophylaxis at this hospital. The occurrence of MRSA amongst inpatients in Thika Hospital was measured in a cross-sectional study and the occurrence of hospital-acquired bacteraemia in children in Kilifi Hospital, Kenya was measured using surveillance data from 2002-2009.

Results: The epidemiological characteristics of the SSI surveillance programme in Thika Hospital were examined including: the consistency of parameter scoring by surgeons and anaesthetists; the sensitivity and specificity of telephone-based post-discharge surveillance; the performance of risk indicators in predicting SSI after major Obstetric+Gynaecological surgery.

The process, outcome and balancing effects of changing the use of surgical antibiotic prophylaxis at Thika Hospital were evaluated, showing that there was rapid and sustained uptake of pre-operative antibiotic prophylaxis use and a more gradual reduction in use of post-operative antibiotics. There was evidence of a modest reduction in the risk of superficial SSI, and an overall reduction in the use of antibiotics, with accompanying cost and time savings.

The risk, rate, aetiology and morbidity and mortality impacts associated with paediatric hospital-acquired bacteraemia in Kilifi Hospital were examined. In a subsequently published correspondence, questions regarding Coagulase-negative staphylococci, premature infants and competing risks were addressed.

MRSA carriage rate amongst inpatients in Thika Hospital was estimated. This organism was relatively rare, and carriage was largely confined to patients with burns. All MRSA isolates obtained were in the ST239-t037 clone, suggesting within-hospital transmission.

Conclusion: The work of this thesis suggests that the problem of hospital-acquired infections in sub-Saharan Africa is substantial, although there are some simple and achievable steps that can be taken to reduce their occurrence.

Declaration

Statement of Own Work

I declare that this thesis is my own work, and that I have acknowledged all results and quotations from the published or unpublished work of other people. I have read and understood the School's definition of plagiarism and cheating given in the Research Degrees Handbook.

Signed:

Date:

Full name: **Alexander Aiken**

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My final thank you is to Charlotte, who gave up a huge amount to support me on this quixotic and difficult journey – it couldn't have been done without her.

Preface

This PhD thesis consists of a collection of research papers, both published and as-yet-unpublished, relating to the subject of hospital-acquired infections in sub-Saharan Africa. Although these papers all address the same broad subject area, they are intended to be able to stand alone as independent research contributions. Thus there are several repetitions of descriptions and definitions which I hope will not prove too burdensome for the reader. My aim is to "tell the story" of my journey through this research area over the past three years, so that it presents my contributions to this field as a coherent body of work. Each paper is prefaced with a title page that gives the publication status of the paper, as of January 2013.

Chapter 1 gives an introduction to this thesis by providing the historical backdrop to this subject area and describing the sequence of research papers in some detail. Chapters 2 to 4 give three papers relating to Surgical Site Infections – the order of these three papers reflects the progressive stages of the research process, from reviewing the literature, to establishing research methods and finally to attempting to measure the effects of a deliberately introduced change in practice. Chapters 5 relates to an observational study of paediatric nosocomial bacteraemia, with one major paper accompanied by a subsequently published correspondence. Chapter 6 reports a study into the extent and typing of MRSA and *S. aureus* carriage in a single hospital. Chapter 7 provides a final discussion and outlines future directions for research, policy and clinical practice in this area.

Contents

Chapter 1. Introduction

1.1. A brief historical preamble

Histories of the epidemiology of hospital-acquired (nosocomial) infections normally begin with reference to the work of Ignaz Semmelweis, the 19th century Hungarian physician who deduced that contamination on the hands of medical practitioners was transmitting the causative agent of puerpual fever between women in obstetric hospitals in Vienna. As is widely known, his contemporaries largely rejected his conclusions and Semmelweis was ultimately committed to an asylum. He died at the age of 47 from septicaemia, thought to have come from a wound infection sustained in a beating from asylum guards. Posthumously, Semmelweis' conclusions were vindicated by Pasteur's confirmation of the germ theory of disease causation and Lister's pioneering use of sterile surgery – his legacies earn him the title "the father of hospital epidemiology".

This thesis focuses on nosocomial diseases in developing countries, and specifically in countries in sub-Saharan Africa, with the fieldwork reported from studies in two hospitals in Kenya. Therefore, a more appropriate place to begin a history of nosocomial infections in Africa would be with one of the earliest reports of nosocomial disease transmission in this region – which, like this thesis, is a tale of two hospitals in Africa. Much of this information is drawn from reports from the WHO investigating teams in Sudan and Zaire (1-2).

In June and July 1976, in the town of Nzara, Sudan (now South Sudan), close to the border with the Republic of Zaire (now Democratic Republic of Congo) and on the edge of an area of tropical rain-forest, three employees in a cotton factory fell sick with a severe influenza-like illness. Although all three men were employees in the same section of the factory, their lifestyles were otherwise quite different and they lived well apart. The first two cases (YG and BZ) both lived with their families and had few contacts outside their homes. During their illnesses, they were both predominantly nursed by close family members, and both men developed extensive haemorrhagic complications and died within two weeks of becoming ill. The brother of YG developed similar symptoms approximately 10 days later, though he recovered from the illness. The wife of BZ became ill and died five days after her husband. The third factory employee (PG) was a sociable bachelor living in the centre of Nzara town. During his illness, he was visited by many friends, including Samir S and Sallah S (the sons of a local merchant), and nursed by two women, HW and CB. The epidemic

principally propagated from this point and subsequent investigations related 48 cases and 27 deaths in Nzara to the infection in PG, usually involving close nursing or care of an infected individual. Notably, whilst all three primary cases were admitted to the small hospital in Nzara in the later stages of their illnesses, only a minority (26%) of all the cases occurring in Nzara were themselves admitted to hospital. Ultimately, only two patients in Nzara (2/67; 3%) were associated with nosocomial acquisition of infection.

The disease spread out from Nzara in various directions, including to the town of Maridi, 128km away, when Samir S was admitted to the Maridi Hospital in early August 1976. Subsequently, AI, a nurse who had administered injections to Sallah S, in his home was also admitted to Maridi Hospital at the end of August. Although the towns of Nzara and Maridi were of similar sizes, the hospital in Maridi was a much larger teaching facility with approximately 230 staff members, plus a body of student nurses, whereas the hospital in Nzara was limited to a few admitted patients.

In Maridi Hospital in August 1976, staff members began to fall ill with the same disease and were themselves admitted to various different hospital wards – in Maridi, almost three-quarters of cases were admitted to hospital. The number of cases increased gradually until mid-September, and towards the end of the month there was a surge of cases, mainly occurring amongst hospital staff. Before the outbreak could be recognized as such, there were infected, haemorrhagic patients in most of the hospital wards. At least one third of staff at Maridi Hospital became infected, including the doctor-in-charge and 61 of 154 nursing staff. In total, 41 staff members died, including all six medical assistants and over 40% of student nurses. Other patients, carers of acutely ill patients and hospital visitors also were involved and seeded the infection out into the general community. The number of cases declined in early October, possibly as a result of the use of protective clothing – but supplies ran out in mid-October and this was followed by another surge in cases in late October and early November. At the end of October 1976, the WHO team arrived in Maridi with an ample supply of disposable gowns, gloves, masks and other personal protective equipment – and were able to instruct the remaining hospital staff on the use of such clothing and its subsequent decontamination. The disease was, of course, Ebola Virus Disease, which was named after a small river in Zaire, close to Yambuku where an outbreak of disease occurred from September 1976 onwards. Although the outbreak in Zaire was initially thought to have been spread from Sudan by truck drivers – there was extensive commercial traffic between the two areas – it later appeared that the Sudan and Zaire Ebola viruses were of different

species. The disease was deliberately named after a virtually unknown river as it was felt to be insensitive to follow the convention of naming the organism after the town or country from whence the first specimens were obtained (3).

The epidemic curves of disease in the two towns in Sudan are shown below in Figure 1-1:

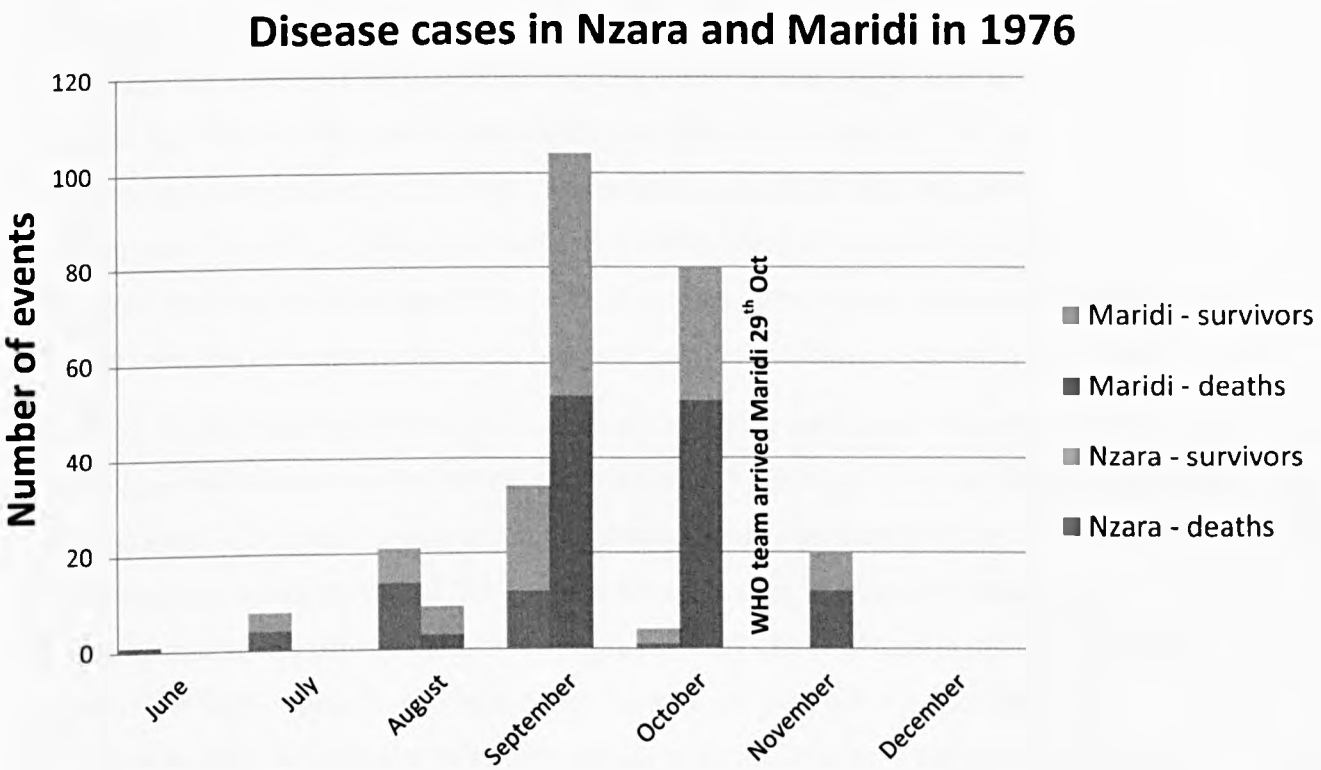


Figure 1-1: Epidemic curves for outbreaks in two towns in Sudan

Overall, more than three times as many Ebola cases occurred in Maridi as in Nzara and almost half of all cases (93/213, 44%) in Maridi were inferred to have the hospital as a source. In the words of the WHO report, "*The* [Maridi] *hospital served as both the focus and amplifier of infection... the hospital served as an efficient amplifier from which the virus was disseminated throughout the town*" (1).Why did the larger, better-staffed hospital serve as the more efficient amplifier of infection? Firstly, as already mentioned, in Maridi, patients were much more likely to be admitted to hospital than in Nzara, though this trend may have reversed once it became evident to the local population that the hospital was the source of disease. Secondly, patients generally only remained admitted in Nzara Hospital for a few days, whereas patients in Maridi Hospital often remained admitted for more than two weeks. Thirdly, the original report described differential transmission risk by type of contact – touching an infected patient was associated with a much lower risk of transmission (5/23:

23%) than performing nursing care (39/48: 81%). We can speculate that in Maridi Hospital, greater efforts were probably being made to provide full nursing care to patients, with the result that more staff were being exposed to the level of contact required for transmission. The concept of barrier nursing would almost certainly not have existed in Maridi Hospital at that time and it is evident (from the allocation of incoming cases to different wards) that in the early stages of the outbreak, patients were not being cohorted by symptoms on admission. Finally, there was probably more widespread access to and use of needles, syringes and intravenous access devices in Maridi Hospital and some of these devices may have been shared between patients – this was the principal mode of Ebola transmission around Yambuku Hospital in Zaire (2). Needlestick and other sharps-related injuries may also have played a part in transmission of Ebola from patients to healthcare workers in Maridi Hospital – this was retrospectively discovered to have occurred in Zaire in the early 1970's (4).

In healthcare epidemiology, outbreaks of highly pathogenic organisms with clearly recognisable clinical syndromes represent the most visible and alarming form of nosocomial infections. Whilst occurrences of such outbreaks always garners much public attention – at the time of writing in August 2012, an Ebola outbreak in Kampala, Uganda was causing major concern in hospitals in Kenya – these outbreaks have generally affected relatively small numbers of people, and have rarely lasted more than a few weeks. In developing countries, other nosocomial infections whose impact is less immediately visible might be having a larger, though less well-recognised impact. Recently, estimations of disease transmission resulting from unsafe injections have suggested that this has played a major role in the transmission of several important bloodbourne viruses including Hepatitis B, Hepatitis C and HIV (5). In sub-Saharan Africa in 1999, it was estimated from a modelling approach that unsafe injections might cause between 780,000 and 1.5 million Hepatitis B infections, between 255,000 and 510,000 Hepatitis C infections and between 51,000 and 102,000 HIV infections annually (6) – though some of these injection-related infections would have been occurring outside of the formal healthcare sector. On this basis, we might suspect that whilst reported outbreaks of noscomial infection in sub-Saharan African are particularly notorious, these probably only represent the "tip of the iceberg" of hospital-acquired infections (HAI) in the region.

Bloodborne viruses are one part of the "rare-but-severe" end of the nosocomial disease spectrum – other infections in this category would include nosocomial bacteraemias which are often associated with implanted medical devices. At the "common-but-treatable"

end of the spectrum are urinary tract infections (usually catheter-related), surgical site infections and diarrhoeal diseases. In between the two ends of the spectrum are several "less-common-but-more-serious" diseases, including nosocomial tuberculosis infection, ventilator-associated and hospital-acquired pneumonias. Underpinning all of these forms of disease is the issue of antibiotic (or more strictly, antimicrobial) resistance – this is often closely related to the nosocomial acquisition of infection, especially for bacterial infections. Addressing whole the spectrum of nosocomial infection research in developing countries as an entirety, the WHO Patient Safety group published a systematic review in 2011 (7), cataloguing the published studies in all the different fields and geographic areas that related to nosocomial infection – see Figure 1-2.

Figure 1-2: Studies describing different forms of HAI in developing countries – adapted from Allegranzi et al (7).

	Africa		Americas		Eastern Med'ean		Europe		Southeast Asia		Western Pacific		Internat'l		Total		
	Adult	Paed	Adult	Paed	Adult	Paed	Adult	Paed	Adult	Paed	Adult	Paed	Adult	Paed	Adult	Paed	All
General HAI	3	1	28	17	12	3	26	2	14	4	3	2	3	0	89	29	118
SSI	6	2	15	1	8	0	8	0	12	0	5	0	0	0	54	3	57
Ventilator-ass'd pneumonia	1	0	2	0	6	0	4	1	5	1	0	0	0	0	18	2	20
Bloodstream infection	0	0	2	0	0	0	3	0	3	3	0	0	0	0	8	5	13
Healthcare-ass'd pneumonia	0	0	2	0	0	0	2	0	2	1	0	0	0	0	6	1	7
UTI	1	0	1	0	1	0	2	0	0	0	0	0	0	0	5	0	5
Totai	11	3	49	19	28	4	45	3	36	9	8	2	3	0	180	40	220

Data represent number of published studies

The results of this literature review, especially the columns relating to studies conducted in Africa, illustrate the extremely limited extent of research in this field in developing countries. Furthermore, much of the limited existing research was found to be of poor quality: according to the reviewers' criteria, over half of all studies included in the review were of low overall quality and *"health-care-associated infection was recorded poorly in some regions, particularly Africa and the western Pacific region."* Additionally, *"very few articles reported antimicrobial resistance"*, although in the few articles that did address this topic, methicillin-resistant *Staphylococcus aureus* (MRSA) was frequently described. However, to some extent, this literature review may actually understate the amount of research conducted in some fields of nosocomial infection in developing countries - the review limited its scope to purely observational work. As we describe in Chapter 2 of this thesis, there is actually a sizeable literature describing interventional studies for the prevention of surgical site infection (SSI) conducted in sub-Saharan Africa – although this is of highly diverse methodological quality. Furthermore, by limiting the review period to 1995-2008, some relevant older work has been omitted. For example, in Chapter 5 of this thesis, we made comparison to a publication relating to hospital-acquired bacteraemia published in South Africa in 1992. Nonetheless, this review, and a subsequent publication by the same group focusing specifically on Africa (8) provide a comprehensive overview of HAI research – or the lack thereof – in developing countries. A commentary piece that accompanied the first review stated *"Healthcare-associated infection in developing countries is a serious issue that is scarcely addressed in the scientific literature"*(9).

The history of epidemiology of hospital-acquired (or healthcare-associated) infection in Africa is limited – very few researchers have tackled this issue, but on the basis of the limited existing research, we would suspect that both the size of the problem and also the scope for improvements might be considerable.

1.2. Scope of this thesis

In the WHO reviews of this topic mentioned above, studies relating to SSI were the most commonly identified form of HAI research undertaken in Africa. The authors in the first review noted "*Surgical-site infection was the leading infection in hospitals,* [...] *strikingly higher than proportions recorded in developed countries*". The review of HAI research in African countries also emphasised the same finding. The major part of this thesis relates to the epidemiology of SSI in an African context. The two other components of this thesis relate to nosocomial bacteraemia and MRSA transmission. Each of these three topics shares some common elements in the broader context of HAI in Africa, and in Figure 1-3 below I have outlined where these are covered in the thesis. This figure repeated at the start of each chapter to help the reader navigate the different subject areas of the thesis.

Figure 1-3: Themes of research

	SSI	Nosocomial bacteraemia	MRSA
Previous research in sSA (or lack thereof)	Ch2	Ch 5	Ch 6
HAI surveillance methods in an African context	Ch 3	Ch 5	Ch 6
Antibiotic use and resistance in sSA	Ch 4		Ch 6
Impacts of HAI in sSA	Ch 4	Ch 5	

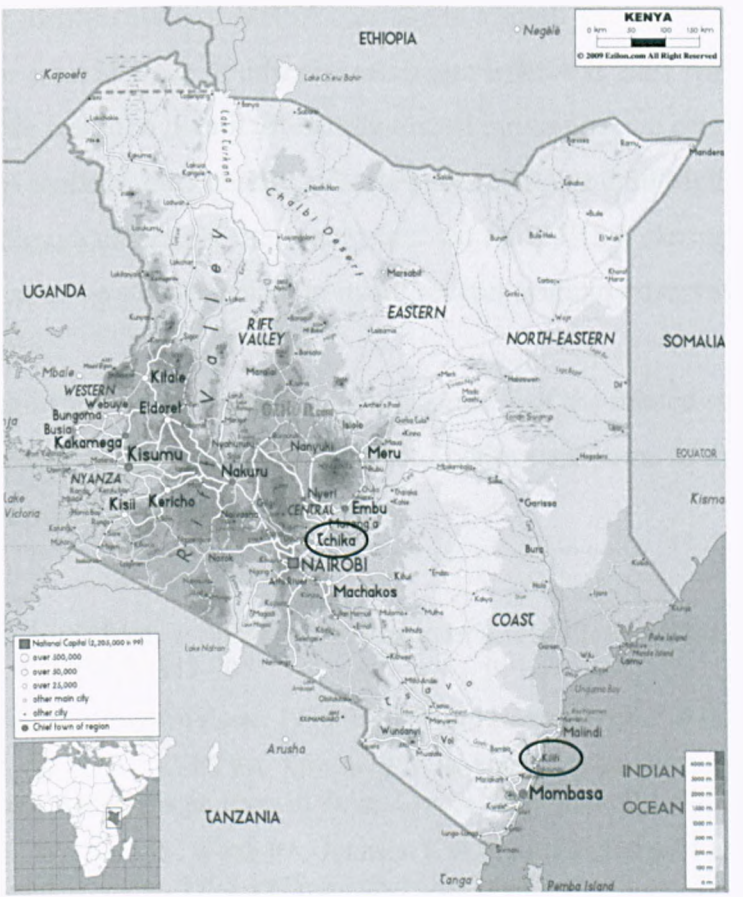
sSA = sub-Saharan Africa

In Chapter 2 of this thesis, I performed a systematic review of publications relating to interventions to prevent SSI in an African context, with the assistance of several surgical colleagues. We felt that it was useful to summarise this existing research in a way that made it easily accessible to the surgeon working in Africa, as much to illustrate the methodological pitfalls encountered in this kind of research as to summarise the actual results of the studies. This review was published in March 2012.

Although several published studies have shown the frequent occurrence of SSI in African hospitals, I was not aware of any studies that examined the methods associated with performing surveillance for this form of HAI in an African context. For the major work of this thesis, I introduced SSI surveillance at a single hospital in Kenya. This work was

conducted in Thika Level 5 Hospital, in Central Province of Kenya, approximately 50km North-East of Nairobi – see Figure 1-4. In Chapter 3 of this thesis, I examine some of these methods that were used in this surveillance in detail, focussing on consistency of scoring of key parameters relating to SSI risk, use of a telephone-based post-discharge SSI surveillance method and performance of the CDC-NHNS Risk Index in major O+G surgery.

Figure 1-4: Location of two hospital study sites in Kenya



In Chapter 4, I describe the process of implementing a change in the use of antibiotic prophylaxis in Thika Hospital to bring this into line with national guidelines and the international evidence base. We used the same surveillance methods described in the previous chapter to assess the impact of this change in practice on the risk of SSI and also consider the impact on resource utilization in the hospital.

In Chapter 5, I switch the focus to paediatric nosocomial bacteraemia and using a continuous 7-year period of inpatient surveillance data from Kilifi Hospital in Coast Province (see Figure 1-4 above), I describe some of the basic epidemiological and microbiological parameters relating to this form of HAI – this was published in December 2011. This is

followed by an appendix that accompanied publication of this report which gives further details about Kilifi Hospital, and then by a published correspondence that followed from the publication of the original article.

In Chapter 6, I describe an investigation into the occurrence of MRSA carriage in adult inpatients in Thika Hospital, coupled with laboratory-based description of all the *S.aureus* isolates obtained. Further laboratory investigations were performed at the University Medical Centre Groningen (UMCG), in the Netherlands. The original idea for this piece of work arose with the identification of MRSA carriage in a small number of inpatients in Thika Hospital. In the near-total absence of other research into MRSA in East Africa, we believed that MRSA was more common than it ultimately turned out to be – we originally envisaged collecting 50 MRSA isolates, but actually collected six MRSA and 80 Methicillin-sensitive *S. aureus* isolates. Although ultimately the conclusion was that MRSA carriage in Thika Hospital was quite rare, we still were able to make several original observations about this pathogen in this setting.

I conclude this thesis with a discussion in Chapter 7 of the related strands of work in healthcare epidemiology in Africa and outline what I believe are some of the important research, policy and practice issues for the future.

References

1. Ebola haemorrhagic fever in Sudan, 1976. Report of a WHO/International Study Team. Bull World Health Organ. 1978;56(2):247-70.

2. Ebola haemorrhagic fever in Zaire, 1976. Bull World Health Organ. 1978;56(2):271-93.

3. Johnson KM, Lange JV, Webb PA, Murphy FA. Isolation and partial characterisation of a new virus causing acute haemorrhagic fever in Zaire. Lancet. 1977 Mar 12;1(8011):569-71.

4. Heymann DL, Weisfeld JS, Webb PA, Johnson KM, Cairns T, Berquist H. Ebola hemorrhagic fever: Tandala, Zaire, 1977-1978. J Infect Dis. 1980 Sep;142(3):372-6.

5. Simonsen L, Kane A, Lloyd J, Zaffran M, Kane M. Unsafe injections in the developing world and transmission of bloodborne pathogens: a review. Bull World Health Organ. 1999;77(10):789-800.

6. Kane A, Lloyd J, Zaffran M, Simonsen L, Kane M. Transmission of hepatitis B, hepatitis C and human immunodeficiency viruses through unsafe injections in the developing world: model-based regional estimates. Bull World Health Organ. 1999;77(10):801-7.

7. Allegranzi B, Bagheri Nejad S, Combescure C, Graafmans W, Attar H, Donaldson L, et al. Burden of endemic health-care-associated infection in developing countries: systematic review and meta-analysis. Lancet. 2011 Jan 15;377(9761):228-41.

8. Bagheri Nejad S, Allegranzi B, Syed SB, Ellis B, Pittet D. Health-care-associated infection in Africa: a systematic review. Bull World Health Organ. 2011 Oct 1;89(10):757-65.

9. Rosenthal VD. Health-care-associated infections in developing countries. Lancet. 2011 Jan 15;377(9761):186-8.

Chapter 2.

Research paper I: Interventional studies for preventing surgical site infections in sub-Saharan Africa - a systematic review

Author(s): Alexander M. Aiken, David M. Karuri, Anthony K. Wanyoro, Jana Macleod

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	SSI	Nosocomial bacteraemia	MRSA
Previous research in sSA (or lack thereof)	Ch2	Ch 5	Ch 6
HAI surveillance methods in an African context	Ch 3	Ch 5	Ch 6
Antibiotic use and resistance in sSA	Ch 4		Ch 6
Impacts of HAI in sSA	Ch 4	Ch 5	

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Review

Interventional studies for preventing surgical site infections in sub-Saharan Africa – A systematic review

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ABSTRACT

Background: There is a great need for safe surgical services in sub-Saharan Africa, but a major difficulty of performing surgery in this region is the high risk of post-operative surgical site infection (SSI).
Methods: We aimed to systematically review which interventions had been tested in sub-Saharan Africa to reduce the risk of SSI and to synthesize their findings. We searched Medline, Embase and Global Health databases for studies published between 1995 and 2010 without language restrictions and extracted data from full-text articles.
Findings: We identified 24 relevant articles originating from nine countries in sub-Saharan Africa. The methodological quality of these publications was diverse, with inconsistency in definitions used for SSI, period and method of post-operative follow-up and classification of wound contamination. Although it was difficult to synthesise information between studies, there was consistent evidence that use of single-dose pre-operative antibiotic prophylaxis could reduce, sometimes dramatically, the risk of SSI. Several studies indicated that alcohol-based handrubs could provide a low-cost alternative to traditional surgical hand-washing methods. Other studies investigated the use of drains and variants of surgical technique. There were no African studies found relating to several other promising SSI prevention strategies, including use of checklists and SSI surveillance.
Conclusions: There is extremely limited research from sub-Saharan Africa on interventions to curb the occurrence of SSI. Although some of the existing studies are weak, several high-quality studies have been published in recent years. Standard methodological approaches to this subject are needed.

1. Introduction

Performing surgery in sub-Saharan Africa has many challenges different from those encountered in high-income countries: costs are usually severely constrained; numbers of trained theatre staff are generally low and facilities are often rudimentary. However, one of the principal difficulties for the surgeon in sub-Saharan Africa is the high risk of post-operative surgical site infection (SSI). In two recent WHO-led review papers, the risk of SSI in developing countries was *"strikingly higher than in equivalent surgical procedures in high-income countries"*[1] and the problem was found to be particularly acute in sub-Saharan Africa.[2] Although extensive research into SSI prevention has been conducted in high-income countries, we were aware of few interventional studies that had been conducted in sub-Saharan Africa. As SSI constitutes a major challenge for surgeons in African countries, we felt this might represent a significant "knowledge gap" in clinical science.

We therefore set out to summarise interventional studies conducted in sub-Saharan Africa that had attempted to reduce the risk of SSI. We systematically reviewed publications relating to this topic to collate the existing African research for the general surgical audience, and also outline the way forward for future studies addressing this important issue.

2. Methods

2.1. Search strategy

We aimed to identify all recent publications giving information on interventions used to reduce the risk of SSI where the research was conducted in countries in sub-Saharan Africa (sSA), without restriction to type of surgery or intervention.

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We searched Medline, Embase and Global Health databases for reports published between January 1995 and December 2010 with no language restrictions. We used search terms as shown in Fig. 1.

Each title/abstract was screened by two of the authors and a decision on which full-text articles to retrieve was reached after discussion amongst all authors. Additional searches were performed using the reference sections of identified publications and the authors' own knowledge of the area. Articles were defined as "interventional" studies if the full-text manuscript contained information on at least two groups of patients for whom different management (of whatever type) had been used in an attempt to reduce the risk of SSI after any type of surgical procedure. "Interventional studies" were not limited to randomised controlled trials (RCT) – other direct comparisons (e.g. "before and after" studies) were also included.

2.2. Inclusion + exclusion criteria

We included interventional studies conducted in sSA, published between 1995 and 2010. We excluded studies where occurrence of SSI was not a major focus of the intervention. We excluded multicentre studies where data from African sites was not presented separately. We did not exclude any surgical specialities or reject any articles based on quality criteria.

3. Results

3.1. Search findings

Our search yielded 3105 abstracts, of which 247 were judged to be of possible relevance. From these 247, further abstracts were excluded as they contained purely descriptive data (i.e. no comparison of treatments/managements; $n = 199$) or microbiological reports of SSI in sSA ($n = 19$) (Fig. 2). Full-text articles were retrieved for 29 studies, of which seven made use of external comparison groups and therefore did not meet our definition of "interventional". Two further studies were identified from additional searches. A total of 24 studies in English and French were included.

Studies originated from nine different countries, most frequently Nigeria ($n = 8$), followed by South Africa ($n = 5$), Côte d'Ivoire ($n = 2$), Kenya ($n = 2$), Tanzania ($n = 2$) and Uganda ($n = 2$). There was one study included from each of Ethiopia, Ghana and Mozambique. Studies were written in English ($n = 22$) and French ($n = 2$). For ease of presentation, we separated the studies identified into those relating to the use of antibiotic prophylaxis ($n = 10$), pre-operative interventions ($n = 4$), intra-operative interventions, including different surgical techniques and devices ($n = 6$) and post-operative interventions ($n = 4$) – see Tables 1–4, respectively, arranged by year of publication.

3.2. Comparison of studies: methodology

3.2.1. Study design

Patients undergoing a variety of surgical procedures formed the subjects for these studies: the majority of studies examined the effects of an intervention in a single type of surgery, most frequently Caesarean sections ($n = 11$). Most studies were conducted in a single centre and used an individually randomised, controlled trial (RCT) design. One study used cluster randomisation (by operating theatre), two studies used a "before and after intervention" design and one study allowed surgeons to select their operating technique (relating to peritoneal closure) and passively observed results. Two studies of antibiotic prophylaxis used a placebo-control group, whilst all other studies used a recognised standard treatment as the control or baseline arm.

3.2.2. RCT components

There were marked variations in the key elements of RCT design and execution. Some studies clearly described the efforts made to achieve single blinding (investigator only) or double blinding (investigator and participant), although for some operative procedures, it would clearly be impossible to blind the surgeon to the treatment status. A well-conducted RCT of an antibiotic prophylaxis intervention in South Africa achieved double blinding by using a placebo solution with the same appearance as the antibiotic agent.[3] The actual method used for randomisation was reported in 77% of RCTs (17/21), although two RCTs randomised by allocating alternate patients to the intervention and control arms (alternating assignment).[4,5] No RCTs were designed from the outset as therapeutic equivalence studies, but several studies finding no significant difference between intervention and standard treatments were interpreted by the authors as providing evidence of equivalence. Only one study[6] reported adherence to the CONSORT guidelines, which were first published in 1996.[7]

3.2.3. Study size

The total number of patients included ranged from 50 to 3317 subjects, and most studies (17/24, 71%) did not include a sample size calculation.

3.2.4. SSI definitions

There was no consistent usage of any standard schema for defining or classifying surgical site infections. Eight studies provided their own definitions of what they judged to be an SSI, seven studies made reference to a schema described elsewhere and nine studies did not provide any (clear) definition of what they considered as an SSI. The most commonly referenced external schema for SSI classification was that of the Centres for Disease Control (CDC)[5] – this was referred to by 3 studies.

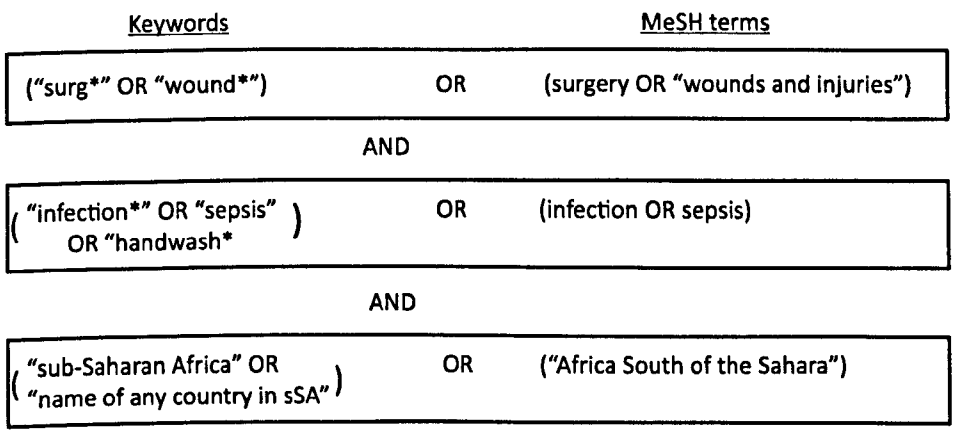

Fig. 1. Search items used for systematic review.

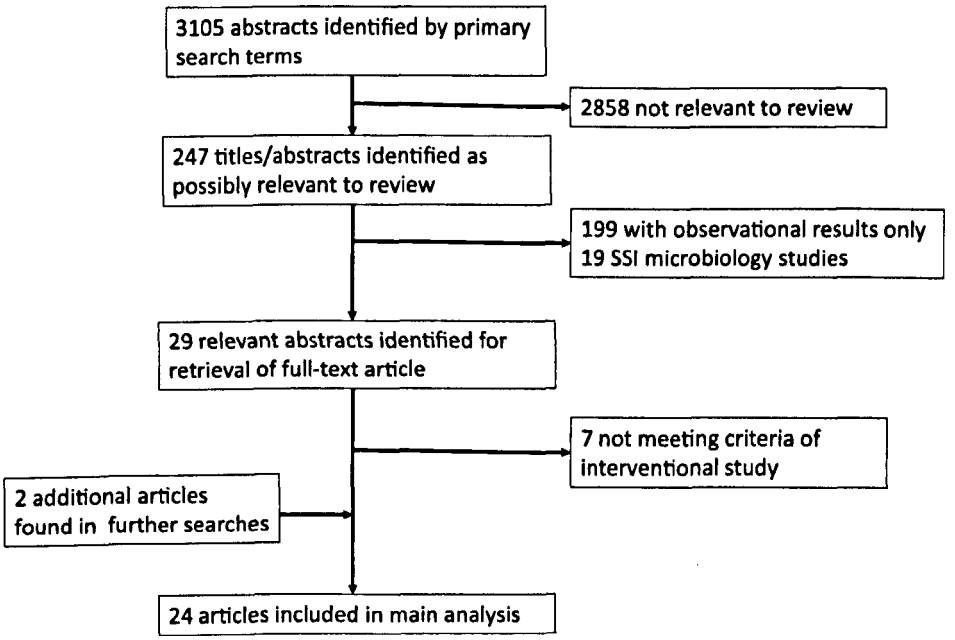

Fig. 2. Flow diagram for selection of articles.

3.2.5. Follow-up

The post-operative follow-up period and the methods employed to achieve this were also highly variable. Follow-up periods used ranged from 5 days to 12 months. In most studies the follow-up period included both inpatient and outpatient periods (15/24, 63%), though the intensity of effort in outpatient follow-up was diverse. Five studies only followed up patients until discharge and five studies did not report how follow-up was performed. In order to achieve high levels of post-discharge follow-up, one study in Côte d'Ivoire reviewed patients on alternate days up to 30 days after their operation [8] and a study in Tanzania provided the transport fare and a free meal for participants who attended their 30-day post-operative review.[9] A study in Kenya used telephone calls to contact patients after discharge,[6] though no information was provided on the sensitivity or specificity of this method with respect to a gold standard of "in-person" physician or nurse review.

3.2.6. Wound contamination

Few studies ($n = 4$) made use of a schema for stratifying patients by degree of wound contamination, such as the Surgical Wound Class,[10] though some studies stated that they excluded patients with unusually contaminated surgical wounds.

3.3. Comparison of studies: effects of interventions

It is challenging to summarise the effects of these different interventions due to the variation in SSI definitions, follow-up periods and methods between studies and the failure of most studies to describe the extent of wound contamination.

3.3.1. Antibiotic prophylaxis (Table 1)

The most commonly examined intervention for preventing SSI was the use of antibiotic prophylaxis ($n = 10$), either in comparison to a placebo treatment, or more normally in comparison to an alternative prophylaxis regime. Many different drug regimes were examined, in the context of a variety of different surgical procedures. Precise information about actual timing of dose administration and re-dosing during long procedures was only given in 2/10 studies. Several studies compared the use of a single-dose pre-operative intravenous administration regime against a "standard" regime of prolonged post-operative antibiotic prophylaxis. All of these studies found that a single-dose pre-operative dosing regime was superior to a prolonged post-operative regime, either in terms of reduced use of drugs[9,11–15] or reduced risk of SSI.[9,16] One study in Tanzania showed a pronounced effect of implementation of a single-dose pre-operative amoxillin/clavulanate prophylaxis regime: the risk of SSI declined from 21.6% to 4%.[9] Studies where the use of post-operative antibiotic prophylaxis was avoided or restricted reported no adverse effects of such a restriction. Both the placebo-controlled trials, including one study of cefoxitin prophylaxis for C-section patients in South Africa,[3] found no benefit of use of antibiotic prophylaxis over placebo.

3.3.2. Pre-operative interventions (Table 2)

Amongst the (non-antibiotic) pre-operative interventions ($n = 4$), two studies on the use of an alcohol-based handrub as an alternative to the traditional surgical hand-washing agents gave consistent results. A large cluster-randomised trial conducted in Kenya[6] showed no significant difference in the risk of SSI when an alcohol-based handrub was substituted for the traditional soap + water used for the pre-operative surgeon's hand-wash. Costs for the alcohol handrub were found to be similar to traditional hand-washing method, and the authors noted that alcohol handrub might be much more convenient for institutions where water supply was erratic. A "before and after" study in Côte d'Ivoire[8] provided similar results and judged that alcohol handrub would be much more cost-effective for an institution to provide. A study in Nigeria[17] examined the use of a locally produced soap + methylated spirit preparation for use in cleaning the patient's skin pre-operatively, in comparison to (much more expensive) povidone-iodine – no difference in the risk of SSI was detected. No studies examined the use of pre-operative checklists as a tool for making surgery safer.

3.3.3. Intra-operative interventions (Table 3)

Studies relating to intra-operative interventions ($n = 6$) mainly related to different operative techniques. Four studies[5,18–20] examined two alternative surgical techniques that might reduce

Table 1
Antibiotic prophylaxis studies ($n = 10$).

Country, year of publication	Surgical procedure(s)	Intervention	Study design and RCT components	Study size	SSI definitions	Use of SWC	Follow-up period + methods	Results/notes
Uganda, 1996[11]	Variety of "abdominal" procedures	Antibiotic prophylaxis	RCT, randomized within procedure	850	From Karl et al.	No	14 days initially as IP, then via OP clinic	Single-dose pre-op ampicillin (±metronidazole) (intervention) was cheaper than extended post-op penicillin (standard) with similar rates of SSI
South Africa, 2001[3]	Caesarean section	Antibiotic prophylaxis	RCT, double blind, placebo-controlled	480	Own	No	6 weeks – as inpatient and at post-natal visit	No difference in SSI risk with pre-op cefoxitin (intervention) versus placebo.
Mozambique, 2003[12]	Caesarean section	Antibiotic prophylaxis	RCT, outcome assessor blinded	288	Own	No	7 days follow-up, r/v in OP clinic on d7	Single-dose pre-op gentamicin + metronidazole was much cheaper and as effective as extended post-op antibiotic regime (standard)
Côte d'Ivoire, 2003[32]	Orthopaedic procedures	Antibiotic prophylaxis	RCT, double blind	162	Own	NRC class used	1 yr follow-up, with r/v at d1, d8, d15, d30, 6 months, 1yr.	No difference in SSI risk between pre-op oxacillin and pre-op perfloxacin, but oxacillin cheaper.
Nigeria, 2006[4]	Clean paediatric surgery	Antibiotic prophylaxis	RCT, double blinded, placebo-control	278	Not described	No	Assessed on d5, d7, d10 by doctor	No benefit to use of ampiclox (intervention) over placebo (control) in preventing SSI in clean surgery, additional costs with use of antibiotics.
Ghana, 2007[13]	Caesarean section	Antibiotic prophylaxis	RCT, no blinding reported	320	Own	No	Not reported	Significantly lower risk of infection with intra-op amoxicillin/clavulanate (intervention) than with intra-op "ampicillin + gentamicin + metronidazole" (standard).
Nigeria, 2008[14]	Caesarean section (elective)	Antibiotic prophylaxis	Multicentre RCT, patients blinded	200	Own	No	7 days IP follow-up, with r/v on d3 and d5	No significant difference between single-dose intra-op ceftriaxone (intervention) versus post-op gentamicin + ampiclox + metronidazole (standard)
Nigeria, 2008[16]	Inguinal hernia	Antibiotic prophylaxis	RCT, no blinding reported	88	NRC	No	32 day follow-up with r/v on d4, d11, d32	Pre-op single-dose gentamicin (intervention) was associated with significantly less risk of wound infection than no antibiotic (control).
Tanzania, 2009[9]	Wide variety of procedures	Antibiotic prophylaxis	"Before and after" intervention	803	CDC	Yes	30 day, with travel expenses + meal paid for follow-up OP visit	Compared various post-op antibiotics ("before") with single-dose pre-op amoxicillin/clavulanate ("after") with 80% reduction in SSI risk for "after" arm.
Ethiopia, 2010[15]	Obstetric fistula repair	Antibiotic prophylaxis	RCT, single blinded	722	Own	No	Not clear from paper	Single-dose pre-op gentamicin (intervention) as effective as extended post-op regime of antibiotics (control).

Note: the following abbreviations are used in Tables 1–4: RCT, randomised controlled trial; IP, inpatient; OP, outpatient; r/v, review; SSI, surgical site infection; CDC, Centres for Disease Control; d5, 5th post-operative day; w4, 4th post-operative week; 3m, 3 months; 1yr, 1 year; NRC, National Research Council, USA; O + G, Obstetrics and Gynaecology; SWC, Surgical Wound Class (=Altemeier Class); and VP, ventriculo-peritoneal.

Table 2
Pre-operative intervention studies ($n = 4$).

Country, year of publication	Surgical procedure(s)	Intervention	Study design and RCT components	Study size	SSI definitions	Use of SWC	Follow-up period + methods	Results/notes
South Africa, 2001[33]	Caesarean section	Adhesive plastic drapes	Double blind RCT	605	Own	No	Wound assessed by clinician on post-op d2, d3, d4, d5	No evidence of any benefit from use of plastic drapes (no reduction of SSI nor reduction in admission length).
Nigeria, 2001[17]	Inguinal hernia	Skin preparation	RCT, no report of randomization method	200	Not described	No	R/v at d5–d10 (suture removal) and w4–w8	No difference in SSI risk between market soap + methylated spirit (intervention) and povidone-iodine (control), but former (presumed) cheaper
Côte d'Ivoire, 2009[8]	Various O + G proceedures	Surgical hand-wash	"Before and after" intervention	318	CDC	Yes	30 days – seen on alternate days	No difference in SSI risk between alcohol handrub (intervention) and povidone-iodine (standard). Alcohol handrub much more cost-effective.
Kenya, 2010[6]	Wide variety of procedures	Surgical hand-wash	Cluster RCT, crossover design	3317	CDC	Yes	30 days, OP clinic r/v and telephone calls for follow-up	No significant difference in SSI risk between soap + water (standard) and alcohol handrub (intervention), with similar costs.

Table 3
Intra-operative intervention studies ($n = 6$).

Country, year of publication	Surgical procedure(s)	Intervention	Study design and RCT components	Study size	SSI definitions	Use of SWC	Follow-up period + methods	Results/notes
Tanzania, 2000[19]	Caesarean section	Misgav-Ladach technique	RCT, no blinding reported	339	Not described	No	Inpatient period only	No difference in SSI risk between ML technique (intervention) and standard midline incision. Less blood loss, sutures and shorter op with ML technique
Kenya, 2001[5]	Caesarean section	Misgav-Ladach technique	RCT but weak randomization method	160	From Karl et al	No	6 weeks – seen on d7 (discharge) and at 6w	ML technique (intervention) had lower risk of SSI than standard midline incision. Shorter op and less analgesia with intervention.
Uganda, 2005[21]	VP shunt insertion	Comparing VP shunt systems	RCT, no blinding reported	90	Not described	No	1yr follow-up: OP review at 1w, 3m and 1yr	No difference in any outcome (inc SSI) between 2 types of VP shunt, but one shunt system much cheaper (US$35) than the other (US$650).
Nigeria, 2006[18]	Caesarean section	Peritoneal non-closure	RCT, blinding not explicitly stated	54	Not described	No	Not described	No significant difference found between peritoneal closure (standard) and non-closure (intervention), but non-closure cheaper and shorter surgery duration.
South Africa, 2009[22]	Circumcision	Tara-KLamp technique	RCT, no blinding used	69	Own	No	Wound examined by clinician on d3 and 6w. Self-report at 2w.	High rate of refusal of TK technique. More adverse events with TK technique (intervention) including wound infection.
South Africa, 2009[20]	Caesarean section	Peritoneal non-closure	Observational – surgeons choice of 3 methods	692	Not described	No	10 days post-partum	Compared double, single and non-closure of peritoneum. No significant difference in risk of SSI between method, but faster surgery with non-closure

Table 4
Post-operative intervention studies ($n = 4$).

Country, year of publication	Surgical procedure(s)	Intervent	Study design and RCT components	Study size	SSI definitions	Use of SWC	Follow-up period + methods	Results/notes
South Africa, 2000[23]	Caesarean section (emergency)	Wound drainage	RCT, no blinding used	440	From Wells et al	No	Assessed daily while IP until discharge/up to d7	No difference in SSI risk or admission length between use of drain (intervention) and no drain (standard).
Nigeria, 2000[24]	Caesarean section	Early discharge	RCT, outcome assessor blinded	100	Not described	No	Wound examined on d3 and d7 only.	No difference in SSI risk with early discharge and marked psychological benefit of early discharge.
Nigeria, 2008[24]	Mastectomy	Wound drainage	RCT, no blinding used	50	Not described	No	At least 1 month via OP clinic	No difference in wound infection risk or other outcomes between suction drain and simple drain, but simple drain much cheaper
Nigeria, 2010[25]	Thyroid surgery	Wound drainage	RCT, no blinding reported	67	Not clearly described	No	Not described	Higher incidence of wound infection with use of drains, resulting in increase inpatient stay and costs.

the operating time in Caesarean sections (peritoneal non-closure and the Misgav-Ladach incision) – all studies reported shorter duration of surgery without elevated SSI risk in the experimental arm of the study with elevated SSI risk. One study in Uganda[21] compared the use of two different ventriculo-peritoneal (VP) shunts – one system was almost 20 times cheaper than the other with an equivalent risk of shunt complications including blockage, device infection and SSI. One study in South Africa[22] described an experimental technique for circumcision of adults (Tara-Klamp) – this was found to have many drawbacks, including higher risk of SSI.

3.3.4. Post-operative interventions (Table 4)

Amongst studies examining post-operative interventions to reduce the risk of SSI ($n = 4$), three studies examined the use of wound drains in the post-operative period[23–25] – we considered these as a "post-operative" intervention, although drains were inserted intra-operatively. None of these studies found a benefit in terms of reduced risk of post-operative complication with more extensive use of drains, and one study found higher risk of SSI in patients with drains (for thyroid surgery). There appears to be consistent evidence that the use of post-operative wound drains should be as conservative as possible in an African surgical setting. No studies on post-operative SSI surveillance as a method of reducing SSI risk at the institutional level were found.

4. Discussion

Over a 15-year review period, we found only 24 studies describing interventional studies conducted in sub-Saharan Africa for reducing the risk of post-operative SSI, although ten of these were from the last three years of the review period (2008–2010).

4.1. Limitations of studies

There were many common errors in designing interventional research studies relating to SSI in Africa. For example, two studies used alternating assignment to "randomise" patients – this is not a suitable method as it allows easy prediction of which treatment the patient will receive. Many studies were likely to be too small to properly evaluate the effect of their intervention on the primary outcome (under-powered) – this could have addressed by performing proper sample size calculations or by combining studies across several sites. However, larger trials are more expensive and multicentre studies present their own logistical challenges. A common misunderstanding in trial interpretation was that failure to find a difference does not mean proof of equivalence – special trial designs (non-inferiority or equivalence trials) are needed to prove equivalence.

The lack of consistency of SSI definitions, follow-up methods and time-periods makes comparisons between these existing studies difficult. Few studies used comparable definitions of what was considered as an SSI and how these were detected. The degree of contamination of the surgical wound is known to be an extremely strong predictor of the risk of SSI in low-income settings,[1] so use of such a standard stratification system would have facilitated comparisons of the effect of interventions.

4.2. Potential future improvements

Some solutions to these problems that could be applied in the future are as follows: adoption of the standard definitions and classification of SSI as provided by the CDC[26] and of the Surgical Wound Class as used in various studies.[10] The CDC defines SSI as an infection at the site of the operation within 30 days of the procedure or within 12 months if there is implanted material – universal

adherence to this follow-up period would facilitate comparison between studies. In low-resource settings in sSA, it may be difficult to achieve post-operative follow-up when travelling to clinic appointments is prohibitively expensive for patients. Some innovative approaches to post-discharge follow-up (such as contacting patients by telephone) identified in this review may be suitable for further examination in an African context – these need further examination of their sensitivity and specificity in detecting SSI in this context.

4.3. Research findings

The existing African research on SSI prevention does provide some important messages which need wide dissemination. Correct use of surgical antibiotic prophylaxis (i.e. single dose, pre-operative delivery) can, in some circumstances, lead to very dramatic reductions in the risk of SSI and can also reduce costs for the patient or institution. This goes directly against the widely held belief amongst African surgeons [in our experience] that "poor hygiene" or crowding in their wards necessitates prolonged post-operative antibiotic usage. Two studies showing no benefit of pre-operative antibiotic prophylaxis over placebo serve to remind prophylaxis regimes are not universally efficacious – locally appropriate agents must be determined. Improved use of antibiotic prophylaxis across sub-Saharan Africa could cut the risk of SSI and simultaneously conserve precious (antibiotic) resources. Use of alcohol handrubs has been shown in two studies to be equivalent (in terms of SSI risk) to traditional soap + water for pre-operative hand-washing by the surgeon and may lead to cost-savings for the institution – this low-cost technology deserves further evaluation across the continent. Use of post-operative drains should be sparing and early discharge should be encouraged, where possible. Some variations in surgical technique were found to be promising, but need more extensive evaluation of their acceptability to surgeons and patients. Some "low-cost" alternative surgical implants and consumables appeared to be equivalent to the standard versions.

Many of these findings are consistent with research and guidelines for preventing SSI originating from high-income settings.[27–31] No research studies examining the use of checklists or post-operative SSI surveillance were identified – these are promising areas for future work.

5. Conclusions

Although little research on how to prevent SSI in surgical practice in sub-Saharan Africa has been published, there are some encouraging signs – several high-quality studies have been undertaken in recent years and promising new methodologies and technologies are apparent. This review highlights the inconsistency of SSI definitions and follow-up methods that have been used in studies in sub-Saharan Africa in the past, and suggests that these could be resolved in the future by use of standard international definitions of SSI, such as those provided by the CDC. Important lessons can be drawn from the existing research – proper use of antibiotic prophylaxis in surgery can dramatically reduce the risk of SSI and alcohol-based preparations may provide a low-cost alternative to traditional surgical hand-washing and skin preparation methods.

Ethical approval

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Conflicts of interest

All authors declare that they have no conflicts of interest. JM and AW are currently practicing surgeons and DK is a resident (trainee) surgeon in sub-Saharan Africa.

Author contributions

AA designed the review methodology. All authors screened a portion of the titles and abstracts, and participated in discussion regarding inclusion and exclusion of papers. AA and DK extracted key data from the identified publications. AA wrote the manuscript and all authors reviewed and approved this prior to submission.

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References

1. Allegranzi B, Nejad SB, Combescure C, Graafmans W, Attar H, Donaldson L, et al. Burden of endemic health-care-associated infection in developing countries: systematic review and meta-analysis. *Lancet* 2011;**377**(9761):228–41.
2. Bagheri Nejad S, Allegranzi B, Syed SB, Ellis B, Pittet D. Health-care-associated infection in Africa: a systematic review. *Bull World Health Organ* 2011;**89**(10): 757–65.
3. Bagratee JS, Moodley J, Kleinschmidt I, Zawilski W. A randomised controlled trial of antibiotic prophylaxis in elective caesarean delivery. *BJOG* 2001;**108**(2):143–8.
4. Osuigwe AN, Ekwunife CN, Ihekowba CH. Use of prophylactic antibiotics in a paediatric day-case surgery at NAUTH, Nnewi, Nigeria: a randomized double-blinded study. *Trop Doct* 2006;**36**(1):42–4.
5. Ansaloni L, Brundisini R, Morino G, Kiura A. Prospective, randomized, comparative study of Misgav Ladach versus traditional cesarean section at Nazareth Hospital, Kenya. *World J Surg* 2001;**25**(9):1164–72.
6. Nthumba PM, Stepita-Poenaru E, Poenaru D, Bird P, Allegranzi B, Pittet D, et al. Cluster-randomized, crossover trial of the efficacy of plain soap and water versus alcohol-based rub for surgical hand preparation in a rural hospital in Kenya. *Br J Surg* 2010;**97**(11):1621–8.
7. Begg C, Cho M, Eastwood S, Horton R, Moher D, Olkin I, et al. Improving the quality of reporting of randomized controlled trials. The CONSORT statement. *JAMA* 1996;**276**(8):637–9.
8. Adjoussou S, Ble RK, Seni K, Fanny M, Toure-Ecra A, Koffi A, et al. Value of hand disinfection by rubbing with alcohol prior to surgery in a tropical setting. *Med Trop* 2009;**69**(5):463–6 [in French].
9. Saxer F, Widmer A, Fehr J, Soka I, Kibatala P, Urassa H, et al. Benefit of a single preoperative dose of antibiotics in a sub-saharan district hospital: minimal input, massive impact. *Ann Surg* 2009;**249**(2):322–6.
10. Culver DH, Horan TC, Gaynes RP, Martone WJ, Jarvis WR, Emori TG, et al. Surgical wound infection rates by wound class, operative procedure, and patient risk index. National Nosocomial Infections Surveillance System. *Am J Med* 1991;**91**(3B):152S–7S.
11. Reggiori A, Ravera M, Cocozza E, Andreata M, Mukasa F. Randomized study of antibiotic prophylaxis for general and gynaecological surgery from a single centre in rural Africa. *Br J Surg* 1996;**83**(3):356–9.
12. Kayihura V, Osman NB, Bugalho A, Bergstrom S, Kayihura V, Osman NB, et al. Choice of antibiotics for infection prophylaxis in emergency cesarean sections in low-income countries: a cost–benefit study in Mozambique. *Acta Obstet Gynecol Scand* 2003;**82**(7):636–41.
13. Opoku BK. Prophylactic antibiotic during Caesarean sections at Komfo Anokye Teaching Hospital, Kumasi. *Ghana Med J* 2007;**41**(2):48–51.
14. Alekwe LO, Kuti O, Orji EO, Ogunniyi SO. Comparison of ceftriaxone versus triple drug regimen in the prevention of cesarean section infectious morbidities. *J Matern Fetal Neonatal Med* 2008;**21**(9):638–42.
15. Mulu M, Biruk T, Aytenfisu HG. Antibiotic use in obstetric fistula repair: single blinded randomized clinical trial. *Ethiop Med J* 2010;**48**(3):211–7.
16. Usang UE, Sowande OA, Adejuyigbe O, Bakare TIB, Ademuyiwa OA. The role of preoperative antibiotics in the prevention of wound infection after day case surgery for inguinal hernia in children in Ile Ife, Nigeria. *Pediatr Surg Int* 2008;**24**(10):1181–5.
17. Meier DE, Nkor SK, Aasa D, OlaOlorun DA, Tarpley JL. Prospective randomized comparison of two preoperative skin preparation techniques in a developing world country. *World J Surg* 2001;**25**(4):441–3.
18. Malomo O, Kuti O, Orji E, Ogunniyi S, Sule S. A randomised controlled study of non-closure of peritoneum at caesarean section in a Nigerian population. *J Obstet Gynaecol* 2006;**26**(5):429–32.
19. Bjorklund K, Kimaro M, Urassa E, Lindmark G. Introduction of the Misgav Ladach caesarean section at an African tertiary centre: a randomised controlled trial. *BJOG* 2000;**107**(2):209–16.

20. van Bogaert LJ, Misra A. Peritoneal closure or non-closure at caesarean section. *J Obstet Gynaecol* 2009;**29**(3):217–9.
21. Warf BC. Comparison of 1-year outcomes for the Chhabra and Codman-Hakim micro precision shunt systems in Uganda: a prospective study in 195 children. *J Neurosurg* 2005;**102**(4):358–62.
22. Lagarde E, Taljaard D, Puren A, Auvert B. High rate of adverse events following circumcision of young male adults with the Tara KLamp technique: a randomised trial in South Africa. *S Afr Med J* 2009;**99**(3):163–9.
23. Maharaj D, Bagratee JS, Moodley J. Drainage at caesarean section – a randomised prospective study. *S Afr J Surg* 2000;**38**(1):9–12.
24. Ezeome ER, Adebamowo CA. Closed suction drainage versus closed simple drainage in the management of modified radical mastectomy wounds. *S Afr Med J* 2008;**98**(9):712–5.
25. Musa AA, Agboola OJ, Banjo AA, Oyegunle O. The use of drains in thyroid surgery. *Niger Postgrad Med J* 2010;**17**(1):15–8.
26. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control* 2008;**36**(5):309–32.
27. Owens CD, Stoessel K. Surgical site infections: epidemiology, microbiology and prevention. *J Hosp Infect* 2008;**70**(Suppl. 2):3–10.
28. National Collaborating Centre for Women's and Children's Health. *Prevention and treatment of surgical site infection*. UK: National Institute for Clinical Excellence; 2008.
29. Kirby JP, Mazuski JE. Prevention of surgical site infection. *Surg Clin North Am* 2009;**89**(2):365–89. viii.
30. Anderson DJ, Kaye KS, Classen D, Arias KM, Podgorny K, Burstin H, et al. Strategies to prevent surgical site infections in acute care hospitals. *Infect Control Hosp Epidemiol* 2008;**29**(Suppl. 1):S51–61.
31. Reichman DE, Greenberg JA. Reducing surgical site infections: a review. *Rev Obstet Gynecol* 2009;**2**(4):212–21.
32. Gogoua RD, Mambo M, Anoumou M, Kouame M, Fal A, Kone B, et al. Pefloxacin compared with oxacillin in short term antibiotic prophylaxis in orthopaedic surgery and traumatology unit at the Treichville university teaching hospital [French]. *Medecine d'Afrique Noire* 2003;**50**(1):17–21.
33. Ward HR, Jennings OG, Potgieter P, Lombard CJ. Do plastic adhesive drapes prevent post caesarean wound infection? *Journal of Hospital Infection [Clinical Trial Randomized Controlled Trial]* 2001 Mar;**47**(3):230–4.
34. Fasubaa OB, Ogunniyi SO, Dare FO, Isawumi AI, Ezechi OC, Orji EO. Uncomplicated Caesarean section: is prolonged hospital stay necessary? *East African Medical Journal* 2000 Aug;**77**(8):448–51.

Chapter 3.

Research paper II: Evaluation of surveillance for surgical site infections in Thika Hospital, Kenya

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	SSI	Nosocomial bacteraemia	MRSA
Previous research in sSA (or lack thereof)	Ch2	Ch 5	Ch 6
HAI surveillance methods in an African context	Ch 3	Ch 5	Ch 6
Antibiotic use and resistance in sSA	Ch 4		Ch 6
Impacts of HAI in sSA	Ch 4	Ch 5	

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Evaluation of surveillance for surgical site infections in Thika Hospital, Kenya

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SUMMARY

Background: In low-income countries, surgical site infections (SSIs) are a very frequent form of hospital-acquired infection. Surveillance is an important method for controlling SSI but it is unclear how this can best be performed in low-income settings.

Aim: To examine the epidemiological characteristics of various components of an SSI surveillance programme in a single Kenyan hospital.

Methods: The study assessed the inter-observer consistency of the surgical wound class (SWC) and American Society of Anesthesiologists (ASA) scores using the kappa statistic. Post-discharge telephone calls were evaluated against an outpatient clinician review 'gold standard'. The predictive value of components of the Centers for Disease Control and Prevention – National Healthcare Safety Network (CDC-NHNS) risk index was examined in patients having major obstetric or gynaecological surgery (O&G) between August 2010 and February 2011.

Findings: After appropriate training, surgeons and anaesthetists were found to be consistent in their use of the SWC and ASA scores respectively. Telephone calls were found to have a sensitivity of 70% [95% confidence interval (CI): 47–87] and a specificity of 100% (95% CI: 95–100) for detection of post-discharge SSI in this setting. In 954 patients undergoing major O&G operations, the SWC score was the only parameter in the CDC-NHNS risk index model associated with the risk of SSI (odds ratio: 4.00; 95% CI: 1.21–13.2; $P = 0.02$).

Conclusions: Surveillance for SSI can be conducted in a low-income hospital setting, although dedicated staff, intensive training and local modifications to surveillance methods are necessary. Surveillance for post-discharge SSI using telephone calls is imperfect but provides a practical alternative to clinic-based diagnosis. The SWC score was the only predictor of SSI risk in O&G surgery in this context.

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Introduction

A World Health Organization (WHO) systematic review in 2011 on hospital-acquired infections (HAIs) highlighted the scarcity of studies from low-income countries and from African countries in particular.[1] From limited information, surgical site infections (SSIs) were identified as a significant problem: the risk in developing countries was 'strikingly higher than in equivalent surgical procedures in high income countries'.

Conducting surveillance for SSIs is recognized as making an important contribution to reducing the risk of these infections. Establishing high-quality surveillance with timely feedback to surgeons can lead to reduction in risk of SSI.[2] A systematic review of interventions for preventing SSI in sub-Saharan Africa found no examples of surveillance being conducted with the primary purpose of reducing the risk of SSI.[3]

The SENIC project (Study on the Efficacy of Nosocomial Infection Control) had demonstrated that the critical components of SSI surveillance were: (i) accurate collection and reporting of information; (ii) appropriate stratification of risk.[4] For the first component, methods for accurate collection of information for SSI surveillance have been extensively researched in high-income countries.[5,6] However, these methods are not applicable in hospitals in low-income settings where data extraction from inpatient records is challenging and electronic linkage to primary healthcare records is impossible. In all settings, many SSI cases occur after discharge from hospital.[6] Incorporating these cases into surveillance systems is especially problematic in low-income settings, where surgical patients are often dispersed over a wide area.

For the second component of SSI surveillance, an appropriate system of risk stratification is needed to make comparisons of the risk of SSI between centres or over time. The Centers for Disease Control and Prevention – National Healthcare Safety Network (CDC-NHSN) risk index provides one such system. A score of 0–3 is assigned based on the sum of values derived from the American Society of Anesthesiologists physical status classification (ASA) score, the surgical wound class (SWC) and operation duration in relation to a procedure-specific length (time T).[7] Although these components of the risk index are, in principle, readily transferable to low-income settings, an important question is whether accuracy of scoring in routine clinical practice in such settings is adequate to reliably predict risk of SSI.

The aim was to evaluate epidemiological characteristics of various components of SSI surveillance in a low-income hospital setting in sub-Saharan Africa. We evaluated: the inter-observer consistency of SWC and ASA scoring; the sensitivity and specificity of telephone calls for identifying SSI against a clinician review 'gold standard'; the association of CDC-NHSN risk index components with the risk of SSI in this setting.

Methods

Thika Level 5 Hospital is a 300-bed government hospital in the town of Thika, about 50 km north east of Nairobi, in Central Province of Kenya. At Thika Hospital there are six consultant surgeons and a rotating pool of 16–20 medical officers (junior doctors) and clinical officers (vocationally trained clinicians) who carry out a range of elective and emergency surgical procedures. There are four operating theatres and about 300 major and minor operations take place monthly. Caesarean sections are the most commonly performed procedure. Surgical instruments are reprocessed in a steam autoclave with monitoring by a change in colour of sealant tape. Prior to February 2011, antibiotic prophylaxis was normally administered to patients postoperatively, as is standard practice in many government hospitals in the region. Thika Hospital is not a university hospital, nor does it have an extensive history of research collaborations. It is a typical mid-sized Kenyan government hospital.

As a collaborative project between the Ministry of Medical Services, the Kenya Medical Research Institute and Thika Hospital, SSI surveillance was conducted at Thika Hospital for a continuous period from August 2010 to December 2011.

All patients gave written consent to participation in surveillance, which included contact by phone after discharge from hospital. This study was approved by the KEMRI National Ethical Review Committee.

Postoperative patient reviews, data and sample collection, phone calls and data entry were performed daily by a team of hospital staff members (two clinical officers and four support staff). All data for CDC-NHNS risk index criteria were recorded by hospital surgeons and anaesthetists. We diagnosed SSI in accordance with CDC-NHSN definitions as far as possible given the diagnostic facilities available.[8] Microbiological criteria were not used for SSI diagnosis, although microbiology services at Thika Hospital were upgraded as part of the surveillance. All diagnoses of SSI were discussed with the relevant surgical team and an infectious diseases physician. Feedback of ongoing surveillance results was given in writing and discussed in a series of multidisciplinary seminars.

In our surveillance, we included all surgical operations where a surgical wound was created during the procedure and the patient stayed overnight in hospital. We therefore excluded patients having day-case surgery (including all ear/nose/throat, ophthalmic and minor gynaecological procedures) and debridement of traumatic or infected wounds. During their inpatient stay, postoperative patients were reviewed at every dressing change, normally starting on the third postoperative day and on alternate days thereafter. Patients remained in SSI surveillance for 30 days after all eligible surgical operations, including both inpatient and outpatient periods. Postoperative readmissions to Thika Hospital were actively sought daily. After discharge, telephone-based surveillance was conducted as described below. Patients were encouraged to contact the surveillance team if they received treatment for wound complications at another facility.

All information for SSI surveillance was recorded in a custom-made PHP-MySQL database. Statistical analyses were performed using Stata v12 software (Stata Corp., College Station, TX, USA).

Consistency of SWC and ASA scores

Scoring consistency tests were conducted with the Surgery, Obstetrics and Gynaecology (O&G) and Anaesthetics departments in Thika Hospital. In each department, a series of 10 case histories was developed describing patient scenarios similar to those encountered in local practice. After revision of the relevant scoring system, all departmental members independently scored the SWC or ASA for these case histories. These results were presented to each department and the need to

ensure inter-observer consistency was explained. Various different approaches to improving consistency were employed: departmental discussions, educational meetings and written guidelines and posters in departments. Among surgeons, a second round of this exercise was conducted with actual patients; in the O&G and Anaesthetics departments, a second round of this exercise used different paper-based case histories.

As the scoring depended on making a clinical judgement, no answer was considered 'correct': the kappa statistic (κ) was employed to assess inter-observer consistency. A weighted κ was used to account for the ordered nature of the scoring categories.

Sensitivity and specificity of telephone-based surveillance

At discharge, patients (or their guardians) were asked to give a mobile phone number where they could be contacted during the next 30 days. More than 90% of patients provided this. Patients were contacted twice by mobile phone on approximately the 14th and 28th postoperative days to inquire about wound complications since discharge. Surveillance staff asked a standard series of questions regarding current condition of the wound, and distinguished between presence of (normal) postoperative mild pain, itching and serous ooze and (abnormal) severe pain, wound breakdown and purulent discharge. Patients could also contact the SSI surveillance team by phone. Patients reporting current symptoms consistent with wound infection were asked to re-attend Thika Hospital for free outpatient review.

Using clinician review in the outpatient clinic as the diagnostic gold standard, paired observations of telephone interview and direct clinician review were analysed when these were performed within 48 h of each other to determine the sensitivity and specificity of telephone calls as a diagnostic test. It was assumed that 'wound infection status' could not change within a 48 h period.

Performance of CDC-NHSN risk index

To analyse the predictive performance of the CDC-NHNS risk index, all forms of SSI were re-categorized (including those occurring after discharge) into a single outcome variable. Exposure variable data were extracted from medical notes at the time of the operation. Logistic regression was used to analyse risk index components in a group consisting of caesarean sections and major gynaecological operations conducted between August 2010 and February 2011. Time *T* represented 1 h for all of these procedures. We did not include other procedures in this modelling as the risk index is only intended to be applied to groups of similar procedures – there were insufficient numbers of any other operative group for adequate evaluation.

Results

Following extensive development, training and piloting, SSI surveillance was conducted at Thika Hospital for a 16-month continuous period from August 2010 to December 2011). All consecutive adult and paediatric patients undergoing eligible operative procedures were enrolled.

Consistency of SWC and ASA scores

Consistency studies were conducted for the SWC and ASA score as shown in Table I. Junior staff rotated between departments every three months, so this exercise could not be repeated in the surgical departments at intervals longer than this. The second exercise was performed in the Anaesthetics department after a 13-month interval.

Whereas consistency of scoring between clinicians initially ranged from fair (within the O&G department) to excellent (within the Surgery department), after a period of routine use of these scoring systems, the consistency between clinicians improved in all departments. The high degree of consistency achieved in the Surgery department in a 'paper-based' exercise ($\kappa = 0.81$) was replicated when the same approach was applied with actual patients ($\kappa = 0.83$, based on 55 paired observations). Subsequently, continuous training of incoming staff was used to maintain these high levels of consistency.

Validity of telephone-based surveillance

There were a total of 89 pairs of outpatient clinician reviews and telephone interviews within 48 h of each other. For 23 patients diagnosed in outpatients by a clinician as having SSI, 16 of these had been judged to have SSI in their telephone interview. For 66 patients seen in outpatients by a clinician and considered not to have SSI, none of these had been considered to have SSI in their telephone interview. On the basis of these results, the sensitivity of telephone calls was 69.6% [95% confidence interval (CI): 47.1–86.8%] and the specificity was 100% (95% CI: 95–100%).

Table I
Results of scoring consistency projects

Department	Test	No. of staff	First exercise		Second exercise[a]	
			Date	Average weighted κ score	Date	Average weighted κ score
Anaesthetics	ASA	5[b]	Jun 2010	0.68	Sep 2011	0.89
O&G	SWC	6	Jun 2010	0.48	Sep 2010	0.72
Surgery	SWC	7	Jun 2010	0.81	Aug–Oct 2010	0.83

ASA, American Society of Anesthesiologists; SWC, surgical wound class.
There are no *P*-values associated with κ as it does not test a particular hypothesis.
[a] All exercises compared paper-based scenarios except the second exercise in surgery which examined actual patients.
[b] Only four of the five participants undertook the second exercise.

Description of surveillance operations and performance of CDC-NHSN risk index

Between August 2010 and February 2011, a total of 1172 operations conducted at Thika Hospital were followed up in SSI surveillance. The characteristics of these operations are given in Table II. As caesarean sections predominated among these procedures (75% of operations), surveillance mainly included women of child-bearing age. A wide variety of other operations were also included in surveillance including laparotomies, hysterectomies, hernia repairs, appendicectomies and amputations. There was a high risk of SSI in orthopaedics and neurosurgery (14%), reflecting the high incidence of extensively contaminated road-accident trauma in this hospital. Surgery performed by clinical officers (vocationally trained clinicians) did appear to have elevated risk of SSI (15%) although this is based on a very small number of procedures. Antibiotic prophylaxis was normally delivered as a postoperative regime, as is widely used in hospitals in Kenya. We have not calculated an overall risk of SSI in the surveillance cohort – this is strongly dependent on the mix of procedures, which is outside of institutional control.

The performance of the CDC-NHSN risk index in predicting the outcome of SSI (of any type, including post-discharge infections) in caesarean sections and major gynaecological operations is given in Table III. For individual components of the risk index, only the parameter derived from the SWC (odds ratio: 3.93; 95% CI: 1.25–12.4; $P = 0.02$) was significantly associated with the risk of SSI – this remained the case in a multivariate model. Parameters relating to the ASA score and the duration of the operation were not associated with the risk of SSI in these operations.

Table II
Risk of surgical site infection (SSI) in operations at Thika Hospital, Kenya: August 2010–February 2011

Variable	Total no.	SSI events (% of all)
Patient age (years)		
≤14	32	0 (0)
15–39	1015	76 (7.5)
40–65	110	16 (14.6)
≥65	15	1 (6.7)
Patient sex		
Female	1060	82 (7.7)
Male	112	11 (9.8)
Type of surgery[a]		
Caesarean section	882	64 (7.3)
General surgery	144	12 (8.3)
Orthopaedic/neurosurgery	36	5 (13.9)
Gynaecological	110	12 (10.9)
Surgeon grade		
Consultant	198	17 (8.6)
Medical officer	685	51 (7.5)
Medical officer intern	266	21 (7.9)
Registered clinical officer	20	3 (15.0)
Preoperative antibiotic prophylaxis[b]		
Given	18	2 (11.1)
Not given	1154	91 (7.9)
Postoperative antibiotic prophylaxis/treatment[c]		
Given	1169	91 (7.8)
Not given	3	1 (33.3)
Total operations followed up	1172	93 (7.9)

[a] Includes caesarean section with tubal ligation ($N = 36$) and with hysterectomy (4); general surgery includes laparotomy (61), hernia repair (19), appendicectomy (10); orthopaedic/neurosurgery includes open reduction internal fixations (9), limb amputations (7) and plating procedures (5); gynaecological surgery includes hysterectomy (43), salpingectomy (11), cystectomy (8).

[b] Antibiotics administered in the 60 min before the start of surgery.

[c] Any antibiotic prescription written up to start/continue immediately after surgery.

Discussion

There are very few previous reports that have studied SSI surveillance methods in sub-Saharan Africa, and we are unaware of any that have examined either the consistency of scoring of risk index components or the characteristics of telephone calls as a surveillance method for SSI.[9,10] This study represents the largest SSI surveillance cohort reported in sub-Saharan Africa.

After appropriate training and with ongoing feedback, surgeons and anaesthetists in Thika Hospital were consistent in categorization of SWC and ASA scores in paper-based evaluations. This consistency improved over time and was similar when applied to actual patients. On this basis, the scoring of these indices by clinicians in this setting can achieve an adequate consistency to make them suitable for use as SSI risk stratification variables.

The sensitivity and specificity of telephone calls as a post-discharge follow-up tool for SSI surveillance were 70% and 100% respectively. Although this was based on a relatively small number of paired observations, the analysis was restricted to those observations within 48 h of each other to maximize accuracy. Specificity was high as there were no false-positive telephone-based diagnoses (type 1 errors) among our paired observations. The moderate sensitivity obtained means that some genuine SSI cases may have been missed (type 2 errors) in surveillance. This combination of high specificity and moderate sensitivity are satisfactory characteristics for a 'stand-alone' test where the outcome is rare. During the pilot phase of surveillance, we had found that in Thika Hospital the actual attendance at postoperative outpatient appointments was extremely poor (<25%). Researchers in Tanzania had also found poor attendance (54%) at postoperative follow-up appointments.[9] Telephone calls have also been used for post-discharge SSI detection in a cluster-randomized trial of a surgical handwashing intervention in Kenya, although that study did not examine the sensitivity or specificity of the method.[11] Telephone calls appear to be a reasonable method of detecting post-discharge SSI in this setting, although this should be further evaluated as a diagnostic tool.[12] This method may be population-specific as Kenya has very high penetration of mobile phone services.

Surgical wound class was predictive of risk of SSI in the univariate and multivariate models in major O&G operations. This is consistent with studies from Tanzania and Ethiopia and with findings from elsewhere in the world, where SWC remains a cornerstone of SSI risk stratification.[1,8,10,13]

Few studies in Africa have examined the use of the ASA score as a predictor of SSI risk. The ASA score approximates 'global'

Table III
CDC-NHSN risk index in Thika Hospital, Kenya in major Obstetrics and Gynaecology surgery[a] ($N = 954$)

Variable	Total no.	SSI (any)	Individual component		Full risk index	
			OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Surgical wound class						
Clean	103	9				
Clean-contaminated	834	59				
Contaminated	13	2				
Dirty-infected	4	2				
CDC-NHSN categorization						
Clean or clean-contaminated	937	68	1.0		–	
Contaminated or dirty-infected	17	4	3.93 (1.25–12.4)	0.02	4.00 (1.21–13.2)	0.02
ASA score						
ASA 1	629	44				
ASA 2	294	25				
ASA 3	27	3				
ASA 4–5	4	0				
CDC-NHSN categorization						
ASA 1–2	923	69	1.0		–	
ASA 3–5	31	3	1.32 (0.39–4.47)	0.65	0.88 (0.24–3.22)	0.85
Operation duration (min)						
<30	162	9				
30–60	616	46				
60–120	171	16				
≥120	5	1				
CDC-NHSN categorization						
<60 min	778	55	1.0		–	
≥60 min	176	17	1.41 (0.79–2.49)	0.24	1.25 (0.77–2.04)	0.37
Total operations	954	72				

CDC-NHSN, Centers for Disease Control and Prevention – National Healthcare Safety Network; SSI, surgical site infection; OR, odds ratio; CI, confidence interval; ASA, American Society of Anesthesiologists.
[a] Includes all types of caesarean section, hysterectomy, salpingectomy, cystectomy and oophorectomy.

patient health at the time of the operation, and is a reliable predictor of the risk of SSI in high-income settings.[14] However, it provided no useful predictive information in this setting when applied to major O&G operations. This may be because these procedures were mainly performed on healthy young women among whom higher scores were rarely assigned, which may limit the utility of the ASA score as a discriminator of risk. In other African studies, the ASA score was strongly predictive of risk in a mixture of obstetric and general surgical procedures in Tanzania but only weakly predictive of risk in a study of paediatric surgery in Nigeria.[10,15]

The duration of an operation gives an indication of the complexity of performing that specific procedure. When this is compared to a standard length, this can predict the risk of subsequent complications. Operation duration was predictive of SSI risk in several studies in low-income settings, though using 'local' values for standard operation length was found to improve the predictive power.[9,10,16,17] The duration of surgery in this study was not associated with the risk of SSI in major O&G operations.

There are limitations to our study. Both the evaluation of the consistency of SWC and ASA scores and the sensitivity and specificity of telephone calls are based on relatively small numbers of observations. However, these are the most detailed examinations of these topics in the region to date. The evaluation of the CDC-NHNS risk index in O&G surgery is the largest such group ever reported in sub-Saharan Africa.

Six full-time staff with salaries equivalent to entry-level nurses were required to conduct this surveillance. About 250 procedures were followed up each month. The high cost of supporting these staff meant that surveillance could not be sustained beyond the duration of this collaborative project. Commercially available software for SSI surveillance might have been a cheaper alternative to our bespoke, locally programmed database.

The value of surveillance is providing surgeons with comparative data about their specific performance. Combining many different types of procedure with different intrinsic risks of infection is therefore of no real value. In the smaller throughput types of surgery, it would be necessary to collect surveillance data for much longer periods or across many sites in order to adequately evaluate the risks of SSI.

In conclusion, surveillance is an important method of measuring and controlling SSIs, which are recognized to be a significant form of HAI in sub-Saharan Africa. In a low-income hospital setting it was found that surgeons and anaesthetists can assign consistent scores for the SWC and ASA; ongoing training and feedback are required. Telephone calls appear to be a reasonable method of detecting post-discharge SSI cases, although further evaluation is needed. Of the components of the CDC-NHNS risk index, only the SWC provided useful predictive information on the risk of SSI in our hospital, where caesarean sections represent the bulk of operations.

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Conflicts of interest

None declared.

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References

1. Allegranzi B, Bagheri Nejad S, Combescure C, *et al.* Burden of endemic health-care-associated infection in developing countries: systematic review and meta-analysis. *Lancet* 2011;**377**:228–241.
2. Gaynes R, Richards C, Edwards J, *et al.* Feeding back surveillance data to prevent hospital-acquired infections. *Emerg Infect Dis* 2001;**7**:295–298.
3. Aiken AM, Karuri DM, Wanyoro AK, Macleod J. Interventional studies for preventing surgical site infections in sub-Saharan Africa – a systematic review. *Int J Surg* 2012;**10**:242–249.
4. Haley RW. The scientific basis for using surveillance and risk factor data to reduce nosocomial infection rates. *J Hosp Infect* 1995;**30**(Suppl):3–14.
5. Rosenthal R, Weber WP, Marti WR, *et al.* Surveillance of surgical site infections by surgeons: biased underreporting or useful epidemiological data? *J Hosp Infect* 2010;**75**:178–182.
6. Petherick ES, Dalton JE, Moore PJ, Cullum N. Methods for identifying surgical wound infection after discharge from hospital: a systematic review. *BMC Infect Dis* 2006;**6**:170.
7. Culver DH, Horan TC, Gaynes RP, *et al.* Surgical wound infection rates by wound class, operative procedure, and patient risk index. National Nosocomial Infections Surveillance System. *Am J Med* 1991;**91**:152S–157S.
8. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control* 2008;**36**:309–332.
9. Fehr J, Hatz C, Soka I, *et al.* Risk factors for surgical site infection in a Tanzanian district hospital: a challenge for the traditional National Nosocomial Infections Surveillance system index. *Infect Control Hosp Epidemiol* 2006;**27**:1401–1404.
10. Eriksen HM, Chugulu S, Kondo S, Lingaas E. Surgical-site infections at Kilimanjaro Christian Medical Center. *J Hosp Infect* 2003;**55**:14–20.
11. Nthumba PM, Stepita-Poenaru E, Poenaru D, *et al.* Cluster-randomized, crossover trial of the efficacy of plain soap and water versus alcohol-based rub for surgical hand preparation in a rural hospital in Kenya. *Br J Surg* 2010;**97**:1621–1628.
12. Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Med Res Methodol* 2003;**3**:25.
13. Taye M. Wound infection in Tikur Anbessa hospital, surgical department. *Ethiop Med J* 2005;**43**:167–174.
14. Woodfield JC, Beshay NM, Pettigrew RA, Plank LD, van Rij AM. American Society of Anesthesiologists classification of physical status as a predictor of wound infection. *Aust NZ J Surg* 2007;**77**:738–741.
15. Kesah CN, Egri-Okwaji MT, Iroha E, Odugbemi TO. Aerobic bacterial nosocomial infections in paediatric surgical patients at a tertiary health institution in Lagos, Nigeria. *Niger Postgrad Med J* 2004;**11**:4–9.
16. Koigi-Kamau R, Kabare LW, Wanyoike-Gichuhi J. Incidence of wound infection after caesarean delivery in a district hospital in central Kenya. *East Afr Med J* 2005;**82**:357–361.
17. Ameh EA, Mshelbwala PM, Nasir AA, *et al.* Surgical site infection in children: prospective analysis of the burden and risk factors in a sub-Saharan African setting. *Surg Infect (Larchmt)* 2009;**10**:105–109.

Chapter 4.

Research paper III: Changing use of surgical antibiotic prophylaxis in Thika Hospital, Kenya – a quality improvement intervention with an interrupted time series design.

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	SSI	Nosocomial bacteraemia	MRSA
Previous research in sSA (or lack thereof)	Ch2	Ch 5	Ch 6
HAI surveillance methods in an African context	Ch 3	Ch 5	Ch 6
Antibiotic use and resistance in sSA	Ch 4		Ch 6
Impacts of HAI in sSA	Ch 4	Ch 5	

Title: Changing use of surgical antibiotic prophylaxis in Thika Hospital, Kenya – a quality improvement intervention with an interrupted time series design.

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Abstract

Background

In low-income countries, Surgical Site Infection (SSI) is a common form of hospital-acquired infection. Antibiotic prophylaxis is an effective method of preventing these infections, if given immediately before the start of surgery. Although several studies in Africa have compared pre-operative versus post-operative prophylaxis, there are no studies describing the implementation of policies to improve prescribing of surgical antibiotic prophylaxis in African hospitals.

Methods

We conducted SSI surveillance at a typical Government hospital in Kenya over a 16 month period between August 2010 and December 2011, using standard definitions of SSI and the extent of contamination of surgical wounds. As an intervention, we developed a hospital policy that advised pre-operative antibiotic prophylaxis and discouraged extended post-operative antibiotics use. We measured process, outcome and balancing effects of this intervention in using an interrupted time series design.

Outcome

Following introduction of the policy in February 2011, there was rapid adoption of the use of pre-operative antibiotic prophylaxis and a substantial immediate decrease in the use of post-operative antibiotics in Clean and Clean-Contaminated surgery which also declined over time thereafter. There was no immediate step-change in risk of SSI, but overall, there appeared to be a moderate reduction in the risk of superficial SSI across all levels of wound contamination. There were marked reductions in the costs associated with antibiotic use, the number of intravenous injections performed and nursing time spent administering these.

Lessons learned

Implementation of a locally developed policy regarding surgical antibiotic prophylaxis is an achievable quality improvement target for hospitals in low-income countries, and can lead to substantial benefits for individual patients and the institution.

Keywords: surgical site infection; antibiotic prophylaxis; antibiotic stewardship; quality improvement; Kenya.

This paper is written specifically to meet the requirements of the Health in Action format of the journal PLoS Medicine. The following are descriptions of this format, from various different sources:

"The Health in Action section focuses on innovative health improvement projects. These pieces are often written by health activists, non-governmental organizations, or researchers in low income settings. We are particularly interested in featuring articles by groups or individuals who rarely have a voice in medical journals.

The piece should be up to 2500 words, with up to 20 references and 2-3 display items. We ask authors to first set the scene (why was your project needed?), then describe the project itself and discuss any early results of the project and the barriers and difficulties you have faced. Finally, we ask authors to end by looking to the future: where is the project heading next?"

"Health in Action articles focus more on implementation and lessons learned than straight reporting of a study. If you are interested to revise and submit your article in this format, you would need to resubmit the full article as a new submission and make sure that you choose Health in Action as the article type."

"A Health in Action article is restricted to 2500 words with up to 3 graphics (tables, figures, box). You will need to revise your article so that it no longer follows the Introduction, Methods, Results, and Discussion (IMRaD) format and instead focus on the lessons and messages for others who wish to implement a similar protocol."

Background

A World Health Organisation (WHO) systematic review in 2011 on hospital-acquired infections (HAI) highlighted the scarcity of studies from developing countries (1). On the basis of limited information, Surgical Site Infections (SSIs) were identified as a particular problem: the risk in developing countries was *"strikingly higher than in equivalent surgical procedures in high income countries"*. A further WHO review confirmed the extremely high risk of SSI in African surgical patients (2).

Antibiotic prophylaxis in surgical patients is an effective means of reducing the risk of post-operative SSI (3) and a recent systematic review found that research studies conducted in sub-Saharan Africa supported this finding (4). The most effective dosing for antibiotic prophylaxis is achieved by giving a single intravenous injection approximately 30 minutes before the start of the procedure (5), though the WHO Safe Surgery checklist indicates that it is acceptable to give prophylaxis between 0 and 60 minutes pre-operatively. There is no evidence to support the use of post-operative antibiotics in a prophylactic role: scientific opinion has reached the consensus that these confer no benefit and should be avoided (6). Nonetheless, many surgeons in both high- and low-income settings continue to use antibiotics in this way: such prescribing increases costs and contributes to the selective pressure driving antibiotic resistance.

Achieving measureable and sustained improvements in the quality of healthcare is challenging in any setting, but in low-income countries examples of effectively introducing evidence-based practices are scanty (7). Although the emergence of antimicrobial resistance could reverse much of the health gains achieved in Africa in the last half century (8, 9), there is a dearth of reports from African countries of antibiotic stewardship interventions: a 2009 Cochrane Review of interventions to improve antibiotic prescribing for hospital inpatients found no reports from African countries (10).

We report our experience of developing and implementing a Surgical Antibiotic Prophylaxis (AP) policy as an intervention to change healthcare practitioners' prescribing behaviour in a single Government hospital in Kenya. We prospectively measured the effects of this intervention in terms of process, outcome and balancing measures.

Setting and Methods

Thika Level 5 Hospital is a 300-bed Government Hospital in the town of Thika, approximately 50km NE of Nairobi, in Central Province of Kenya. It has six consultant surgeons and a rotating pool of 16-20 junior doctors and clinical officers (clinically-trained healthcare professionals) who carry out approximately 300 elective and emergency operations monthly. As a collaborative project between the Ministry of Medical Services, the Kenya Medical Research Institute and Thika Hospital, we conducted SSI surveillance at Thika Hospital from August 2010 to December 2011 for all patients undergoing surgical procedures involving overnight admission to Thika Hospital. Patients remained in SSI surveillance for 30 days after all operations, encompassing both inpatient and outpatient periods. Information regarding patients, operations, prescribed and administered drugs were extracted from patient medical records within 24 hours of recording. After discharge from hospital, we contacted patients by phone to determine the occurrence of post-discharge SSI. Further examination of these methodological approaches used for this SSI surveillance is described elsewhere (11).

Surveillance activities were performed daily by a team of hospital staff members (2 clinical officers and 4 support workers) throughout the period with on-site supervision by a clinical epidemiologist. Surgical wound class (Clean, Clean-Contaminated, Contaminated, Dirty) was assigned by the operating surgeon. No changes to surveillance methods or staff were made during this period. Surveillance staff, although not blinded to the introduction of the Antibiotic Prophylaxis policy, performed no role in its development or implementation such that policy introduction did not affect data collection.

We diagnosed SSI in accordance with CDC-NHSN definitions (12) within the constraints of the diagnostic facilities available. All SSI diagnoses were based on clinical and radiological criteria - microbiological criteria were not used, although microbiology services at Thika Hospital were upgraded as part of the surveillance project. All SSI diagnoses were discussed with the relevant surgical team and an infectious diseases physician. For analytic purposes, we only considered the single anatomically deepest form of SSI (organ-space > deep > superficial) diagnosed in a patient during the 30 day surveillance period.

As process indicators, we analysed the proportion of patients undergoing surgical procedures who were documented to receive AP within 60 minutes of the start of the operation, and the

proportion of patients prescribed post-operative antibiotics. Using weekly datapoints (26 pre- and 40 post-intervention), we used segmented regression analysis to determine if there were significant step or slope changes in antibiotic prescribing behaviour associated with policy introduction.

As outcome measures, the risk of different forms of SSI within 30 days of the operation were recorded. We examined a time series plot of monthly datapoints (6 pre- and 9 post-intervention) for SSI risk. We looked for a step change associated with initial policy introduction and for overall trends in risk over time by performing linear regression analyses for the periods before (August 2010 – January 2011) and after (March – November 2011) policy introduction. In the absence of aclear patterns to the month–to –month variation in SSI risk, the overall risk in these periods was compared in a before-and-after format by calculating a risk ratio. Patients whose surgery was classified as "Contaminated" or "Dirty" were considered separately as work in Thika Hospital (11) and elsewhere (1) has shown that high levels of wound contamination to be strongly associated with increased SSI risk.

As balancing measures, we assessed financial costs and staff time requirements from the point of view of a hospital administrator. Costs were evaluated by comparing the average cost (per 100 operations) for purchasing and administering intravenous (iv) antibiotics based on usage in Thika Hospital during surveillance. The monetary values of drugs and other consumables were obtained from the awarded prices for medical products in Thika Hospital for 2011-12. We estimated the difference in nurse-hours based on assumption of an average of 10 minutes of nursing time per dose of intravenous medication administered.

Ethics statement: SSI Surveillance at Thika Hospital was approved by the Kenya Medical Research Institute National Ethics Review Committee. All patients gave assent to participation in surveillance, which included contact by phone after discharge from hospital.

This study is reported in accordance with the ORION guidelines (13). All statistical analyses were done using STATA v12 except for the segmented regression analysis which was done using SAS v9.

Outcomes

Surveillance. We conducted SSI surveillance at Thika Hospital for all operations performed between the 16th August 2010 and the 20th November 2011 for patients who spent at least one post-operative night in hospital. We followed all patients for a 30-day post-operative period, with contact by telephone after discharge. A total of 3,343 patients were followed up in surveillance over this time, with the most commonly performed procedures being Caesarean section, hysterectomy, laparotomy and hernia repair.

Policy development and implementation. As our intervention, we developed an Antibiotic Prophylaxis (AP) policy for Thika Hospital over a series of multi-disciplinary seminars held between November 2010 and January 2011. This was based on a review of African (14-16) and international research (17) papers and relevant national policy documents. The resulting AP policy recommended that for most routine operations (including Caesarean sections, hysterectomies and laparotomies), a combination of ampicillin (2g iv) and metronidazole (500mg iv) should be given pre-operatively and that no antibiotics should be prescribed post-operatively. No restrictions were placed on use of antibiotics for post-operative prophylaxis, but it was agreed that there was no evidence to support this practice. Full details of the policy are given in Appendix 1; this policy was endorsed by all consultant surgeons and anaesthetists working at Thika Hospital, the Medicines+Therapeutics Committee and the Medical Superintendant. As there was no regular supply of ampicillin from the Kenya Medical Supplies Agency (KEMSA) at this time, hospital pharmacists purchased this medicine locally.

Following extensive training of medical, nursing and theatre staff, this AP policy was implemented in Thika Hospital from the 7th February 2011 onwards. Following an initial evaluation meeting, a patient information poster was used (Appendix 2) and personalised feedback was used to alert individual clinicians to substantial deviations from the practice of their colleagues. We estimate that a total of approximately 600 hours of staff time were used in meetings relating to development, implementation and evaluation of the AP policy.

Results: process measures. In the pre-intervention phase of this study (prior to Feb 2011), less than 2% of patients were given pre-operative antibiotic prophylaxis – this was only used for patients having orthopaedic procedures involving implanted material – whilst over 99% of surgical patients were prescribed post-operative antibiotic regimes, typically a combination of penicillin, gentamicin and metronidazole given intravenously (iv) for three to five days,

followed by a course of oral antibiotics. The implementation of the AP policy is illustrated in Figure 1, based on the weekly proportions of patients undergoing Clean or Clean-Contaminated surgery. Documented adherence to the AP policy (in terms of giving pre-operative prophylaxis) was 60% in week 1 and 98% in week 6 of policy introduction. Use of post-operative prophylactic antibiotics in Clean and Clean-Contaminated surgery fell to 40% in week 1 and 10% in week 6 of policy introduction. Segmented regression analysis indicated that both the step change ($p<0.0001$) and the post-intervention downward trend ($p=0.001$) were highly significant changes.

Results: outcome measures. Over the surveillance period, the monthly risk of developing any form of SSI (superficial, deep or organ-space) ranged between 3 and 13% in patients whose surgery was classified as Clean or Clean-Contaminated (see Figure 2) with marked month-to-month variation. With linear regression, there was no clear evidence of a trend in risk prior to policy introduction (6 monthly datapoints; monthly change: -0.5%; 95%CI -2.5 to +1.4%, $p=0.49$). After policy introduction there was some evidence of a downward trend in risk (9 monthly data points; monthly change: -0.7%; 95%CI -1.2 to -0.1%, $p=0.027$).

Evaluation of the effects of the AP policy on SSI risk in a before-and-after comparison showed reduction in the risk of superficial SSI in both Clean/Clean-Contaminated surgery (RR 0.66; 95%CI 0.49-0.91; $p=0.01$) and in Contaminated/Dirty surgery (RR 0.17; 95%CI 0.04-0.74; $p=0.005$) – see Table 2. Changes in the risk of deep or organ-space SSI were found to be non-significant ($p>0.1$).

Results: balancing measures. The financial and time impacts associated with the introduction of the AP policy in Thika Hospital, based on recorded usage before and after AP policy introduction are given in Table 3. There was a net reduction in the costs for iv antibiotics and associated consumables of approximately $2.50/operation, and the number of iv injections administered and the nursing time spent performing these were both reduced by approximately 70%, leading to a saving of approximately 450 nurse-hours per month.

Discussion

We believe this is the first report of implementation of a quality improvement intervention in antibiotic use accompanied by process, outcome and balancing measures reported from sub-Saharan Africa. It is also the largest single-institution study of SSI risk in this region.

Our intervention, a locally-developed surgical antibiotic prophylaxis policy, rationalised clinicians' prescribing, substantially reduced the use of intravenous antibiotics and saved both money and nursing time. Furthermore, there was some evidence of a modest reduction in risk of superficial SSI across all levels of wound contamination (RR 0.66, 95%CI 0.49-0.91 in Clean/Clean-Contaminated surgery; RR0.17, 95%CI 0.04-0.74 in Contaminated/Dirty surgery).

We note that there was marked month-to-month variation in the overall risk of SSI during surveillance, principally due to changes in the recorded risk of superficial SSI. The highest overall risk of SSI was seen in the month of February 2011: this was both the month of the AP policy implementation and also the month that the annual intake of newly qualified junior doctors commenced work in Thika Hospital in 2011. This may have obscured the immediate effect of the changeover in AP use and may also account for the spike in SSI cases that occurred that month. Junior doctors (who perform the majority of uncomplicated Caesarean sections) rotated between hospital departments on a 3-monthly basis throughout the surveillance period; no other changes in staffing levels, equipment, facilities or operative techniques took place in Thika Hospital during this period.

Limitations: Surgical Site Infections are inherently difficult to measure – these must be detected over a prolonged post-discharge period and largely rely on clinical judgement for diagnosis. We believe the outcomes measured in this study were assessed objectively and that we achieved the best level of post-discharge follow-up that is feasible for SSI surveillance in this setting.

Although this study represents the largest report of SSI surveillance in a single institution in sub-Saharan Africa, it still remains relatively small in comparison to SSI surveillance studies in high-income settings. There are not sufficient data points in this surveillance to determine if there were cyclical patterns to SSI risk which could relating to hospital crowding or changes in average levels of staff experience. Some circumstantial evidence, as described above, suggests that the latter could be important. This could be contributing bias to this study, though this would probably lead to underestimation of the effectiveness of the

intervention as junior doctors were, on average, less experienced in the period after policy introduction. The numbers of patients undergoing surgery that was classified Contaminated or Dirty operations was small, typically between 5 and 15 operations per month, so there were insufficient data to evaluate the effects of the intervention on these procedures.

Selection of antibiotics for use in the AP policy in Thika Hospital was difficult. Gentamicin was not used due to concerns about possible interactions with long-acting muscle relaxants. Co-amoxiclav might have been a better agent (15) as resistance to amoxicillin/ampicillin is widespread in Kenya (18) which might have lead to a more pronounced reduction in the risk of SSI, but at greater cost.

Barriers and pathways to change. Inappropriate antibiotic use is a multi-dimensional problem. What barriers existed to prevent this change in timing of antibiotic prophylaxis being implemented in Thika Hospital prior to 2011, when both research evidence and national guidelines supported such a change? Firstly, there was very limited awareness of national clinical policy documents, resulting in a marked policy-to-practice gap. Secondly, there was poor access to appropriate medicines for surgical prophylaxis – for example, although the Kenya Essential Medicines List describes ampicillin as "essential" for Government hospitals, in practice, this antibiotic was never received from official suppliers. Thirdly, amongst clinicians there was a marked concern about negative outcomes, especially regarding nosocomial infections, that hindered changes in antibiotic usage. The belief that prolonged post-operative antibiotic use mitigated the risk of HAI (in turn principally ascribed to overcrowding and poor hygiene) was widespread. Finally, there was a lack of awareness amongst hospital management of the overall potential for cost-savings associated with such a policy change.

Why did this AP policy intervention succeed in changing local practice and sustaining this throughout the study period? Contributing factors to success were:

1) A strong evidence base – including some local studies – to support the proposed changes and national infection control guidelines were already in place.
2) "Buy-in" to this project from senior clinicians and hospital management
3) Collaborative policy development involving staff from different professions and departments.
4) Locally-relevant written training materials for both staff and patients.
5) Extensive staff and patient sensitization prior to an after implementation.

6) Data collection for both process and outcome measures with timely feedback, including personalized feedback to persistent policy non-compliers.
7) Upgrade of SSI microbiology services as part of surveillance.
8) An appreciable saving of nurse-time and resources as a result of policy implementation.

Informal feedback from staff at Thika Hospital suggested that factors 5 and 8 were judged to have been most important, but all other factors played a contributing role. The change in practice with regard to use of surgical prophylaxis was reported to have been sustained as of August 2012, although no further data were collected.

Conclusion

Antibiotic stewardship, evidence-based practice and infection control are all important issues in healthcare. Achieving lasting improvements in any one of these fields is difficult – but this intervention made an improvement in a typical Government hospital in Kenya in all three areas whilst also saving both nursing-time and resources. Many factors contributed to achieving successful implementation of policy – most importantly, local engagement with clinicians and support of the process of change.

Our report demonstrates that changing from the outdated practice of post-operative prophylaxis is an achievable quality improvement intervention for hospitals in low-income settings. The looming threat of widespread antibiotic resistance means that there is a pressing need to improve antimicrobial use in low-resource settings (19). Better use of antibiotics for surgical prophylaxis is a "low-hanging fruit"(20) that is worth picking for antibiotic stewardship programmes in hospitals in sub-Saharan Africa.

Acknowledgments

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Author contributions

AA, JAGS and AJH designed and conducted the surveillance for SSI at Thika Hospital. JM and FJ lead surgical and anaesthetic services at Kilifi Hospital respectively. IM assisted with setting planning and setting up Thika Hospital as a surveillance site. AA and AJH planned the analysis. AA wrote the manuscript and all authors reviewed and approved this prior to submission.

Data access and responsibility to submit

AA declares that he had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Ethical approval

SSI Surveillance at Thika Hospital was approved by the Kenya Medical Research Institute National Ethics Review Committee. All patients gave assent to participation in surveillance, which included contact by phone after discharge from hospital.

Conflicts of interest

All authors declare that they have no conflicts of interest.

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References

1. Allegranzi B, Bagheri Nejad S, Combescure C, Graafmans W, Attar H, Donaldson L, et al. Burden of endemic health-care-associated infection in developing countries: systematic review and meta-analysis. Lancet. 2011;377(9761):228-41. Epub 2010/12/15.

2. Bagheri Nejad S, Allegranzi B, Syed SB, Ellis B, Pittet D. Health-care-associated infection in Africa: a systematic review. Bull World Health Organ. 2011;89(10):757-65. Epub 2011/11/16.

3. Bowater RJ, Stirling SA, Lilford RJ. Is antibiotic prophylaxis in surgery a generally effective intervention? Testing a generic hypothesis over a set of meta-analyses. Ann Surg. 2009;249(4):551-6. Epub 2009/03/21.

4. Aiken AM, Karuri DM, Wanyoro AK, Macleod J. Interventional studies for preventing surgical site infections in sub-Saharan Africa - A systematic review. Int J Surg. 2012;10(5):242-9. Epub 2012/04/19.

5. Classen DC, Evans RS, Pestotnik SL, Horn SD, Menlove RL, Burke JP. The timing of prophylactic administration of antibiotics and the risk of surgical-wound infection. N Engl J Med. 1992;326(5):281-6. Epub 1992/01/30.

6. Hedrick TL, Sawyer RG. The end of postoperative antimicrobial prophylaxis? Lancet Infect Dis. 2012;12(5):357-8. Epub 2012/02/03.

7. Siddiqi K, Newell J, Robinson M. Getting evidence into practice: what works in developing countries? Int J Qual Health Care. 2005;17(5):447-54. Epub 2005/05/06.

8. Laxminarayan R, Heymann DL. Challenges of drug resistance in the developing world. BMJ. 2012;344:e1567. Epub 2012/04/12.

9. Okeke IN, Aboderin OA, Byarugaba DK, Ojo KK, Opintan JA. Growing problem of multidrug-resistant enteric pathogens in Africa. Emerg Infect Dis. 2007;13(11):1640-6. Epub 2008/01/26.

10. Davey P, Brown E, Fenelon L, Finch R, Gould I, Hartman G, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database Syst Rev. 2009(4):CD003543. Epub 2005/10/20.

11. Aiken AMW, A.K.; Mwangi, J.; Mulingwa, P.; Wanjohi, J.;, Njoroge JGJ, F.; Mugoya, I.K.; Scott, J.A.G.; Hall, A.J. Evaluation of surveillance for surgical site infections in Thika Hospital, Kenya. Journal of Hospital Infection. 2012;in press.

12. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control. 2008;36(5):309-32. Epub 2008/06/10.

13. Stone SP, Cooper BS, Kibbler CC, Cookson BD, Roberts JA, Medley GF, et al. The ORION statement: guidelines for transparent reporting of outbreak reports and intervention studies of nosocomial infection. Lancet Infect Dis. 2007;7(4):282-8. Epub 2007/03/23.

14. Reggiori A, Ravera M, Cocozza E, Andreata M, Mukasa F. Randomized study of antibiotic prophylaxis for general and gynaecological surgery from a single centre in rural Africa. Br J Surg. 1996;83(3):356-9. Epub 1996/03/01.

15. Saxer F, Widmer A, Fehr J, Soka I, Kibatala P, Urassa H, et al. Benefit of a single preoperative dose of antibiotics in a sub-saharan district hospital: minimal input, massive impact. Ann Surg. 2009;249(2):322-6. Epub 2009/02/13.

16. Kayihura V, Osman NB, Bugalho A, Bergstrom S. Choice of antibiotics for infection prophylaxis in emergency cesarean sections in low-income countries: a cost-benefit study in Mozambique. Acta Obstet Gynecol Scand. 2003;82(7):636-41. Epub 2003/06/07.

17. Owens SM, Brozanski BS, Meyn LA, Wiesenfeld HC. Antimicrobial prophylaxis for cesarean delivery before skin incision. Obstet Gynecol. 2009;114(3):573-9. Epub 2009/08/25.

18. Bejon P, Mwangi I, Ngetsa C, Mwarumba S, Berkley JA, Lowe BS, et al. Invasive Gram-negative bacilli are frequently resistant to standard antibiotics for children admitted to hospital in Kilifi, Kenya. J Antimicrob Chemother. 2005;56(1):232-5. Epub 2005/05/21.

19. WHO. The evolving threat of antimicrobial resistance - options for action. 2012.

20. Goff DA, Bauer KA, Reed EE, Stevenson KB, Taylor JJ, West JE. Is the "Low-Hanging Fruit" Worth Picking for Antimicrobial Stewardship Programs? Clin Infect Dis. 2012. Epub 2012/05/23.

Table 1 – Overall risk of SSI with and without use of pre-operative antibiotic prophylaxis

Surgical Site Infections	Post-operative antibiotics only (%)		Pre-operative AP +/- post-operative antibiotics (%)		Risk Ratio (95%CI)	p-value[a]
Clean and Clean-Contaminated surgery						
number of operations	1,130	(100)	2,046	(100)		-
superficial	69	(6.1)	83	(4.1)	0.66 (0.49-0.91)	0.01
deep	10	(0.9)	13	(0.6)	0.72 (0.32-1.63)	0.43
organ-space	3	(0.3)	6	(0.3)	1.10 (0.28-4.41)	0.89
total [b]	82	(7.3)	102	(5.0)		-
Contaminated and Dirty surgery						
number of operations	76	(100)	91	(100)		-
superficial	10	(13.2)	2	(2.2)	0.17 (0.04-0.74)	0.006
deep	6	(7.9)	13	(14.3)	1.81 (0.72-4.53)	0.20
organ-space	2	(2.6)	2	(2.2)	0.83 (0.12-5.79)	0.86
total [b]	18	(23.7)	17	(18.7)		-

a = p-value from χ^2-test with 1 degree of freedom.

b = no RR calculated for all SSI combined as these represent diverse forms of infection

Table 2: Financial and other impacts associated with provision of surgical antibiotic prophylaxis, per 100 operations.

Item	Baseline August 2010 – Jan 2011	Intervention April 2011 – Nov 2011	Change associated with AP policy (% change from baseline)
Costs (US$)			
All iv antibiotic agents used †	394.21	293.14	-101.07 (-26)
Consumables for iv administration	223.01	71.02	-151.99 (-68)
Total costs	617.22	364.16	-253.06 (-41)
Other impacts			
Doses of iv medications (number)	1221	367	-854 (-70)
Nursing time giving iv antibiotics (hrs)*	204	61	-143 (-70)

Exchange rate of Ksh85 = US$1 used

† based on documented prescriptions and number of doses administered in these time-periods

* based on an estimate of 10 minutes of nursing time / dose of iv medication.

Figure 5: Weekly prescribing practices for surgical antibiotic prophylaxis

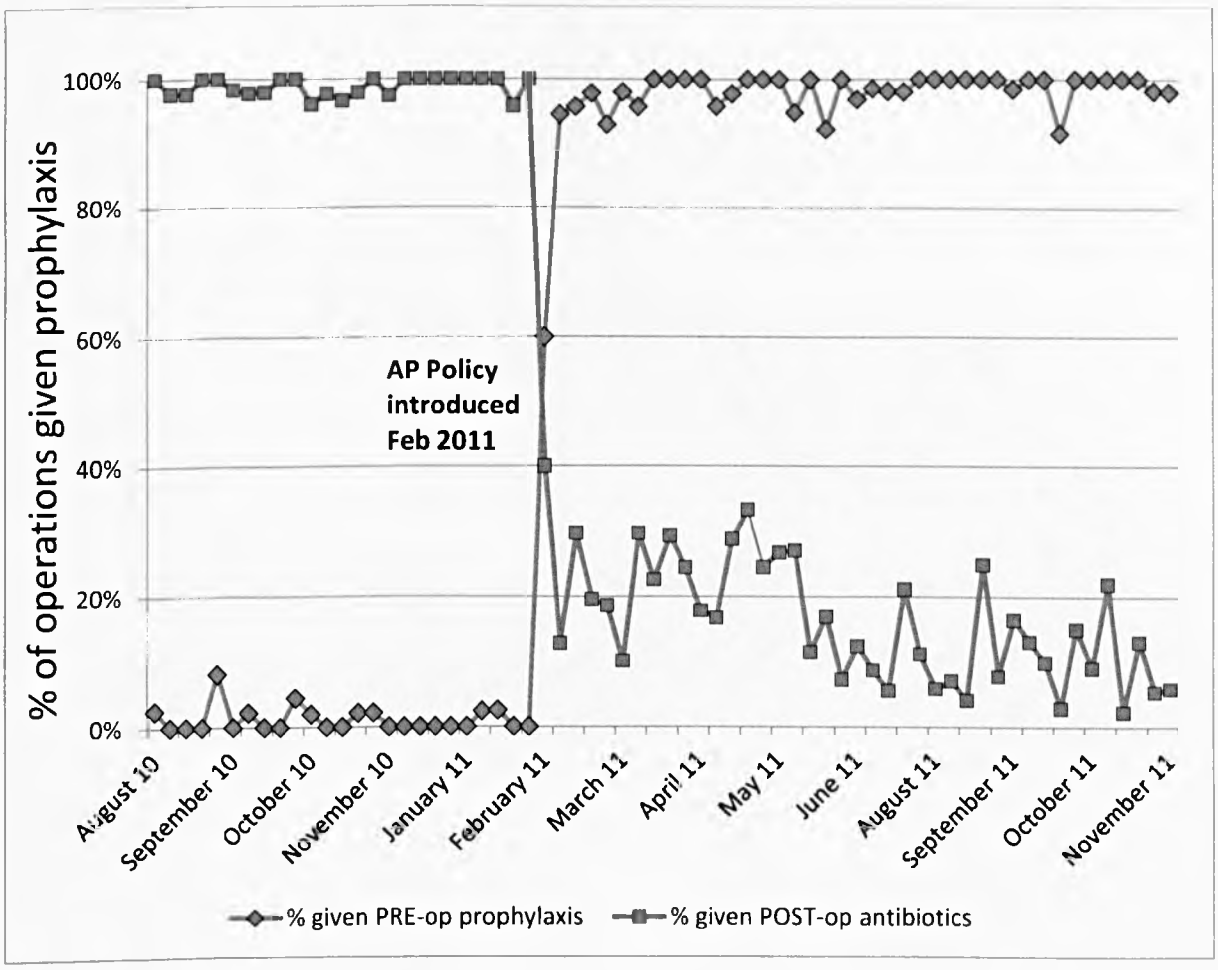
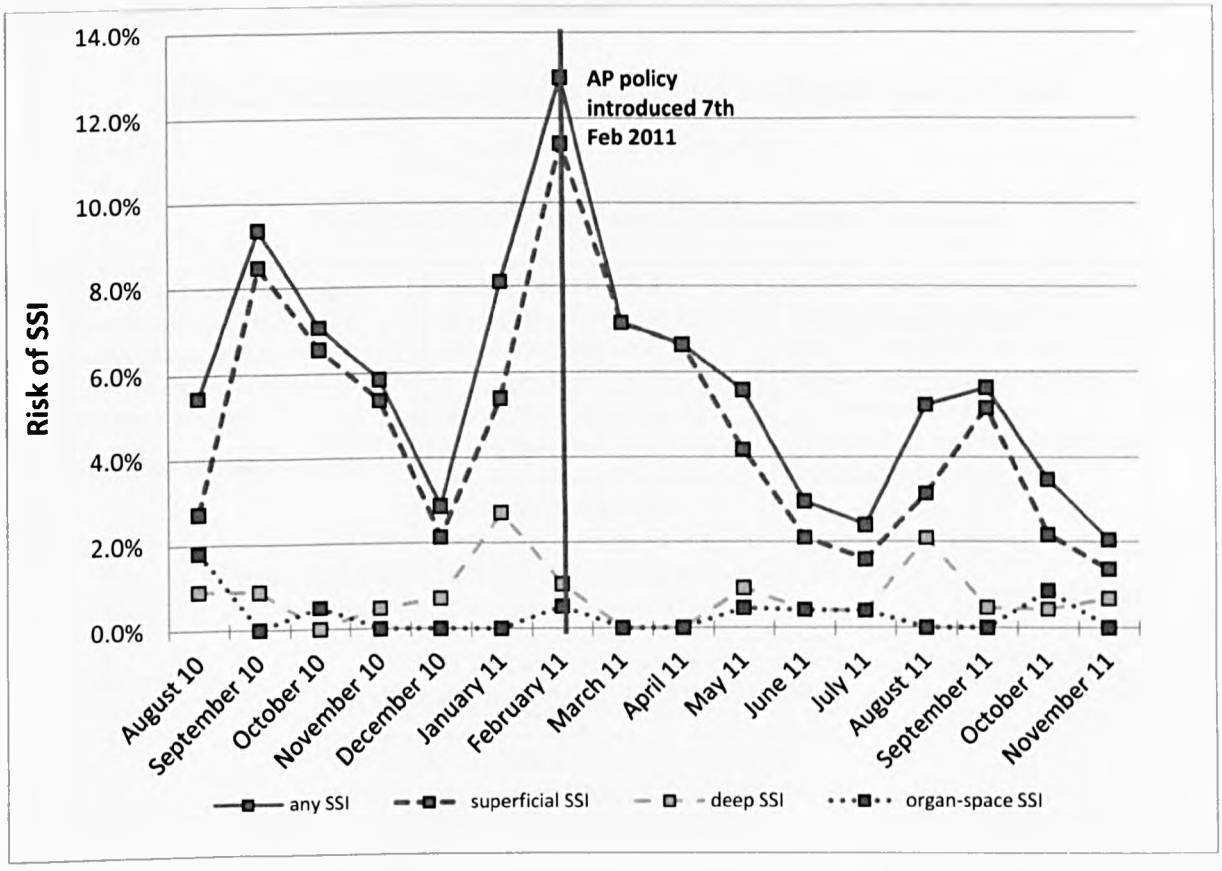
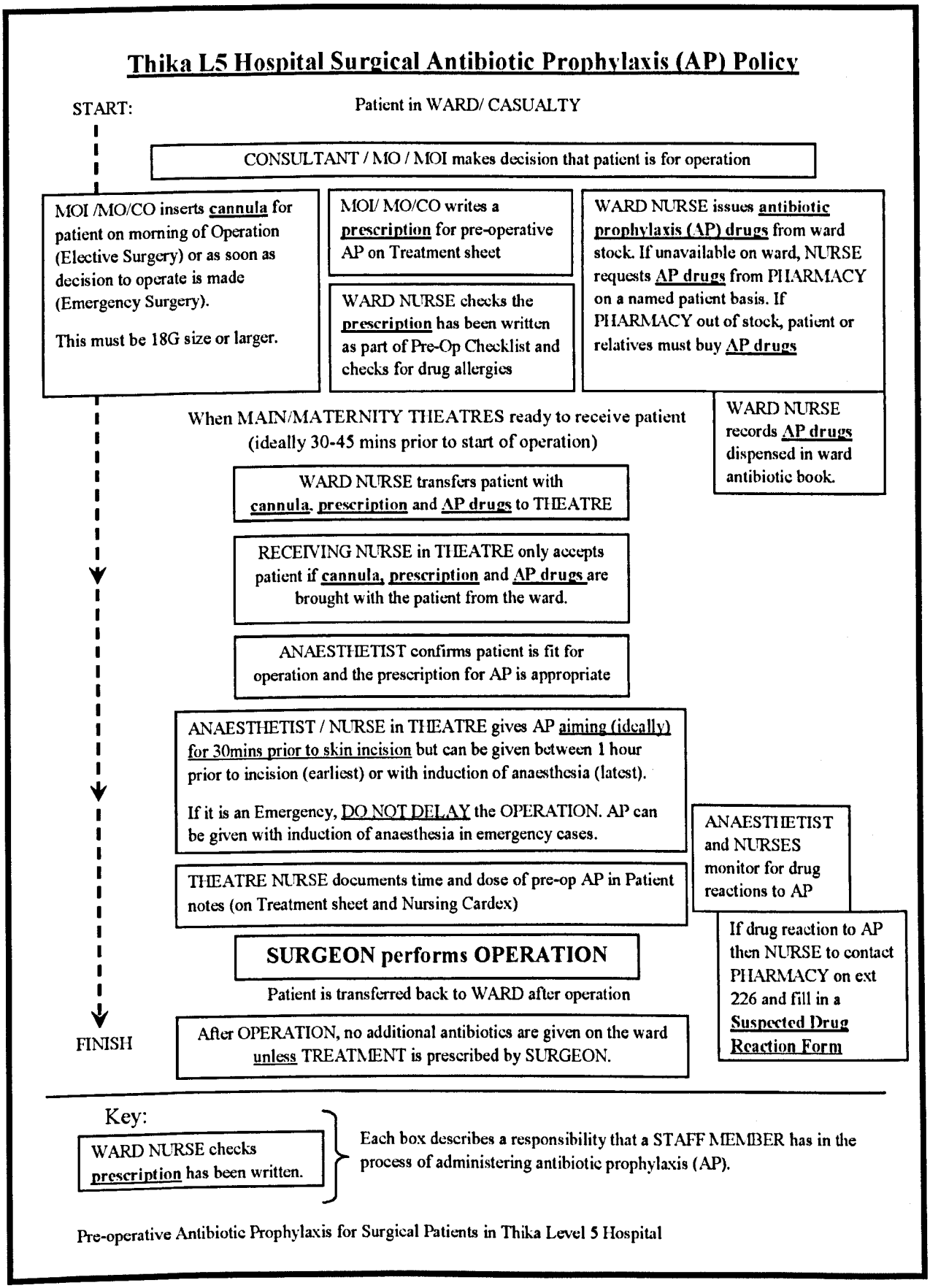


Figure 6: Monthly risk of SSI in Thika Hospital, 2010-11



Appendix 1:



Pre-operative Antibiotic Prophylaxis for Surgical Patients in Thika Level 5 Hospital

Thika L5 Hospital Surgical Antibiotic Prophylaxis (AP) Policy

Operation Group	Antibiotics for PROPHYLAXIS	Dose Timing
Caesarean section: Elective OR Emergency* *= Unless ruptured uterus / Prolonged ROM / Prolonged labour / other complication – see below	Ampicillin 2g Flagyl 500mg	Single pre-op dose, no post-operative antibiotics
Gynaecological Surgery – major procedures (eg hysterectomy, oophorectomy, cystectomy)	Ampicillin 2g Flagyl 500mg	Single pre-op dose, no post-operative antibiotics
General Surgery "abdominal" (eg laparotomy, appendisectomy (if no perforation), biliary tract surgery, colorectal surgery	Ampicillin 2g Flagyl 500mg	Single pre-op dose, no post-operative antibiotics
General Surgery "non-abdominal" (eg hernia repair, mastectomy, thyroidectomy, burns grafting , fasciotomy)	Ampicillin 2g	Single pre-op dose, no post-operative antibiotics
CLEAN Orthopaedic surgery and Neurosurgery (eg ORIF, craniotomy, interlocking nail)	Ceftriaxone 2g	Single pre-op dose, no post-operative antibiotics
EYE Surgery – Extensive EYE operations (eg. Dacryocystorhinostomy (DCR), Enucleation of eye, repair of major eye trauma)	Ampicillin 2g Flagyl 500mg	Single pre-op dose, Give post-op Gentamycin + steroid eye drops
Local EYE surgery (cataract removal, glaucoma surgery)	Subconjunctival Gentamycin injection at end of op.	Give post-op Gentamycin +steroid eye drops
ENT Surgery – Extensive ENT operations (eg parotidectomy, thyroglossal cyst removal)	Ampicillin 2g Flagyl 500mg	Single pre-op dose, no post-operative antibiotics
Local ENT operations (eg. Tonsillectomy, adenoidectomy)	No pre-operative AP	Post-op oral augmentin or azithromycin
Minor Gynaecology Procedures (on Ward or in theatre) Eg. MVA, D+C. (ESB and MacDonald stitch do not require AP)	Ampicillin 2g Flagyl 500mg	Single dose before procedure, Nil further treatment.
ANY Contaminated or Dirty/Infected operation Including • Surgical Toilet, Abscess drainage, arthrotomy for septic arthritis, traumatic wound closure, any gastro-intestinal perforation, amputation for gangrene. • *C/S with ruptured uterus/ Macerated Stillbirth/ PROM/Prolonged Labour.* • Any patient with an infection at the time of surgery (eg chorioamnionitis, infected wound, abscess).	Ampicillin 2g Flagyl 500mg	Pre-operative PROPHYLAXIS AND then to received TREATMENT after operation as per clinicians prescription.
Patient with reported allergy to penicillin, for any surgery *Note: there is a small risk of cross-allergy between Penicillins and Cephalosporins (approx 10% risk)	Omit Ampicillin from AP **if good history of allergy.** Can use Ceftriaxone* (2g) instead if necessary.	Single pre-op dose, no post-operative antibiotics

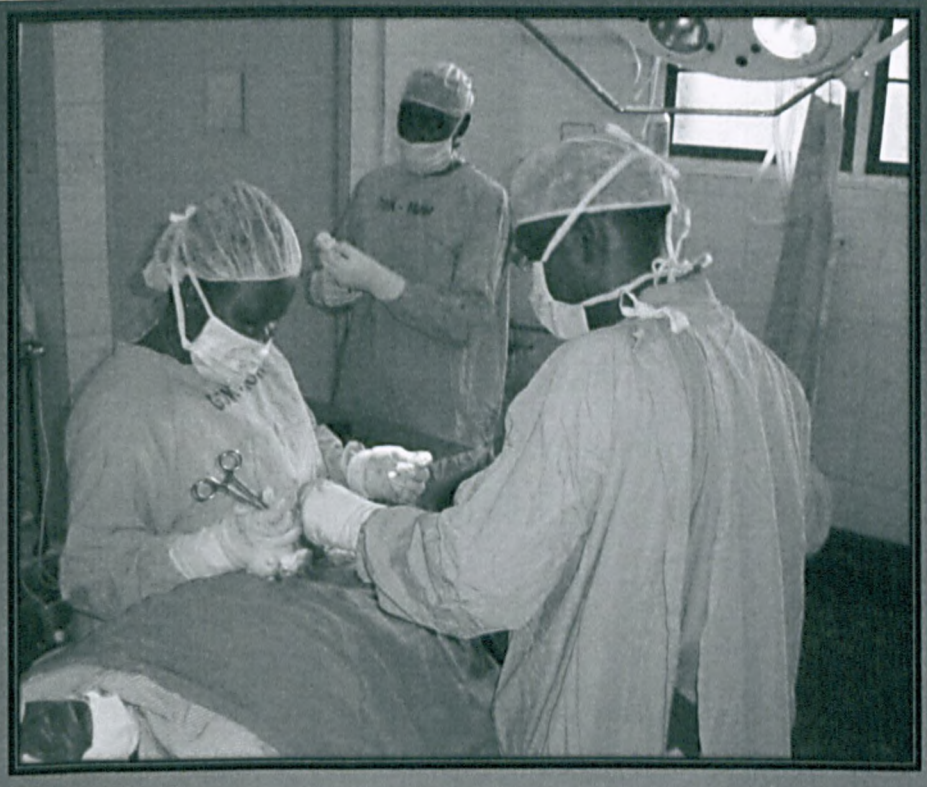
Notes

- Patients should receive pre-operative Antibiotic Prophylaxis even if they are already on antibiotic treatment on the wards- these medicines are very unlikely to cause significant overdose.
- For children under the age of 10 years or adult patients less than 30kg, doses of antibiotics should be adjusted to the weight of the patient as follows: Ampicillin 50mg /kg, Metronidazole 7.5mg /kg.
- Repeat doses of AP should be given in operations lasting > 4 hours, or if major blood loss occurs.
- No additional post-operative treatment is required for immunosuppressed patients unless they have "Contaminated" or "Dirty" operation sites.
- Ampicillin is for use as Antibiotic Prophylaxis in Surgical patients. If an infection subsequently develops after surgery, different antibiotics should be prescribed for treatment of the infection as the organism(s) may be Ampicillin resistant. First line treatment for wound infections should be X-pen, Gentamicin, Flagyl.
- No oral antibiotics are needed on discharge if a patient had pre-operative AP and has no signs of wound infection at time of discharge. Prescribing further antibiotics wastes money and promotes drug resistance!

Pre-operative Antibiotic Prophylaxis for Surgical Patients in Thika Level 5 Hospital

Appendix 2: Patient education poster in Kiswahili and English.

Dawa baada ya upasuaji ?



Hivi karibuni, hospitali ya Thika imebadilisha mfumo wa utumizi wa dawa kwa wagonjwa wanaofanyiwa upasuaji.

Hapo mbeleni, wagonjwa walikuwa wakipewa dawa za kukabiliana na baktiria kwa njia ya sindano pamoja na tembe kwa siku kadha BAADA ya upasuaji ili kuzuia maambukizi. Utaratibu huu unafuatwa katika hospitali nyingi kote nchini lakini ni mfumo wa kutumia hizi dawa uliopitwa na wakati.

Kwa sasa, wagonjwa katika hospitali ya Thika wanapewa DOZI MOJA ya dawa za kukabiliana na baktiria KABLA ya upasuaji, kuambatana na mwongozo uliotolewa na kanuni za kitaifa za matibabu (National Clinical Guidelines) 2009. Desturi ya kutumia dawa za kukabiliana na baktiria baada ya upasuaji haimo tena.

Kwa hiyo,wengi wa wagonjwa hawahitaji dawa za kukabili baktiria baada ya upasuaji, ziwe za sindano au za tembe. Unahitaji kuzitumia hizi dawa baada ya upasuaji iwapo yamezuka maambukizi kwenye kidonda chako baada ya upasuaji. Unaweza kutumia dawa zingine kama paracetamol na diclofenac kwa minajili ya kupunguza maumivu baada ya upasuaji, hili halitaathiri kupona kwa kidonda chako.

Idadi ndogo ya wagonjwa ambao tayari wana maambukizi wakati wa upasuaji watapewa dawa za kukabili baktiria baada ya upasuaji ili kulitibu ambukizi hili. Daktari wako atafanya uamuzi iwapo utahitaji matibabu haya.

Thika Hospital has recently changed the way that medicines are used for patients having surgery.

Previously, patients were given antibiotic injections and tablets for several days AFTER the operation to prevent infections. This is used in hospitals nationwide, but this is an old-fashioned way of using these medicines.

Now, patients in Thika Hospital are given a SINGLE DOSE of antibiotics IMMEDIATELY BEFORE the start of the operation – this is what is advised by the National Clinical Guidelines (2009). No antibiotics are routinely used after surgery.

So, most patients do not need any antibiotics after their operation, either as injections or as tablets. You only need to have antibiotics after your operation if an infection develops in your wound after the operation. You can still take medicines such as paracetamol or diclofenac to reduce pain after your operation – this will not affect the healing of your wound.

A small number of patients who already have an infection at the time of their operation will be given antibiotics after the operation to treat this infection. Your doctor will decide if you need to have this treatment.

Thika Hospital – Infection Prevention+Control Committee, May 2011

Title translates to "Medicines after surgery?"

Technical Appendix

An assumption of linear regression is that the data series is normally distributed ($-1 \leq$ skew ≤ 1 AND $-1 \leq$ kurtosis ≤ 1). Before the post-operative antibiotic prescribing series was analysed using segmented regression, a check was made to assess the normality of the series. When the data was found to be non-normal (kurtosis = -1.759), we also explored the use of fortnightly and monthly time points.

Post Op Prophylaxis Given	Skew	Kurtosis
Weekly Time Points	0.413	-1.759
Log Weekly Time Points	-0.396	-0.679
Fortnightly Time Points	0.473	-1.799
Log Fortnightly Time Points	0.054	-1.510
Monthly Time Points	0.715	-1.619
Log Monthly Time Points	0.254	-1.477

The time series of weekly data points is not normally distributed, and collapsing data to fortnightly or monthly time points did not achieve normalisation. The underlying reason for this non-normality is likely to be the large scale of the effect of the intervention – essentially this makes the data points appear bimodal, which then gives the high degree of kurtosis ("peakedness") seen above. Therefore, a log transformation was performed to achieve normality (skew = -0.396, kurtosis = -0.679) in weekly datapoints.

Segmented regression analysis was performed on the log transformed series to assess pre intervention trend, change in level and change in trend. As the series has been log transformed the direction of the change (+ or -) only can be determined and assessed for statistical significance.

	Log transformed Regression Co-efficients	p-value
Intercept	4.6054	<0.0001
Trend (Before Intervention)	-0.001772	0.8623
Change In Level	-1.1727	<0.0001
Change In Trend	-0.0360	0.0010

These results indicate that there was no statistically significant change in % of patients receiving post-operative antibiotics before the intervention which is fairly static at ~96%. There was a statistically significant decrease in level (-1.1727, $p<0.0001$) which indicates an abrupt intervention effect. There was a statistically significant change in trend (-0.0360, $p=0.0010$) following the intervention which indicates a gradual intervention effect.

As the data series has been log transformed the data series is not appropriate for use in the Multivariate Delta Method (as described by Zhang et al, J Clin Epi 2009) so it is not possible to construct confidence intervals around the intervention effects.

Chapter 5.

Research paper IV: The risk and causes of paediatric hospital-acquired bacteraemia in Kilifi District Hospital, Kenya: a prospective cohort study

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Candidate: signed: Alex Aiken

Supervisor: signed: Andrew J Hall

	SSI	Nosocomial bacteraemia	MRSA
Previous research in sSA (or lack thereof)	Ch2	Ch 5	Ch 6
HAI surveillance methods in an African context	Ch 3	Ch 5	Ch 6
Antibiotic use and resistance in sSA	Ch 4		Ch 6
Impacts of HAI in sSA	Ch 4	Ch 5	

Risk and causes of paediatric hospital-acquired bacteraemia in Kilifi District Hospital, Kenya: a prospective cohort study

*Alexander M Aiken, Neema Mturi, Patricia Njuguna, Shebe Mohammed, James A Berkley, Isaiah Mwangi, Salim Mwarumba, Barnes S Kitsao, Brett S Lowe, Susan C Morpeth, Andrew J Hall, Iqbal Khandawalla, J Anthony G Scott, Kilifi Bacteraemia Surveillance Group**

Summary

Background In sub-Saharan Africa, community-acquired bacteraemia is an important cause of illness and death in children. Our aim was to establish the magnitude and causes of hospital-acquired (nosocomial) bacteraemia in African children.

Methods We reviewed prospectively collected surveillance data of 33 188 admissions to Kilifi District Hospital, Kenya, between April 16, 2002, and Sept 30, 2009. We defined bacteraemia as nosocomial if it occurred 48 h or more after admission. We estimated the per-admission risk, daily rate, effect on mortality, and microbial cause of nosocomial bacteraemia and analysed risk factors by multivariable Cox regression. The effect on morbidity was measured as the increase in hospital stay by comparison with time-matched patients without bacteraemia.

Findings The overall risk of nosocomial bacteraemia during this period was 5·9/1000 admissions (95% CI 5·2–6·9) but we recorded an underlying rise in risk of 27% per year. The incidence was 1·0/1000 days in hospital (0·87–1·14), which is about 40 times higher than that of community-acquired bacteraemia in the same region. Mortality in patients with nosocomial bacteraemia was 53%, compared with 24% in community-acquired bacteraemia and 6% in patients without bacteraemia. In survivors, nosocomial bacteraemia lengthened hospital stay by 10·1 days (3·0–17·2). *Klebsiella pneumoniae, Escherichia coli, Staphylococcus aureus, Acinetobacter* spp, group D streptococci, and *Pseudomonas aeruginosa* accounted for three-quarters of nosocomial infections. Nosocomial bacteraemia was significantly associated with severe malnutrition (hazard ratio 2·52, 95% CI 1·79–3·57) and blood transfusion in children without severe anaemia (4·99; 3·39–7·37).

Interpretation Our findings show that although nosocomial bacteraemia is rare, it has serious effects on morbidity and mortality, and the microbiological causes are distinct from those of community-acquired bacteraemia. Nosocomial infections are largely unrecognised or undocumented as a health risk in low-income countries, but they are likely to become public health priorities as awareness of their occurrence increases and as other prominent childhood diseases are progressively controlled.

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Introduction

"Health-care-associated infection in developing countries is a serious issue that is scarcely addressed in the scientific literature".[1] In sub-Saharan Africa, community-acquired paediatric bacteraemia imposes a major health burden.[2–6] However, almost no regional information is available about hospital-acquired (nosocomial) bacteraemia. The WHO Patient Safety programme[7] did a systematic review of health-care-associated infection in developing countries between 1995 and 2008 and found no reports about nosocomial bacteraemia in adults or children in Africa, and only five studies of paediatric nosocomial bacteraemia from developing countries worldwide. A review focusing on infections in hospital-born neonates suggested a high risk of disease in this age group across the region.[8] Untreated maternal HIV infection is an important risk factor for neonatal nosocomial sepsis.[9] Outbreak reports[10–12] show that this disease occurs in the region but do not provide the denominator data necessary for estimation of risk or incidence.

We aimed to assess the risk, rate, effect on mortality and morbidity, microbiological causes, and risk factors for paediatric nosocomial bacteraemia by analysing surveillance data obtained prospectively for a continuous period at one Kenyan hospital.

Methods

Study design and patients

Kilifi District Hospital is in a rural area in Coast Province of Kenya. The Kenya Medical Research Institute-Wellcome Trust Research Programme has undertaken surveillance for invasive bacterial disease in children admitted to this hospital for more than a decade. Further information about Kilifi District Hospital is available in the webappendix. Throughout the analysis period between April 16, 2002, and Sept 30, 2009, we obtained specimens from all paediatric inpatients (except those with minor trauma or undergoing elective surgery) to investigate clinical illness both on admission and during the hospital stay. All children (except those described above) admitted to the paediatric ward were investigated

See Online for webappendix

with blood cultures on admission. We systematically obtained detailed clinical and laboratory information from all patients at admission. We used WHO standard techniques to take anthropometric measurements and we calculated weight-for-age *Z* scores using American National Centre for Health Statistics reference data.

We investigated patients with persistent or new fever, or clinical deterioration after admission, with a septic screen consisting of blood cultures, urine testing, and other samples as clinically indicated. Blood samples were taken by the admitting clinician, or by a ward aide (ie, a clinical support worker with phlebotomy training) after cleansing of the child's skin with 70% alcohol. Blood was inoculated into a culture bottle (BACTEC Peds Plus, Becton Dickinson, Franklin Lakes, NJ, USA) after the top of the bottle had been disinfected. We used an automated culturing system (BACTEC 9050, Becton Dickinson) to process blood cultures. We subcultured positive samples onto standard media and used standard microbiological techniques to identify the microorganisms. Laboratory procedures were internally controlled, and quality was monitored externally by the UK National External Quality Assessment Service. The monthly performance score for culturing of simulated specimens and identification of test organisms was higher than 95%.

Our study included an analysis of bacterial surveillance data that were drawn from two studies of invasive bacterial diseases at Kilifi District Hospital. Parents or guardians of all patients gave written informed consent for participation in these studies, which included cultures of blood taken at admission and routine investigations of clinical care. Both studies were approved by the Kenya Medical Research Institute National Ethics Review Committee.

Case definition

We defined an episode of nosocomial bacteraemia as isolation of a pathogenic organism (bacterial or fungal) from the blood of a child when the sample was taken more than 48 h after admission. We classified bacteraemia on readmission (within 28 days of discharge or hospital birth) as health-care-associated and all other positive blood cultures as community acquired. We regarded repeated isolation of the same pathogen in blood cultures within 14 days as one disease episode, whereas we regarded isolation of a different pathogen as a distinct disease episode. Coagulase-negative staphylococci, *Bacillus* spp, *Micrococcus* spp, viridans group streptococci, and coryneform bacteria were regarded as contaminants.

Statistical analysis

We did analyses in STATA version 11.0. We calculated the risk of at least one episode of nosocomial bacteraemia per admission and the incidence per 1000 days of inpatient hospital stay. We used log-linear binomial regression to characterise trends in the yearly risk of nosocomial bacteraemia and the probability of identifying a pathogen if a blood sample for culture had been taken. We analysed change in duration of hospital stay by year using Cox regression.

We used multivariable Cox regression to investigate the association of risk factors with the development of nosocomial bacteraemia. This approach is independent of length of hospital stay and is suitable for analysis of nosocomial infections in inpatient cohort data[13] even if the outcome is rare.[14] We used adjustment of variance for clustering within individuals with several admissions, and log-log plots for each variable to graphically confirm the validity of the proportional hazards assumption. We converted risk factor data, originally recorded in continuous variables, to binary or categorical variables before examining the effects of risk factors. Variables were included in a multivariable model if they showed a univariate association of $p<0\cdot1$. We tested for interactions between biologically associated variables in the final model.

To produce unbiased estimates of the additional length of hospital stay attributable to nosocomial bacteraemia, we used a confounder and time matching approach.[15] When possible, we randomly selected four patients who survived to discharge without nosocomial bacteraemia and matched by age and nutritional status to a patient with nosocomial bacteraemia, with the further constraint that they had been in hospital at least as long as the index patient at the point he or she developed bacteraemia. With an assumed mean hospital stay of 20 days (SD 25 days) in unexposed patients, matching of four patients to each case provides more than 90% power to detect an increased duration of 10 days in the exposed group.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

35 143 admissions were made to Kilifi District Hospital in the study period, of which 1316 (4%) were excluded because no blood was taken for culture, and 639 (2%) were excluded because of missing data or errors in the dates of admission or discharge. We analysed 33 188 admissions (94%) in 26 721 patients.

The median length of hospital stay was 3·7 days (IQR 2·0–6·8 days) and the median age at admission was 1·3 years (range 0 days to 15 years, IQR 157 days to 3·0 years). About 14% of the children admitted were neonates (age ≤28 days, table 1), though the proportion increased from 11% (904 of 8547) in 2002–03 to 18% (1219 of 6889) in 2008–09.

We identified 212 episodes of nosocomial bacteraemia. 13 children had two episodes and one child had three episodes during the same admission, so the total number

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of admissions with at least one episode of nosocomial bacteraemia was 197. Most episodes of nosocomial bacteraemia were preceded by one or more negative blood cultures (88%, 186 of 212) or by an admission blood culture isolating a different pathogen (5%, 11 of 212), supporting the inference of hospital-acquired disease. The risk of development of nosocomial bacteraemia at least once during a hospital stay was 5·9 per 1000 admissions (95% CI 5·2–6·9).

We included 212 933 inpatient days of observation in the study period, giving an overall rate of nosocomial bacteraemia of 1·00 episode per 1000 person-days (0·87–1·14) or 36 340 episodes per 100 000 person-years (31 777–41 639). In children younger than 2 years at admission, the rate was 42 398 episodes per 100 000 person-years (36 222–49 626). The estimated incidence of community-acquired bacteraemia in children younger than 2 years living in the same community is 1080 per 100 000 person years,[1] which suggests that the incidence rate ratio for acquisition of bacteraemia in hospital compared with in the community is about 40. The rate of nosocomial bacteraemia was higher than at baseline (day 2–7) in the second week (relative risk [RR] 1·61, 95% CI 1·16–2·23) and third week (1·77, 1·18–2·66) of hospital stays but not thereafter. The rate of nosocomial bacteraemia increased progressively throughout the study from 0·59 per 1000 person-days (95% CI 0·44–0·78) in 2002–04, to 1·66 per 1000 person-days (1·34–2·04) in 2008–09. The number of blood samples for culture taken more than 48 h after admission increased progressively from 163 in 2003, to 408 in 2008, with an annual increase of 19% (17–22%). Duration of hospital stay also increased throughout the study period. The average annual increase in duration of admissions was 3·8% (3·3–4·4%); the median duration was 3·15 days (IQR 1·90–5·92) in 2002 and 3·98 days (2·06–7·96) in 2009. We recorded no difference in this trend when the analysis was restricted to children who survived to discharge. The probability of detection of nosocomial bacteraemia when blood samples were taken more than 48 h after admission increased slightly during the study (RR per year=1·07, 95% CI 1·00–1·14).

Table 1 shows the distribution of children with nosocomial bacteraemia by each risk factor, together with univariable hazard ratios (HRs). Notably, nosocomial bacteraemia was not associated with age group (p=0·18). A multivariable proportional hazards model showed significant effects for nutritional status defined in terms of weight-for-age *Z* score, prescription of a blood transfusion, and study period. We recorded a significant interaction between transfusion and severe anaemia. To elucidate the factors behind this interaction, we re-examined the multivariable model in two exclusive age strata, patients aged 28 days or younger (neonates), and patients older than 28 days (infants and children). The pattern of risk factors differed sufficiently between these strata to justify separate presentation of the results (table 2). Severe anaemia and blood transfusion were not risk factors for nosocomial bacteraemia in neonates. In infants and children, blood transfusion (as prescribed at admission) was a highly significant risk factor for nosocomial bacteraemia, but only in children who did not have severe anaemia (table 2). Poor nutritional status was a risk factor at all ages but it showed a more pronounced association in neonates than in infants and children (table 2).

In 197 patients who developed one or more episodes of nosocomial bacteraemia, the case-fatality rate was 53% (105 of 197; 95% CI 46–60), compared with 24% (372 of 1528; 22–26) in patients with community-acquired

	Number of admissions (% of all admissions)	Outcome events	Univariable hazard ratio (95% CI)
Age group			
0–28 days	4668 (14%)	53	1·38 (0·97–1·94)
29–59 days	1056 (3%)	6	1·18 (0·46–3·00)
60–365 days	8275 (25%)	49	1·40 (0·97–2·01)
Older than 366 days	19 189 (58%)	104	1·0
Sex			
Female	14 552 (44%)	97	1·0
Male	18 636 (54%)	115	0·98 (0·74–1·31)
Nutritional status (WAZ)			
>–3	26 050 (79%)	78	1·0
–3 to –4	4179 (13%)	52	2·06 (1·42–2·99)
<–4	2692 (8%)	77	2·52 (1·79–3·57)
Missing	267 (1%)	5	3·52 (1·20–10·29)
HIV status			
Known negative	8150 (25%)	71	1·0
Known positive	696 (2%)	20	1·60 (0·97–2·66)
Unknown	24 342 (73%)	121	0·67 (0·49–0·92)
Transfusion prescribed			
No	30 563 (92%)	153	1·0
Yes	2573 (8%)	58	2·73 (1·98–3·76)
Unknown	52 (<1%)	1	3·90 (0·53–28·7)
Severe malaria*			
No	30 205 (91%)	208	1·0
Yes	2789 (9%)	4	0·45 (0·13–1·51)
Severe anaemia†			
No	30 132 (91%)	189	1·0
Yes	2167 (7%)	11	0·75 (0·40–1·43)
Unknown or not tested	889 (3%)	12	2·00 (0·97–4·14)
Burns on admission			
No	32 724 (99%)	202	1·0
Yes	464 (1%)	10	0·81 (0·41–1·60)
Time admitted			
2002–04	13 300 (40%)	48	1·0
2005–07	12 998 (39%)	78	1·58 (1·07–2·32)
2008–09	6890 (21%)	86	2·53 (1·74–3·68)
Total			
All admissions	33 188 (100%)	212	

WAZ=weight-for-age *Z* score. *Defined as per WHO criteria[14] for clinically severe malaria. †Defined as haemoglobin <50 g/L (for patients older than 28 days) or haemoglobin <90 g/L (for neonates).

Table 1: **Risk factors in study patients and univariable hazard ratios**

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	Age younger than 28 days* (HR [95% CI])	Age older than 28 days (HR [95% CI])
Nutritional status (WAZ)		
>-3	1·00	1·00
-3 to -4	1·73 (0·71–4·23)	1·99 (1·31–3·04)
<-4	3·40 (1·60–7·26)	1·95 (1·29–2·97)
Missing	5·22 (0·93–29·4)	1·78 (0·42–7·48)
Severe anaemia and transfusion		
No severe anaemia, not transfused		1·00
Severe anaemia, not transfused		1·04 (0·33–3·26)
No severe anaemia, transfused		4·99 (3·39–7·37)
Severe anaemia, transfused		0·62 (0·23–1·66)†
Time admitted		
2002–04	1·00	1·00
2005–07	1·87 (0·73–4·82)	1·43 (0·93–2·20)
2008–09	2·34 (0·89–6·14)	2·01 (1·29–3·12)

Severe anaemia and receipt of a blood transfusion had no significant effect in neonates and were not included in this model for this age group. WAZ=weight-for-age Z score. HR=hazard ratio. *Patients with missing data for blood transfusion or anaemia status on admission were excluded from this analysis. †Likelihood ratio test for inclusion of interaction term has p=0·015.

Table 2: **Risk factors for nosocomial bacteraemia analysed with multivariable Cox regression models**

	Nosocomial (total [%])	Health-care-associated* (total [%])	Community-acquired (total [%])
Gram-negative organisms			
Escherichia coli	44 (21%)	16 (11%)	144 (9%)
Proteus mirabilis	3 (1%)	1 (1%)	6 (<1%)
Klebsiella pneumoniae	43 (20%)	2 (1%)	37 (2%)
Klebsiella spp (other)	9 (4%)	1 (1%)	5 (<1%)
Pseudomonas aeruginosa	16 (8%)	8 (6%)	31 (2%)
Pseudomonas spp (other)	3 (1%)	1 (1%)	24 (2%)
Acinetobacter spp	19 (9%)	12 (9%)	159 (10%)
Non-typhi *Salmonella* spp	3 (1%)	10 (7%)	136 (9%)
Salmonella typhi	2 (1%)	0 (0%)	12 (1%)
Other enterobacteriaceae	8 (4%)	4 (3%)	26 (2%)
Haemophilus influenzae	2 (1%)	4 (3%)	99 (6%)
Other Gram-negative organisms	4 (2%)	0 (0%)	59 (4%)
Gram-positive organisms			
Staphylococcus aureus	20 (9%)	22 (16%)	198 (13%)
Streptococcus pneumoniae	3 (1%)	23 (16%)	459 (29%)
Group A streptococci	1 (1%)	5 (4%)	71 (5%)
Group B streptococci	2 (1%)	18 (13%)	26 (2%)
Group D streptococci	18 (9%)	12 (9%)	53 (3%)
Other gram-positive organisms	1 (1%)	2 (1%)	37 (2%)
Fungi			
Yeasts	11 (5%)	1 (1%)	8 (1%)
Total pathogens†	212 (100%)	141 (100%)	1590 (100%)

Data are number of episodes. *Health-care-associated infection was defined as bacteraemia within the first 48 h of admission to hospital when within 28 days of discharge from hospital or hospital birth. †Contaminants were grown from 19·5% of samples collected in the first 48 h after admission and 18·1% of samples obtained 48 h or more after admission. These proportions did not differ significantly (p=0·11).

Table 3: **Pathogens causing paediatric bacteraemia in Kilifi District Hospital, 2002–09**

bacteraemia and 6·2% (1930 of 31347; 5·9–6·4) in patients with no detected episodes of bacteraemia in this period. The median interval from sample collection to death for patients with nosocomial bacteraemia was 44 h (IQR 17–120 h). During the study, 4·3% (105 of 2423) of all hospital inpatient deaths occurred in patients in whom nosocomial bacteraemia was identified.

89 patients developed nosocomial bacteraemia and survived to discharge; the median length of hospital stay for these patients was 28·9 days (IQR 13·0–41·6). In 353 matched patients without nosocomial bacteraemia, whose hospital stay lasted at least as long as the time when bacteraemia developed in the index child, the median duration was significantly shorter (18·8 days; 8·1–30·9; difference between medians 10·1 days, p=0·006). Three patients with nosocomial bacteraemia were transferred to other facilities, and their eventual outcome is unknown.

Gram-negative organisms caused 74% of episodes of nosocomial bacteraemia (table 3); *Escherichia coli* and *Klebsiella pneumoniae* accounted for 21% and 20% of all episodes, respectively. Gram-positive organisms, of which *Staphylococcus aureus* was the most common, accounted for 21% of cases. Yeasts accounted for 5% of episodes of nosocomial bloodstream infection. Health-care-associated (readmission after recent discharge) pathogens were much the same as those causing community-acquired bacteraemia.

In patients with nosocomial bacteraemia the case-fatality rate varied significantly by organism class (χ^2 test p=0·023), being 61% in Gram-negative infections, 38% in Gram-positive infections, and 45% in fungal infections. Case-fatality rates were highest in patients infected with *Acinetobacter* spp (74%), *Pseudomonas aeruginosa* (75%), and *E coli* (77%). We detected no evidence of increased mortality in patients with isolates considered to be contaminants compared with all other patients (χ^2 test p=0·49).

Discussion

Our large study provides a comprehensive description of the epidemiology and microbiological causes of nosocomial bacteraemia in a representative paediatric service in sub-Saharan Africa. With a conventional case definition,[17] the risk of nosocomial bacteraemia was 5·9 per 1000 admissions. This finding is consistent with a risk of 5·0 per 1000 admissions recorded in a study in South Africa in 1989,[18] although the cutoff used to define infections as nosocomial in that study was 72 h after admission rather than 48 h as we used. The risk of nosocomial bacteraemia increased significantly throughout the study, which could be attributable, in part, to increased length of hospital stay in the later years of the study. This increase in turn is probably attributable to declining numbers of short admissions for malaria[19] and an increasing proportion of neonatal admissions. These factors suggest that the 2008–09 nosocomial

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bacteraemia rate (1·66 per 1000 days in hospital) is a better estimate of the present rate in Kilifi District Hospital than the study mean (1·00 per 1000 days in hospital). The effect of admission is clear from the fact that the incidence of nosocomial bacteraemia was about 40 times greater than the previously estimated incidence of community-acquired bacteraemia.[1]

Nosocomial bacteraemia is associated with high mortality; more than half of all patients (53%) died in hospital. Particular pathogens (such as *P aeruginosa* and *E coli*) were associated with very high case-fatality rates. Although other factors might have contributed to the risk of both bacteraemia and death, such as nutritional status, the case-fatality rate for nosocomial bacteraemia was more than double that for community-acquired bacteraemia (24%). The interval between detection of nosocomial bacteraemia and death (median 44 h) means that in many cases bacteraemia could have been the cause of death. The crude mortality of paediatric nosocomial bacteraemia at 49 hospitals in the USA between 1995 and 2001 was 14%.[20] At Kilifi District Hospital, survivors of nosocomial bacteraemia had a substantial morbidity burden, leading to an additional 10·1 days in hospital per case.

The factor most strongly associated with nosocomial bacteraemia in our study was prescription of blood transfusion, though this association was confined to children who did not have severe anaemia. We assume that most children prescribed transfusions at admission subsequently received the same, although data were not collected on the actual administration of transfusions. Overall, 2% (52 of 2573) of transfusion recipients subsequently developed nosocomial bacteraemia, which is similar to a rate of 3·5% of post-transfusion bacteraemia recorded in Malawi.[21] In African hospitals, clinicians often use blood transfusions to resuscitate shocked patients and for treatment of severe anaemia. In this study, 55% of patients prescribed a transfusion were severely anaemic (1408 of 2573), 27% (689 of 2573) were clinically shocked (as per WHO criteria), and 33% were neither severely anaemic nor shocked (847 of 2573). One possible explanation for the association of bacteraemia with transfusion is that these nosocomial infections were, in fact, delayed detection of community-acquired septicaemic shock. A second possible explanation for the reported association is contamination of blood for transfusion. In a study in Mombasa, Kenya, 8% of blood packs in the transfusion service had bacterial contamination.[22] The absence of transfusion-associated risk in severely anaemic patients argues against this interpretation. However, the combination of a strong association in patients without severe anaemia and local evidence of blood contamination supports a critical assessment of the role of blood transfusion in nosocomial bacteraemia in Africa.[23]

Malnutrition was a risk factor for nosocomial bacteraemia at all ages. This finding is consistent with studies of both community-acquired bacteraemia[24] and late hospital mortality in the region.[25] Other factors previously identified as risks for bacteraemia in general are (neonatal) age,[8] HIV infection, and anaemia.[26] That HIV infection was not significant in the multivariable model is indicative of underascertainment of HIV status in our study population—more than 70% of patients were of unknown HIV status because universal HIV testing was not implemented in Kilifi District Hospital until 2008. Furthermore, some of the risk of HIV infection might be indicated through nutritional status. Unexpectedly, patients with unknown HIV status seemed to be at decreased risk of disease in the univariable analysis—this finding is largely attributable to the confounding effect of the time period. Anaemia was not a risk factor after the effects of blood transfusion had been incorporated in the model, though, notably, children admitted to Kilifi District Hospital are much more anaemic than the general population.[27] No data were available for peripheral intravenous catheter use, which is likely to be an important risk factor in paediatric nosocomial bacteraemia.[20]

Our study might have underestimated the true risk of nosocomial bacteraemia for two reasons. First, the sensitivity of paediatric blood cultures is inherently poor, especially when antibiotic use is common and only one small-volume culture is collected.[1] Second, not all children who deteriorate in Kilifi District Hospital are investigated with blood cultures. For example, blood for culture was obtained during the 48 h before death from less than 50% of children dying in hospital. Even if only 10% of these children had had hospital-acquired bacteraemia, the calculated risk of nosocomial bacteraemia would have doubled.

We used a standard 48 h cutoff to separate hospital and community acquisition, which might have misclassified some community-acquired infections as hospital-acquired. The low sensitivity of blood cultures[1]

Panel: Research in context

Systematic review

A systematic review by WHO in 2010 identified no reports about paediatric or adult nosocomial bacteraemia in African countries between 1995 and 2008.[7] We searched PubMed using the MeSH terms ("nosocomial" OR "hospital-acquired") AND ("bacteraemia" OR "septicaemia") AND (Africa) in July, 2011, and found no subsequent studies of relevance.

Interpretation

As far as we are aware, our study is the only recent description of hospital-acquired paediatric bacteraemia in sub-Saharan Africa, other than outbreak reports. Although this form of disease is rare, it has serious effects on morbidity and mortality, and the microbiological causes are distinct from those of community-acquired bacteraemia. Malnutrition is a risk factor for hospital acquired bacteraemia.

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could have contributed to this misclassification—some community-acquired pathogens might have been missed on admission cultures. However, we believe that this 48 h threshold is validated, post hoc, by the distribution of pathogens isolated. Organisms that are usually acquired in the community (such as *S pneumoniae*) were very rarely classified as hospital-acquired in our analysis. Organisms such as *K pneumoniae*, which are typically associated with hospital acquisition,[11] were mainly classified as nosocomial cases.

Concerns about generalisability naturally arise with any single centre study. The risk of paediatric nosocomial bacteraemia at Kilifi District Hospital is substantial but it is probably even higher in other regional district hospitals. Clinical care at Kilifi District Hospital is supported by sustained research funding from the Kenya Medical Research Institute-Wellcome Trust Research Programme. Although the hospital has difficulties of overcrowding and high patient to staff ratios, the clinical services (including infection prevention and control) are probably of a higher standard in this institution than in other regional facilities.

To what extent are cases of nosocomial bacteraemia preventable in a setting such as Kilifi District Hospital? The WHO Patient Safety programme[28] argues that nosocomial disease should never be regarded as an unavoidable part of care, even in settings in which funds are limited. Indeed, measures to prevent nosocomial disease could be some of the most cost-effective interventions in low-income hospital settings.[29] In our study, many nosocomial bacteraemia cases occurred in easily identifiable high-risk groups of patients, so the efficiency of interventions could be increased through targeting. Promotion of hand hygiene, safe blood transfusions, and appropriate care of intravascular catheters could all greatly reduce the spread of invasive bacterial infections. In Kenya, national guidelines for infection prevention and control were published by the Ministry of Medical Services in December, 2010;[30] enforcement of these basic infection control principles could achieve substantial reductions in the burden of nosocomial disease.

As far as we are aware, our study is the largest analysis of nosocomial bacteraemia in sub-Saharan Africa (panel) and it provides the information base both for future research and for immediate efforts to tackle this disease. In Kilifi District Hospital, nosocomial bacteraemia occurs in six of every 1000 paediatric inpatients and accounts for almost 5% of deaths in hospital and extended hospital stay in survivors. The inherent insensitivity of paediatric blood cultures means that these findings are probably substantial underestimates. As the major paediatric infectious diseases of developing countries are brought under control by insecticide-treated bednets, effective antimalarial drugs, and vaccines against *Haemophilus influenzae* type b, pneumococcus, and rotavirus, the importance of hospital-acquired infections will become increasingly apparent and an effective response from doctors, nurses, hospital managers, and policy makers will be essential.

Contributors

JAGS, JAB, IMW, IK, and the Kilifi Bacteraemia Surveillance Group designed and did the surveillance for paediatric bacteraemia at Kilifi District Hospital. NM, PN, and SM led paediatric clinical services at Kilifi Hospital. SM, BCL, BSK, and SCM were responsible for microbiological parts of surveillance. AA, AJH, and JAGS planned the analysis. AA wrote the report and all authors reviewed and approved it before submission.

The Kilifi Bacteraemia Surveillance Group

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Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

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References

1 Rosenthal VD. Health-care-associated infections in developing countries. *Lancet* 2011; 377: 186–88.

2 Walsh AL, Phiri AJ, Graham SM, Molyneux EM, Molyneux ME. Bacteremia in febrile Malawian children: clinical and microbiologic features. *Pediatr Infect Dis J* 2000; 19: 312–18.

3 Berkley JA, Lowe BS, Mwangi I, et al. Bacteremia among children admitted to a rural hospital in Kenya. *N Engl J Med* 2005; 352: 39–47.

4 Hill PC, Onyeama CO, Ikumapayi UN, et al. Bacteraemia in patients admitted to an urban hospital in West Africa. *BMC Infect Dis* 2007; 7: 2.

5 Bahwere P, Levy J, Hennart P, et al. Community-acquired bacteremia among hospitalized children in rural central Africa. *Int J Infect Dis* 2001; 5: 180–88.

6 Blomberg B, Jureen R, Manji KP, et al. High rate of fatal cases of pediatric septicemia caused by gram-negative bacteria with extended-spectrum beta-lactamases in Dar es Salaam, Tanzania. *J Clin Microbiol* 2005; 43: 745–49.

7 Allegranzi B, Bagheri Nejad S, Combescure C, et al. Burden of endemic health-care-associated infection in developing countries: systematic review and meta-analysis. *Lancet* 2011; 377: 228–41.

8 Zaidi AK, Huskins WC, Thaver D, Bhutta ZA, Abbas Z, Goldmann DA. Hospital-acquired neonatal infections in developing countries. *Lancet* 2005; 365: 1175–88.

9 Aiken CG. HIV-1 infection and perinatal mortality in Zimbabwe. *Arch Dis Child* 1992; 67: 595–99.

10 Iregbu KC, Anwaal U. Extended spectrum Beta-Lactamase-producing *Klebsiella pneumoniae* septicaemia outbreak in the Neonatal Intensive Care Unit of a tertiary hospital in Nigeria. *Afr J Med Med Sci* 2007; 36: 225–28.

11 Murphy SA, Lowe B, Maghenda JK, Apollo JG. An outbreak of intravenous cannulae associated nosocomial septicaemia due to multidrug-resistant *Klebsiella pneumoniae*. *East Afr Med J* 1994; 71: 271–72.

12 Vaagland H, Blomberg B, Kruger C, Naman N, Jureen R, Langeland N. Nosocomial outbreak of neonatal Salmonella enterica serotype *Enteritidis meningitis* in a rural hospital in northern Tanzania. *BMC Infect Dis* 2004; 4: 35.

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13 de Irala-Estevez J, Martinez-Concha D, Diaz-Molina C, Masa-Calles J, Serrano del Castillo A, Fernandez-Crehuet Navajas R. Comparison of different methodological approaches to identify risk factors of nosocomial infection in intensive care units. *Intensive Care Med* 2001; **27**: 1254–62.

14 Callas PW, Pastides H, Hosmer DW. Empirical comparisons of proportional hazards, poisson, and logistic regression modeling of occupational cohort data. *Am J Ind Med* 1998; **33**: 33–47.

15 Schulgen G, Kropec A, Kappstein I, Daschner F, Schumacher M. Estimation of extra hospital stay attributable to nosocomial infections: heterogeneity and timing of events. *J Clin Epidemiol* 2000; **53**: 409–17.

16 Severe falciparum malaria. World Health Organization, Communicable Diseases Cluster. *Trans R Soc Trop Med Hyg* 2000; **94** (suppl 1): S1–90.

17 Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control* 2008; **36**: 309–32.

18 Cotton MF, Burger PJ, Bodenstein WJ. Bacteraemia in children in the south-western Cape. A hospital-based survey. *S Afr Med J* 1992; **81**: 87–90.

19 O'Meara WP, Bejon P, Mwangi TW, et al. Effect of a fall in malaria transmission on morbidity and mortality in Kilifi, Kenya. *Lancet* 2008; **372**: 1555–62.

20 Wisplinghoff H, Seifert H, Tallent SM, Bischoff T, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in pediatric patients in United States hospitals: epidemiology, clinical features and susceptibilities. *Pediatr Infect Dis J* 2003; **22**: 686–91.

21 Walsh AL, Molyneux EM, Kabudula M, Phiri AJ, Molyneux ME, Graham SM. Bacteraemia following blood transfusion in Malawian children: predominance of Salmonella. *Trans R Soc Trop Med Hyg* 2002; **96**: 276–77.

22 Hassall O, Maitland K, Pole L, et al. Bacterial contamination of pediatric whole blood transfusions in a Kenyan hospital. *Transfusion* 2009; **49**: 2594–98.

23 Tagny CT, Mbanya D, Tapko JB, Lefrere JJ. Blood safety in Sub-Saharan Africa: a multi-factorial problem. *Transfusion* 2008; **48**: 1256–61.

24 Bejon P. Fraction of all hospital admissions and deaths attributable to malnutrition among children in rural Kenya. *Am J Clin Nutr* 2008; **88**: 1626–31.

25 Berkley JA, Ross A, Mwangi I, et al. Prognostic indicators of early and late death in children admitted to district hospital in Kenya: cohort study. *BMJ* 2003; **326**: 361.

26 Calis JC, Phiri KS, Faragher EB, et al. Severe anemia in Malawian children. *N Engl J Med* 2008; **358**: 888–99.

27 Pedro R, Akech S, Fegan G, Maitland K. Changing trends in blood transfusion in children and neonates admitted in Kilifi District Hospital, Kenya. *Malar J* 2010; **9**: 307.

28 Pittet D, Allegranzi B, Storr J, et al. Infection control as a major World Health Organization priority for developing countries. *J Hosp Infect* 2008; **68**: 285–92.

29 Allegranzi B, Pittet D. Healthcare-associated infection in developing countries: simple solutions to meet complex challenges. *Infect Control Hosp Epidemiol* 2007; **28**: 1323–27.

30 Ministry of Medical Services, Kenya. National infection prevention and control guidelines for health care services in Kenya; 2010.

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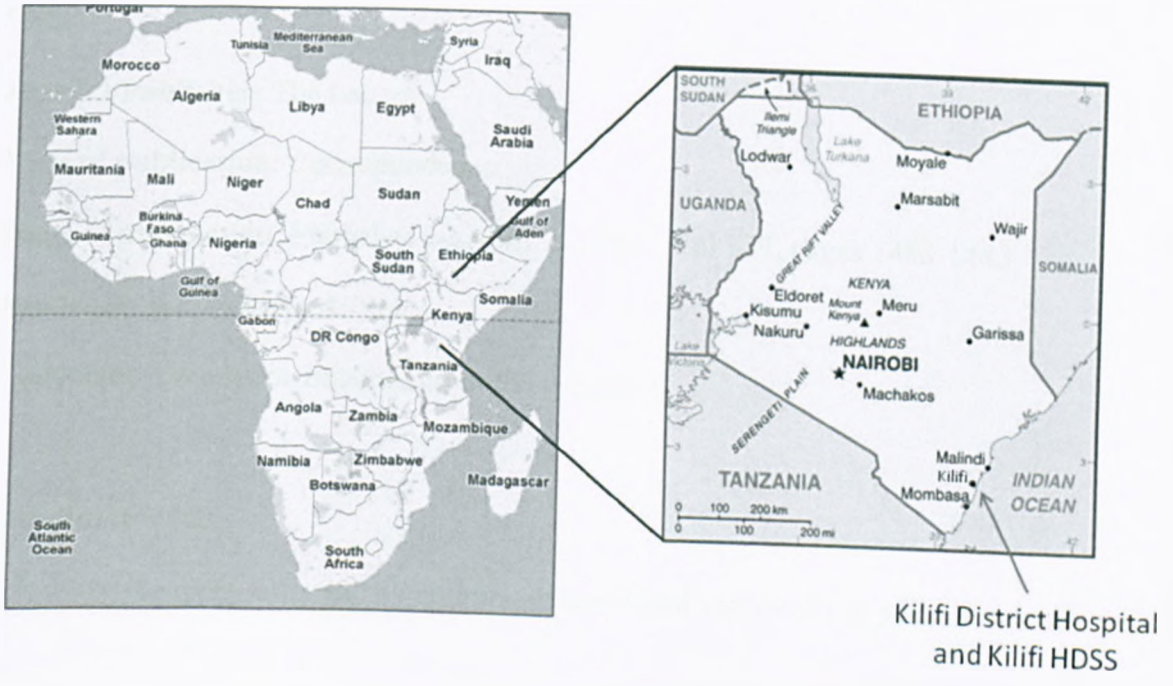
Webappendix to paper IV: Background information for Kilifi District Hospital, Kenya

Kilifi District Hospital (KDH) is a Government facility situated in Kilifi town on the Indian Ocean coast of Kenya – see figure 1. The KEMRI-Wellcome Trust Research Programme (KWTRP) was established in 1989 as a collaboration between the Kenya Medical Research Institute (KEMRI), the Wellcome Trust and the University of Oxford to conduct medical research on infectious diseases of children. During the 1990s, the Programme developed longitudinal clinical surveillance in the paediatric wards of KDH. Since 2000, Kilifi Health and Demographic Surveillance System (KHDSS) has been established to create a longitudinal community-based cohort study linked, at inception, to hospital morbidity surveillance by integrating the existing clinical and field-based research infrastructure. Further information about the Kilifi HDSS is available at _____

Figure 1: Location of Kilifi District Hospital, Kenya



The paediatric wards at KDH consist of a 54 bed "general ward", divided into 5 cubicles, where patients are cohorted by diagnosis, a 9 bed high-dependency unit and a 20 cot newborn unit. The bed occupancy in these units is normally between 150 and 200%: two children often share a bed/incubator, with an average of 80-90 inpatients, depending on time of the year.

There are normally 6 nurses on duty during daytime-shifts and 2 overnight (in the general ward). The same staffing pattern applies in the High Dependency Unit in a 3-3-2 shift system. Children are admitted via the outpatient department during the day and via Casualty at night. Blood samples are taken by the admitting clinician, or may be taken by a ward aide (a clinical support worker who has had phlebotomy training). The admitting clinician may be either a Medical Officer (a junior doctor) or a Clinical Officer (a vocationally-trained medical professional who performs similar duties to a junior doctor). During the day, blood cultures are taken to the main KWTRP laboratory within the hour, whilst at night, they are taken to a "satellite" laboratory adjacent to the paediatric ward, where a BACTEC machine is available for immediate incubation.

Correspondence I

Title: Paediatric hospital-acquired bacteraemia in developing countries

Author(s):

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Letter 2: Martin Wolkewitz, Susanna Di Termini, Ben Cooper, Joerg Meerpohl, Martin Schumacher

Reply: Alexander M Aiken, Neema Mturi, Susan C Morpeth, Anna C Seale, J Anthony G Scott

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AA wrote the reply letter and all authors reviewed and approved this prior to submission.

Candidate: signed: Alex Aiken

Supervisor: signed: Andrew J Hall

Correspondence

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Paediatric hospital-acquired bacteraemia in developing countries

April 13, 2012
DOI:10.1016/S0140-6736(12)60576-5

Although Alexander Aiken and colleagues (Dec 10, p 2021),[1] address an important issue, I have a few major concerns about their paper on the risk and causes of paediatric hospital-acquired bacteraemia.

First I am surprised that Aiken and colleagues excluded coagulase-negative staphylococci so hastily as a contaminant. In the developing world, such organisms constitute 12% of all Gram-positive organisms that cause hospital-acquired infection in neonates, and 17% of those in all age-groups.[2,3] Although often regarded as contaminants, coagulase-negative staphylococci can cause systemic instability resulting in temporary cessation of enteral feeding or escalation of ventilatory support, and are associated with longer hospital stay and poorer overall outcome, especially in neonates.[4] With the growing infrastructure of paediatric and neonatal intensive-care units and increasing survival of low birthweight babies in developing countries, these organisms will definitely become more important, as they are in developed countries currently.

Second, Aiken and colleagues have calculated weight-for-age Z scores using National Centre for Health Statistics (NCHS) reference data. This

Correspondence

method is fallacious in preterm low-birthweight neonates. An intrauterine or postnatal growth chart should be used until a preterm infant is full-term, after which one of the growth charts (WHO, NCHS, or US Centers for Disease Control and Prevention) should be used, corrected for gestational age.[5] This factor is even more important in a developing country where preterm birth rates are high. Aiken and colleagues' lack of attention to this point might therefore mean that the association they found between nosocomial bacteraemia and malnutrition, which is more pronounced in neonates than in infants and children, has been overestimated.

I declare that I have no conflicts of interest.

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1 Aiken AM, Mturi N, Njuguna P, et al, Kilifi Bacteraemia Surveillance Group. Risk and causes of paediatric hospital-acquired bacteraemia in Kilifi District Hospital, Kenya: a prospective cohort study. *Lancet* 2011; 378: 2021-27.

2 Zaidi AK, Huskins WC, Thaver D, Bhutta ZA, Abbas Z, Goldmann DA. Hospital-acquired neonatal infections in developing countries. *Lancet* 2005; 365: 1175–88.

3 Allegranzi B, Bagheri Nejad S, Combescure C, et al. Burden of endemic health-care-associated infection in developing countries: systematic review and meta-analysis. *Lancet* 2011; 377: 228-41.

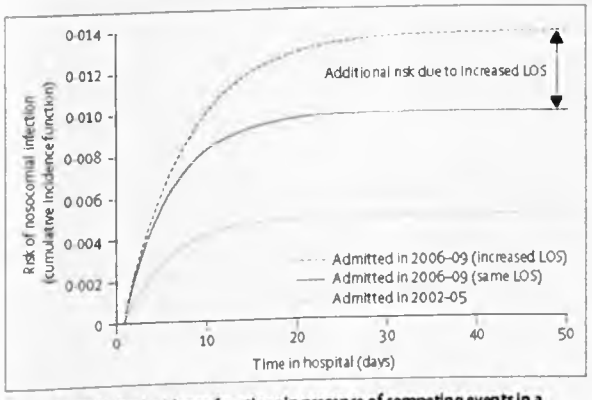

Figure: Cumulative incidence functions in presence of competing events in a hospital setting
We assume that the incidence is 2 per 1000 admission days for 2006-09 and 1 per 1000 for 2002-05. Further, we assume an average length of stay (LOS) of 5 days (discharge rate=0·2) for the whole period (solid lines). In another scenario, which reflects the situation mentioned by Aiken and colleagues,[1] we assume an extended LOS of 7 days (discharge rate=0·14) in 2006-09 (dashed line). The formula to calculate the cumulative incidence function can be found in Grambauer and colleagues.[5]

4 Klein JO. From harmless commensal to invasive pathogen: coagulase-negative staphylococci. *N Engl J Med* 1990; 323: 339-40.

5 Effard D, Anderson DM. Nutrition. In: Cloherty JP, Eichenwald EC, Stark AR, eds. Manual of neonatal care, 6th edn. New Delhi: Wolters Kluwer (India), 2009: 114-15.

We congratulate Alexander Aiken and colleagues[1] on their important study, which addresses two under-researched areas of hospital epidemiology: paediatrics and sub-Saharan Africa. The paper brings to light a subtle statistical issue that has been largely neglected in published studies on hospital infection, but which could lead to bias when assessing risk factors for nosocomial infection.

In survival analyses, as presented by Aiken and colleagues, patients who do not have bacteraemia are often regarded as censored when they are discharged. However, hospital discharge is a competing event for nosocomial infection.[2,3] Risk factors should then be assessed in two ways: an event-specific hazard regression (one for nosocomial bacteraemia and one for the hospital discharge), and a subdistribution approach.[4] These approaches will estimate different effects for risk factors than a simple survival analysis if the same risk factor has an effect on both infection and discharge.[5]

In the reported survival analysis, admission during 2005–09 was associated with an increased instantaneous risk of acquiring bacteraemia. Accounting for competing events, we find that the effect will be even larger when length of stay is increasing over time (as reported). The difference can be explained by the fact that patients with an increased length of stay acquire bacteraemia more frequently than patients with shorter stays (even though the infection rates remain the same). The figure shows this indirect effect with hypothetical values.

Thus, the optimum strategy for analysis of such data would be to treat discharge and bacteraemia as competing events.

We declare that we have no conflicts of interest.

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wolke

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1 Aiken AM, Mturi N, Njuguna P, et al, Kilifi Bacteraemia Surveillance Group. Risk and causes of paediatric hospital-acquired bacteraemia in Kilifi District Hospital, Kenya: a prospective cohort study. *Lancet* 2011; 378: 2021-27.

2 Beyersmann J, Wolkewitz M, Allignol A, Grambauer N, Schumacher M. Application of multistate models in hospital epidemiology: Advances and challenges. *Biometr J* 2011; 53: 332–50.

3 Wolkewitz M, Vonberg RP, Grundmann H, et al. Risk factors for the development of nosocomial pneumonia and mortality on intensive care units: application of competing risks models. *Crit Care* 2008; 12: R44.

4 Lau B, Cole SR, Gange SJ. Competing risk regression models for epidemiologic data. *Am J Epidemiol* 2009; 170: 244–56.

5 Grambauer N, Schumacher M, Dettenkofer M, Beyersmann J. Incidence densities in a competing events analysis. *Am J Epidemiol* 2010; 172: 1077–84.

Authors' reply

Rashmi Das raises the issue of whether coagulase-negative staphylococci could, in some cases, be acting as pathogens causing nosocomial bacteraemia rather than being contaminants. We agree that, in specific circumstances, coagulase-negative staphylococci can act as pathogens, most commonly when indwelling central vascular access devices are used in intensive-care settings. The US Centers for Disease Control and Prevention define bacteraemia caused by coagulase-negative staphylococci as occurring if the patient has symptoms or signs of systemic infection, if these symptoms or signs are not related to infection elsewhere, and if coagulase-negative staphylococci are cultured from two or more separate blood cultures.[1] In Kilifi District Hospital, where our study took place, central

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vascular access devices were not in use in the study period and there were no neonatal or paediatric intensive-care facilities. However, it is possible that coagulase-negative staphylococci could enter through peripheral intravenous access. We therefore analysed data for children with two or more detected episodes of bacteraemia with coagulase-negative staphylococci in blood cultures and found no increase in either morbidity or mortality above baseline. On this basis, we felt it best to exclude all coagulase-negative staphylococci as likely contaminants, although we acknowledge it is possible that a small number were acting as pathogens.

Das also highlights that calculation of weight-for-age Z scores with reference data from the National Centre for Health Statistics is inappropriate in preterm neonates, resulting in overestimation of malnutrition as a risk factor for hospital-acquired infection in neonates. Preterm birth is likely to be an important risk factor for nosocomial bacteraemia, and a limitation of this study is the inability to assess and adjust for it. However, determination of gestational age after delivery on the basis of the date of last menstrual period is imprecise and antenatal ultrasound dating scans were not available in this study.

Martin Wolkewitz and colleagues draw attention to the important issue of competing risks in nosocomial infections. Essentially, a competing risks analysis format should be used when a mode of exit from an analysis cohort is not independent of the main outcome—in such a situation, the assumption of non-informative censoring is not met.

Two events might compete for nosocomial bacteraemia in our analysis: discharge from hospital and inpatient death. With regard to discharge, we circumvented this problem by defining nosocomial bacteraemia as being detected before discharge. In reality, some hospital-acquired infections only manifest after discharge and many of these are missed by hospital-based surveillance. We agree that in ideal circumstances a subdistribution model would provide a better (and probably higher) estimate of overall disease risk. We note that another study[2] found high risk of death soon after discharge from Kilifi District Hospital for malnourished children.

Inpatient death could plausibly bias risk-factor estimates in this analysis: for example, the risk associated with malnutrition might have been underestimated, since malnourished children are more likely to die (and be removed from the at-risk set) during inpatient admission. This potential bias can be dealt with by treating death as a competing event for nosocomial bacteraemia, by use of the stcrreg command in STATA (versions 11+), giving cause-specific hazard ratios. However, this function cannot be done for data in which there are multiple failures per patient, so the analysis must be restricted to the first episode of nosocomial bacteraemia. If this is done for the univariate analysis of the nutritional status variable (weight-for-age Z score), we see that the parameter estimates from Cox regression (as we originally used) are reasonable (table). For our analysis, we chose to present the data incorporating all episodes of nosocomial bacteraemia to maximise the power of the study, precluding a competing events analysis in STATA.

We declare that we have no conflicts of interest.

*Alexander M Aiken, Neema Mturi, Susan C Morpeth, Anna C Seale, J Anthony G Scott

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1 Horan TC, Andrus M, Dudeck M, et al. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infection in the acute care setting. *Am J Infect Control* 2008; 36: 309–32.

2 Morsi JC, Gatakaa H, Berkley JA, et al. Excess child mortality after discharge from hospital in Kilifi, Kenya: a retrospective cohort analysis. *Bull World Health Organ* 2011; 89: 725–32.

	Cox regression	Cause-specific Cox regression with inpatient death as competing event
Types of failure included	Multiple failures per patient	Single failure per patient
Number of bacteraemia cases included	212 (original results)	197
Univariable hazard ratio (95% CI)		
Z score >–3	1·0	1·0
Z score –3 to –4	2·06 (1·42–2·99)	2·05 (1·42–2·95)
Z score <–4	2·52 (1·79–3·57)	2·54 (1·81–3·54)
Missing data	3·52 (1·20–10·29)	2·72 (0·98–7·58)

Both analyses use all 33 188 admissions included in original report.

Table: **Effect of treating death as a competing event on univariable hazard ratio for nutritional status (weight-for-age Z score)**

Chapter 6.

Research paper V: Carriage of *Staphylococcus aureus* in Thika Level 5 Hospital, Kenya: a cross-sectional study.

Author(s): Alexander M Aiken, Irene M Mutuku, Artur J Sabat, Viktoria Akkerboom, Jonah Mwangi, J Anthony G Scott, Susan C Morpeth, Alexander W Friedrich, Hajo Grundmann

Journal/Publisher: Journal of Hospital Infection

Type of publication: Research paper.

Stage of publication: submitted to journal but not yet reviewed

URL: N/A

Academic peer-reviewed: No

Candidate's role: as described in paper

Candidate: signed: Alex Aiken

Supervisor: signed: Andrew J Hall

	SSI	Nosocomial bacteraemia	MRSA
Previous research in sSA (or lack thereof)	Ch2	Ch 5	Ch 6
HAI surveillance methods in an African context	Ch 3	Ch 5	Ch 6
Antibiotic use and resistance in sSA	Ch 4		Ch 6
Impacts of HAI in sSA	Ch 4	Ch 5	

Title: Carriage of *Staphylococcus aureus* in Thika Level 5 Hospital, Kenya: a cross-sectional study.

Authors:

Alexander M Aiken[1,2], Irene M Mutuku[2], Artur J Sabat[3], Viktoria Akkerboom[3], Jonah Mwangi[4], J Anthony G Scott[2,5], Susan C Morpeth[2,5], Alexander W Friedrich[3], Hajo Grundmann[3].

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short title: Carriage of *S. aureus* in Thika Hospital, Kenya

ABSTRACT

Background. Methicillin-resistant *Staphylococcus aureus* (MRSA) is an important nosocomial pathogen but little is known about its circulation in hospitals in developing countries.

Methods. We measured the prevalence of *S. aureus* and MRSA carriage amongst adult inpatients in Thika Hospital, Kenya by means of repeated cross-sectional ward surveys. For all *S. aureus* isolates, we performed antibiotic susceptibility tests, genomic profiling using a DNA microarray and *spa* typing and MLST.

Findings. In this typical mid-sized Kenyan Government hospital, we screened 950 inpatients for prevalent carriage of *S. aureus* over a four month period. We detected *S. aureus* carriage (either MSSA or MRSA) in 8.9% (85/950; 95%CI 7.1-10.8) of hospital inpatients. MRSA carriage was relatively rare amongst hospital inpatients – only 7.0% (6/86; 95%CI 1.5-12.5%) of all *S. aureus* isolates were MRSA. Most MRSA (5/6) were obtained from burns patients with prolonged admissions, who only represented a small proportion of the inpatient population. All MRSA strains were of the same clone (MLST ST239; *spa* type t037) with concurrent resistance to multiple antibiotic classes. MSSA isolates were diverse and rarely expressed antibiotic resistance except against benzyl-penicillin and co-trimoxazole.

Interpretation. Although carriage rates for *S. aureus* and the MRSA prevalence in this Kenyan hospital were both low, burns patient were identified as a high risk group for carriage. The high frequency of genetically indistinguishable isolates suggests that there was local transmission of both MRSA and MSSA carriage.

Keywords: *Staphylococcus aureus*; MRSA; Kenya; hospitals; carriage prevalence

INTRODUCTION

Staphylococcus aureus is both a human commensal and an important pathogen (1). Methicillin-resistant *S. aureus* (MRSA) is a common cause of healthcare-associated infections in both developed and developing countries, though limited information is available from the latter (2). In hospital wards in developing countries, the risk of nosocomial transmission is likely to be high due to close physical proximity of patients, inadequate staffing, unreliable water-supply for handwashing, lack of alcohol hand-rub, isolation facilities or expertise for infection control (3) - these could represent near-ideal conditions for nosocomial circulation of drug-resistant bacteria. In sub-Saharan Africa, screening for MRSA carriage during hospital admission is rarely considered a healthcare priority and is infrequently performed, so patients carrying MRSA in hospitals in this region are unlikely to be identified or isolated.

Carriage of *S. aureus* is most commonly detected in the anterior nares (nostrils), though other sites on the body are frequently colonised, most commonly the groin and the axillae (1). Isolates from the nares are normally indistinguishable by molecular typing from those found on other body sites (4). Most *S. aureus* infections originate from self-carried strains, although disease only develops in a small minority of carriers (4-5). Cross sectional studies in adult populations have found nasal carriage rates of around 25%, although much of this work has been conducted in high-income settings (1). Carriage of *S. aureus* (either MRSA or methicillin-sensitive *S. aureus* (MSSA)) often lasts from months to years, and tends to be longer amongst individuals with chronic skin disease (6).

MRSA expresses resistance to all β-lactam antibiotics (penicillins, cephalosporins, carbapenems) by producing a penicillin-binding protein (PBP2a) from the *mecA* gene in the staphylococcal cassette chromosome (SCC*mec*). MRSA was first described in 1961 in the UK, very soon after the introduction of anti-staphylococcal penicillins (7). Some of the earliest reports of MRSA in sub-Saharan African came from various Kenyan Hospitals (including Thika Hospital) in the early 1990's, where it was principally found amongst burns patients (8). The prevalence of MRSA is the percentage of a collection of *S.aureus* isolates expressing resistance to methicillin – a marker for the presence of *mecA*. This has been estimated in a small number of studies in sub-Saharan Africa over the past 20 years, mostly based on clinical (disease-causing) isolates obtained at university teaching hospitals in major cities – see table 1. These studies have shown considerable variation: a relatively high

microbiological prevalence was found in clinical isolates in Ibadan, Nigeria in 2006-7 (9), but no MRSA was found amongst 45 *S. aureus* carriage isolates from healthcare workers in a large private hospital in Nairobi, Kenya in 2010 (10). Much more information about the nature of MRSA strains in circulation is available in South Africa (11), but data from this country is unlikely to be regionally representative. We are not aware of any previous estimates of the carriage rate of MRSA or *S.aureus* for an inpatient population in sub-Saharan Africa outside of South Africa. Most MRSA strains in Africa appear to derive from a small number of common ancestors: a recent study examining 86 MRSA isolates from five hospitals in West Africa and Madagascar found that 88% of these isolates were from one of three clonal strains (12). By contrast, there was wide diversity amongst MSSA clones from the same institutions (13). No similar studies have been reported from East Africa. The types of MRSA circulating in East Africa are unknown.

We aimed to describe the prevalence and diversity of MSSA and MRSA carriage amongst inpatients in a typical mid-sized public-service hospital in Kenya.

MATERIALS AND METHODS

Study setting and patient procedures: Thika Level 5 Hospital is a 300-bed Government Hospital in the town of Thika, approximately 50km north-east of Nairobi, in Central Province, Kenya. It provides medical, surgical, gynaecological, obstetric and paediatric services to a mixed urban and rural population and has a total of seven inpatient wards. Throughout this study there was no full-time infection control nurse in Thika Hospital, though a Hospital Infection Prevention and Control Committee met monthly. Daily bed occupancy rates in adult wards in 2011 were typically between 120 and 140% and all patients were nursed in communal bays.

Between the 11th July and 7th November 2011, all patients in adult inpatient medical, surgical and gynaecological wards were screened on alternate weeks for carriage of *S. aureus*. Any patients who stayed in the ward overnight prior to screening were eligible for inclusion, provided that they (or a family member) were able to give consent. The surgical wards included some paediatric patients receiving treatment for surgical conditions, who were also included in screening. Patients who were MRSA-negative were repeatedly screened throughout their entire period of hospitalisation. Results regarding MRSA carriage were relayed to patients and clinicians as soon as these became available. Patients found to have carriage of MRSA were subsequently treated with vancomycin if an infection with *S. aureus* was suspected. Patient data were collected from patient notes or by direct interview during screening and single-entered into a local database. Statistical analysis was carried out using STATA v12 (StataCorp, College Station, Texas, USA).

Ethics statement: This study was approved by the Kenya Medical Research Institute (KEMRI) National Ethical Review Committee. All patients (or their relatives) gave written informed consent to nasal and skin swab collection.

Swab processing: Paired nasal and axillary skin swabs were collected from each patient and were immediately transferred to Mannitol Salt broth (HiMedia Laboratories, Mumbai, India) for overnight selective enrichment. The following day, aliquots were plated onto Blood Agar (BA) media. Single colonies from plates which showed suspected *S. aureus* colony growth, were further processed by Gram stain, catalase and coagulase test, and checked for the ability to hydrolyse DNA. Disc diffusion tests with cefoxitin (10μg) were used to identify suspected MRSA according to British Society for Antimicrobial Chemotherapy guidelines.

All media were locally prepared and batch controlled using appropriate internal quality control strains (*S. aureus* ATCC 25923, *S. epidermidis* ATCC 12228, *E. coli* ATCC 25922). Isolates were initially kept at -20°C and then transferred to -80°C for storage. Isolates were shipped to the University Medical Centre Groningen for further investigations.

Antimicrobial susceptibility testing. Susceptibility to a standard panel of antibiotics plus chloramphenicol was performed using the automated Vitek 2 system (bioMerieux, Marcy l'Etoile, France). The results were interpreted in accordance with the 2012 guidelines of the Clinical and Laboratory Standards Institute. Isolates positive for inducible clindamycin resistance were assumed to be resistant to lincosamines and macrolides.

Extraction of genomic DNA. Total DNA was prepared from a loop of *S. aureus* cells lifted from blood agar plates and transferred to 2-ml tubes containing 500µl of water and zirconia/silica beads. The tubes were fixed in a TissueLyser homogenizer (Qiagen, Venlo, Netherlands) and the cells were disrupted by vortexing for 5min at 30Hz. The suspensions were clarified by centrifugation (14,000 rpm for 10min), and the supernatant was used for DNA extraction with the DNeasy Blood & Tissue kit (Qiagen) according to the manufacturer's protocol. The DNA concentration was quantified using a NanoDrop spectrophotometer (NanoDrop Technologies, Wilmington, DE) at 260nm.

Genotyping. *Spa* typing (14) and Multi Locus Sequence Typing (MLST) (15) were performed as described previously. *Spa* types were assigned by Ridom StaphType software version 1.4.6 (Ridom GmbH, Würzburg, Germany) and the Ridom SpaServer (http://www.spaserver.ridom.de) (16) after adhering to the SeqNet.org quality procedure (17). Sequences of each MLST locus were compared to the data in the *S. aureus* MLST database (http://saureus.mlst.net/), and resulting allelic profiles were assigned to particular sequence types (STs) for each isolate. eBURST software (v3, http://eburst.mlst.net) was used to classify related Sequence Types (STs) into clonal complexes (CCs) A singleton was defined as a sequence type that did not group with any clonal complex. The diagnostic DNA microarrays (StaphyType; Alere Technologies, Jena, Germany) and StaphyType DNA microarray kit were used for study of the presence of genes encoding species markers, agr types and virulence factors as described previously (18).

RESULTS

Carriage of *S. aureus*

A total of 950 screening swabs were obtained from inpatients in the medical, surgical and gynaecological wards of Thika Hospital. Patients ranged in age between 1 and 90 years and 52% were male. A total of 85 patients (85/950; 8.9%; 95%CI 7.1-10.8) were found to carry *S. aureus*. One patient had two distinct *S. aureus* strains (one MRSA and one MSSA). Thus, a total of 86 *S. aureus* isolates were collected. Species identification was confirmed by the presence of the *S.aureus*-specific genes (*spa*, *coA*, *nuc1*) and *mecA* for MRSA. We found no association between carriage of *S. aureus* and either age group or sex (χ^2test; $p>0.1$).

Among the *S. aureus* isolates obtained, six (6/86; 7.0%; 95%CI 1.5-12.5%) were MRSA. All of these were obtained from surgical patients, comprising three adult men and one male child (male surgical ward) and one woman and one female child (female surgical ward). All of these patients had been hospitalised for a prolonged period, five with extensive burns and one with a fractured femur. The median admission length prior to MRSA detection was 27 days (range 25 - 172 days).

Antibiotic resistance

All six MRSA isolates were co-resistant to gentamicin, ciprofloxacin, tetracycline and co-trimoxazole and five were also resistant to lincosamine and macrolide antibiotics. All MRSA isolates were susceptible to chloramphenicol, vancomycin and mupirocin. Amongst the MSSA isolates obtained, resistance to penicillin, tetracycline and SXT was common, but not to any other antibiotics – see table 2.

Diversity of isolates established by *spa* typing and MLST analyses

The 86 *S. aureus* isolates were assigned to 29 *spa* types, ranging in length between four (t10499) and 12 (t005) repeats. Two new repeats, r558 and r559, and five new *spa* types, t10496, t10497, t10498, t10499 and t10960, were found and assigned over the course of this study. Sixteen *spa* types were represented by 2 or more isolates (73 isolates in total), while 13 *spa* types contained a single isolate. All six MRSA isolates identified were of *spa* type t037. Among the MSSA isolates, t223 ($n = 15$) was the most frequent *spa* type, followed by t064 ($n = 10$) and t131 ($n = 10$). Other *spa* types ($n = 25$) were represented by four or less MSSA isolates.

A *single representative* of each *spa* type was analyzed by *MLST*. Twenty STs were identified. Five new MLST allelic profiles and three new STs were found; the latter were assigned as ST2429, ST2430, and ST2431. All six MRSA isolates belonged to international clone ST239. The correspondence between MLST and *spa* typing is shown in table 3.

Using eBURSTv3, all MLST STs obtained in the study were assigned to CCs. This method identified ST2430 as a single locus variant of CC121; the remaining 18 STs were unrelated. Subsequently, MLST data obtained in this study were compared to the *S. aureus* MLST database. Of the 68 isolates which were grouped into 14 CCs, the majority of these (64/68, 94%) had a founder sequence type – see Table 3.

Microarrays

The distribution of genes of the core variable genome and the identification of the allelic variants of genes of the core genome varied between MLST sequence type – full details of these results including profiles for all MSSA isolates are given as supplementary material in appendix S1.

All six MRSA isolates carried the SCCmec III element, the mercury resistance operon, ccrC, the virulence genes *sek* and *seq*, the protease *splA*, *splB* and *splE* genes but phage-associated genes *sak, scn* and *chp* were present only in four isolates. Five isolates carried the haemolysins genes, *hla* and *hlb*. All isolates had the same set of the MSCRAMM genes (*bbp*, *cna*, *ebh*, *fib*, *fnbA*, *fnbB*, *map*, *sdrC*, *sdrD*, and *sasG*).

DISCUSSION

In this typical mid-sized Kenyan government hospital, carriage of *S. aureus* amongst inpatients was found to be relatively infrequent (8.9%; 95%CI 7.1-10.8). MRSA constituted only 6.9% (95%CI 1.5-12.5%) of all *S. aureus* isolates obtained. Both of these results were surprisingly low, given that nasal carriage of *S. aureus* in the general population is typically thought to be around 25% (1) and the crowded conditions in Thika Hospital should lead to frequent transmission of MRSA. The small number of MRSA isolates obtained leaves us with a wide confidence interval for the true microbiological prevalence.

Almost all MRSA carriage was confined to patients with burns who constituted approximately 10% of adult inpatients admitted to the surgical wards and approximately 5% of inpatients overall. In sub-Saharan Africa, prolonged hospital admission after burns injuries are common (19), and as specialist burns units are rarely available, these patients often make up a sizeable proportion of the general inpatient population. Burns patients are at increased risk of invasive bacterial disease (20) and hence colonisation of these patients with a multi-drug resistance organism is of particular concern. Chloramphenicol is a widely used 2nd line antibiotic in sub-Saharan Africa and as all isolates in Thika Hospital were found to be susceptible to this drug, this might be a suitable empirical alternative to vancomycin for suspected MRSA infections in this setting.

These Thika MRSA isolates belong to the widespread ST239 strain, formerly known as the Hungarian/Brazilian epidemic strain which is typically associated with hospital-acquisition. This has been documented to occur in sub-Saharan Africa in Senegal, Niger (12), South Africa (11) and was noted to be common amongst hospitalised burns patients in Nigeria (9). The pattern of multi-class antibiotic resistance that we found in Thika Hospital is typical of this strain in African settings (12). A recent study described the intercontinental transmission of this strain from Europe to Asia and the Americas, but did not include any African isolates (21).

When designing this study, we expected the prevalence of *S. aureus* and MRSA to be considerably higher than we actually found. The only previous study of MRSA carriage in hospital inpatients in sub-Saharan Africa was conducted in TB patients hospitalised in KwaZulu-Natal in South Africa (22) where MRSA carriage was found to be 21% on admission. Many of these MRSA colonised patients had recent hospitalisations and advanced

HIV disease, which may have contributed to the high carriage prevalence. In this study, a standard cross-sectional approach for detecting carriage was used, but this may have missed some cases of nosocomial acquisition occurring late in admission, which could have been detected by additional screening on discharge.

The reason for the surprisingly low overall rate of *S. aureus* carriage (8.9%) in our study is unclear. We feel that is it unlikely that procedural errors with swab collection could account for this – all swab collection was supervised in person and regularly quality controlled by one investigator (AA) and an experienced researcher (HG) made an on-site review of the collection and processing methods in the first month of the study. Genetic differences could provide an explanation for this low carriage rate – human genetic factors are thought to be important determinants for persistent colonisation with *S. aureus* (23). In the USA, one study found people of African ethnicity to have low *S. aureus* carriage rates (3/9 individuals) in comparison to White non-Hispanic (27/50) or Hispanic (8/20) individuals (24). It is also possible that carriage of coagulase-negative staphylococci (CoNS) or other members of the human skin microbiota may have been competitively inhibiting *S. aureus* colonisation, as has recently been demonstrated in animal models (25) – but our study did not set out to examine this possibility.

Many of the *spa* types (17%; 5/29) and MLST profiles (15%, 3/20) identified in this population were novel. This reflects the fact that very few African sites have previously contributed typing information to the relevant databases. The lack of diversity amongst the MRSA and MSSA isolates obtained in our institution over a four month period suggests that these were probably being transmitted by local (i.e. within-hospital) routes rather than repeated introduction from external sources, though without greater knowledge of the diversity of strains circulating in Kenya or East Africa as a whole, we cannot be certain of this. Due to overcrowding, lack of isolation facilities and awareness of the problem, eliminating nosocomial transmission of organisms such as MRSA in institutions like Thika Hospital will be challenging.

CONCLUSION

Antibiotic resistance is a growing concern in developing countries (26) and local studies are needed to understand the transmission of drug-resistant organisms and guide strategies for

containment (27). MRSA is an important nosocomial pathogen in developed countries but little is known about it in sub-Saharan Africa. This is the largest study examining prevalent inpatient carriage of *S. aureus* in sub-Saharan Africa and it was conducted in a typical mid-sized Kenyan Government Hospital. Most of the existing studies of MRSA in Africa have examined clinical isolates in large hospitals in major cities and these are unlikely to be representative of hospitals in the region. We found inpatient carriage of MRSA to be relatively infrequent and was mainly confined to patients with burns. The lack of genetic diversity of these isolates obtained suggests "within-hospital" transmission. The multiple drug resistance of the MRSA found in Thika hospital coupled with the vulnerability of burns patients to invasive bacterial infection is a cause for concern. Thika Hospital faces many infection control challenges that are typical of those encountered in African healthcare facilities. Much work is needed in Kenya and throughout the region to formulate national and local policies on appropriate Infection Prevention and Control (28) to tackle issues such as MRSA and, more importantly, to put these into effect practice.

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Author contributions

Conceived and designed the study: AMA, JAGS, SCM, AWF and HG. Performed collection of samples from inpatients in Thika Hospital, Kenya: AMA, JM. Performed isolation of *S.aureus* in Thika Hospital, Kenya: IMM, SCM. Performed further analysis in UMCG, the Netherlands: IMM, AJS, VA and AWF. Wrote the final manuscript: AMA. Reviewed and approved of final manuscript prior to submission: all authors.

Data access and responsibility to submit

AA declares that he had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Ethical approval

This study was approved by the Kenya Medical Research Institute (KEMRI) National Ethical Review Committee. All patients (or their relatives) gave informed consent to nasal and skin swab collection.

Conflicts of interest

All authors declare that they have no conflicts of interest.

References

1. Wertheim HF, Melles DC, Vos MC, van Leeuwen W, van Belkum A, Verbrugh HA, et al. The role of nasal carriage in Staphylococcus aureus infections. Lancet Infect Dis. 2005 Dec;5(12):751-62.

2. Allegranzi B, Bagheri Nejad S, Combescure C, Graafmans W, Attar H, Donaldson L, et al. Burden of endemic health-care-associated infection in developing countries: systematic review and meta-analysis. Lancet. 2011 Jan 15;377(9761):228-41.

3. Okeke IN, Laxminarayan R, Bhutta ZA, Duse AG, Jenkins P, O'Brien TF, et al. Antimicrobial resistance in developing countries. Part I: recent trends and current status. Lancet Infect Dis. 2005 Aug;5(8):481-93.

4. Reighard A, Diekema D, Wibbenmeyer L, Ward M, Herwaldt L. Staphylococcus aureus nasal colonization and colonization or infection at other body sites in patients on a burn trauma unit. Infect Control Hosp Epidemiol. 2009 Aug;30(8):721-6.

5. Nouwen JL, van Belkum A, Verbrugh HA. Determinants of Staphylococcus aureus nasal carriage. Neth J Med. 2001 Sep;59(3):126-33.

6. Hoeger PH, Lenz W, Boutonnier A, Fournier JM. Staphylococcal skin colonization in children with atopic dermatitis: prevalence, persistence, and transmission of toxigenic and nontoxigenic strains. J Infect Dis. 1992 Jun;165(6):1064-8.

7. Cookson B. Five decades of MRSA: controversy and uncertainty continues. Lancet. 2011 Oct 8;378(9799):1291-2.

8. Muthotho JN, Waiyaki PG, Mbalu M, Wairugu A, Mwanthi B, Odongo B. Control of spread of Methicillin Resistant Staphylococcus aureus (MRSA) in Burns Units. Afr J Health Sci. 1995 Feb;2(1):232-5.

9. Ghebremedhin B, Olugbosi MO, Raji AM, Layer F, Bakare RA, Konig B, et al. Emergence of a community-associated methicillin-resistant Staphylococcus aureus strain with a unique resistance profile in Southwest Nigeria. J Clin Microbiol. 2009 Sep;47(9):2975-80.

10. Omuse G, Kariuki S, Revathi G. Unexpected absence of meticillin-resistant Staphylococcus aureus nasal carriage by healthcare workers in a tertiary hospital in Kenya. J Hosp Infect. 2012 Jan;80(1):71-3.

11. Moodley A, Oosthuysen WF, Duse AG, Marais E. Molecular characterization of clinical methicillin-resistant Staphylococcus aureus isolates in South Africa. J Clin Microbiol. 2010 Dec;48(12):4608-11.

12. Breurec S, Zriouil SB, Fall C, Boisier P, Brisse S, Djibo S, et al. Epidemiology of methicillin-resistant Staphylococcus aureus lineages in five major African towns: emergence and spread of atypical clones. Clin Microbiol Infect. Mar 13.

13. Breurec S, Fall C, Pouillot R, Boisier P, Brisse S, Diene-Sarr F, et al. Epidemiology of methicillin-susceptible Staphylococcus aureus lineages in five major African towns: high prevalence of Panton-Valentine leukocidin genes. Clin Microbiol Infect. Jul 29.

14. Aires-de-Sousa M, Boye K, de Lencastre H, Deplano A, Enright MC, Etienne J, et al. High interlaboratory reproducibility of DNA sequence-based typing of bacteria in a multicenter study. J Clin Microbiol. 2006 Feb;44(2):619-21.

15. Enright MC, Day NP, Davies CE, Peacock SJ, Spratt BG. Multilocus sequence typing for characterization of methicillin-resistant and methicillin-susceptible clones of Staphylococcus aureus. J Clin Microbiol. 2000 Mar;38(3):1008-15.

16. Harmsen D, Claus H, Witte W, Rothganger J, Turnwald D, Vogel U. Typing of methicillin-resistant Staphylococcus aureus in a university hospital setting by using novel software for spa repeat determination and database management. J Clin Microbiol. 2003 Dec;41(12):5442-8.

17. Friedrich AW, Witte W, de Lencastre H, Hryniewicz W, Scheres J, Westh H. A European laboratory network for sequence-based typing of methicillin-resistant Staphylococcus aureus (MRSA) as a communication platform between human and veterinary medicine--an update on SeqNet.org. Euro Surveill. 2008 May 8;13(19).

18. Monecke S, Coombs G, Shore AC, Coleman DC, Akpaka P, Borg M, et al. A field guide to pandemic, epidemic and sporadic clones of methicillin-resistant Staphylococcus aureus. PLoS One. 2011;6(4):e17936.

19. Albertyn R, Bickler SW, Rode H. Paediatric burn injuries in Sub Saharan Africa--an overview. Burns. 2006 Aug;32(5):605-12.

20. Cook N. Methicillin-resistant Staphylococcus aureus versus the burn patient. Burns. 1998 Mar;24(2):91-8.

21. Harris SR, Feil EJ, Holden MT, Quail MA, Nickerson EK, Chantratita N, et al. Evolution of MRSA during hospital transmission and intercontinental spread. Science. 2010 Jan 22;327(5964):469-74.

22. Heysell SK, Shenoi SV, Catterick K, Thomas TA, Friedland G. Prevalence of methicillin-resistant Staphylococcus aureus nasal carriage among hospitalised patients with tuberculosis in rural Kwazulu-Natal. S Afr Med J. 2011 May;101(5):332-4.

23. van Belkum A, Melles DC, Nouwen J, van Leeuwen WB, van Wamel W, Vos MC, et al. Co-evolutionary aspects of human colonisation and infection by Staphylococcus aureus. Infect Genet Evol. 2009 Jan;9(1):32-47.

24. Cole AM, Tahk S, Oren A, Yoshioka D, Kim YH, Park A, et al. Determinants of Staphylococcus aureus nasal carriage. Clin Diagn Lab Immunol. 2001 Nov;8(6):1064-9.

25. Park B, Iwase T, Liu GY. Intranasal application of S. epidermidis prevents colonization by methicillin-resistant Staphylococcus aureus in mice. PLoS One. 2011;6(10):e25880.

26. Laxminarayan R, Heymann DL. Challenges of drug resistance in the developing world. BMJ. 2012;344:e1567.

27. Okeke IN, Klugman KP, Bhutta ZA, Duse AG, Jenkins P, O'Brien TF, et al. Antimicrobial resistance in developing countries. Part II: strategies for containment. Lancet Infect Dis. 2005 Sep;5(9):568-80.

28. National Infection Prevention and Control Guidelines for Health Care Services in Kenya. In: Services MoM, editor. Nairobi2010.

29. Kesah C, Ben Redjeb S, Odugbemi TO, Boye CS, Dosso M, Ndinya Achola JO, et al. Prevalence of methicillin-resistant Staphylococcus aureus in eight African hospitals and Malta. Clin Microbiol Infect. 2003 Feb;9(2):153-6.

30. Shittu AO, Lin J. Antimicrobial susceptibility patterns and characterization of clinical isolates of Staphylococcus aureus in KwaZulu-Natal province, South Africa. BMC Infect Dis. 2006;6:125.

Table 1 – Estimates of microbiological prevalence of MRSA in sub-Saharan Africa

Study location	Year(s)	Isolates from	Number of MRSA/*S.aureus*	MRSA %
Lagos, Nigeria (29)	1996-7	Clinical specimens	42/142	29.6
Nairobi, Kenya (29)	1996-7	Clinical specimens	38/137	27.7
Yaounde, Cameroon (29)	1996-7	Clinical specimens	27/127	21.3
Abidjan, Côte d'Ivoire (29)	1996-7	Clinical specimens	26/155	16.8
Dakar, Senegal (29)	1996-7	Clinical specimens	21/168	12.5
KwaZulu-Natal Province, South Africa (30)	2001-3	Clinical specimens	61/227	26.9
Ibadan, Nigeria (9)	2006-7	Clinical + carriage specimens	70/346	20.2
5 major cities in Africa* (12)	2007-8	Clinical specimens	86/555	15.5
Nairobi, Kenya (10)	2010	HCW nasal carriage specimens†	0/45	0.0

* Data from hospitals in capital or largest cities of Senegal, Morocco, Niger, Cameroon, Madagascar.

† HCW = Health Care Workers

Table 2 – Overall sensitivity patterns of MRSA and MSSA carriage isolates from Thika Hospital

Antibiotic	Proportion susceptible (%)	
	MSSA (n=80)	MRSA (n=6)
Cefoxitin	100	0
Benzylpenicillin	26	0
Co-trimoxazole	60	0
Tetracycline	85	0
Gentamicin	99	0
Ciprofloxacin	100	0
Erythromicin / Clindamycin	99	17
Rifampicin	99	83
Chloramphenicol	100	100
Vancomycin	100	100
Mupirocin	100	100

Table 3 –MLST and spa types from 86 *S. aureus* isolates obtained at Thika Hospital, Kenya

MLST CC*	ST within CC (number of isolates)	*spa* types (number of isolates, if >1 *spa* type)
CC22	ST22 (17)	t223 (15), t005 (1), t10498 (1)
CC8	ST8 (14)	t064 (10), t121 (3), t10497 (1)
CC121	ST2430 (4)	t645
	ST121 (3)	t314
CC239	ST239 (6)	t037
CC97	ST97 (5)	t359 (2), t1965 (2), t267 (1)
CC5	ST5 (3)	t002
CC30	ST30 (3)	t318 (2), t1130 (1)
CC7	ST7 (3)	t091
CC6	ST6 (2)	t701
CC15	ST15 (2)	t084 (1), t491 (1)
CC25	ST25 (2)	t3772
CC72	ST72 (2)	t148 (1), t4353 (1)
CC1	ST1 (1)	t127
CC45	ST45 (1)	t015
singletons	ST1290 (10)	t131
	ST152 (4)	t355
	ST2431 (2)	t10496
	ST2019 (1)	t10499
	ST2429 (1)	t10960

* = Clonal Complex nomenclature derived from MLST database.

APPENDIX 1: SUPPLEMENTARY MATERIAL.

This section describes full microarray results from the MSSA isolates from Thika Hospital.

Factors present in all isolates were as follows: virulence genes *hld*, *sspA* and *sspB* encoding hemolysin delta, serine protease V8 and cysteine protease, respectively; immune evasion gene *isaB* encoding immunodominant antigen B; adhesion factors genes *clfA*, *clfB*, *eno*, *ebpS* and *vwb* encoding clumping factor A, clumping factor B, enolase, cell wall associated fibronectin-binding protein and von Willebrand factor, respectively; the intercellular adhesion locus (*ica*) responsible for biofilm production, however only the *icaA* gene from this locus was present in all isolates.

ST22-MSSA

All isolates carried the enterotoxin gene cluster *egc* (*seg*, *sei*, *sem*, *sen*, *seo*, and *seu*) and almost all, with the exception of a single isolate with the spa type t005, were positive for the gene encoding the toxic shock syndrome toxin (*tst1*). All isolates were characterized by the lack of the protease genes *splA*, *splB* and *splE* but contained β-haemolysin-converting phages (*sak, chp* and *scn*), however, in 2 isolates only *sak* was detected. The *hla* and *hlb* genes encoding alpha- and beta-hemolysins, respectively, were found in all isolates with the exception of a single isolate in which the *hla* gene was absent. In all isolates the MSCRAMMs genes such as *cna*, *fib*, *sdrC* and *sasG* were present, while carriage of the *bbp*, *fnbA*, *fnbB*, *map*, and *sdrD* genes was variable.

ST8-MSSA

The majority of isolates (12 out of 14) from this group possessed the enterotoxin profile (*sea+seb+sek+seq*) characteristic for the strain of CC8-MRSA-IV which is known as USA500. Moreover, one of the MSSA USA500 isolates possessed the *tst1* gene. Two remaining isolates from this group were equipped with the *sea* gene, and one of them additionally had the *sek* gene. All ST8-MSSA isolates from Thika Hospital showed homogenous distribution of the hemolysins genes (*hla* and *hlb*, with the exception of a single isolate in which the *hla* gene was not detected), immune evasion genes (*sak, scn, splA, splB,*and *splE*), and the MSCRAMMs genes (*bbp*, *ebh*, *fib*, *fnbA*, *fnbB*, *map*, *sdrC*, *sdrD*, and *sasG*).

ST1290-MSSA

The enterotoxin genes were not detected in this group but majority of the isolates (6 out of 10) harboured the exfoliative toxin gene *eta*. All isolates had either the *hla* or *hlb gene*. The immune evasion genes *sak, scn, splA, splB,* and *splE* were found in all isolates and a single isolate had additionally the *chp* gene. The MSCRAMMs profile *bbp+ebh+fib+fnbA+fnbB+ sdrC+sdrD+sasG* was found in all isolates, while the *map* gene was additionally found in seven isolates.

CC121-MSSA

All isolates carried the bi-component toxin Panton-Valentine leukocidin (PVL) genes and carried *seb, sec,* and the *egc* enterotoxin locus (*seg, sei, sem, sen, seo,* and *seu*). The *hla* and *hlb* genes coding for hemolysins alpha and beta were found in all isolates of this clonal complex. The genes associated with beta-haemolysin converting phages such as *sak* and *scn* were present, while *chp* was absent in all CC121 MSSA isolates. The distribution of the protease genes in this clonal complex was sequence type specific. The isolates of ST2430 possessed the *splA* and *splB* genes, whereas the isolates of ST121 had only the *splB* gene. All isolates had the MSCRAMMs genes as follows: *bbp, cna, ebh, fnbA, fnbB, map, sdrC,* and *sdrD*. Moreover, 4 out of 7 isolates possessed additional adhesion gene encoding the *S. aureus* surface protein G (*SasG*), and this distribution was not ST specific.

ST97-MSSA

This group of isolates was characterized by the lack of the toxin genes. All other groups of genes were homogeneously distributed among the isolates: hemolysins (*hla* and *hlb*), immune evasion (*sak, scn, splA, splB,* and *splE*) and MSCRAMMs (*bbp, ebh, fib, fnbA, fnbB, map, sdrC, sdrD,* and *sasG*)

ST152-MSSA

All isolates were PVL-positive and enterotoxins-negative. The only toxin detected was *EdinB* which structural gene was present among 3 out of 4 isolates. Two isolates possessed the *hla* and *hlb* genes, one had the *hla* gene and one isolate had neither *hla* nor *hlb*. The protease genes *splA, splB* and *splE* were not detected in all isolates. Two MSCRAMMs profiles, *bbp+can+ebh+fnbA+fnbB+sdrD* and *bbp+can+ebh+fnbA+fnbB+sdrD+sasG*, were equally found in ST152 MSSA isolates.

ST7-MSSA

The *sea* gene was detected in all three isolates from this group. Moreover, one of the ST7 isolates was positive for the *sed* gene. All isolates had the same hemolysin and immune evasion gene profiles (*hla*, *hlb* and *sak*, *scn*, *splA*, *splB*, *splE*, respectively). Almost all isolates had the same MSCRAMM gene profile (*bbp+ebh+fib+fnbA+fnbB+map+sdrC+sdrD*) and the only difference was found for a single isolate which possessed additionally the *sasG* gene.

ST5-MSSA

All three isolates shared the same hemolysin and immune evasion gene content (*hla*, *hlb*, *sak*, *chp*, *scn*, *splA*, and *splB*). Two isolates showed the same distribution of superantigens (*seb*, *sek*, *seq*, and the cluster *egc*) and MSCRAMMs (*bbp*, *ebh*, *fib*, *fnbA*, *fnbB*, *map*, *sdrC*, *sdrD*, and *sasG*). Third isolate harbored the enterotoxin gene cluster *egc* and almost the same MSCRAMM genes with the exception of *sdrD* which was not detected in the genome.

ST30-MSSA

All 3 isolates had the same content for genes encoding hemolysins (*hla* and *hlb*) immune evasion (*sak, chp, scn, splE*) and superantigens (*egc* cluster: *seg*, *sei*, *sem*, *sen*, *seo*, and *seu*). Moreover, all isolates were characterized by the presence of genes encoding PVL. The only difference between isolates was in the MSCRAMM content: two isolates possessed the *bbp*, *cna*, *ebh*, *fib*, *fnbA*, *fnbB*, *map*, *sdrC* and *sdrD* genes. The third isolate had almost the same MSCRAMM gene content like two other isolates with the exception of the *fnbB* gene which was not detected in the genomic DNA.

ST2431-MSSA

Two isolates of this group did not have any toxin gene. They shared the same immune evasion genes, *sak* and *scn*, but differed in the content of the hemolysin (*hla+/ hlb+* and *hla+/ hlb-*) and MSCRAMM (*bbp*, *ebh*, *fnbA*, *fnbB*, *sdrC*, *sdrD* and the same content plus *sasG*) genes.

ST6-MSSA

Both isolates shared exactly the same gene content. They showed the gene content as follows:

hla, hlb, sak, scn, splA, splB, splE, sea, bbp, cna, ebh, fib, fnbA, fnbB, map, sdrC, sdrD, and *sasG.*

ST72-MSSA

This group was composed of 2 isolates with different *spa* types. The isolates shared the same hemolysin (*hla* and *hlb*), immune evasion (*sak,scn,splA,splB,splE*) and MSCRAMM (*bbp, ebh, fib, fnbA, fnbB, map, sdrC, sdrD,* and *sasG*) genes but differed substantially in the content of the superantigen genes. One of the isolates (with the *spa* type t148) harbored the enterotoxin *egc* genes, while second one (with the *spa* type t4353) possessed the *egc* cluster and also the *tst1, sec, sel* genes.

ST15-MSSA

Both isolates were characterized by the presence of the same gene content and they did not have any toxin genes. They yielded hybridisation signals for the hemolysin gene *hla,* immune evasion genes *chp, scn, splA, splB, splE,* and the MSCRAMM genes *bbp, ebh, fib, fnbA, fnbB, map, sdrC, sdrD, sasG.*

ST25-MSSA

Two isolates showed almost the same gene content. The exceptional situation was found for the hemolysin genes. One isolate had both the *hla* and *hlb* genes, while in genomic DNA of second isolate these genes were not detected. The immune evasion (*sak,chp,scn,splA,splB,splE*), superantigen (*sec, sel,* and the egc cluster) and MSCRAMM (*bbp, ebh, fib, fnbA, fnbB, map, sdrC, sdrD*) genes were the same in both isolates. The very characteristic feature of the isolates from this group was the presence of the *etd* gene coding for exfoliative toxin D. This gene was not found in other isolates in this collection. Another exfoliative toxin gene detected in the ST25 isolates was *edinB.*

ST2429-MSSA

The one isolate of this group did not show any hybridization signal for the toxin genes. It revealed hybridization signals for: the *hla* gene; phage-associated genes *sak, scn* and *chp;* protease genes *splA* and *splE;* and the adhesion genes *cna, ebh, fib, fnbA, fnbB, sdrC* and *sasG.*

ST2019-MSSA

The one isolate did not have genes for enterotoxins and exfoliative toxins. However, the PVL genes were detected in its genomic DNA. The isolate possessed the *hla* and *hlb* genes for hemolysins alpha and beta, respectively. Immune evasion genes genes *chp* and *scn* were present, whereas *sak* and protease *splA*, *splB* and *splE* genes were absent. The MSCRAMM genes *bbp*, *ebh*, *fnbA*, *fnbB*, *sdrC*, and *sdrD* were detected in this isolate.

ST1-MSSA

Genomic content of the MSSA ST1 representative showed the presence of the superantigen *sea*, *seh*, *sek*, and *seq* genes. The hybridization results also revealed that this isolate harbored the PVL genes, the hemolysin genes *hla* and *hlb*, immune evasion genes *sak*, *scn*, *splA*, *splB*, *splE*, and the MSCRAMM genes *bbp*, *cna*, *ebh*, *fib*, *fnbA*, *fnbB*, *sdrC*, *sdrD*, *sasG*.

ST45-MSSA

The only isolate of this group possessed the genes encoding enterotoxins *seb* and that of the *egc* cluster (*seg*, *sei*, *sem*, *sen*, *seo*, and *seu*). Moreover, it revealed hybridization signals for the hemolysins alpha and beta genes (*hla* and *hlb*) and phage-associated genes *sak*, *scn* and *chp*. Protease genes *splA*, *splB* and *splE* were not detected. The adhesion genes detected in the genomic DNA were as follow: *bbp*, *cna*, *ebh*, *fib*, *fnbA*, *fnbB*, *map*, *sdrC* and *sdrD*.

Chapter 7. Discussion and conclusion

This final chapter draws together all the different strands of nosocomial infection research that I have undertaken in the course of this thesis. I have done this by looking at a series of issues or questions that arise from my work and exploring how each of the three main project areas (SSI, nosocomial bacteraemia and MRSA) has contributed to my thoughts on the topic. I also have tried to highlight some of the interesting contrasts between these projects and how this body of work, as a whole, points towards the future.

7.1. Previous nosocomial infection research in Africa – or lack thereof

As we have seen, historically, there has been very little research into most forms of hospital-acquired infection in developing countries – but some progress is now being made. In Kenya, as in most African countries, research in Infection Control has had to compete for funding and attention with a wide range of other pressing, and often more high-profile, public health problems. But the dearth of research is also, in part, due to an intellectual impasse – without original work, the scale of the problem and the potential benefits remain largely unknown and hence new researchers are not attracted into the area and no new work is undertaken. All three research areas in this thesis made reference to the two recent systematic reviews by the WHO Patient Safety Group on nosocomial infections in developing countries – I think these reviews will represent a turning point in attention devoted to this topic. The coverage of these WHO reviews was by no means exhaustive - the systematic review of SSI interventions in Africa was an attempt to address one notable omission - but given the huge breadth of topics that they did cover, these reviews provided a useful starting-point for all the different components of my own work and will probably continue to serve the same purpose for many others in diverse areas of nosocomial infection research for many years to come.

Although much of the existing research in hospital-acquired infections in Africa has been in the form of burden-of-disease studies, I think these will continue to be important for some time to come – as many Infection Control professionals are fond of quoting: "*If you cannot measure it, you cannot improve it.*" There were no African publications identified in the WHO systematic review for health-care associated pneumonia and only one for urinary tract infections – these are important forms of disease that need a better understanding in the context of African hospitals. In the future, wider adoption of more advanced medical technologies in African healthcare systems (e.g. kidney dialysis, chemotherapy, radiotherapy,

Intensive Care Units) and progressively increasing numbers of patients on long-term Anti-Retroviral Therapy for HIV will produce an expanding population of immunocompromised individuals requiring frequent hospitalisations – these patients will be extremely vulnerable to various types of hospital-acquired infections.

The lack of background research in this field has given me both opportunities and challenges. Despite their various limitations, all three projects that I undertook were respectively the "largest-ever" studies of their particular type in sub-Saharan Africa, which gave me a unique position from which to make original observations on each of these topics. When working on nosocomial bacteraemia, I was able, to some extent, to create a new set of definitions for "nosocomial", "healthcare-associated" and "community-acquired" infections, which may prove useful for enabling future comparative work in this field. Conversely, the challenge of researching in such unexplored territory was that little could be learned from the previous work of others and many of the trial-and-error processes that I engaged in concerned quite elementary research questions. For example, the issue of how to follow-up a patient for 30 days after their surgery seems basic, but it took much fruitless attendance at outpatient clinics to conclude that telephone calls might be a more profitable approach to this question. A more fundamental study limitation arose when my projected sample size for the S. aureus carriage study substantially overestimated the likely prevalence of both MSSA and MRSA carriage – neither the estimates obtained from other African research nor those from high-income countries were in line with the ultimate results. This meant that a study originally planned as a case-control and modelling project ultimately evolved into quite a different format.

7.2. Methodological challenges – limitations of surveillance

Two of the three projects that I worked on (SSI and nosocomial bacteraemia) revolved around the use of surveillance data for measuring the burden of HAI, whereas the MRSA project set out from the beginning to measure prevalence as a pure research exercise. Over the period of conducting SSI surveillance at Thika Hospital, I found these to be a difficult outcome measure to work with as an epidemiologist essentially because of the lack of an entirely objective diagnostic method. This subjectivity means that continuous effort must be devoted to ensuring the reliability of observations within and between observers – although within a single institution a practical way to achieve this was by having close oversight of all diagnoses by a single individual. In larger-scale research or multi-site surveillance it would obviously be impossible to achieve this – the difficulty of standardising a subjective

diagnosis between individuals would then become considerable. A second difficulty of working with SSI is the extreme heterogeneity of the different forms of SSI – superficial SSIs, whilst common, are usually no more than a minor inconvenience whilst organ-space SSI are likely to be life-threatening but occur rarely – to consider these as comparable events is illogical. The obvious solution to this issue is to stratify the single entity of SSI into various subtypes – adherence to the standard diagnostic definition of the CDC-NHNS also gives a sensible sub-classification system.

A major limitation of HAI surveillance systems is that these are an imperfect tool for assessing the impact of an Infection Control intervention. This is because all forms of HAI surveillance system are particularly vulnerable to what I call a "surveillance-effort paradox". This paradox is that the more effort that is made to perform comprehensive HAI surveillance, the higher the apparent rate of infection and the more extensive the disease appears to be – essentially, the old adage "the harder you look, the more you find". Conversely, with minimal effort to perform HAI surveillance accurately, very few cases are apparent. Whilst this paradox probably exists for all forms of disease surveillance, I think it is especially problematic for SSI, as the cases occurring after discharge from hospital are hard to detect. This surveillance effort-paradox is illustrated in figure 7-1, drawn from work done in the UK by the Health Protection Agency on developing SSI surveillance after Caesarean sections. In this figure, where each point represents one hospital trust, there is a clear correlation between the percentage of Post Discharge Questionnaires (PDQ) returned in each hospital (which I posit approximates an institutional "level of effort") and the measured SSI rate. In this example, the problem was thought to have arisen because the surveillance system was newly-implemented and had not yet established mechanisms to account for differential questionnaire return rates – but it seems likely that even in well-established HAI surveillance systems, the same issue is likely to exist.

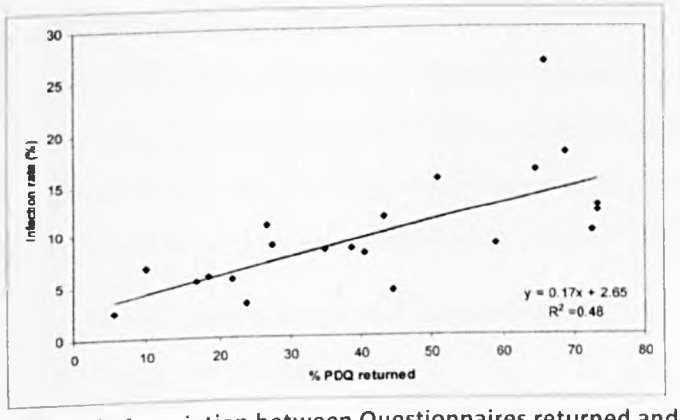

Figure 7-1: Association between Questionnaires returned and SSI rate, courtesy of Catherine Wloch, HPA, UK

The problem that arises from this paradox is that if the level of "surveillance-effort" varies between the intervention and control arms of a comparative study, or between sites in a

multi-centre surveillance program, this in itself could be sufficient to lead to an apparent effect of the intervention or differential rate between centres, leading to bias in the study. This bias might occur quite subtlety – an investigator who puts much effort into introducing a change in a hospital practice might unconsciously relax the effort put into their surveillance, leading to an apparent success of the intervention. I was very conscious of this risk when organising the change in antibiotic prophylaxis policy at Thika Hospital and was careful to make no changes to the staffing or procedures of the SSI surveillance team at any point during the surveillance. However, it was obviously impossible to keep myself or the SSI surveillance staff blinded to the fact that a significant change in a relevant clinical practice had taken place – could we have unknowingly altered our approaches to surveillance after implementation of the change in policy? I found no evidence of such changes in terms of coverage of post-operative follow-up (telephone contact remained high throughout the study), or thresholds for diagnosis of SSI (I reviewed all patients diagnosed with SSI), but I wasn't able to sustain the same level of personal oversight for the SSI surveillance for the whole period of working in Kenya. One alternative approach to this issue would have been to conduct this work as a randomised double-blinded trial – but as there is no doubt that pre-operative antibiotic prophylaxis is superior to post-operative antibiotic use, I feel that it would clearly have been unethical to conduct such a trial.

Nosocomial bacteraemia is a rare outcome to work with in an epidemiological study and requires a well-functioning microbiology service – but it has the major advantage of being an objectively defined outcome. Collecting sufficient data to make useful epidemiological conclusions on this subject requires technical expertise in several domains and a considerable investment of time and money. I was very fortunate to be in the position to analyse a 7-year period of high-quality clinical and laboratory data without having been involved in the original establishment of the surveillance – this was a very satisfying analysis to conduct. In some ways, nosocomial bacteraemia is a

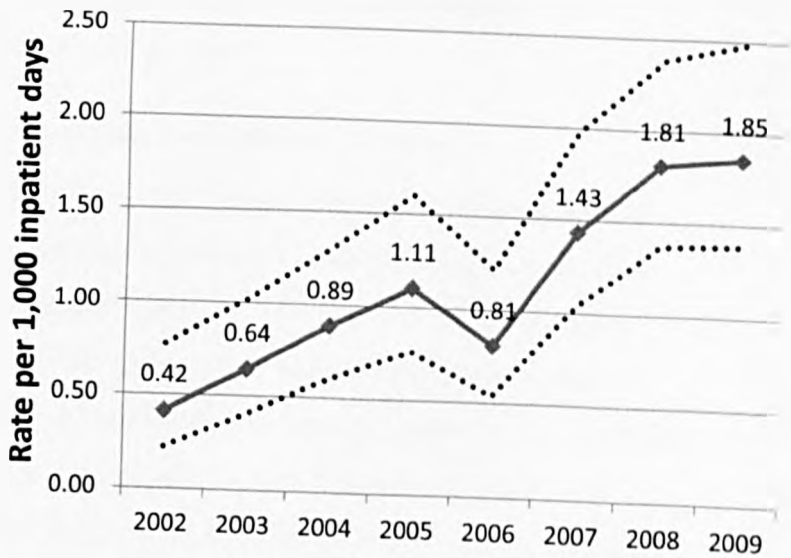

Figure 7-2: Trend in rate of nosocomial bacteraemia

much better epidemiological outcome to work with than SSI – there is little doubt about the seriousness of the illness nor of the diagnostic objectivity in the vast majority of these cases. The dramatic changes in the risk of nosocomial bacteraemia observed during the course of the surveillance (figure 7-2), exemplifies my earlier observation about the "surveillance-effort paradox" – but more post-admission blood cultures were being taken in later years (figure 7-3), which partially may partially explain the increase in disease rate over this period.

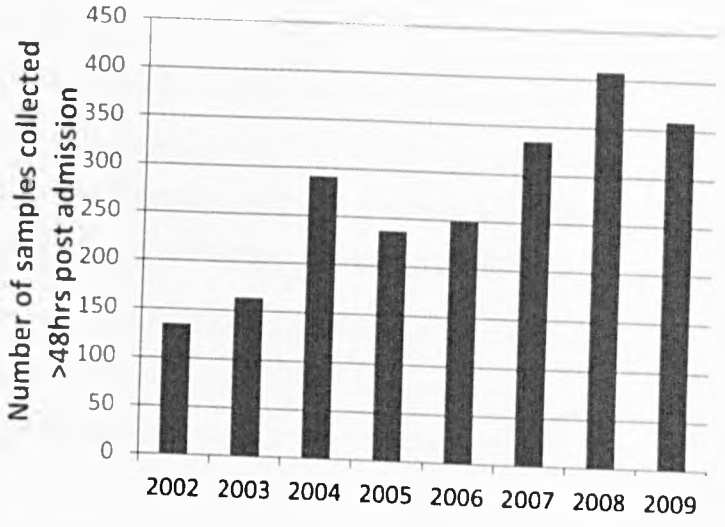

Figure 7-3: Trend in post-admission BC collection

By contrast to the work on SSI and nosocomial bacteraemia, the MRSA study used no surveillance data and made use of a very clear outcome state (the presence of the mecA gene in S.aureus isolates), which could be tested phenotypically with reasonable accuracy in the laboratory at Thika Hospital and was subsequently definitively confirmed by microarray testing. The obvious drawback of this outcome state was that it was actually quite rare, or at least much rarer than anticipated, which limited the scope of the epidemiological investigations that could be performed with resulting data.

7.3. Challenges in IT system construction for HAI surveillance

One of the important decisions to make when designing any surveillance program is to determine how the data being collected will be inputted, handled, stored and accessed by a computer system. Although generic database packages (e.g. Microsoft Access, Filemaker Pro) can be used for this purpose and several commercial software packages specifically designed for HAI or SSI surveillance also exist, for the SSI surveillance that I set up at Thika Hospital, I made the decision to create a modular extension onto a pre-existing piece of locally-written software that was already in use at Thika Hospital in 2010. The pre-existing system, called the Integrated Medical Records System (IMRS) was used on a within-hospital network of computers in the paediatric, maternity, laboratory and administrative buildings, and the network progressively expanded to other areas also. This system was designed,

installed and administered by another KEMRI-Wellcome Trust Research Programme (KWTRP) scientist working in Thika Hospital (Moses Ndiritu) whose work focussed on paediatric pneumococcal bacteraemia. A central hospital server hosted the IMRS system and performed daily back-ups of its databases. Other software used by the hospital primarily for financial purposes also operated on the same network and server. I organised for extension of the physical network in the hospital to operating theatres and surgical wards and employed a programmer (Geoffrey Mimano) to write the "surgical" extension module of IMRS.

The extension module of the IMRS was known as ESURG. The whole of IMRS was coded using the PHP scripting language, the Zend framework for the "front-end" user-interactions and server components and a MySql database system for data management. MySql was originally selected since it is an open-source, robust data management suite that is able to handle large data sets. Computers set up to use the IMRS in the hospital system ran on the Ubuntu operating system, which is also open-source and generally extremely resistant to viruses and other malware. The actual interactions between computer terminals and the main database on the central server were mediated via web-browser software (Mozilla Firefox), although data were only transmitted within the hospital intranet and never over the wider internet. Thus all the components of the surveillance system made use of freely available software which were able to operate on low-specification computers, and provided excellent data security in a system that was highly resistant to virus attack, power failure and slow or intermittent internet access – all significant daily risks in Kenya. Additionally, it was possible to design some simple reporting components to produce live summaries of data. More complex analyses could be performed after downloading a copy of the database to an external machine running specialist data-analysis software.

The drawbacks of using this bespoke, locally-programmed distributed database system for surveillance were as follows:

- the time and expense of developing this ESURG software were considerable: an experienced and skilled programmer took 4 months of full-time work to write a basic package for collecting data for SSI surveillance, and then a further 2 months to introduce and trouble-shoot this software. Part of the difficulty arose from the need for the second programmer to understand how the first programmer had configured the layout of the original IMRS system and then to understand how to frame the SSI surveillance system within the same format – the important lesson being that any newly designed system needs adequate documentation when they are being designed and implemented.

- as the system was designed using a specific software language (PHP) and format (Zend frameworks), it was impossible for me (with only a basic understanding of computer programming) to make adjustments to the system as the surveillance progressed, once the programmer had completed his 6 month contract.

- making use of a multi-computer system operating over the shared space of the hospital intranet and hosted on the hospital server, rather than using a single stand-alone machine under my control, gave me a de facto responsibility to ensure adequate maintenance of the hospital intranet, regulation of internet-usage and the upkeep (and eventual replacement) of the hospital server. Whilst there may have been some benefits of having a "shared stake" in upkeep of the hospital IT systems, this oversight was very time-consuming and expensive to perform.

On balance, I think it would almost certainly have been better to have used a commercial-available piece of dedicated SSI surveillance software, which could have been used with multiple terminals across the hospital intranet. I think this would have been preferable to batched double-entry of paper forms by data-entry clerks as this would distance the clinical members of the surveillance team from the resulting data – my sense is that well-motivated clinical staff are better at controlling errors than software validation scripts.

7.4. Novel descriptions of bacterial diseases and their plausibility

Two of the projects described in this thesis (nosocomial bacteraemia and MRSA) make, to some extent, a new description of the rate of a form of bacterial disease in an African context; by contrast, SSI is already well-known to be a considerable problem in many low-income countries. How plausible are these two new descriptions in epidemiological and microbiological terms? Firstly, considering the three classic forms of epidemiological error – bias, confounding and random error – we can eliminate each of these on the following grounds. With regard to bias, as large proportions of the target populations in both studies were sampled systematically, it seems unlikely that bias relating to inclusion in studies could be playing a major role. With regard to confounding, although both of these studies did find associations between the particular form of disease and a clinical exposure (MRSA with burns; nosocomial bacteraemia with blood transfusions), whether or not these associations were confounded by other variables is irrelevant to the question of the underlying rate of occurrence of the disease. With regard to random error, the overall number of cases in the nosocomial bacteraemia study was sufficiently large to give quite narrow confidence

intervals, though this was not the case in the MRSA study – in the latter study we might have considerably under or over estimated the scale of this disease. With regards to microbiological sources of error, these seem unlikely in either project as both studies made use of laboratories that were working to very high internal and external quality control standards. Furthermore, within both studies, there were several pieces of corroborating evidence to back up the reliability of the primary identification of the bacterial pathogens: in the nosocomial bacteraemia work, there was clear epidemiological evidence of both morbidity and mortality burdens imposed by disease whilst in the MRSA study, the microarray studies supported the primary phenotypic identifications. In addition to the internal reliability of both of these studies, other scientific research, albeit on a smaller scale or in a different format, lends further plausibility to these novel descriptions: in the work relating to nosocomial bacteraemia, we referred several previous reports of outbreaks of nosocomial in sub-Saharan Africa and in the MRSA field, there is clearly previous evidence to suggest that this pathogen is widely dispersed in the region.

7.5. Antibiotic resistance – the coming storm in African hospitals?

Antibiotic resistance and antibiotic stewardship are high profile topics at this time – World Health Day in 2011 was devoted to this issue (Figure 7-4). From what we know in high-income settings, the extent of antibiotic resistance is inversely correlated with the overall consumption of antibiotics in the population – this is probably most famously illustrated by an ecological study observing antibiotics resistance rates in different European countries (1). As hospitals are inevitably the locations were antibiotic use is most highly concentrated, selective pressure will almost invariably make these foci of resistance. Little is known about the overall extent of antibiotic resistance in hospital populations in developing countries, but worryingly, extensive antibiotic resistance has often been uncovered when inpatients have been transferred from hospitals in developing countries to high-income settings – most notoriously, with the discovery of the NDM-1 allele of the bla gene following the transfer of a patient from India to Sweden (2). Anecdotal reports from colleagues working in private hospitals in Mombasa and Nairobi suggest that same combination of circumstances that appear to have led to the generation and widespread environmental distribution of novel

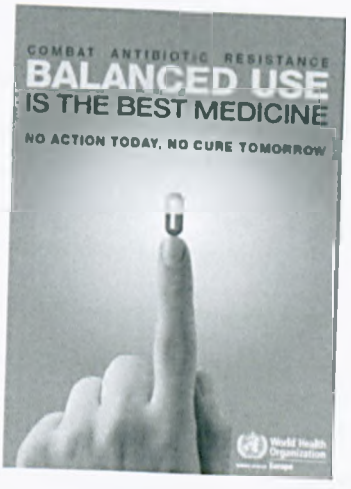

Figure 7-4: Poster from World Health Day 2011

antibiotic resistance genes in New Delhi (3) are probably also present in large cities in Kenya. Currently, in the public-service hospitals such as Thika Hospital, my sense is that the extremely limited supply of most advanced antibiotic agents is probably the most effective restriction on their usage – but this is unlikely to remain the case indefinitely.

All three strands of my work in nosocomial infection had a close relationship with issues of antibiotic use and resistance. In the work relating to nosocomial bacteraemia, we made a decision not to include any report of antibiotic resistance amongst the isolates identified when we submitted this work for publication. Further analysis of these isolates is currently ongoing – preliminary analysis of surveillance data had suggested a marked difference in the extent of antibiotic resistance between isolates of the same species acquired in the hospital and the community.

Investigation of the spread of antibiotic resistance between continents has been greatly facilitated by use of DNA sequencing technologies – the spread of the MRSA ST239 clone has been investigated in some detail, although not in Africa (4). We hope to conduct whole genome sequencing of MRSA isolates from Thika Hospital with the Sanger Institute in the near future and aim to use this approach to place these East African isolates in an intercontinental evolutionary tree of MRSA ST239 isolates. Hopefully we may also obtain some insights as to why this organism was so rarely being transmitted (other than amongst patients with burns) in Thika Hospital.

The work relating to use of antibiotic prophylaxis raises an interesting and (to my knowledge) unanswered question: what is the importance of antibiotic resistance when an antibiotic is being used for prophylaxis purposes? This was of great relevance when we were selecting drugs to use for antibiotic prophylaxis in Thika Hospital as ampicillin, which was in many other respects an ideal agent, was known to have widespread drug resistance in disease-causing isolates in Kenya. The role of antibiotic prophylaxis in surgery is to reduce the bacterial innoculum introduced into the operation wound at the time of surgery – it is not intended to entirely sterilize the patient, but just to sufficiently reduce the number of bacteria so that the immune system can deal with any remaining organisms. The important characteristic of this bacterial innoculum is that it is a heterogeneous population of bacteria, derived from a mixture of the patient's own microflora, plus some from the operating theatre environment and the operating team. This means that antibiotic resistance in this innoculum is also likely to be heterogeneous – and the variation in bacterial species will also mean that different agents are useful against different subsets of the bacterial population. In my mind,

this situation probably means that even if a moderate proportion of bacteria in the bacterial innoculum do have resistance against the agents used in prophylaxis, the drugs for prophylaxis should still be effective against the remainder. An increasing proportion of resistance in the innoculum might then be expected to lead to a gradual diminution of the effectiveness of prophylaxis, but this effect might be non-linear. We should also bear in mind that use of prophylaxis against a partially resistant bacteria population will select in favour of resistant strains, making it more likely that any SSI that do develop at resistant to this agent. This situation is totally different to the effect of antibiotic resistance in treating an established bacterial infection – in an infection, the bacterial population is largely homogenous, and the response to antibiotic treatment (if delivered in the appropriate doses and duration) will be either all or nothing. As far as I am aware, the effect of increasing proportions of antibiotic resistance on the effectiveness of antibiotic prophylaxis has not been explored, either in animal or clinical studies. As antibiotic resistance becomes ever-more widespread, this would be a useful question to investigate.

7.6. Why so little *Staphylococcus aureus*?

It remains a puzzle to me why carriage of MRSA in Thika Hospital was so rare and almost entirely confined to patients with burns – what could have prevented this organism from spreading to other patients in these crowded wards where healthcare workers (in my experience) rarely washed their hands? In many respects, these were ideal circumstances for frequent cross-infection of patients with MRSA, yet carriage was extremely uncommon. My suspicion is that there is something fundamentally different about the biology of the organism-host interactions for S.aureus carriage in this setting to that seen in high-income countries. The main reason for believing this is that we found an overall S.aureus carriage rate of only 9% - a more typical value in a "western" setting would be around 25%, although this appears to be declining over time (5) - and researchers working in Coast Province of Kenya had also found S.aureus nasal carriage to be rare (personal communication, Donald Akech, KEMRI-Wellcome Trust). In the work relating to SSI, out of the wound samples where a likely pathogen was identified by the microbiology laboratory in Thika Hospital, S.aureus only accounted for about 25% of these pathogens – a much smaller proportion than is seen in high income countries, but consistent with the (small number) of high quality studies of SSI microbiology done in the region (refs needed). A review of studies of community-acquired bacteraemia in Africa found S.aureus to account for 9.5% of these infections (6), similar to the figure of 13% that we found in Kilifi. In bacteraemia, it is hard to

compare proportions of pathogens as whether or not possible contaminants (such as Coagulase-negative Staphylococci) have been excluded exerts a large influence on the proportions and is very variable between studies.

On this basis, it does seem possible that S.aureus might be less prevalent in carriage and as a cause of disease in East Africa than in other regions of the world – are there plausible explanations for this? Regional and temporal variation in rates of bacterial carriage is not unusual – paediatric S.pneumoniae carriage is much more common in low-income countries and carriage was observed to decline in high-income countries over the course of the 20th century. Between S.aureus, other epidermal micro-organisms and the human host, there is a wide range of "push" and "pull" forces that determine carriage of bacteria (5) – I cannot say which of these is playing the important role here. Perhaps there is a good evolutionary reason why regional differences in the human skin-surface microbiome occur. For example, the populations of enteric bacteria from rural Malawians and Amazonian Indians tend to be different to those of US residents of similar ages, and have more genes that process (and release) important carbohydrates and micronutrients (7), which seems an obvious symbiotic adaptation to local conditions – regional variations in the skin-surface microbiome could well have a similar co-evolutionary explanation.

7.7. How can we influence national infection control policy?

In terms of producing published national policy documents relating to nosocomial infections, Kenya is doing rather well: paired National IPC Policy and Guidelines were published in December 2010 and these documents contain many sensible provisions for government hospitals - any other low-income countries wishing to develop such policies would do well to use the Kenyan documents as a starting point. These documents cover issues relating to antibiotic prophylaxis in surgery (several times), spread of drug-resistant organisms and describe the possibility of hospital-acquired bacteraemia. On the issue of antibiotic prophylaxis, these documents are very clear that pre-operative prophylaxis is preferable to post-operative use – hence making it quite impossible to consider a randomised trial on this question. The policy documents establish that tackling HAI is a priority for everyone working in hospitals and encourage the open acknowledgement that these types of infections do occur and can be prevented.

One issue that may present a substantial obstacle to establishing the need for national infection control policies in countries in sub-Saharan Africa is the extremely limited number

of estimates of the burden of nosocomial disease, in terms of deaths, disability or economic impacts. Producing such estimates is difficult as most studies of nosocomial diseases in the region derive from a single institution and without standardised methods or definitions across a representative series of sites, it is hard to produce a geographically representative estimate. Without an appreciation of the "large-scale" impacts of this issue, formulation or enforcement of infection control policy, whether at the national or local level, is likely to be weak.

There is actually good reason to think that the regional burden of nosocomial infection in Africa could be a considerable health problem. If we take nosocomial bacteraemia – which is a single rare-but-severe form of HAI – and multiply the risk-per-admission and the mortality-per-case that we found in Kilifi Hospital by the local average rate of hospital admission (approximately 1 in 20 per year for under 5s) and the population of under-5s in sub-Saharan Africa (2005 UN data), this brings a very basic estimate of approximately 20,000 deaths per year for under-5s in sub-Saharan Africa. This estimated number of deaths, albeit very crude, would put the disease on a par with African Trypanosomiasis - how much larger would the problem be if all forms of HAI across all ages were included? One useful future piece of future work would be to apply the approaches used in Kilifi Hospital across a larger number of sites in Africa to obtain an estimate with the appropriate degree of representation of different areas of the continent.

7.8. What changes clinical practice?

Although there extremely limited research into improving hospital infection control practices in low-income countries, lessons on getting research into practice can be drawn from other fields of health systems research. One Kenya-based group focussing on paediatric care has been very productive in recent years, recently concluding a major project based on evaluation of the implementation of training and guideline programs on improving the quality of acute paediatric care (8-9). Interesting reports from this group include a report of using clinical guidelines to achieve an improvement in the performance of clinicians in individual tasks, although there were no improvements in the performance in tasks requiring sustained efforts of teams (10). Another study described some evidence for a reduction in inappropriate antibiotic prescribing as a result of a multi-faceted intervention over an extended period (11). A common theme across much of the work from this group is the need for close involvement with clinicians over an extended period and for delivery of training and guidelines in a variety of modalities, primarily performed face-to-face.

In my studies, getting clinicians in Thika Hospital to change any of their practices – whether documentation standards for surgical procedures or use of antibiotic prophylaxis – was difficult. For many clinicians, continuing to do what had always been done was the preferred option regardless of evidence presented and any suggestion that a change in practice might achieve better results was met with intense scepticism. I used a wide variety of approaches to overcome this resistance to change: seeking management-level support and endorsement at every step; recruiting departmental advocates for the desired change; whole-hearted engagement in discussions over the minutiae of the planned change; intensive and sustained educational activities for all hospital staff in a variety of formats regarding the planned changes; providing feedback to individuals and departments about adherence to the agree changes. Ultimately, one positive aspect of this organisational resistance to change was that once a change (in this case, the different format of antibiotic prophylaxis use) had become the norm, this subsequently remained the standard practice long after my surveillance project finished. The same cannot be said of standards of documentation or activities of the Hospital Infection Prevention and Control Committee – these appear to have reverted to their former state after I left Thika Hospital. For achieving lasting changes in Infection Control in Kenyan hospitals, I think there is no substitute for ongoing hard work at the local level by highly-motivated specialists.

New technology can be instrumental in driving changes in healthcare and for Infection Control in developing countries the introduction of alcohol hand-rub is an enormously important innovation. In Kenya, it was exciting to see the start of local manufacture and marketing of such a product (fig 7-5 – courtesy of James Kimotho, KEMRI-CDC) while I was based there, although the evidence-base unpinning the effectiveness of this product in preventing transmission of HAI is currently somewhat scanty. Alcohol hand-rubs were in occasional use at Thika Hospital at the time I was working there – though it seems unlikely to me that their use was sufficiently widespread to be substantially impeding the transmission of MRSA.

Figure 7-5: KEMrub alcohol hand-rub

HAI research in high-income countries is far ahead of work in African settings, so other pragmatic research in adapting processes or methods from high to low-income settings is likely to be fruitful for some time to come: two examples are radio-frequency ID tags and

checklists. Radio-frequency ID (RFID) tags are starting to be used in hospitals in high-income countries for tracking the physical movements of hospital staff members, including their visits to patient bedside areas and to hand-washing basins – these could easily be deployed in low-income settings on a research-basis to investigate the spread of infections in hospital wards. Checklist also a current area of much interest: this approach to complex tasks has some merits for adaptation to medical procedures in low-income setting where much routine work is delegated from doctors to less expensively trained nurses other clinicians. A checklist relating to childbirth was recently found to be very effective in improving process measures in an Indian setting (12) – but I am not aware of any checklist-based studies conducted exclusively in African hospitals. Interestingly, one of the most influential studies investigating the use of a general surgical checklist involved eight (extremely diverse) hospital sites around the world, including one hospital in Tanzania (13). The report of the study anonymised the hospital sites, but it was clear that one of the hospitals made an enormous improvement in the appropriate use of antibiotic prophylaxis as a result of introduction of the surgical checklist, which probably accounted for much of the overall benefit reported in the study.

7.9. A discussion on Infection Control in Africa

At the time I first arrived at Thika Hospital in 2009, there was no active Hospital Infection Prevention and Control Committee (HIPCC) – this had lapsed after the sudden death of the member of staff who had led this. As part of my involvement with Thika Hospital, I chaired the HIPCC for the time I was based at Thika Hospital, which primarily involved holding monthly meetings to discuss current Infection Control issues. Major IPC achievements included writing and launching a Hospital Infection Control Policy, getting an Infection Control professional to sit on the Hospital Management Team and getting a (small) budgetary allocation for infection control work in the hospital. We conducted various training sessions and presentations to hospital staff members, and were invited to talk at hospitals elsewhere in the District. However, we never managed to achieve having a full-time infection control nurse permanently employed by the hospital – despite the Ministry of Medical Services mandating (in mid-2011) that a hospital of this size should have at least two full-time nurses in this role.

Beyond Thika Hospital, it was apparent to me that Infection Control was an issue that many clinicians, policy makers and researchers in Kenya were beginning to take seriously. As previously mentioned, in 2010, the Kenyan Government launched a National Infection

Control Policy and accompanying Guidelines and following this in 2011, a National Infection Control secretariat was formed by the Ministry of Medical Services to look into the implementation of the Infection Control Policy. As part of the process of raising awareness about this work, I worked with several colleagues including Linus Ndegwa and Daniel Kimani at the KEMRI-Centres for Disease Control (KEMRI-CDC) and many others to run an Infection Prevention and Control conference, which was held in Mombasa in November 2011. There were 25 scientific presentations and approximately 90 attendees, including several high-level Ministry representatives. We received several sizeable donations from commercial organisations and the conference turned a small profit, although substantial "start-up" funding had been provided by KEMRI-CDC. I was the Scientific Chair of this conference, and in the course of the meeting, we presented both the work done in Thika Hospital regarding SSI and the work in Kilifi Hospital regarding nosocomial bacteraemia – these were both received with great interest.

Figure 7-6: Attendees at the IPNET-K conference – Whitesands Hotel, Mombasa, 28-29 November 2011

7.10. Conclusion – HAI monitoring as an index of healthcare quality

In many important respects, rates of hospital-acquired infections and the extent of efforts to prevent their occurrence are most usefully considered as a marker of quality in a health system. As the work of this thesis has shown, their occurrence, if unmanaged, is inevitable, but efforts to minimize or prevent their occurrence can be highly effective if local practitioners engage with the issue. Rates of HAI disease, if properly measured over an extended period, are sensitive indicators of quality-of-care in the institution. However, as the

work of this thesis has shown, the measurement of HAI in a low-income setting is itself a complex and demanding task. A marker of any effective healthcare system is that they perform continuous self-assessment and improvement through internal audit cycles – in a well-run hospital, the more common forms of HAI can be detected and prevented by internal auditing processes in the system. Thus if HAI are an indicator of the general quality of a health system (14), reducing their occurrence in low-income countries will require system-wide improvements above and beyond any steps being taken to purely tackle the HAI symptoms of the underlying systemic problems.

1. Goossens H, Ferech M, Vander Stichele R, Elseviers M. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. Lancet. 2005 Feb 12-18;365(9459):579-87.

2. Yong D, Toleman MA, Giske CG, Cho HS, Sundman K, Lee K, et al. Characterization of a new metallo-beta-lactamase gene, bla(NDM-1), and a novel erythromycin esterase gene carried on a unique genetic structure in Klebsiella pneumoniae sequence type 14 from India. Antimicrob Agents Chemother. 2009 Dec;53(12):5046-54.

3. Walsh TR, Weeks J, Livermore DM, Toleman MA. Dissemination of NDM-1 positive bacteria in the New Delhi environment and its implications for human health: an environmental point prevalence study. Lancet Infect Dis. 2011 May;11(5):355-62.

4. Harris SR, Feil EJ, Holden MT, Quail MA, Nickerson EK, Chantratita N, et al. Evolution of MRSA during hospital transmission and intercontinental spread. Science. 2010 Jan 22;327(5964):469-74.

5. Wertheim HF, Melles DC, Vos MC, van Leeuwen W, van Belkum A, Verbrugh HA, et al. The role of nasal carriage in Staphylococcus aureus infections. Lancet Infect Dis. 2005 Dec;5(12):751-62.

6. Reddy EA, Shaw AV, Crump JA. Community-acquired bloodstream infections in Africa: a systematic review and meta-analysis. Lancet Infect Dis. Jun;10(6):417-32.

7. Yatsunenko T, Rey FE, Manary MJ, Trehan I, Dominguez-Bello MG, Contreras M, et al. Human gut microbiome viewed across age and geography. Nature. 2012 Jun 14;486(7402):222-7.

8. Barasa EW, Ayieko P, Cleary S, English M. A multifaceted intervention to improve the quality of care of children in district hospitals in Kenya: a cost-effectiveness analysis. PLoS Med. 2012;9(6):e1001238.

9. English M, Irimu G, Wamae A, Were F, Wasunna A, Fegan G, et al. Health systems research in a low-income country: easier said than done. Arch Dis Child. 2008 Jun;93(6):540-4.

10. Irimu GW, Gathara D, Zurovac D, Kihara H, Maina C, Mwangi J, et al. Performance of health workers in the management of seriously sick children at a Kenyan tertiary hospital: before and after a training intervention. PLoS One. 2012;7(7):e39964.

11. Opondo C, Ayieko P, Ntoburi S, Wagai J, Opiyo N, Irimu G, et al. Effect of a multi-faceted quality improvement intervention on inappropriate antibiotic use in children with non-bloody diarrhoea admitted to district hospitals in Kenya. BMC Pediatr. 2011;11:109.

12. Spector JM, Agrawal P, Kodkany B, Lipsitz S, Lashoher A, Dziekan G, et al. Improving quality of care for maternal and newborn health: prospective pilot study of the WHO safe childbirth checklist program. PLoS One. 2012;7(5):e35151.

13. Haynes AB, Weiser TG, Berry WR, Lipsitz SR, Breizat AH, Dellinger EP, et al. A surgical safety checklist to reduce morbidity and mortality in a global population. N Engl J Med. 2009 Jan 29;360(5):491-9.

14. Murray E, Holmes A. Addressing healthcare-associated infections and antimicrobial resistance from an organizational perspective: progress and challenges. J Antimicrob Chemother. 2012 Jul;67 Suppl 1:i29-i36.