Orthopaedic Trauma Surgery in Low-Income Countries

Follow-up, Infections and HIV

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Scientific environment

The studies included in this thesis were carried out at Haukeland University Hospital, Bergen, Norway, and Kamuzu Central Hospital, Lilongwe, Malawi. Data for the first two studies was supplied by SIGN Fracture Care International from the SIGN Online Surgical Database. The third study was wholly conducted at Kamuzu Central Hospital between 2009 and 2013. Supervision was provided by staff from the Department of Orthopaedic Surgery and the Norwegian Arthroplasty Register (NAR) at Haukeland University Hospital. Medical statisticians from NAR provided statistical support for all three studies in this thesis.

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The Norwegian
Arthroplasty Register

Kamuzu Central Hospital
Lilongwe, Malawi.

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List of abbreviations

AIDS	Acquired Immunodeficiency Syndrome
AO	Arbeitsgemeinschaft für Osteosynthesefragen
C-arm	The same as II. The arm of an II x-ray machine is C-shaped
CI	95% Confidence Interval
CME	Continuing Medical Education
DALY	Disability Adjusted Life-Years
FDA	United States Food and Drug Administration, USA
gam	Generalized Additive regression Model
GNI	Gross National Income per capita
HIC	High-Income Country (definition page 57)
HIV	Human Immunodeficiency Virus
HUH	Haukeland University Hospital
II	Image Intensifier; low-dose x-ray machine used during surgery
IM	Intramedullary, ie. inside the medullary canal of a long bone
K-nail	Küntscher nail
KCH	Kamuzu Central Hospital
LIC	Low-Income Country (definition page 57)
LMICs	Low- and Middle-Income Countries (definition page 57)
MDGs	Millennium Development Goals
NAR	The Norwegian Arthroplasty Register
OR	Odds Ratio
ORIF	Open Reduction and Internal Fixation
PE	Pulmonary Embolism
SIGN	SIGN Fracture Care International
SOSD	SIGN Online Surgical Database
UK	The United Kingdom of Great Britain and Northern Ireland
UN	The United Nations
USA	The United States of America
VTE	Venous Thromboembolism
WHO	The World Health Organization

Abstract

This thesis is based on three published papers about complications after intramedullary (IM) nailing of fractures of the long bones in low- and middle-income countries (LMICs). The first two studies were register studies using data from the SIGN online surgical database (SOSD). The third study was a prospective study of patients treated for femoral fractures at Kamuzu Central Hospital in Malawi. The SOSD is, to my knowledge, currently the largest database in the world containing data on orthopaedic trauma surgery in LMICs. It was established to ease communication between SIGN Fracture Care International (SIGN) and surgeons using their IM nail. SIGN provides hospitals in LMICs with IM nails free of charge for the treatment of fractures in poor people. Being operated with an IM nail for a fracture of the thigh bone (femur) will have a patient out of bed in a few days, and this has been the obvious treatment of choice in high-income countries for more than half a century now. In many LMICs, however, femoral fractures are still treated with the patient in bed on traction for one and a half to three months. There are still many myths about the risks of doing surgery in LMICs. We wished to document the results and complications of IM nailing in LMICs so that better informed decisions can be made when planning surgical services in these countries. Lack of sufficient follow-up is a challenge in research in LMICs. We also wished to see how this influences results.

We found that returning for follow-up in LIC can be difficult and very expensive for many patients. The motivation for returning for follow-up is therefore very low if a patient does not have any complaints. Insisting on very high follow-up rates in clinical research from low-income countries is unrealistic and can exclude important information from the literature. It does, however, seem as if people in low income countries mostly do return for follow-up if they have a complaint after surgery even if total follow up rates are low. This implies that results based only on the patients that returned for follow-up in LIC will be negatively biased. This should be kept in mind when interpreting results in research from LIC.

Infection rates after IM nailing in LMIC are acceptable and infections, when they occur, usually manageable. The risk of infection should not be used as an argument against well-proven surgical treatment of fractures by properly trained surgeons in LMICs. Patients with femoral fractures in particular have a great deal to gain from IM nailing as opposed to spending months in hospital on skeletal traction.

Patients registered in the SOSD undergoing IM nailing for a non-union had a more than doubled risk of postoperative infection. This further supports that, at least femoral fractures, should be treated early with IM nailing also in LMIC. Data from the SOSD suggests that there is a statistically increased risk of postoperative infection with decreasing income level of a country. However, infection rates are still low and this should not be used as an argument against the practice of orthopaedic trauma surgery in low-income countries.

We found no statistically significant increase in infection rates when open reduction was used compared to closed reduction. The need for open reduction because of the lack of expensive equipment such as orthopaedic traction tables, C-arm image intensifiers etc. is no contraindication to the use of IM nailing in LMICs.

People living with HIV do not seem to have a much increased risk of postoperative infection. This certainly is no argument against surgical treatment of fractures in HIV positive trauma patients. They might, however, have an increased postoperative mortality risk due to venous thromboembolism (VTE) after prolonged preoperative traction when low molecular weight heparin VTE prophylaxis is not available. This needs to be confirmed in larger studies, but in my opinion further strengthens the argument for the earliest possible IM nailing of femoral fractures in HIV positive trauma patients.

List of publications

This thesis is based on the following three papers. They are referred to in the text by their roman numeral.

Paper I:

Young S, Lie SA, Hallan G, Zirkle LG, Engesæter LB, Havelin LI. Low infection rates after 34,361 intramedullary nail operations in 55 low- and middle-income countries. Validation of the Surgical Implant Generation Network (SIGN) Online Surgical Database. Acta Orthopaedica 2011; 82 (6): 737-43.

Paper II:

Young S, Lie SA, Hallan G, Zirkle LG, Engesæter LB, Havelin LI. Risk Factors for Infection after 46,113 Intramedullary Nail Operations in Low- and Middle-income Countries. World Journal of Surgery 2013; 37 (2): 349-55.

Paper III:

Young S, Banza L, Hallan G, Beniyasi F, Manda K, Munthali B, Dybvik E, Engesæter LB, Havelin LI. Complications after trauma surgery in a low-income country. A prospective study of follow-up, HIV and infection rates after IM nailing of 141 femoral fractures at a central hospital in Malawi. Acta Orthopaedica 2013; Accepted for publication 22.08.2013.

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“The Patient”

Woodcarving by Patrick Kaliati.
On display at Mua Mission Art Gallery, Mua, Malawi, 2009.
(Photo Sven Young)

1. Background

1.1 A Brief History of Intramedullary Nailing of the Femur

"…this method of introducing a long internal peg into the femur from the trochanter is one of some value…"
Ernest W. Hey Groves, 1918.

Femoral fractures have been treated for many centuries by extensive periods of traction and bed rest. The outcomes were in many instances acceptable, but often terrible. Though improvements in traction (or "extension" as it was often called) techniques in the 19th and early 20th century improved outcomes a great deal, treatment still meant bed rest for months, and doctors were continually searching for better ways to treat femoral fractures. Lister's principles of antiseptic surgery and the discovery of anaesthesia in the mid 19th century opened the way for modern orthopaedic surgery.

The idea of stabilizing a fracture by inserting a peg in the medullary canal of a long bone is not a new one. In Mexico the Aztec apparently inserted wooden pegs into the medullary canal of non-united bones. This practice was described by Bernardino de Sahagún who travelled with Hernando Cortes to Mexico in the 16th century.[1,2] The Aztec seem to have used some kind of numbing anaesthesia (at least for human sacrifice…) and the use of "very resinous wood"[1] for the intramedullary peg possibly acted as an anti-infectant after the peg was inserted. A method of drilling holes in the bone near to a non-union and inserting ivory pegs to stimulate healing was attempted by several surgeons from the mid 19th century,[3,4] but this was not really IM nailing as we think of it. Bircher was probably one of the first to suggest a more systematic use of intramedullary implants when reduction could not be held by traction or plaster. He inserted short intramedullary ivory pegs into the intramedullary canal through the fracture site to hold the fracture in place while it healed and published a well illustrated paper of his technique in 1886.[5]

Hey Groves used ivory pegs similar to those described by Bircher to treat femoral fractures after gun shot injuries during the First World War, but realized that they did not give sufficient stability to allow mobilization of the joints. He experimented using a long metal "peg" introduced from the trochanter. He published a series of 60 patients treated with different methods for non-union after gun shot wounds in 1918.[6] In this article he argued that fixation of fractures and motion of the joints promoted healing, and that rigid immobilization with casts, operations with stripping of the periosteum and plating without compression or good contact across the fracture, led to non-union, essentially spelling out the problems facing the AO half a century later. Hey Groves was dealing with infected non-unions and did not have access to stainless steel or antibiotics. Consequently the results also of the four IM fixations in his series were not good. However, he concluded that "…this method of introducing a long internal peg into the femur from the trochanter is one of some value in special cases…".[6]

By the 1920s, however, stainless steel was available, and after Smith Peterson's paper popularizing nailing of neck-of-femur fractures with stainless steel nails in 1931, more people started to experiment with metal implants. Rush and Rush published a series using their rods for proximal ulna and proximal femur fractures in 1939.[7] Though the rods held the position of the fragments in subtrochanteric fractures, the technique did not give sufficient stability to allow full mobilization of the patient and this treatment did not gain much popularity. However, "Rush Rods" were widely used in the upper extremity until the introduction of AO plating techniques in the 1960s.

In Germany, Müller-Meernach used stainless steel nails with an X-shaped cross-section introduced from the fracture site from the early 1920s and reported good results with early mobilization of the patients.[8] Gerhard Küntscher was well acquainted with this work and had extensive experience with Smith Peterson Nailing of hip fractures.[9] He was impressed with how well his own first 132 patients using the Smith Peterson technique for hip fractures did. Out of the 132 patents there were 9 infections (7%), and only one he describes as deep, but they all resolved. Küntscher realized this was much less than in other open techniques used at the time and attributed this to the fact that the fractures had not been opened. He also believed that leaving the fracture haematoma, periosteal- and endosteal blood supply intact was beneficial to good healing.

Küntscher had trained briefly in an x-ray department as a young doctor and knew the method of fluoroscopy. He used a long nail that could be inserted away from the fracture site through the trochanter major of the femur. To obtain sufficient stability for the fracture to heal and to mobilize the patients quickly he wanted the nail to impinge in the bone much like a nail that is driven into wood gains purchase because of the elastic and frictional forces of the wood on the nail. Since bone is hard and brittle Küntscher used a nail with a v-shaped cross section that could be elastically compressed instead of the bone, which is why he chose the name "nail". Before he tried the method on humans he did a series of surgeries on the fractured femurs of dogs. The dogs were able to stand on their hind legs alone ("Männchen zu machen") after only 8 days. He refined the technique for use in humans and used a traction table and fluoroscopy to pass the nail into the distal fragment without opening the fracture, much as we do today. He operated his first patient with the technique in 1939 and published his first results after 11 femoral IM nails in 1940,[9] including all the above information and the name of the instrument maker, Ernst Pohl

Figure 1. Küntscher's first design of intramedullary nail had a V-shaped cross section (nail on the right). Later on he advocated the use of a nail with a cloverleaf shaped cross section. The nails had a hole near the end for ease of removal. (Photo Sven Young)

of Kiel, who made and sold the nails and instruments. Though his technique at first met some resistance from his peers, the Second World War was raging and there were large numbers of young men with fractures filling the hospitals. The patients treated with the "Küntscher-nail", or "K-nail", were out of bed in a matter of days rather than months and the technique quickly spread through Germany and Austria during the War.[10] It quickly became apparent how much better the patients did compared to patients treated with traction. Hospital stays were reduced from months to a few weeks and the average number of working days lost were reduced from up to three years (!) to around three months.[11]

In the UK and America, Küntscher's technique first became known through returning allied prisoners of war who had been treated during captivity in Germany. At first there was great scepticism towards the technique, but people quickly saw how well these patients did and publications of cases treated by the Germans appeared both in the UK and the US during and just after the war.[2,12]

After the war Küntscher developed the guide wire technique for closed nailing, a Y-nail for trochanteric fractures,[11] flexible intramedullary reaming, and changed the cross-sectional profile of his nails from the V-shape to a cloverleaf shape so it could be compressed from all sides.[13] The V-shape only allows compression in one plane. (Figure 1) His technique spread quickly throughout Europe and the US. However many surgeons were, understandably, concerned about the use of the head mounted fluoroscopy used at the time. Essentially the surgeon wore a fluorescent piece of glass in front of his eyes and an x-ray beam was aimed straight at the surgeon's head through the patient's thigh. This, and the fact that penicillin was now available, led to the return to the old technique of open reduction and retrograde nailing from the fracture site that some surgeons still erroneously call the "K-nail technique". This had nothing to do with Küntscher. He was the first to systematically leave open reduction of femoral fractures behind. Not until the introduction of the C-arm image intensifier in 1955[14] (Figure 2) did the technique of closed nailing on a traction table regain acceptance. By that time, many surgeons had forgotten that this was in fact the original K-nail technique.

In the 1960s, the popularity of IM nailing diminished as a result of the AO organization promoting the use of exact reduction and compression plating, but by the 1980s surgeons were again realizing the superior results of nailing, especially in femoral fractures. The problem of shortening and rotational instability was solved by using interlocking screws through the nail above and below the fracture. One of the earliest versions of an interlocking IM nail was described as early as 1953.[15]

Figure 2. The introduction of the C-arm image intensifier in the 1950s and -60s made the use of closed x-ray guided nailing safer for the surgical staff. Before this you would wear a box on your head with a piece of fluorescent glass in front of your eyes. The x-ray beam would be aimed straight at your face. The picture shows the Philips BV20 C-arm introduced in 1955 and in use until the late 1960s. This one was used at Haukeland University Hospital. (Photo Sven Young)

Küntscher's nailing principle with a compressible nail was used even after interlocking screws had become the gold standard of care, and his design of a slotted stainless steel nail with a cloverleaf cross section was integrated into the AO and Grosse-Kempf nails. However, in the 1990s surgeons and designers of new nails realized the use of interlocking screws had removed the necessity for a "nail" that impinged in the medullary canal. The use of titanium, which is lighter, stronger and closer to the bone's own rigidity was introduced. Most nails used in high-income countries today are rigid titanium nails with a built in curve to match the anatomy of the femur. Though we still use the word "nail", modern "nails" are more an internal splint or rod, where the rotational and shortening forces are held by the locking screws when the fracture does not have integral stability.

Intramedullary nailing has now been used for over a century and has been the established treatment of choice for femoral fractures in Europe and the USA for over half a century. Yet in many low-income countries today traction is still the only available treatment.[16-18] History, I think, gives this fact some perspective.

1.2 The Growing Burden of Trauma in LMICs

Nearly six million people die annually from injuries, more people than die of HIV/AIDS, tuberculosis and malaria combined.[19,20] Over 90% of these fatal injuries occur in low- and middle income countries (LMIC). For every death from injury, between 3 to 10 more people survive an injury with a permanent disability.[21,22] If you look only at young people between the ages of 10 and 24 years, and thereby exclude expected deaths due to old age, as many as 97% of deaths occur in LMICs, over 40% of deaths are related to injuries, and road traffic injuries are the most common cause of death.[23] Injuries not only disproportionately affect the younger segment of the population in LMICs, they have a serious impact on the family of the injured as a whole. Low- and middle income countries often have no functioning social security systems and the injury of a young mother or father, often the breadwinner of the family, can be devastating to their economic situation and push them further into poverty.[24]

The global burden of injuries is growing rapidly, and almost entirely in LMICs. The main cause of this is the rapid increase in road traffic injuries.[25,26] By 2030, the World Health Organization (WHO) expects road traffic accidents (RTAs) to have risen from the 9th to the 5th leading cause of all deaths globally,[27] only surpassed by the diseases of old age such as cardiovascular, cerebrovascular and pulmonary disease. Despite these compelling facts, surgery is not mentioned at all in the Millennium Development Goals[28,29] (MDGs: http://www.un.org/millenniumgoals/). To be fair, we are currently seeing the beginnings of an increasing awareness of surgery as an integral part of the global public health effort to reach the MDGs,[28,30-33] but over 40 times as many research articles have been published on HIV in Africa than on road traffic accidents,[26] and nearly 190 times as much money was donated to LMICs for treatment of HIV than for unintentional injuries in 1990.[34]

1.3 The Global Distribution of Surgical Health Services

Africa has 24% of the global burden of disease, but has only 3% of the World's health workers and commands less than 1% of world health expenditure.[20] As a concrete illustration of the realities of these facts, the Ministry of Health in Malawi has the very modest target of 40 government employed surgeons for the whole of its 15 million inhabitants. In February 2013, only 3 of these 40 posts were filled, a vacancy rate of 92.5%.[35] The Central Region of Malawi has a population similar to that of Norway, around 5 million inhabitants. Central Region has only two orthopaedic surgeons, both funded from outside the country. In July 2013 there were 957 registered orthopaedic surgeons in Norway,[36] nearly 500 times more.

Weiser et al. reported that an estimated 234 million major surgical operations were performed in the world in 2004.[37] Of these only 3.5% were performed in the poorest 35% of the World's population. The number of performed major operations is already twice the number of annual births and seven times the number of people living with HIV.[38] However, the actual surgical workload is probably many times larger than this, as minor surgical procedures and non-operative treatment were not included in the study by Weiser and his colleagues. A cluster randomized nation-wide survey in Sierra Leone, published in The Lancet in 2012,[39] found that 25% of the population were living with a condition that could be treated by surgery, and that 25% of the reported deaths of family members in the last year could possibly have been avoided by surgical intervention. This is one of the first papers of its kind to document the huge need for surgical services in low-income countries.

1.4 Realities of Trauma Care in Low-Income Countries

The realities of trauma care in low-income countries can be very harsh. No pre-hospital trauma care, or even a simple pick-up service ambulance, is usually available, and most patients are brought to hospital by "good Samaritans", family members or the Police.[40] By that time the most severely injured are already dead. Transport is difficult and very expensive for the rural poor in LICs. This often stops people from seeking help until it is obvious they are not going to get better by themselves - or with the help of a local traditional healer. The next step is for the family to transport the patient to a local health care facility. The patient will most likely be referred to the nearest district hospital, but there will often only be the choice of Plaster of Paris (POP) casting or traction. By the time the patient is seen at a central hospital often many weeks – or even months – will have passed. Even obvious emergencies such as severe open fractures often come late and are infected by the time they reach a facility that can help. Consequently, a large proportion of the fractures treated by orthopaedic surgeons in a LIC will be neglected fractures.[16] Operating time is scarce even in referral hospitals, and prioritizing which patients to offer treatment can be hard. All this makes orthopaedic trauma surgery even more challenging in LICs than in high-income countries.

Despite half a century's experience with the good results of IM nailing, and increasing new evidence that IM nailing is more cost effective than traction,[41,42] femoral fractures are still treated in traction in most hospitals in sub-Saharan Africa, and in many other LMICs around the world. This confines the patients to bed for one and a half to three months,[17,43] and makes them dependent on walking aids for another six to twelve weeks. Contrary to some surgeons' belief, complications are common, with up to 42% pin tract infections, 22% non-union and 14% mal-union.[41,43] Pulmonary embolism[44] and serious infections[18] are also seen while on traction. People's perception of the suffering involved in being treated on traction in a Malawian hospital are well illustrated by Patrick Kaliati's wood carving, "The Patient" (see page 17).

Hospitals in LICs lack many basic services that we take for granted in high-income countries (HIC). VTE prophylaxis in the form of low-molecular-weight heparin is expensive and usually not available. Simple blood tests such as Haemoglobin (Hb) might not be available all the time.[18] There is often no equipment for postoperative monitoring of patients. Oxygen is often not available and even the supply of water and electricity might be erratic.

In surgery in general, but especially in orthopaedic surgery, some specialized equipment is needed. Lack of equipment forces surgeons to improvise and compromise and, though many surgeons can make this work through good knowledge of historical techniques and adherence to proper surgical and mechanical principles, this also leads to many bad results. Many people who have experienced these conditions wish to help, and under the principle that "something is better than nothing" a lot of old equipment is donated to hospitals in LICs. When these donations are well thought through they can be very helpful, but incomplete donations of implants etc can also tempt inexperienced surgeons to do surgery with inappropriate equipment.[16] The reason electro-medical equipment is decommissioned in HICs is that it is getting to an age where maintenance and repairs are becoming more necessary and more expensive. When this equipment is sent as it is, without a thorough overhaul to a LIC with no funds or systems for maintenance, it invariably breaks down quickly and becomes a new problem for the recipient.[45] They now also have a growing mountain of environmentally harmful scrap.

When we are comparing results from low-income countries with those from high-income countries we need to have in mind the setting in which the surgery was carried out. However, despite often being overwhelmed by the situation they find themselves in, short-term visitors to a LIC should not automatically conclude that it is unsafe to do surgery there. This has unfortunately probably been the case for many years, and has given rise to many myths used as arguments opposed to surgery in LICs. More research is urgently needed to confront these myths and to focus attention on the important contribution of surgery in global health.

1.5 Malawi and Kamuzu Central Hospital

Malawi is a small land-locked country lying along the western shore of Lake Malawi bordered by Tanzania, Mozambique and Zambia in southern Africa. It has a population of around 15 million and one of the highest population densities in Africa. In 2012 Malawi was ranked number 170 out of 186 countries on the United Nations' Human Development Index. Norway was ranked as number 1. (http://hdrstats.undp.org/en/countries/profiles/MWI.html)

Because of the surgical workforce situation in LICs mentioned earlier, Haukeland University Hospital has been supporting Kamuzu Central Hospital in the capital city of Malawi, Lilongwe, to develop a postgraduate surgical training programme since 2007.[46] Through involvement in this cooperation I have had the privilege of working at KCH for several shorter and longer periods. The introduction of SIGN intramedullary nails to KCH in 2008 secured a steady supply of implants for the treatment of femoral fractures and laid the foundation for the study in Paper III.

Surgeons at KCH have done approximately 75 SIGN IM nail operations a year so far. Because of the severe lack of surgeons and theatre time at KCH, this is far below the actual number needed. At district hospitals in Malawi there are no surgeons and there is no equipment for IM nailing. Consequently all patients are still treated with traction. Even at our referral hospital in the capital city we are still forced to treat most patients with femoral fractures with traction while they wait for surgery.

For many, this becomes the definitive treatment. By the time we have available theatre time, many weeks may have gone by and some fractures are already healing. If this is the case, we are forced to give priority to other patients, sometimes patients with similar injuries who have waited a much shorter time. This will, of course, seem very unfair to the patients - and will no doubt also seem questionable to outside observers. However, in order to get the maximum amount of benefit for patients out of our limited resources, it is often necessary to prioritize cases that have a predictable outcome and will benefit the most people – not necessarily those who have the worst injury or have waited the longest. Many clinical decisions might, like this, be different in a low-resource setting compared to in high income countries, and it can be very difficult to adapt to this for a surgeon trained in a high income country.

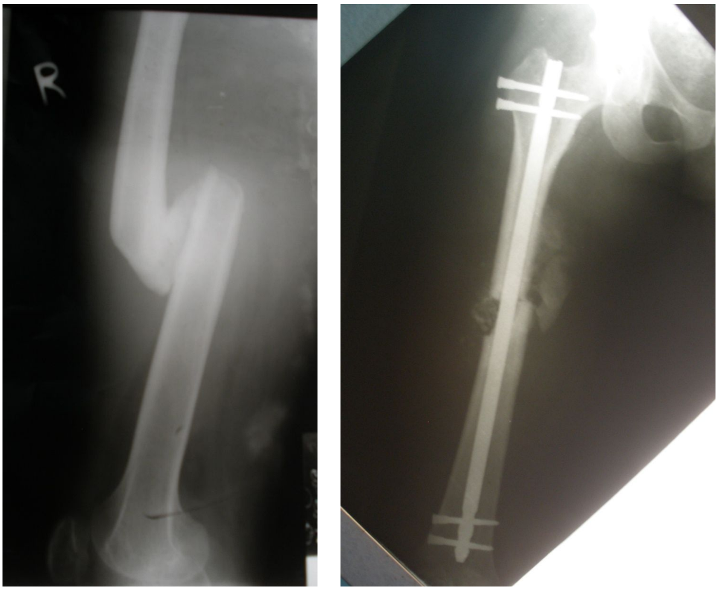

Figure 3. X-rays of a 20 year old man treated for a femoral fracture at Kamuzu Central Hospital. He was treated on traction for two and a half months. The fracture healed with shortening (x-ray on the left) and he was discharged home on crutches. He stopped using the crutches three months later or nearly half a year after the fracture but was still limping when walking. One year later his femur re-fractured while walking normally along the road. This time he was operated with a SIGN IM nail and was up on crutches within a few days and ambulating without crutches a few weeks later.
(Photos Sven Young)

1.6 Postoperative Infection after surgery in LMICs

"Postoperative infection is the saddest of all complications..."
Sir John Charnley, 1982.

Deep infection after orthopaedic implant surgery can be disastrous. It invariably leads to prolonged hospitalization, more operations, increased suffering for the patient and increased costs to society. To address this, orthopaedic surgeons have continuously tried to increase the sterility of the operating field, even through reducing the number of microscopic particles in the air in the theatre with special types of ventilation. It might be understandable, then, that when surgeons from high income countries meet the realities of surgery in hospitals in LICs they assume results will be bad. Visiting surgeons to LICs will see many cases of acute and chronic osteomyelitis, septic joints, neglected open fractures and many amputations done on septic indications. Naturally there will be more surgical site infections in this setting.[47] They will also, most likely, see badly performed ORIF done with inappropriate implants by undertrained visiting and local surgeons.[16] All this, unfortunately, seems to have led to a widespread belief among many surgeons and policy makers in high income countries that postoperative infection rates are very high in LICs and that orthopaedic implant surgery is best avoided there. Several reports of high infection rates after abdominal and gynaecological surgery in LICs have added to this perception.[48-51] There is, however, no scientific basis for the assumption that modern orthopaedic trauma surgery, when done in a well-organized manner by well-trained surgeons, will have the same high infection rates. In fact several papers have reported similar outcomes in LMICs and HICs.[52,53] Most hospitals, even in LICs, have the basic requirements for sterile surgery such as autoclaves, antiseptic wash and prophylactic antibiotics. If the surgeon receives the correct implants and good training, such as through a SIGN programme, is there really any reason why results should not be good? This is one of the questions I have attempted to address in this thesis.

1.7 The HIV pandemic and Trauma Surgery

Since the first reports of Acquired Immune Deficiency Syndrome (AIDS) in California in 1981 and the discovery of the Human Immuno-deficiency Virus (HIV) in 1983,[54] HIV/AIDS has been high on the global public health agenda, and for good reason. Currently an estimated 34 million people are living with HIV; 23 million of these, more than two thirds, live in sub-Saharan Africa.[55] In Malawi, where we conducted the study in Paper III, the HIV prevalence in the adult population between 15 and 49 years is 10%. Internal audits in the medical department at Kamuzu Central Hospital (KCH) have revealed an HIV prevalence among the patients of up to 30%.

In the 1980s HIV/AIDS was a semi-acute lethal infection. With the development of anti-retroviral therapy (ART) from the 1990s, HIV infection can now be supressed so efficiently that the virus is undetectable in the blood and CD4 T-lymphocyte levels are in the normal range. Consequently, HIV positive patients no longer need to develop AIDS and die of opportunistic infections after only a few years. HIV infection has become more of a chronic disease, with the possibility of a normal lifespan, in countries where affordable ART and good follow-up is available.

Unfortunately, the stigma of the 1980s HIV scare still hangs over the disease. The logical assumption has been that HIV positive trauma patients will have more postoperative infections and worse outcomes than HIV negative patients. The fear of patient to surgeon transmission of HIV has also probably contributed to some surgeons being sceptical of the use of internal fixation in HIV positive patients. This has even led to recommendations that ORIF should be avoided in the treatment of closed fractures in HIV positive patients.[56] However, there is very little documentation to support this policy. In Paper III we sought to shed more light on this issue.

Another aspect of the HIV pandemic in sub-Saharan Africa, is its direct and indirect impact on the health workforce. In parts of southern Africa where prevalence rates of HIV in many places are above 10% there is, of course, a similar HIV prevalence among the health care workers themselves. This and other factors has lead to a high mortality rate also among health workers,[57] and is devastating to an already minimal and overworked health workforce. In addition, the fear of patient to surgeon transmission during surgery can be an extra “push factor” leading to “brain drain” of health workers from sub-Saharan LMICs.

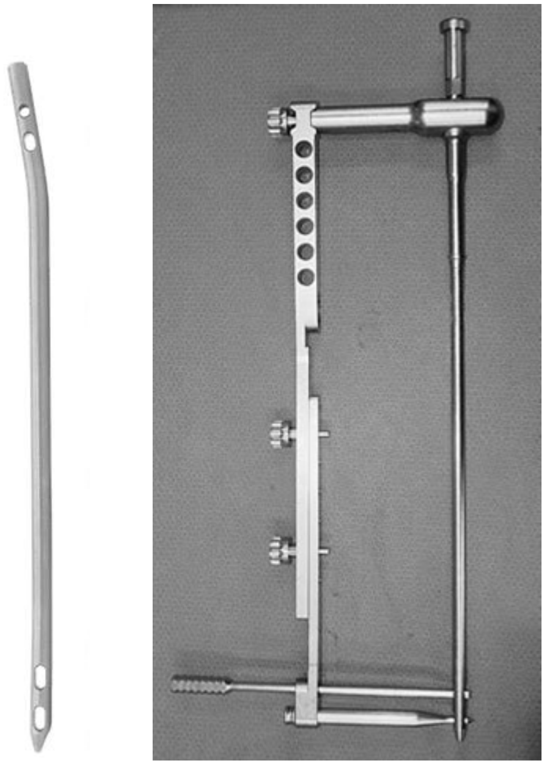

Figure 4. The SIGN intramedullary nail has a proximal bend like a traditional Tibia nail. However, it is used without problems both antegrade and retrograde in the femur and antegrade in the humerus. The fact that it is a solid stainless steel nail makes it stiffer, so the target arm is more likely to indicate the correct position of the distal screw slots in the nail.
(Image © SIGN Fracture Care International. Used with permission.)

1.8 SIGN Fracture Care International

SIGN Fracture Care International (SIGN) is a non-profit organization based in Washington State, USA, that provides orthopaedic surgical implants and instruments to hospitals in low-income countries free of charge (www.signfracturecare.org). Dr Lewis G. Zirkle was drafted as a young resident orthopaedic surgeon in the Vietnam War. He was appalled by the difference in care given to civilians and soldiers and insisted on treating the local civilian population the same as the American soldiers. After the war he returned to Asia many times and helped train orthopaedic surgeons in Vietnam and Indonesia over many years. One day he came across a patient in Indonesia that had been treated in traction for three years because he could not afford to buy the implants needed to treat his fracture. It then became clear to Dr Zirkle that it was useless to train surgeons to treat fractures unless they also had access to the equipment needed.[58]

Since then SIGN has developed an FDA approved intramedullary nail that can be used without expensive equipment such as an orthopaedic traction table, C-arm image intensifier (II) or surgical power tools.[44,59-61] The SIGN nail instruments include an external target arm (Figure 4) used to drill the holes for the distal interlocking screws, and specially designed instruments ("slot-finders") are used to ensure the screws are placed through the slots in the IM nail (Figures 4 & 5).

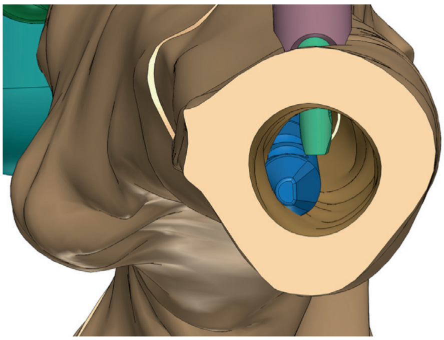

Figure 5. The SIGN nail (blue) is solid, i.e. has no cannulation. "Slot finder" instruments (green) are used with the SIGN IM nail to find the screw slots in the nail. When the nail does not lie centrally these instruments allow the surgeon to feel for the slot by twisting the nail and changing the angle of the slot finder. Once the "slot finder" is placed in the slot, the opposite cortex can be drilled through the instrument.
(Image © SIGN Fracture Care International. Used with permission.)

The SIGN nail itself is a solid stainless steel nail with a bend proximally like a traditional tibial IM nail (Figure 4). This allows its use for tibia fractures as well as in antegrade and retrograde femoral nailing and humerus nailing. The fact that the nail is solid makes it stiffer so the target arm is more likely to indicate the correct position of the distal slots in the nail. Also it reduces the surface area of the nail and dead space in the IM canal, possibly reducing the risk of infection. The design of the holes in the nail as oval slots, not round holes, makes the use of the "slot-finder" instruments possible and allows some dynamic compression of the fracture on weight bearing. The top hole in the nail is, however, round so that a screw placed here will statically lock the nail in place. This, amongst other things, prevents the nail backing out into the joint when used retrograde in the femur or antegrade in the humerus.

In LMICs traction tables and C-arm IIs are rare. In addition, one is often dealing with neglected or late-presented fractures. Therefore open reduction is usually necessary and reaming of the distal fragment is done from the fracture site. Since 1999, SIGN has supplied over 80 000 IM nails and provided training to surgeons in the correct use of the nail in over 200 hospitals in low- and middle-income countries.[62]

1.9 The SIGN Online Surgical Database

The SIGN Online Surgical Database (SOSD) was established in 2003 to ease communication between SIGN and the surgeons using SIGN IM nails. Since then, when a SIGN nail is used the operation is reported to SIGN via the SIGN Online Surgical Database (SOSD) so SIGN can send a replacement nail and locking screws of the right size to the hospital.

In addition to being a fast and effective way to report what nails have been used and need to be replaced, SIGN has realized that the SOSD is an important tool for communicating with surgeons that use the system. The fact that broken instruments or nails are also replaced motivates surgeons to report difficulties with the system so SIGN can constantly evaluate and improve the system. The surgeon also uploads pre- and postoperative x-rays, and all x-rays are reviewed by an orthopaedic surgeon at SIGN in the USA. When the surgical technique does not seem to have been up to scratch or there have been technical problems with the operation SIGN discusses this with the surgeons at that specific hospital. In effect SIGN is also probably the largest single provider of continuing medical education (CME) to surgeons in many of the countries using their nails. Not all problems and complications are apparent immediately postoperatively, though, and SIGN also realizes the need for research on longer term outcomes. Surgeons are therefore strongly encouraged to register follow-up visits in the SOSD, including a few basic clinical parameters and x-rays. A copy of both the SIGN Postoperative Data Collection Form and the SIGN Follow-up Form have been included in the Appendix to show what data is included in the SOSD.

The SOSD in October 2010 contained over 36 000 IM nail operations in 55 low- and middle-income countries.[63] By November 2011 another 10 000 operations had been added to the SOSD,[62] making it one of the largest and fastest growing databases of orthopaedic trauma surgery in the world. SIGN kindly allowed us to use this data in the first two studies included in this thesis.[62,63] The SOSD has one problem, however; a very low rate of registered follow-up. In 2009 it was reported to be only 12.6%.[64] This is why we wished, in Paper I, to validate the data in the SOSD to see if it could be used for further scientific research.

1.10 Follow-up and research in LICs

The achievement of high enough follow-up rates is a concern in clinical research all over the world, but is especially difficult in low-income countries. Surgeons in LICs often tell you that their patients do not return unless they feel they have a problem. The reason usually given for this is the availability and cost of transport. In Malawi over 80% of the population still live in rural villages and depend on subsistence farming. People have very little cash income and transport is expensive. When someone needs to go to hospital in town this can lead to the family having to borrow money or sell off some of their property.[24] For someone who has very little this is a considerable investment, and it would be understandable if people did not want to use money on this if they had no complaints.

Lack of follow-up after surgery in low income countries is problematic in many ways. Most importantly, it may result in inferior results for patients where early postoperative complications are not addressed in a timely or proper manner. But also, studies with low follow-up rates are less likely to be published, contributing to the exclusion of studies from LICs from the literature.

In research we cannot trust our results fully unless we actually confirm progress of the people in the study. In reality, we always lose some patients to follow-up. This is often addressed by excluding all patients in a study who did not return for follow-up. However, if the proportion of people who do not return for follow-up is large, and it is true that patients in LMICs do not return if they are feeling well, this will give the results a strong negative bias; you will be looking at a group of patients with an over representation of those that came back because they had a problem. This negative "selection bias" may also have contributed to the perception that surgery results in bad outcomes in LMICs.

In papers I and III we wished to see if we could get a clearer picture of the pattern of follow-up and its effect on results after IM nailing in LMICs.

2. Study Aims

The overall aim of this thesis was to contribute to the current knowledge on follow-up patterns and infection rates after intra-medullary nailing in low- and middle-income countries.

The specific aims of each paper were:

Paper I: To describe the pattern of follow-up in the SIGN Online Surgical Database (SOSD) and discuss whether the registered data, in light of the low reported follow-up rates, could be used in future in-depth research into infection rates and risk factors.

Paper II: To use the data in the SOSD to investigate whether the follow-up and infection rates were changing over time and to identify risk factors for infection after IM nail operations in LMICs.

Paper III: To examine the possibility of approaching 100% follow-up in a low-resource setting in Malawi, and to clarify whether patients who did not return for follow-up after femoral nailing really did have fewer complications than those that returned as scheduled. Considering the regional impact of HIV, we also wished to compare outcomes in HIV-positive and HIV-negative patients.

3. Methods

In this chapter I wish to explain briefly the basic methods used in this thesis and in our three papers. I do not wish merely to repeat the method sections from the papers, but rather to rephrase these descriptions and the thoughts behind the methods in simpler language. Papers I-III are reprinted in chapter 9, and I refer the reader to these for a more detailed description of the methods used in each paper.

3.1 Paper I. Validation of the SOSD for Research on Trauma Surgery in LMIC. Lack of Follow-up.

SIGN kindly supplied our research group with a data file containing an anonymous export of all surgeries registered in the SOSD from the start of the registry in 2003 to October 8th 2010. The SOSD then contained surgeries using 36,454 SIGN IM nails. After exclusion of humerus and hip fractures and cases with missing data, there were 34 361 IM nail operations of the tibia or femur remaining for analysis. These operations were performed in 55 different low- and middle-income countries with widely differing follow-up rates. With the belief mentioned in chapter 1.10 in mind, that patients in LICs do not return for follow up if they have no complaints, this offered the possibility to study if there is a relationship between the amount of follow-up and the infection rate in different countries. In other words: Do most people with postoperative infections in LMICs actually come back for follow-up, or do countries with higher follow-up rates find more infections and therefore get higher infection rates?

To visualize the relation between the follow-up rates and the risk of infection, Professor Stein Atle Lie used a generalized additive regression model (gam), with spline smoothing of the follow-up rates compared to the risk of infection to generate a graph (Figure 8). He calculated follow-up rates over time based on fixed effects in a mixed effects Poisson regression model (Paper I, Figures 1 & 2). The analyses were done using the lme4 and the mgcv libraries in the statistical computer program R, version 2.12.2 (R Development Core Team 2010).

3.2 Paper II. Risk Factors for Postoperative Infection in LMIC. Data from the SOSD.

Having to some extent established in our first paper that the SOSD could be used for research into risk factors for infection after IM nailing in LMICs, in our second study we wished to do just that. One year after our first study validating the data in the SOSD, it contained data on 46 722 IM nail operations, 10 000 more than the year before. SIGN provided us with a new anonymous export of all surgeries registered in the database from the start of the registry up to November 29th 2011. This time we also included humerus fractures and only excluded the relatively few hip fractures and the very few operations done in high income countries, leaving 46 113 IM nail operations of the humerus, femur or tibia for analysis. In this paper, simpler (logistic regression) statistics were employed to calculate both crude and adjusted risk, odds ratio (OR), of postoperative infection after IM nailing for different risk factors.

3.3 Paper III. Postoperative Complications after IM nailing in Malawi. Lack of Followup and impact of HIV.

The introduction of SIGN intramedullary nails for the treatment of long bone fractures in 2008 at last allowed Kamuzu Central Hospital to step into the modern era of orthopaedic trauma surgery. It gave us the opportunity to prospectively follow up in more detail a local series of SIGN nail patients to determine the infection rate after surgery in our specific setting in Malawi. Also, if we could trace the patients that did not return for follow-up of their own accord, we might find out if these patients really did have fewer complications than those who returned for scheduled follow-up.

In addition to the data recorded for the SOSD, a separate Study Data Collection Form was used for all patients to record additional information. A copy of this form is included in the Appendix. Information about patients who returned for follow-up was recorded on the SIGN follow-up form and uploaded to the SOSD. For the patients who needed to be contacted as they did not have a registered follow-up visit we used a separate follow-up form that contained some more information than the SOSD allows. A copy of this form has also been included in the Appendix.

Patients who did not return for follow-up were, if possible, contacted by phone and given a follow-up appointment. If patients refused to come for follow-up when contacted by phone, we interviewed them by phone only. Some patients could not be reached by phone. Though mobile phones are rapidly becoming very common even in low-income countries, in Malawi many patients do not own a phone or even know someone who does. Also phone numbers are often discontinued if people lose or sell their phone or cannot pay for phone credits over a long period. In cases where people could not be reached by phone, but had an accurate address recorded, we tried to examine them at home on outreach visits. Where we found the right village and family but the patient was not at home, we obtained a phone number to reach the patient if possible. Where the patient was not reachable for some reason (e.g. had died), we interviewed the family to get as much information as possible. We

Figure 6. In our study from Malawi (Paper III) we drove 2006km over 8 days on very rough, some times hardly passable roads to follow up 11 patients; 182km per patient contacted. The difficulties facing people in the districts in Malawi to return for follow up at a hospital became quite apparent to us during these outreach visits. (Photo Sven Young.)

drove a total of 2006 km on very rough, sometimes scarcely passable, roads over 8 days to find these 11 patients; 182 km per patient found (Figure 6).

Of the 137 patients included in this study 79 (58%) returned for follow-up as scheduled, in itself not a bad number in our setting. Of the remaining 58 patients who did not return for follow-up we managed to contact or obtain information about exactly half, i.e. 29. Of these, 11 returned for an outpatient visit after being contacted by phone, an additional 7 were only available for interview by phone, 7 more patients were found on outreach visits and examined at home, while 4 were contacted through relatives or friends found on these visits.

3.4 Ethical Considerations

Papers I and II were both register studies carried out on anonymous data provided by SIGN from the SIGN Online Surgical Database. The study proposal was reviewed and approved by the Norwegian Regional Committee for Medical and Health Research Ethics (20.09.10, 2010/2040).

Paper III is based on a prospective registration of SIGN nail operations at Kamuzu Central Hospital in Lilongwe, Malawi. The research proposal for this study was reviewed and approved by the National Health Sciences Research Committee in Malawi (approval # 753). All patients were counselled and asked for their consent to be included in the study. All patients were also asked to take an HIV test. They received the same treatment regardless of their answers to these requests.

Research on femoral fractures in a low resource setting had its ethical challenges. At KCH the patients lie in large open wards with up to 18 patients listening in on the conversation with the patient. This makes patient confidentiality next to non-existent. There are no treatment rooms for more discrete counselling, and even if the room and time were available the patients are confined to bed in traction, and most beds have no wheels. On outreach visits too, it was difficult to talk to the patient alone. Driving into some of the most remote villages brought the whole extended family and many neighbours to the scene (Figure 7). However, patients seem to be used to this lack of privacy in Malawi and they all accepted that we talked to them in front of other people.

Figure 7. Patient confidentiality is difficult to uphold both in the hospital and on rural outreach visits in Malawi. Here Mr Fletcher Beniyasi is interviewing a patient. The extended family and neighbors have all joined in to greet the visitors. The patient gave consent to the use of the image. (Photo Sven Young)

4. Summary of Papers I - III

Paper I. Young S, Lie SA, Hallan G, Zirkle LG, Engesæter LB, Havelin LI. **Low infection rates after 34,361 intramedullary nail operations in 55 low- and middle-income countries.** Acta Orthop 2011; 82 (6): 737-43.

Background The Surgical Implant Generation Network (SIGN) supplies intra-medullary (IM) nails for the treatment of long bone fractures free of charge to hospitals in low and middle-income countries (LMIC). Most operations are reported to the SIGN Online Surgical Database (SOSD). Follow-up, however, has been reported to be low. We wished to examine the pattern of follow-up and assess if infection rates could be trusted.

Patients and methods The SOSD contained 36,454 IM nail surgeries in 55 LMIC. Humerus and hip fractures, and fractures without a registered surgical approach were excluded. This left 34,361 IM nails operations of the femur and tibia for analysis. A generalized additive regression model (gam) was used to explore the association between follow-up rates and infection rates.

Results The overall follow-up rate in the SOSD was 18.1% (CI: 17.7-18.5) and national follow-up rates ranged from 0% to 74.2%. The overall infection rate was 0.7% (CI: 0.6-0.8) for femoral and 1.2% (CI: 1.0-1.4) for tibial fractures. If only nails with a registered follow-up visit (n=6224) were included, infection rates were 3.5% (CI: 3.0-4.1) for femoral and 7.3% (CI: 6.2-8.4) for tibial fractures. We found an increase in infection rates with increasing follow-up rates up to a level of 5%. Follow-up above 5% in a country did not result in increased infection rates.

Interpretation Reported infection rates after IM nailing in the SOSD seem to be reliable and could be used for further research. The low infection rates suggest that IM nailing is a safe procedure also in low and middle-income countries.

Paper II. Young S, Lie SA, Hallan G, Zirkle LG, Engesæter LB, Havelin LI. **Risk Factors for Infection after 46,113 Intramedullary Nail Operations in Low- and Middle-income Countries.** World J Surg 2013; 37 (2): 349-55.

Background The fields of surgery and trauma care have largely been neglected in the global health discussion. As a result the idea that surgery is not safe or cost effective in resource-limited settings has gone unchallenged. The SIGN Online Surgical Database (SOSD) is now one of the largest databases on trauma surgery in low- and middle-income countries (LMICs). We wished to examine infection rates and risk factors for infection after IM nail operations in LMICs using this data.

Methods The SOSD contained 46 722 IM nail surgeries in 58 different LMICs. 46 113 IM nail operations of the humerus, femur and tibia were included for analysis.

Results The overall follow-up rate was 23.1%. The overall infection rate was 1.0%; 0.7% for humerus, 0.8% for femoral and 1.5% for tibial fractures. If only nails with registered follow-up (n=10 684) were included in analyses, infection rates were 2.9% for humerus, 3.2% for femoral and 6.9% for tibial fractures. Prophylactic antibiotics reduced the risk of infection by 29%. Operations for non-union had a doubled risk of infection. Risk of infection was reduced with increasing income level of the country.

Conclusions The overall infection rates were low, and well within acceptable levels, suggesting IM nailing is safe also in low-income countries. The fact that operations for non-union have twice the risk of infection compared to primary fracture surgery, further supports the use of IM nailing as the primary treatment for femoral fractures in low- and middle-income countries.

Paper III. Young S, Banza L, Hallan G, Beniyasi F, Manda K, Munthali B, Dybvik E, Engesæter LB, Havelin LI. **Complications after trauma surgery in a low-income country.** Acta Orthop 2013

Background Some surgeons believe that internal fixation of fractures carries too high a risk of infection in low-income countries (LIC) to merit its use there. However, too few studies from LIC with sufficient follow-up to answer this are available. We wished 1) to explore whether complete follow up could be achieved in a LIC, and 2) to find the true infection rate at Kamuzu Central Hospital in Malawi, and 3) to examine the influence of HIV and lack of follow-up on patient outcomes.

Patients and methods 137 patients with 141 femoral fractures that were treated with intra-medullary (IM) nails were included. We compared outcomes in patients who returned for scheduled follow-up and patients who did not return and therefore needed to be contacted by phone or visited on outreach visits to their home villages.

Results 79 patients returned for follow-up as scheduled, 29 of the remaining patients were reached by phone or outreach visits giving a total follow-up rate of 79%. 7 nails (5.0%) were complicated by a deep postoperative infection, all of whom returned for scheduled follow-up. There were no infections among patients who did not return for follow-up, compared to 9.6% in the group that did return as scheduled ($p=0.11$). Two deaths occurred among HIV positive patients (8.7%), while no HIV negative patients died < 30 days postoperatively ($p=0.031$).

Interpretation There was an acceptable infection rate in this study. The risk of infection should not be used as an argument against IM nailing of femoral fractures in LIC. Many patients in Malawi did not return for follow-up because they had no complaints about the fracture. There was an increased postoperative mortality rate in HIV positive patients.

5. Discussion

The main findings from the three papers on which this thesis is based were:

1 People in LMIC do, mostly, seem to return for follow-up if they have complaints after an IM nail operation, but often choose not to return if they have no complaints.

2 Postoperative infection rates after IM nailing in LMIC are not alarmingly high.

3 HIV positive trauma patients did not have a greatly increased risk of infection, but might have an increased early postoperative mortality rate in resource limited settings with long preoperative traction times and no available VTE prophylaxis.

5.1 Follow-up

In our analysis of the follow-up and infection rates in the 55 LMICs in the SOSD in Paper I, we found that registered infection rates in a country increased with increasing follow-up rates up to a level of 5%. However, countries with follow-up rates higher than this did not show correspondingly increased infection rates (Figure 8). This, of course, does not mean that a follow-up rate of 5% in any given country is enough to register all infections. There could be many factors influencing this finding. In Paper II we found that infection rates fell the higher the income level of a country (Paper II, Table 2). One might be tempted to think that more prosperous countries will have both higher follow-up and lower infection rates and that this might explain the plateau of the curve in Figure 8. However, this does not seem to be the case as low-income countries actually had higher follow-up rates than middle-income countries in our first study (Paper I, Table 2). The plateau in Figure 8 might in fact reflect the possibility that a large proportion of infections were being registered in the SOSD at the time. In that case it would seem to support the notion that people in LMICs return for follow-up if they have complications after an IM nail operation and choose not to if they have no complaints. Another finding that might support this is the fact that the follow-up rate in the SOSD went up by 28% from 18% to 23% between 2010 and 2011. This however had very little effect on the recorded infection rates in the SOSD.

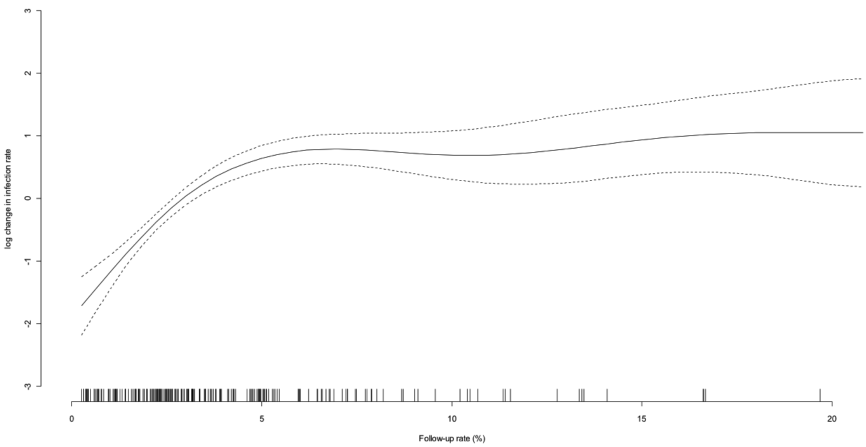

Figure 8. Follow-up rate plotted against log change in the infection rate. The curve is based on a generalized additive regression model (gam). Dotted lines represent 95% CI. With follow-up over 5%, there is very little increase in infection rate and the curve is consequently nearly horizontal. Short vertical lines on x-axis represent observations in different countries.

Figure from: Young S et al. Low infection rates after 34,361 intramedullary nail operations in 55 low- and middle-income countries. Acta Orthop 2011; 82 (6): 737-43.

It seems that the cost and availability of transport can be an important factor stopping people in Malawi from coming for follow-up.[65,66] However, to our knowledge, no studies have been done specifically asking trauma patients why they did not return for review after surgery. In Paper III we attempted to look more closely at this when we followed up our own patients in Malawi. We found that the main reasons given by our patients were that the cost of transport was high and that they did not have any complaints. Considering the challenges we had, even in a 4-wheel-drive vehicle, of getting to the few patients we were able to locate on outreach visits (see 3.3 & Figure 6), and the fact that people in rural Malawi have very little cash income, it is hardly surprising that people do not prioritize returning for review after surgery (see 1.10).

Nearly one third (9/29) of the patients who did not have registered follow-up actually claimed to have returned once. Some of them said that they had been seen by a clinical officer and told not to come back. In these cases it is, of course, a lack of registration that is the problem. At KCH, this can result from several factors, even at times as basic as the lack of writing paper. Others said they were sent away because the doctor was not there, or the x-ray department was closed because of lack of film or water, both plausible explanations in our setting. If someone has made a considerable effort at great expense to come for review and experienced this kind of problem, it is even more understandable that they, or even others they tell about this, would not be motivated to come back.

In this last study (Paper III) we managed to contact half of the 58 patients who did not return for follow-up. None of these (0/29) had a postoperative infection, compared to 8 infections in the 83 patients who did return (9.6%). Despite this finding not reaching statistical significance (p=0.11) with this study's size, I believe this finding supports the idea that people often do not return for follow-up in low-income countries unless they have a complaint. As a consequence, research from LICs should be interpreted with this in mind. Complication rates based only on the number of patients that returned for follow up are likely to be negatively biased, i.e. too high.

5.2 Infections

Femoral fractures

Contrary to traditional perceptions of the risk of infection after surgery in low-income countries (see 1.6), our studies from the SOSD and first-hand in Malawi have shown acceptable infection rates. In Paper II the overall postoperative infection rate after IM nailing of femoral fractures across all the 55 low and middle-income countries in the SOSD was 0.8%. If only patients with follow-up were used in the analysis the rate was 3.2%.

The postoperative deep infection rate after femoral nailing at Kamuzu Central Hospital was 5% (Paper III). This is considerably higher than the average infection rates in the SOSD. This, however, has to be seen in the context of the limited resource setting at KCH and the severity of the trauma being treated. In this study 87% of the fractures were the result of high-energy trauma, 25% of patients were polytrauma victims, and 7% of fractures were open. In the SOSD, the risk of infection increased with decreasing resources in a country (Paper II, Table 2). Malawi was ranked number 170 of 186 countries on the United Nations' Human Development Index (http://hdrstats.undp.org/en/countries/profiles/MWI.html) in 2012, making it one of the poorest countries in the world. Limited resources lead to many risks for postoperative infection. In Malawi wards are overcrowded and under-staffed. Stock-outs are frequent, even of antibiotics, anaesthetic drugs, painkillers and antiseptic preparation wash. Surgical drapes and gowns frequently have holes in them and the supply of water and electricity is erratic. In such a situation infections are bound to be more frequent than in high-income countries. However, an infection rate of 5% is not alarmingly high and should not be used as an argument to avoid IM nailing of femoral fractures in LICs. Similar infection rates have been reported after IM nailing in high-income countries. In the UK, Malik et al. found a deep infection rate of 4.1% after 122 femoral nailings.[67] In the USA, Bone and Johnson reported 6.3% infections after nailing of 112 tibial fractures.[68] In Oslo, Norway, a recent study by Westberg et al. found an infection rate of 9% after hemiarthroplasty for femoral neck fractures in elderly patients.[69] Deep postoperative infection of an IM nail is a serious, potentially life-threatening, complication. Even when successfully treated, an infected nail often leads to knee stiffness. This was also seen in our last study (Paper III, Table 3) from Lilongwe. However, in most cases the infection can be controlled with early debridement and suppressive antibiotics until the fracture has healed.[70] The nail can then be removed and the IM canal reamed to remove any dead or poorly vascularized infected tissue.[71]

Though an infection rate of 5% might not be an argument against the use of IM nailing of femoral fractures in LIC, there is definitely room for improvement. Winquist et al.[72] reported an infection rate of 0.9% in a series of 520 IM nails with 17% open fractures nearly 30 years ago, and in a prospective series of 172 IM nail operations in Boston,[73] no infections were seen at all. Efforts should be made to reduce the infection rate where possible through the training of surgeons and specialist theatre nurses, increased hospital ward staffing, and the improvement of infrastructure and supply chains in hospitals in LICs.

Tibia and humerus fractures

In Paper II we found that the infection rate for tibial fractures in the SOSD was 1.5% overall and 6.9% if only patients with registered follow-up were included in analyses. The equivalent rates for humerus fractures were 0.7% and 2.9%. The true infection rates probably lie somewhere between these two extremes, but most likely closer to the lower figure. The doubled crude risk of infection after nailing of tibial fractures compared to antegrade nailing of the femur can partially be explained by the higher number of open tibial fractures, but even after adjusting for this in the analyses tibial fractures had a 71% increased risk of infection, compared to antegrade femoral nailing. Whereas the femur and the humerus are entirely surrounded by well circulated muscle, the tibia has much less muscle cover with the whole medial surface of the bone lying subcutaneously.

The increased risk of postoperative infection after tibial nailing should be considered when selecting treatment for tibial fractures in resource-limited settings. Whereas the benefit to patients with femoral fractures from IM nailing is obvious and large, good results can be achieved with functional bracing of closed tibia and humerus fractures.[74] The patients can be treated as outpatients and need not be admitted for long periods as with femoral fractures. In a setting of severe resource limitations it is probably best to reserve IM nailing of the tibia and humerus for cases of mal- and non-union. In Gustilo grade 2-3 open fractures of the tibia, external fixation and early soft tissue cover is probably the best option. However, if external fixation is not available, good results have been reported with IM nailing of open tibial fractures.[59]

Open fractures

As discussed earlier, the spectrum of trauma is severe in LMICs, largely due to the increasing number of road traffic accidents involving vulnerable road users (i.e. pedestrians, bicyclists, motorcyclists, passengers on the back of lorries etc.). This leads to a large number of open fractures. In the SOSD 17% of the registered fractures were open fractures at the end of 2011 (Paper II), and at Kamuzu Central Hospital in Malawi we found that 7% of femoral fractures were open (Paper III). Other authors have shown a clear correlation between increasing severity of the open fracture (Gustilo grade) and the rates of infection.[71,75] We found this to be the case also in the SOSD. Previous research from high income countries has shown very little increased risk of infection in Gustilo grade 1 injuries and some authors even group these fractures with closed fractures.[71] However, our results in Paper II suggest that also grade 1 injuries have a clinically significant increase in infection risk of 86% compared to closed fractures after IM nailing (OR 1.86, 95% CI 1.32-2.62; $p<0.001$). Proper treatment protocols for open fractures including intravenous antibiotics, debridement and irrigation should also be followed in grade 1 open fractures.

Open reduction

Küntscher realised over 70 years ago, before penicillin was available in normal clinical practice, that closed reduction reduced the risk of infection and non-union after IM nailing (see 1.1). However, the fear of harmful irradiation from early versions of x-ray fluoroscopy in the operating theatre made many surgeons revert to open reduction when doing IM nailing. The technique was widely used until the 1980s with good results and few reported infections.[76] There is a conspicuous absence of good quality studies actually showing an increase in infections after open reduction. Though it is logical and probable that there would be at least some more infections after opening the fracture site, this risk is probably small due to the widespread use of prophylactic antibiotics. A few studies have compared infection rates after open and closed reduction in IM nailing of the tibia, but the studies were too small and underpowered to prove differences in outcomes.[77,78] Large studies are needed to show any small differences in outcomes, and the SOSD therefore offers a rare opportunity to study this. In Paper II we found an increase in the crude risk of infection (OR 1.34, 95% CI 1.07-1.66; $p = 0.010$) after open reduction. However, after adjusting for other risk factors such as open fractures, surgical approach, prophylactic antibiotics etc., the difference marginally lost its statistical significance (OR 1.23, 95% CI 0.97-1.55; $p = 0.083$). Also, the actual increase in the infection rate was only from 0.8% to 1.1% and as such is probably of little clinical significance. The need for open reduction because of the lack of expensive equipment such as orthopaedic traction tables, C-arm II etc. is no contraindication to the use of IM nailing in LMICs.

Non-union

In literature from high-income countries a non-union, a fracture that has not united, is usually seen as a complication of surgery. In low-income countries, however, non-union is a separate and common indication for surgery as non-operative management is still widely used. Any orthopaedic surgeon will tell you that operating a delayed- or non-union is more difficult and takes longer than operating a fresh fracture, but actual evidence of this is difficult to find in the literature. In Paper III we confirmed that this seems to be the case at Kamuzu Central Hospital in Malawi. Fractures defined by the surgeon preoperatively as a delayed or non-union had a mean operating time of 130 (SD 36) minutes and estimated blood loss of 400 (SD 309) ml. Fractures that were defined as primary fracture treatment had a mean operating time of 112 (SD43) minutes, mean difference 18 minutes (95% CI 0.6-35, p=0.04) and an estimated blood loss of 279 (SD 202) ml, mean difference 121 ml (95% CI -10-252, p=0.07). The fact that differences were not larger can probably be explained by the fact that even the patients with "acute" fractures had waited on average 17 days for surgery in this study. Muscles soon start contracting when a bone is left with shortening and many of these fractures were therefore already difficult to reduce at the time of surgery. Despite these differences we found no difference in infection rates in these two groups in Paper III with this study's relatively small size (OR 0.47, 95% CI 0.1-4.0, p=0.68). In Paper II, however, we looked at this in the SOSD and found that patients undergoing IM nailing for a non-union had a more than doubled risk of postoperative infection (OR 2.31, 95 % CI 1.83-2.91; p<0.001). The operating time and blood loss are not recorded in the SOSD, but other authors have shown a correlation between increased operating time and infection rates in total hip replacement surgery.[79] The increased infection rate in operations of non-unions in the SOSD may be an indirect measure of this, or there might be biological factors with the non-union itself affecting the outcomes. Either way, in my opinion, this further supports that, at least femoral fractures, should be treated early with IM nailing. It also shows that the large proportion of neglected fracture patients treated in LICs (see 1.4) can lead to inferior results. This must be considered when interpreting results from such countries.

Prophylactic antibiotics

After the Second World War, antibiotics became readily available and the use of prophylactic antibiotics quickly became the standard before bone surgery. In a large multicentre study from the 1980s of over 8000 hip and knee replacements a reduction in the risk of infection of 75% was seen when prophylactic antibiotics were given before surgery.[80] Though, few people will advocate not using antibiotic prophylaxis before IM nailing these days, the consequences of not providing this is at least of interest. Data from the SOSD (Paper II, Table 2) showed a reduction in the risk of infection of nearly one third for those that received prophylactic antibiotics (OR 0.71, 95 % CI 0.55-0.91; p = 0.008).

Income level

The World Bank classifies a country into one of four income groups based on its gross national income (GNI) per capita (http://data.worldbank.org/about/country-classifications). The groups are: low-income, lower middle-income, higher middle-income and high-income countries. Low-income countries have a GNI per capita of below US$ 1000, whereas high-income countries have a GNI per capita over US$ 12000 (2012 figures). The fewer resources a country has, the more unfavourable one would expect the condition of its hospitals to be, as described earlier for KCH in Malawi (see 1.5). As a consequence, one might expect results to be poorer in low-income countries than in high-income countries. The data in the SOSD does seem to support this to some degree, as we did find a lower adjusted risk of infection the higher the income level of a country in Paper II (Table 2). The risk of infection in higher middle-income countries was half that of low-income countries in that study. This does show that there is clear room for improvement of infection control in low-income countries, but the rates of infection are still low and should not be used to as an argument against the use of surgical treatment in LIC.

5.3 HIV

In our study of patients at Kamuzu Central Hospital in Lilongwe, Malawi, 17% of the patients were HIV positive and 6.6% had an unknown HIV status (Paper III). The HIV positive patients had an infection rate of 8.7% (2/23) and the HIV negative patients 4.8% (5/105). This seemingly doubled risk of infection was not statistically significant with our study's size, however (OR 1.9, 95% CI 0.3-10, p=0.61). Bates et al. followed 609 patients after internal fixation of different fractures in Blantyre, Malawi.[81] 132 of these patients were HIV-positive. They found no difference in infection rates in HIV-positive and HIV-negative trauma patients. In a paper from Rwanda in 1991, Hoekman et al. found an increased risk of postoperative infection after fracture surgery in HIV seropositive patients with "symptomatic disease".[82] However, they did not use systemic prophylactic antibiotics before surgery, and if all HIV positive patients were combined in one group no significant difference in infection rate was seen. A recent meta-analysis did suggest that there might be more postoperative infections in HIV positive patients,[83] but the findings were based on many old and small studies and were not conclusive. Infection does seem to be more common in HIV-positive patients after open fractures,[84] but the increased risk is probably more influenced by the severity of the injury[85] and contamination of the wound,[86]or with the life style of the patients.[87] There is increasing evidence both from high-income countries and LMICs that clean implant surgery in HIV-positive patients is safe and that the long-term outcomes after surgery in general are no worse for HIV-positive patients than for other patients.[88-91] However, there is still a lack of good studies of the results of surgery in HIV-positive trauma victims and this has unfortunately even led to poorly founded general recommendations that closed fractures in HIV patients should be treated non-operatively in low-income settings.[56]

HIV positive trauma patients at KCH had an increased over all risk of death (OR 16, CI 1.5-158, p=0.018) in the study period (Paper III, Table 4). The 30 day postoperative mortality was 8.7% (2/23) in HIV-positive patients compared to 0% (0/105) in HIV-negative patients (p=0.03). Numbers were small and care must be taken in concluding from these. However, there is available literature that may support this finding. HIV-positive patients are reported to have an up to tenfold increased risk of venous thromboembolism (VTE).[92] Immobilization in traction can also lead to VTE, including pulmonary embolism (PE). In a study of the use of SIGN nails in Uganda, Sekimpi at al. diagnosed and treated two patients for pulmonary embolism (PE) while they were waiting for surgery for femoral fracture.[44] In their study patients waited an average 13 days for surgery. A prospective randomized study by Bone et al. from 1989 found that delayed stabilization of femoral fractures over 24 hours increased the incidence of pulmonary complications.[93] At KCH patients waited on average 17 days (nearly two and a half weeks) for surgery of acute fractures. Due to economic constraints we did not have available VTE prophylaxis with low-molecular-weight heparin. All three postoperative deaths were suspected to be pulmonary embolisms with sudden onset hypotension and respiratory distress, though definitive diagnosis or post-mortem examination were not available. The lack of VTE prophylaxis could, together with the seriousness of the trauma in our patients and the long period of immobilization, explain the increased postoperative mortality recorded in Paper III. As HIV-positive patients have an increased risk of VTE, this might disproportionately affect this group. HIV-positive patients did not have increased time to ambulation or length of stay postoperatively in this study and therefore seem to have the same potential for rehabilitation postoperatively as other patients with femoral fractures. In my opinion, these findings further strengthen the argument for early IM fixation of femoral fractures in HIV positive patients. Surgeons should also try to provide VTE prophylaxis in some other form (e.g. compressive stockings or Aspirin) to these patients if low molecular weight heparin is not available.

5.4 Study design and limitations

Papers I and II are based on the SOSD and are in essence register studies, or prospective observational studies, using a large database of intra medullary nail surgery registering data on the use of one specific implant. The SOSD gathers systematic prospective data on trauma surgery on a large scale and is probably the largest and fastest growing database of its kind in the world. It is also unique because all operations recorded are carried out in LMICs giving us the opportunity to study outcomes in countries with fewer resources and higher burdens of disease than in high-income countries.

Randomised controlled trials (RCTs) are generally considered to generate the highest level of evidence for differences between treatment modalities. However, this trial design is not always practical or even sensible. Large RCTs are difficult and expensive to implement, even in high-income countries. Register studies are likely to include much larger numbers of patients and are therefore better suited to study rare outcomes, such as infection and death. An RCT comparing outcomes of skeletal traction and IM nailing in a high-income country would be considered completely outrageous by most surgeons and would not be likely to pass ethical review. The benefits of IM nailing over traction are obvious and well proven over the last 70 years, and there is absolutely no reason why a study of this kind should be ethically acceptable in a low-income country either.

Despite this being the focus of our interest in our first paper, the most obvious limitation in our two register studies was the lack of follow-up in the SOSD. This was discussed in more detail at the beginning of this chapter (5.1). Infection is registered as superficial or deep in the SOSD. However, the definition of this is at the discretion of the surgeon reporting, and in a register study from 55 countries we had no way of auditing the reporting practice. We assumed that infections reported in an environment of resource and time constraints would be clinically significant, e.g. not just a stitch abscess or passing inflammation of the wound that cleared with a few days of oral antibiotics. We therefore grouped superficial and deep infections together. In calculating infection rates, we assumed that people who had infections returned for follow-up. This, of course, is not correct in all cases, but the statistical model used in Paper I, and our findings in Paper III, seem to support that this assumption holds to some degree. We also assumed that if patients returned they would be registered in the SOSD. This also is not always the case, as we found in

Paper III where a third of patients who were not registered as having come for follow-up actually claimed to have returned as requested (Paper III, Table 3). Assumptions like these introduce uncertainty into the analyses and conclusions. However, in light of our findings in Papers I and III that a large proportion of patients with complaints did return, the large size of the register studies (Papers I and II) and the fact that we have done all calculations of infection rates both including and excluding patients without follow-up, I believe that the reported figures give a good indication of the true infection rates in low- and middle-income countries.

Our prospective study of femoral fractures at KCH (Paper III) also had its own clear limitations, including the relatively small number of included patients limiting that study's power to prove small differences in relatively rare complications. Despite considerable effort we did not achieve our goal of 100% follow-up in this study either. However, in the light of the setting in which this study was conducted, and the fact that we managed to get close to 80% follow-up despite huge resource challenges, I do believe this study has brought some new information to the field of orthopaedic trauma care in low-income countries.

6. Conclusions

Returning for follow-up in LICs can be difficult and very expensive for many patients. The motivation for returning for follow-up is therefore very low if a patient does not have any complaints. Insisting on very high follow-up rates in clinical research from low-income countries is unrealistic and can exclude important information from the literature. It does, however, seem as if people in low income countries mostly do return for follow-up if they have a complaint after surgery, even if total follow up rates are low. This implies that results based only on the patients who returned for follow-up in LICs will be negatively biased. This should be kept in mind when interpreting results in research from LICs.

Infection rates after IM nailing in LMICs are acceptable and infections, when they occur, are usually manageable. The risk of infection should not be used as an argument against well-proven surgical treatment of fractures by properly trained surgeons in LMICs. Patients with femoral fractures in particular have a great deal to gain from IM nailing as opposed to spending months in hospital on skeletal traction. Patients with tibia and humerus shaft fractures can in most cases be treated effectively by functional bracing. In a setting of severe resource constraints with limited operating time it is probably best to reserve IM nailing of the tibia and humerus for cases of mal- and non-union.

Patients undergoing IM nailing for a non-union had a more than doubled risk of postoperative infection in the SOSD. This further supports that, at least femoral fractures, should be treated early with IM nailing also in LMIC. The large proportion of neglected fractures treated can also explain inferior results in research from LICs. This must be considered when interpreting results from these countries.

Data from the SOSD suggests that there is a statistically increased risk of postoperative infection with the decreasing income level of a country. However, infection rates are still low and should not be used as an argument against the practice of orthopaedic trauma surgery in low-income countries.

We found no statistically significant increase in infection rates when open reduction was used compared to closed reduction. The need for open reduction because of the lack of expensive equipment such as orthopaedic traction tables, C-arm image intensifiers etc. is no contraindication to the use of IM nailing in LMICs.

There is a large potential for decreasing the length of hospital stay both pre- and postoperatively for femoral fracture patients in Malawi. Increased surgical capacity and better availability of affordable crutches could realistically reduce the length of stay at Kamuzu Central Hospital from the current average of 30 days to around 10 days. At hospitals where IM nailing has not yet been introduced this reduction in length of hospital stay would be even larger.

People living with HIV do not seem to have a much increased risk of postoperative infection. This certainly is no argument against the surgical treatment of fractures in HIV-positive trauma patients. They might, however, have an increased postoperative mortality risk due to venous thromboembolism (VTE) after prolonged preoperative traction when low-molecular-weight heparin VTE prophylaxis is not available. This needs to be confirmed in larger studies, but in my opinion further strengthens the argument for the earliest possible IM nailing of femoral fractures in HIV-positive trauma patients. Surgeons should also try to provide VTE prophylaxis in some other form (e.g. compressive stockings or acetylsalicylic acid) to these patients if low-molecular-weight heparin is not available.

7. Future Research

7.1 The SOSD

The SOSD is already probably the largest database on orthopaedic trauma surgery in the world. The increasing numbers and follow-up rates in the SOSD offer exciting prospects for future research. However, the SOSD was set up for ease of reporting and feedback on surgery and was not primarily designed for research. As a consequence some data that would be of interest is not recorded in the database. This includes epidemiological data such as mechanism of injury, risk factors for surgery such as other medical conditions and smoking, operation time, blood loss, surgical positioning, use of C-arm, draping material etc. Also a clear way of registering a reoperation and connecting it to the primary surgery is missing. Minor changes and additions to the SOSD could greatly increase its importance in orthopaedic trauma research.

The information registered at follow-up also limits the use of the SOSD for research. With slight changes to the follow-up form, such as automatically adapting the form to the bone operated, more reliable and interesting end points could be registered. For the femur, differentiating between knee, trochanter and fracture pain would be interesting in looking at results after retrograde and antegrade nailing. For tibias, it would be interesting to record anterior knee pain, ankle pain and peroneal nerve / anterior compartment function. For humerus fractures, abductor power, shoulder pain and radial nerve function could easily be recorded. One must of course realize that increasing or complicating the reporting process can affect surgeons' motivation to report follow-up, but improving the follow-up form does not necessarily mean it would take longer to fill in.

Even without changes to the SOSD, there are still many areas of interest to be studied with the current data set. As the database grows and follow-up hopefully increases, results will be more reliable and the SOSD promises to continue to be an important source of information on trauma surgery in LMIC.

7.2 Documenting the need for and cost effectiveness of surgery in LIC.

Despite the large burden of trauma and surgical disease in LMICs, surgery has not been a priority in global health. Though several reports have documented the need for surgery in LICs (see 1.2 and 1.3) there is an urgent need for more documentation to bring surgery into the mainstream of the global health discussion. Unless a larger body of research is produced in this field from LICs, surgery is bound to continue to lose in the competition for funds with communicable diseases like HIV, TB and malaria. There is a pressing need for more documentation of the negative consequences of the absence of surgical services in LIC, as well as demonstrating that surgery in LICs is cost effective.

7.3 Stimulating clinical research on surgery in LIC.

Though surgical techniques introduced to a low-income country usually are well proven in high-income countries, documenting outcomes after the introduction of the same techniques to a LIC can be important for several reasons. First, it can identify problems that need to be addressed for the safe introduction of specific techniques in low-resource settings. Secondly, documenting outcomes of surgery in LICs similar to those in HICs is important in advocating inclusion of surgery as an essential part of national and global health planning. Thirdly, stimulating research in LICs is a way of empowering local clinicians and academic institutions to take charge and search for information important in their own setting. On-going clinical research is necessary to check the quality of services being provided and the consequences of a service not being provided in a country. Lastly, orthopaedic surgery in high-income countries is heavily influenced by the surgical implant industry. This affects both indications for surgery and the choice of implants. In LMICs one is forced to pay much more attention to the cost of the surgery, and one is more likely to end up with older technology, and perhaps inferior quality implants. The research being done now in HICs, on implants that are usually not available in LICs, might therefore not be as relevant to surgeons in LICs. On the other hand, results from LMICs might in the future show equally good results with much cheaper technology.

7.4 Documenting results in HIV positive patients

Our knowledge on the outcomes of surgery in HIV-positive patients is largely based on a few small studies with inconclusive results (see 1.7). Many of these studies are old and based on cohorts of haemophilia patients further making the validity of the results uncertain. Larger prospective studies, including data on CD4/CD8 and viral load values and duration and type of ART medication, are needed to document the real risks of complications for HIV patients undergoing surgery, so that we can address risk factors and improve the outcomes for these patients. With sufficient funding a prospective international multicentre study using the SOSD in Southern Africa, possibly under the umbrella of the College of Surgeons of East, Central and Southern Africa (COSECSA), could give reliable results in a relatively short timeframe.

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9. Papers I – III

I

Paper I:

Young S, Lie SA, Hallan G, Zirkle LG, Engesæter LB, Havelin LI. Low infection rates after 34,361 intramedullary nail operations in 55 low- and middle-income countries. Validation of the Surgical Implant Generation Network (SIGN) Online Surgical Database. Acta Orthop 2011; 82 (6): 737-43.

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Low infection rates after 34,361 intramedullary nail operations in 55 low- and middle-income countries

Validation of the Surgical Implant Generation Network (SIGN) Online Surgical Database

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Background The Surgical Implant Generation Network (SIGN) supplies intramedullary (IM) nails for the treatment of long bone fractures free of charge to hospitals in low- and middle-income countries (LMICs). Most operations are reported to the SIGN Online Surgical Database (SOSD). Follow-up has been reported to be low, however. We wanted to examine the pattern of follow-up and to assess whether infection rates could be trusted.

Patients and methods The SOSD contained 36,454 IM nail surgeries in 55 LMICs. We excluded humerus and hip fractures, and fractures without a registered surgical approach. This left 34,361 IM nails for analysis. A generalized additive regression model (gam) was used to explore the association between follow-up rates and infection rates.

Results The overall follow-up rate in the SOSD was 18.1% (95% CI: 17.7–18.5) and national follow-up rates ranged from 0% to 74.2%. The overall infection rate was 0.7% (CI: 0.6–0.8) for femoral fractures and 1.2% (CI: 1.0–1.4) for tibial fractures. If only nails with a registered follow-up visit were included (n = 6,224), infection rates were 3.5% (CI: 3.0–4.1) for femoral fractures and 7.3% (CI: 6.2–8.4) for tibial fractures. We found an increase in infection rates with increasing follow-up rates up to a level of 5%. Follow-up above 5% did not result in increased infection rates.

Interpretation Reported infection rates after IM nailing in the SOSD appear to be reliable and could be used for further research. The low infection rates suggest that IM nailing is a safe procedure also in low- and middle-income countries.

Approximately 2.6 million people between the ages of 10 and 24 died globally in 2004. 97% of these lived in low- and middle-income countries (LMICs). 259,000 people in the same age group died in traffic accidents alone. 22% of all deaths in young people are a result of injury, twice as many as those from HIV/AIDS and tuberculosis combined (Patton et al. 2009). For every death resulting from injury, one can expect 3–50 times as many people living with disability as a result of the same injury (Kobusingye et al. 2001, Peden 2004, Gosselin et al. 2009b). Many of these deaths and disabilities could be prevented with better surgical trauma care. However, the funding of this has been neglected by policy makers and international donors, who in previous decades have focused almost entirely on the prevention of communicable disease and primary care (Debas et al. 2006, Mock and Cherian 2008, Ozgediz and Riviello 2008). As an answer to the challenge of increasing orthopedic trauma globally, since 1999 the Surgical Implant Generation Network (SIGN) has been supplying orthopedic implants and training free of charge to over 130 hospitals in more than 50 low- and middle-income countries (Zirkle 2008). SIGN produces a solid stainless steel, interlocking intramedullary (IM) nail for the treatment of long bone factures; it can be inserted and locked without the use of an image intensifier (Ikem et al. 2007, Feibel and Zirkle 2009). Initially, re-ordering of used implants was done by mail. This was a slow and cumbersome process, and from 2003 the SIGN online surgical database (SOSD) was set up to register the surgeries done and to ease communication with SIGN surgeons worldwide (Shearer et al. 2009). To date, over 36,000 SIGN nail surgeries have been registered in the SOSD. To our knowledge, this makes the SOSD the biggest database on trauma in LMICs in the world. With the exception of some relief organizations that buy the nails from SIGN at the price of the production costs, all surgeons must report their operations to ensure re-supply of the used nails and locking screws free of charge from SIGN. There is therefore a strong

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incentive to register all surgeries, and the degree of reporting in 2009 was over 95% (SIGN 2011). However, reporting of follow-up carries no real incentive and Shearer et al. (2009) reported a minimum 1-month follow-up rate of only 12.6% in 2009. For this reason, some previous researchers have questioned the validity of using the SOSD for outcome measures (Shearer et al. 2009, Clough et al. 2010).

A strong argument against the use of modern orthopedic surgical trauma care, apart from the cost of the implants and the lack of personnel, has been the fear of infection. There have, however, been very few studies of good quality determining the infection rates after orthopedic surgery in low-income countries. Even though some authors have reported disturbingly high rates of postoperative infections in general and in gynecological surgery in LMICs (Reggiori et al. 1996, Eriksen et al. 2003), others have shown infection rates in orthopedic surgery matching those in high-income countries (Saris et al. 2006, Gross et al. 2010).

If it can be trusted, the huge amount of data available in the SOSD might help to give a better picture of the real risk of infection after IM nailing in LMICs. The object of this study was to describe the pattern of follow-up in the SOSD and to discuss whether the data registered—in light of the low reported follow-up rates—can be used in future in-depth research into infection rates and risk factors.

Patients and methods

Following ethical approval by the Norwegian regional research ethics committee (20.09.10, no.2010/2040), SIGN supplied us with a data file containing an anonymous export of all surgeries registered in the SOSD from the start of the registry to October 8, 2010. The SOSD then contained surgeries involving 36,454 SIGN IM nails. 834 nails did not have the surgical approach registered. 1,228 of the nails registered involved hip, humerus, or other fracture operations. They were excluded because the numbers in each country were low, and inclusion of only tibia and femur fractures was considered more reliable for analysis. Only 2 high-income countries had registered use of SIGN nails in the SOSD. USA and Australia had registered 22 and 9 nails, respectively, and only 1 of the nails had follow-up data. Nails from these countries were therefore excluded. Remaining for analysis were 34,361 nails of the tibia or femur in 55 low- and middle-income countries with widely differing follow-up rates. Infection at follow-up in the SOSD is registered as being superficial or deep. The definition of these is at the discretion of the surgeon. Because of unclear definitions and diagnostics, and because the total infection rate was sufficient for the validation of the data in the SOSD, we did not make a distinction between the two in this study.

Statistics

The Chi-square test was used to compare the rates of follow-up in 2 different groups. Where data were insufficient to use the Chi-square test, Fisher's exact test was used. The Student t-test was used to compare means in 2 groups. Logistic regression was used to compare rates in more than 2 groups. All p-values were 2-tailed and the level of statistical significance was set to 5% ($p < 0.05$). Simple descriptive statistics were used using SPSS software version 18.0.

Calculations of the follow-up rates over time were based on fixed effects in a mixed-effects Poisson regression model. The follow-up rates were analyzed using the number of follow-ups in a given time interval, and for a specific country, as a dependent variable in the analysis and the log of the total number of fractures at risk at a given time as offset in the analyses. Country was entered in the model as a random factor. Infection rates were calculated in the same way, with infection as outcome. To visualize the relation between the follow-up rates and the risk of infection, we used a generalized additive regression model (gam), with a spline smoothing of the follow-up rates compared to the risk of infection. These analyses were done using the lme4 and the mgcv libraries in the statistical program R, version 2.12.2 (R Development Core Team 2010).

Results

The total follow-up rate (i.e. the percentage of IM nail operations with at least 1 registered follow-up visit) for all nails registered in the SOSD in October 2010 was 18.1% (CI: 17.7–18.5), and national rates ranged from 0% to 74.2%. The overall infection rate, expressed as the percentage of all registered nails that had a registered infection at follow-up, was 0.7% (CI: 0.6–0.8) for femoral fractures and 1.2% (CI: 1.0–1.4) for tibial fractures. When only nails with at least one registered follow-up visit ($n = 6,224$) were counted in the calculation of infection rates, the rates of infection were 3.5% (CI: 3.0–4.1) for femoral fractures and 7.3% (CI: 6.2–8.4) for tibial fractures. Countries that reported SIGN surgeries to the SOSD are listed in Table 1, along with the total number of operations registered, follow-up, and infection rates.

No large differences in follow-up rates were seen between men and women, although we found that in Asia there was a statistically significant tendency for more women than men to return for follow-up. There were also regional differences in the proportion of female patients operated (Table 2).

Mean age at surgery in patients returning for follow-up was 33 (SD 14) years; in patients who did not have a registered follow-up it was 35 (SD 15) years ($p < 0.001$) (Table 3). Logistic regression analysis showed that there was a statistically significant association between increasing age and less follow-up.

The mixed-effects Poisson regression model showed that most follow-up in the SOSD occurred in the first 2 months after surgery (Figure 1). Most infections were detected in a bimodal pattern at this time, and between 6 and 12 months after surgery (Figure 2).

Table 2. Total number of SIGN nails and follow-up according to sex, geographic region, and income level of country

Region / income level [a]	Total no.	No. of women (%)	Total no. followed up (%)	No. of females followed up (%)	p-value [b]
Africa	8,146	1,815 (22.3)	1,811 (22.3)	403 (22.3)	1.0
Asia	23,484	3,828 (16.3)	4,207 (17.9)	785 (18.7)	< 0.001
Latin America	2,552	390 (15.3)	200 (7.8)	26 (12.5)	0.3
Europe	179	64 (34.6)	6 (3.4)	1	0.7 [c]
Low-income	18,152	3,496 (19.3)	4,365 (24.1)	889 (20.4)	0.03
Lower middle-income	13,391	2,032 (15.2)	1,645 (12.3)	283 (17.2)	0.01
Higher middle-income	2,818	567 (20.1)	214 (7.6)	42 (19.6)	0.9
Total SOSD	34,361	6,095 (17.7)	6,224 (18.1)	1,214 (19.9)	< 0.001

[a] Income level as defined by the World Bank 2009.
[b] Chi-square test, gender against follow-up.
[c] Fisher's exact test.

Table 3. Follow-up for each age group compared to the < 20-year age group

Age group	n	Follow-up (%)	p-value [a]
< 20 years	4,237	824 (19.4)	< 0.001 [b]
20–29 years	11,645	2,161 (18.6)	0.2
30–39 years	7,770	1,510 (19.4)	1.0
40–49 years	4,940	902 (18.3)	0.2
50–59 years	2,823	451 (16.0)	< 0.001
≥ 60 years	2,946	376 (12.8)	< 0.001
Total	34,361	6,224 (18.1)	

[a] logistic regression.
[b] overall test.

The relationship between the follow-up rates and the risk of infection, when examined in the generalized additive regression model (gam), showed that increasing national follow-up rates resulted in increasing infection rates up to a follow-up rate of approximately 5%. Follow-up rates above this did not give higher infection rates (Figure 3). This was apparent also when looking at each point in time separately.

Discussion

Our main findings were that the infection rates in the SOSD were low and that, when we used a generalized additive regression model (gam) to look at the effects of increasing follow-up, countries with follow-up exceeding approximately 5% in the SOSD did not have statistically significantly increased infection rates with increasing follow-up. This can probably not be interpreted as if 5% follow-up in itself, in any individual center or country, is enough to catch all infections. However, it might lend support to a common notion among surgeons in low-income countries that a large proportion of people who have complaints come back for review, whereas those who do not have complaints do not return because of—among other things—the high cost of transport (Shearer et al. 2009). In some low-income countries, where large proportions of the population live on sustenance farming and have little or no cash income, many villagers will not have the money even for a local bus ticket (Gosselin 2009). It is understandable that walking many kilometers to sit in a hospital queue, sometimes for several days before being seen, may not be a high priority if people do not have a serious problem. On the other hand, a low-grade infection of an IM nail leads to pain, swelling, joint stiffness, and fistula secretion—and an acute, deep infection will make the patient very ill. In both of these situations, it is more likely that the patients will try to return to the hospital.

In a limited resource setting, one cannot expect the same follow-up rates in research as in high-income countries and a higher level of uncertainty must be accepted. If interpretation of our findings as we do above is valid, then the average national follow-up rates of approximately 18% would imply that a large (but unknown) proportion of patients with infections have returned for follow-up and in effect that the infection rates in the SOSD appear to be relatively trustworthy. However, the infection rates of 0.7% (for the femur) and 1.2% (for the tibia) in countries where the frequency of open fractures, delayed surgery, nonunions, malnutrition, and immunosuppression is known to be high may be difficult to believe for most orthopedic surgeons. When all nails without follow-up were excluded, the rates of postoperative infection were 3.5% for femoral fractures and 7.3% for tibial fractures. Even these rates are acceptable in this context, but the true infection rates probably lie somewhere between these rates. If patients with complaints really do return for follow-up more than those without complaints, this conservative estimate should be biased towards worse outcomes. On the other hand, some patients with infection are most probably lost to follow-up either because poverty forces them to live with their low-grade infection, they get treated elsewhere, or they migrate or die, and the true figures are bound to be somewhat higher than 0.7% and 1.2%. In our opinion, this is not likely to be a large

Table 1. Number of femur and tibia SIGN nail operations, follow–up, and infection rates by country in the SOSD in October 2010

Country	Bone	Nails N	Follow-up n	%	(95% CI)	Infected %	(95% CI)
Afghanistan	Femur	893	138	16	(13–18)	1.6	(0.8–2.4)
	Tibia	698	109	16	(13–18)	1.7	(0.7–2.7)
Bangladesh	Femur	1,111	299	27	(24–30)	1.2	(0.6–1.8)
	Tibia	211	48	23	(17–28)	4.7	(1.8–7.6)
Belarus	Femur	28	1	4	(0–11)	0.0	(0.0–0.0)
	Tibia	150	5	3	(0.4–6)	0.0	(0.0–0.0)
Bhutan	Femur	39	8	21	(8–33)	2.6	(0.0–7.6)
	Tibia	126	29	23	(16–30)	1.6	(0.0–3.8)
Cambodia	Femur	2,478	550	22	(21–24)	0.7	(0.4–1.0)
	Tibia	1,587	275	17	(15–19)	0.6	(0.2–1.0)
Cameroon	Femur	309	35	11	(8–15)	0.3	(0.0–0.9)
	Tibia	116	12	10	(5–16)	1.7	(0.0–4.1)
Dominican Republic	Femur	847	22	3	(2–4)	0.5	(0.0–1.0)
	Tibia	168	4	2	(0.1–5)	0.0	(0.0–0.0)
Egypt	Femur	47	4	9	(1–17)	0.0	(0.0–0.0)
	Tibia	120	9	8	(3–12)	0.0	(0.0–0.0)
Ethiopia	Femur	347	142	41	(36–46)	1.7	(0.4–3.1)
	Tibia	139	52	37	(29–45)	2.9	(0.1–5.7)
Guatemala	Femur	320	10	3	(1–5)	0.3	(0.0–0.9)
	Tibia	200	8	4	(1–7)	1.5	(0.0–3.2)
Haiti	Femur	297	37	13	(9–16)	0.7	(0.0–1.7)
	Tibia	90	1	1	(0–3)	0.0	(0.0–0.0)
India	Femur	348	12	3	(2–5)	0.3	(0.0–0.9)
	Tibia	652	22	3	(2–5)	0.2	(0.0–0.5)
Indonesia	Femur	434	57	13	(10–16)	0.0	(0.0–0.0)
	Tibia	239	37	16	(11–20)	0.0	(0.0–0.0)
Iran	Femur	223	0	0	(0–0)	0.0	(0.0–0.0)
	Tibia	254	1	0.4	(0–1)	0.0	(0.0–0.0)
Iraq	Femur	137	69	50	(42–59)	0.7	(0.0–2.1)
	Tibia	71	38	54	(42–65)	8.5	(2.0–15)
Kenya	Femur	1,849	250	14	(12–15)	0.8	(0.4–1.2)
	Tibia	742	169	23	(20–26)	3.2	(1.9–4.5)
Malawi	Femur	236	46	20	(15–25)	1.3	(0.0–2.8)
	Tibia	66	10	15	(7–24)	1.5	(0.0–4.4)
Mongolia	Femur	229	9	4	(1–6)	0.9	(0.0–2.1)
	Tibia	306	12	4	(1–6)	0.3	(0.0–0.9)
Mozambique	Femur	131	11	8	(4–13)	0.8	(0.0–2.3)
	Tibia	12	1	8	(0–24)	0.0	(0.0–0.0)
Myanmar	Femur	1,508	343	23	(21–25)	0.7	(0.3–1.1)
	Tibia	1,234	232	19	(17–21)	1.1	(0.5–1.7)
Nepal	Femur	624	251	40	(36–44)	1.0	(0.2–1.8)
	Tibia	909	435	48	(45–51)	3.0	(1.9–4.1)
Nicaragua	Femur	165	12	7	(3–11)	0.0	(0.0–0.0)
	Tibia	238	18	7	(4–11)	0.0	(0.0–0.0)
Niger	Femur	122	16	13	(7–19)	0.0	(0.0–0.0)
	Tibia	43	6	14	(4–24)	0.0	(0.0–0.0)
Nigeria	Femur	412	49	12	(9–15)	0.0	(0.0–0.0)
	Tibia	147	23	16	(10–22)	0.0	(0.0–0.0)
Pakistan	Femur	1,493	313	21	(19–23)	0.9	(0.4–1.4)
	Tibia	1,187	203	17	(15–19)	1.2	(0.6–1.8)
Philippines	Femur	1,295	367	28	(26–31)	0.6	(0.2–1.0)
	Tibia	450	130	29	(25–33)	1.8	(0.6–3.0)
Russian Federation	Femur	380	56	15	(11–18)	0.3	(0.0–0.9)
	Tibia	420	49	12	(9–15)	0.0	(0.0–0.0)
South Africa	Femur	169	4	2	(0.1–5)	0.6	(0.0–1.8)
	Tibia	20	0	0	(0–0)	0.0	(0.0–0.0)
Swaziland	Femur	128	13	10	(5–15)	0.8	(0.0–2.3)
	Tibia	108	9	8	(3–14)	1.9	(0.0–4.5)
Tanzania	Femur	1,206	462	38	(36–41)	0.7	(0.2–1.2)
	Tibia	297	116	39	(34–45)	2.0	(0.4–3.6)
Thailand	Femur	91	25	28	(18–37)	0.0	(0.0–0.0)
	Tibia	72	8	11	(4–18)	1.4	(0.0–4.1)
Uganda	Femur	909	295	33	(30–36)	0.8	(0.2–1.4)
	Tibia	147	28	19	(13–25)	0.7	(0.0–2.1)

proportion of patients and should not dramatically affect the estimated infection rates. There might also be situations in which patients with an infection did in fact return for follow-up, but the surgeon did not report this. Even so, the analysis did not show increased infection rates in centers where the surgeons registered more follow-up.

We believe that our findings using the above statistical model give an indication that infection rates after IM nailing in LMIC are perhaps considerably lower than many surgeons think. The overall infection rates in the SOSD are comparable to results from the literature in high-income countries (Court-Brown et al. 1992, Jenny et al. 1994, Wolinsky et al. 1999), even in the higher end of the range indicated above (Malik et al. 2004). However, most centers in high-income countries are likely to have even lower infection rates. Winquist et al. (1984) reported an infection rate of 0.9% in a series from Seattle with 520 IM nails with 17% open fractures over 25 years ago, and in a prospective series of 172 IM nail operations in Boston (Tornetta and Tiburzi 2000), no infections were seen at all.

The established perception that postoperative infection rates are high in low-income countries might be fueled by surgeons' personal experiences of the many serious infections that are encountered in an orthopedic ward in many low-income countries. However, the abundance of chronic osteomyelitis, late-presented infected open fractures, and badly done internal fixation that one can experience in these settings should not let us conclude that properly done surgery, in correctly selected patients, with modern equipment, by well trained surgeons will have poor results. The necessary basis for safe orthopedic surgery such as autoclaves, antiseptic wash, and prophylactic antibiotics has become available at most hospitals, even in

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Table 1. Continued

Country	Bone	Nails N	Follow-up n	Follow-up %	Follow-up (95% CI)	Infected %	Infected (95% CI)
Vietnam	Femur	1,609	29	2	(1–3)	0.1	(0.0–0.3)
	Tibia	2,105	29	1	(1–2)	0.0	(0.0–0.0)
Countries with n < 100 [a]	Femur	393	99	25	(21–30)	0.8	(0.0–1.7)
	Tibia	230	62	27	(21–33)	4.3	(1.7–6.9)
Total	Femur	20,807	4,034	19.4	(18.9–19.9)	0.7	(0.6–0.8)
	Tibia	13,554	2,190	16.2	(15.6–16.8)	1.2	(1.0–1.4)
Total: femur andtibia combined		34,361	6,224	18.1	(17.7–18.5)	0.9	(0.8–1.0)

The 95% confidence intervals are based on linear calculations based on approximations to the normal distribution.
[a] To reduce the size of the table, all countries with less than 100 registered cases are grouped together.

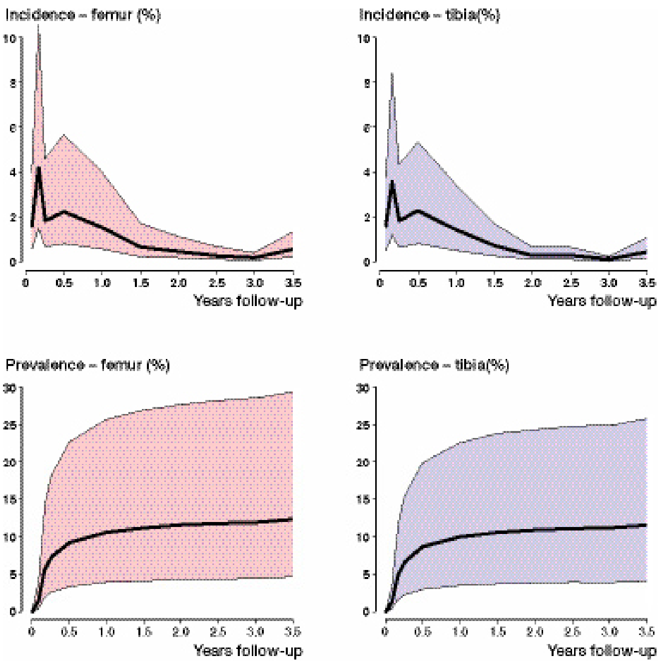

Figure 1. Poisson regression analysis. Pattern of follow-up rate over time for femur and tibia fractures in the SOSD. The color band signifies the 80% range of values between countries.

the poorest countries, and hospitals that insert SIGN nails have motivated surgeons well-trained in the technique. This has been shown to be the case in general surgery in a large randomized study of prophylactic antibiotics use in Uganda, where the rate of infection after inguinal hernia repair dropped from 7.5% to 0% with correct antibiotic usage (Reggiori et al. 1996).

Even with a high prevalence of complicated cases, we really see no reason why the infection rates should not be in the same range as those in high-income countries. In fact, a prospective multicenter study comparing results of a standardized IM nailing technique between a trauma center in South Africa and Europe showed lower complication rates in South Africa and identical infection rates despite more serious injuries (Gross et al. 2010). Follow-up at 3 months in that study was 81% in South Africa and 95% in Europe. One explanation for these good results might be the lower mean age and better general health of trauma victims in South Africa. Trauma is a growing epidemic among young people in LMICs (Peden 2004, Patton et al. 2009). In the SOSD, nearly half of the patients are below the age of 30 years. The young age of the victims makes it even more important to offer modern orthopedic trauma treatment in LMICs. Perhaps it might also promise good results.

The follow-up rate in the SOSD was relatively consistent across the younger age groups, but appeared to fall off in people over 50 years. The SOSD does not contain data that can answer why this might be. One might speculate that there may be cultural reasons for this or that older people—even less than young people—are willing or have the resources to return for follow-up without having serious complaints. However, both a lower complication rate in older people with low-energy fractures and wider IM canals, and a higher mortality rate because of age related diseases, could explain this finding.

There appear to be some regional differences in follow-up patterns in the SOSD. In Africa, more than one-fifth of patients return for follow-up whereas less than 1 in 12 return for review in Latin America. In the SOSD, a marginally larger proportion of women than men return for follow-up. When stratified by

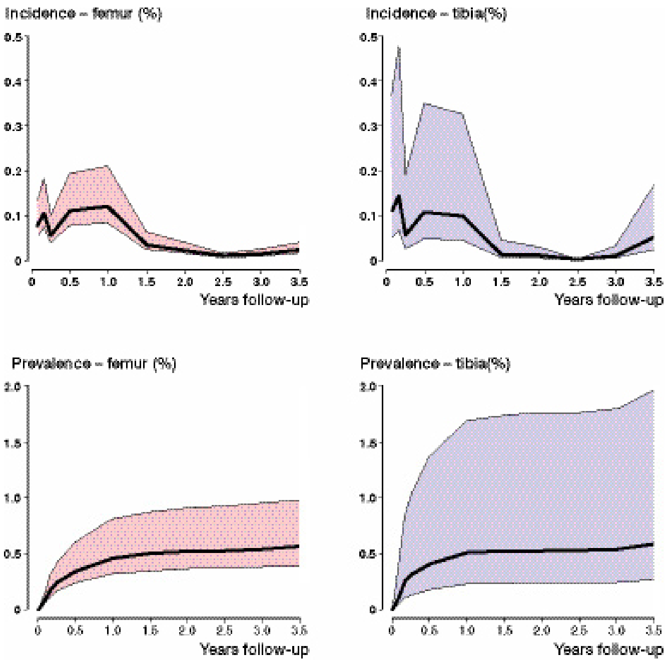

Figure 2. Poisson regression analysis. Pattern of infection rate for femur and tibia fractures over time in the SOSD. The color band signifies the 80% range of values between countries.

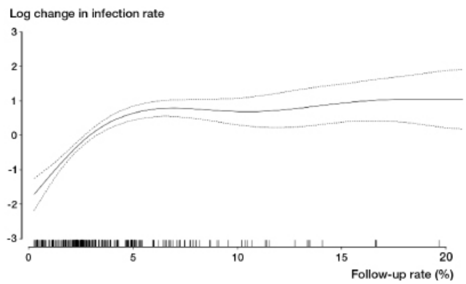

Figure 3. Follow-up rate plotted against log change in the infection rate. The curve is based on a generalized additive regression model (gam). Dotted lines represent 95% CI. With follow-up over 5%, there is very little increase in infection rate and the curve is consequently nearly horizontal. Short vertical lines on x-axis represent observations in different countries.

regions, however, this tendency could only be seen in Asia. In Africa there was no difference in follow-up according to gender, and in Latin America there was seemingly a lower proportion of women who returned for follow-up than men. This, however, was not statistically significant with the current number of cases in the SOSD. Whether these small regional differences in women's return for follow-up are the result of cultural differences or of the economic and political state of the countries involved is not possible to answer with our study design. Stratification of countries according to income level does not appear to give more information, although the small differences seen in Table 2 were statistically significant for low-income and lower middle-income countries.

The present study had obvious limitations, the largest one being the low follow-up rate itself; which is the subject of this paper. We had to make several assumptions that may or may not be correct. We grouped superficial and deep infections together on the assumption that if they are reported, they are serious enough to be of clinical importance and we assumed that if a patient returns with a complaint it will be registered in the SOSD. All these factors introduce uncertainty into the analyses and conclusions, but we believe that the statistical models we used give strong indications that the data is complete enough to use for further studies into results and risk factors of IM nailing in LMIC. In addition, the SIGN is working hard to increase the level of follow-up. This, combined with the ever-increasing numbers in the SOSD, should help to give us more precise figures in future studies.

Very little research has been published on the results of the use of IM nails in a low-resource setting. Those studies that have been published, however, indicate that this is cost-effective treatment (Gosselin et al. 2009a) with results comparable to those found in high-income countries (Shah et al. 2004, Ikem et al. 2007, Ikpeme et al. 2011). In a world in which the growing burden of orthopedic trauma is occurring mostly in LMICs, and the safety of doing orthopedic procedures in a low-resource setting is not yet universally accepted, it is important to encourage good-quality research in order to shed light on these issues. Registry studies with large numbers of patients can demonstrate small differences in treatment outcomes sooner than smaller studies. To our knowledge, the SOSD is the largest orthopedic trauma database containing information on surgery in LMICs. It contains a wealth of information on intramedullary nail operations in over 50 countries, and presents a unique opportunity for future research to evaluate the safety and effect of orthopedic trauma surgery in general, and in low- and middle-income countries in particular. However, results from trauma registries, including the SOSD, should be confirmed by more detailed prospective studies with better follow-up. We are currently conducting such a study in Malawi.

In conclusion, it seems safe to use the data in the SOSD for studies examining infection after IM nailing in limited-resource settings, and the low infection rates in the SOSD indicate that IM nailing is a safe procedure also in low- and middle-income countries. We consider it important that more research is published on surgery in LMICs to inform policy makers and the large multilateral donors in these countries of the impact of many years of neglect of the surgical field, and the safety and good effect of modern treatment.

SY: study design, descriptive statistics, first manuscript draft, and revisions. SAL: study design, statistical modeling, Poisson regression analysis, writing of statistics section, and manuscript revision. GH, LGZ, LBE, LIH: study design and manuscript revisions. All authors contributed to critical analysis and interpretation of the data and statistics.

We thank all the surgeons who register operations and follow-up in the SOSD, and who make it possible to do research into the safety of modern orthopedic trauma surgery in low- and middle-income countries.

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II

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Risk Factors for Infection after 46,113 Intramedullary Nail Operations in Low- and Middle-income Countries

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Abstract

Background The fields of surgery and trauma care have largely been neglected in the global health discussion. As a result the idea that surgery is not safe or cost effective in resource-limited settings has gone unchallenged. The SIGN Online Surgical Database (SOSD) is now one of the largest databases on trauma surgery in low- and middle-income countries (LMIC). We wished to examine infection rates and risk factors for infection after IM nail operations in LMIC using this data.

Methods The SOSD contained 46,722 IM nail surgeries in 58 different LMIC; 46,113 IM nail operations were included for analysis.

Results The overall follow-up rate was 23.1 %. The overall infection rate was 1.0 %, 0.7 % for humerus, 0.8 % for femur, and 1.5 % for tibia fractures. If only nails with registered follow-up ($n = 10{,}684$) were included in analyses, infection rates were 2.9 % for humerus, 3.2 % for femur, and 6.9 % for tibia fractures. Prophylactic antibiotics reduced the risk of infection by 29 %. Operations for non-union had a doubled risk of infection. Risk of infection was reduced with increasing income level of the country.

Conclusions The overall infection rates were low, and well within acceptable levels, suggesting that it is safe to do IM nailing in low-income countries. The fact that operations for non-union have twice the risk of infection compared to primary fracture surgery further supports the use of IM nailing as the primary treatment for femur fractures in LMIC.

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Introduction

Approximately 5.8 million people die annually as the result of injuries, more people than die of HIV/AIDS, tuberculosis, and malaria combined [1, 2]. Over 90 % of these fatal injuries occur in low- and middle-income countries (LMIC). For every death from injury, 3–10 more people survive injury with a permanent disability [3, 4]. In young people between the ages of 10 and 24 years as many as 97 % of deaths occur in LMIC, over 40 % of deaths are related to injuries, and road traffic injuries are the most common cause [5]. The global burden of injuries is growing rapidly, and almost entirely in LMIC. By 2030 the World Health Organization (WHO) expects traffic accidents to have risen from the ninth to the fifth leading cause of all deaths globally [6]. Despite these compelling facts, surgery is not mentioned at all in the Millennium Development Goals (MDGs: http://www.un.org/millenniumgoals/) [7, 8]. At present, however, we are seeing increasing awareness of surgery as an integral part of the global public health effort to reach the MDGs [8–12]. Injuries disproportionately affect the younger segment of the population in LMIC and have a serious impact on the whole families of the injured. In LMIC with no functioning social security systems, the injury of a young mother or father, often the breadwinner of the family, can be devastating to their economic situation and push them further into poverty [13].

In high-income countries intra-medullary (IM) nailing of femoral shaft fractures is an established gold standard. However, the cost of IM nails and the fear of postoperative infection has prohibited their use in most LMIC, where traction most often still is the only treatment offered for femoral fractures [14, 15]. In orthopedic surgery, skills and training are useless without the equipment to do the job. This is recognized by SIGN Fracture Care International (SIGN) which has developed a US Food and Drug Administration (FDA) approved IM nail specifically designed for use in resource- poor settings without the use of an image intensifier [16]. SIGN has provided over 80,000 IM nails, and training in their use, to over 200 hospitals in LMIC free of charge since 1999 (numbers; personal communication from SIGN, February 2012) [17]. Although there is growing evidence that orthopedic trauma surgery is necessary, safe, and cost-effective also in LMIC [18–21], more research is needed to confirm these findings and to bring this knowledge into the mainstream global health discussion. As a part of the resupply service for the hospitals supported by SIGN, the SIGN online surgical database (SOSD) was started in 2003. There are now over 46,000 registered IM nail operations in this database, making it possibly the largest available database on orthopedic trauma care in LMIC. Despite a fairly limited follow-up rate (18.1 % in 2010), validation of the data in the SOSD has suggested that it is reliable and can be used for further research [21]. The aim of the present study was to use the data in the SOSD to investigate whether the follow-up and infection rates are changing, and to identify risk factors for infection after IM nail operations in LMIC.

Methods

SIGN provided us with an anonymous export of all surgeries registered in the SOSD from the start of the registry in 2003 up to November 29, 2011. Ethical approval for this study was given by the Norwegian regional research ethics committee (20.09.10, 2010/2040). The SOSD at the time of export contained data on 46,722 IM nail operations. 562 operations were for hip fractures or did not have a registered surgical approach and were excluded. As only 47 operations were done in high-income countries (USA 38, Australia 9), and only one of these cases had a registered follow-up, these cases were also excluded. This left 46,113 IM nail operations of the humerus, femur, or tibia to be included for analysis. An overview of the included cases and risk factors is presented in Table 1.

Infection was registered in the SOSD at the time of follow-up. Possible risk factors for infection after orthopedic trauma surgery, including age, gender, surgical approach, use of antibiotics, and operating techniques were included as variables in the analyses. Open fractures in the SOSD were classified according to Gustilo and Anderson [22]. Surgeons classified infections as superficial or deep in the SOSD; however, this distinction did not follow a strict classification. We therefore grouped all registered infections together on the assumption that registered infections are likely to be clinically significant. The duration of the operative procedure was not registered in the SOSD, but surgeons did subjectively classify a fracture as a non-union or not at the time of surgery. Non-union may be a risk factor in itself, or it might be an indirect measure of increased operating time, and it was therefore analyzed as a separate risk factor. The SIGN IM nail system uses an external target arm and “slot finder” instruments to place the distal locking screws in the nail. This technique can be challenging at times and can prolong operating time. The number of distal locking screws (0, 1, or 2) was therefore also included as another possible indirect measure of operating time.

Statistics

The χ^2 test was used to compare rates in two different groups, and Student’s *t* test was used to compare means in two groups. Logistic regression was used to compare rates in more than two groups and to calculate both crude and adjusted risk, odds ratio (OR), of infection. All *p* values were two-tailed, and the level of statistical significance was set to 5 % ($p < 0.05$). Analyses were performed with IBM SPSS Statistics version 19.0 (SPSS Inc., Chicago, IL).

Results

A total of 46,133 IM nail operations were included, 1,381 operations of the humerus, 27,350 of the femur, and 17,382 of the tibia. Only 18.8 % of operations were in women. The mean age of the patients was 34.7 (SD 15.2) years, 40.6 (SD 18.6) years for women and 33.3 (SD 14.0) years for men ($p < 0.001$).

The total follow-up rate, defined as the percentage of IM nail operations with at least one registered follow-up visit, for all nails registered in the SOSD in November 2011 was 23.1 % (95 % CI: 22.7–23.5), this is an increase from one year before, when the follow-up rate in the SOSD was 18.1 %. The mean time to follow-up was 215 (SD 293) days, median 100 (range: 1–3,309) days. The over all infection rate was 1.0 % (95 % CI: 0.9–1.1); 0.7% (95 % CI: 0.6–0.8) for the humerus, 0.8 % (95 % CI: 0.7–0.9) for

Table 1 Overview of included cases in the SIGN online surgical database

	Number of operations (%)	Number with follow-up (rate in %)	Number of open fractures (rate in %)	Number of infections (rate in %)
Included operations in SOSD	46,113 (100)	10,684 (23.1)	7,831 (17.0)	479 (1.0)
Age				
<30 years	20,896 (45.3)	5,029 (24.1)	3,822 (18.3)	216 (1.0)
≥30 years	25,217 (54.7)	5,655 (22.4)	4,009 (15.9)	263 (1.0)
Gender				
Female	8,664 (18.8)	2,213 (25.5)	1,080 (12.5)	71 (0.8)
Male	37,449 (81.2)	8,471 (22.6)	6,751 (18.0)	408 (1.1)
Approach				
Antegrade humerus	1,381 (3.0)	310 (22.4)	110 (8.0)	9 (0.7)
Antegrade femur	17,450 (37.8)	4,355 (25.0)	1,431 (8.2)	130 (0.7)
Retrograde femur	9,900 (21.5)	2,292 (23.2)	1,230 (12.4)	84 (0.8)
Tibia	17,382 (37.7)	3,727 (21.4)	5,060 (29.1)	256 (1.5)
Prophylactic antibiotics				
No	6,538 (14.2)	8,666 (21.9)	7,478 (18.9)	78 (1.2)
Yes	39,575 (85.8)	2,018 (30.9)	353 (5.4)	401 (1.0)
Fracture reduction				
Closed	12,216 (26.5)	8,314 (19.4)	5,814 (17.1)	102 (0.8)
Open	33,897 (73.5)	2,370 (24.5)	2,017 (16.5)	377 (1.1)
Reaming method				
None	3,996 (8.7)	472 (11.8)	1,169 (29.2)	31 (0.8)
Hand	41,593 (90.2)	10,033 (24.1)	6,592 (15.8)	440 (1.1)
Power	524 (1.1)	179 (34.2)	70 (13.3)	8 (1.5)
Operation for non-union				
No	41,441 (89.9)	1,350 (28.9)	470 (10.0)	379 (0.9)
Yes	4,672 (10.1)	9,334 (22.5)	7,361 (17.8)	100 (2.1)
Gustilo–Anderson grade				
Closed	38,297 (83.1)	8,881 (23.2)	–	293 (0.8)
Open grade 1	2,777 (6.0)	595 (21.4)	2,777 (6.0)	40 (1.4)
Open grade 2	2,936 (6.4)	681 (23.2)	2,936 (6.4)	69 (2.4)
Open grade 3a	1,562 (3.4)	383 (24.5)	1,562 (3.4)	48 (3.1)
Open grads 3b	467 (1.0)	125 (26.8)	467 (1.0)	24 (5.1)
Open grade 3c	74 (0.2)	19 (25.7)	74 (0.2)	5 (6.8)
Country income level [a]				
Low-income countries	25,751 (55.8)	7,197 (27.9)	4,192 (16.3)	309 (1.2)
Lower middle- income countries	17,083 (37.0)	3,168 (18.5)	3,231 (18.9)	153 (0.9)
Higher middle-income countries	3,279 (7.1)	319 (9.7)	393 (12.0)	17 (0.5)

[a] Country income level according to World Bank 2009

the femur, and 1.5 % (95 % CI: 1.4–1.6) for the tibia. Crude and adjusted risks of infection for different risk factors are presented in Table 2. If only nails with registered follow-up ($n = 10\,684$) were included, infection rates were 2.9 % for fractures of the humerus (95 % CI: 2.6–3.2), 3.2 % (95 % CI: 2.9–3.5) for those of the femur, and 6.9 % (95 % CI: 6.4, 7.4) for those of the tibia.

The crude risk of infection for men was 33 % higher than for women (OR 1.33, 95 % CI 1.04–1.72; $p = 0.026$), but this apparent increased risk marginally lost statistically significance when adjusted for the other risk factors in Table 2 (OR 1.29, 95 % CI 1.00–1.66; $p = 0.053$).

There were 17.0 % open fractures in this study. An open fracture of any grade gave a 3.16 times increased adjusted risk of infection (OR 3.16, 95 % CI 2.62–3.80; $p < 0.001$). The increased risk of infection rose from 1.86 times for a Gustilo type 1 fracture to 7.61 times increased risk for Gustilo type 3c fracture (Table 2). Fractures defined by the

Table 2 Crude and adjusted risk of infection

	No. operations (%)	No. infections (rate in %)	Crude odds ratio (95 % CI)	*p* value	Adjusted odds ratio (95 % CI)	*p* value
All included operations in SOSD	46,113 (100)	479 (1.0)				
Age (years)						
<30	20,896 (45.3)	216 (1.0)	1		1	
≥30	25,217 (54.7)	263 (1.0)	1.01 (0.84–1.21)	0.92	1.01 (0.84–1.21)	0.96
Gender						
Female	8,664 (18.8)	71 (0.8)	1		1	
Male	37,449 (81.2)	408 (1.1)	1.33 (1.04–1.72)	0.026	1.29 (1.00–1.66)	0.053
Approach						
Antegrade humerus	1,381 (3.0)	9 (0.7)	0.87 (0.44–1.72)	0.70	0.88 (0.45–1.75)	0.72
Antegrade femur	17,450 (37.8)	130 (0.7)	1	<0.001[a]	1	<0.001[a]
Retrograde femur	9900 (21.5)	84 (0.8)	1.14 (0.87–1.50)	0.35	1.13 (0.86–1.50)	0.38
Tibia	17,382 (37.7)	256 (1.5)	1.99 (1.61–2.46)	<0.001	1.71 (1.36–2.15)	<0.001
Prophylactic antibiotics						
No	6,538 (14.2)	78 (1.2)	1		1	
Yes	39,575 (85.8)	401 (1.0)	0.85 (0.66–1.08)	0.19	0.71 (0.55–0.91)	0.008
Fracture reduction						
Closed	12,216 (26.5)	102 (0.8)	1		1	
Open	33,897 (73.5)	377 (1.1)	1.34 (1.07–1.66)	0.010	1.23 (0.97–1.55)	0.083
Reaming method						
None	3,996 (8.7)	31 (0.8)	1	0.14[a]	1	0.14[a]
Hand	41,593 (90.2)	440 (1.1)	1.37 (0.95–1.97)	0.093	1.41 (0.96–2.06)	0.076
Power	524 (1.1)	8 (1.5)	1.98 (0.91–4.34)	0.086	1.92 (0.86–4.25)	0.11
Operation for non-union						
No	41,441 (89.9)	379 (0.9)	1		1	
Yes	4,672 (10.1)	100 (2.1)	2.37 (1.90–2.96)	<0.001	2.31 (1.83–2.91)	<0.001
Gustilo–Anderson grade						
Closed	38,297 (83.1)	293 (0.8)	1	<0.001[a]	1	<0.001[a]
Open grade 1	2,777 (6.0)	40 (1.4)	1.90 (1.36–2.64)	<0.001	1.86 (1.32–2.62)	<0.001
Open grade 2	2,936 (6.4)	69 (2.4)	3.12 (2.40–4.07)	<0.001	2.98 (2.25–3.94)	<0.001
Open grade 3a	1,562 (3.4)	48 (3.1)	4.11 (3.02–5.60)	<0.001	4.00 (2.90–5.50)	<0.001
Open grads 3b	467 (1.0)	24 (5.1)	7.03 (4.59–10.77)	<0.001	6.08 (3.92–9.43)	<0.001
Open grade 3c	74 (0.2)	5 (6.8)	9.40 (3.77–23.47)	<0.001	7.61 (3.01–19.25)	<0.001
Country income level[b]						
Low-income countries	25 751 (55.8)	309 (1.2)	1	<0.001[a]	1	<0.001[a]
Lower middle-income countries	17 083 (37.0)	153 (0.9)	0.74 (0.61–0.90)	0.003	0.71 (0.58–0.86)	0.001
Higher middle-income countries	3,279 (7.1)	17 (0.5)	0.43 (0.26–0.70)	0.001	0.49 (0.30–0.81)	0.005

Crude odds ratio only compares the risk of infection for the particular risk factor in question. The adjusted odds ratio is adjusted for all the other factors in the table

[a] Overall test

[b] Country income level according to World Bank 2009

surgeon preoperatively as a non-union had an adjusted risk of infection 2.31 times higher (OR 2.31, 95 % CI 1.83–2.91; $p < 0.001$) than fractures that were not classified as a non-union. There was no apparent effect of the number of distal locking screws on the rate of infection (OR 0.95–1.25; $p = 0.80$–0.30), and this variable did not affect the adjusted risks of the other risk factors. It was therefore not included in Table 2. The method of reaming did not significantly affect the risk of infection (Table 2).

The use of prophylactic antibiotics at the time of surgery reduced the adjusted risk of infection by 29 % (OR 0.71, 95 % CI 0.55–0.91; $p = 0.008$). The apparent increase in the crude risk of infection after open reduction (OR 1.34, 95% CI 1.07–1.66; $p = 0.010$) was not statistically significant after adjusting for other risk factors (OR 1.23, 95% CI 0.97–1.55; $p = 0.083$).

Age and gender did not significantly affect the risk of infection on more thorough sub-analysis. The same was the case when analyses were done after exclusion of countries with less than 5 % follow-up, except that the difference in infection risk according to a country's income level was then no longer present ($p = 0.68$). Sub-analysis was also done after exclusion of all patients without follow-up. This left 10,684 surgeries for analysis. Also here results were mostly unchanged. However, once again the difference in risk of infection according to the income level of the country where the surgery was performed ($p = 0.30$) was no longer statistically significant. In addition the effect of prophylactic antibiotics ($p = 0.99$) was no longer seen on exclusion of patients without follow-up.

Discussion

The main findings in the present study were that infection rates in the SOSD were low, and that the risk of infection is doubled for the delayed surgery of non-unions. When the results of this study were compared to results from the SOSD one year before [21] an increase in the follow-up rate from 18.1 % (95 % CI: 17.7– 18.5) in 2010 to 23.1 % (95 % CI: 22.7–23.5) in 2011 was observed. Despite this 27.6 % increase in the follow-up rate, the infection rates in the SOSD have not risen notably. The findings that the changes in infection rates are small despite a fairly large increase in follow-up might support the observation many surgeons in low-income countries have made; that a large proportion of the patients who have specific complaints do return for follow-up, whereas patients with no complaints do not return, due, among other things, to the high cost of transport [23]. In the previous article mentioned above, we looked at the effect of the low follow-up rate in the SOSD on the infection rates [21]. In that article the statistical model suggested that the data in the SOSD might support this, as countries registering more than 5 % follow-up had very little difference in infection rates, and no increase in infection rates was found with increasing follow-up rates over 5 %.

The infection rates in the present study are comparable to published infection rates in high-income countries [24–26], even in the higher end of the range [27]. However, there is a widespread belief among surgeons that the risk of postoperative infection is very high in LMIC. This probably stems from the personal experiences of many visiting surgeons through the years who have seen an abundance of osteomyelitis, late-presenting open fractures, and badly performed internal fixations done by undertrained local and visiting surgeons in LMIC. SIGN, however, trains surgeons in the correct setup, indications, and techniques, and all reported X-rays are reviewed and commented on by SIGN staff if they show results that are not satisfactory. There is no reason that infection rates should be much higher in a low resource setting when well-trained surgeons with modern equipment have access to the basic requirements for surgery, such as autoclaves, antiseptic wash, and the right prophylactic antibiotics, as they increasingly have in even the poorest countries. In a large randomized study of prophylactic antibiotic use in Uganda, the rate of infection after inguinal hernia repair dropped from 7.5 to 0 % with correct antibiotic usage [28]. In our study prophylactic antibiotics reduced the risk of infection by 29 % (OR 0.71, 95 % CI: 0.55–0.91). A prospective multi-center study comparing results of a standardized IM nailing technique between a South African trauma center and European centers showed lower complication rates in South Africa and a near-identical infection rate despite more serious injuries in the South African patients [19]. One explanation for this can be a lower mean age of the patients in South Africa. Trauma is a growing epidemic among the young people of LMIC [4, 5]. This can also be seen in the SOSD, where the mean age is only 34.7 years.

The second interesting finding in this study was that fractures defined by the surgeon as a non-union prior to surgery had a 2.3 times increased adjusted risk of infection (OR 2.31, 95 % CI: 1.83–2.91). It is no news to orthopedic surgeons that operating to repair a non-union of the femur is a lot more work than operating on an acute fracture. The exposure is larger, the operating time longer, and the expected bleeding greater than with primary fracture surgery. In addition, it is possible that unknown factors regarding the biology of the fracture may be less favorable in non-unions. Though the definition of a non-union was at the discretion of the surgeons reporting the surgery, and might not reflect exactly the common definition of a fracture not healed at 6 months, it nevertheless is an expression of the surgeon's doing surgery for a fracture at a delayed point in time when healing is not expected to occur. As such, in the authors' opinion, this is an important finding, suggesting that outcomes are better when primary fracture surgery is done in LMIC, and in consequence that primary IM nailing should be offered for femur fractures in centers where the infrastructure and training of the surgeons allows. In uncomplicated closed tibia and humerus fractures, where there are good results of primary functional bracing that does not necessitate long-term hospital stay, this should probably still be the first-line treatment of choice [29–32].

Infection risk decreased with increasing country income level in this study, with higher middle-income countries having half the adjusted risk of infection that was seen in low-income countries (OR 0.49, 95 % CI: 0.30–0.81).

Although this is a common preconception among surgeons, to our knowledge this has not been shown in an isolated study before. This would support the notion that the lack of infrastructure and the high prevalence of malnutrition and immunosuppression in low-income countries leads to an increased risk of infection in orthopedic trauma surgery. However, the numbers registered in higher middle-income countries are low, and these figures should be interpreted with caution. Even if these risk estimates are accurate, the risk of infection in low-income countries is still low and should not prohibit the use of modern orthopedic trauma surgery in these countries.

Tibia fractures had a twofold increased crude risk of infection and a 71 % increased adjusted risk of infection when an IM nail was used compared to antegrade nailing of the femur. As the adjusted risk of postoperative infection was adjusted for the increased incidence of open fractures of the tibia compared to the femur, this increase in infection risk is probably attributable to the subcutaneous localization of the tibia in contrast to the femur, which is surrounded by large, well-perfused muscles. No significant difference in the risk of infection was found between retrograde and antegrade nailing of the femur or between humerus and femur fractures.

There were 17 % open fractures in this study. This relatively high proportion of open fractures can possibly be seen as an expression of the severity of trauma in patients selected for IM nailing in LMIC. Open fractures had a 3.2 times increased risk of infection overall compared to closed fractures. The adjusted risk of infection rose with increasing severity of the injury from an OR of 1.9 for Gustilo grade 1 injuries to 7.6 for grade 3C injuries (Table 2). This is in line with other published reports and further supports that the data in the SOSD can be trusted [22, 33, 34]. No effect was seen on the adjusted risk of infection from age, gender, open reduction, number of distal locking screws, or method of reaming in this study.

There are some obvious limitations to this study, the most important being the low follow-up rate in the SOSD. Limited follow-up in studies in resource-constrained settings is a well-known problem. However, this might be necessary to accept if a large body of important information from poor countries is not to be kept out of the literature. In our above-mentioned earlier article validating the data in the SOSD in late 2010, we reported a follow-up rate of 18.1 % [21]. In that article we argued the case that the whole database can be used to estimate risk of infection based on the assumption that patients who have not returned for follow-up do not have infection. The present study builds on that assumption. We have also had to make several other assumptions that may not be correct. We have grouped superficial and deep infections together on the assumption that if they are reported they are serious enough to be of clinical importance, and we have assumed that if a patient returns with a complaint it will be registered in the SOSD. All this introduces uncertainty into the analyses and conclusions. However, in light of our former study, the large numbers in the SOSD, and the fact that we have analyzed the data both including and excluding patients without follow-up, we believe the reported figures give a good indication of where the true figures lie.

Conclusions

This study seems to confirm the expected increase in postoperative infection risk in low-income countries compared to countries with higher income levels, and presumably better infrastructure, but the increase in infection rates was small (0.5–1.2 %). The overall infection rates were low, and well within acceptable levels, suggesting that it is safe to do IM nailing in low-income countries. The fact that operations for non-union have twice the risk of infection compared to primary fracture surgery further supports the use of IM nailing as the primary treatment for femur fractures in LMIC.

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Conflict of interest L.G.Z. is president and founder of SIGN Fracture Care International, a registered not-for-profit organization based in Richland, Washington, that supplies hospitals in LMIC with orthopedic surgical equipment and implants free of charge for use in the treatment of poor people.

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Paper III:

Young S, Banza L, Hallan G, Beniyasi F, Manda K, Munthali B, Dybvik E, Engesæter LB, Havelin LI. Complications after trauma surgery in a low-income country. A prospective study of follow-up, HIV and infection rates after IM nailing of 141 femoral fractures at a central hospital in Malawi. Accepted for publication in Acta Orthopaedica, 22. August 2013.

III

Complications after intra-medullary nailing of femoral fractures in a low-income country

A prospective study of follow-up, HIV and infection rates after IM nailing of 141 femoral fractures at a central hospital in Malawi

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Background Some surgeons believe that internal fixation of fractures carries too high a risk of infection in low-income countries (LIC) to merit its use there. However, there are too few studies from LIC with sufficient follow-up to support this belief. We wished, first, to explore if complete follow up could be achieved in a LIC, and second, to find the true infection rate at our hospital, and to examine the influence of HIV and lack of follow-up on outcomes.

Patients and methods 137 patients with 141 femoral fractures that were treated with intra-medullary (IM) nails were included. We compared outcomes in patients who returned for scheduled follow-up and patients that did not return but could be contacted by phone or visited in their home villages.

Results 79 patients returned for follow-up as scheduled, 29 of the remaining patients were reached by phone or outreach visits giving a total follow-up rate of 79%. 7 patients (5%) had a deep postoperative infection. All these returned for scheduled follow-up. There were no infections among patients that did not return for follow-up compared to 8/83 in the group that did return as scheduled ($p=0.1$). 2 deaths occurred in HIV positive patients (2/23), while no HIV negative patients (0/105) died < 30 days postoperatively ($p=0.03$).

Interpretation We found an acceptable infection rate. The risk of infection should not be used as an argument against IM nailing of femoral fractures in LIC. Many patients in Malawi did not return for follow-up because they had no complaints about the fracture. There was an increased postoperative mortality rate in HIV positive patients.

Introduction

Even though Africa has 24% of the global burden of disease, it has only 3% of health workers and commands less than 1% of world health expenditure (WHO 2006). Of the estimated 234 million major surgical operations performed world wide in 2004 only 3.5% were performed in the poorest 35% of the World's population (Weiser et al. 2008). Globally 5.8 million people die annually as the result of injuries. That is more people than die of HIV/AIDS, tuberculosis and malaria combined (WHO 2006, Mathers et al. 2008). Of the 2.6 million young people between 10 and 24 years that died in the world in 2004, 97% died in low- and middle-income countries (LMIC). Over 40% of these deaths were due to injuries and, among these, road traffic injuries were the most common cause (Patton et al. 2009). Possibly more than 20 times as many as are killed by injuries survive and need treatment for their injuries (Peden 2004), and probably at least 3 times as many as are killed end up with a permanent disability (Kobusingye et al. 2001). The resulting long hospital stays and disability pushes poor people in LMICs further into poverty (Mock et al. 2003).

Kamuzu Central Hospital (KCH) is the referral hospital for 5.5 million people in the Central Region of Malawi. Despite being situated in the capital city, Lilongwe, KCH is drastically under funded and lacks many basic facilities and human resources. Malawi is seriously affected by the HIV pandemic and the national HIV prevalence in adults between 15 and 49 years was 10% in 2011 according to the UN (http://www.unaids.org/en/regionscountries/countries/malawi/). Internal audits at KCH have at times shown an HIV prevalence above 30% for patients admitted to the medical wards. Before 2007 only very basic orthopedic surgery was carried out and essentially all femoral fractures admitted to the hospital were treated in traction. From 2007 KCH has cooperated with Haukeland University Hospital in Norway and other international partners to improve surgical services and to start a surgical training program for general and orthopedic surgeons (Qureshi et al. 2012).

Orthopedic trauma surgery can prevent and treat disability and is increasingly being shown to be as cost effective as other essential health interventions in LMIC (Mock et al. 2003, Ozgediz and Riviello 2008, PLoS Medicine Editors 2008). However, there is still a prevailing belief among many surgeons and policy makers that infection rates are too high, and therefore results not good enough, to recommend orthopedic implant surgery in low resource settings. This perception is based mostly on papers about abdominal and gynecological surgery (Ibeziako et al. 1977, Ansaloni et al. 2001, Fehr et al. 2006), and probably on the individual experience of visiting surgeons who experience the stark contrast in infrastructure in hospitals in LIC to their home setting. Several studies have shown, however, that this is not necessarily the case in orthopedic surgery (Gross et al. 2010, Bates et al. 2012), but follow-up rates as low as 20% and below in some studies from LMIC make infection rates uncertain (Shearer et al. 2009, Young et al. 2011).

Low follow-up rates are a continuous problem in research in LMIC. In Malawi patients often do not know their date of birth. People spell their names differently from one visit to another and even use a different surname from one visit to the next, some times using their "clan name", other times their father's first name - or surname. It is not unusual for patients even to start using a different name all together. Though mobile phones are increasingly common among people in Malawi not everyone has a phone, or even knows someone who owns a phone, and numbers are often discontinued because of loss of the phone or lack of payment. Addresses are imprecise and many villages have the same names. The roads in rural Malawi are bad, especially during and after the rainy season, making transport difficult and finding patients on outreach visits challenging. Surgeons working in low-income countries (LIC) often have the impression that patients do not return for follow-up if they have no complaints, but that they do return if they have a serious problem. A frequent reason given by patients for not returning for review in Malawi is the cost of transport (Yu et al. 2007, Bedford et al. 2011). In an earlier study of the SIGN Online Surgical Database (SOSD) we found a statistical model supported the notion that patients who do not return for follow-up after trauma surgery in LMIC have few infections (Young et al. 2011), but prospective studies with better follow-up rates are needed to shed more light on this.

In the present study we wished to see if it was possible to get close to 100% follow-up in a low-resource setting, and to answer whether the patients that did not return for follow-up after femoral nailing really did have less complications than those that returned as scheduled. Considering the regional impact of HIV, we also wished to compare outcomes in HIV positive and negative patients.

Patients and methods

All patients presenting to Kamuzu Central Hospital with a femoral fracture eligible for treatment with an IM nail between January 1st 2010 and April 3rd 2012 were asked to participate in the study. Participation required giving informed consent to recording data concerning their accident, health status, the IM nail operation and follow up. All patients were asked to do an HIV test. They were all thoroughly counseled about the reasons for testing, the consequences of the result and possibilities for treatment. Treatment of their femoral fracture was the same irrespective of compliance with HIV testing, the result or whether included in the study or not. No patients refused inclusion in the study. However, 6 patients that had incompletely filled out study forms and did not have a recorded address or telephone number were excluded from the study.

Data, including as accurate a birth date, name and physical address as possible and a phone number for the patient, a relative or friend, was recorded in a data collection form. Primary end points at follow up were the same as for the SIGN online surgical database (SOSD) and included: presence of infection, partial weight bearing, painless full weight bearing, knee flexion over 90 degrees and signs of healing on radiographs (Young et al. 2011, Young et al. 2013). Surgeons classified infections, if present, as superficial (just involving skin) or deep (involving bone / the implant).

All patients were operated using a SIGN IM nail (Zirkle 2008). SIGN Fracture Care International (SIGN) is a not-for-profit organization based in Washington State, USA, that supplies intra-medullary nails for the treatment of long bone fractures free of charge to hospitals in low-income countries. The SIGN IM nails are specifically designed to be used in a low resource setting without a C-arm image intensifier or power tools. SIGN has supplied IM nails to KCH since 2008. Patients were mobilized with crutches as soon as possible after surgery and discharged when they could ambulate without assistance.

All patients were given a follow-up appointment 6 weeks after discharge, and actively encouraged to come for this checkup however happy they were with the result.
Patients that did return for this first follow-up visit were asked to return for a new visit and attempted followed up until the fracture had clinically and radiographically healed. All patients that had returned for at least 1 follow-up visit were classified as having returned for scheduled follow-up. Those that had not returned for follow-up and needed to be actively contacted by phone or outreach were classified as not having returned for follow-up. Patients were, if possible, contacted by phone and given a follow-up appointment. Patients who refused to come for follow-up when contacted by phone were interviewed by phone only. Patients that could not be reached by phone but had an accurate address were examined at their home on outreach visits if they could be found. Where we found the right village and family but the patient was not at home, we interviewed the family and if possible got a phone number to reach the patient on.

Infection was defined as any clinical infection relating to the operating incisions or the fractured bone. Possible risk factors for infection after orthopedic trauma surgery, including age, sex, surgical approach, time from injury to surgery, duration of surgery, open fractures, use of antibiotics and operating techniques were included as variables in the analyses. Open fractures were classified according to Gustilo-Anderson (1976). Non-union is usually seen as a complication of surgery in literature from high-income countries. In low-income countries, however, it is a separate and common indication for surgery as non-operative management is still widely used. Non-union has been shown to be a risk factor for infection in itself (Young et al. 2013) or might be an indirect measure of increased operating time, and was therefore analyzed as a separate risk factor. Delayed or non-union was simply defined as a fracture that had no signs of healing in the expected time with conservative treatment. These patients were mostly referrals from other hospitals that had no other option than conservative management. They were defined as a separate group in contrast to the patients where IM nailing was the intention from the start of treatment.

Ethical approval for this study was given by the National Health Sciences Research Committee of Malawi (approval # 753).

Statistics

The Chi-Square Test was used to compare rates in 2 different groups. When any expected cell frequency as less than 5 we used Fisher's Exact Test. Independent samples t-tests were used to compare means in 2 groups. Based on Levene's test for equality of variances we used Student's t-test for equal variances and Welch t-test when unequal variances. All p-values were 2-tailed and the level of statistical significance set to $p<0.05$. Analyses were done using IBM SPSS Statistics versions 19.0 and 21.0 (SPSS Inc., Chicago, Illinois 60606, USA.).

Results

137 patients were included in this study. 32 fractures (23%) were classified as delayed or non-union at operation. 4 patients had bilateral femoral fractures giving 141 IM nail operations, 125 antegrade nails (89%) with a trochanteric approach and 16 retrograde nails. Of the included patients 17% were female. The median age of the patients was 30 (12 - 78) years. For females the mean age was 40 (SD 16) years and for males 32 (SD 12) years, mean difference 8 (95% CI 3-14). 60% of fractures occurred in the right femur. 25% of patients were poly-trauma victims and 87% of fractures were due to high-energy trauma. 7% were open fractures (Gustilo grade 1, 2.8%; grade 2, 2.8%; grade 3, 1.4%). 71% of injuries were due to road traffic accidents (Table 1). 114 fractures were shaft fractures, 20 subtrochanteric and 7 distal metaphyseal fractures.

Mean waiting time from injury to surgery in acute fractures primarily planned for surgery was 17 (SD 10) days. In patients with fractures defined as delayed or non-unions surgery was performed a median 11 weeks (5 weeks – 11 years) after the injury. Mean time from injury to discharge in acute fractures was 30 (SD 15) days. Median time from surgery to discharge was 8 (1-90) days. The patients were ambulating with crutches a median 6 (1-72) days postoperatively. Open reduction was used in 96% of cases and IV prophylactic antibiotics were given preoperatively in all but 2 cases. Mean operating time was 115 (SD 42) min and mean estimated blood loss 306 (SD 234) mL. Fractures defined by the surgeon preoperatively as a delayed or non-union had a mean operating time of 130 (SD 36) min and estimated blood loss of 400 (SD 309) mL. Fractures that were defined as primary fracture treatment had a mean operating time of 112 (SD43) min, mean difference 18 min (95% CI 0.6-35) and an estimated blood loss of 279 (SD 202) mL, mean difference 121 ml (95% CI -10-252).

Follow-up
Of the 137 included patients 108 had at least 1 registered follow-up contact, including those with study or outreach contacts, giving a total follow-up rate of 79%. The mean time from surgery to final follow-up was 381 (SD 310) days. 79 patients (58%) returned for follow-up as scheduled on postoperative discharge from hospital. Of the remaining 58 patients who did not return for follow-up, 11 returned for an outpatient visit after being contacted by phone. An additional 7 were only available for interview by phone. 7 more patients were found on outreach visits and examined in their home, while 4 were contacted through relatives or friends found on these visits. We drove 2006 km over 8 days to find these 11 patients; 182km per patient found. As a result we were able to contact 29 patients (or their relatives in the case of 2 late deaths) that did not return for follow-up before.

All the registered postoperative infections occurred in patients who returned for follow-up. No infections were registered in patients that did not return for follow-up as scheduled. No statistical differences were found in patient or operation characteristics, or in outcomes, between patients that returned for follow-up and those that did not (Table 2). Only 1 other major complication, an asymptomatic non-union of the femoral shaft discovered on the check x-ray in a 43 year old HIV negative man 2 years after surgery, was found among the patients that did not return for scheduled follow-up. The nail was dynamized by removal of the distal locking screws and healed without further treatment.

28 of the patients that did not return for follow-up gave different, and some times several, reasons for not returning. 19 patients stated that they could not afford the transport, 18 patients reported that they had no problems and 4 did not think it necessary. 9 patients claimed to have come back, despite no follow-up being registered for them. Some of these patients reported that they were turned back because the x-ray department was closed or the doctor was not available. Some of them, however, seem to have been seen and the follow-up not reported.

Infection
No infections were found in the patients that did not return for scheduled follow-up. 8 infections, 7 deep and 1 superficial, were registered making the over all total infection rate in this study 6%, or 5% deep infections (Table 3). If only nails with registered follow-up (n=112) were included in the analysis, the infection rate was 7%, or 6% deep infections. There was only one infection (1/32) among the fractures defined as delayed or non-unions at the time of operation in this study. The other 7 infections were seen in fractures intended for primary treatment (6%, OR 0.5, 95% CI 0.1-4). 10 fractures (7%) were open. Of these only 1 developed an infection (OR 2, 95% CI 0.2-17). This was an open knee injury with comminuted patella and femoral condyle fractures combined with a distal femur fracture. He waited 12 days for surgery (Table 3).

HIV
17% of patients were HIV positive and 7% had an unknown HIV status (Table 4). No statistical difference was found in infection rates between HIV positive (2/23, 9%) and negative (5%) patients. For HIV positive patients mean time from injury to surgery in acute fractures primarily planned for surgery was 19 (SD 11) days and for HIV negative patients 17 (SD 9) days, mean difference 2 days. Mean time from surgery to ambulation with crutches was 6 (SD 3) days in HIV positive and 8 (SD 10) days in HIV negative patients, mean difference 2 days. None of these differences were statistically significant. The mean time to discharge from surgery was 8 (SD 3) days in HIV positive patients and 11 (SD 10) days in HIV negative patients, mean difference 3 days (95% CI 0.7 - 5.6). Operating time and estimated blood loss in HIV positive and HIV negative patients were similar.

5 deaths (4%) were recorded. 3 deaths occurred in HIV positive patients (3/23) and 2 in other patients (2/114, p=0.03). 3 deaths occurred within 30 days postoperatively and were as such defined as postoperative complications. 2 of these deaths were in HIV positive patients (2/23) and 1 in a patient with unknown sero-status. No confirmed HIV negative patients died in the first 30 days postoperatively (p=0.03). If the patients with unknown sero-status were grouped with the HIV negative patients this difference in postoperative mortality did not quite reach statistical significance (0.9%, p=0.07). Both HIV patients that died postoperatively, a 50-year-old woman and a 47-year-old man, died of sudden onset respiratory distress and hypotension a few days postoperatively and before they were discharged, probably from pulmonary embolism (PE). The third HIV positive patient, a 32-year-old man, died of pneumonia 3 months postoperatively. A 33-year-old man with unknown HIV sero-status died before discharge from hospital from respiratory problems of a less sudden nature than the 2 others. The only HIV negative patient that died was a 75 year old man that according to family died of malaria 10 months after surgery. He had recovered fully after the surgery according to the family.

Discussion

In the present study with 79% follow-up from one of the poorest countries in the world the deep infection rate was 5%. There were no infections found among the patients that did not return for scheduled follow-up but were reached by phone or outreach visits. These main findings support the idea that patients that do not return for follow-up in low-income countries have fewer complications than those that do return. HIV positive patients did well after femoral nailing, but there might be an increased 30-day mortality rate in these patients in our setting.

Follow-up

In our previous paper validating the data in the SOSD in late 2010 we reported a follow-up rate of 18% (Young et al. 2011). In that paper we argued the case that the whole database can still be used to estimate risk of infection based on the assumption that patients that have not returned for follow-up are unlikely to have infections. In the present study we went to considerable lengths to try to find as many of the patients that did not return for follow-up as possible. We drove over 2000 km on, at times, hardly passable roads to try to find patients at home in their villages. As a result we found 7 patients at home and managed to contact 4 more by phone. The extreme difficulty of getting to some of the villages, even in a good 4-wheel-drive vehicle, illustrates the patients' problems of returning for follow-up. Even before considering the cost of transport to people who have close to no cash income at all, it is understandable that many do not return if they feel well anyway. We believe insisting on very high follow-up rates in clinical research from low-income countries is unrealistic and can exclude important information from the literature.

The most common reason given by patients for not returning for follow-up in the present study was the cost of transport. Other studies have also shown that transport expenses are a major barrier to follow-up in Malawi (Yu et al. 2007, Bedford et al. 2011). The present study lends some support to the assumption that patients that do not have problems do not return for review, at least in Malawi, as no infections were found in the 29 patients that did not return for follow-up on their own accord.

Infection rates

We found a deep infection rate of 5% after femoral IM nailing at Kamuzu Central Hospital. This has to be seen in the context of the severe trauma being treated. 9 out of 10 femoral fractures were the result of high-energy trauma, 25% of patients were poly trauma victims and 7% of fractures were open. An analysis of risk factors for infection after 46 113 IM nail operations in the SIGN Online Surgical Database (SOSD) (Young et al. 2013) found an increasing risk of infection with decreasing resources in a country. Malawi is rated at number 170 of 186 countries on the United Nation's Human Development index (http://hdrstats.undp.org/en/countries/profiles/MWI.html) and as such is one of the poorest countries in the World. Limited resources increase the waiting time for surgery and introduce many other risk factors for infection such as stock outs of antiseptic solutions, old surgical drapes with holes, donated expired consumables, lack of bandages and linen in the wards, intermittent water supply etc. Though a postoperative deep infection rate of 5% might seem high to surgeons working in high-income countries, rates of deep infection up to 4% after IM nailing of femoral fractures have been reported even in the UK (Malik et al. 2004) where the severity of trauma is likely to be much less and there are few resource constraints. In Oslo, Norway, a recent study showed an infection rate of 9% after hemiarthroplasty for femoral neck fractures in elderly patients (Westberg et al. 2013). Infection after IM nailing of the femur is a serious complication and often leads to reduced range of knee motion, as was seen in several of our patients (Table 3). However, early debridement, suppressive antibiotic treatment until union and subsequent removal of the nail and reaming of the IM canal is usually successful in eradicating the infection in our experience from Malawi. This is supported by a paper from 2010 describing the use of this treatment in the USA (Berkes et al. 2010). In our opinion the infection risk after IM nailing in the present study is acceptable and the advantages of IM nailing over skeletal traction by far outweigh this risk (Gosselin et al. 2009, Young et al. 2012).

We do not think the risk of infection should be used as an argument against IM nailing of femoral fractures in low-income countries, but efforts must be made to reduce the infection rate where possible through improvement of hospital infrastructure and supply chains, and systematic training of surgeons and theatre staff. Where good alternatives for functional bracing exist, such as in closed tibia and humerus shaft fractures, this should still be the mainstay of treatment in our setting. This saves already limited operative resources and reduces the risk of infection in these patients.

HIV

Though there was an apparent increased risk of infection in HIV positive patients (9%) compared to HIV negative patients (5%), the differences did not reach statistical significance. This is in line with an increasing number of publications from the region (Harrison et al. 2004, Harrison 2005, Bates et al. 2012), but most available studies, including the present study, are small and under-powered. A recent meta-analysis did suggest that there might be an increased risk of postoperative infections in HIV patients, but the analysis was based on many small and old studies, mostly of hemophilic patients, and the findings were not conclusive (Kigera et al. 2012). Larger prospective studies will be needed to shed more light on this, but the available literature, including this study, suggests that the risk of postoperative infection is not, at least, greatly increased in HIV positive trauma patients.

Postoperative mortality, however, did seem to be increased in HIV positive patients (2/23) compared to HIV negative patients (0%, p=0.03) in our study. Numbers were small, and care has to be taken in concluding from these, but there is literature that might support this finding. HIV positive patients have an up to 10 times increased risk of venous thromboembolism (VTE) (Ahonkhai et al. 2008) and immobilization in traction can lead to pulmonary embolism (Sekimpi et al. 2011). Because of economic constraints we did not have available VTE prophylaxis with low-molecular-weight heparin or compressive stockings at our hospital. Aspirin is a cheap alternative but was not used systematically in the study period. All 3 postoperative deaths were suspected to be pulmonary embolisms with sudden onset hypotension and respiratory distress, though definitive diagnosis or post-mortem examination was not available at the time. The lack of VTE prophylaxis could, together with the seriousness of the trauma spectrum in our patients and the long period of immobilization while waiting for surgery, explain the overall postoperative mortality of 2.2% in this study. Patients waited on average 2.5 weeks for surgery of acute fractures in this study. As HIV positive patients have an increased risk of VTE this might disproportionately affect this group.

HIV positive patients did not have increased time to ambulation or length of stay postoperatively and as such seem to have the same potential for rehabilitation postoperatively as other patients with femoral fractures. In our opinion, this, coupled with the possibility for increased risk of VTE with long preoperative traction times, supports early IM fixation of femoral fractures in HIV positive patients.

Time from surgery to discharge was median 8 days. At KCH crutches are made for the patients by a carpenter and the patients have to pay a fee (approximately 2 US$) to receive them. This fee is waived for patients that cannot find the funds. However, it often takes time for the patients to try to find money, and for the carpenter to make the crutches, and this contributes to the length of stay postoperatively. Once the patients have received crutches they are discharged within a median of 2 days. There is a large potential for decreasing the length of hospital stay both pre- and postoperatively for femoral fracture patients at KCH. Increased surgical capacity (more theatres and staff for orthopedic surgery) and better availability of affordable crutches could realistically reduce the length of stay for operated patients from the current average of 30 days to around 10 days.

The length of stay for patients with femoral fractures treated with traction can be expected to average between 6 and 8 weeks (Gosselin and Lavaly 2007, Doorgakant and Mkandawire 2012). However, many patients will need to stay longer. Complications are common with up to 14% mal-union and 22% non-union (Gosselin and Lavaly 2007, Gosselin et al. 2009). Pulmonary embolism (Sekimpi et al. 2011) and serious infections (Young et al. 2012) have been reported. It has even been shown that IM nailing can be more cost effective than traction (Gosselin et al. 2009). In our opinion, it is high time that IM nailing of femoral fractures is accepted as an essential part of health care delivery also in low income countries.

There are some obvious limitations to this study, including the relatively small number of included patients limiting the power. However, the fields of surgery and trauma care have largely been neglected in the global health discussion and as a result the idea that surgery is not safe or cost effective in resource-limited settings has gone unchallenged. In light of the setting in which this study has been conducted, and the fact that we have managed to get close to 80% follow-up amidst huge resource challenges, we do believe our study brings some new information to the field of orthopedic trauma care in low-income countries in general and more specifically in HIV positive patients.

Conclusions

100% follow-up is not realistic in research in low-income countries. In the present study patients often did not return for follow-up if they had no problem. The most frequent reason given for this was the cost of transport. Low follow-up rates must, to some degree, be accepted in research from this region or we could be excluding new knowledge from these countries from the literature.

The 5% infection rate is acceptable, considering the spectrum of serious trauma in this study. Risk of infection should not be used as an argument against IM nailing of femoral fractures in low-income countries.

HIV positive trauma patients had a higher postoperative mortality rate than other patients. If confirmed in larger studies, this might possibly be explained by the increased risk of venous thromboembolism in people living with HIV. HIV positive trauma patients otherwise did just as well, or better, postoperatively and did not have a significantly increased risk of infection. We recommend early IM fixation of femoral fractures in HIV positive patients.

SY: study design, data collection, statistics. LB, FB, KM, BM: data collection. ED: independent review of statistics. GH, LBE, LIH: study design. All authors contributed to critical analysis and interpretation of data and statistics, and to writing and revision of the manuscript.

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Table 1. Registered mechanism of injury. 71% of injuries were due to road traffic accidents.

Mechanism of injury	n	%
Road Traffic accidents	96	71
Minibus	22	16
Passenger in private vehicle	21	15
Pedestrian hit by motor vehicle	17	13
Cyclist hit by motor vehicle	17	13
Passenger on pick-up or lorry*	16	12
Oxcart	3	2
Other injuries	40	29
Fall	16	12
Collapsing structure	9	7
Assault	8	6
Sports	4	3
Pathological fracture	2	1
Crocodile bite	1	1

*"Passenger on pick-up or lorry" refers to patients that were passengers on the rear open loading area of a pick-up truck or lorry, a common mode of public transport in Malawi.

Table 4. Outcomes in HIV positive and negative patients

	HIV+	HIV-	OR	95% CI	p-value
Patients	23	105			
Infection	2	5	1.9	0.3 – 10	0.6
Over all mortality	3	1	16	1.5 - 158	0.02
<30 day mortality	2	0	*	*	0.03
Returned for scheduled follow-up	16	56	1.8	0.5 - 6	0.3

OR=Odds Ratio. *Undefined, zero in 1 cell.

Table 2. Overview of operations and patients with recorded follow-up information, with comparison between patients that returned for scheduled follow-up and those that did not.

	Scheduled follow-up	No follow-up before study	p-value
Patient characteristics			
No. of patients	79	29	-
Mean age, years	33	37	0.2
Sex, n			
Female	15	4	0.8*
Male	64	25	-
HIV, n			
HIV +	17	4	0.4
HIV – / unknown status	66	25	-
No of nails	83	29	
Approach, n			
Antegrade Femur	71	27	0.5*
Retrograde Femur	12	2	-
Fracture reduction, n			
Open	79	28	1.0*
Closed	4	1	-
Proph. Antibiotics, n			
Yes	82	28	0.5*
No	1	1	-
Indication, n			
Acute fracture	63	22	1.0
Delayed / non-union	20	7	-
Open fracture, n			
Yes	6	1	0.7*
No	77	28	-
Outcomes			
No of nails	83	29	
Infections, n	8	0	0.1*
Death < 30 days postop.	3	0	0.3*
Mean operating time (min)	117	113	0.7
Mean estimated blood loss (mL)	291	367	0.2

* Fisher's Exact Test

Case no.	age	sex	HIV +/-	CD4	Time of diagnosis*	risk factors?	Deep?	Treatment	outcome
9	14	M	negative	-	5 days postop.	-	Superficial	Oral antibiotics for 2 weeks	Completely recovered, and no infection at follow-up after 2 months
11	20	M	negative	-	1 month postop. (IV antibiotics 20 days)	Same side open grade 2 comminuted patellar and femoral condyle fx. Waited 12 days for surgery.	Deep	Oral antibiotics until healing, then removal of nail and other hardware.	Infection resolved. Painless weight bearing, but stiff knee, ROM 0-15 degrees only.
40	40	F	unknown	-	5 days postop.	Psyciatric patient, non-compliant. Early postop. Infection	Deep	Oral antibiotics, Nail removed 14 months post surgery.	Wound dry on discharge after nail removal. Ambulating without support.
56	65	F	negative	-	Not recorded	Cellulitis distally on same leg preop. Treated with IV antibiotics 10 days.	Deep	Nail removal.	Neck of femur fracture opposite side a few months after surgery.
93	25	M	negative	-	2 months postop.	Old patellar ligament injury same side. Stiff knee. 3 hour operation.	Deep, discharging sinus	On list for removal of nail.	Fully weight bearing w/o pain. ROM 0-60 deg.
96	19	M	positive	-	17 months postop.	-	Deep, discharging sinus	On list for removal of nail.	Fully weight bearing w/o pain. ROM 0-100 deg.
116	37	M	positive	334	2 months postop.	-	Deep	Oral antibiotics until healing, then removal of nail	Infection resolved. Fully weight bearing w/o pain. ROM 0-70 deg.
128	28	M	negative	-	1 month postop.	Sub-optimal surgery. Nail too short & locking screws missed nail distally. Unstable.	Deep. Wound break down	Debridement in theatre & suppressive antibiotics. Nail removed when healed.	Infection resolved. Fully weight bearing w/o pain. ROM 0-90 deg.

Table 3 Overview of the 8 patients with postoperative infections.

* Time from surgery to postoperative infection diagnosis.

Appendices

10. Appendix

10.1 Postoperative SOSD registration form:

SIGN SURGICAL DATABASE
Data Collection Sheets
For Data Entry In The SIGN Surgical Database
www.signsurgery.org

PATIENT CASE INFORMATION: (All fields are required unless otherwise noted.)			
Patient Name:	**Age:**	**Gender:**	**Injury Date:**
Hospital Name:		**Case Number:** (optional)	
Optional Patient Contact Information: *(This information will be available only to the applicable hospital).*			
Address:			
Phone Number:	**Email Address:**		

Postoperative SOSD registration form (page 2 of 4):

SURGERY INFORMATION: Copy this page for each additional surgery for this patient.
Date (month/day/year):
Surgeon Name(s):

1. Antibiotics Used? ☐ **Yes** ☐ **No**

If yes:

How long from time of injury? _____ hours _____ days

Name of Antibiotic: ____

Duration of Antibiotic Coverage: _____ hours _____ days

2. Surgery Comments:

____

____

____

____

____

____

____

____

____

____

Postoperative SOSD registration form (page 3 of 4):

FRACTURE INFORMATION: (Copy pages 3 - 4 for each additional fracture.)
Patient Name:
Case Number:

1. Fracture Side: ☐ Left ☐ Right

2. Surgical Approach: ☐ Tibia ☐ Retrograde Femur ☐ Antegrade Femur ☐ Antegrade Humerus
Other: ____

3. Location of Fracture: (check all that apply) ☐ Proximal ☐ Middle ☐ Distal ☐ Segmental ☐ Femoral Neck ☐ Intertrochanteric

4. Type of Fracture: ☐ Closed ☐ Gustilo IIIa ☐ Gustilo I ☐ Gustilo IIIb ☐ Gustilo II ☐ Gustilo IIIc

5. Time from injury to Debridement: ____hours ____days

6. Time from injury to Skin Closure: ____days

7. Method of Wound Closure:
(check all that apply) ☐ Primary ☐ Skin Graft ☐ Muscle Flap ☐ Secondary Other: ________________________

8. Previous Implant Used: ☐ Yes ☐ No
If Yes, check all that apply: ☐ External Fixation ☐ Plate ☐ IM Nail ☐ Wire
If External Fixation: 1. How long was external fixation in place? ____days
2. Time between removal of ext. fixation and SIGN? ____days

9. Method of Reaming: ☐ None ☐ Power ☐ Hand

10. Fracture Reduction: ☐ Open ☐ Closed

11. Comments:
____
____
____
____
____
____
____
____

Postoperative SOSD registration form (page 4 of 4):

FRACTURE INFORMATION (continued from page 3)
Patient Name:
Case Number:

13. Nail Type Used: (Please mark the type of nail used to treat this fracture.)

Standard Nails	200 mm	220 mm	240 mm	260 mm	280 mm	300 mm	320 mm	340 mm	360 mm	380 mm	400 mm	420 mm
8 mm												
9 mm												
10 mm												
11 mm												
12 mm												

Fin Nails	160 mm	190 mm	240 mm	280 mm
7 mm				
8 mm				
9 mm				
10 mm				
11 mm				
12 mm				

14. Screw Quantities Used: (Please enter the quantity of each type of screw used with this nail.)

Length in mm	25	30	35	40	45	50	55	60	65	70	75
#Proximal											
#Distal											

15. X-Rays Taken: (Please list the names of the digital image files for all x-rays of this fracture.)

Digital Image X-Ray File Name(s)	Pre-Op	Post-Op	Date Taken
	☐	☐	
	☐	☐	
	☐	☐	
	☐	☐	
	☐	☐	
	☐	☐	
	☐	☐	

Notes on uploading digital image x-ray files:

1. This table is provided for you to keep track of digital x-ray images so that the process of uploading these images to the online database goes smoothly.
2. The time required to upload image files is determined by the size of your digital image files and your internet connection speed.
3. VERY IMPORTANT: You can reduce the size of your digital image files by converting them to grayscale (remove all color) and by reducing the dimensions of your pictures to approximately 640 x 480 pixels. Many digital cameras come with software programs capable of these tasks.

10.2 SOSD follow-up visit registration form:

FOLLOW-UP INFORMATION: (Copy this sheet for each additional follow-up.)	
Patient Name:	
Case Number:	**Date (month/day/year):**
If multiple fractures, which fracture is this a follow-up for?	

1. Infection: ☐ Yes ☐ No
If yes:
Incision of the wound: ☐ Yes ☐ No
Infection depth: ☐ Superficial ☐ Deep (patient returns to surgery)
Duration of infection: _____ weeks
☐ Osteomyelitis ☐ Amputation

3. Partial weight bearing: ☐ Yes ☐ No
4. Painless full weight bearing: ☐ Yes ☐ No
5. Healing by x-ray: ☐ Yes ☐ No
6. Knee flexion greater than 90 degrees: ☐ Yes ☐ No
7. Screw breakage: ☐ Yes ☐ No
8. Screw loosening: ☐ Yes ☐ No
9. Nail breakage: ☐ Yes ☐ No
10. Nail loosening: ☐ Yes ☐ No

11. Deformity: ☐ Yes ☐ No (under 10 degrees)
If yes:
Alignment: ☐ Over 10 degrees varus ☐ Over 10 degrees valgus
☐ Over 20 degrees varus ☐ Over 20 degrees valgus

Rotation: ☐ Over 30 degrees

12. Repeat Surgery: ☐ Yes ☐ No
If Yes, check all that apply: ☐ For Infection ☐ For Deformity ☐ For Non-union

If For Non-Union, check all that apply: ☐ Dynamize ☐ Exchange Nail
☐ Iliac Crest Bone Graft
Other:___________________________________

13. Comments:
____
____
____

14. X-Rays Taken: (Please list the names of the digital image files for all x-rays during this follow-up.)

Digital Image X-Ray File Name(s)	Date Taken

10.3 Data Collection form, KCH study (Paper III):

Prospective registration of SIGN intramedullary nails at Kamuzu Central Hospital 2010-2011

Data collection sheet.

Please fill in ALL fields at latest on discharge of patient. Circle all appropriate choices.

Patient must sign consent form on reverse.

<table>
<tr><td>Name:</td><td colspan="2">Gender: F / M</td></tr>
<tr><td>SIGN database case no.:</td><td colspan="2">Age:</td></tr>
<tr><td>Current address / Contact details:</td><td colspan="2">Phone no of pt. or guardian:</td></tr>
<tr><td>Date of injury (D/M/Y):</td><td colspan="2">Date of surgery (D/M/Y):</td></tr>
<tr><td>Mechanism of injury:
Pedestrian run down by motor vehicle
Bicyclist run down by motor vehicle
Driver or passenger in private car
Driver or passenger in Minibus
Passenger on back of pick up or lorry</td><td colspan="2">
Wall or roof of house fell down
assault by thugs / robbers
domestic violence
pathological fracture
other (please state below):</td></tr>
<tr><td>Fracture site:
subtrochanteric / midshaft / distal shaft / supracondylar</td><td>Fracture config.:
transverse / oblique / spiral / segmental / comminuted</td><td>Side of injury:
Right / Left</td></tr>
<tr><td>Fracture type:
Closed
Open, grade 1 / 2 / 3a / 3b / 3c</td><td colspan="2">Treatment before surgery:
Skin traction / skeletal traction / ExFix / No treatment</td></tr>
<tr><td>Indication for surgery:
Primary fracture treatment
Delayed union
Non-union
Malunion: valgus / varus / rotation / shortening (circle all that apply)
Palliative care / pathological fracture</td><td colspan="2">Symptoms preop. (circle all that apply):
Pain on manipulation /
Pain on weight bearing /

completely loose /
stiff but some movement on manipulation /
no movement at # site on manipulation</td></tr>
<tr><td>Other diseases / risk factors (circle all that apply):
Diabetes: Yes / No
Heart disease: Yes / No
Hypertension: Yes / No
Asthma / chronic lung disease: Yes / No</td><td colspan="2">
Malnutrition (pt under weight): Yes / No
Obesity: Yes / No
Smoker: Yes / No
Cancer (state type): Yes / No
HIV (see next page): Yes / No</td></tr>
</table>

Data collection form used in KCH study (Paper III). Page 2 of 2:

HIV: Non-reactive / reactive / unknown	**ART:** Yes / No If yes how long:
CD4 count / date:	**Preoperative Hb / date:**
Antibiotic(s): Yes / No	**Type and dose of antibiotics:**
Date antibiotic(s) started (D/M/Y):	**Date of last antibiotic dose (D/M/Y):**
Operating time (skin to skin):	**Estimated peroperative blood loss (ml):**
Date up on crutches (D/M/Y):	**Date of discharge (D/M/Y):**
Knee range of motion (ROM) at discharge (degrees ext. and flex., eg.: 0° – 30°):	**Wounds clean and dry on date of discharge?** Yes / No
Planned follow up / review date (D/M/Y):	**Form filled out by (name):**

Consent form:

I have been informed of the current study on the use of SIGN nails at Kamuzu Central Hospital by Mr / Mrs : ______________________________ and give my consent to the above information being used for research purposes in an anonymous form.

Nda dziwitsidwa za maphunziro a kagwiritsidwe ka SIGN nail ku Kamuzu Central Hospital ndi Mr / Mrs: ________________________________ ndi kubvomereza ndondomeko yogwiritsidwa mu kafukufuku mosatchulidwa dzina langa.

Name: Signature:

Date:

10.4 Follow-up registration form used for patients that had not returned for follow-up in KCH study (Paper III):

FOLLOW-UP FORM

SIGN intra-medullary nails at Kamuzu Central Hospital

Please fill in ALL fields. Circle all appropriate choices. One form for each IM nail if >1.

<table>
<tr><td colspan="3">Circle one: Follow-up visit / telephone interview</td><td colspan="2">Follow-up date (D/M/Y):</td></tr>
<tr><td colspan="2">Name:</td><td colspan="2">Gender: F / M</td><td>Age:</td></tr>
<tr><td colspan="2">SIGN case no.:</td><td colspan="3">Date of surgery (D/M/Y):</td></tr>
<tr><td colspan="2">Reason for this follow-up:
Study / Problem / routine postop. visit
Other (specify):</td><td colspan="3">Returned for follow-up before?
Yes / No</td></tr>
<tr><td colspan="5">Reason if not returned for follow-up before (circle all that apply):
Had no problem / could not afford / did not think it necessary / was not told to come back /
Other reason (specify):</td></tr>
<tr><td colspan="2">Place of stay:
Urban / rural</td><td colspan="3">Cost of transport to KCH, one way:</td></tr>
<tr><td colspan="2">Fractured bone:
humerus / femur / tibia</td><td colspan="2">Fracture type:
Closed / Open</td><td>Side of injury:
Right / Left</td></tr>
<tr><td colspan="2">HIV:
Non-reactive / reactive / unknown</td><td colspan="2">ART: Yes / No
If yes, no. months:</td><td>CD4 count / date:</td></tr>
<tr><td>Infection at this follow-up?
Yes / No</td><td>Deep?
Yes / No</td><td>Infection at earlier follow-up?
Yes / No</td><td colspan="2">Treatment for infection:</td></tr>
<tr><td colspan="2">Partial weight bearing?
Yes / No</td><td colspan="3">Painless full weight bearing?
Yes / No</td></tr>
<tr><td colspan="2">Healing on x-ray?
Yes / No</td><td>Broken / loose screws? Yes / No</td><td colspan="2">Broken / loose nail?
Yes / No</td></tr>
<tr><td colspan="3">Deformity? No / Yes
If yes specify degrees or cm and circle direction
___ degrees: varus / valgus / external / internal
___ cm shortening</td><td colspan="2">Knee pain? Yes / No
Crepitation in knee? Yes / No
Trochanter pain? Yes / No
Tenderness over screws? Yes / No</td></tr>
<tr><td colspan="2">Knee range of motion (ROM) at follow-up (degr. ext. and flex., eg.: 10°- 0° – 150°):</td><td colspan="3">Happy with result? Yes / No
Other complaints / problems: Yes / No
If yes, specify:</td></tr>
<tr><td>Pictures of x-rays taken?</td><td>Follow-up reported to SIGN?
Date:</td><td colspan="3">Form filled out by (name):</td></tr>
</table>