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# Wounds of War

## Surgical care for conflict-related injuries among civilians in resource-limited settings

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# Wounds of war

Surgical care for conflict-related injuries among civilians in resource-limited settings

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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To Elsy, Frank, Bill and Lina

*The story is not in the words; it's in the struggle*

Paul Auster, The New York Trilogy

# ABSTRACT

Background: Armed conflicts significantly contribute to the global burden of injury and death. Armed conflicts shocks health systems, deprive its resources and reduce its function, as well as limits access to civilian hospital care. In such resource-limited settings, the evidence on how to optimally manage the injuries sustained by civilians remains scarce.

Objectives: To generate knowledge on how wound infection affects outcomes for civilian patients treated for conflict-related injuries, to explore the challenges associated with the treatment of such patients, and to evaluate the safety, effectiveness, and cost-effectiveness of negative pressure wound therapy (NPWT) for conflict-related extremity wounds.

Methods: All patients were wounded in armed conflicts in Syria and Iraq. The studies were performed at two civilian hospitals in Jordan and Iraqi Kurdistan. In a cohort study (*Paper I*), utilising routinely collected clinical data from consecutive patients surgically treated for conflict-related injuries, we compared patients with wound infection to those without, in terms of clinical outcome and resource consumption. *Paper II* was a qualitative study where treating physicians in Jordan were interviewed to explore the perceived main challenges in conflict wound management. *Paper III* was a randomised controlled trial on the safety and effectiveness of NPWT compared to standard treatment for conflict-related extremity wounds. In *Paper IV* we used clinical outcome data from *Paper III* to perform a health economic evaluation of NPWT in resource-limited settings.

Main Findings: Wound infection was associated with poor clinical outcomes and excess resource consumption. In addition, three out of four infected wounds contained multidrug-resistant bacteria. The main challenges in conflict wound management related to protocol adherence. Reasons for protocol deviations included resource scarcity, high patient loads, and limited compliance among patients and caregivers. Neither time to wound closure nor net clinical benefit was improved by NPWT compared to standard treatment for conflict-related extremity wounds. Treatment-related healthcare costs were higher for NPWT compared to standard treatment

Conclusions: Wound infection was associated with poor clinical outcomes and an excess resource consumption among patients receiving surgery for conflict-related injuries. Physicians found protocol adherence to be the main challenge in the management of conflict-related wounds. NPWT did not result in superior clinical outcomes compared to standard treatment. In addition, costs were higher, indicating that NPWT is not a cost-effective treatment option.

# LIST OF ABBREVIATIONS

| | |
|---|---|
| CHEERS | Consolidated Health Economic Evaluation Reporting Standards |
| CONSORT | Consolidated Standards of Reporting Trials |
| CRF | Case report form |
| DPC | Delayed primary closure |
| EMC | Emergency Management Center, Erbil, Iraq |
| GCP | Good Clinical Practice |
| GCS | Glasgow Coma Scale |
| HAI | Healthcare-associated infection |
| ICRC | International Committee of the Red Cross |
| ISIS | Islamic State of Iraq and Syria |
| MDR | Multidrug-resistance |
| MSF | Médecins Sans Frontières/Doctors Without Borders |
| NGO | Non-governmental organisation |
| NPWT | Negative pressure wound therapy |
| RCT | Randomised controlled trial |
| RTSc | Revised Trauma Score, coded |
| SRQR | Standards for Reporting Qualitative Research |
| STROBE | Strengthening the Reporting of Observational Studies in Epidemiology |

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# LIST OF PAPERS

This thesis is based on the following papers, referred to in the text by their Roman numerals.

I. **Infection with high proportion of multidrug-resistant bacteria in conflict-related injuries is associated with poor outcomes and excess resource consumption: a cohort study of Syrian patients treated in Jordan.**
Älgå A, Wong S, Shoaib M, Lundgren K, Giske CG, von Schreeb J, Malmstedt J.
BMC Infectious Diseases. 2018 Dec;18(1):233.

II. **"Reality rarely looks like the guidelines": a qualitative study of the challenges hospital-based physicians encounter in war wound management.**
Älgå A, Herzog KK, Alrawashdeh M, Wong S, Khankeh H, Lundborg CS.
Scandinavian journal of trauma, resuscitation and emergency medicine.
2018 Dec;26(1):52.

III. **Negative pressure wound therapy versus standard treatment in patients with acute conflict-related extremity wounds: a pragmatic, multisite, randomised controlled trial.**
Älgå A, Haweizy R, Bashaireh K, Wong S, Conneryd Lundgren K, von Schreeb J, Malmstedt J. (Submitted)

IV. **Health economic evaluation of negative pressure wound therapy vs standard treatment of conflict-related extremity wounds within a randomized clinical trial.**
Älgå A, Löfgren J, Haweizy R, Wong S, von Schreeb J, Malmstedt J.
(Manuscript)

# PREAMBLE

I tried to avoid getting involved with research. I wanted to focus my working hours on being a good doctor, and on my training to become a skilled surgeon. Then, after my first mission with Médecins Sans Frontières (MSF), I met Johan. At a debriefing session at the Swedish MSF office, I was trying to make sense of my overwhelming first encounters with extreme poverty. Johan summarised it for me in a few clear sentences that made me think that maybe there was, after all, a way to make sense of the senseless. The following years we stayed in touch, and I found myself slowly being drawn into the world of research.

My first attempts included a systematic review of crush injuries following earthquakes and an observational study assessing the primary healthcare flood preparedness in the Vietnamese countryside. None of which proved to be suitable areas for a doctoral thesis. Then I got an email from Eugene at MSF, asking if I wanted to be part of the implementation of a new treatment method for Syrian civilians with acute conflict-related injuries. After some thinking I figured that a randomised controlled trial could be a straight-forward approach. However, I was not sure how to go about this task. At my new position at the Department of Surgery at Södersjukhuset I met Jonas and we almost immediately started discussing research. His enthusiasm convinced me of the feasibility to conduct a randomised clinical trial in a conflict-affected area. The combination of Johan's sense of context and relevance, and Jonas' tenacity and methodological knowledge soon proved to be a recipe for success.

Throughout this thesis project, I have struggled with limitations and shortcomings; mostly my own, but also external factors out of my control. During the running of our clinical trial in Jordan, for example, the Syrian border was suddenly closed due to a violent border control attack. This left injured Syrian patients with limited access to healthcare and us with no study participants. After six months of trying to figure out what to do, we managed to expand the trial and opened an additional site in Erbil, Iraq. Not long after, Iraqi Kurdistan voted for independence. Baghdad officials did not appreciate this, so they closed the Erbil airport. This time it was not the patients but me who could not access the hospital.

Then there is the issue of working with war surgeons, lone wolves who have seen everything, done everything, and were not easily impressed by my enthusiasm and ambitious research ideas. I never thought that getting involved with research would bring such challenges. If I had known, I would never have hesitated. It has truly been an interesting and rewarding journey. Now I have arrived. This is the result.

# INTRODUCTION

During the war between Sweden and Russia in the early 1800s, mortality due to wound complications was high. To improve the surgical management of the injured, the Swedish King Karl XIII founded Karolinska Institutet in 1810 as an 'academy for the training of skilled army surgeons'.[1] During the following two centuries, global medical research has evolved immensely. However, its focus has shifted away from those wounded during armed conflict.[2]

A starting point for research is the creation of an inventory of the existing evidence and an assessment of the knowledge gaps. Initiatives to increase the use of the best available evidence in the response to armed conflict include utilising the thousands of reviews available in the *Cochrane Database of Systematic Reviews*.[3] However, when the available studies that might be included in a review article or meta-analysis are few and have a low evidence value, the conclusions that can be drawn are limited. The burden of conflict-related injuries among civilians is increasing.[4] The predominant source of information on which to base the care for civilians with conflict-related injuries is anecdotal military experiences.[5,6] Some of the treatment strategies utilised in conflict-affected areas are based on data from high-resource settings; however, such a transfer of evidence is not uncomplicated.[7,8] Although research initiatives do exist, there is an urgent need for context-specific evidence to guide the development of best treatment strategies.[2,9,10]

Research projects in conflict-affected areas are faced with three main sets of challenges: *i)* practical, related to insecurity, a damaged infrastructure, and limited resources; *ii)* ethical; and *iii)* methodological, as many of the available research methods are not adapted to these contexts.[11] The overarching objective of this thesis is to explore the challenges of conducting research on civilians with acute conflict-related injuries, to generate new knowledge to inform best practices for these patients, and to assess the utility of different research methods in resource-limited settings.

# BACKGROUND

## Armed Conflict and Public Health

Armed conflict is no longer understood exclusively as a war declared between countries and fought by national armed forces. Today the term includes asymmetric warfare, internal conflicts with civilian combatants, and attacks by terrorist groups. The year 2017 was one of the most violent since the end of the Cold War, with 49 state-based armed conflicts and 82 non-state conflicts.[12] The global number of direct fatalities caused by armed conflict and terrorism is increasing, reaching an estimated 129 700 in 2017.[13] The number of indirect fatalities is unknown but armed conflicts cause societal harm far beyond that of direct and indirect fatalities. In 2017, the non-fatal outcomes of conflict and terrorism were estimated to be 2.1 million years lived with disability worldwide, which is almost equivalent to that of motor vehicle road injuries.[4] In addition to the direct effects of armed conflict, indirect effects are generated by displacement, the destruction of infrastructure, and the disruption of healthcare delivery (Textbox 1). The direct and indirect effects of armed conflict have significant negative consequences for the development and can halt affected countries' ambitions to reach the universally-accepted Sustainable Development Goals.[14,15]

**Textbox 1.** Direct and Indirect Health Effects of Armed Conflict

**Direct effects** are death and injuries directly linked to the conflict, such as those that result from gunshots and bombings.

**Indirect effects** are secondary to factors such as displacement, forced migration, the destruction of infrastructure, and the disruption of healthcare delivery.

Armed conflicts mainly occur in low- and middle-income countries.[16] Armed conflict settings are characterised by instability and rapid changes in circumstances. With a sudden influx of critically injured patients, resources for healthcare will be limited, regardless of income level (Textbox 2).[17] Conflict-affected settings generally have a significant burden of disease and injury, and a low health system resilience with insufficient infrastructure, equipment, and personnel.[18] The extra burden generated by a conflict often leads to devastating consequences for the population, which are determined more by pre-conflict fragility than by the intensity of the conflict (Figure 1).[19] In addition, warfare tactics have shifted towards targeting the civilian population, healthcare workers and facilities.[20] The assessed proportion of civilian casualties of armed conflict vary, from 35% to as high as 70%.[21,22]

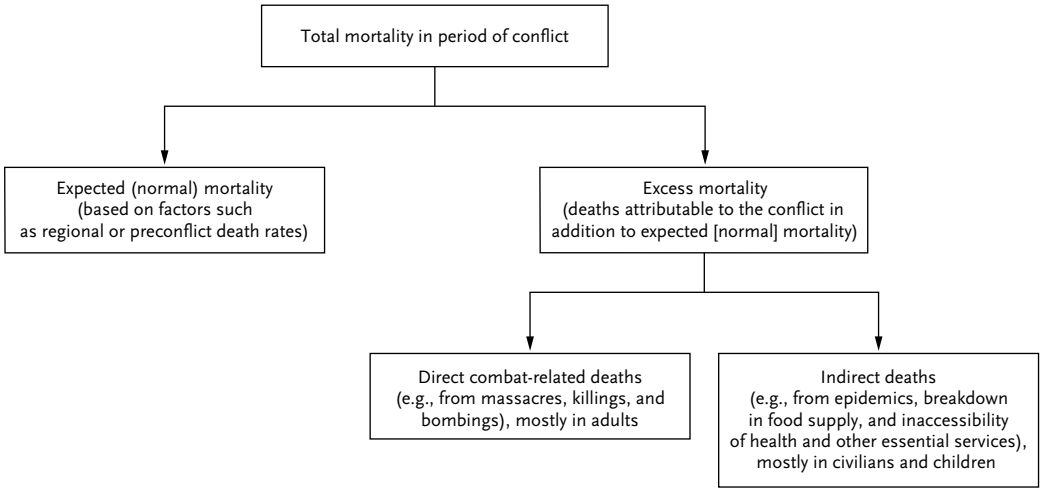


**Figure 1.** Conflict-related Deaths. Reproduced with Permission from Leaning and Guha-Sapir,[19] Copyright Massachusetts Medical Society.

**Textbox 2.** Armed Conflict and Resource-limited Settings

**Armed conflicts** can, according to the International Humanitarian Law, be either international (opposing two or more states) or non-international. Non-international armed conflicts are fought 'between governmental forces and non-governmental armed groups, or between such groups only'.[23]

**Resource-limited settings** have scarce material and financial means, and exist in either low-income countries or subareas within countries.[24] In healthcare, this term can be used for settings with 'limited access to medication, equipment and supplies, under-developed infrastructure and a lack of trained personnel'.[25]

Healthcare in all contexts entails choices about resource allocation, which should be made based on how the population is best served. Interventions need to be planned from the patient's perspective but should also be guided by public health considerations. This requires that the quality of care is maintained, the effectiveness of treatments is guaranteed, and the costs are justified. When resources are scarce, making informed decisions regarding allocation becomes all the more significant.

Surgery has been called 'the neglected stepchild of global public health'.[26] However, new initiatives aim towards the improvement of outcomes and equity for people in need of surgical care.[27] The publication of the *Lancet commission on global surgery* in 2015 provided evidence on the importance of surgery and possibilities to improve global health with wide-scale dissemination.[28] Further, the published research on surgery in low-income areas has increased substantially during the last decade.[29] Recently published results of interventions

have exemplified the possibilities to improve health and change policies through a shift towards surgical care delivery and research in resource-limited areas.[30,31]

## Conflict-related Injuries

Conflict-related injuries are heterogenic and their characteristics change with the evolution of warfare.[32] The two main types of injury mechanisms are blasts and gunshots. Globally, the proportion of gunshot injuries has gradually decreased, and today up to 80% of conflict-related injuries are caused by explosions or fragments from aerial bombs, hand grenades, land mines or improvised explosive devices.[32,33] Death is often caused by exsanguination or central nervous system injuries. Most non-fatal injuries are musculoskeletal, impacting muscles, bones, and soft tissues.[34,35]

Military combatants have a different injury pattern compared to civilians, in part due to their use of protective equipment and access to more advanced medical support.[36] Research initiatives for the management of combat injuries exist within the armed forces. This thesis is limited to civilian injuries. However, as the studies were performed at the hospital level, not all injury types are represented. Patients with severe injuries to the central nervous system, thorax or major blood vessels are absent as they generally do not survive the transport to the hospital.[37-39] Patients with severe burns or injuries that require neurosurgery are also omitted as the hospitals under study do not offer this care. Consequently, these patients were transferred to other facilities.

### *Wounds*

A wound disrupts the skin's function as a protective barrier against the environment.[40] Normal wound healing follows a path with three overlapping stages towards wound closure, a mature scar, and re-epithelialisation.[41] These stages are *i)* inflammation (days), *ii)* new tissue formation (weeks), and *iii)* remodelling (months). Healing is influenced by patient-related and wound-related factors.[42] Patient-related factors include age, smoking, nutrition, anaemia, medications, and diseases, such as diabetes mellitus. Wound-related factors include wound size, ischemia, the extent of devitalised tissue, and the presence of any foreign material or infectious agents. In addition, wound healing is affected by healthcare-related factors, such as surgical and antimicrobial treatment, and patient compliance with treatment protocols (Figure 2).

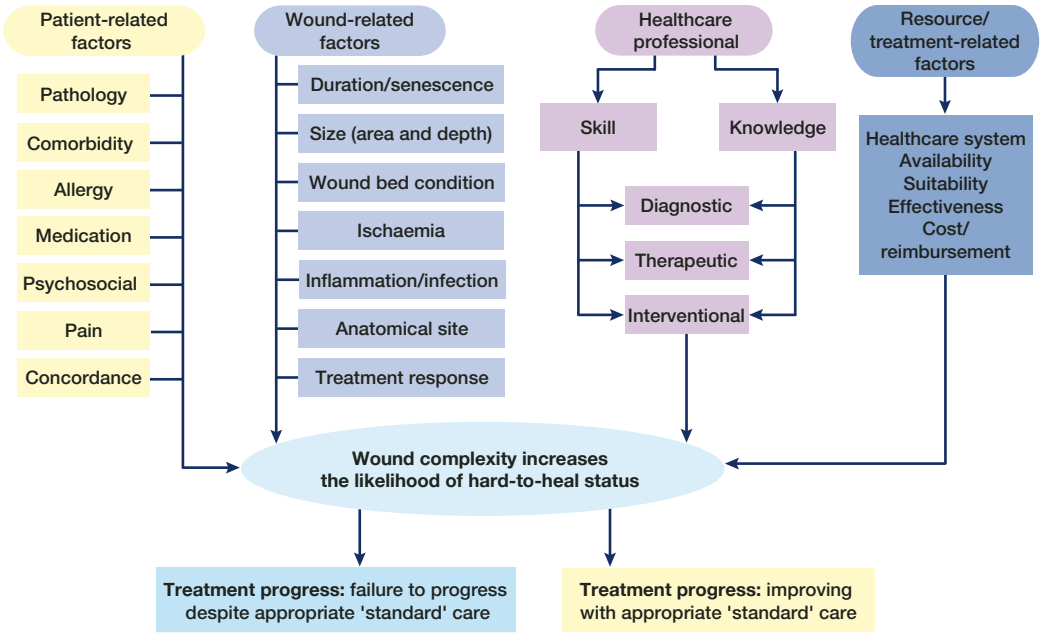


**Figure 2.** Factors Influencing Wound Healing. Modified with Permission from Wounds International,[43] Copyright Wounds International.

Conflict-related wounds are mainly caused by an explosion or a projectile. A projectile is a fragment or a bullet penetrating the body causing a wound tract. This tract is surrounded by devitalised tissue caused by the pressure wave. In addition, the pressure wave generates a vacuum, drawing contaminated particles, including bacteria and foreign materials, into the wound tract.[32]

## Wound Infection

The devitalised tissue and contaminating particles lead to an increased risk of infection.[44,45] Irrigation, mechanical cleaning, and antibiotic treatment limit infectious complications. Still, infection remains a major risk for short- and long-term morbidity and mortality.[46] It is essential to differentiate between contamination, colonisation and infection and refrain from overuse of antibiotics. Contamination and colonisation differ in the presence of non-replicating or replicating microorganisms, respectively. Infection is characterized by the presence of replicating microorganisms that cause a host response, leading to tissue damage and subsequent host injury.[42] Local signs of infection include purulent discharge, increased pain, and redness.[47,48]

The pathogenic microbiota of a wound in a hospitalised patient evolves with time and can be summarised in three stages: environmentally acquired, self-contamination from the skin or gastrointestinal tract, and healthcare-associated infections (HAIs).[32] There are three main groups of bacteria that contaminate conflict-related wounds: *i)* Gram-positive pyogenic cocci, part of the normal skin flora, including *Staphylococcus aureus* and β-haemolytic streptococci; *ii)* Gram-negative bacilli, primarily from the gastrointestinal tract, such as *Escherichia coli*, *Proteus*, *Klebsiella*, *Pseudomonas*, and *Bacterioides*. This group also includes *Acinetobacter*

*baumannii*, found on the skin and in the soil, commonly found in HAIs; and *iii)* Gram-positive bacilli found in the environment, including the *Clostridium* species, causing tetanus and gas gangrene.[32]

### *Antibiotic Resistance*

Antibiotic resistance is increasing worldwide,[49] owing to the overuse and misuse of antibiotics.[50] This development threatens the effectiveness of antibiotics, used both as prophylaxis and as treatment for infections. Multidrug-resistant (MDR) bacteria is a risk factor for persistent infection in conflict-wounded patients.[51] The incidence of MDR organisms in civilians was found to be high, both when systematically screening all patients[52-54] and when culturing chronic conflict wounds.[55,56] MDR organisms were common in infected wounds among Syrian civilians with conflict-related injuries.[52,55] The suggested sources of MDR infection in conflict-related wounds include colonisation of the patients and HAIs.[57] A high MDR prevalence in the study setting could partly be explained by the easy access to antibiotics without a prescription.[58]

## Surgical Management

### *A Short History of Conflict-related Wound Management*

The struggle against bacterial infection can be traced throughout the history of conflict-related wound management.[59] Prior to the era of antibiotics, antiseptic techniques were developed which, together with effectively disinfecting surgical instruments, reduced mortality.[60,61] The principle of removing devitalised or infected tissue and contamination, so-called wound debridement,[62] was further developed during the First World War, as described by the Belgian Army surgeon, Antoine Depage.[63] The Penicillium mould, accidentally discovered by Alexander Fleming when he recognised that the mould inhibited the growth of staphylococci,[64] was not mass-produced in the early years of the Second World War. Instead, the oral prophylactic administration of sulphonamides was recommended after an injury. Gradually, penicillin and streptomycin came into use.[65] The knowledge on the bacteriology of wounds increased as a result of the research conducted during the war.[65] In the Korean and Vietnam Wars, thorough debridement was found to decrease the risk of infection.[66,67] Other management developments led to improved outcomes for wounded combatants, such as forward surgical care, helicopter evacuations, and vascular repairs.

### *Modern Surgical Management*

The modern management of conflict-related wounds relies on irrigation, debridement,[68] and antibiotic therapy, used both as perioperative prophylaxis and to treat wound infections.[32,69] After the stabilisation of fractures and management of any damage to vital structures, the wound is dressed and monitored until ready for so-called delayed primary closure (DPC), as early closure of the wound after debridement is associated with a greater risk of local infection and septic complications.[70] The optimal time for DPC has not been determined and is based on clinical judgement, with signs of sepsis or offensive smell from the wound

prompting early return to the operating theatre for re-assessment.[71] Current practice guidelines recommend DPC three to five days following injury, depending on wound status.[32,70]

There are treatment guidelines and established best practices for traumatic injuries in high-resource settings.[72] However, a major challenge lies in how to manage high numbers of patients when resources are limited. To support prioritisation and allocation of resources, the effectiveness, utility, and cost-effectiveness of available treatment methods must be carefully evaluated. To assess the specific challenges related to resource-limited settings, context-specific evidence is needed.

### Negative Pressure Wound Therapy

Since its introduction in the early 1990s, negative pressure wound therapy (NPWT) has been adopted as a widespread technique in wound management.[73] The technique involves a sterilised sponge that is fitted into the wound and covered with a plastic sheet. A hole is cut in the plastic and a suction device is attached, creating negative pressure. Any tissue fluid is drawn away and collected in a canister. Expert consensus supports NPWT for use in a variety of indications, including as a bridge from debridement to DPC.[74] Claimed benefits include shortened healing time and fewer infectious complications. The airtight plastic sheet might, however, increase the risk of anaerobic bacterial infections. Additional risks include pain during dressings changes[75] and bleeding from granulation tissue.[76]

Attempts have been made to study the potential benefits of NPWT. However, more systematic reviews than randomised controlled trials (RCTs) have been published, and the majority of existing RCTs contain quality-related issues.[77] In addition, many trials are financially supported and initiated by the medical device industry and are often terminated prematurely.[78] This generates a risk of publication bias as "negative" results, i.e. results without evidence of effectiveness, are less likely to be published.

Cochrane reviews of NPWT for chronic and surgical wounds have emphasised the need for high-quality, adequately powered clinical trials to assess effectiveness.[79-81] A systematic review of RCTs of NPWT for the treatment of open traumatic wounds concluded that evidence of the technique's effectiveness is lacking.[82] Consequently, evidence from a carefully designed and performed RCT is necessary to establish best practices.

Reports have been written regarding NPWT in the treatment of acute conflict-related wounds[83-85] and the technique is now being introduced as a treatment alternative for these patients. However, the decision to implement a costly treatment method should be based on high-quality, context-specific evidence of its effectiveness as a remedy as well as its cost-effectiveness. For NPWT, there is little such evidence to date.

# AIMS

**The overall aim** of this thesis is to generate knowledge on the management of conflict-related injuries among civilians in resource-limited settings.

**The specific aims** were:

I. To compare the outcome and resource consumption of civilian patients, recieving surgical treatment for acute conflict-related injuries, with and without wound infection.

II. To explore the challenges hospital-based physicians encounter in the management of conflict-related wounds among civilians, focusing on surgical intervention and antibiotic use.

III. To compare the safety and effectiveness of NPWT against that of standard wound treatment, specifically in patients with acute conflict-related extremity wounds.

IV. To determine the treatment-related costs and cost-effectiveness of NPWT for acute conflict-related extremity wounds in civilian hospital care.

# METHODOLOGY

Conflict-related wound management is a complex topic that is not well-studied. Therefore, the most suitable research methods remain to be defined. For this thesis, I have utilised different approaches. Through observational research methods (*Paper I*), my colleagues and I assessed how wound infection is associated with outcomes. In *Paper II*, we used qualitative methods to explore the main challenges in conflict-related wound management. In a randomised clinical trial, we evaluated an intervention for wound treatment, specifically regarding its effectiveness and safety (*Paper III*), and its associated costs and cost-effectiveness (*Paper IV*). Figure 3 depicts the research framework for this thesis.

By combining different methods, each with different possible biases, the methods will ideally complement each other and thus result in an improved overall body of evidence. This rationale is in line with the concept of methodological triangulation.[86]

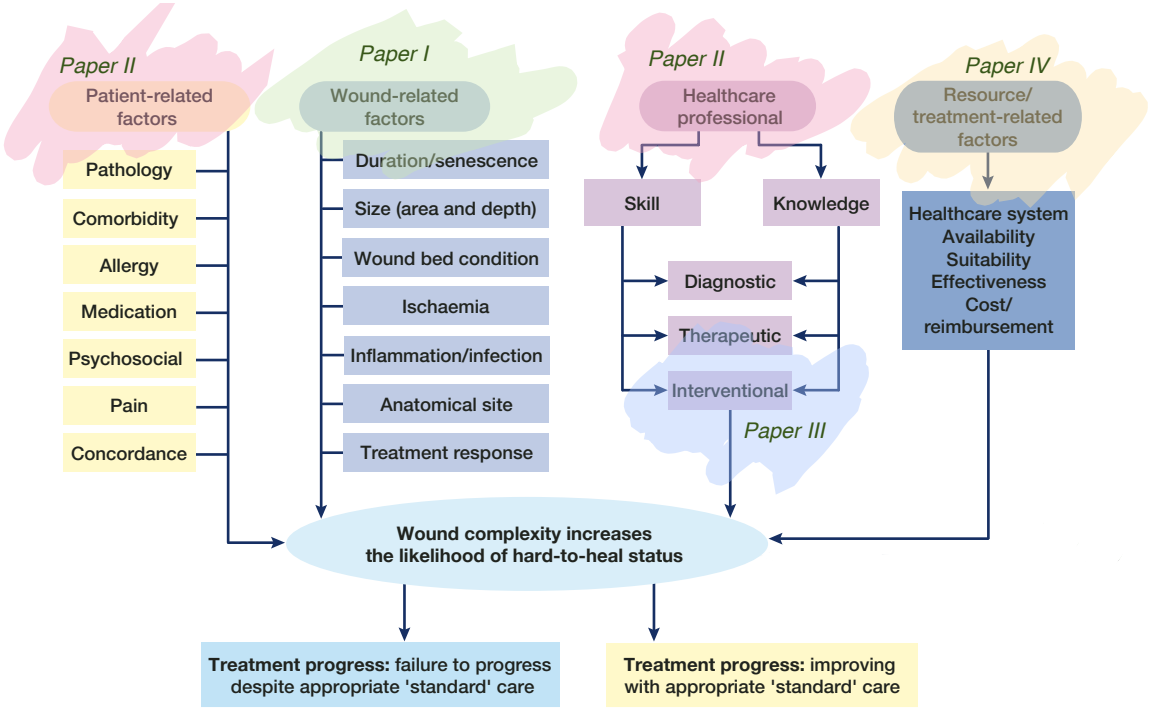


**Figure 3.** Research Framework. Modified with permission from Wounds International,[43] Copyright Wounds International.

## Study Areas

Data collection for all papers (*I–IV*) was initiated in 2015 at the civilian Ministry of Health hospital in Ar Ramtha, Jordan (Figure 4). This hospital is located near the Syrian border and is supported by the international non-governmental organisation (NGO) Médecins Sans Frontières/Doctors Without Borders (MSF). In June 2016, the Syrian border was closed following a border control attack. At that time, data collection was complete for *Papers I* and *II*; however, we had not yet reached the target number of patients for the randomised trial (*Papers III* and *IV*). We began searching for an additional location at which the trial could be

expanded. An opportunity arose in Erbil, Iraq, at a civilian hospital run by the local NGO Emergency Management Center (EMC) (Figure 5). This hospital received patients from Mosul during the armed conflict between 2016 and 2017.[87] When the Syrian border was re-opened in November 2016, we resumed patient enrolment in Jordan, but this was suspended again in February 2017.

**Figure 4.** Ar Ramtha Hospital, Jordan. Photo: Andreas Älgå


**Figure 5.** Emergency Management Center, Iraq. Photo: Andreas Älgå

Consequently, the patients included in this thesis were from Syria and Iraq. These countries are heavily affected by armed conflict, with a life expectancy approximately 15 years shorter than that of Sweden (Figure 6). We chose study areas with reasonable stability and security, albeit with proximity to armed conflict, providing unique preconditions for a clinical research project. Both EMC and Ar Ramtha Hospital were equipped with an operating theatre, autoclave, and computer tomography. Each hospital had a basic laboratory but did not have the facilities to perform microbiological cultures or analyses. For *Paper I*, an external laboratory was used. Specialist doctors were anaesthesiologists and general or orthopaedic surgeons. Angiography or endovascular capabilities were not available, nor were specialists in vascular-, thoracic-, plastic-, or neurosurgery. Prophylactic antibiotics were available. However, more advanced antibiotics, such as the rifampicin, were unavailable (*Paper II*).

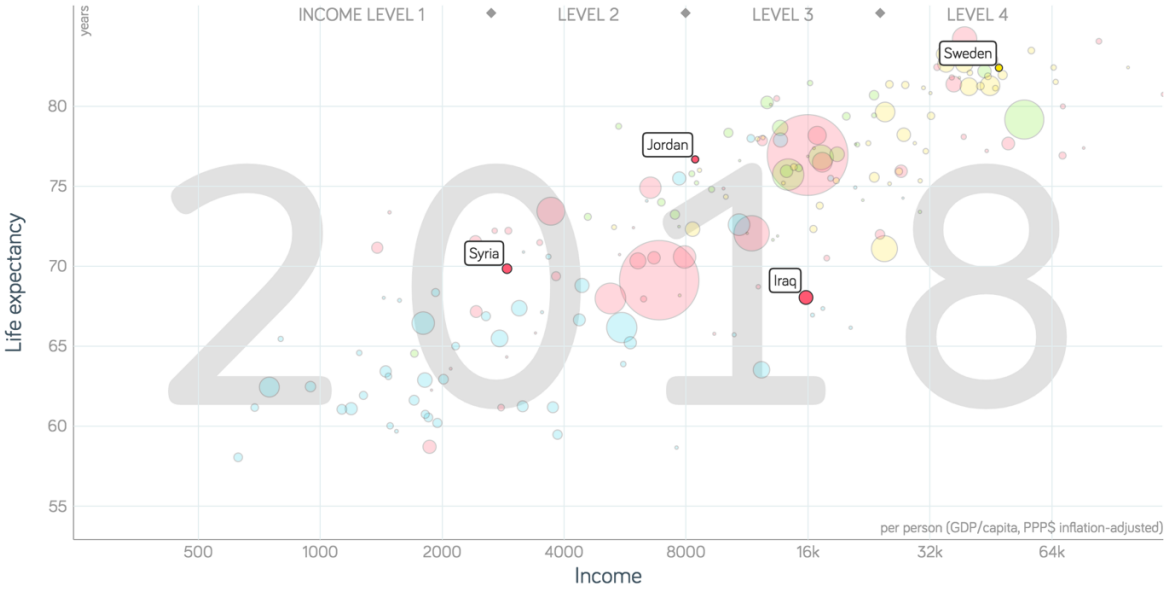


**Figure 6.** Life Expectancy and Income per Capita Arranged by Country, 2018. Free material from www.gapminder.org.

### *Jordan and the Syrian Armed Conflict, Papers I–IV*

Syria is a low-income country (Figure 7).[88] The Syrian armed conflict started in 2011 and rapidly deteriorated into what has been described as 'the worst man-made disaster the world has seen since World War II'.[89] To date, the conflict has claimed 350 000 lives; over 4 million Syrians have been forced to migrate, primarily to neighbouring countries.[16] The upper-middle-income country, Jordan, now hosts 655 000 Syrian refugees.[88,90] At Ar Ramtha Hospital, patients with acute injuries from the Syrian armed conflict are treated. Wounds are managed in accordance with the International Committee of the Red Cross (ICRC) protocols.[32]


**Figure 7.** Study Areas. Copyright Google Maps.

*Iraqi Kurdistan and the Battle of Mosul, Papers III–IV*

Iraq is an upper-middle-income country.[88] Since the current state of Iraq was formed in the early 1930s, not one decade has passed without the country experiencing armed conflict. In the mid-2010s, militant Islamist groups like Al-Qaeda and the Islamic State of Iraq and Syria (ISIS) increasingly gained control in Iraq. Between 2016 and 2017, an Iraqi-led coalition reclaimed the city of Mosul from ISIS. EMC was a key medical facility that received people injured in the conflict.[87] The hospital is designated to treat patients with conflict-related injuries.

## Study Populations

The population in *Paper I* consists of 457 consecutive patients who were admitted to Ar Ramtha Hospital from September 17, 2014, to June 21, 2016, and received surgical treatment for acute conflict-related trauma (Table 1). The availability of standardised culture results established the start of the study, and closure of the Syrian border determined the end.

**Table 1.** Overview of the Included Papers

| | ***Paper I*** | ***Paper II*** | ***Paper III*** | ***Paper IV*** |
|---|---|---|---|---|
| **Study Period** | 2014–2016 | 2015 | 2015–2018 | 2015–2018 |
| **Design** | Cohort study | Qualitative interview study | Randomized controlled trial | Health economic evaluation |
| **Participants** | Patients having surgery for conflict-related injuries, Ar Ramtha | Physicians, Ar Ramtha | Patients with conflict-related extremity wounds, Ar Ramtha and EMC | Patients with conflict-related extremity wounds, Ar Ramtha and EMC |
| **Number** | 457 | 10 | 165 | 165 |
| **Data Sources** | Routinely collected clinical data | Semi-structured, face-to-face interviews | Case report forms | Case report forms, hospital end-of-year report |
| **Main Analysis Methods** | Logistic regression models | Content analysis | Standard analysis in accordance with CONSORT[91] | Cost and cost-effectiveness analyses[92] |
| **Main Outcome Measures** | Clinical outcomes and resource consumption | Perceptions of challenges in wound management | Wound closure by day five and net clinical benefit | Treatment-related costs and cost-effectiveness |

EMC, Emergency Management Center. CONSORT, Consolidated Standards of Reporting Trials.

The ten participants in *Paper II* were recruited in 2015. They all worked for MSF at Ar Ramtha Hospital, five as general or orthopaedic surgeons and five as general doctors in the emergency room or on the ward. The participants were selected through purposeful sampling aiming at heterogeneity in terms of age, sex, country of origin, medical specialty, and years of work experience (Table 2).

**Table 2.** Characteristics of the Ten Participants in *Paper II*

| | | |
|---|---|---|
| Age, median (IQR) | 31 | (29–39) |
| Male, n (%) | 6 | (60) |
| Origin, Jordan (non-Jordan) | 6 | (4) |
| Medical specialty, general or orthopaedic surgeon (not specialised) | 5 | (5) |
| Years of work experience, median (IQR) | 6 | (4–13) |

IQR, interquartile range.

For *Papers III* and *IV*, participants were recruited between June 9, 2015, and October 24, 2018, at Ar Ramtha Hospital and EMC. A total of 278 patients were eligible for participation (Figure 8). One patient declined. Some 103 patients were either deemed unsuitable by the responsible surgeon or were not included for other reasons, i.e. they were admitted during a mass-casualty situation, were transferred to other hospitals, or the study nurses were not informed when they arrived at the hospital. Consequently, 174 patients were randomised. Nine patients were excluded; either because we could not obtain delayed consent, or because the patients did not fulfil the inclusion criteria, died, or left the hospital against medical advice. A total of 165 patients (67 from Ar Ramtha, 98 from EMC) remained for the intention-to-treat analysis.

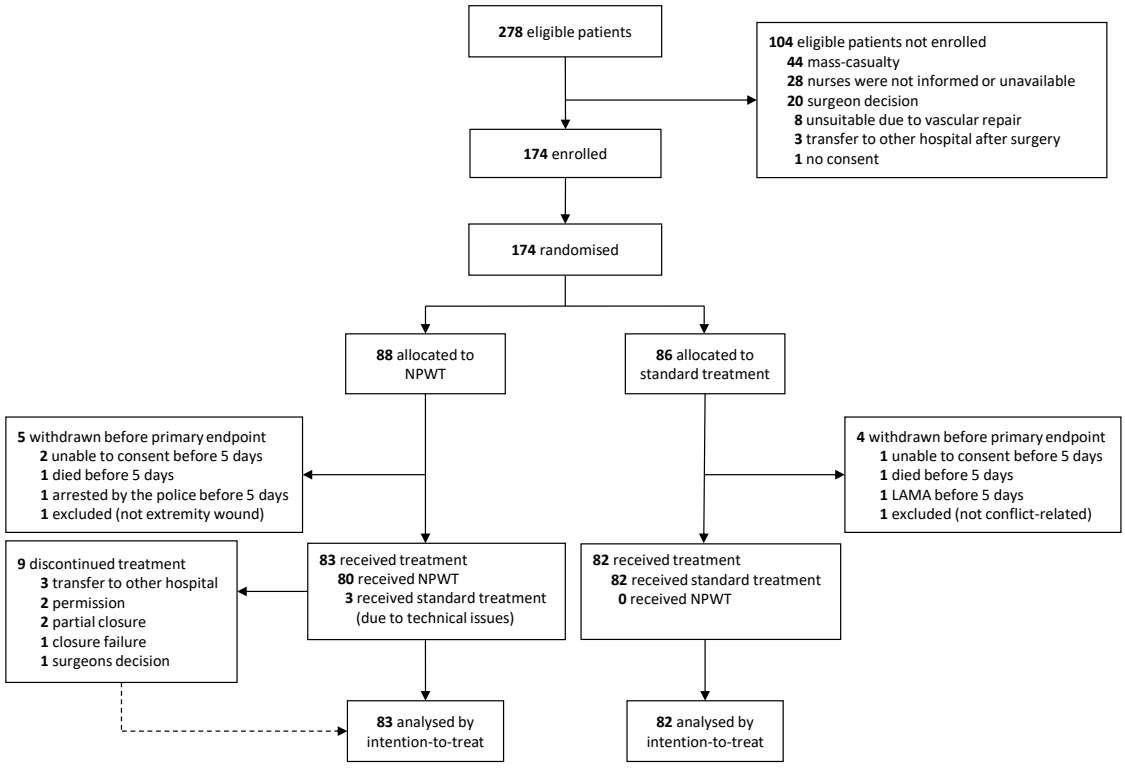


**Figure 8.** Flow Chart. NPWT, negative pressure wound therapy. LAMA, left against medical advice.

## Study Design and Methods

### *Paper I*

The seed of *Paper I* was planted during my first visit to Ar Ramtha. At the MSF office next to the hospital, I was presented with a folder containing wound cultures for all patients with clinically infected conflict-related injuries treated at the hospital. Inspired by the potential of this data set, we developed a cohort study protocol to compare patients with wound infection to those without, and to assess if the groups differed in terms of clinical outcomes and resource consumption. After ethical approval, we started building a database of these culture results and clinical information extracted from a pre-existing MSF database. We collected both retrospective and prospective data.

Surgeons obtained intraoperative samples (fluid, soft tissue, or bone) only from wounds with clinical signs of infection. Details on bacterial species and their resistance patterns were extracted from wound culture reports. MDR was defined as resistance to at least one antibiotic from three or more relevant antibiotic groups.[93] Methicillin-resistant *Staphylococcus aureus* (MRSA) was considered as MDR.

One strength of using routine clinical data was that, to a large extent, it was readily available in a computer database; however, there were some limitations. First, outcome measures were limited. Available data included length of hospital stay, number of surgeries, limb amputations, and inpatient death. Outcome measures that would have been interesting to study involved data on the type and duration of antibiotic treatment, septic complications, and the number of days spent in the intensive care unit. Second, limited baseline characteristics were available. Details on previous medical history and medications, vital signs on admission, injury mechanism, and injury severity score would have been relevant to include. With the aim to assess injury severity as a confounder, one of our study nurses localised the paper files for all 49 patients with wound infection, and non-infected controls were matched according to age and sex. We then calculated the coded Revised Trauma Score (RTSc)[94] from the respiratory rate, systolic blood pressure, and Glasgow Coma Scale (GCS)[95] scores. The mean RTSc in cases was then compared to the controls. Third, we had to rely on local definitions of clinical signs of infection and trust the adherence to those guidelines. Wound infection was defined as clinical signs of infection and at least one positive culture. This definition, however, might have been too strict and was adjusted for *Paper III* to only include clinical signs, defined as purulent discharge,[47] disregarding confirmation by wound culture. Another strength of the study was the use of an accredited clinical microbiology laboratory that utilised well-established analysis techniques and interpretation guidelines.[96] The findings in *Paper I* were reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[97]

*Paper II*

Due to the explorative nature of *Paper II*, we concluded that a qualitative study design using interviews and subsequent content analysis would be suitable. Qualitative methods enable the researcher to describe, interpret, and generate theories on the experiences of individuals and the specific contexts in which they took place.[98] These methods are used to answer questions difficult to approach quantitatively, mainly focusing on the 'how?' and 'why?'.[99] Data is often gathered through interviews. An inductive analysis is commonly used to derive the broader meaning from the interview material. A deductive approach will utilise a pre-existing perception, guideline or theory for continuous comparison throughout the condensation and abstraction processes. We used the protocols for wound care, hygiene, and antibiotic treatment from Ar Ramtha Hospital for the deductive analysis. Subsequently, our goal was to analyse both manifest and latent content. Manifest content is defined as the concrete meaning of a text, whereas latent content refers to the interpreted underlying meaning.

In the area of conflict-related wound management in civilians, there is a dearth of qualitative research and no studies have been published as yet on the experiences of physicians in this context. Our aim was to explore physicians' experiences by letting the participants freely present their views and then elaborate. This has been shown to be an effective design to generate knowledge that cannot be obtained through quantitative methods.[100] We reported our findings in accordance with the standards for reporting qualitative research (SRQR).[101]

*Paper III*

Expatriate surgeons from the United States who were working for MSF at Ar Ramtha Hospital had requested the introduction of NPWT for patients with hard-to-heal traumatic wounds. I was approached by MSF Sweden and asked to facilitate the evaluation of NPWT in terms of feasibility, safety, and effectiveness. At first, I was somewhat reluctant due to the costs associated with NPWT and the limited evidence of its effectiveness. However, I concluded that an uncertainty of effect, i.e. clinical equipoise, is to be considered an ideal starting point for an RCT.[102] In addition, the introduction of NPWT for civilians with conflict-related wounds was discussed at the time, both within MSF and the ICRC. Once an intervention has been established as part of routine treatment, questioning its indication and conducting a clinical trial becomes much more problematic. Therefore, the time was limited to initiate an adequately powered RCT to evaluate the safety and effectiveness of NPWT for this patient group.

We designed a pragmatic, randomised, controlled, superiority trial (*Paper III*). The purpose of a pragmatic trial is to inform real-world healthcare decisions by designing the trial so that most patients with the studied condition will be eligible, using non-strict inclusion criteria and few exclusion criteria.[103] We considered adult patients (≥18 years) with acute conflict-related extremity wounds (≤72 h) in need of surgical debridement as eligible (Figure 9). Patients with a wound suitable for primary closure were not included. We used block randomisation with three fixed block sizes (4, 6, 8). Paper envelopes were prepared by one member of the research team who was not involved with randomisation or treatment. At the end of the first

surgery, the participants were randomly assigned to NPWT (a commercial NPWT device with a continuous negative pressure of 125 mm Hg) or standard wound treatment (wound dressings with non-adhesive sterile gauze covered with a bandage) according to the ICRC war surgery protocol.[32] Apart from the wound treatment methods, the same perioperative routines and materials were used for all participants. Fractures were immobilised by using external fixation. All participants received narrow-spectrum antibiotic prophylaxis.

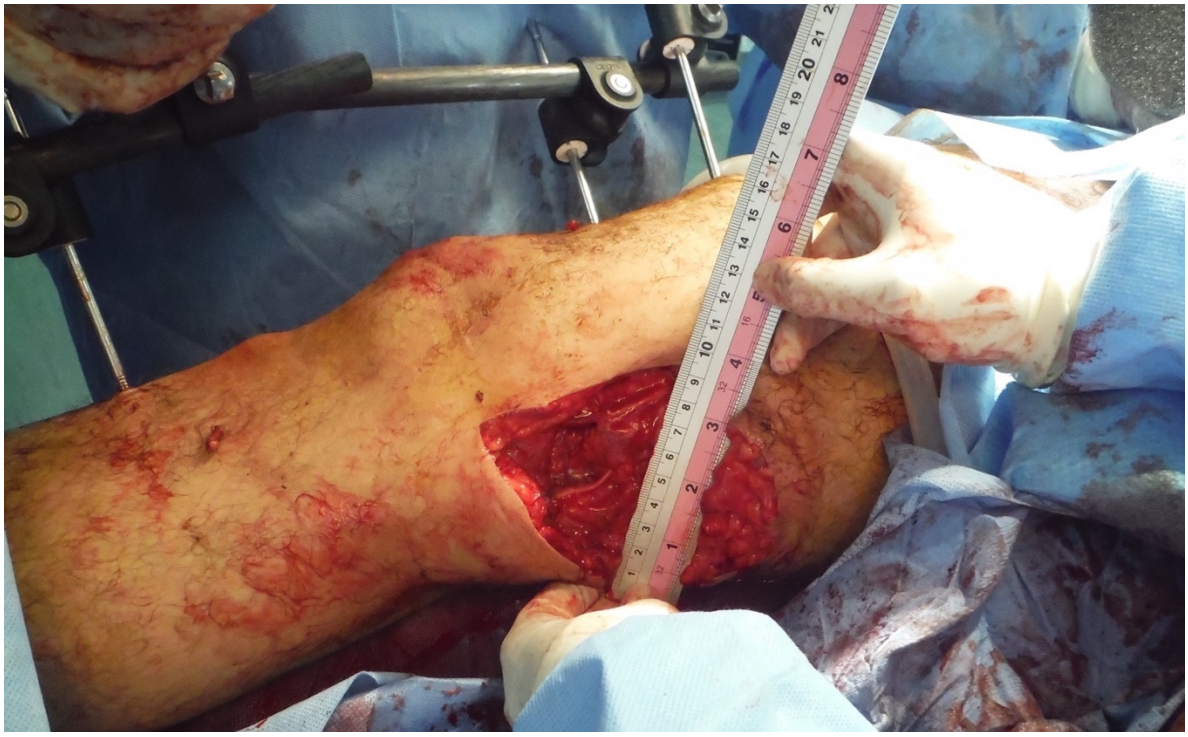

**Figure 9.** Patient with an Acute Conflict-related Extremity Wound. Published with Patient Permission. Photo: Murad Alrawashdeh

Patients were sometimes transported from the emergency room to the operating theatre for emergency surgery without full consciousness, circumstances that often provided insufficient time and opportunity to obtain informed consent before surgery. We therefore utilised the principle of delayed consent.[104] Participants undergoing acute surgery entered the study under presumed consent. They were subsequently informed as soon as appropriate during the postoperative period and written consent for continuation in the trial was collected. Three patients were unable to provide delayed informed consent within five days after randomization; these patients were excluded from the intention-to-treat analysis.

The nature of the treatment methods precluded blinding of the patients or staff involved. Two independent clinicians, blinded to treatment allocation, evaluated the wound photographs. Data were collected at each dressing change, at hospital discharge, and at days 14 and 30 following the day of randomisation. We defined wound closure as closure by flap, suture, or split-thickness skin graft. The primary endpoint was wound closure by day five. The coprimary endpoint was net clinical benefit, defined as a composite of wound closure by day five, and freedom from any bleeding, wound infection, sepsis, or amputation of an index limb. The trial was registered online at ClinicalTrials.gov (NCT02444598)[105] and the research

protocol was peer-reviewed and published.[106] The study was carried out, analysed, and reported in accordance with Consolidated Standards of Reporting Trials (CONSORT) guidelines for randomised and pragmatic trials.[91,103]

The observational study design of *Paper I* is often used to measure the effectiveness of an intervention in a 'real-world' scenario, as compared to the controlled study setting of an RCT. In general, observational studies are considerably less costly and time-consuming compared to RCTs and have been shown to result in similar findings.[107] However, some biases and confounders cannot be controlled for without randomisation.[108] The random allocation to treatment groups accounts for known and unknown confounders and generates two groups with balanced characteristics. In a large enough RCT, the only thing that should be non-identical between the groups is treatment allocation. The intention-to-treat analyses aim to preserve this random allocation by basing the analyses on the original treatment assignment and not the treatment (if any) received. This strategy should minimise the effect of non-random dropouts or treatment crossover. In conclusion, the randomisation process and intention-to-treat analyses should assure clear, unbiased evidence. RCTs are therefore considered a robust method to assess the effectiveness of an intervention, while real-world studies can be viewed as hypothesis-generating.[109]

Surgical research generally consists of retrospective case series.[110,111] In the peer-reviewed literature, it has been reported that less than 10% of all surgical articles report the results of RCTs.[112] Surgical interventions are half as likely to be based on RCTs than medical therapies.[113,114] In a field with rapid technological advances and new surgical interventions, it is largely the responsibility of the research community to generate high-quality evidence to evaluate the safety and effectiveness of such new techniques. In a recent a review of the evidence on NPWT, less than 1% (n=27) of the 3 287 identified publications were RCTs with clearly defined endpoints.[73]

### *Paper IV*

Health economic evaluations may be defined as 'comparative analyss of alternative courses of action in terms of both their costs and consequences'[92] and can help guide the allocation of healthcare resources. Before a treatment method is implemented in a resource-limited setting, its effectiveness should be *i)* proven and *ii)* found to justify the costs involved. When designing *Paper III*, we concluded that the logical next step after the assessment of the safety and effectiveness of NPWT would be a health economic evaluation. Health economic evaluations of NPWT versus standard wound treatment exist, but as most of these analyses are based on trials with methodological weaknesses, the evidence value of their conclusions are limited, hence, cost and cost-effectiveness of NPWT need to be further analysed.[77] Economic evaluations of NPWT, as an alternative to the standard treatment of traumatic wounds, are scarce. To date, there are only two analyses based on randomised data and one is included in this thesis (*Paper IV*). The other found no evidence of cost-effectiveness.[82]

Within the health economy framework, the three alternative assessment methods available were a cost-benefit analysis, a cost-minimisation analysis, or a cost-effectiveness analysis. For cost-benefit analyses, health effects are valued in monetary terms. Based on the nature of the outcome data from *Paper III*, we concluded that this method was not a suitable option. A cost-minimisation analysis implies that two treatments result in equivalent health effects, and is typically utilised for data derived from non-inferiority trials.[115] Although *Paper III* reports 'negative' results, we cannot exclude the possibility of important differences in treatment effects. It is important to bear in mind that 'absence of evidence is not evidence of absence'.[116] Consequently, a cost-minimisation analysis was not considered an appropriate methodological choice.[117] Cost-effectiveness calculations incorporates both the cost and the health effects of two treatments. The health effects are valued in nonmonetary units. We decided to perform a cost-effectiveness analysis, despite a non-significant difference in treatment effects (*Paper III*).

We conducted an analysis of costs from the perspective of the healthcare provider,[92] covering overhead and capital costs, and costs for staff, medicines and materials. We included the costs of services delivered to the participants admitted to the hospital, including the costs of surgeries and care given on the ward. Costs per surgical procedure were calculated based on the total number of procedures per year. Costs for postoperative care were calculated as cost per hospital day based on the yearly costs for all admitted patients. We used cost data from EMC, where the information was readily available. In addition, EMC exclusively treats patients with conflict-related injuries, thus reducing the risk of a larger surgical panorama that might have affected the health economic analysis. We used outcome data until 30 days after randomisation. We excluded costs for the treatment of chronic wounds (defined as non-closure within 30 days) in the analysis. The primary and coprimary endpoints of *Paper III* were used as health outcomes. To challenge the data used in the analysis, we performed sensitivity analyses for hospital productivity level, staff and hospital costs, the capital cost for the NPWT pumps, and the depreciation time of the NPWT pumps. The study findings were reported in accordance with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines.[118]

### Data Collection and Management

Data for this thesis were stored at a protected server at Karolinska Institutet. The use of identification numbers ensured the anonymity of the data. With the use of encryption methods, all data remained confidential throughout the data entry and analysis process.

The data used in *Paper I* was limited to routinely collected clinical data. Data were extracted from a clinical patient database, paper-based patient files and wound culture reports. To ensure full quality control and traceability of our data, we used designated data management software, Epidata Entry (The Epidata Association, Odense, Denmark). This software is free to download (www.epidata.org) and thus suitable for use in resource-limited settings. An extensive data-check operates during the data entry process. By tracking all changes, random errors can be identified and corrected.

The data for *Paper II* were collected through semi-structured, face-to-face interviews. We constructed an interview guide with questions and probing areas. I handled all interviews and thus was able to observe each interviewee's body language and gestures. The interviews were recorded, and the interview guide was discussed within the research group. When necessary, the guide was adjusted in-between interviews. We included participants until saturation was reached, i.e. when further data collection was not found to contribute new information regarding the main topics. Eleven medical doctors were invited to participate and they all consented to the study. The recorder malfunctioned during one interview, which had to be excluded. One interview was terminated in advance because the participant needed to attend clinical work. As a consequence, this interview is shorter than the others, but it was included in the analysis process. In total, ten interviews were analysed. The duration of the interviews ranged from 13 to 50 minutes, with a mean duration of 32 minutes.

In *Paper III*, all data were primary data, collected prospectively on paper-based case report forms (CRFs) in accordance with Good Clinical Practice (GCP).[119] The data were quality-controlled for completeness by the primary investigator; an external monitor regularly reviewed unblinded data. The paper-based data were entered into a database using the Epidata Entry software. Through double entry, we minimised the risk of random errors from manual entry. Data were thoroughly checked for consistency and plausibility.

In *Paper IV,* we utilised clinical outcome data derived from *Paper III*. Data used for the cost analysis were collected from the EMC end-of-year report, payroll, and measurements of the hospital area. The participating surgeons and nurses provided additional information, for example, meal costs and land-leasing prices in Erbil city.

### Statistical Analysis

For *Paper I*, the mean with standard deviation (SD) was used for summarising scale variables, and proportions with 95% confidence intervals (95% CI) for categorical variables. We used t-test to compare scale variables and bivariate analyses with Chi-square to compare two categorical variables. Binary logistic regression models were used to evaluate differences in outcomes and resource consumption between patients with and without infections.

For *Paper III*, we based the sample size calculation on the expected rate of participants reaching the primary endpoint of 75% in the NPWT group and 50% in the control group. We considered a 25% difference clinically significant. At a significance level of 5%, we calculated that 58 participants per treatment group would give the study 80% power. Considering the nature of the study setting, we anticipated dropout levels higher than what might be expected in other trials. To adjust for dropouts, we therefore aimed to enrol a total of 200 participants.

The analysis was done by intention to treat and no interim analyses were carried out. We reported continuous variables as a median with an interquartile range (IQR), and categorical variables as numbers and proportions. We computed the between-group differences in categorical variables by employing Fisher's exact test. Two-sided 95% CIs were calculated

for the absolute differences in the proportions of the outcomes, according to the method of Jeffreys.[120] We estimated time-to-closure with the Kaplan-Meier (KM) method, and we used the Mantel-Haenszel log-rank test to compare the KM cumulative incidence curves. We applied a standard Cox proportional hazards model for estimating the relative chance of closure (hazard ratios [HRs] and 95% CIs) with the standard dressing group used as the reference. Inspection of log–log plots and a global test based on Schoenfeld residuals indicated that the proportional hazards assumption was not violated.

The analysis in *Paper IV* was by intention to treat. We used the Mann-Whitney U test or a two-sample test for equality of proportions to detect differences in characteristics and outcomes between the two study arms. For this thesis, a two-sided P<.05 was considered to indicate statistical significance. We analysed data using SPSS Statistics (IBM Corp., Armonk, New York, USA) and R version 3.5.0 software.[121]

### Qualitative Analysis

For *Paper II*, we used content analysis as described by Graneheim and Lundman.[122] The interviews were transcribed verbatim. Subsequently, the transcribed interviews were read and re-read in their entirety to grasp the overall content and to correct mishearing and misinterpretations. For the content analysis, we first identified meaning units, defined as words, sentences or paragraphs related by their context or meaning. If needed, we then condensed the meaning units. Subsequently, we developed codes, sub-categories, and categories by both deductive and inductive approaches. We conducted the analysis primarily using tables in Microsoft Word® 2011 (Microsoft, Redmond, Washington, USA). We implemented member-check during the interview period, where I continuously reviewed the material and, if clarification was needed, went back to the participants to completely understand the content. We used peer-check during the analysis and the writing processes through consultation with experienced qualitative researchers.

### Role of the Funding Source

This is an investigator-initiated research project. No commercial companies were involved in the study design, the interpretation of data, or the writing of the reports, nor did any companies contribute funding.

### Ethical Considerations

The procedures for *Paper I* were limited to the analysis of routinely collected clinical data. The primary risk generated by the retrospective data analysis was a breach of data confidentiality. With the above-described data protection strategies, the risks of harm were considered minimal. The potential benefit for future patients by the generated knowledge therefore justified proceeding with the study. The participants of *Paper II* all provided written informed consent, and were informed that they could withdraw from the study at any time. It could be argued that some of the matters discussed could be considered as sensitive.

However, anonymity and confidentiality were assured. As the participants were physicians, the power between the researcher and the participants was considered well-balanced.

The main ethical considerations pertain to *Paper III*. The introduction of a relatively new intervention in resource-limited settings must be done with care. 'Failing to match technology to local needs and abilities' has been mentioned as one of the seven sins of humanitarian medicine.[123] However, it may be considered unethical to exclude casualties of armed conflict from research and thus refrain from the generation of knowledge imperative for the optimisation of the relevance and effectiveness of the healthcare provided to these populations.[124] In areas where a local ethics committee is absent or sub-standard, an external independent committee might be useful. For our studies (*Papers I–IV*), in addition to the Jordanian and Iraqi ethics committees, we utilised the independent MSF ethics review board.[125]

It has been argued that moving clinical trials to low- and middle-income countries to minimise research costs could be a violation of international human rights or humanitarian law.[126] There is a need of research within these populations; however, it should be health-promoting and not lead to excess risks. A thorough risk-benefit analysis with identified benefits for the population studied is essential before initiating such research projects. In addition, attention should be paid to the dissemination of study results. To reach the actors involved in improving the care for patients with conflict-related injuries, publication in open-access journals is an option to be considered.

Patients eligible for inclusion in the RCT were sometimes illiterate or in a position of dependence, and thus were at a risk of feeling obliged to participate in the trial. We provided written and oral information in English and Arabic to eligible patients, including details on their right to withdraw from the study and issues concerning confidentiality. No incentives were provided to any participant. We collected written informed consent from each participant before randomisation or obtained delayed consent within five days of randomisation.

The principle of delayed consent has been established in large trials that include critically ill participants.[127-129] Ethically, the use of delayed consent has been questioned, and some ethics committees do not allow this practice.[127] Researchers have used hypothetical scenarios to confirm the acceptability of delayed consent among relatives of critically ill patients.[130-132] One questionnaire study among patients enrolled in a trial using delayed consent found that it was considered acceptable from participants' perspectives.[104] The intervention under investigation in *Paper III*, NPWT, is a well-established treatment and not to be considered experimental. In addition, prior to study initiation, the implementation of NPWT in Ar Ramtha as a standard treatment option was discussed, making the use of delayed consent less controversial. All trial procedures adhered to the GCP guidelines and an external monitor regularly reviewed unblinded data in confidence.

*Paper IV* was limited to secondary analyses of aggregated outcome data derived from *Paper III* and additional non-sensitive data for cost calculations. The potential risks for study participants are therefore considered to be minimal.

Formal competencies were acquired through courses in GCP and ethics in global and public health research. We held regular ethical discussions at the research sites, and local researchers received online GCP training.

All study procedures adhered to the Declaration of Helsinki.[133] Ethics approval was obtained from the Ethics Review Committee of the Jordanian Ministry of Health (MOH REC 150037) (*Papers I–IV*), the Ethics Review Board of MSF (ID 1520) (*Papers I–IV*), the Research Ethics Committee, Kurdistan Regional Government in Iraq (2:10 6/3/2017) (*Papers III–IV*), and the Swedish Ethical Review Authority (2019-01975) (*Papers III–IV*). The proceedings in the MSF ethics approval included a yearly re-application for renewal.

### Personal Fieldwork Reflections

I came into this project with a rather naïve idea that things would work out easily, and that the studies would run smoothly. This feeling was enforced by the positive attitude expressed by the MSF staff, especially within the MSF Sweden Innovation Unit. However, research will probably never have priority within an MSF project, and rightly so.

The opportunity to conduct research in cooperation with an international NGO has been a privilege but also a challenge in many ways. MSF is an organisation full of action-driven, passionate people who do not fear starting new projects. This has been a very helpful approach on this journey towards a common goal: to find an answer to the question of whether NPWT is better than standard treatment. However, sometimes there is a sense that NGOs and medical universities speak two different languages. It is understandable that a humanitarian organisation accustomed to making quick decisions will expect a clinical study to provide results that are directly applicable at the patient level. However, a research project is not a quick fix. The initial assessment by the Ar Ramtha office was that data collection would take six months at the most. In the end, a study period of over 40 months, including the expansion into another country, was required before data collection was finally complete. By the time we had cleaned the data and could present some preliminary results, the Ar Ramtha project had been closed for more than a year.

It should be noted that, considering the complexity of the project and study settings, the length of the data collection period is not surprisingly long. However, expectations on both sides of the collaboration could have been more realistic and more thoroughly discussed during the planning stage.

In June 2014, I had never heard about the MSF project in Ar Ramtha, Jordan. The idea of performing an RCT there was first discussed with the MSF Sweden Innovation Unit in July 2014, and quickly developed into a collaborative effort. In January 2015, I embarked on my first field visit to Ar Ramtha and, in February 2015, the first draft version of the study

protocol was finalised. After ethical approvals were gained, the first patient was recruited in June 2015. Without enthusiasm, a strong will, and local support, going from first discussions to patient enrolment in an RCT within an armed conflict setting in less than one year would never have been possible.

### *Challenges*

The main challenges of this project were related to patient enrolment, a high turnover of surgeons, the sudden influx of high numbers of wounded patients, unanticipated complicated injuries, the transfer of information, and, at times, limited access to the hospital—both for patients and for researchers.

### *Lessons Learned*

For a complex research project like this one, it is essential to base decisions on first-hand information. I had begun drafting a study proposal based on emails, internal reports, and Skype conferences only to find that, when I finally reached the capital of Amman, Jordan, this information was, to a large extent, obsolete. I met with the Head of Mission and the medical coordinator and was thoroughly briefed. The next day, I travelled to the hospital in Ar Ramtha. Upon arrival, I quickly realised that only at the study site would I be able to understand the whole picture.

I talked to the patients spent time with the doctors and nurses at the hospital. Many had questions and some were sceptical, but most were enthusiastic. I made sure to take the time to answer all questions and to explain, and I tried to earn their trust. The idea of testing this specific new method for wound treatment came from the surgeons at Ar Ramtha Hospital. This proved to be a major advantage when seeking acceptance for this type of project, which requires advocates at the study site—especially when the primary investigator may be somewhere else, in my case on another continent.

Another necessity is a strong local research team, if possible with a link to local academia. This was in our case, Jordan University of Science and Technology in Irbid. However, the most critical factor for this type of project is the study nurses. They engage in the day-to-day challenge of enrolling patients in the study. By taking the time to recruit dedicated study nurses, half the battle is won. Right after my return from Ar Ramtha, I started working on the study protocol, applications for the ethical review committee, and a study-nurse job description. At the second visit, we recruited our first study nurse and initiated patient enrolment. We had developed a study protocol with a pragmatic design—just a few clear inclusion and exclusion criteria, proceedings free of computers with everything paper-based. However, even though attempted to foresee all eventualities, I quickly learned that a clinical trial requires continuous supervision and regular visits.

When not on-site, it is important to provide regular support and feedback to the study nurses and local researchers by ensuring technical support for data checks and trial oversights, and by maintaining a clear and consistent communication, with an emphasis on strict adherence to

the study protocol. It is, however, equally necessary to refrain from interfering with clinical decisions. I came close a couple of times but managed to stay out of the discussion. The treating surgeons must do their job and trust that all their treatment decisions will be respected.

If feasible, education and training will serve the project well. Investments in capacity building and knowledge sharing among partners can lead to long-term collaborations. In this, international and local NGOs should be considered key actors, but most important are the local healthcare workers and researchers. They are the greatest assets for the project and should, together with the patients, benefit the most from the research.

# MAIN FINDINGS AND DISCUSSION

## Population Characteristics

The patients receiving surgical treatment for acute conflict-related injuries were predominantly male (88%) in their twenties and thirties (*Papers I* and *III*) (Table 3). Similar overrepresentation of young males has previously been reported, both in trauma cases[134] and civilians in armed conflict settings.[135] In our study settings, selection bias could have been introduced by males having better access to transportation, as the patients were often brought to the hospital without the assistance of an ambulance. We cannot exclude the possibility of the presence of civilian combatants, which would also drive the data towards an overrepresentation of young males. Another factor contributing to the overrepresentation might be cultural differences. It is noticeable that, in many Middle Eastern cities, men are outside more commonly than women and might therefore to be considered at a higher risk for injury.

The majority of those killed and injured due to armed conflict can be found in the working-age population; direct fatalities are predominantly male.[136] Men are often the main, and sometimes the sole, breadwinners in the family. Morbidity and mortality in this group will lead to devastating consequences for households and entire societies already burdened by limited resources. In addition, there is an ongoing change in warfare tactics, with conflicts being increasingly fought in urban areas, resulting in more civilians placed in the line of fire.

The median number of surgeries was three (*Paper I*), indicating the complexity of injury among the patients. In contrast, a report from a high-resource setting, patients with extremity gunshot injuries had an average of 1.8 surgeries.[137] Contrary to previous reports, gunshot was the injury mechanism for the majority (61%) of the patients (*Paper III*). The amputation rate (8%) was in line with previous studies (*Papers I* and *III*).[138,139] Research indicates that the rate of amputations remains unchanged over time in resource-limited conflict settings,[140] whereas in high-resource areas the rates are declining.[141,142]

**Table 3.** Baseline Characteristics and Outcomes for Civilians who Received Surgical Treatment for Acute Conflict-related Injuries

| | ***Paper I*** **(n=457)** | ***Paper III*** **(n=165)** |
|---|---|---|
| Age, median (IQR) | 24 (19–33) | 28 (21–34) |
| Male, n (%) | 395 (86) | 155 (94) |
| Infection, n (%) | 49 (11) | 29 (18) |
| Number of surgeries, median (IQR) | 3 (1–5) | 2 (2–5) |
| Amputation, n (%) | 48 (11) | 2 (1) |
| Inpatient mortality, n (%) | 37 (8) | 1 (1) |
| Days in hospital, median (IQR) | 26 (11–54) | 10 (5–38) |

IQR, interquartile range.

### Wound infection was associated with poor outcomes and high resource consumption among patients receiving surgery for conflict-related injuries

Wound infection was diagnosed in 78/622 patients (12%) (*Papers I* and *III*). MDR bacteria was detected in 36/49 of the patients (73%) who had positive wound cultures (*Paper I*). It is unknown whether this unexpectedly high rate is due to colonisation during pre-admission or due to HAI. The mean time from hospital presentation to detection of MDR bacteria was 16.5 days (IQR 8–30). The most commonly detected bacteria were *Staphylococcus aureus* (73% MRSA), *Pseudomonas* (17% MDR), *Klebsiella pneumoniae* (82% MDR), *Enterobacter* (78% MDR), and *Escherichia coli* (100% MDR).

In *Paper I*, the mean RTSc did not differ between matched patients with and without infection, indicating that injury severity was similar in the two groups. Wound infection was associated with worse patient outcomes and an increased burden of care. Patients with an infection had more surgeries, including amputations compared to those without an infection. The mean number of days in hospital was higher for patients with (77 days), compared to patients without an infection (35 days), P=.000001. This association has previously been found in both military and civilian settings.[143,144]

### The main challenges hospital-based physicians encounter in the management of civilians with conflict-related wounds were related to protocol adherence

Physicians interviewed in *Paper II* described that the main challenge in the management of acute conflict-related wounds was adherence to established treatment protocols. We found a consensus and adherence to protocols in certain areas. These areas could be considered commonly agreed-upon principles of trauma surgery, such as the use of wound debridement and the evaluation of the systemic state of the patient before initiating antibiotic treatment. However, we identified factors that made it difficult to follow the protocols. The main reasons for protocol deviation were *i)* limitations imposed on the physicians (lack of space and materials, and the unfavourable behaviour of patients and caregivers); *ii)* a lack of consensus on hygiene routines; and *iii)* deliberate deviations (either to ensure a good doctor-patient relationship or when medical reasons prevented adherence to the established protocols). Qualitative studies on physicians' adherence to clinical guidelines have shown that the approaches to the implementation of clinical guidelines vary substantially[145] and that guidelines are sometimes viewed as a mere influence on clinical decision making.[146] Often, other factors such as convenience, malpractice concerns, and physician experience overrule clinical guidelines.[147] The wording of the guidelines and any disparities with reality will influence perceived relevance and, consequently, the adherence.[146] The perceived simplicity and practicality of the guidelines have been shown to positively affect implementation.[148]

Antibiotic-resistant organisms causing HAI are a major concern in resource-limited settings.[149] Considering the high levels of MDR (73% of infected wounds in *Paper I*), it was surprising that participants described how issues related to HAI were not being prioritised. When analysed further, these findings found to be linked to a high workload in combination with limited resources.[150] A previous study found that the main obstacles to antibiotic protocol adherence related to issues of workflow, both inherent and unexpected, and to conflicts over the responsibility for the administration of antibiotics.[151] In a study of the factors influencing the prescription of antibiotics, personal experience influenced prescribing decisions, while hospital guidelines did so to a lesser degree.[152] Previous research also indicated that the hospital design influences the adherence to isolation routines,[153] and that hygiene protocol compliance tends to go down when patient numbers go up.[154]

We found that participants had difficulties differentiating between bacterial contamination and infection at presentation after injury, and that this affects the certainty of assessments regarding HAI levels. This has also been seen in previous studies.[70,155] Clinical guidelines are considered essential for providing safe, evidence-based healthcare. However, their implementation in daily practice is filled with challenges[156] and it remains unclear which guideline dissemination and implementation strategies to use in different circumstances.[157]

### NPWT failed to reduce the time to wound closure and the incidence of wound infection in patients with acute conflict-related extremity wounds

Overall, the groups were well-balanced in terms of their baseline characteristics. However, the wounds in the NPWT group had a larger median wound area and a higher rate of injury to major blood vessels, exposed bone, nerves or tendons, and fracture at the site of the studied wound.

The wound closure rate by day five was 41/83 (49%) among participants treated with NPWT, compared to 49/82 (60%) for those who received standard treatment. Hence, NPWT was not superior to standard treatment. In fact, the absolute difference was -10 percentage points, indicating that NPWT may be a less effective treatment, 95% CI -5–25, P=.212. It should be noted that the power calculation was based on a 25% difference in the rate of participants reaching the primary endpoint. The mean time to wound closure did not differ between the groups, nor did the net clinical benefit, HR 0.90, 95% CI 0.56–1.45.

NPWT did not result in an increased chance of wound closure, even after adjusting for the imbalances in baseline characteristics, HR 1.17, 95% CI 0.82–1.65, P=.385. A review of the available wound photographs for the primary endpoint did not change the initial assessments. Wound infection was diagnosed in 10/83 participants (12%) in the NPWT group, and 19/82 participants (23%) in the standard treatment group with an absolute difference of 11 percentage points, 95% CI -0.5–23, P=.068. This indicates that NPWT may decrease the infection rate, but at the cost of a lower wound closure rate. However, wound infection was a secondary endpoint not considered in the sample size calculation.

In recent years, we have seen large non-governmental actors, such as the ICRC and MSF, implementing NPWT in the treatment of civilians with injuries sustained in armed conflict. This is concerning, as the evidence grade supporting NPWT as an effective means of promoting wound healing is low,[82] the technique is expensive, and it requires resources that are limited in conflict-affected areas.

RCTs are considered the gold standard in medical research and represent the highest evidence grade.[158] However, RCTs are costly, time-consuming, and the generalizability of their results has been questioned. Traditionally, patients in resource-limited settings have received treatments based on evidence generated in another context or based on the best available evidence from observational studies. With the development of the pragmatic randomised trials design, this has changed. Data derived from pragmatic randomised trials are often considered ‘real-world evidence’, a term used increasingly and associated with sources other than RCTs. It has been argued that, compared to conventional RCTs, the pragmatic trial is more suitable for the support of real-world healthcare decision making.[103]

RCTs in surgical care are rare[159] though it has been shown that high-quality RCTs can be conducted in trauma settings.[160-162] In the context of armed conflict, I have only managed to identify one RCT.[163] In this trial, 76 military combatants, wounded in Afghanistan and treated at a military hospital, were randomised to receive either silver dressings or plain gauze

dressings, the standard of care. No difference between the treatment groups was found in the primary endpoint of wound colonisation.

### Compared to standard treatment, NPWT was associated with higher treatment-related costs, and is unlikely to be a cost-effective treatment

For the primary endpoint, wound closure by day five, the cost of NPWT was $1 332 above that of standard treatment (*Paper IV*). In addition, treatment-related costs were higher for the NPWT group. Overall, results were robust in a sensitivity analysis. As we found no evidence of superiority for NPWT compared to standard treatment of traumatic extremity wounds (*Paper III*) and costs were higher, NPWT is unlikely to be a cost-effective treatment. These conclusions are in line with the results from the only previous cost-effectiveness analysis from an RCT of NPWT for traumatic open wounds.[164] It should be noted that the health outcomes used in the health economic evaluation (*Paper IV*) were derived from *Paper III*. Consequently, the analysis in *Paper IV* risks being underpowered to detect meaningful differences in economic outcomes.

The significance of the costs related to the dressings and technology greatly differs between settings. In a resource-limited setting, the costs of advanced technology are often a substantial part, while in high-income settings, these costs are almost negligible in comparison with costs linked to staff time, overhead, and capital expenditures. It is therefore essential for the calculations to incorporate nursing time, the number of surgeries or dressing changes, and the length of hospital stay in addition to outcomes such as wound closure and wound infection rates.

## Research in Resource-limited Settings

Relative to the high burden of disease in resource-limited settings, the number of clinical researchers is low.[165] One fundamental requirement to initiate a research project and to be granted funding is that the research is deemed relevant. Relevance, however, is a relative term. To healthcare workers and researchers in a resource-limited setting, it might be obvious which questions would be most relevant. However, when research in resource-limited settings is performed by an institution from a high-income country, the funders will often need to see its relevance for a high-income context. This may generate a dilemma among researchers, often resulting in an unfortunate paradox where resources are allocated to research on topics that are of minor importance to the people in the areas where the project is being conducted.[166]

Consequently, researchers from high-income countries risk the temptation to initiate projects that hold relevance for their institutions and funders. In addition, an insufficient will or ability to engage local researchers and appropriately credit their involvement will lead to data and academic prestige being retained by high-income institutions.[167,168] These risks may be diminished through thorough planning and partnerships with local institutions and international and local NGOs. The identification and engagement of local healthcare workers and researchers already at the planning stage is of the outmost importance.[2] If possible, pose

the question, ‘What would be relevant for you to investigate?’. Subsequently, the identified areas could be explored by using qualitative methods to generate hypotheses. The quantitative methods used to test these hypotheses might need adaptation to the study setting but it is essential that this adaptation does not lead to a substantial loss in evidence quality. To perform substandard research is both unethical and a waste of resources.

There is a concern that knowledge generated in one context cannot be transferred to another without a risk of distortion and misinterpretation. Additionally, RCTs of health interventions generally fail to report the generalizability of their results.[169] Preconditions differ between a trauma centre in the United Kingdom and an ad hoc hospital close to a Syrian battlefield. At the hospital level, there will most likely be differences in terms of resources, experiences, patient load, culture, traditions, and patient behaviour. In addition, the microbiota and antimicrobial resistance patterns often vary between two settings, as well as the availability of prehospital care, access to healthcare, and transport time to definitive treatment. When evidence generated in a stable high-income setting is being directly transferred to a different environment without validation, it risks being misinterpreted, leading to a misuse of the limited resources available and, in the end, doing more harm than good. In the words of R. M. Coupland, ‘Inadequate surgery is worse than nothing’.[170]

There are, however, examples of knowledge being transferrable between contexts.[171] The similarities of two seemingly different settings, armed conflict and urban violence in a resource-limited setting, have proven able to use the same standardised package of care.[172] In this case, the armed conflict setting is probably more closely related to resource scarcity, compared to a high-income setting, with a higher chance of cross-cultural validity and generalizability.[173] This approach should, however, be used with care and requires the evaluation and validation of methods.

# METHODOLOGICAL CONSIDERATIONS

## Strengths and Limitations

In *Papers I* and *III*, injured patients were, at times, not able to access the hospital, and, at other times, the research team was unable to reach the study site. Consequently, potentially eligible patients were missed, leading to a risk of selection bias, and impaired trial oversight. Delays in the transportation of severely injured patients, due to long distances, damaged infrastructure, checkpoints, and insecurity, might have negatively affected prehospital mortality and, as a consequence, generated survival bias.

Language was a potential barrier. Interviews in *Paper II* were conducted in English. However, English was neither the first language of the interviewer nor of the participants. In addition, most patients enrolled in the randomised trial (*Papers III* and *IV*) did not speak English, which was the language spoken among the expatriates at Ar Ramtha Hospital and among the researchers at both study sites. This language barrier might have generated information bias due to misclassification. Misclassification bias could also have been introduced by the use of a clinical database in *Paper I*. The hospital's use of paper files, non-strict definitions, and the fact that doctors had limited time to report data may have led to the misclassification of exposures and outcomes.

The overall strengths of this thesis include the collaboration with two civilian hospitals, international and local NGOs, healthcare workers, and researchers affiliated with academic institutions in Jordan and Iraq. This collaboration has been essential in the development of relevant research questions, the implementation of the research, and the interpretation of the results. The independence from the medical device industry eliminates bias that may otherwise be introduced when corporate interests are allowed to influence the design, conduct, analysis, and reporting of a trial.[174]

## Generalizability

The classical understanding of generalizability, or external validity, is extrapolating results from a sample to a wider or unspecified population.[175] To form a representative sample of the population, participants are ideally selected at random. In reality, the starting point for a study is most commonly the sample, not the population. The importance of generalizability is acknowledged in the STROBE, SRQR, CONSORT, and CHEERS guidelines.

As pointed out in the STROBE statement, adequate reporting is a prerequisite for the reader to assess a study's generalizability.[97] This includes details on when and where the study took place. In addition, readers need information on the study participants, the exposures examined, and the outcomes assessed. In *Paper I* we used a pre-existing database of routine clinical data. As previously mentioned (Study Design and Methods), the information of the patients' baseline characteristics exposures and outcome measures was limited. Consequently, the generalizability of the study findings can be questioned. In addition, the above-mentioned risk of misclassification bias may affect the study's internal validity and, in

turn, limit the external validity. Details on wound microbiota and resistance patterns are context-specific and thus, the generalizability of these results is limited to the specific geographical area.

The randomisation process in an RCT balances patient characteristics between treatment groups, securing high internal validity. However, the external validity, and thereby generalizability, of traditional RCTs has been questioned pertaining to strict inclusion criteria, the exclusion of 'non-ideal' patients, and a controlled environment.[176] Participants of such trials are often highly selected and followed more closely than they would be in a real-world setting. To overcome the limitations of a traditional RCT, we used a pragmatic trial design in *Paper III*, with broad inclusion criteria and minimal exclusion criteria, aiming for a representative study population with minimal selection bias, and thus, yielding results that are more relevant for routine care use.[177] We obtained power in excess of the calculated 80% due to the low number of dropouts and the high enrolment rate among eligible patients (>60%). The study population was heterogeneous, which improves generalizability, at the cost of statistical power for subgroup analyses.

Cost-effectiveness analyses based on RCTs usually struggle with external validity.[178] Limitations can be generated by the specific trial setting, the inclusion criteria and endpoints chosen or the length of the follow-up. By using a real-world setting and a pragmatic study design, the external validity of *Paper IV* may have been improved. Other strategies used to enable the reader to assess a study's external validity included a sensitivity analysis and transparency in reporting.

Generalizability is a limitation in qualitative research.[100] Since data is generated from a select population, it is often difficult to generalize the findings outside of the specific context studied.[179] In qualitative research it is common to instead use the terms 'trustworthiness' and 'transferability'.[122] We acknowledged the interpretations included in *Paper II*, and aimed for comprehensive reporting of the context and research methodology to achieve trustworthiness. Findings were presented in detail, with quotations to allow for alternative interpretations among the readers. However, the study findings are derived from a small group of participants at one single hospital, limiting generalizability. Due to diversity among the participants in *Paper II*, the study findings might be considered transferrable to similar conflict-affected hospital settings in the same geographical area.

The combination of relative stability and proximity to armed conflict renders our study sites and populations suitable for research. Jordan and Iraq are middle-income countries. However, in armed conflict, the healthcare services of the affected areas are often overburdened and thus considered resource-limited.[24] As an illustration, at Ar Ramtha we found insufficiencies in hospital infrastructure, medication, and supplies (*Paper II*). In addition, both study hospitals were understaffed, and lacked equipment and trained personnel for reconstructive surgery.

Both Ar Ramtha Hospital and EMC are civilian hospitals but the distinction between civilian and combatant is not clear, especially so in internal armed conflicts.[180] Asking patients in conflict-affected areas for their combatant status is unethical and risk hurting the patient-doctor relationship. In addition, there are numerous reasons why a patient would not want to disclose such information, including fear of retaliation, persecution or being denied access to healthcare. Through interviews with local researchers and healthcare personnel, we found that the patients included in the studies did not wear helmets or body armour and were not supported by military field-hospitals, forward surgical teams or rapid casualty evacuation. Although our studies have limitations and biases, we suggest that the results may be valid for civilian patients with acute conflict-related extremity wounds treated in other resource-limited settings.

# CONCLUSIONS

**Wound infection** was associated with poor clinical outcomes and an excess resource consumption among patients receiving surgery for conflict-related injuries. In addition, these patients had a higher incidence of MDR infection than has previously been shown.

**Wound management is complex,** and physicians treating conflict-related wounds found protocol adherence to be the main challenge. Reasons for protocol deviations included resource scarcity, high patient loads, and limited compliance among patients and caregivers.

**Neither time to wound closure nor net clinical benefit** was improved by NPWT compared to standard treatment for conflict-related extremity wounds.

**Treatment-related healthcare costs** were higher for NPWT compared to standard treatment, indicating that NPWT is not a cost-effective treatment option.

# CLINICAL IMPLICATIONS AND FUTURE PERSPECTIVES

Hopefully, this thesis will serve as a step towards improving the evidence base for the care of civilians with conflict-related injuries in terms of results and the reporting of research methods. Keeping in mind the methodological considerations regarding limitations and generalizability, as alluded to previously, this section discusses the potential clinical implications of this thesis, as well as future research.

The strong overrepresentation of young males in *Papers I* and *III* implies that our study populations probably do not represent the full picture. The true epidemiology for civilians wounded in a conflict-affected area cannot be understood at the hospital level but needs to be studied closer to the population. Most suitable would be a mixed-methods approach, including quantitative as well as qualitative data collection and analysis. Potential biases must also be considered, such as selection bias by the patients' limited access to healthcare (transportation, security checkpoints) and survival bias, generated by severely injured patients who die before they reach the hospital. One strategy towards the inclusion of these patients would be to cooperate with the local prehospital services and morgues and incorporate their data into the analysis.

Microbiota and their resistance patterns will vary depending on the setting. Antibiotic strategies therefore need to be locally adapted to be effective. In this thesis, I report methods used to generate context-specific knowledge on the microbiota in infected conflict-related wounds. An advantage with this approach compared to screening is that the results are more likely to represent clinically-relevant pathogens and thus, could be more useful as an aid in treatment decisions. However, the development and validation of a rapid assessment method could prove to be a more feasible means of directly guiding clinicians in their treatment strategies.

We have mapped the challenges physicians experience in the management of conflict-related wounds. Hopefully, these results can provide some insights for resource allocation and the development of protocols for wound care, hygiene, and antibiotic use in similar settings. However, many questions are left unanswered. The factors affecting adherence to protocols could be explored in more depth along with why there were split views on the significance of HAI and antibiotic resistance development. Focus group discussions could serve as a first step towards resolving the identified discrepancies between protocol recommendations and actual practice.

For our primary endpoint, wound closure by day five, NPWT did not prove to be superior to standard treatment. In fact, the absolute difference in wound closure rate was 10% in favour of standard treatment (P=.212). NPWT had a lower wound infection rate than standard treatment; however, these results were not statistically significant (P=.068). It should be noted that our power calculation was made for our primary endpoint. A larger trial might find a statistically significant difference in wound infection rate. There could even be a link between the two, with the risk of infectious complications being limited by decisions not to close

wounds prematurely. The hypothesis of NPWT being a better treatment for some patients at risk of wound infection, but unsuitable for routine use could be inferred from the results in *Paper III*, although the number of included patients did not allow for further subgroup analyses. However, this hypothesis would be realistic to study in a non-pragmatic RCT. Through the widespread use of mobile phones, we were able to reach many of our patients for follow-up after hospital discharge. However, the displacement of the study populations rendered return visits nearly impossible to organise.

Regarding the health economic evaluation of NPWT, the non-significant differences in clinical effect make it difficult to draw any clear conclusions. *Paper III* was a superiority trial which was not designed to detect equivalence in terms of outcomes. If there is, in fact, a true equivalence, this would have to be proven in a non-inferiority trial. Subsequently, a cost-minimisation analysis could be performed. However, the analysis performed based on our health outcomes in *Paper III* shows that NPWT is unlikely to be a cost-effective treatment for these patients.

NPWT may serve purposes not studied in this thesis, such as improving the quality of life for injured patients. Neither *Paper III* nor *Paper IV* discussed the patients' experiences, e.g. wound-associated pain and health-related quality of life. Consequently, potentially important aspects of the treatment methods could have been neglected. However, we have collected patient-reported data on psychological distress[181] and wound-specific details, e.g. discharge, foul smell, movement impairment, pain, discomfort, and sleep quality. Further analyses are ongoing to help clarify these issues.

To perform an RCT in resource-limited settings is challenging. The GCP offers guidance to some extent. However, GCP instructions and training are generally directed towards research by pharmaceutical companies acting in controlled environments and hence are not always applicable to a real-world setting.[182] The CONSORT guidelines for pragmatic trials proved to be helpful both for planning and conducting the trial, as well as in reporting our findings.[103] I recommend that research projects in challenging settings make use of these guidelines.

I have reported the utility of observational and qualitative research methods, as well as the pragmatic randomised trial design, to generate evidence in conflict-affected settings. In these settings, access to populations over time is a major challenge. Insecurity, insufficient infrastructure and human resources, and difficulties allocating resources to research all call for the utilisation of a pragmatic adaptation of research methodologies and adjustments to fit the local conditions. Visits to the study site and collaboration with local researchers is essential in the planning phase. Ideally, a feasibility analysis should be conducted before initiating a study. If possible, dedicated local research personnel, e.g. study nurses, should be given relevant training, such as GCP. The high turnover rate of expatriate staff made it difficult to deeply engage them in the trial proceedings in Ar Ramtha. At both EMC and Ar Ramtha Hospital, we involved local healthcare workers in the research and subsequent publication of scientific articles. Hopefully, this will assist local capacity development and stimulate future research projects.

There are many important aspects related to conflict-injury management in resource-limited settings not covered in this thesis, including prehospital management and access to healthcare, postoperative care, functional outcomes, and rehabilitation. These areas are all in need of further investigation.

Retrospective analyses, as utilised in *Paper I*, requires sufficient data quality. Prospective collection of original data (*Paper III*) is considerably costlier and more time-consuming. However, given an adequate study design and thorough execution, the data collected will be of high quality. The publication of the first-ever randomised clinical trial performed in resource-limited civilian settings close to armed conflict should call attention to the feasibility of the development of high-quality trials to generate level-one evidence in similarly challenging settings. Hopefully, this thesis may serve to inspire other researchers and change the current paradigm in which limited data is used to justify the scarcity of evidence-based treatment protocols for civilians in conflict-affected areas.

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# SAMMANFATTNING PÅ SVENSKA

Effekterna av väpnade konflikter drabbar civilbefolkningen världen över. Konfliktområden har ofta en eftersatt folkhälsa och en begränsad motståndskraft mot den extra börda som en väpnad konflikt medför. Dessutom saknas forskning rörande hur konfliktrelaterade skador hos civila skall handläggas på bästa sätt.

Syftet med denna avhandling är att generera ny kunskap om de människor som skadas vid väpnade konflikter i resursknappa miljöer, hur sårinfektion påverkar utfall och vilka de huvudsakliga utmaningarna är när det gäller behandlingen av dessa skador. Därutöver ville vi utvärdera en ny metod, lokal undertrycksbehandling, gällande säkerhet, effektivitet, användbarhet, och kostnadseffektivitet vid behandling av konfliktrelaterade extremitetssår.

Alla patienter i denna avhandling skadades i väpnade konflikter i Syrien och i Irak. Studierna utfördes på två civila sjukhus i Jordanien och irakiska Kurdistan. I en kohortstudie inkluderade vi alla patienter med akuta konfliktrelaterade skador som genomgått kirurgisk behandling vid ett sjukhus i Jordanien. Vi jämförde patienter med sårinfektion mot de utan sårinfektion avseende kliniskt utfall och resursåtgång. Vi fann att patienter med infektion vårdades längre och behövde fler operationer, inklusive amputationer. Därutöver så fann vi att tre av fyra infekterade sår innehöll multiresistenta bakterier. I en kvalitativ studie intervjuade vi läkare på sjukhuset i Jordanien. De beskrev att de huvudsakliga utmaningarna i behandlingen av konflikt-relaterade skador rörde följsamhet till behandlingsriktlinjer. Dels upplevde läkarna att resursbrist försvårade följsamheten, dels var bristen på följsamhet relaterad till beteenden hos patienter och anhöriga. I en randomiserad kontrollerad prövning jämförde vi lokal undertrycksbehandling med standardbehandling för konfliktrelaterade extremitetssår. Vuxna patienter med akuta skador randomiserades i samband med deras första operation. Lokal undertrycksbehandling förkortade inte tid till sårförslutning men medförde högre kostnader jämfört med standardbehandling. Våra resultat talar således emot att lokal undertrycksbehandling skulle vara en effektiv eller kostnadseffektiv behandling för patienter med konfliktrelaterade extremitetssår. Dessa patienter bör därför erhålla standardbehandling.

Den höga frekvensen av multiresistenta bakterier i sår hos patienter med konfliktrelaterade skador samt att sårinfektion var associerat med försämrat kliniskt utfall indikerar att riktlinjer för sårbehandling bör anpassas till lokala förutsättningar. Resurser krävs för att öka följsamheten till dessa riktlinjer.

# PAPERS I–IV