

Management of fracture-related infection in low resource settings: how applicable are the current consensus guidelines?

Elizabeth K Tissingh^{1,2}, Leonard Marais³, Antonio Loro⁴, Deepa Bose⁵, Jamie Ferguson^{1,6}, Mario Morgensten⁷ and Martin McNally¹

¹The Bone Infection Unit, Nuffield Orthopaedic Centre, Oxford University Hospitals, Oxford, UK

²King's Global Health Partnerships, School of Life Course and Population Sciences, King's College London, London, UK

³Department of Orthopaedic Surgery, School of Clinical Medicine, University of KwaZulu-Natal, KwaZulu-Natal, South Africa

⁴Comprehensive Rehabilitation Services for People with Disability in Uganda (CoRSU) Hospital, Kisubi, Uganda

⁵University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

⁶Oxford Trauma Unit, Oxford University Hospitals, Oxford, UK

⁷Centre for Musculoskeletal Infections, Department of Orthopaedic and Trauma Surgery, University Hospital Basel, Basel, Switzerland

Correspondence
should be addressed
to E K Tissingh
Email
Elizabeth.tissingh1@nhs.net

- The global burden of fracture-related infection (FRI) is likely to be found in countries with limited healthcare resources and strategies are needed to ensure the best available practice is context appropriate. This study has two main aims: (i) to assess the applicability of recently published expert guidance from the FRI consensus groups on the diagnosis and management of FRI to low- and middle-income countries (LMICs); (ii) to summarise the available evidence on FRI, with consideration for strategies applicable to low resource settings.
- Data related to the International Consensus Meeting Orthopaedic Trauma Work Group and the International Fracture Related Infection Consensus Group FRI guidelines were collected including panel membership, country of origin, language of publication, open access status and impact factor of the journal of publication. The recommendations and guidelines were then summarised with specific consideration for relevance and applicability to LMICs. Barriers to implementation were explored within a group of LMIC residents and experienced workers.
- The authorship, evidence base and reach of the FRI consensus guidelines lack representation from low resource settings. The majority of authors (78.5–100%) are based in high-income countries and there are no low-income country collaborators listed in any of the papers. All papers are in English.
- The FRI consensus guidelines give a clear set of principles for the optimum management of FRI. Many of these – including the approach to diagnosis, multidisciplinary team working and some elements of surgical management – are achievable in low resource settings. Current evidence suggests that it is important that a core set of principles is prioritised but robust evidence for this is lacking. There are major organisational and infrastructure obstacles in LMICs that will make any standardisation of FRI diagnosis or management challenging. The detail of how FRI consensus principles should be applied in low resource settings requires further work.
- The important work presented in the current FRI consensus guidelines is relevant to low resource settings. However, leadership, collaboration, creativity and innovation will be needed to implement these strategies for communities who need it the most.

Keywords

- consensus
- fracture
- fracture-related infection
- definition
- diagnosis
- infection
- low- and middle-income countries (LMICs)

EFORT Open Reviews
(2022) 7, 422–432

Introduction and aims

The global burden of fracture-related infection (FRI) is likely to be concentrated in countries with limited healthcare resources. Conditions associated with FRI (road injuries, other musculoskeletal disorders, falls and self-harm) are among the top 25 leading causes of disability-adjusted life years in the world (1). Studies have looked at the burden of musculoskeletal disease (including infection) in low- and middle-income countries (LMICs) (2, 3) but the focus in low- and middle-income settings is often on vertical, communicable disease programmes.

While there is a significant body of literature on the global surgical burden of disease (4, 5, 6), the burden of disease related to FRIs remains poorly characterised. The Lancet Commission on Global Surgery recognised the importance of orthopaedic trauma by including external fixation for an open fracture as a ‘bellwether procedure’ (6, 7). Others have proposed that a complete ‘basket’ of procedures should include internal and external fixation for fractures (open or closed) and amputation (8).

Injuries cause more than 5 million deaths per year (9) and it is estimated that 88% of injury-related deaths occur in LMICs (10). For every death, between 10 and 50 people are estimated to survive trauma and approximately half of these survivors will suffer permanent disability. A recent systematic review by Cordero *et al.* calculated an overall mean fracture incidence ranging from 779 (95% CI: 483.0–1188.7) to 1574 (95% CI: 1285.1–1915.1) per 100 000 person-years, across 14 countries (11). An epidemiological study in Rwanda carried out a national household survey and found a musculoskeletal impairment prevalence of 5.2%. Of these, 4% had a diagnosis of musculoskeletal infection (12). This suggests a high burden of FRI across LMICs.

The majority of FRI is seen and managed in LMICs and there are particular considerations for these populations and contexts compared to high resource settings. These differences – such as delays in accessing care, resource constraints, population demographics, pathogen patterns and host comorbidities – may have an impact on how applicable guidelines are to these different contexts. In LMICs where fracture fixation with metalwork is possible, infection rates may be high (13, 14, 15, 16, 17).

There are significant delays in accessing care in underserved populations and these delays can impact significantly on the disease course. Patients with limited access to care – for economic, geographical and cultural reasons – may present with a more complex disease that is more difficult to manage. Upfront, out-of-pocket costs may result in catastrophic health expenditure and may make treatment impossible.

While many of the same pathogens have been identified in LMICs (18, 19, 20, 21), there is insufficient evidence to

fully quantify the differences that are likely to be present. Musculoskeletal presentations of infectious diseases – such as from *Echinococcus granulomatosus* or Actinomycetoma or tuberculosis (TB) – are more common. In addition, co-infection with TB and human immunodeficiency virus (HIV) may be more common.

The pattern of patient comorbidities differs across populations. In low resource settings, malnutrition, anaemia of chronic disease (malaria, gastrointestinal parasites and sickle cell disease), dermatitis, HIV/acquired immunodeficiency syndrome and TB may all play a significant role. A systematic review of FRI in HIV-positive patients found a non-significant increased risk overall for FRI in HIV-positive patients for operatively managed fractures (open and closed). Infection rates ranged from 3.1 to 100% in these 11 papers that cover the pre- and post-anti-retroviral era (22).

Given the importance and complexity of managing FRI well, experts came together to discuss definitions and management principles. The International Consensus Meeting (ICM) Orthopaedic Trauma Work Group and the International Fracture Related Infection Consensus Group were born out of the need to bring clarity to a complex problem for patients and clinicians and to share the best practice. These groups were largely made up of individuals from high resource settings and it is not clear how applicable their recommendations are for low resource settings. The management of musculoskeletal infection and FRI in particular in these contexts is challenging but possible (23, 24) and should be guided by the best available evidence. Given that high and low resource settings differ in significant ways, how are we to interpret the current FRI consensus guidelines?

This paper has two main aims:

1. To assess the applicability of recently published expert guidance from the FRI consensus groups on the diagnosis and management of FRI to LMICs.
2. To summarise the available evidence on FRI, with consideration for strategies applicable to low resource settings.

Methods

Elements of the ICM Orthopaedic Trauma Work Group (25) and the International FRI Consensus Group publications were analysed to define the applicability of the groups’ recommendations to LMICs. Data were collected on panel membership, language of publication, open access status and impact factor of the journal of publication as documented in the Journal Citation Report.

The authors who contributed to the consensus documents were then categorised according to the

income status of their country of origin. Countries of the listed authors and authors from the consensus groups were recorded and analysed using the World Bank Country and Lending Groups Database for the 2022 fiscal year (26). Income is measured using gross national income (GNI) per capita, in US dollars, converted from local currency using the World Bank Atlas method. The four groups the World Bank recognises are as follows: low-income economy GNI \$1045 or less, lower middle-income economies GNI \$1046–4095, Upper middle-income economies GNI \$4096–12,695 and high-income economies GNI \$12 696 or more.

For the narrative component of this review, the recommendations and guidelines that were produced by the ICM Orthopaedic Trauma Work Group and the International FRI Consensus Group were summarised with specific consideration for relevance and applicability to LMICs.

Results

Consensus panels and publications

Table 1 illustrates the composition of the FRI consensus groups and the articles that emanated from these meetings. The majority of authors (78.5–100%) are based in high-income countries and there are no low-income country collaborators listed in any of the papers. It is worth highlighting that all papers are in English. Most of the papers are open access (87.5%).

General considerations on FRI

The consensus guides and systematic reviews highlight that the available literature on the management of FRI is heterogenous with few standardised guidelines. The consensus guides aim to address this by agreeing on a core set of general principles. There is, however, an ongoing need for more robust evidence.

The ICM Orthopaedic Trauma Work Group addressed 49 key questions on the prevention, diagnosis and treatment of FRI (25). They documented the strength of evidence reviewed and the degree of consensus reached

in discussions. A systematic review from an expert group in 2018 (27) highlighted that ‘standardised guidelines for the treatment of FRI are lacking’. They summarise the epidemiology and treatment described in 93 studies. A later paper from the International FRI Consensus Group (28) presents Level 5 evidence on the management of FRI and emphasises the importance of a multidisciplinary approach for all aspects of FRI management.

Definition and diagnosis

The consensus definition from the FRI expert group with suggestive and confirmatory criteria (29) was adopted by the ICM Orthopaedic Trauma Work group for musculoskeletal infection (26). A subsequent guide from the International FRI Consensus Group has further expanded on this, in particular making recommendations around diagnostic adjuncts (30).

A FRI is an infection in the presence of a bone fracture. The definition intentionally does not stipulate a temporal relationship between the two. Neither does it stipulate that the fracture was open or closed or has undergone surgical fixation with metalwork; this is important, particularly in low resource settings. The definition also allows a clear distinction between FRI and osteomyelitis or prosthetic infection. It also removes the ambiguity that previously surrounded terms such as postoperative or post-traumatic osteomyelitis, surgical site infection and infection following fracture fixation.

Figure 1 outlines the diagnosis of FRI with confirmatory and suggestive criteria. Alongside this are outlined recommendations from Disease Control Priorities 3rd edition (DCP3) (31). The infrastructure, equipment and supplies and human resources required for surgical services at a Level 2 Hospital (100 bed district hospital) listed include the essential elements required to diagnose an FRI.

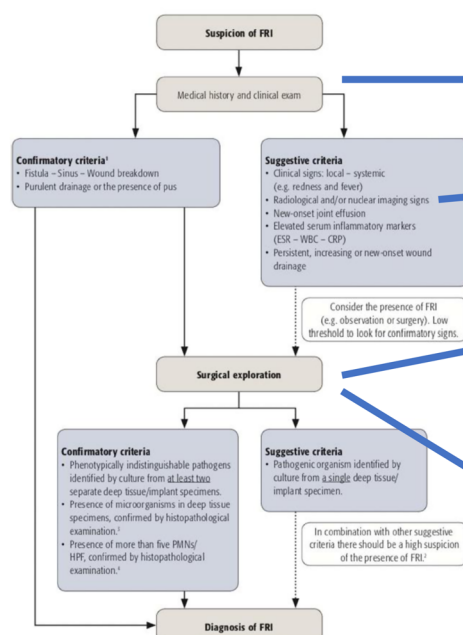
The confirmatory diagnostic criteria include clinical signs and microbiological or histological examinations that are neither complex nor difficult to access and therefore applicable to low resource settings. Some of the laboratory diagnostic adjuncts are relatively low in cost and widely

Table 1 Key characteristics of the FRI consensus papers.

Article	Consensus group	Percentage HIC	Percentage UMIC/LMIC	Language	Impact factor	Open access
Obremskey <i>et al.</i> (26)	ICM	78.5	21.5	English	5.284	N
Metsemakers <i>et al.</i> (29)	Early FRI group	94.7	5.3	English	2.586	Y
Depypere <i>et al.</i> (39)	FRI group	93.3	6.7	English	2.512	Y
Metsemakers <i>et al.</i> (51)	FRI group	93.3	6.7	English	2.512	Y
Metsemakers <i>et al.</i> (28)	FRI group	93.3	6.7	English	3.067	Y
Govaert <i>et al.</i> (30)	FRI group	93.3	6.7	English	2.512	Y
Bezstarosti <i>et al.</i> (27)	Review	100	0	English	3.067	Y
Bezstarosti <i>et al.</i> (53)	Review	87.5	12.5	English	3.067	Y

World Bank Country and Lending Groups: HIC, high-income country; UMIC, upper-middle-income country; LMIC, lower-middle-income country. There are no LIC, low-income countries listed. Impact factor from Journal Citation Report 2020.

Descriptive flow chart of the diagnostic criteria of FRI



Resource requirements for surgical services at second-level hospital

Requirements	Infrastructure	Equipment and supplies	Human resources
Qualified staff in appropriate clinical environment	Clean water supply Power supply Inpatient facility Outpatient facility	Furniture Materials for record keeping Wireless communication equipment	Nurse (50+) General surgeon
Imaging	Storage space Clean water supply Power supply Radiology and ultrasonography suite		Radiology technician (1) Radiologist (1)
Surgical procedure	Clean water supply Power supply Inpatient facility Outpatient facility	Autoclave Sterile dressings Anaesthetic machines and inhalation gases Fully equipped operating room Fully equipped recovery room Pharmaceuticals Blood products and intravenous fluids Surgical materials	Nurse (50+) General surgeon (2) Anaesthetist (2-3)
Laboratory investigation	Storage space Clean water supply Power supply Pharmacy Clinical laboratory	Basic microbiology equipment	

Figure 1

Diagnosis of fracture-related infection with surgical service provision recommendations in DCP3. Adapted from Govaert *et al.* (30) and DCP3.

available: full blood count, erythrocyte sedimentation rate and presence of micro-organisms on histopathological examination. Blood test C-reactive protein and detailed culture and sensitivity analysis require more investment in infrastructure that may not be present in all clinical settings in low-income countries. Tissue sampling for histological and microbiological analysis is discussed below.

Plain radiographs are accessible in many hospitals, even in low resource settings. They are relatively cheap and do not require specialist interpretation. CT scanners are also available in some low resource settings. More detailed imaging for the diagnosis of FRI (nuclear imaging such as FDG-PET/CT or WBC scintigraphy +SPECT/CT) or planning its management (MRI) as discussed by the consensus group (30) are unlikely to be available in low resource settings. However, as pointed out by the consensus group the investigations listed under the suggestive criteria are not essential to make the diagnosis of FRI. If uncertainty remains about the presence of infection, tissue can be collected by biopsy for microbiological and histopathological examination. While this procedure can be performed in most settings, limited theatre time and associated costs may represent a challenge.

Classification

A systematic review of the literature identified 13 different classification systems for osteomyelitis (32),

some of which have applicability in low resource settings. The Cierny and Mader classification is the most widely used (33). It is based on host characteristics and morphological features of the diseased bone and is well suited to a low resource setting but may not provide all the information required in the management of FRI. The BACH classification provides a more complete picture and includes detail on antimicrobial options and soft tissue coverage (34, 35).

The BACH classification was evaluated in high resource settings where most patients had infection after fracture (FRI). Full utilisation of the BACH classification may be limited in very low resource settings. For example, the determination of the antimicrobial categories requires additional infrastructure and expertise. Nevertheless, the general principles it highlights in guiding the management of FRI by considering the bone, the antimicrobial options, soft tissue cover and the host are valuable. As a classification system, it is a useful guide for predicting outcomes. Osteomyelitis classified as 'uncomplicated' is a good prognostic indicator for improved quality of life following intervention (36).

Marais *et al.* present a useful staging system that was developed in a low resource setting (37). The modification of the host element of the Cierny and Mader classification allows for a more pragmatic definition of a type C host and places the emphasis on host optimisation prior to surgery

to improve outcomes. Their work in South Africa is equally applicable to other middle- and low-income countries.

Host optimisation

The consensus guide (28) emphasis on host optimisation is applicable to low resource settings. The spectrum of conditions may be different depending on context but there is likely to be a need to optimise patients with poor nutrition, anaemia of chronic disease and infectious diseases such as HIV and TB. There is a well-recognised increase in non-communicable disease in LMICs – particular among wealthy and urban populations (38) who may be the population with more access to FRI treatment. Many patients who require optimisation of communicable disease (such as HIV, TB or malaria) will at the same time require optimisation of non-communicable disease (such as diabetes or ischaemic heart disease). The importance of host optimisation is echoed in Marais *et al.*'s paper (37).

Systemic antibiotic use

The consensus guide on systemic antimicrobial therapy (39) describes general treatment principles and the synergy between surgical approach and administration of systemic antimicrobials. The applicability of not only the type of antibiotic but also the method of its administration needs to be considered in low resource settings.

Specific recommendations are given on antibiotic regimes for FRI caused by specific pathogens. Some, but not all, of these antibiotics will be available in low resource settings and some will be prohibitively expensive for most patients, especially if prolonged courses of intravenous antibiotics are required. The duration and route of antibiotic administration impact on treatment efficacy. Evidence from the OVIVA trial (40) found that oral antibiotic therapy was non-inferior to intravenous antibiotic therapy. However, oral therapy regimes may not be taken by patients, due to side effects, relative high cost and distance to healthcare facilities to supply medication and do the required monitoring. There is little evidence around the duration of antimicrobial therapy in FRI. Trials looking at shorter courses would be helpful in guiding practical treatment options in LMICs.

Local antibiotic use may offer a significant advantage in the antimicrobial management of FRI in low resource settings. Low-cost local antibiotic delivery, such as the addition of locally sourced antibiotic to calcium sulphate, negates the challenges of cost, compliance and availability associated with systemic antibiotics. There is precedent for this approach (23, 41). The SOLARIO trial (42) is currently comparing very short versus long systemic antimicrobial treatment for bone infection, in patients who have had local antibiotics implanted. Shorter courses of systemic antibiotics, with an early switch to oral options, or no

continuation of therapy, will be particularly advantageous in low resource settings.

Although pathophysiology and antimicrobial mechanisms of action are universal, not enough is known about causative organisms in musculoskeletal infection in LMICs. A few studies describe microbiology results in osteomyelitis case series but in most low-income countries, infrastructure and expertise are lacking to identify and characterise causative organisms (21). A study from Tanzania (43) highlights the lack of availability of bacterial cultures as a risk factor for recurrence in a cohort of osteomyelitis cases.

A study from India (44) reports isolates from 100 patients being predominantly *Staphylococcus aureus*. Of concern, they note 75% of isolates were resistant to gentamicin, 81% to ciprofloxacin and 50% were methicillin-resistant *Staphylococcus aureus* (MRSA). Work from the UK (45), describing two patient cohorts from 2001 to 2004 and from 2013 to 2017 describes similar pathogens but different resistance patterns. In particular, they note the fall in MRSA from 11.4 to 8.3% of the *S. aureus* identified.

While a pragmatic approach to antibiotic choice and duration of systemic antibiotic cover may be reasonable, it is important to be mindful of the huge variation in pathogen distribution and in resistance patterns, much of which has not yet been studied. Addressing the contrast between the cohorts from India and from the UK, Dudareva *et al.* highlight the important regional differences in micro-organisms responsible for bone infections and their significance in managing musculoskeletal infection. However, they also note that increasing rates of antimicrobial resistance are not inevitable if proper antibiotic stewardship can be implemented (46).

Surgical principles

Full implementation of the surgical principles outlined in the consensus guides is the most resource intense element of the recommendations. The primary aims of surgical management of FRI are outlined in Table 2.

The steps to achieve these aims include five principles: sampling, excision of non-viable bone and irrigation, local antibiotic therapy and dead space management, bone defect management and soft tissue management are adaptable to be implemented in different contexts. Supportive training may be needed to introduce these principles to centres without previous experience and this may be facilitated by international collaboration (47).

Table 2 Primary aims for surgical treatment of FRI (51).

1. Fracture consolidation
2. Eradication of infection as the final outcome (in certain cases, initial suppression of infection until fracture consolidation is achieved)
3. Healing of the soft-tissue envelope
4. Restoration of function
5. Prevention of chronic infection/osteomyelitis

The method of bone and soft tissue sampling should minimise skin contamination and cross-contamination of samples. The use of separate sampling instruments and meticulous aseptic technique helps achieve this and is achievable in low resource settings although is more resource intensive (additional instruments and increased sterilisation costs). Evidence from high-income country laboratories suggests that the optimum number of microbiology samples in FRI is five (48). It is difficult to say with certainty that the same will hold true for less well-equipped laboratories with different infrastructure and culture methods. Additional routine testing for TB may increase costs. It is recommended that at least two samples are sent for histology, particularly in cases where the diagnosis is not clear. Analysing the number of neutrophils per high power field has high sensitivity and specificity to diagnose infection in the context of non-union (49). This is a technique that is well suited to low resource settings as the infrastructure and reagents needed for this are low cost and similar to those needed to do malaria blood films.

Debridement principles and techniques can be universally applied and do not require additional equipment or infrastructure but do require theatre time which may be limited (due to other competing cases) or not accessible (due to prohibitive costs). The use of tourniquets and diathermy is helpful but not essential. Normal saline at low pressure is recommended for irrigation. There is insufficient evidence to recommend any other irrigation solution.

It is widely accepted that managing the dead space created by debridement is important in reducing infection recurrence and promoting fracture healing. There is insufficient evidence to make firm recommendations about specific techniques or materials for dead space management. Filling defects with living tissue is advocated but is not always possible. The use of antibiotic-loaded materials (such as PMMA or inorganic calcium salts) has been extensively studied (50). One type of antibiotic carrier cannot be recommended over another on the basis of current evidence (51) and costs of some of these commercially available products are likely to be prohibitive. However, the use of local antibiotics may offer overall cost savings by reduction in the use of systemic antimicrobials (41, 42). This approach facilitates a one-stage treatment which may be more cost-effective and pragmatic in low resource settings.

Significant debridement and segment resection to achieve the important aim of removing all dead and poorly vascularised tissue may compromise stability or result in a critical size bone defect which requires additional stability. Stability is important for the management of FRI (52) and treatment options for these defects include cancellous bone grafting, induced membrane technique, vascularised graft or bone transport (53). Individual techniques need to be tailored to the clinical case and

the resource available to the treating team. Examples of low-cost Ilizarov techniques demonstrate that these treatment modalities are feasible in low resource settings (54, 55). It is also possible to perform some microvascular reconstructions (56) but this is rare.

When the preceding surgical stages of sampling, non-viable bone excision, dead space management and bone stability have been achieved, soft tissue coverage is paramount. Single-stage bone excision and soft tissue reconstruction should be undertaken whenever possible (57). Single-stage procedures require significant expertise, infrastructure and resource. In a low resource setting, this initial upfront investment, even if it leads to overall reduced cost per patient, may be prohibitive. Soft tissue reconstruction with local, pedicled and free flaps may be required in complex cases and the complications associated with these cases and their reconstructive treatment requires significant expertise and resource (58) but is achievable in a low resource setting (56).

Multidisciplinary team

A recurring theme throughout the consensus guidelines, and the scientific literature which informs them, is the importance of multidisciplinary team (MDT) working. The recommendations are that this team should include microbiologists, surgeons (orthopaedic and plastic) and radiologists. Any health service plan to offer care for FRI patients should include MDT working but this may be a challenge to implement in low resource settings where specialty-trained clinicians may be few and not always present at the same geographical location. Team members often have a high burden of disease to deal with and many competing interests and thus cannot prioritise FRI. The use of technology – such as internet messaging groups – to facilitate virtual team working may help but internet costs are often prohibitive. Centralising care for patients with musculoskeletal infection may facilitate MDT working and has been recommended in some high resource settings (59) but comes at a significant cost to patients, who in low resource settings already face catastrophic out-of-pocket costs. Low resource settings may have specific considerations around community involvement and the role of traditional medicine and ‘bone setters’ (60).

Overall treatment pathway

The FRI treatment pathway described by Metsemakers *et al.* can be considered alongside the infrastructure, equipment and supplies and human resources described in DCP3. The resource required to deliver the optimum patient pathway is achievable with the resource described in the ideal Level 2 health facility in DCP3. Figure 2 illustrates this. It is important to note that DCP3 presents ‘the ideal’ and this is not always the reality.

Discussion

The consensus FRI guidelines provide a good basis on which to build good practice in low resource settings. Key themes arise that will help guide this discussion and further work.

Adaptability of a set of principles

The FRI consensus guidelines give a clear set of principles for the optimum management of FRI. Evidence suggests that it is important that this core set of principles is prioritised in order to achieve optimum outcomes but robust evidence for this is lacking and the detail of how these principles should be applied in low resource settings requires further work. The additional detail associated with the basic set of principles, where the evidence is less clear (which antibiotic carrier to use for example) should be less of a priority. It is important that the basics of diagnosis and surgery are done well and this is achievable in low resource settings. Additions to this provide marginal gains and can be considered further down the line (Illustrated in Fig. 3).

Mutual learning

The authorship and reach of the FRI consensus guidelines, and the evidence base from which it draws, lack representation from low resource settings. Guidelines with 78.5–100% HIC authorship and no LIC authors are likely to miss out on the wealth of knowledge and experience

found in LMICs. It is likely that the published epidemiology and evidence for FRI does not reflect the global burden of disease or the best strategies to address the challenge. The experience, creative solutions and novel technology found in low resource settings treating musculoskeletal infection need to be better represented in scientific literature so that valuable lessons can be shared.

The inequity in research representation is seen across healthcare with less than 10% of global investment in health research spent in LMICs (61) and author representation in the published collaborative papers is often poor with less than a quarter of first authors being from the country of focus in the paper in one review (62). There is very limited data on the burden of disease related to FRI and there is a real need for the characterisation of the extent of the problem in LMIC's. Available data are often not digitised and an emphasis is placed on data related to donor priorities—often mother and child health or communicable disease. There is a need for a broad-based collaborative effort to determine the prevalence and impact of FRI in LMICs.

Funding considerations

Musculoskeletal infection (including prosthetic joint infection and FRI) and surgical site infection related to trauma and orthopaedic surgery have significant cost implications for a health service (63). The management of FRI can be resource intensive and remuneration often not

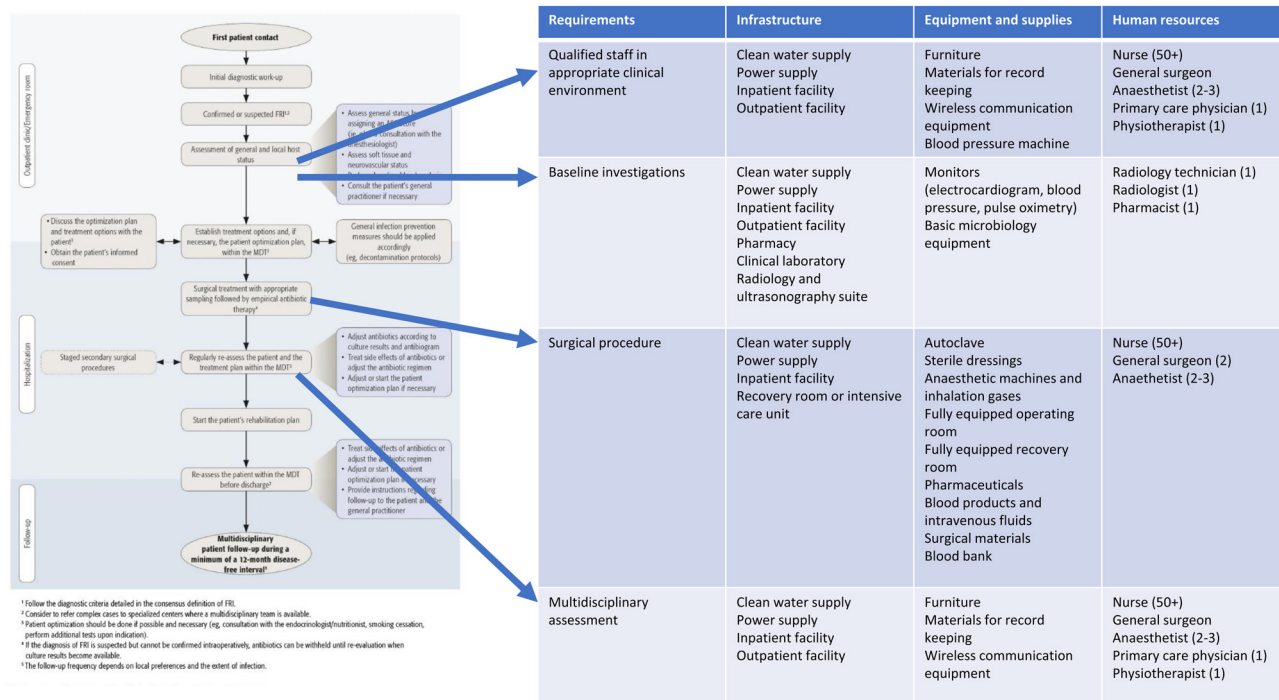


Figure 2

FRI patient pathway with resource available described in DCP3.

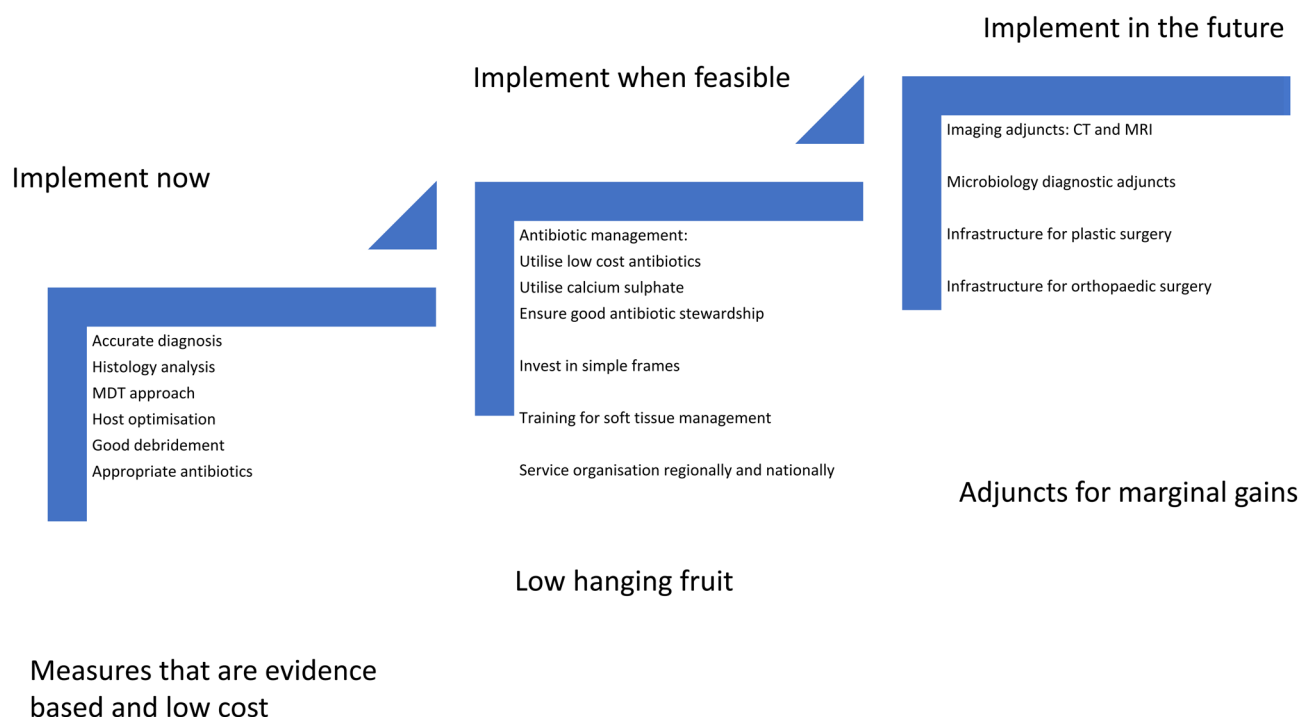


Figure 3

A stepwise approach to improving the quality of care delivered in the management of fracture related infection.

adequate. A case has been made in a high-income setting for centralising services to improve the quality of care and reduce costs overall (59).

Advocacy for health care provision in low resource settings has often relied on economic arguments utilising return on investment calculations and cost-benefit analyses. This has historically been used to campaign for medication for HIV, TB and malaria. More recently, cost-benefit calculations for surgical procedures such as cleft palate surgery and caesarean sections have been included in DCP-3 (64). It may be that similar work would be helpful for musculoskeletal infection care worldwide.

Innovation and technology

Innovation and appropriate technology have a role to play in providing high-quality care for FRI in low resource settings. Reverse innovation – where best practice from LMICs is brought to HICs – should be encouraged, and an emphasis placed on the experience of centres delivering high quality care in low resource settings. The Ganga Hospital delivering orthoplastic care in India (65), the Narayana Health Model delivering low-cost cardiac surgery and the orthoplastic centre in Uganda (66) are a few examples.

Measuring FRI treatment outcomes

Although patient follow-up is often challenging, outcome measures – including for longer-term follow-up – are

important. Treatment aims, and patient expectations, may be different across cultures. Further work on FRI management should consider outcomes measures suited to a broad range of settings. This work should actively involve patients. It may be possible to consider a similar set of outcome measures for trauma patients, but it is likely that markers of more chronic musculoskeletal pathology will also need to be included. Marais *et al.* (37) utilise amputation as an end point but clearly more nuance is needed for other outcomes.

Conclusion

The important work presented in the current FRI consensus guidelines is relevant to low resource settings and this paper sets out the salient aspects that can be applied in LMICs in a stepwise manner. There is, however, a need to build a robust evidence base for certain aspects of management and the best implementation strategies.

Treating the growing burden of FRI requires the best minds and the most innovative solutions. The lessons we need to learn are likely to be found in low resource settings. We need leadership, collaboration, creativity and innovation to implement the best knowledge and evidence available to us today to serve the communities who need it most.

ICMJE Conflict of Interest Statement

E H T reports that the receiving funding was not related to this work from Africa grants Programme, Johnson and Johnson Tropical Health and Education Trust Covid Relief Fund, Else Kroner Fresenius Stiftung; M Mc N has offered consultancy to Bonesupport Ab and received royalties from Oxford university Press. Both of these are not related to the work reported here; D B and M M have nothing to disclose.

Funding Statement

The work reported here did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

References

1. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020 **396** 1204–1222. ([https://doi.org/10.1016/S0140-6736\(20\)30925-9](https://doi.org/10.1016/S0140-6736(20)30925-9))
2. Beveridge M & Howard A. The burden of orthopaedic disease in developing countries. *Journal of Bone and Joint Surgery: American Volume* 2004 **86** 1819–1822. (<https://doi.org/10.2106/00004623-200408000-00029>)
3. Salomon JA, Vos T, Hogan DR, Gagnon M, Naghavi M, Mokdad A, Begum N, Shah R, Karyana M, Kosen S, *et al.* Common values in assessing health outcomes from disease and injury: disability weights measurement study for the Global Burden of Disease Study 2010. *Lancet* 2012 **380** 2129–2143. ([https://doi.org/10.1016/S0140-6736\(12\)61680-8](https://doi.org/10.1016/S0140-6736(12)61680-8))
4. Ozgediz D & Riviello R. The ‘other’ neglected diseases in global public health: surgical conditions in sub-Saharan Africa. *PLoS Medicine* 2008 **5** e121. (<https://doi.org/10.1371/journal.pmed.0050121>)
5. Grimes CE, Bowman KG, Dodgion CM & Lavy CB. Systematic review of barriers to surgical care in low-income and middle-income countries. *World Journal of Surgery* 2011 **35** 941–950. (<https://doi.org/10.1007/s00268-011-1010-1>)
6. Meara JG, Leather AJ, Hagander L, Alkire BC, Alonso N, Ameh EA, Bickler SW, Conteh L, Dare AJ, Davies J, *et al.* Global Surgery 2030: evidence and solutions for achieving health, welfare, and economic development. *International Journal of Obstetric Anesthesia* 2016 **25** 75–78. (<https://doi.org/10.1016/j.ijoa.2015.09.006>)
7. O'Neill KM, Greenberg SL, Cherian M, Gillies RD, Daniels KM, Roy N, Raykar NP, Riesel JN, Spiegel D, Watters DA, *et al.* Bellwether procedures for monitoring and planning essential surgical care in low- and middle-income countries: caesarean delivery, laparotomy, and treatment of open fractures. *World Journal of Surgery* 2016 **40** 2611–2619. (<https://doi.org/10.1007/s00268-016-3614-y>)
8. Odland ML, Nepogodiev D, Morton D, Martin J, Bekele A, Ghosh D, Ademuyiwa AO, Davies JI & Weiser TG. Identifying a basket of surgical procedures to standardize global surgical metrics: an International Delphi Study. *Annals of Surgery* 2021 **274** 1107–1114. (<https://doi.org/10.1097/SLA.0000000000004611>)
9. Gosselin RA, Spiegel DA, Coughlin R & Zirkle LG. Injuries: the neglected burden in developing countries. *Bulletin of the World Health Organization* 2009 **87** 246–246a. (<https://doi.org/10.2471/blt.08.052290>)
10. Kotagal M, Agarwal-Harding KJ, Mock C, Quansah R, Arreola-Risa C & Meara JG. Health and economic benefits of improved injury prevention and trauma care worldwide. *PLoS ONE* 2014 **9** e91862. (<https://doi.org/10.1371/journal.pone.0091862>)

11. Cordero DM, Miclau TA, Paul AV, Morshed S, Miclau T, 3rd, Martin C & Shearer DW. The global burden of musculoskeletal injury in low and lower-middle income countries: a systematic literature review. *OTA International* 2020 **3** e062. (<https://doi.org/10.1097/OI9.0000000000000062>)
12. Atijosan O, Rischewski D, Simms V, Kuper H, Lingana B, Nuhu A, Foster A & Lavy C. A national survey of musculoskeletal impairment in Rwanda: prevalence, causes and service implications. *PLoS ONE* 2008 **3** e2851. (<https://doi.org/10.1371/journal.pone.0002851>)
13. Young S, Banza LN, Hallan G, Beniyasi F, Manda KG, Munthali BS, Dybvik E, Engesaeter LB & Havelin LI. Complications after intramedullary nailing of femoral fractures in a low-income country. *Acta Orthopaedica* 2013 **84** 460–467. (<https://doi.org/10.3109/17453674.2013.850014>)
14. Saris CG, Bastianen CA, Mvan Swieten EC & Wegdam HH. Infection rate in closed fractures after internal fixations in a municipal hospital in Ghana. *Tropical Doctor* 2006 **36** 233–235. (<https://doi.org/10.1258/004947506778604689>)
15. Whiting PS, Galat DD, Zirkle LG, Shaw MK & Galat JD. Risk factors for infection after intramedullary nailing of open tibial shaft fractures in low- and middle-income countries. *Journal of Orthopaedic Trauma* 2019 **33** e234–e239. (<https://doi.org/10.1097/BOT.0000000000001441>)
16. Madu KA, Enweani UN, Katchy AU, Madu AJ & Aguwa EN. Implant associated surgical site infection in orthopaedics: a regional hospital experience. *Nigerian Journal of Medicine* 2011 **20** 435–440.
17. Stanley CM, Rutherford GW, Morshed S, Coughlin RR & Beyeza T. Estimating the healthcare burden of osteomyelitis in Uganda. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2010 **104** 139–142. (<https://doi.org/10.1016/j.trstmh.2009.05.014>)
18. Callistus KB, Alhassan A, Majeed S & Mogre V. Chronic osteomyelitis in a Ghanaian Specialist Hospital. *Advances in Applied Science Research* 2015 **6** 150–153.
19. Ikem ICF, Oginni LM, Bamgboye EA, Ako-Nai AK & Onipede AO. The bacteriology of open fractures in Ile-Ife, Nigeria. *Nigerian Journal of Medicine* 2004 **13** 359–365.
20. Ma X, Han S, Ma J, Chen X, Bai W, Yan W & Wang K. Epidemiology, microbiology and therapeutic consequences of chronic osteomyelitis in northern China: a retrospective analysis of 255 patients. *Scientific Reports* 2018 **8** 14895.
21. Mthethwa P & Marais LC. The microbiology of chronic osteomyelitis in a developing world setting. *SA Orthopaedic Journal* 2017 **16** 39–45. (<https://doi.org/10.17159/2309-8309/2017/v16n2a4>)
22. Nieuwoudt L, Rodseth RN & Marais LC. Fracture-related infections in HIV infected patients: a systematic review and meta-analysis. *Journal of Orthopaedics* 2020 **18** 248–254. (<https://doi.org/10.1016/j.jor.2020.01.023>)
23. Geurts J, Hohnen A, Vranken T & Moh P. Treatment strategies for chronic osteomyelitis in low- and middle-income countries: systematic review. *Tropical Medicine and International Health* 2017 **22** 1054–1062. (<https://doi.org/10.1111/tmi.12921>)
24. Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, Shibuya K, Salomon JA, Abdalla S, Aboyans V, *et al.* Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012 **380** 2163–2196. ([https://doi.org/10.1016/S0140-6736\(12\)61729-2](https://doi.org/10.1016/S0140-6736(12)61729-2))
25. Obremeskey WT, Metsemakers WJ, Schlatterer DR, Tetsworth K, Egol K, Kates S, McNally M, ICM Orthopaedic Trauma Work Group* & ICM Orthopaedic Trauma

Work Group*. Musculoskeletal infection in orthopaedic trauma: assessment of the 2018 International Consensus Meeting on Musculoskeletal Infection. *Journal of Bone and Joint Surgery: American Volume* 2020 **102** e44. (<https://doi.org/10.2106/JBJS.19.01070>)

26. World Bank. World Bank country and lending groups 2022. (available at: <https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups>)

27. Bezstarosti H, Van Lieshout EMM, Voskamp LW, Kortram K, Obremskey W, McNally MA, Metsemakers WJ & Verhofstad MHJ. Insights into treatment and outcome of fracture-related infection: a systematic literature review. *Archives of Orthopaedic and Trauma Surgery* 2019 **139** 61–72. (<https://doi.org/10.1007/s00402-018-3048-0>)

28. Metsemakers WJ, Morgenstern M, Senneville E, Borens O, Govaert GAM, Onsea J, Depypere M, Richards RG, Trampuz A, Verhofstad MHJ, et al. General treatment principles for fracture-related infection: recommendations from an International Expert Group. *Archives of Orthopaedic and Trauma Surgery* 2020 **140** 1013–1027. (<https://doi.org/10.1007/s00402-019-03287-4>)

29. Metsemakers WJ, Morgenstern M, McNally MA, Moriarty TF, McFadyen I, Scarborough M, Athanasou NA, Ochsner PE, Kuehl R, Raschke M, et al. Fracture-related infection: a consensus on definition from an International Expert Group. *Injury* 2018 **49** 505–510. (<https://doi.org/10.1016/j.injury.2017.08.040>)

30. Govaert GAM, Kuehl R, Atkins BL, Trampuz A, Morgenstern M, Obremskey WT, Verhofstad MHJ, McNally MA, Metsemakers WJ & Fracture-Related Infection (FRI) Consensus Group. Diagnosing fracture-related infection: current concepts and recommendations. *Journal of Orthopaedic Trauma* 2020 **34** 8–17. (<https://doi.org/10.1097/BOT.0000000000001614>)

31. McCord C, Kruk ME, Mock CN, Cherian M, von Schreeb J, Russell S & English M. Organization of essential services and the role of first-level hospitals. In *DCP-3 Essential Surgery*, pp. 213–230, 2017.

32. Hotchen AJ, McNally MA & Sendi P. The classification of long bone osteomyelitis: a systemic review of the literature. *Journal of Bone and Joint Infection* 2017 **2** 167–174. (<https://doi.org/10.7150/jbji.21050>)

33. Cierny G & Mader JT. Adult chronic osteomyelitis. *Orthopedics* 1984 **7** 1557–1564. (<https://doi.org/10.3928/0147-7447-19841001-07>)

34. Hotchen AJ, Sendi P & McNally M. BACH: a new classification system for long-bone osteomyelitis. *Orthopaedic Proceedings* 2018 **99-B**.

35. Hotchen AJ, Dudareva M, Ferguson JY, Sendi P & McNally MA. The BACH classification of long bone osteomyelitis. *Bone and Joint Research* 2019 **8** 459–468. (<https://doi.org/10.1302/2046-3758.810.BJR-2019-0050.R1>)

36. Hotchen AJ, Dudareva M, Corrigan RA, Ferguson JY & McNally MA. Can we predict outcome after treatment of long bone osteomyelitis? *Bone and Joint Journal* 2020 **102-B** 1587–1596. (<https://doi.org/10.1302/0301-620X.102B11.BJJ-2020-0284.R1>)

37. Marais LC, Ferreira N, Aldous C, Sartorius B & Le Roux T. A modified staging system for chronic osteomyelitis. *Journal of Orthopaedics* 2015 **12** 184–192. (<https://doi.org/10.1016/j.jor.2015.05.017>)

38. Asogwa OA, Boateng D, Marza-Florensa A, Peters S, Levitt N, van Olmen J & Klipstein-Grobush K. Multimorbidity of non-communicable diseases in low-income and middle-income countries: a systematic review and meta-analysis. *BMJ Open* 2022 **12** e049133. (<https://doi.org/10.1136/bmjopen-2021-049133>)

39. Depypere M, Kuehl R, Metsemakers WJ, Senneville E, McNally MA, Obremskey WT, Zimmerli W, Atkins BL, Trampuz A & Fracture-Related Infection (FRI) Consensus Group. Recommendations for systemic antimicrobial therapy in fracture-

related infection: a consensus from an International Expert Group. *Journal of Orthopaedic Trauma* 2020 **34** 30–41. (<https://doi.org/10.1097/BOT.0000000000001626>)

40. Li HK, Rombach I, Zambellas R, Walker AS, McNally MA, Atkins BL, Lipsky BA, Hughes HC, Bose D, Kümin M et al. Oral versus intravenous antibiotics for bone and joint infection. *New England Journal of Medicine* 2019 **380** 425–436. (<https://doi.org/10.1056/NEJMoa1710926>)

41. Masrouha KZ, Raad ME & Saghie SS. A novel treatment approach to infected nonunion of long bones without systemic antibiotics. *Strategies in Trauma and Limb Reconstruction* 2018 **13** 13–18. (<https://doi.org/10.1007/s11751-018-0303-4>)

42. Dudareva M, Kumin M, Vach W, Kaier K, Ferguson J, McNally M & Scarborough M. Short or long antibiotic regimes in orthopaedics (SOLARIO): a randomised controlled open-label non-inferiority trial of duration of systemic antibiotics in adults with orthopaedic infection treated operatively with local antibiotic therapy. *Trials* 2019 **20** 693. (<https://doi.org/10.1186/s13063-019-3832-3>)

43. Ali AM, Maya E & Lakhoo K. Challenges in managing paediatric osteomyelitis in the developing world: analysis of cases presenting to a tertiary referral centre in Tanzania. *African Journal of Paediatric Surgery* 2014 **11** 308–311. (<https://doi.org/10.4103/0189-6725.143136>)

44. Vijayakumar AB, Reddy YP, Suphala B, Gopalakrishnan A & Vinod Kumar CS. Microbiological and antibiotic profile of osteomyelitis in tertiary care hospital. *International Journal of Surgery* 2021 **8** 910–914.

45. Dudareva M, Hotchen AJ, Ferguson J, Hodgson S, Scarborough M, Atkins BL & McNally MA. The microbiology of chronic osteomyelitis: changes over ten years. *Journal of Infection* 2019 **79** 189–198. (<https://doi.org/10.1016/j.jinf.2019.07.006>)

46. Corrigan RA, Dudareva M & McNally M. Increasing antimicrobial resistance is not inevitable: in reply to microbiological and antibiotic profile of osteomyelitis tertiary care hospital. *International Surgery Journal* 2021 **8** 1967–1968. (<https://doi.org/10.18203/2349-2902.isj20212304>)

47. Midlau T, MacKechnie MC, Born CT, MacKechnie MA, Dyer GSM, Yuan BJ, Dawson J, Lee C, Ishmael CR, Schreiber VM et al. International Orthopaedic Volunteer Opportunities in Low and Middle-Income Countries. *Journal of Bone & Joint Surgery American Volume* 2021 In press. (<https://doi.org/10.2106/JBJS.21.00948>)

48. Dudareva M, Barrett LK, Morgenstern M, Atkins BL, Brent AJ & McNally MA. Providing an evidence base for tissue sampling and culture interpretation in suspected fracture-related infection. *Journal of Bone and Joint Surgery: American Volume* 2021 **103** 977–983. (<https://doi.org/10.2106/JBJS.20.00409>)

49. Morgenstern M, Athanasou NA, Ferguson JY, Metsemakers WJ, Atkins BL & McNally MA. The value of quantitative histology in the diagnosis of fracture-related infection. *Bone and Joint Journal* 2018 **100-B** 966–972. (<https://doi.org/10.1302/0301-620X.100B7.BJJ-2018-0052.R1>)

50. Ferguson J, Diefenbeck M & McNally M. Ceramic biocomposites as biodegradable antibiotic carriers in the treatment of bone infections. *Journal of Bone and Joint Infection* 2017 **2** 38–51. (<https://doi.org/10.7150/jbji.17234>)

51. Metsemakers WJ, Fragomen AT, Moriarty TF, Morgenstern M, Ego KA, Zalavras C, Obremskey WT, Raschke M, McNally MA & Fracture-Related Infection (FRI) Consensus Group. Evidence-based recommendations for local antimicrobial strategies and dead space management in fracture-related infection. *Journal of Orthopaedic Trauma* 2020 **34** 18–29. (<https://doi.org/10.1097/BOT.0000000000001615>)

52. Foster AL, Moriarty TF, Zalavras C, Morgenstern M, Jaiprakash A, Crawford R, Burch MA, Boot W, Tetsworth K, Midlau T et al. The influence of

biomechanical stability on bone healing and fracture-related infection: the legacy of Stephan Perren. *Injury* 2021 **52** 43–52. (<https://doi.org/10.1016/j.injury.2020.06.044>)

53. Bezstarosti H, Metsemakers WJ, van Lieshout EMM, Voskamp LW, Kortram K, McNally MA, Marais LC & Verhofstad MHJ. Management of critical-sized bone defects in the treatment of fracture-related infection: a systematic review and pooled analysis. *Archives of Orthopaedic and Trauma Surgery* 2021 **141** 1215–1230. (<https://doi.org/10.1007/s00402-020-03525-0>)

54. Bakhsh K, Atiq Ur R, Zimri FK, Mohammad E, Ahmed W & Saaiq M. Presentation and management outcome of tibial infected non-union with Ilizarov technique. *Pakistan Journal of Medical Sciences* 2019 **35** 136–140. (<https://doi.org/10.12669/pjms.35.1.67>)

55. Islam DMS, Hossain DMA, Sobhan DMA, Pramanik DSK, Rahman DMM, Rahman DMM & Haque DO. Management of infected non-union tibia with Ilizarov external fixator: study on tertiary hospital in Bangladesh. *SAS Journal of Surgery* 2022 **8** 34–39. (<https://doi.org/10.36347/sasjs.2022.v08i01.010>)

56. Loro A, Hodges A, Galiwango GW & Loro F. Vascularized fibula flap in the management of segmental bone loss following osteomyelitis in children at a Ugandan hospital. *Journal of Bone and Joint Infection* 2021 **6** 179–187. (<https://doi.org/10.5194/jbji-6-179-2021>)

57. Chan JKK, Ferguson JY, Scarborough M, McNally MA & Ramsden AJ. Management of post-traumatic osteomyelitis in the lower limb: current state of the art. *Indian Journal of Plastic Surgery* 2019 **52** 62–72. (<https://doi.org/10.1055/s-0039-1687920>)

58. Muller SLC, Morgenstern M, Kuehl R, Muri T, Kalbermatten DF, Clauss M, Schaefer DJ, Sendi P & Osinga R. Soft-tissue reconstruction in lower-leg fracture-related infections: an orthoplastic outcome and risk factor analysis. *Injury* 2021 **52** 3489–3497. (<https://doi.org/10.1016/j.injury.2021.07.022>)

59. Ferguson J, Alexander M, Bruce S, O'Connell M, Beecroft S & McNally M. A retrospective cohort study comparing clinical outcomes and healthcare resource utilisation in

patients undergoing surgery for osteomyelitis in England: a case for reorganising orthopaedic infection services. *Journal of Bone and Joint Infection* 2021 **6** 151–163. (<https://doi.org/10.5194/jbji-6-151-2021>)

60. Card EB, Obayemi JE, Shirima O, Lazaro M, Massawe H, Stanifer JW, Premkumar A & Sheth NP. Practices and perspectives of traditional bone setters in Northern Tanzania. *Annals of Global Health* 2020 **86** 61. (<https://doi.org/10.5334/aogh.2878>)

61. Viergever RF. The mismatch between the health research and development (R&D) that is needed and the R&D that is undertaken: an overview of the problem, the causes, and solutions. *Global Health Action* 2013 **6** 22450. (<https://doi.org/10.3402/gha.v6i0.22450>)

62. Hedt-Gauthier BL, Jeufack HM, Neufeld NH, Alem A, Sauer S, Odhiambo J, Boum Y, Shuchman M & Volmink J. Stuck in the middle: a systematic review of authorship in collaborative health research in Africa, 2014–2016. *BMJ Global Health* 2019 **4** e001853. (<https://doi.org/10.1136/bmjgh-2019-001853>)

63. Parker B, Petrou S, Masters JPM, Achana F & Costa ML. Economic outcomes associated with deep surgical site infection in patients with an open fracture of the lower limb. *Bone and Joint Journal* 2018 **100-B** 1506–1510. (<https://doi.org/10.1302/0301-620X.100B11.BJJ-2018-0308.R1>)

64. Alkire BC, Meara JG & Vincent JR. Benefit-cost analysis for selected surgical interventions in low- and middle-income countries. In *DCP-3 Essential Surgery*, pp. 361–380, 2017.

65. Boriani F, Ul Haq A, Baldini T, Urso R, Granchi D, Baldini N, Tigani D, Tarar M & Khan U. Orthoplastic surgical collaboration is required to optimise the treatment of severe limb injuries: a multi-centre, prospective cohort study. *Journal of Plastic, Reconstructive and Aesthetic Surgery* 2017 **70** 715–722. (<https://doi.org/10.1016/j.bjps.2017.02.017>)

66. Loro A. External fixation used in the management of septic non-union of long bones in a low resources setting. *Uganda Orthopaedic Journal* 2016 **1**.