Paediatric Surgery across Sub-Saharan Africa: A Multi-Centre Prospective Cohort Study

PaedSurg Africa

PaedSurg Africa Research Collaboration:
A multi-centre research collaboration, constituting surgeons and allied health professionals working with neonates and children requiring surgery across sub-Saharan Africa.

paedsurg.research@gmail.com

@PaedsSurgeon

Study Protocol v5

1st Oct 2016

Contents

1. Abstract 3
2. Introduction 4
3. Aim and Objectives 9
4. Methodology: 10
    - Authorship
    - Data collection tool
    - Questionnaire data
    - Patient data and outcome measures
    - Validity
    - Data analysis
    - Ethics
5. References 13
6. Appendix 1: Patient data collection 20
7. Appendix 2: Summary of the questionnaire for research collaborators 24
8. Appendix 3: Kings College London ethical approval 25

Abstract

Background: Five billion people worldwide do not have access to safe, affordable surgical care. A significant proportion live in sub-Saharan Africa (SSA), where up to 50% of the population are children. There is limited literature on neonatal and paediatric surgery in SSA and children's surgery does not appear on any of the National Health Strategic Plans for the 47 independent countries across SSA.

Objectives: To form a collaboration of surgeons and allied health professionals involved in children's surgery across SSA and collectively undertake the largest prospective cohort study of paediatric surgery in this region.

Materials and Methods: Data will be collected via REDCap website on all patients with gastroschisis, anorectal malformation, appendicitis, inguinal hernia and intussusception, during a 1-month period between October 2016 to April 2017. Estimated study population: 1450 patients from 50 institutions. Local ethics approval will be required for participation. All collaborators will be co-authors.

Primary outcome will be in-hospital mortality. Secondary outcomes will include post-intervention complications. Data will be collected on institutional facilities, patient demographics, duration from condition onset to presentation, peri-operative resuscitation, intervention and outcome.

Differences in outcomes between SSA and high-income countries will be calculated using chi-squared analysis. Multi-level multivariate logistic regression analysis will be used to identify interventions and peri-operative factors associated with improved outcomes; $p<0.05$ will be deemed significant.

Outcome: Results will be used to advocate for enhanced children's surgical services in SSA. We shall identify context-appropriate interventions associated with improved outcome. The collaboration will help to enhance research capacity in the region.

Introduction

Research Collaboratives

PaedSurg Africa aims to recruit surgeons and allied health professionals undertaking neonatal and paediatric surgery (PS) across sub-Saharan Africa (SSA) - an area heavily neglected in global health prioritisation. Such research collaboratives are being increasingly utilised as a highly effective and efficient method of collecting large volume prospective data in a short period of time. Utilising a similar methodology, GlobalSurg recruited surgeons from 375 centres around the world, collecting data on 10,745 patients in just 2-weeks, highlighting the feasibility of this study[1]. A great recruitment incentive will be ethical group co-authorship of published results for all research collaborators.

Global Paediatric Surgery

In 2015, the Lancet Commission on Global Surgery (LCoGS) highlighted that 5 billion people worldwide do not have access to safe, affordable surgical care[2]. The same year, the World Health Assembly (Resolution 68/31) incorporated 'emergency and essential surgery and anaesthesia care' within 'Universal Health Coverage'[3]. In concordance with this, plans have arisen to exponentially scale up access to surgical care in low- and middle-income countries (LMICs)[2]. Children's surgery has yet to be formally recognised within these plans despite children forming up to 50% of the population in LMICs[4].

SSA has the highest unmet need for surgical care in the world at 41 million cases per year (29% of the worlds unmet need)[2]. 9% of the global surgical burden of disease is attributable to congenital anomalies[5]. It is estimated that 2.6 million children are born with a congenital anomaly in SSA each year[4,5].

Hence, in order for the world to achieve the LCoGS goal of 80% coverage of surgical care by 2030, there must be a focus on scaling up neonatal and PS care in SSA where a significant proportion of the burden of surgical disease lies.

To date there has been limited data published on neonatal and PS in SSA. Nwomeh et al undertook a systematic review and meta-analysis of neonatal surgery in SSA and identified just 13 prospective studies and 38 retrospective studies between 1995 – 2014[6]. The majority of these were single institutional studies, many with limited numbers. The results highlight poor outcomes with mortality rates of over 50-100% for conditions such as gastroschisis, which has mortality rates consistently under 4% in high-income countries[6,7]. Similarly, the limited literature on PS in SSA highlights significantly poorer outcomes for common conditions such as appendicitis, intussusception and inguinal hernia[8-13].

Surgery has largely been overlooked in global health prioritisation and funding, likely because of the perception of prohibitive cost and complexity of care. Conversely, recent health economic studies have amply demonstrated the overall cost-effectiveness of PS procedures; for instance investing in a paediatric inguinal hernia repair is similar to administering a tetanus vaccine or treating a patient with malaria in terms of disability-adjusted life years (DALYS)/ US$[14].

Our study aims to collect prospective data on 5 common neonatal and PS conditions across SSA, all of which have low morbidity and mortality (M&M) in high income countries (HIC), but reported poorer outcomes in SSA. It will be the first neonatal and PS cohort study across SSA and will undoubtedly form one of the largest prospective data sets in this region of the world.

This project aims to provide vital information required to advocate for enhanced children's surgical services in SSA and to identify context appropriate interventions to improve the outcome of a selection of the commonest neonatal and general paediatric surgical conditions. Participation in this project will help to enhance research capacity amongst surgeons and allied healthcare professionals in SSA. Formulation of PaedSurg Africa Research Collaboration will provide the infrastructure for future research projects and interventions to help improve outcome.

The 5 conditions to be studied are gastroschisis, anorectal malformation, appendicitis, inguinal hernia and intussusception.

Gastroschisis

The incidence of gastroschisis is increasing worldwide, as are the number of these patients presenting to hospital in SSA[16]. In Pretoria, South Africa, there was a 35-fold increase in patients presenting with gastroschisis from the early 1980's to late 1990s[17]. Centres such as Harare, Zimbabwe, report receiving up to 3-4 cases per week[18]. The true incidence of gastroschisis is unknown in SSA, however studies suggest the incidence, at least in some regions, appears to be similar to HICs[18]. With a prevalence of 5.4/10,000 births, we can estimate that 1440 cases will be born each month in SSA[18,19].

Mortality rates for gastroschisis have fallen dramatically in HICs from 60% in the 1960's to less than 4% today[7,18]. This has resulted from improvements in neonatal resuscitation and peri-operative management, awareness of complications such as abdominal compartment syndrome, and the provision of parenteral nutrition (PN). Gastroschisis has been suggested as a Bellwether procedure for neonatal surgery capacity in low resource settings because there are usually no co-morbidities, yet the condition tests all the key elements that go into the successful management of a newborn with a surgical condition[20].

The data available regarding gastroschisis in SSA suggests significantly poorer outcomes than in HIC. Mortality rates have been reported as: 60% Malawi, 57-75% Nigeria, 84-100% Zimbabwe, 100% Uganda, 100% Cote'd'Ivoire[16,20-24]. Mortality in South Africa is lower at 12-43%[17,20,25,26]. In an international survey of gastroschisis,

two thirds of the 25 institutions in SSA stated their mortality rate was >75% and the remaining third stated it was between 50-75%[18].

There is great variation in the management of gastroschisis across the globe and even between surgeons within the same institution[18,27,28]. Primary closure rates vary from 16%, particularly in centres where routine use of preformed silos (PFS) have been adopted, to 92%[18,20,27]. The majority of staged closure in SSA is undertaken using a surgical silo; PFS are utilised less due to lack of availability and training[18,20]. Some surgeons recommend primary palliative care in SSA[18,20,25]. A randomised control trial of primary closure versus PFS had reported they have similar outcomes, however there is a trend towards fewer ventilator days with the latter[29]. A meta-analysis highlighted that the studies with least selection bias show that PFS is associated with fewer ventilator days ($P<0.0001$), reduced time to first feed ($p=0.04$) and lower infection rates ($p=0.03$)[30].

There are many challenges faced by a surgeon in SSA. Patients are often outborn with no antenatal diagnosis, and hence presentation is delayed resulting in hypothermia, sepsis, hypovolaemia and bowel compromise[18,25]. There is a natural tendency for babies with gastroschisis to be born early; in Harare 43% were preterm and 72% were <2.5kg[22]. Similarly in Durban 64% were preterm and 72% <2.5kg[25]. Many centres lack a neonatal intensive care unit (NICU) and have limited anaesthetic resources[18,20]. Exposure of the bowel to amniotic fluid results in dysmotility and problems with absorption of nutrients; in the UK the average duration of parenteral (PN) requirement in simple gastroschisis is 23 days and 51 days in complex gastroschisis (gastroschisis associated with bowel perforation, necrosis or atresia)[7]. PN was only available in 36% of SSA centres when surveyed[18]. However, in Harare the median hospital stay was 4.5days for the 85% who died, suggesting death was related to inadequate resuscitation and support rather than lack of PN [7]. A multi-centre Gastroschisis International (GiT) study showed septicaemia to be the leading cause of death[20].

Some centres such as the University of Nigeria Teaching Hospital have introduced a protocol to ensure efficient pre and post operative resuscitation and care, preservation of body heat, decompression of the stomach with a nasogastric tube, evacuation of meconium, respiratory support and parental nutrition[16]. As a result their mortality rate has fallen from 65% to 35%. However, Hadley notes that in Durban, despite access to NICU and PN, the overall mortality is still 43%, with sepsis being the leading cause[25]. They stress the importance of meticulous central line care and a need for improved antenatal care and delivery within a tertiary paediatric surgery centre. A protocol focussed on early and aggressive resuscitation, avoidance of compartment syndrome, appropriate IV access and proactive nutritional interventions may help SSA start to realise the improvements in outcome as seen in HIC over the last 55-years. Implementing such interventions should have a knock on effect to strengthen the neonatal healthcare system in SSA and hence help to improve outcomes for all newborns with surgical conditions[20].

Anorectal Malformation

The birth prevalence of anorectal malformations (ARMs) has been reported as 1:1,500 – 1:5,000 in South Africa[31]. In institutional publications from around SSA,

caseload varies from 1-3 cases/ month[37-41]. ARMs are one of the most common neonatal emergencies presenting to hospitals in SSA: 9.5% surgical neonates in Tanzania, 13.4% congenital malformations in Nigeria[37-41].

Mortality in HIC has fallen from 23% in the 1940's to less than 3% today[42]. Mortality has been documented at 18.5 – 20% in Nigeria, with most deaths related to overwhelming sepsis, respiratory insufficiency and cyanotic heart disease[35,40]. Unlike gastroschisis, 50% cases are associated with other anomalies: VACTERL (vertebral, anorectal, cardiac, tracheoesophageal, renal and limb). Other challenges include late presentation (2-5 days), low birth weight (38% < 2.5kg) and lack of adequate NICU facilities.

Management is dependent on the type of anomaly with low ARM typically being managed with a primary anoplasty and higher anomalies requiring a primary colostomy followed by a posterior sagittal anorectoplasty (PSARP) within the first year of life, and subsequent colostomy closure. Divided sigmoid colostomy is preferred to avoid overspill of stool from the proximal limb into the distal pouch, however some centres in SSA undertake loop colostomies[32]. Lukong et al highlighted their improvement in outcome following a change in practice from a transverse loop colostomy to divided sigmoid colostomy with delayed PSARP[43]. In some centres local anaesthesia is utilised to undertake the colostomy, reducing the risks associated with general anaesthesia where resources are limited[40].

Udefiagbon et al, highlight the problems with a colostomy, particularly in a low income setting: skin excoriation, wound infection, sepsis, prolapse, fluid and electrolyte losses and poor acceptance by care givers[44]. They present impressive outcomes for primary PSARP undertaken during the first week of life[44]. Authors advocate the benefits of reduced infection rate due to the sterile nature of the meconium and avoidance of a prolonged 3-stage procedure, which is more expensive and often unfeasible for African families. However, this practice requires safe neonatal anaesthesia, skilled surgeons and good standards of peri-operative care. Olivieri et al have described a modified PSARP technique utilised in Eritrea to reduce the risk of perianal wound infection where they leave a 3cm rectal stump, which is trimmed after 2 weeks[37]. Poenaru et al advocate performing a wider anoplasty, which is less prone to stenosis, as regular dilatation and following-up can be challenging in this context[45].

This study will capture the primary peri-operative management and outcomes for patients presenting with ARM. Longer-term morbidity including faecal incontinence, anal stenosis, constipation, urinary and ejaculatory problems and outcomes of subsequent surgery are beyond the remit of this study.

Appendicitis

Acute appendicitis is one of the commonest causes for acute abdomen in children worldwide. In Ethiopia appendicitis accounts for 12% of emergency paediatric surgery and in the Congo it constitutes 30% of paediatric visceral surgery[12,46]. Mortality from appendicitis is up to 4% in some SSA settings and morbidity high with wound infection rates up to 60% and wound dehiscence in up to 25%[8-10]. Conversely, mortality from appendicitis in HICs is 0.04% and only 0.006% in children aged 9-19-years[9]. The LCoGS has listed laparotomy as one of 3 Bellwether

procedures that must be safe and available at all institutions providing first level care[2].

There are a number of challenges for managing children with acute appendicitis in the SSA setting. Children present late with 25-67% perforation rates; re-operation for intra-abdominal sepsis is as high as 40%[2,5,8,47,48]. Differential diagnoses in SSA are more varied. In America, 82% of peritonitis in children is secondary to appendicitis whereas in SSA children present with peritonitis secondary to typhoid perforation, tuberculosis and ascariasis [53,55]. There is often a lack of appropriate antibiotics, paediatric intensive care, blood products and parental nutrition[9]. HIV may impact on the spectrum and severity of surgical infection in African children[10].

Inguinal Hernia

Paediatric inguinal hernia repair (PIHR) is the most commonly performed operation worldwide[11,14]. The incidence is up to 5% of term infants and 30% of preterm[49]. It is widely considered a basic and essential procedure that should be available to all and yet is largely unavailable in SSA[14,50]. Complicated inguinal hernias pose a threat to the life of the child and considerable morbidity, which could be avoided by timely management of what is otherwise a straightforward procedure[11]. Infants are at greatest risk of delay; Zamakhshary found that waiting over 2 weeks for a PIHR doubled the risk of incarceration in this age group[51].

In Ein's study of 6361 paediatric inguinal hernia repairs in Canada there were no deaths, recurrence rate of 1.2%, wound infection rate of 1.2% and testicular atrophy rate of 0.3%[49]. In this study, 12% presented as incarcerated, but only 1% required emergency surgery for an irreducible hernia and 2/6361 required a bowel resection[49]. Ergogan reported similar outcomes in Turkey[52].

In SSA, delays in presentation and lack of surgical capacity often result in a higher proportion of complicated paediatric hernias. In Nigeria, outcomes have been reported as: mortality 2.4%, intestinal resection 7%, testicular gangrene 15% and wound infection 15%[11]. Another centre reported that in their cohort of infants presenting <42days of age, 52% were incarcerated, 36% required a bowel resection and 18% underwent an orchidectomy for testicular infarction[53]. Strangulated hernias constitute 22% of the emergency visceral surgery in the Congo[12]. A randomised controlled trial in Nigeria reported a reduction in infection rate following PIHR from 4.8% to 0% with the use of prophylactic IV gentamycin at induction[54].

Intussusception

Intussusception is a leading cause of intestinal obstruction (IO) in children. A study from Nigeria reported 29% of IO from intussusception, 22% from ARM and 17% from obstructed PIH[55]. The incidence is South Africa is comparable to HICs at 56/100,000 < 1-year compared to 33-49/100,000 < 1-year in the US[13]. Published studies suggest institutions in SSA see at least one case/ month[13].

In HIC mortality is low at 0.1% in Europe and 0.4% in the US[13,56]. Mortality rates in SSA vary widely and have been reported at 0 – 55%[13,57-72]. The average mortality rate across SSA is 9.4%[13,73]. There are a number of challenges to managing a child

with intussusception in SSA. They often present late; 92% patients in Ile-Ife, Nigeria, present >24 hours. In Kenya the main duration of symptoms at presentation was 5 days (1-14)[63]. It was noted that the median delay for those who died (6.4%) was 5-days versus 3-days in those who survived[57]. Surgical site infections following laparotomy for intussusception have been reported as high as 37.5%[74].

Management varies widely in SSA. In HICs most centres undertake air enema reduction (AER) as primary management in cases without peritonitis, perforation or non-responsive shock. This has been shown to be 1.48 times more effective than hydrostatic reduction (61% and 44% respectively)[75]. Centres in SSA with access to AER report good success rates; in a study in Ghana AER was successful in 59-67% cases and their mortality rate was 2%[62,76]. They note that AER costs 20% of the fee for surgical management[76]. A study from Nigeria reports offering hydrostatic reduction to 40% of cases, where it is successful in 64%[71]. They also highlight the significant cost savings.

Ahmed et al in Egypt describe their simple AER equipment with a pressure release value at 120mmHg[77]. They report an 88.2% success rate with no complications. Wiersma and Hadley advocate the use of AER in the operating theatre, which has improved their reduction rate to 53% from 22%[78].

Aim:

To compare outcomes of five common neonatal and paediatric surgical conditions between SSA and HICs.

Objectives:

1) To undertake the first multi-centre prospective cohort study across SSA to compare outcomes of common paediatric surgical conditions with benchmark data from HICs.

2) To identify context appropriate interventions and peri-operative factors associated with an improved outcome.

3) To form a research collaboration of paediatric surgeons and allied health professionals across SSA and help to enhance research capacity.

4) To raise awareness and provide advocacy for neonatal and paediatric surgical care within global health prioritisation, planning and funding.

Methodology

Authorship

PaedSurg Africa constitutes a network of surgeons and allied health professionals who work with children requiring surgery across sub-Saharan Africa. This methodology is based on an equal partnership model previously described in the Lancet and utilised by a number of national and international collaboratives[1,79].

We will ask publishing journals to make all co-authors PubMed citable. Articles will be published under 'PaedSurg Africa Research Collaboration'. At the end of the article co-authors will be listed under the following headings:

- Lead investigators: collaborators who have contributed to the study protocol, data analysis and write-up of the manuscript.
- Country leads: collaborators who have recruited several sites in their country to contribute to the study.
- Local investigators: collaborators who have gained ethical approval for the protocol in their centre and collected data at their site including patient identification and data completion with follow-up of mortality and complications. The study invites up to three local investigators per institution.

Collaborator recruitment:

Primary recruitment will be through the lead investigators' personal contacts, which span many centres and countries across SSA, and the Pan-African Paediatric Surgical Association (PAPSA) mailing list. Research collaborators were recruited at the Global Initiative for Children's Surgery (GICS) Conference hosted by the Royal College of Surgeons of England, May 2016. A further recruitment drive will be undertaken at the PAPSA Conference in Nigeria (September 2016) where the research proposal will be presented, investigators actively sought, and REDCap sign-up, app download and project set-up achieved.

Data collection tool

Prospective data will be collected over a 1-month period utilising the free, user-friendly, secure database, REDCap[80]. The tool includes a Smartphone app that allows offline data collection. Data collection sheets that can be printed for written data collection and later uploaded will also be provided. Data collection will be open for any continuous 1-month period between October 2016 to April 2017, to optimise uptake. A pilot study will be run in August/ September 2016 at 5 institutions in SSA.

Conditions studied:

The 5 conditions selected are common congenital or acquired neonatal and paediatric surgical conditions with low M&M in HICs. Consequently surgical interventions for these conditions carry high avertable DALYs and cost-effectiveness ratios, as saving the life of a neonate or child with minimal long-term disability can permit a lifetime of labour and income for their family and their country's economy.

Limited, mostly retrospective, individual institutional studies suggest significantly poorer outcomes of these conditions in SSA.

Patient data and outcome measures:

Primary outcome will be all cause in-hospital mortality. For patients hospitalised for > 30-days, a 30-day mortality will be utilised.

Secondary outcomes will include post-operative complications and length of hospital stay.

Data will be collected on: patient demographics, referral source, duration from onset of condition to presentation, reason for delay if present, pre-operative resuscitation, intervention and outcome [Appendix 1].

Validation:

At 5% of collaborating centres, one research collaborator will be asked to identify patients and upload the study data independent to the other research collaborator(s) at their centre. This data will be collected on a separate REDCap validation database and the inputted data will be cross-checked with that entered into the main database. The database will be programmed to only permit datasets to be submitted if a minimum of 90% of the data has been completed. Data can be initially uploaded and completed at a later date prior to submission if any data is missing.

Questionnaire data:

A short questionnaire will be undertaken by all research collaborators at the time of project sign up regarding the facilities and resources available at their institution [Appendix 2].

Estimated population:

Estimated patient numbers per centre during a 1-month study period are: 1-2 gastroschisis[16-18], 1-2 anorectal malformations[32-36], 11 appendicitis[46,81], 14 inguinal hernias[11,14,51,53,54,82,83], 1 intussusception[13] (29 patients per centre). We aim to include a minimum of 50 centres, which would generate 1450 patients. Estimates were calculated using the mean number of patients presenting per month to all institutions from SSA who have published data on these conditions.

Data Analysis

Power calculations were undertaken to determine the minimum detectable differences between mortality in SSA and benchmark data from HICs. The minimum differences that can be detected at the 5% significance level with 80% power are summarised in the table 1.

Table 1: The minimum detectable differences in mortality between SSA and HICs.

	High income country		Sub-Saharan Africa		
	Patient population	Mortality rate	Expected study population size	Mortality rate in SSA at minimum detectable difference	Minimum detectable difference in mortality
Gastroschisis[7]	301	4%	75	14.5%	10.5%
ARM[42]	410	3%	75	12.2%	9.2%
Appendicitis[84]	24665	0.004%	550	0.43%	0.426%
Inguinal hernia[49,52]	10137	0%	700	0.40%	0.4%
Intussusception[13]	9186	0.2%	50	5%	4.8%

Outcomes in SSA compared to HICs will be presented as relative risks and significant differences determined using Chi-Squared analysis.

Multi-level, multivariate logistic regression analysis will be utilised to identify context appropriate interventions and peri-operative factors associated with improved outcomes. For example: does availability of air enema reduction significantly reduce mortality from intussusception in the SSA context and if so, by how much? Results will be presented as odds ratios. Data will be adjusted for confounding factors such as delay in presentation. $P<0.05$ will be deemed significant.

Ethics:

We have received full ethical approval for the project by the Kings College London Ethics Committee [Appendix 3]. Research collaborators in SSA will be required to receive approval for the project at their own centres according to local ethical regulations and provide evidence of this in order to submit data.

If no formal ethics or audit committee exists, collaborators must provide written consent from the Director of the Hospital or Head of Surgical Department. All data will be anonymous and remain confidential. Data will not be identifiable at individual surgeon, institution or country level.

Outcome:

The results from this study can be used to advocate for enhanced neonatal and paediatric surgical care in SSA, both at country level via 'National Health Strategic Plans' and at an international level[15]. This is vital to ensure neonatal and paediatric surgery are appropriately prioritised over the coming 15-years as access to surgical care in low and middle income countries is exponentially scaled up following publication of the LCoGS and the WHA resolution 68/31, which incorporates surgery within 'universal health coverage'.
Participation in this international project will help to enhance research capacity amongst surgeons and allied healthcare professionals across SSA. Formation of PaedSurg Africa Research Collaboration will provide the infrastructure for future research projects and interventions to help improve outcome.

References

1. GlobalSurg Collaborative. Mortality of emergency abdominal surgery in high-, middle- and low-income countries. BJS, 2016. doi: 10.1002/bjs.10151. [Epub ahead of print]

2. Meara JG, Leather AJ, Hagander L, Alkire BC, Alonso N, et al. Global Surgery 2030: evidence and solutions for achieving health, welfare, and economic development. Lancet, 2015;386(9993):569-624.

3. World Health Organisation. World Health Assembly, 68/31. Strengthening emergency and essential surgical care and anaesthesia as a component of universal health coverage. 2015: http://apps.who.int/gb/ebwha/pdf_files/EB136/B136_CONF1-en.pdf (Accessed 13.6.16).

4. The World Bank. Birth rate crude (per 1000 people): data.worldbank.org (Accessed 8.6.16).

5. Poenaru D, Pemberton J, Frankfurter C, Cameron BH. Quantifying the Disability from Congenital Anomalies Averted Through Pediatric Surgery: A Cross-Sectional Comparison of a Pediatric Surgical Unit in Kenya and Canada. World J Surg, 2015;39(9):2198-206.

6. Ekenze SO, Ajuzieogu OV, Nwomeh BC. Challenges of management and outcome of neonatal surgery in Africa: a systematic review. Pediatr Surg Int, 2016;32(3):291-9.

7. Bradnock TJ, Marven S, Owen A, Johnson P, Kurinczuk JJ, et al; BAPS-CASS. Gastroschisis: one year outcomes from national cohort study. BMJ. 2011;343:d6749.

8. Ademola TO, Oludayo SA, Samuel OA, Amarachukwu EC, Akinwunmi KO, et al. Clinicopathological review of 156 appendicectomies for acute appendicitis in children in Ile-Ife, Nigeria: a retrospective analysis. BMC Emerg Med, 2015;15:7.

9. Hadley GP. Intra-abdominal sepsis--epidemiology, aetiology and management. Semin Pediatr Surg, 2014;23(6):357-62.

10. Ameh EA, Abantanga FA, Birabwa-Male D. Surgical aspects of bacterial infection in African children. Semin Pediatr Surg, 2012;21(2):116-24.

11. Bamigbola KT, Nasir AA, Abdur-Rahman LO, Adeniran JO. Complicated childhood inguinal hernias in UITH, Ilorin. Afr J Paediatr Surg, 2012;9(3):227-30.

12. Mabiala-Babela JR, Pandzou N, Koutaba E, Ganga-Zandzou S, Senga P. [Retrospective study of visceral surgical emergencies in children at the University Hospital Center of Brazzaville (Congo)]. [Article in French] Med Trop (Mars), 2006;66(2):172-6.

13. Jiang J, Jiang B, Parashar U, Nguyen T, Bines J, et al. Childhood intussusception: a literature review. PLoS One, 2013;8(7):e68482.

14. Eeson G, Birabwa-Male D, Pennington M, Blair GK. Costs and cost-effectiveness of pediatric inguinal hernia repair in Uganda. World J Surg, 2015;39(2):343-9.

15. Citron I, Chokotho L, Lavy C. Prioritisation of Surgery in the National Health Strategic Plans of Africa: A Systematic Review. World J Surg, 2016;40(4):779-83.

16. Agugua NE, Nwako FA. Gastroschisis a fifteen-year experience. West Afr J Med, 1990;9(2):147-50.

17. Arnold M. Is the incidence of gastroschisis rising in South Africa in accordance with international trends? A retrospective analysis at Pretoria Academic and Kalafong Hospitals, 1981-2001. S Afr J Surg, 2004;42(3):86-8.

18. Wright NJ, Zani A, Ade-Ajayi N. Epidemiology, management and outcome of gastroschisis in Sub-Saharan Africa: Results of an international survey. Afr J Paediatr Surg, 2015;12(1):1-6.

19. Springett A, Morris JK. Congenital Anomaly Statistics 2010: England and Wales. London: British Isles Network of Congenital Anomaly Registers 2012.

20. Ford K, Poenaru D, Moulot O, Tavener K, Bradley S, Bankole R, Tshifularo N, Ameh E, Alema N, Borgstein E, Hickey A, Ade-Ajayi N. Gastroschisis: Bellwether for neonatal surgery capacity in low resource settings? J Pediatr Surg, 2016. pii: S0022-3468(16)00204-9.

21. Iliff PJ. Neonatal surgery in Harare Hospital. Cent Afr J Med, 1990;36(1):11-5.

22. Apfeld JC, Wren SM, Macheka N, Mbuwayesango BA, Bruzoni M, Sylvester KG, Kastenberg ZJ. Infant, maternal, and geographic factors influencing gastroschisis related mortality in Zimbabwe. Surgery, 2015;158(6):1475-80.

23. Abdur-Rahman LO, Abdulrasheed NA, Adeniran JO. Challenges and outcomes of management of anterior abdominal wall defects in a Nigerian tertiary hospital. Afr J Paediatr Surg, 2011;8(2):159-63.

24. Apfeld JC, Wren SM, Macheka N, Mbuwayesango BA, Bruzoni M, et al. Infant, maternal, and geographic factors influencing gastroschisis related mortality in Zimbabwe. Surgery, 2015158(6):1475-80.

25. Sekabira J1, Hadley GP. Gastroschisis: a third world perspective. Pediatr Surg Int. 2009;25(4):327-9.

26. Davies MR, Beale PG. The pivotal role of the surgeon in the results achieved in gastroschisis. Pediatr Surg Int, 1996;11(2-3):82-5.

27. Zani A, Ruttenstock E, Davenport M, Ade-Ajayi N. Is there unity in Europe? First survey of EUPSA delegates on the management of gastroschisis. Eur J Pediatr Surg, 2013;23(1):19-24.

28. Weil BR, Leys CM, Rescorla FJ. The jury is still out: changes in gastroschisis management over the last decade are associated with both benefits and shortcomings. J Pediatr Surg, 2012;47(1):119-24.

29. Pastor AC, Phillips JD, Fenton SJ, Meyers RL, Lamm AW, et al. Routine use of a SILASTIC spring-loaded silo for infants with gastroschisis: a multicenter randomized controlled trial. J Pediatr Surg, 2008;43(10):1807-12.

30. Kunz SN, Tieder JS, Whitlock K, Jackson JC, Avansino JR. Primary fascial closure versus staged closure with silo in patients with gastroschisis: a meta-analysis. J Pediatr Surg, 2013;48(4):845-57.

31. Theron A, Loveland J. Birth prevalence of anorectal malformation in the referral area for the University of the Witwatersrand tertiary hospitals, South Africa. Eur J Pediatr Surg, 2015;25(2):220-5.

32. Safavi A, Skarsgard E, Butterworth S. Bowel-defect disproportion in gastroschisis: does the need to extend the fascial defect predict outcome? Pediatr Surg Int, 2012;28(5):495-500.

33. Govender S, Wiersma R. Delayed diagnosis of anorectal malformations (ARM): causes and consequences in a resource-constrained environment. Pediatr Surg Int, 2016;32(4):369-75.

34. Kigo CN, Ndung'u JM. Bowel function following primary repair of anorectal malformations at Kenyatta National Hospital. East Afr Med J, 2002;79(3):124-7.

35. Chirdan LB, Uba FA, Ameh EA, Mshelbwala PM. Colostomy for high anorectal malformation: an evaluation of morbidity and mortality in a developing country. Pediatr Surg Int, 2008;24(4):407-10.

36. Lawal TA, Olulana DI, Ogundoyin OO. Spectrum of colorectal surgery operations performed in a single paediatric surgery unit in sub-Saharan Africa. Afr J Paediatr Surg, 2014;11(2):128-31.

37. Olivieri C, Belay K, Coletta R, Retrosi G, Molle P, Calisti A. Preventing posterior sagittal anoplasty 'cripples' in areas with limited medical resources: a few modifications to surgical approach in anorectal malformations. Afr J Paediatr Surg, 2012;9(3):223-6.

38. Nandi B, Mungongo C, Lakhoo K. A comparison of neonatal surgical admissions between two linked surgical departments in Africa and Europe. Pediatr Surg Int, 2008;24(8):939-42.

39. Adeyemo AA, Gbadegesin RA, Omotade OO. Major congenital malformations among neonatal referrals to a Nigerian university hospital. East Afr Med J, 1997;74(11):699-701.

40. Ameh EA, Chirdan LB. Neonatal intestinal obstruction in Zaria, Nigeria. East Afr Med J, 2000;77(9):510-3.

41. Shah M, Gallaher J, Msiska N, McLean SE, Charles AG. Pediatric intestinal obstruction in Malawi: characteristics and outcomes. Am J Surg, 2016;211(4):722-6.

42. Rintala R, Pakarinen M. Imperforate anus: long- and short-term outcome. Sem Pediatr Surg, 2008;17:79-89.

43. Lukong CS, Ameh EA, Mshelbwala PM, Jabo BA, Gomna A, et al. Management of anorectal malformation: Changing trend over two decades in Zaria, Nigeria. Afr J Paediatr Surg, 2011;8(1):19-22.

44. Osifo OD, Osagie TO, Udefiagbon EO. Outcome of primary posterior sagittal anorectoplasty of high anorectal malformation in well selected neonates. Niger J Clin Pract, 2014;17(1):1-5.

45. Poenaru D, Borgstein E, Numanoglu A, Azzie G. Caring for children with colorectal disease in the context of limited resources. Semin Pediatr Surg, 2010;19(2):118-27.

46. Derbew M, Ahmed E. The pattern of pediatric surgical conditions in Tikur Anbessa Unversity Hospital, Addis Ababa, Ethiopia. Ethiop Med J, 2006;44(4):331-8.

47. Momoh JT. External hernia in Nigerian children. Ann Trop Paediatr, 1985;5(4):197-200.

48. Daniel E, Mersha D. Childhood appendicitis: factors associated with its incidence and perforation in Ethiopian children. Ethiop Med J, 1991;29(1):15-9.

49. Ein SH, Njere I, Ein A. Six thousand three hundred sixty-one pediatric inguinal hernias: a 35-year review. J Pediatr Surg, 2006;41(5):980-6.

50. Ohene-Yeboah M1, Abantanga FA. Inguinal hernia disease in Africa: a common but neglected surgical condition. West Afr J Med, 2011;30(2):77-83.

51. Zamakhshary M, To T, Guan J, Langer JC. Risk of incarceration of inguinal hernia among infants and young children awaiting elective surgery. CMAJ, 2008;179(10):1001-5.

52. Erdoğan D1, Karaman I, Aslan MK, Karaman A, Cavuşoğlu YH. Analysis of 3,776 pediatric inguinal hernia and hydrocele cases in a tertiary center. J Pediatr Surg, 2013;48(8):1767-72.

53. Ameh EA. Morbidity and mortality of inguinal hernia in the newborn. Niger Postgrad Med J, 2002;9(4):233-4.

54. Usang UE, Sowande OA, Adejuyigbe O, Bakare TI, Ademuyiwa OA. The role of preoperative antibiotics in the prevention of wound infection after day case surgery for inguinal hernia in children in Ile Ife, Nigeria. Pediatr Surg Int, 2008;24(10):1181-5.

55. Ogundoyin OO, Afolabi AO, Ogunlana DI, Lawal TA, Yifieyeh AC. Pattern and

outcome of childhood intestinal obstruction at a tertiary hospital in Nigeria. Afr Health Sci, 2009;9(3):170-3.

56. Stolz LA, Kizza H, Little K, Kasekende J. Intussusception detected with ultrasound in a resource-limited setting. Lancet, 2013;381(9882):2054.

57. Omore R, Osawa F, Musia J, Rha B, Ismail A, et al. Intussusception Cases Among Children Admitted to Referral Hospitals in Kenya, 2002-2013: Implications for Monitoring Postlicensure Safety of Rotavirus Vaccines in Africa. J Pediatric Infect Dis Soc, 2015.

58. Talabi AO1, Sowande OA, Etonyeaku CA, Adejuyigbe O. Childhood intussusception in Ile-ife: what has changed? Afr J Paediatr Surg, 2013;10(3):239-42.

59. Mpabalwani EM1, Chitambala P, Chibumbya JN, Matapo B, Mutambo H, et al. Intussusception incidence rates in 9 Zambian hospitals, 2007-2011: prerotavirus vaccine introduction. Pediatr Infect Dis J, 2014;33 Suppl 1:S94-8.

60. Steele AD, Patel M, Cunliffe NA, Bresee JS, Borgstein E, et al. Workshop on intussusception in African countries--meeting report. Vaccine, 2012;30 Suppl 1:A185-9.

61. Moore SW, Kirsten M, Müller EW, Numanoglu A, Chitnis M, et al. Retrospective surveillance of intussusception in South Africa, 1998-2003. J Infect Dis, 2010;202 Suppl:S156-61.

62. Abantanga FA, Amoah M, Adeyinka AO, Nimako B, Yankey KP. Pneumatic reduction of intussusception in children at the Komfo Anokye Hospital, Kumasi, Ghana. East Afr Med J, 2008;85(11):550-5.

63. Kuremu RT. Childhood intussusception at the Moi teaching and Referral Hospital Eldoret: management challenges in a rural setting. East Afr Med J, 2004;81(9):443-6.

64. Carneiro PM, Kisusi DM. Intussusception in children seen at Muhimbili National Hospital, Dar es Salaam. East Afr Med J, 2004;81(9):439-42.

65. Edino ST, Ochicha O, Mohammed AZ, Anumah M. Intussusception in Kano: a 5-year analysis of pattern, morbidity and mortality. Niger J Med, 2003;12(4):221-4.

66. Ameh EA. The morbidity and mortality of right hemicolectomy for complicated intussusception in infants. Niger Postgrad Med J, 2002;9(3):123-4.

67. Ameh EA. The morbidity and mortality of laparotomy for uncomplicated intussusception in children. West Afr J Med, 2002;21(2):115-6.

68. Harouna Y, Tardivel G, Abdou I, Gamatie Y, Mariama S, et al. [Prognosis of acute intestinal intussusception in infants at the national hospital of Niamey (Niger). Eleven cases treated surgically]. Bull Soc Pathol Exot, 1997;90(1):30-

2. [Article in French]

69. Adejuyigbe O, Jeje EA, Owa JA. Childhood intussusception in Ile-Ife, Nigeria. Ann Trop Paediatr, 1991;11(2):123-7.

70. Abdur-Rahman LO, Adeniran JO, Taiwo JO, Nasir AA, Odi T. Bowel resection in Nigerian children. Afr J Paediatr Surg, 2009;6(2):85-7.

71. Ogundoyin OO, Olulana DI, Lawal TA. Childhood intussusception: A prospective study of management trend in a developing country. Afr J Paediatr Surg, 2015;12(4):217-20.

72. Ekenze SO, Mgbor SO, Okwesili OR. Routine surgical intervention for childhood intussusception in a developing country. Ann Afr Med, 2010;9(1):27-30.

73. Carapinha C, Truter M, Bentley A, Welthagen A, Loveland J. Factors determining clinical outcomes in intussusception in the developing world: Experience from Johannesburg, South Africa. S Afr Med J, 2016;106(2):177-80.

74. Chalya PL, Kayange NM, Chandika AB. Childhood intussusceptions at a tertiary care hospital in northwestern Tanzania: a diagnostic and therapeutic challenge in resource-limited setting. Ital J Pediatr, 2014;40(1):28.

75. Khorana J, Singhavejsakul J, Ukarapol N, Laohapensang M, Wakhanrittee J, Patumanond J. Enema reduction of intussusception: the success rate of hydrostatic and pneumatic reduction. Ther Clin Risk Manag, 2015;11:1837-42.

76. Mensah YB, Glover-Addy H, Etwire V, Twum MB, Asiamah S, et al. Pneumatic reduction of intussusception in children at Korle Bu Teaching Hospital: an initial experience. Afr J Paediatr Surg, 2011;8(2):176-81.

77. Ahmed HM, Ahmed O, Ahmed RK. Adding a custom made pressure release valve during air enema for intussusception: A new technique. Afr J Paediatr Surg, 2015;12(4):232-5.

78. Wiersma R, Hadley GP. Minimizing surgery in complicated intussusceptions in the Third World. Pediatr Surg Int, 2004;20(3):215-7.

79. Bhangu A, Kolias AG, Pinkney T, Hall NJ. Surgical research collaboratives in the UK. Lancet, 2013;382(9898):1091-92.

80. REDCap Research Electronic Data Capture. Vanderbilt University. https://redcap.vanderbilt.edu

81. Kong VY, Sartorius B, Clarke DL. Acute appendicitis in the developing world is a morbid disease. Ann R Coll Surg Engl, 2015;97(5):390-5.

82. Ameh EA. Incarcerated and strangulated inguinal hernias in children in Zaria, Nigeria. East Afr Med J, 1999;76(9):499-501.

83. Ohene-Yeboah M, Abantanga F, Oppong J, Togbe B, Nimako B, et al. Some aspects of the epidemiology of external hernias in Kumasi, Ghana. Hernia, 2009;13(5):529-32.

84. Healy DA, Doyle D, Moynagh E, Maguire M, Ahmed I, et al. Systematic review and meta-analysis on the influence of surgeon specialization n outcomes following appendicectomy in children. Medicine (Baltimore), 2015;94(32):e1352.

Appendix 1: Patient Data Collection

* A full glossary of terms will be provided along with guidelines on how to complete the REDCap database in September 2016 prior to data collection.

All conditions: (12 data points)

Demographics:
- Gestational age at birth, current age, sex, weight
- Time from onset of condition to presentation at study institution
- Distance of travel from home to study institution
- Referral site: home, traditional healer, GP, district hospital, other

Primary Outcome:
- In hospital mortality (or 30-day mortality if still an in-patient at 30-days): yes/ no

Secondary Outcomes:
- Post-operative surgical site infection: yes/ no*
- Major complication: yes/ no*
- Need for re-intervention: yes/ no*
- Time to discharge or death in days:

Peri-operative factors:
- American Society of Anaesthesiologists (ASA) score at the time of primary surgery or intervention: I-V
- If surgery was undertaken, was a surgical safety checklist used? yes/ no
- Type of anaesthesia used: general, ketamine, spinal/ epidural, regional, local
  Was pulse oximetry used during the anaesthetic? Yes/ no

Condition specific data:

Gastroschisis (9 data points)

- Type of gastroschisis:
  Simple/ Complex (associated with atresia, necrosis or perforation)

- Inborn: yes/ no

- Septic on arrival: yes/ no*
  Appropriate broad spectrum antibiotics administered: yes/ no

- Hypothermic on arrival: yes/ no*
  Warmed on arrival to achieve normothermia: yes/ no

- Hypovolaemic on arrival: yes/ no*
  Fluid resuscitation administered: yes/ no

- Intravenous access:

None
Umbilical vein catheter
Peripheral cannula
Central line (including all types)

- Methods of closure:
  Not attempted (palliative care)
  Primary closure at the bedside (Bianci technique)
  Preformed silo, reduction and closure at the bedside
  Preformed silo, reduction and closure in theatre
  Surgical silo, reduction and closure in theatre
  Primary closure in theatre
  Other

- Ventilation required: yes/ no. If yes, was it available: yes/ no.
- Parental nutrition required: yes/ no. If yes, was it available: yes/ no.

Anorectal Malformation (7 data points)

- Inborn: yes/ no

- Septic on arrival: yes/ no
  Appropriate antibiotics administered: yes/ no

- Pre-operative bowel perforation: yes/ no

- Type of malformation:
  Perineal/ vestibular – passing stool
  Higher malformation

- Associated with a VACTERL anomaly (vertebral, cardiac, trachea-oesophageal fistula/ oesophageal atresia, renal, limb)? Yes/ no, specify.

- Operative management:
  Not attempted (palliative care)
  Dilation of distal fistula
  Colostomy – loop or divided, transverse, sigmoid or other.
  Primary definitive surgery – anoplasty, PSARP, modified PSARP (provide details), other (provide details).

- Plan for future management:
  No further operative management
  Anoplasty/ pull-through scheduled in the future at study institution
  Anoplasty/ pull-through scheduled in the future at other institution

Appendicitis (7 data points)

- Septic on arrival: yes/no*
  Appropriate pre-operative antibiotics given: yes/ no*
  IV fluid resuscitation given: yes/ no*

- Operative time: day/ night*

- Operation undertaken:
  Open Lanz or Gridiron
  Open Laparotomy, midline or other
  Laparoscopic

- Operative findings:
  Simple appendicitis
  Perforated appendicitis

- Sterile saline used to washout peritoneal cavity prior to closure: yes/ no

- Duration of appropriate post-operative antibiotics (days):

- Post-operative intra-abdominal collection requiring subsequent drainage: yes/ no

Inguinal Hernia (5 data points)

- Hernia type at presentation:
  Easily reducible
  Difficult to reduce
  Incarcerated/ obstructed/ strangulated
  Fistulated

- Bilateral or unilateral

- Operation type: elective/ urgent/ emergency*

- Operation: open/ laparoscopic

- Use of prophylactic antibiotics: yes/ no

Intussusception (6 data points)

- Diagnosis: clinical/ on ultrasound

- Signs of perforation warranting primary surgery: yes/ no

- Other contra-indication to air or hydro enema reduction: yes/ no
  Detail:

- Primary management:
  None attempted (palliative care)
  Air enema reduction
  Hydroenema reduction
  Laparotomy
  Other

- If air or hydroenema reduction, was laparotomy required: yes/ no

- Surgical intervention if undertaken:
  Laparotomy, manual reduction
  Laparotomy, bowel resection and primary anastomosis
  Laparotomy and stoma
  Laparoscopy and manual reduction
  Laparoscopy, bowel resection and primary anastomosis

Appendix 2: Summary of the questionnaire for research collaborators

Research collaborator details:
Job title: general surgeon, paediatric surgeon, anaesthetic doctor, anaesthetic nurse, paediatrician, other (please specify)
Position: medical student, intern/house officer, registrar, consultant, other

Institution details:
Type of healthcare facility: health centre, district, tertiary, private, NGO, other
Population served

Personnel:
Number of Paediatric Surgeons
Number of General Surgeons undertaking Paediatric Surgery
Number Anaesthetic Doctors with paediatric training
Number of Anaesthetic Nurses with paediatric training
Number of Radiologists trained to undertake ultrasound for intussusception

Infrastructure: (yes/ no)
Laboratory for biochemistry and haematology
Blood bank
Functioning ultrasound machine
Paediatric/ neonatal ventilation

Procedures available at study institution: (yes/ no)
Preformed silo application and closure of gastroschisis
Surgical silo application and closure of gastroschisis
Primary closure of gastroschisis
Colostomy
Posterior Sagittal Anorectoplasty (PSARP) for Anorectal malformation
Open/ laparoscopic appendicectomy
Open/ laparoscopic inguinal hernia repair
Air enema reduction of intussusception
Hydrostatic enema reduction of intussusception
Laparotomy for intussusception
Central line insertion
Umbilical vein catheterisation
Peripheral intravenous cannulation of neonates/ children

Anaesthesia/ resuscitation: (yes/ no)
Oxygen, oxygen saturation monitor
Paediatric bag, valve & mask
Anaesthetic machine for neonates/ children
Anaesthesia: ketamine, spinal/ caudal anaesthesia, local

Appendix 3: Kings College London Ethical Approval

Research Ethics
Office

Franklin Wilkins Building
5.9 Waterloo Bridge Wing
Waterloo Road
London SE1 9NH
Telephone 020 7848 4020/4070/4077
rec@kcl.ac.uk

KING'S College LONDON

11 May 2016

LRS-15/16-2949
-PaediatricSurgeryGAPSINAfrica:aPanAfricanProspectiveCohortStudy.

I am pleased to inform you that full approval for your project has been granted by the BDM Research Ethics Panel

Ethical approval is granted for a period of three years from 11 May 2016 . You will not receive a reminder that your approval is about to lapse. It is your responsibility to apply for an extension prior to the project lapsing. You should report any untoward events or unforeseen ethical problems to the panel Chair, via the Research Ethics Office, within a week of occurrence. Information about the panel may be accessed at: http://www.kcl.ac.uk/innovation/research/support/ethics/committees/sshl/reps/index.aspx

If you wish to change your project or request an extension of approval, please complete and submit a Modification Request to crec-lowrisk@kcl.ac.uk. Please quote your ethics reference number, found at the top of this letter, in all correspondence with the Research Ethics Office. Details of how to complete a modification request can be found at: http://www.kcl.ac.uk/innovation/research/support/ethics/applications/modifications.aspx All research should be conducted in accordance with the King's College London Guidelines on Good Practice in Academic Research available at: http://www.kcl.ac.uk/college/policyzone/assets/files/research/good%20practice%20Sept%2009%20FINAL.pdf

Please note that we may, for auditing purposes, contact you to ascertain the status of your research. We wish you every success with your research.

Best wishes,

BDM Research Ethics Panel REP Reviewers