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Authors

Fitzgerald, Tamara N
Zambeli-Ljepović, Alan
Olatunji, Bolusefe T
et al.

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Gaps and Priorities in Innovation for Children's Surgery

Tamara N Fitzgerald [a,b] Alan Zambeli-Ljepović [c], Bolusefe T. Olatunji MD[d],
Abdullah Saleh[e], Emanuel Ameh[f]

[a] Department of Surgery, Duke University, Durham, NC, USA
[b] Duke Global Health Institute, Durham, NC USA
[c] Philip R. Lee Institute for Health Policy Studies, University of California San Fransisco, USA
[d] Department of Surgery, University of California San Fransisco, USA
[e] Department of Surgery, University of Alberta, Canada
[f] Department of Paediatric Surgery, National Hospital, Abuja, Nigeria

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Corresponding Author:

Abstract

Lack of access to pediatric medical devices and innovative technology contributes to global disparities in children's surgical care. There are currently many barriers that prevent access to these technologies in low- and middle-income countries (LMICs). Technologies that were designed for the needs of high-income countries (HICs) may not fit the resources available in LMICs. Likewise, obtaining these devices are costly and require supply chain infrastructure. Once these technologies have reached the LMIC, there are many issues with sustainability and maintenance of the devices. Ideally, devices would be created for the needs and resources of LMICs, but there are many obstacles to innovation that are imposed by institutions in both HICs and LMICs. Fortunately, there is a growing interest for development of this space, and there are many examples of current technologies that are paving the way for future innovations. Pediatric laparoscopy, imaging modalities and new surgical training paradigms are just some of the innovations that could make a major impact in children's surgery around the world.

INTRODUCTION

Children and adolescents make up more that 50% of the population in low- and middle-income countries (LMICs) where surgical morbidity and mortality is disproportionately high compared to high-income countries (HICs).[1] This disparity is multifactorial, but access to pediatric medical devices and innovative technology contributes to this disparity. Medical devices and consumable supplies of appropriate size and function are essential for the diagnosis and treatment of all pediatric surgical conditions. Innovation for children is still under-supported in HICs,[2] but these challenges are greatly magnified by innovation pathways that were designed for the HIC context coupled with the resource limitations found in LMICs.

In previous decades, global health has largely been dominated by public health with a focus on infectious disease.[3] Likewise, biomedical engineering has primarily focused on advancing the cutting edge of life-changing technology in HICs. Unfortunately, for many individuals in LMICs, these technologies have not reached them to change their lives. Multidisciplinary collaboration and cross-cultural advancement have been stifled by these limiting thought patterns. Engineering has the capacity to bring disruptive technology into the problems faced by LMICs.[4] In turn, the design constraints induced by innovating for the LMIC context can bring a much-needed efficiency and frugality to HIC health systems.[5]

There are currently many barriers that prevent access to appropriate pediatric medical devices and consumable supplies in LMICs. Technologies that were designed for the needs of HICs, may not fit the resources available in LMICs. Likewise, obtaining these devices are costly and require supply chain infrastructure. Once these technologies have reached the LMIC, there are many issues with sustainability and maintenance of the devices.[6] Ideally, devices would be created for the needs and resources of LMICs, but there are many obstacles to innovation that are imposed by institutions in both HICs and LMICs.[7] Fortunately, there is a growing interest for innovation in this space, and there are many examples of current technologies that are paving the way for future innovations.[8-11]

PEDIATRIC MEDICAL DEVICE DEVELOPMENT

Relative to adult patients, infants and children have widely ranging physiology and pathology based on age, body size and rare diseases that limit the feasibility of large clinical trials.[12] Although regulatory bodies, such as the Food and Drug Administration in the United States, recognize these differences and stress the importance of targeted device development for children, most medical devices used in pediatric patients are still used off-label with supporting data extrapolated from trials with adult patients.[2,13] This can lead to life-threatening complications.[14,15] Medical devices and supplies for children must therefore be designed specifically for this population.

In 2007, the Pediatric Medical Device Safety and Improvement Act (PMDSIA) was introduced in the U.S. to facilitate development of new devices, establish a pediatric device research agenda, and improve post-market surveillance of devices. In contrast to the pharmaceutical industry, medical device companies tend to be smaller companies which focus on a few products. These devices often undergo multiple iterations of improvement, with changes in patent protection. Thus, market exclusivity is a challenge.[16]

New device development has largely focused on adult patients in HICs, who make up the most profitable addressable market. Pediatric surgical conditions are more rare than adult conditions and many children are financially disadvantaged and underinsured, which further discourages medical device companies and investors from prioritizing pediatric markets, as the return on investment will not be as easily attainable.[17] Upfront costs to develop a device include research and development, pre-clinical testing, clinical trials, and

costs for regulatory approval through most commonly the U.S. Food and Drug Administration (FDA) or the European CE Mark.[18] To attract investors, a sustainable business model must be developed which often involves a significant financial mark-up for use in a large addressable market.

Therefore, even in HICs, significant barriers exist for development of pediatric medical devices. In addition to market considerations, there may be a need for multiple pediatric sizes (ie. gastrostomy tubes, foley catheters, etc.) Clinical trials are expensive and there are barriers to the enrollment of children, ethical complexities, and lack of device trial infrastructure.[19] Clinicians with device ideas often lack the engineering, business and regulatory skills necessary to develop and commercialize products.[17]

OBTAINING AND USING TECHNOLOGIES IN LMICS

The most obvious barrier to obtaining medical equipment and supplies in LMICs is cost. As previously noted, the vast majority of medical devices and supplies have been designed to fit the needs and resources of HICs. Therefore the costing of these technologies has been set to ensure business stability in the HIC. Therefore, inadequate supply of equipment and consumable supplies is a major challenge in LMICs. Most district hospitals do not have routine access to basic monitoring equipment such as blood pressure cuffs and electrocardiogram supplies. Ministries of health have financial limitations, and pediatric care is often not prioritized in the larger health agenda. Therefore, it is common that even larger referral hospitals do not have pediatric-sized supplies such as foley catheters, endotracheal tubes, gastroschisis silos, fine sutures and other surgical equipment.[3]

However, cost is not the only barrier. Weak infrastructure, such as lack of paved roads and delivery services can also limit access to supplies. Lack of running water and inconsistent electrical power may hinder sanitation and device safety.[6] Certain electronic devices may not be able to withstand hot, humid environments, frequent power outages or inconsistencies in electrical current.[20] Many hospitals do not have autoclaves, creating sterilization concerns for many medical products. Single-use equipment that is available is routinely reused after cleaning with antiseptics and the infection transmission rate remains unquantified.[21] Supply chain issues are complex, as recently experienced by HICs during the COVID-19 pandemic, and are more chronic and severe in LMICs.[22]

Technology that has passed rigorous safety testing in HICs is usually believed to be safe for use in LMICs without concerns for patient harm. Donated devices, however, should be scrutinized; well-intentioned donations are often broken and unusable in their destination setting and may stifle local innovation.[23,24]

SUSTAINING TECHNOLOGY IN LMICS

If there in one engineering principle that can be counted upon, it is this: *Everything eventually breaks*. For most LMIC health systems, service contracts are not affordable and there is a lack of qualified maintenance personnel to fix broken devices, due to a shortage of training programs. To complicate matters, medical device repair manuals have previously been kept proprietary and unavailable to the public. Device companies do not share these manuals for patient safety reasons, as they want to ensure that their equipment is repaired properly by their own technicians. However, these service contracts are also a significant source of revenue for their company.[25] For several years, a Tanzanian-based biomedical engineer has maintained a website of medical-device repair manuals, called Frank's Hospital Workshop,[26] which was established to support biomedical engineers in LMICs. In many cases, file downloads have been prohibited by device makers. In August 2020, the Critical Medical Infrastructure Right-to-Repair Act was introduced to the U.S. House of Representatives in response to medical device maintenance issues

encountered by U.S. hospitals during the COVID-19 pandemic. Going forward this new legislation is likely to benefit LMICs by requiring medical device companies to release their repair manuals to the public.[27]

Even when qualified biomedical technicians are available, the broken part may not be readily available in the LMIC, and devices with multiple components will be difficult to maintain. As an example, consider the current standard-of-care laparoscopic equipment, which consists of an endoscope, camera head, light cord, light cord attachment, insufflator, light box and a system of monitors. If any one of these parts breaks, it renders the entire system inoperable.[10]

Medical devices which rely on consumable supplies are also at risk for becoming unusable. Supplies such as glucometer test strips, medical grade carbon dioxide for laparoscopy, and disposable blades for suction rectal biopsy guns are just a few examples of consumable items that are necessary to operate their respective devices.

CULTIVATING INNOVATION IN LMICS

Capacity building in biomedical engineering is desperately needed. There is currently no data regarding the numbers of biomedical engineers and technicians in most LMICs,[28] but those who work in global surgery know from experience that the numbers are low. In 2009, less than 2% of research was based in Africa.[29] Currently, there are a handful of academic partnerships in biomedical engineering between HICs and LMICs. Human capacity is limited, and few engineers are willing to leave their jobs in the private sector to accept faculty positions.[30] Many times there is a lack of institutional space and funding to create such programs.

If we desire to change the innovation landscape, then we must be willing to change our mindset. For HIC actors, we must stop believing that "if it works in my HIC setting, it will work in an LMIC." As previously discussed, technologies that are designed for HICs may not address the needs and resources present in LMICs. Likewise, there are many policies in HIC institutions such as universities, regulatory bodies and private companies that slow progress and inhibit fruitful collaboration with LMICs. Most of these policies were created without the HIC-LMIC partnership in mind, and are applied from a risk-aversion mindset, without an appropriate assessment of the true risk. These policies may include Institutional Review Board procedures, cumbersome financial paperwork, guidelines for the conduct of clinical trials, rules for data ownership, intellectual property management and procedures for oversight of data collection.

Likewise, LMICs must work to streamline and encourage innovation in their institutions. Currently, the process of Institutional Review Board approval is lengthy (taking months to years in many countries) and expensive. Many countries charge several hundred U.S. dollars for local institutional and country-level approval. One could argue that these costs generate revenue for the LMIC institutions, which will be paid by HIC resources. However, these costs make it nearly impossible for local LMIC innovators to pursue independent projects without financial assistance from HIC collaborators, creating a type of dependence.

There is also an underdeveloped regulatory process in many LMICs. For example, most countries in Africa have regulatory approval processes for pharmaceuticals, and simple medical products such as gloves and condoms, but no regulatory process for more substantial medical devices and supplies. There is currently no harmonization between countries. Therefore, if a device has been designed in Africa, for Africans, there is no streamlined solution for making this device available in multiple African countries. Many innovators are currently seeking either CE Mark or FDA approval for their device, which will be

readily accepted in most African nations.[31] However, these processes are cumbersome to navigate, particularly if innovators are trying to navigate these processes outside of their culture, without the assistance of an expert to guide them, and possibly in a foreign language. The costs of obtaining these approvals are substantial and must be absorbed in the future business model. It is not sustainable to pay the upfront and continuing costs for regulatory approval in a HIC, and then keep the purchase price low in the LMIC. Some businesses have dealt with this by also selling the device in HICs, but then often they stop designing the device for use in an LMIC context, and start modifying the device to be attractive to the HIC market.

Mistrust can also be a substantial barrier. Understandably, many LMIC institutions are wary of a first-in-human study being conducted with their patients. Previous ethical abuses have occurred, and institutions may also be fearful of litigation from patients with poor outcomes. Individuals in LMICs may also have biases, and doubt the quality of the medical device if it was designed and manufactured locally. However, it is essential that clinical trials be conducted in LMICs to build local capacity in conducting this type of research.[32] Additionally, standard medical ethics dictate that human studies should be performed in populations that can potentially receive the benefit of the innovation. It may be unethical to test a medical device designed for LMICs in a HIC population, when a suitable medical device already exists in the LMIC and there is no potential benefit to the population.

PRIORITIES FOR INNOVATION IN LMICS

The importance of minimizing costs is just one aspect of appropriate medical device design. Many innovators employ Human-Centered-Design,[33] which is an iterative process whereby the future users of an innovation describe their needs and how they intend to use the product. Design criteria are developed and vetted with future users, and then used to construct prototypes. These prototypes are then delivered to the future users, so that improvements to the design can be made in an iterative fashion.

In LMICs, consideration of the following issues may prove helpful: methods for cleaning or sterilization, reusability, simple design with reduced maintenance, single unit design with minimum spare parts, contextual relevance and attention to cultural sigma, and ecological conservation with methods for recycling. If the device will be manufactured in an LMIC, then it is advisable to choose materials which are locally available.

Feasibility and acceptability testing may need to be performed with various versions of the protype, to ensure that all members of the surgical team would be eager to accept the device into their work flow. New designs for the LMIC setting should be held to a universal standard of safety pre-evaluation, taking into account the local environment and culture.[24] Local stakeholders must be involved at every step of the process to ensure the product will address real needs, be affordable and accessible, and be accompanied by appropriate user education and manageable maintenance requirements.[25] The WHO and other international organizations have published guidelines for the development, dissemination, and outcome evaluation of new devices in LMICs.[26,27]

RECENT GLOBAL INNOVATION

A good example of large-scale development and dissemination of inexpensive durable devices was set by the Lifebox group in 2011. After the establishment of the well-known WHO surgical safety checklist, which identified the pulse oximeter as the single most important piece of equipment for safe surgery monitoring,[34] the World Federation of Societies of Anaesthesiologists demonstrated the feasibility of

disseminating pulse oximeters throughout LMICs.[35] A WHO working group then defined the requirements for sustainability: rechargeable and long-lasting batteries, ability to withstand one-meter falls onto concrete, affordability, and extended warranty. An affordable manufacturer was identified, and the Lifebox team began distribution, with a focus on user education and advocacy for the importance of safe anesthesia practices.[9] More than 33,000 Lifebox oximeters have been distributed across more than 100 LMICs, with follow-up studies demonstrating knowledge retention and ongoing provider usage.[36,37]

Bubble CPAP is another example of a successful innovation for pediatric patients. In Malawi, a CPAP system was developed from a compressor, oxygen concentrator, water bottle and binasal prongs. It was initially tested in 11 neonates and found to be effective.[11] It is now used widely, in several LMICs.[38]

Gastroschisis silos are another need in pediatric surgery. Gastroschisis is one of the most common congenital anomalies encountered in LMICs, and survival is dismally low compared to HICs. The reasons for this disparity are multifactorial, but silos are generally unavailable and cost-prohibitive in LMICs. Investigators have demonstrated construction of silos from locally available materials and performed testing in a porcine model.[8,39] Clinical trials will need to be performed to assess the safety and feasibility.

Minimally invasive surgery has revolutionized children's surgery by reducing postoperative complications, accelerating recovery, and minimizing scarring.[40,41] Initially slow adoption in children (compared to adults) has accelerated recently in HICs,[41] but remains low in LMIC, where the benefits are likely to have more impact because of the significantly larger pediatric population.[42] Several challenges exist including instrument size limitations,[43] anatomical differences in children, limited availability of pediatric-specific instrumentation, and surgeon learning curve.[44,45] In addition, the cost and maintenance requirements for the equipment makes it more challenging to deploy in LMICs. The xenoscope™ and KeyScope[10,46] are examples of inexpensive laparoscopes with high-resolution images, as well as abdominal lift surgeries that preclude the need for gas insufflation.[47-50]

PRIORITIZATION OF FUTURE INNOVATIONS

Further research should consider laparoscopic instruments and training paradigms as essential innovations for pediatric surgical problems. According to LMIC pediatric surgeons, other needed supplies include esophageal dilators, silos for gastroschisis, abdominal wall and perineal retractors, stoma appliances, gastrostomy devices, and vascular access catheters. Some of these devices are currently reusable but prohibitively expensive for LMICs. Others devices are built for single use in the HIC setting but could be redesigned for safe repeat usage after sterilization. Stoma appliances, as designed for HICs, are expensive and difficult to maintain;[51] successful pouching requires accessory pastes or adhesives and is even more challenging in hot, humid environments. Enteral and vascular access devices have more affordable versions designed for LMICs (peripherally-inserted central venous catheters at 10% of HIC price) but experiences with dangerous device failures have raised safety concerns and precluded adoption.

Medical imaging is a key part of diagnosis, preoperative planning, intraoperative guidance, and postoperative evaluation.[52] Compared to adult patients, children are more sensitive to ionizing radiation and more likely to need sedation, both of which carry inherent risks.[53] Innovations in imaging techniques should focus on affordability, reducing radiation exposure, improving image resolution, and developing age-appropriate imaging protocols. Low cost, user friendly portable and durable image intensifiers and X-ray equipment are needed for use in the operating room and intensive care units. A high resolution

portable bedside ultrasound is an affordable, durable, readily available, and affordable innovation that is useful in low resource settings. However, LMIC prenatal diagnosis of congenital anomalies is still limited due to unavailability and cost of ultrasound equipment. Point of care ultrasound is now available but remains under-utilized in LMICs.

Globally, there are simply not enough general pediatric surgeons. The American Pediatric Surgical Association recommends a specialist pediatric surgical density of 1 per 100,000 children age ≤ 15 years; we know that children's perioperative mortality is inversely related to availability of surgical workforce.[54,55] In LMICs, this number is consistently low: 0 to 0.49 across Africa, 0.03 in Indonesia, 0.4 in Colombia, and 0.33 in Iran.[56,57]

Simulation-based training, increasing in popularity over recent years, has been shown to improve technical skills at minimal cost to the program or patient.[58-60] Similarly, immersive virtual reality training has, across multiple studies, demonstrated improved procedural times, increased accuracy, positive user ratings, and cost-effectiveness.[61] These methods could expand training capacity at a lower cost, but success hinges on careful consideration of relevance and feasibility in the contexts in which they are being deployed.

Finally, training of both surgeons and non-surgeon providers, especially through a train-the-trainer model, has been piloted in multiple contexts with resulting improvement in patient survival.[62-65] Further innovation and investment should prioritize supporting existing programs that have local support and proven effectiveness. Skills acquisitiion simulation should incorpoarate self-assessment to track progress.

Innovations should focus on developing comprehensive and context-focused postoperative care guidelines, improving the coordination of multidisciplinary care teams (including wound and stoma care nurses, pain specialists), enhancing telemedicine capabilities for remote consultations, and implementing age-appropriate psychological support services.[66] The ability to provide these services in the face of brain drain hinges on workforce retention strategies: strengthening medical education, investing in postgraduate training, and improving remuneration strategies.[67,68]

CONCLUSION

Increasing awareness of global inequities in children's surgery and the cost-effectiveness of safe surgery has brought international attention to this field. Despite the awareness and attention, large gaps remain, particularly in the availability of surgical equipment, supplies and innovative approaches to surgical training. Evidence-based suggestions to translate passive international attention into concerted, contextually-relevant action is crucial. Investing in innovations to support and strengthen children's surgical care globally would expand access, improve quality, safety and outcomes, as well as yield measurable return on investment.

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