

Medical Devices for Low- and Middle-Income Countries: A Review and Directions for Development

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The development of diagnostics and medical devices has historically been concentrated in high-income countries, despite a significant need to expand healthcare services to low- and middle-income countries (LMIC). Poor quality healthcare extends beyond LMIC to underserved communities in developed countries. This paper reviews diseases and conditions that have not received much attention in the past despite imposing a significant burden on healthcare systems in these circumstances. We review the underlying mechanism of action of these conditions and current technology in use for diagnosis or surgical intervention. We aim to identify areas for technological development and review policy considerations that will enable real-world adoption. Specifically, this review focuses on diseases prevalent in sub-Saharan Africa and south Asia: melioidosis, infant and maternal mortality, schistosomiasis, and heavy metal and pesticide poisoning. Our aim with this review is to identify problems facing the world that require the attention of the medical device community and provide recommendations for research directions for groups interested in this field. [DOI: 10.1115/1.4045910]

Keywords: medical devices, disadvantaged nations, device development, underrepresented diseases

1 Methods

A formal search of peer-reviewed articles pertaining to diseases affecting low- and middle-income countries (LMIC) was performed using Google Scholar and PubMed in order to compile this qualitative systematic review. Keywords used to identify diseases and technologies included, but were not limited to, the following terms: medical devices, low-cost design, global health, low-income countries, low- and middle-income countries, point-of-care diagnostics, neglected tropical diseases (NTD), neonatal mortality. The names of specific health challenges in conjunction with other keywords were also used in the search. Identified conditions were compared based upon the number of affected people, disability adjusted life years, and current research carried out to address the condition. The diseases chosen for this review are melioidosis and neglected tropical diseases such as schistosomiasis. These two diseases combined affect over 500,000 people in south Asia and sub-Saharan Africa [1]. This is a fraction of the number of people affected by mosquito-borne diseases [2], but still presents a significant healthcare burden on developing economies. In contrast to, for example, malaria or HIV, these diseases have not received notable attention nor the development of technological solutions toward their treatment. One of the key aims of this review is to expose this unmet need. A section of this review focuses on neonatal mortality, which accounts for over 4×10^6 deaths worldwide and is a significant economic burden due to the number of productive years of life lost [3]. Finally, a section on policy and implementation is provided to aid researchers in identifying useful areas of study.

2 Melioidosis

Melioidosis (Whitmore's disease) is an infection caused by the bacterium *Burkholderia pseudomallei* and is prevalent in south and east Asia and northern Australia. In major regions where the

disease is endemic, the annual incidence rates are up to 50 cases per 100,000 people [4]. It has been classified as a category B bioterrorism agent by the United States and recent reports indicate that the endemic areas have expanded to southern China, Hong Kong, Taiwan, and parts of the Americas [5].

Although healthcare facilities have seen significant improvements over the past few years, reports suggest that diagnosis of melioidosis is only possible in large regional referral centers. This could lead to a delay in diagnosis and treatment, and an underestimate of the number of people infected with the disease [6]. Diagnosis of melioidosis can be complicated by the presenting symptoms and their similarity to tuberculosis: abscesses in the lungs, liver, spleen, and brain stem encephalitis. The bacterium typically infects the host by inoculation onto the skin, by inhalation, or by ingestion. Inoculation onto the skin can cause subcutaneous abscesses, inhalation can cause pneumonia, and the bacterium can reach internal organs such as the spleen, liver, and the lungs through the blood. The most common presentation of melioidosis is pneumonia, with over 50% of cases either occurring through lung abscess or due to septicemic spread. An additional challenge with melioidosis is that the bacteria, *B. Pseudo-mallei*, is a difficult organism to kill, with studies showing that it is capable of surviving in triple distilled water for years [7]. The disease primarily occurs during the rainy season [8] and people who are in direct contact with wet soil are most vulnerable to the disease. Predispositions such as diabetes mellitus, cirrhosis, and alcoholism, or those who are immunosuppressed increase the risk of contracting the bacterium [9]. Over 50% of patients diagnosed with melioidosis already have diabetes mellitus as a predisposition [10]. This presents a major problem for south Asian countries as the number of patients living with diabetes as an underlying condition is projected to increase by 70% between 2010 and 2030 [11]. An additional risk factor is the age group for contracting diabetes mellitus in these countries is 40–60, with reports showing that incidence of melioidosis peaking in this age group, and most countries of this region exhibiting aging demographics.

The recommended treatment of melioidosis involves the intravenous injection of the antibiotic ceftazidime for at least 10 days

Manuscript received August 15, 2019; final manuscript received December 17, 2019; published online February 5, 2020. Assoc. Editor: Boris Rubinsky.

[12]. The therapeutic response to the drug is slow and physicians tend to prematurely switch antibiotics in a considerable number of cases, with the assumption that the bacterium has developed antibiotic resistance. The mortality for a 2-week administration of the drug is 18% [10]. Although there have been developments over the past 30 years with multiple clinical trials [13–15] in treating melioidosis, the cost of the antibiotics is still high (from US\$70–\$150 a day [16]), imposing a significant economic burden on developing countries. Simpson et al. [17] comment on the price of drug regimens used to treat the disease and cite lack of financial support from pharmaceutical companies for diseases prevalent in rural areas as one of the challenges in developing treatment and diagnostic solutions. Melioidosis has been described as “the great imitator” of other tropical diseases such as malaria, typhoid fever, leptospirosis, and tuberculosis [18]. The varying clinical manifestations of the disease and the multiple affected organs often lead to an incorrect diagnosis. Delayed identification results in the administration of antibiotics that are usually unsuitable to treat melioidosis, which has led to high mortality rates as indicated by multiple studies [18,19]. It is critical that rapid diagnostic solutions are developed to reduce mortality rates. The most widely used method to detect *B. Pseudo-mallei* is culturing in a modified Ashdown medium with colistin [20], but even this technique may yield inaccurate results, especially in nonendemic areas where the clinical suspicion is low. In cases where there is a positive culture, it may be difficult for commercial systems to differentiate between *B. Pseudo-mallei* and phenotypically similar species such as *Burkholderia thailandensis* [21]. Recent reports highlight not only the limitations of bacterial gene amplification and detection but also the development of new screening and amplification techniques [22]. Since the sequencing of the complete genome of *B. Pseudo-mallei* [23], several quantitative polymerase chain reaction (PCR) assays have been developed to identify the species [24]. However, it is still a challenge to identify primers that can differentiate *B. Pseudo-mallei* from closely related species.

Clinical laboratories have recently started adopting matrix-assisted laser desorption/ionization mass spectrometry systems for the identification of bacterium [25–28], with modest clinical success alongside reports that suggest the databases used mass spectrometry require expansion to accurately identify *B. Pseudo-mallei*. This technique shows great potential to be used as a rapid identification technique but has the limitation of requiring skilled personnel, expensive equipment, and the infrastructure to support them. Low-cost molecular profiling and analysis has been a challenge, and advancements in this field would have a significant beneficial impact on healthcare outcomes in endemic areas. Surface acoustic wave-based atomization has been proposed to simplify the sample extraction and filtration process [29]. High-frequency surface acoustic wave-based atomization was used for the formation of micrometer scale droplets of cell lysate, and the purification step was achieved by loading the sample on a porous membrane placed in the direction of propagation of the surface acoustic waves.

Since the main cause of melioidosis spread is through soil during the rainy season, analyzing soil for the presence of *B. Pseudo-mallei* would prevent infection and hospitalization. Environmental samples are difficult to purify via PCR due to the typical presence of a diverse species of bacteria and fungi. Development of better enrichment and purification techniques would enable an increase in the number of relevant DNA templates for amplification to occur. An alternative to sampling environmental specimens is the analysis of relevant clinical samples—blood and sputum [30,31]. The sensitivity of PCR-based techniques is high for sputum and pus, but, by contrast, the sensitivity for blood samples is quite low [32,33].

There may be as many as 165,000 cases of melioidosis every year with an estimated 89,000 deaths [34]. The most commonly used technique for identification, bacterial culture, is 100% specific but has low sensitivity. Slow or incorrect diagnosis results in a significant burden on healthcare systems and can be fatal. Matrix

assisted laser desorption/ionization-time of flight mass spectrometry is increasingly being used as a rapid and accurate technique to identify isolates [35,36], though significant challenges to its adoption remain but likely can be addressed by further research in this field.

3 Heavy Metal and Organophosphate Contamination of Water

This section details the risks associated with poisoning due to metals, such as lead and cadmium, and associated detection techniques. Additionally, we consider the effects and detection of environmental pollutants arising from intensive agricultural and industrial practices. Evidence of the toxicity of lead has been documented in studies conducted as early as 1914 [37] and studies demonstrating the adverse effects of lead on attention, childhood development, and neurological disorders were established in the 1970s [38]. Lead poisoning has been shown to impair cognitive ability and social function [39].

The toxic properties of lead are partially due to its ability to compete with calcium at a cellular level, for neuronal signaling [40] and in inhibiting calcium influx into cells [41]. The neurological effects are due to its inhibitory impact on stimulated neurotransmitter release [42,43]. At high doses, lead can inhibit myelin formation and compromises the integrity of the blood brain barrier. Children are more sensitive to lead than adults due to increased hand-to-mouth activity and increased absorption in the gut. The acceptable thresholds for lead in blood have drastically changed since the 1960s in the United States, from 60 $\mu\text{g}/\text{dl}$ to essentially recognizing that there is no safe level of lead exposure, with amounts under 5 $\mu\text{g}/\text{dl}$ having been shown to adversely impact learning [44]. Significant reduction in lead exposure in the United States has been achieved by eliminating lead in gasoline and paint, but lead contamination of water remains a problem without a commensurate level of attention [45]. The decision in 2014 by the city of Flint to change its primary source of water saw lead levels in water rise to as much as 1000 $\mu\text{g}/\text{dl}$ in some cases [46], with lasting healthcare implications. The only medical treatment for lead exposure is chelation [47], but chelating drugs may not be available in LMIC and in lower income regions of even wealthy countries. In any case, they are not very useful to treat chronic exposure.

Another heavy metal that has adverse health effects is cadmium, commonly used in the electronics industry in batteries and circuit boards. Chronic exposure to cadmium results in accumulation in the kidneys that eventually leads to renal damage [48]. Cadmium can also be absorbed by plants more readily than other heavy metals, presenting another mode of uptake in regions contaminated with industrial waste. The number of people worldwide affected by heavy metal poisoning is difficult to estimate due to the varying sources of poisoning but, given that incidents like the one in Flint that occurred in a developed country with safeguards in place to prevent lead poisoning, there is a need to estimate atmospheric and water-based heavy metal exposure risks across the world.

The daily per-capita supply of calories has increased by over 30% over the last 50 years [49], and as this demand increases, there has been a push toward maximizing agricultural productivity. Increasing agricultural yield has been possible, in part, by the increased use of pesticides. The food and agriculture organization of the United Nations defines pesticides as growth regulators and includes substances that can prevent harm to crop during or after harvest [50]. Exposure to pesticides may occur through direct means through occupational exposure or via indirect means through drinking water, dust and food. The World Health Organization (WHO) estimates that 3×10^6 severe pesticide poisonings occur annually and that at least 300,000 people die as a result of exposure, with 99% of these cases being from LMICs [51]. The effects of pesticide exposure are wide ranging: chronic diseases such as cancer and developmental disorders [52],

immunosuppression, hormone disruption, diminished intelligence, and reproductive abnormalities [53]. Of the various classes of pesticides in use today, organophosphate pesticides have been shown to cause substantial morbidity and mortality [54] but still account for over 25% of fertilizer produced [55,56]. Organophosphates are readily absorbed through the skin, and the gastrointestinal and respiratory tracts. The mechanism of action is by inhibition of acetylcholinesterase, which promotes the production of the neurotransmitter acetylcholine [57]. Overstimulation of nerves due to excess acetylcholine results in autonomic dysfunction, involuntary motor movements, and respiratory depression. Long-term exposure has been shown to result in carcinogenicity [58]. Many farmers in developing countries are exposed to pesticides due to unsafe storage and handling practices, a lack of protective equipment during spraying, or chronic exposure to contaminated soil and water. Although there have been attempts to implement safe handling practices [59] and reduce pesticide use, there is a need to develop protective equipment that can be deployed in developing countries to prevent exposure alongside devices that can detect the presence of harmful pesticides in the local environment.

There is furthermore a need to monitor the presence of heavy metals and organophosphates in water supplies and in soil, particularly in regions of significant industrial or agricultural output. Paper-based microfluidics was first reported by George Whitesides' group [60] and has the advantage of being inexpensive, readily available, and can wick biological fluids without active pumping. A recent point-of-care paper diagnostic assay for the detection of lead and mercury in water was developed by Lewis et al. [61]. The device consists of hydrophobic regions that define where the fluid travels through capillary action. The assay is designed in such a way that the time taken for the fluid to travel from one part of the chip to another is indicative of the concentration of the analyte. This is accomplished by the use of glucose oxidase or streptavidin, which inhibit flow depending on analyte concentration. It has not been determined if time-based assays provide quantitative results for a range of users. More sensitive tests to detect the presence of lead in drinking water have been developed, with one group reporting a fourfold increase in sensitivity over conventional lateral flow assays [62]. The increased sensitivity was achieved by conjugating gold nanoparticles to a

lead-specific monoclonal antibody (Anti-Pb(II)-ITCBE). Organophosphate detection schemes have been considered due to their historical use as chemical warfare agents [63], though there has been a lack of development in the detection of trace amounts of organophosphates, despite knowledge they pose a significant health risk.

4 Neonatal Mortality

As of 2005, about 4×10^6 babies die in the neonatal period (the first 4 weeks of life) and a similar number of babies are stillborn [64]. A majority of these deaths are in low-income and middle-income countries in Africa and southeast Asia [65] as illustrated in Fig. 1. Some estimates show that 38% of all deaths in children under the age of five occur within the first month of life [65]. Assessment of the cause of death is difficult due to a lack of data collection in LMICs, but estimates indicate that complications arising from asphyxia, severe infections, and preterm births are the main causes of death [64]. The WHO defines birth asphyxia as the clinical description of a newborn that fails to initiate or maintain regular breathing at birth [68]. This term applies to a clinical condition and is not a specific cause of death. Advanced resuscitation is needed for less than 1% of babies at birth and babies that typically require advanced resuscitation by intubation typically require a neonatal intensive care unit to recover [69,70]. These are typically not available in regional hospitals in LMICs. Basic resuscitation, however, which only requires bag- and mask-type ventilators, is easy to implement for cases where intrapartum breathing assistance is required. Published guidelines vary on when to provide resuscitation [71], but the WHO recommends resuscitation in cases where the baby does not cry, breathe at all, or is gasping for 30s [68]. It is crucial that these guidelines become widely known, as there is potential for adverse effects such as upper airway damage if respiratory support is provided to healthy babies [72]. Existing devices in use in low-resource settings include mucus extractors with one-way valves and rubber bulb suction devices. The key downside of these devices is that they present an infection hazard for both the neonate and the healthcare provider [73], alongside the potential risk of hypothermia in prolonged resuscitation of a neonate [74,75], and asphyxia.

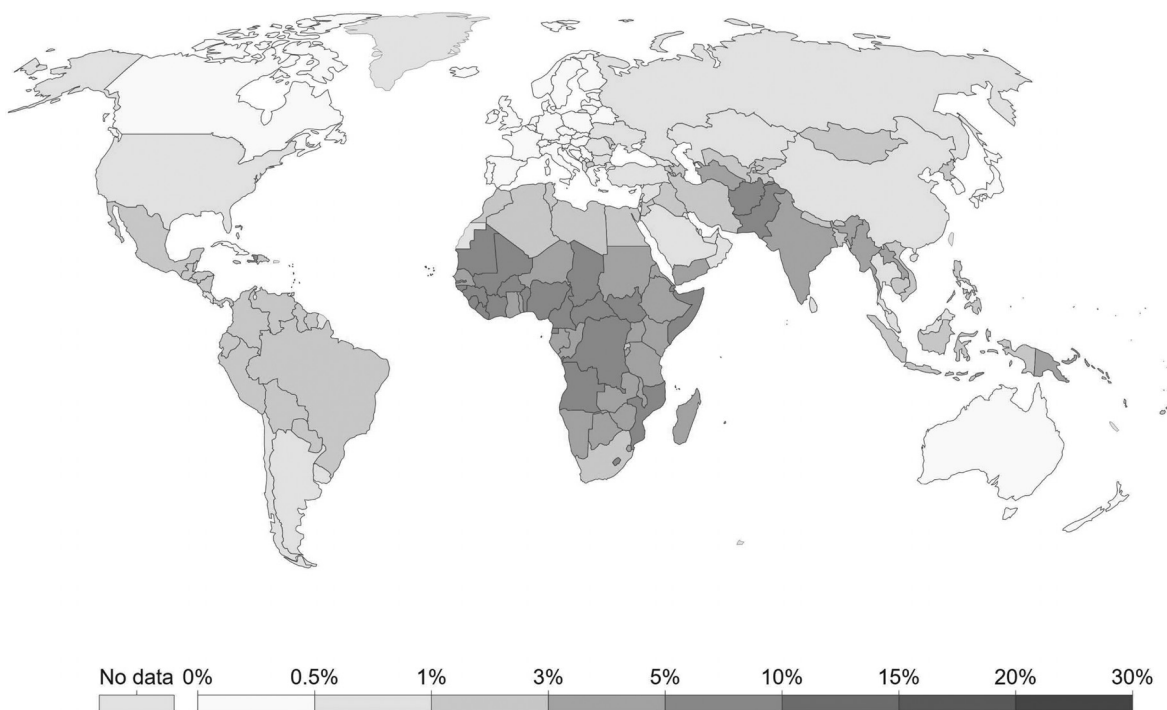


Fig. 1 Infant mortality rates in 2017 [66,67]. Neonatal mortality is double the global average in sub-Saharan Africa.

However, asphyxia may be overcome with expanded care and improved healthcare provider training, but it is crucial that clear protocols for resuscitation be established first.

Congenital abnormalities [64] likewise receive less attention than other medical conditions, especially given that they account for 7% of all neonatal deaths. One of the most common abnormalities in neonates is *spina bifida*, which results from the failure of fusion of the caudal neural tube. A large percentage of cases can be prevented by folic acid supplementation as long as the condition is diagnosed [76]. The underlying cause of the condition is not known but it has been established that women with pregestational diabetes or a high body mass index are at an increased risk of having a child with *spina bifida*. The protein α -fetoprotein (AFP) and ultrasound can each be used to identify fetuses that have the condition [77]. Point-of-care testing of AFP would enable screening and potential early detection of *spina bifida* and allow the patient to seek further medical care in a primary setting. The typical values in maternal serum are under 100 ng/ml until 13–18 weeks of gestation [78]. A quantum-dot-based sensor for the detection of AFP has been reported by Yang et al. [79], with sensitivities to 1 ng/ml. This test, however, relies on comparing the relative fluorescence intensities of the sample with a control, and can be difficult to interpret in the absence of optics and skilled personnel. The WHO compendium of medical devices and technologies for low-resource settings lists two ultrasound scanners, which are priced at US\$24,000 and US\$7,500 [80], still a significant cost in comparison to the annual budget of many hospitals in low-resource settings [81].

Ultrasound is otherwise commonly used to diagnose congenital structural defects during pregnancy. One such condition typically diagnosed using fetal ultrasound is hydrocephalus, a condition where fluid accumulates in the ventricles within the brain. The treatment for this condition involves the implant of a shunt that drains away excess cerebrospinal fluid into the abdominal cavity. The problem with this procedure irrespective of the setting—whether in an LMIC or a high-income country—is that implanted shunts fail due to an obstruction caused by glial and inflammatory cells [82]. A comparison between an inexpensive shunt developed and used in Africa and one currently in use in the United States to treat the condition showed that there was no significant difference in clinical outcomes [83]. The failure rate in the first 2 years for

implanted ventriculoperitoneal shunts remains high, at over 40% [84], indicating that there is a need to evaluate failure due to occlusion in greater detail.

5 Neglected Tropical Diseases

Neglected tropical diseases are a group of thirteen bacterial and parasitic infections that affect around 2.7×10^9 people worldwide [85] as illustrated in Fig. 2. They are highly prevalent in sub-Saharan Africa and south Asia, where over 70% of the population lives on less than \$2 a day [87]. These diseases make it difficult for people affected by them to rise out of poverty as their effects can be chronic or, in some cases, fatal. Schistosomiasis is such an NTD, affecting 192×10^6 people in sub-Saharan Africa alone, accounting for 93% of the world's cases, and associated with increased human immunodeficiency virus transmission [88]. About 75% of the population of sub-Saharan Africa lives near bodies of water that have been contaminated with schistosomiasis hosts [89], with those living near dam reservoirs at higher risk [90]. The population most affected by schistosomiasis is children and young adults.

Schistosomiasis can be caused by two strains of bacterium, one of which affects the urinary tract and the second infecting the intestine. *Schistosoma haematobium* is one of the leading causes for urinary tract infections, and around 150,000 deaths annually [91]. *Schistosoma mansoni* causes bowel ulceration and an estimated 130,000 deaths [92]. Adult male and female worms can live in the human host for an average of 10 years and the disease spreads by the transmission of eggs to an intermediate snail host typically found in water bodies. The worms feed on glucose present in blood and erythrocytes and excrete waste into the blood stream. Biomarkers present in waste may serve as a target for detecting schistosomiasis. The primary treatment for the disease is the drug praziquantel, which is only effective against mature worms [93]. Prolonged treatment for 3–6 weeks is required to completely cure the disease. Although this drug is being employed in the field to treat schistosomiasis, the mechanism of action is still unknown and side effects include abdominal pain and passage of blood in the stool [94]. The current diagnostic standard for schistosomiasis is the presence of viable eggs in urine or fecal matter, but the test has a low sensitivity [95]. The three

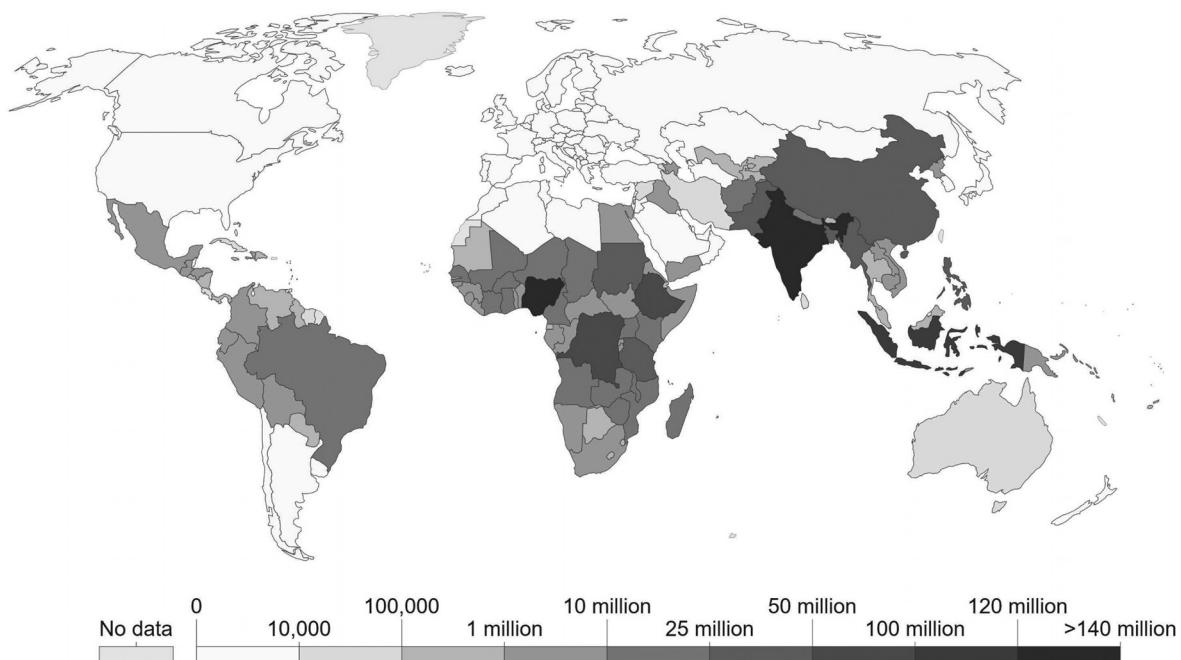


Fig. 2 Number of people requiring interventions for NTD in 2015. These data are a subset of the number of people at risk for NTDs [86].

recommended detection techniques by the WHO are microscopy, a urine-based dipstick assay [96], and the Kato–Katz fecal examination [97]. The Kato–Katz method was developed in the 1970s and uses a cardboard cutout over a glass slide and microscopy to easily count the number of eggs in a sample and quantify the number of eggs per unit weight but this technique, like the others recommended by the WHO, lack sensitivity.

A point-of-care lateral flow assay to detect the presence of circulating cathodic antigen was developed [98], addressing the sensitivity limitations of the Kato–Katz technique, but only for *Schistosoma mansoni*. It did no better than the Kato–Katz technique when used for stool samples. Recent reports on diagnosis of the disease have called for better diagnostic tools [99], one of which is PET (positron emission tomography) imaging. This group made use of glucose intake of the worms in vivo to detect and quantify their presence using a PET scanner. With groups starting to develop handheld PET scanners [100], this might present a novel research direction for groups looking to develop diagnostic technologies. PCR-based techniques have also been developed to analyze cell-free parasite deoxyribonucleic acid in human plasma [101], and the development of microfluidic PCR-based systems [102] for schistosomiasis could lead to improved detection.

Control measures against the disease include preventative therapy using praziquantel [103], issued by schools screening and treating children for this and other diseases. An additional screening technique that has been attempted in the past is to monitor and eliminate snails that serve as intermediate hosts. The WHO in 2012 pledged to control the morbidity caused by the disease by 2020 and eliminate it as a public health problem by 2025, leading to an increased effort in diagnosing and educating the communities most affected by the disease. This has stimulated increased funding and opportunities for novel interventions.

6 Policy and Implementation

There have been significant improvements in healthcare outcomes over the past few decades due to a combination of efforts by public and private organizations, and technological advancements in diagnostics and surgical devices. Despite this, there are some limitations to adoption and implementation of technology.

In some cases, the underlying disease or condition may not have a device or diagnostic solution. This is common in the case of neglected tropical diseases that are a significant health burden but have seen insufficient investment from the private sector. A point-of-care monoclonal antibody-based dipstick for urinary schistosomiasis was developed by a Ghanaian group in 2004 [104] but has not been commercialized [105].

The technology may exist, but other problems such as distribution or energy required to power the devices may not exist [106]. Oxytocin is used to reduce the risk of postpartum hemorrhage but requires refrigeration, unavailable throughout the day in resource-limited settings. Advances in packaging that could extend the shelf life of drugs and vaccines would expand access to available care in these cases.

In the case of diagnostics, a more sensitive and specific test may exist but there could be reluctance to adopt it or mistrust in the results it produces due to past misdiagnosis with old technology. Rapid diagnostic tests for malaria have been shown to have superior sensitivity and specificity than the current gold standard for malaria detection, microscopy [107]. But a study found that doctors prescribed antimalarial drugs—even in the case of a negative test result [108,109]. Skilled healthcare is crucial to improve surgical outcomes. For example, access to skilled surgeons for delivery is as low as 40% in sub-Saharan Africa and less than 30% in south Asia [110].

Designing medical devices for LMIC's presents unique challenges not seen in developed markets. The WHO estimates that 70% of medical equipment coming from developed countries does not work in hospitals in developing countries [68,111] due to lack

of trained personnel, limitations with infrastructure, and the lack of spare parts or support for equipment.

It is evident from these examples that research and development of novel diagnostic tools and devices alone is insufficient for adoption. In the context of the conditions presented in this paper, there is a need to develop an effective way to screen for schistosomiasis and melioidosis. The spread of melioidosis starts through soil in the rainy season and the presence of schistosomiasis can easily be detected in fecal matter. A technique to purify samples coupled with existing point-of-care diagnostics would stop the spread of the disease at the source. This can be extended to detect the presence of environmental contaminants such as organophosphates and heavy metals. An increase in sensitivity can be achieved if adequate processing is done prior to point-of-care diagnosis. The UN's fourth millennium development goal called for a two-third reduction in neonatal mortality by 2015. Although there has been significant progress toward this goal, there are still 4×10^6 neonatal deaths every year, predominantly in south Asia and Africa. Developing medical devices specifically for neonatal care and not having to repurpose devices made for adults would enable easier surgical procedures. Better detection schemes for diseases such as spina bifida or hydrocephalus using low-cost ultrasound transducers would prepare doctors better for surgery. It is critical to rethink what low-cost means for such applications, especially considering the annual budget of hospitals in LMIC's. Frugal technologies that can be used repeatedly can withstand environmental conditions and can be used easily by healthcare workers in target countries should be prioritized.

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