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Important Factors for the Design of Medical Devices for Developing Countries

An Interactive Qualifying Project Report:

Submitted to the Faculty

of the

WORCESTER POLYTECHNIC INSTITUTE

In partial fulfillment of the requirements for the

Degree of Bachelor of Science

By

Boyla O Mainsah

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Approved:

Prof. Robert Peura, Advisor

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Abstract

The high failure rates of imported medical devices in developing countries represent a significant challenge in the fight against world diseases. Developing affordable devices designed with an understanding of health care systems in developing countries is imperative. This project outlines the necessary steps for the development of a lab-on-chip microfluidics test for the detection of diarrhoeal pathogens. A framework is outlined based on the lessons learnt in implementing medical devices and the successes of custom devices designed to meet the needs of the developing world such as auto-disable syringes.

1. Executive Summary

The Declaration of Alma-Ata in 1978 by the World Health Organisation (WHO) highlighted the importance of appropriate and functioning medical technology in healthcare delivery¹. Medical devices are an integral part of health care systems as they facilitate healthcare delivery, diagnosis and treatment for better patient care. Developing countries account for about 80% of the world's population and bear a significant burden (about 93%) of the world's diseases². However, over 95% of medical equipment in developing countries is imported and most don't often meet the needs of their health care systems³. The WHO estimates that 50% of equipment is not in use due to lack of maintenance or spare parts, device over-sophistication or lack of proper use by health personnel³.

Most medical devices are designed for industrialised countries having the high GDP spending to back medical expenditure as well as the adequate infrastructure to incorporate these devices into their healthcare systems. In addition to this difference in target market in design consideration, are socio-economic and regulatory issues that make the application of these imported medical devices problematic in developing countries. Unfortunately, designing for the developing world market presents unique challenges due to the lack of understanding of healthcare systems in developing countries. In addition, there is little incentive for the medical device industry to develop products specifically for developing countries due to the non guarantee of return of investment⁴.

Fortunately, the past few years has seen an increased interest in global health, attracting investments from private and non-governmental organisations for the development of technologies designed specifically to meet the needs of developing countries. For example, an improvement in vaccination coverage and reduction in unsafe injections in developing countries has been observed due to the introduction of auto-disable syringes and cold chains in developing countries, coordinated by the WHO and other global health organisations. Developing affordable devices designed with an understanding of health care systems in developing countries is imperative.

The goal of this project is to develop guidelines for the development and testing of medical devices designed to meet the needs of developing countries, specifically for a diagnostic

test for the detection of diarrhoeal pathogens. This project will examine through literature search, the reasons for the inappropriateness of imported medical devices within the context of developing countries to identify the key areas to consider during the design development process. In addition, the success of auto-disable syringe implementation in immunisation programs in developing countries will serve as a model template to adopt when developing these guidelines. This information will be useful to biomedical engineers, and medical device industry who would like to consider designing devices for the developing world community.

2. Medical Device Challenges in Developing Countries

2.1. Imported Medical Technology

2.1.1. Medical Device Market

The annual global medical device market is worth \$150 billion and is expected to grow by 4-5% over the next few years due to the current medical technology revolution^{1,5,6}. About 50% of all diagnostic and treatment methods used today were nonexistent a decade ago⁷ and the number of medical device patents filed in the U.S. Patent and Trademark Office has more than doubled since 1989⁸. The US is a key player in the development of medical devices; it is the base for 9 of the top 10 world medical device companies, produces over half of the world's medical devices and consumes about 40%^{1,5,6}.

Such growth in the medical device industry creates business opportunities that attract many medical device suppliers and manufacturers. However, due to the high costs involved in developing new medical devices, investors are typically attracted to larger device markets or the more established ones like the adult demographic. The increasing ageing population, emerging middle class markets, and the (unfortunate) spread of the “Western diet” represents areas with unmet clinical needs. Cardiovascular (CDV) and orthopedics device market are some of the leading device markets in most industrialised countries due to the high prevalence of cardiovascular disease and the more active lifestyles of the ageing population⁵. In addition, major medical device companies tend to increase their product portfolios by acquisition of smaller companies or mergers, as opposed to through internal early stage research and development^{5,9}.

Prior to entering a new market, suppliers typically look at industry reports to estimate potential market demand and forecast profits. China's market has been projected to grow faster than the global medical device market. The reasons for this fast growth include its fast growing domestic economy, increased GDP spending on healthcare, increased demand for more advanced medical technologies, the availability of health insurance as well as increased government focus on improving healthcare in the country¹⁰. Although a majority of the Indian population cannot afford healthcare, its growing middle and upper class population (+150 million people) is a promising market due to their changing disease profiles i.e. more sedentary lifestyles and rise in CDV diseases¹¹. Developing countries represent the fastest growing medical device market due to their greater disease burden, with a market size about five times of the developed world¹².

Unfortunately, although developing countries account for about 80% of the world's population and 93% of the world's disease burden, they contribute to only 10-11% percent of total healthcare spending². Ironically, most of the world's population requiring health services are forced to use medical devices designed for high income countries. Over 95% of medical equipment in developing countries is imported and the WHO estimates that 70% of this equipment doesn't work because they don't meet their healthcare needs^{3,12}. This “bundle, package and ship” form of technology transfer without considering the internal capabilities to accept, diffuse, produce and manage medical technology is mainly responsible for this failure of most medical devices in the developing world. Developing countries are thus faced with the challenge of adapting these technologies into their health care systems with direct implications on the appropriateness of these technologies.

There is thus the need to balance this largely supply-driven market and meeting the actual needs of the healthcare population. Despite the wide array of medical devices, this supply-driven market has created inequitable access to medical equipment, especially for countries with small populations, weak socio-economic situations or unstable political conditions. This huge technology divide is thus problematic as deriving maximum benefits from medical devices requires technical knowledge, skills and operation resources which may not be available in most developing countries. The high costs of medical devices can be made more affordable for most developing countries if cost is factored as a main design consideration during the device development process.

Opening a market requires a considerable amount of investment as well as research and development to adapt or develop new products to local conditions e.g. climate, access to electricity and water, transportation conditions etc. Most medical devices assume an existing minimal infrastructure level of electricity and water (e.g. distilled or deionised). For example, although x-ray imaging has existed for more than a century, the unreliability of power in most developing country hospitals makes them impractical for use. In addition to being very expensive, MRI imaging use is unfeasible due to its high power consumption. There is often little local production of medical equipment in most developing countries and if any, it is controlled by multinational corporations with little commitment to local research and development. Setting up production facilities can sometimes be difficult due to import

restrictions, transportation and tariff costs. Investors can also be discouraged that their large investment cannot be supported by the market in developing countries¹³.

Equipment service organisations thus play a significant role in these countries to serve as a bridge between medical device manufacturers and buyers as they provide the necessary information for product purchase, supply spare parts, train buyers to use the product etc. However, the limited number of these organisations can be problematic¹³. Unfortunately, as Figure 1 shows, while a hospital in the U.S. readily available information and the luxury of various choice options prior to making equipment purchase, most developing countries lack this information to help in their decision making and are often faced with only one manufacturer option. This lack of choice in selecting and negotiating suitable terms with suppliers makes them more susceptible to being locked into long contracts as well as inflated prices for services. Robert Malkin notes that the lack of spare parts due to insufficient number of local suppliers in most development significantly reduces the life cycle of medical devices, especially when a first replacement is required¹² (see Appendix A for medical device acquisition flow chart).

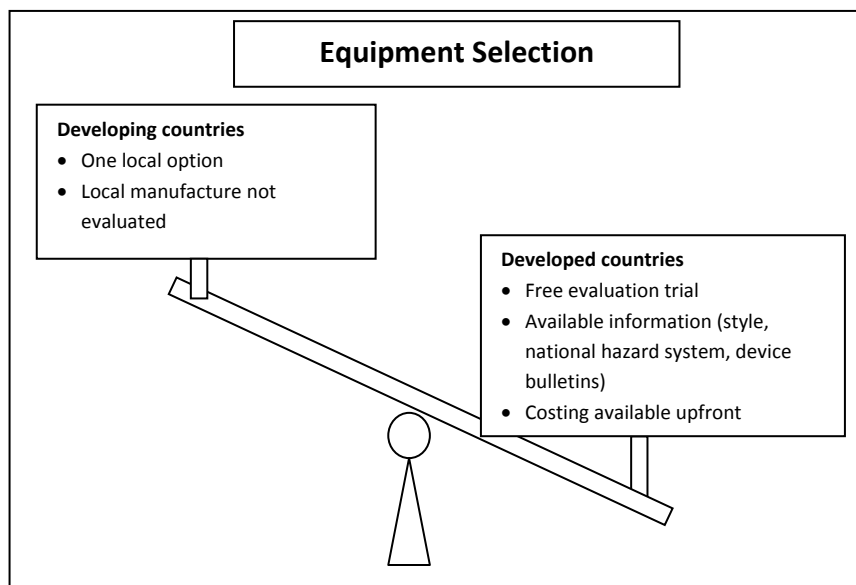


Figure 1: Comparison of equipment selection scenarios between developing and developed countries¹⁵

2.1.2. Medical Device Donations

Due to the high costs of healthcare, donor assistance and foreign aid represents a significant portion of healthcare funding in most developing countries. In 1990, total aid to the healthcare sector was estimated at \$4.8 billion, with over 80% coming as development assistance and the rest through foundations and other sources. In Burkina Faso, Chad, Guinea-Bissau, Mozambique, and Tanzania, foreign aid covers over half of all health expenditures¹⁶. For most donors, medical device donations allow for frequent equipment turnover, tax deductions, or better yet the good benefactor feel of helping people in need. For developing countries, it allows for quicker access to sophisticated technology that might be otherwise unaffordable.

Despite significant investment, this “technical invasion” has led to the inefficient use of most medical device in developing country settings. Investments in expensive equipments with no clear benefits have often proven to be unsustainable as they distort healthcare spending patterns. For example, in the early 90’s, through plenty of foreign aid, the Cuban government was able to purchase the best of medical equipment for its healthcare system. However, when funding ceased, the inability to sustain such equipment resulted in 70% of the equipment being out of service within 7 years¹⁷. Similarly the World Bank invested about \$1.5 billion in medical devices for developing countries between 1997 and 2001, with less than satisfactory results. About 30 % of the equipment proved too sophisticated for use, while those in operation had 25 to 35 % equipment downtime due to inadequate maintainance¹⁸. This was due to the failure of the Bank projects to assess the cost-effectiveness and affordability of these medical devices and to evaluate the real impact of their investment on improving the quality of healthcare.

Also, anaesthesia provision is still challenging in developing countries because this is a technology-based specialty which can be very vulnerable if resources are limited^{19,20,21}. A recent study in Anaesthesia demonstrated that adequate equipment and supplies for safe anaesthesia in Uganda was available in only 6% of C-sections, 13% of children laparotomies and 23% of adult laparotomies²². Unfortunately, the donation of anaesthesia equipment has proven unsuccessful in most cases due to lack of access to equipment supplies such as compressed gas or liquid oxygen systems²³. Table 1 summarises problems with donation of Anaesthesiology equipment in

developing countries by the World Federation Societies of Anaesthesiologists (WFSA), and some of which can be applicable to other medical device donations.

Table 1: WFSA Summary of Problems with Donation of Anesthesiology Equipment Donation ²⁴

<ul style="list-style-type: none">• Limited electrical supply which may be erratic, of a different voltage or not exist.• Lack of compressed gas or component supplies for replacement or expenditure may represent additional cost burden.• It may not stand up to an adverse environment (heat, humidity, dust)• There may be no expertise locally to install, commission or repair the equipment.• It may not be supplied with manuals or, if it is, they may be incomprehensible (not easily understood) or in a language which cannot be understood.• It may be defective on arrival or have part missing• Inadequate sterilising facilities• There may be no reliable or clean water source for cleaning• It may require basic-to-advanced physiological and/or pharmacological knowledge to use it.

The mismanagement of technology, lack of user training and on-going technical support results in the failure of most medical donation programs. Donors can sometimes concentrate on volume, and be anxious to get rid of product without paying attention to condition of equipment, availability of parts, complete device documentation etc. Often, the failure to refurbish or repair used donated medical devices can lead to the shipment of defunct products. This is especially problematic with the practice of “spray and pray” whereby medical devices are aesthetically painted to look new, with no little or no device repair²⁵. Donor policies can fail to recognize recipients as equal partners in the process, can foster dependence and sometimes adopt an ‘anything is better than nothing’ policy if their efforts prove ineffective²⁶. The passive role that recipients play in this process is also problematic, especially as they cannot properly screen incoming devices or assess and plan if they can support the technology.

Due to notoriety of the problems associated with medical device donations, the WHO has set up guidelines to regulate medical donation practices in an effort to better coordinate donor efforts and their recipient countries to obtain maximum benefits from device donations²⁷. Some basic considerations include evaluating the real cost of the technology, as well as considering if the recipient country can sustain the donated technology. When transportation and shipping costs are considered it might sometimes be cheaper to produce or buy materials locally as beneficiaries can often be burdened with custom taxes and importation issues. The costly

nature of purchasing and maintaining medical devices especially those with short life cycles e.g. syringes, catheters etc can represent an added burden to healthcare systems with limited budgets.

2.2. Health Service Organisation and Management

2.2.1. Health Care Policy

2.2.1.1. Economic Aspects of Health Care

Most industrialised (except for the US with mainly private insurance-based healthcare) and developing countries provide most of the healthcare to their citizens through public healthcare systems. Unfortunately, per capita healthcare spending (purchasing power parity) for most developing countries is very low. For example, in the United States, \$ 6,096 (the largest in the world) is spent per capita on healthcare, on average \$2000 per capita in Europe, and less than \$100 per capita in every one of the 35 nations with very low human development²⁸. Chad, Niger and Ethiopia, countries with one of the lowest Human Development Indices, spend less than \$50 per capita on healthcare, with public expenditure of health being less than 5%^{28,29} (see Appendix B for more data details). While most industrialised countries spend about 5% on total annual health care on physical infrastructure, building, equipment, etc, in contrast in developing countries, capital expenditures accounts for about 40% - 50% of the total public health care budget⁷.

Provision of healthcare through the private sector is thriving in developing countries, as it experienced an increase in growth from 8% in 1991 to 27% in 2000¹². However, although these services are comparable to those in developed countries, they are unaffordable to a majority of the population. Thus, with limited budgets, many developing-country governments attempt to offer comprehensive health care for all. Unfortunately this approach often results in inefficient spending. Due to the large disease burden in these countries, medical device purchases are dominated by public health considerations and healthcare professionals may often prioritise social services over medical devices¹². Resources typically get concentrated in urban hospitals and tertiary-care hospitals, which provide the most specialised and sophisticated services, consuming a majority of the healthcare budget. This misallocation of funds leaves very limited funding towards more cost-effective public health measures especially for rural and poorer areas, (with a larger subgroup of the population) that have limited access to these healthcare services³⁰.

The lack of proper knowledge in assessing health care needs can often lead to irrational procurement especially of expensive medical devices. In Columbia, a government-sponsored x-ray distribution project failed due to lack of radiologists and unavailable electricity in some areas leading to equipment sitting idle for over 10 years³¹. Developing countries can provide significant health benefits to a larger population by concentrating public spending on highly cost-effective public health and clinical services, thereby protecting the health sector and its citizens from unnecessary healthcare expenditures. For medical devices, this requires assessing cost-effectiveness of medical device purchases, developing policies on rational procurement and regulating purchasing decisions in both the public and private sectors¹. A strong collaboration between private industry and governments is necessary as without the full support of a country's government, any solution to a country's medical problems will only prove temporary³².

2.2.1.2. Medical Device Regulations

As most developing countries obtain their medical devices via imports, the presence of a regulatory body is important to ensure quality products with pre-market, on-market, and post-market control to ensure device safety, quality and appropriate use. These responsibilities include ensuring incoming devices comply with essential safety/performance principles, are appropriately selected by healthcare providers for use and implementing good medical device management and disposal practices. Unfortunately, for most developing countries, medical devices are perceived as more of a procurement issue as opposed to an integral part of health care policy³.

Few developing countries have an authoritative body with the sole responsibility of regulating medical devices, and this lack of effective regulation can lead to the importation of substandard devices, or illegal re-processing of medical devices. For example, the reprocessing of single use devices such as syringes without proper sterilisation is a major source of disease transmission such as HIV and Hepatitis in most developing countries³³. The lack of post-market surveillance also makes it difficult to monitor device failures and hold manufacturers accountable for adverse device incidents or product recall.

While purchasing refurbished medical equipment can be cost-saving, the lack of adequate medical regulatory control is problematic in most developing countries as they can often pose a safety risk^{34,35}. The U.S. accounts for almost half of the world's market share in used and

refurbished medical devices, this sector is strictly regulated by the U.S. Food and Drug Administration to ensure that equipment is rebuilt and tested to original specifications³⁵. The bad experiences of trading in used/refurbished medical devices such as lack of after-sale technical support or spare parts, adequate documentation etc has led to the partial or complete ban in most developing countries. By 2002, at least 5 countries had imposed a total ban on the import of used equipment and 17 other countries have partial bans³⁵.

In 1993, a Global Harmonisation Taskforce was set up by the major medical device producing and regulatory bodies (Australia, Canada, the European Union, Japan and the U.S.A.) to harmonise standards and regulatory practices across countries. This was done in an effort to reduce regulatory barriers, facilitate trade and improve access to safe and effective technologies. Although in effect for more than a decade, developing countries who import 90% of their medical devices remain sidelined in this process due to their lack of knowledge on best practice guidelines³⁶.

To bridge this gap, the WHO published a global overview and guidance document, with recommendations for countries with limited infrastructure on how to build a more effective regulatory system³⁴. This includes a matrix of the entire life cycle of a medical device, the stakeholders involved at each stage, and policies that should be in place to manage each stage in the medical device life cycle (see Figure 2) Most developing countries should prioritise vendor and product registration, user training and post-market surveillance (correct use, problem alert, recalls) though creation of a database, since most of them import their medical devices. Figure 3 shows the key responsibilities of such a regulatory system during the phases of the life cycle, of a medical device.

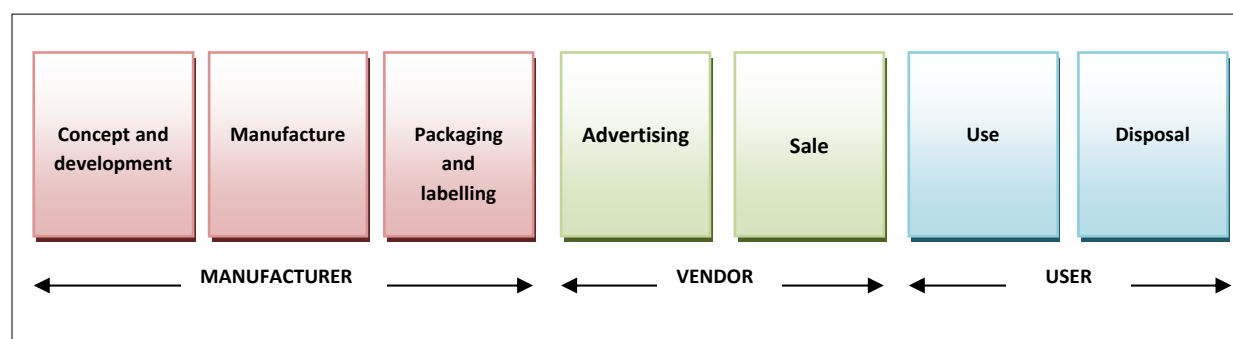


Figure 2: Stake holders during medical device lifecycle

<p>Pre-market control</p> <p>Close cooperation is needed with the manufacturer/importer of the product. Important activities include:</p> <ul style="list-style-type: none"> ● Collaboration on acceptance criteria (see checklist overleaf) ● Collaboration on international quality systems and product-specific standards ● Agreement on systems for conformity assessments ● Clinical trials/testing ● Appropriate and effective customs control system on imported medical devices <p><small>* includes testing and clinical trials</small></p>	<p>Sales monitoring</p> <p>A national database on vendors and products is essential for effective control of medical devices. Important activities include:</p> <ul style="list-style-type: none"> ● Vendor registration ● Product registration ● Prohibition of fraudulent/misleading advertising ● After sales obligations, including: <ul style="list-style-type: none"> — distribution records — complaint handling — problem reporting — recall procedures 	<p>Post-market surveillance</p> <p>Correct use is the ultimate determinant of safety and effectiveness. Important activities include:</p> <ul style="list-style-type: none"> ● Training of user before use ● Regular maintenance of devices in accordance with operation and service manuals ● User networks and medical device vigilance systems to facilitate alert notification ● Adequate management and disposal of discarded devices
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Figure 3: Key elements of a National Medical Device Regulatory or Monitoring Programme ³⁴

2.2.1.3. Medical Device Management

Medical devices are assets that require good management in order to fully utilize their capacity, given their considerable amount of capital investment, high maintenance costs and relatively short life spans. Also the safety and health outcome of a medical device is intimately linked to how well it is managed and its operator's skills (see Figure 4). Unfortunately, the WHO estimates that around 50% of medical equipment in developing countries is not functioning, primarily due to a lack of maintenance culture in these countries^{3, 37}. Medical device management is often reduced to the mere acquisition of up -to-date technology and equipment depreciation and maintenance costs are hardly factored in healthcare provisions. Figure 5 shows (without factoring natural depreciation), the value medical devices can fall to about one tenth of their original value due to inadequate device procurement decisions, over sophistication, misuse, lack of spare parts, inadequate support infrastructure, maintenance and repairs¹.

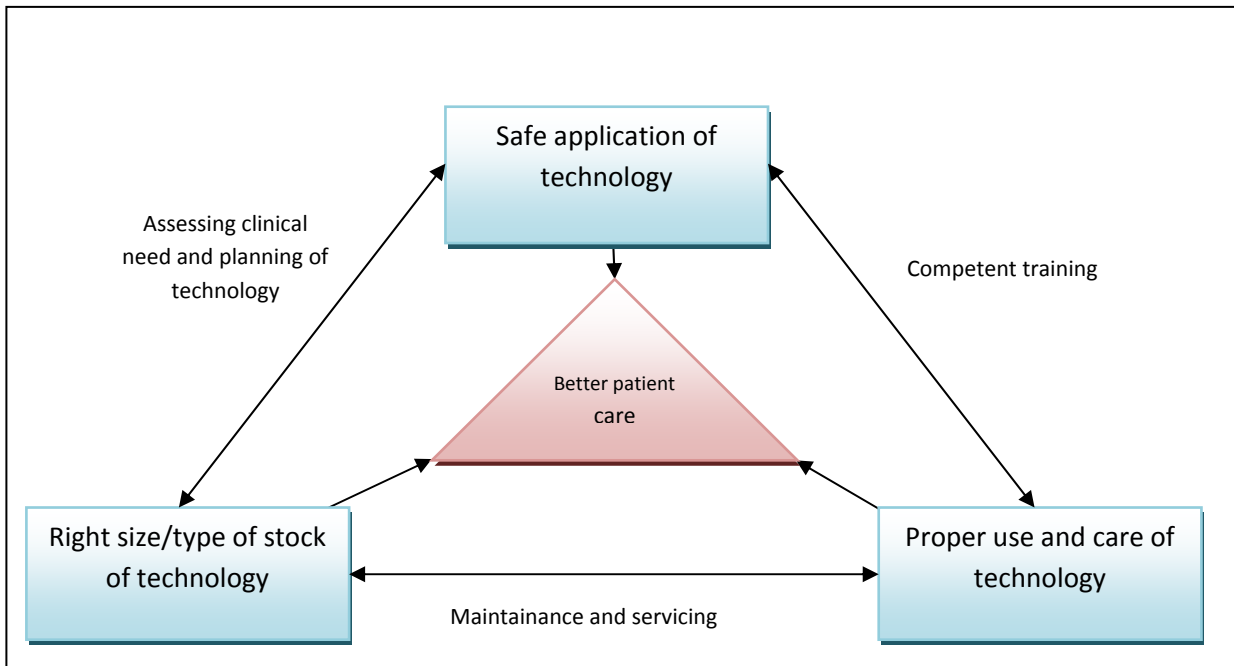


Figure 4: Components of healthcare technology management for better patient care

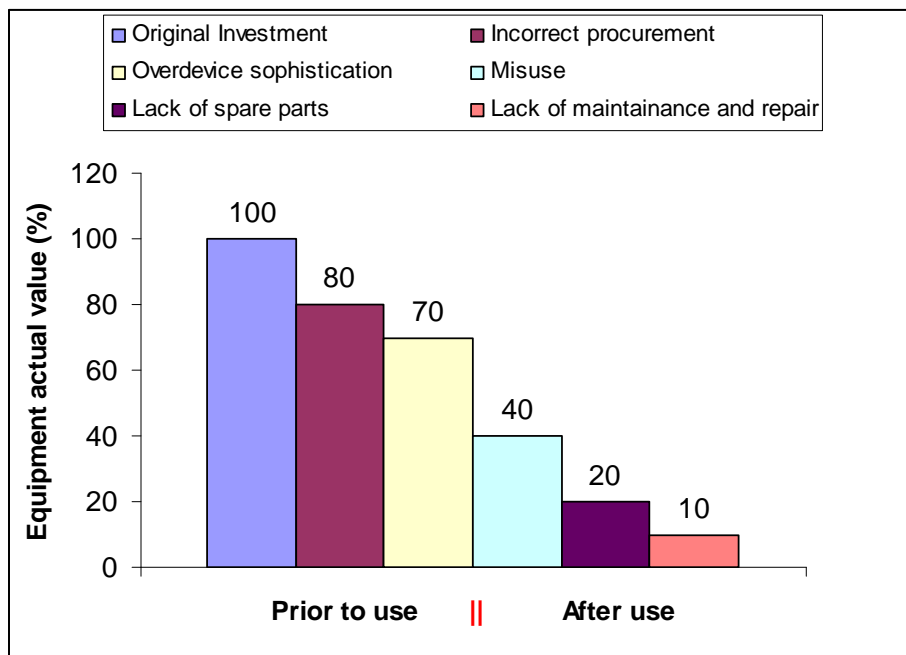


Figure 5: Waste of resources from budget to patient due to lack of medical technology management¹

For example, Table 2 summarises the results of a small survey by Engineering World Health (EWH) of diagnostic x-ray availability in eight hospitals in three countries: Nicaragua, Haiti and Sierra Leone³⁸. The survey documented the number of mobile and stationary, working and non working diagnostic x-ray machines, noting the cause of equipment breakdown where applicable. Only one of the eight hospitals had a working mobile x-ray machine, and approximately half of the hospitals had a working stationary x-ray machine. The most common reason cited for broken equipment was an expired x-ray tube, with unavailable spare parts. Even at La Mascota Hospital, the largest pediatric hospital in Nicaragua, which also conducts thoracic surgeries, there was no functional x-ray of any kind.

Table 2: EWH Survey of X-ray machines in Sierra Leone, Haiti and Nicaragua³⁸

Country	Hospital	Number of Mobile X-ray Machines	Number of Stationary X-ray Machines	Number of Beds
Sierra Leone	Connaught	1 (1)	1 (2)	500
	Good Shepard	0	0 (1)	30
	Bo	0	1 (2)	225
	Kissy	0	0 (1)	150
Haiti	Jacmel	0 (2)	1 (1)	250
	La Vallee	0	0	50
Nicaragua	La Mascota	0 (1)	0 (2)	250
	Leon	0 (1)	1 (2)	400

Numbers in parentheses are the number of broken machines.

It is also important to note that the operating and maintenance costs during the life cycle of a medical device can sometimes be underestimated e.g. for disposables syringes, infusion pumps, test strips. For example disposable, sponge-based self adhesive pads have replaced metallic, reusable ECG electrodes due to their convenience of being faster to use and no requirement for cleaning and sterilising between uses. However, when an ECG machine was donated to a Tanzanian hospital by EWH, reusable metallic electrodes had to be designed and tested due to the lack of disposable ECG electrodes in the area and budgetary constraints of the hospital³⁹. Figure 6 shows that acquisition costs represent a “tip of the iceberg” in the recurrent costs of maintaining a medical device during its lifecycle²⁵. It is thus important to take into account the budgetary constraints of resource limited healthcare settings and consider the total life cycle ownership costs of medical devices, which includes in addition of acquisition costs, costs of accessories and consumables, maintenance, and utilities.

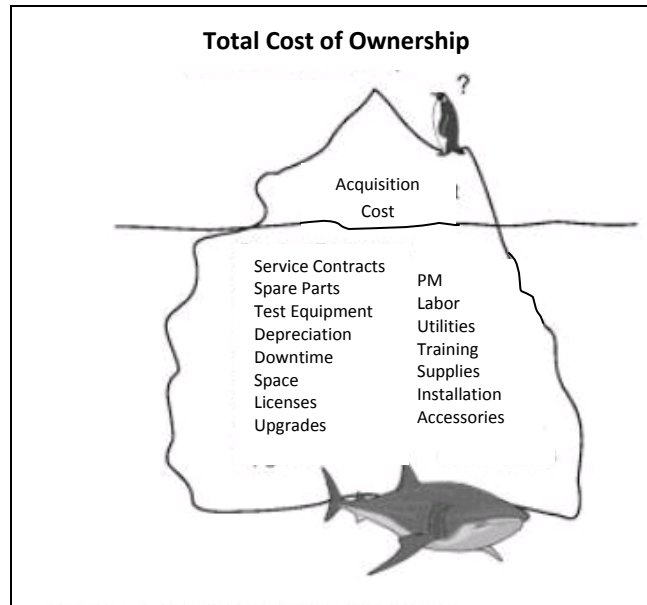


Figure 6: Medical Device Acquisition Iceberg²⁵

2.2.2. Health Technology Transfer

2.2.2.1. Education and Healthcare Personnel

The proper education and training of healthcare personnel is important to ensure the safe and effective use of medical devices. This includes training in preventive and routine maintenance for technicians as well as training of proper use of equipment for healthcare personnel. In most developing countries, the lack of the proper training schools or technically qualified staff contributes to the inadequate maintenance of medical devices. The one-time training by the vendor prior to device use has proven insufficient, especially as the proper use of medical devices requires on-going support and the coordination of efforts of all healthcare personnel. Language barriers also create problems in terms of proper translation of technical documents and training into the native languages of the local population.

In addition, the absence of suitable personnel to integrate knowledge of medical needs with technical expertise presents a challenge when determining what medical devices are suitable for particular healthcare environments. It is important to note the significant impact of brain drain, where most developing countries have lost their skilled workers to greener pastures abroad^{40,41}. In addition, is the phenomenon of “brain leak” where the few people who are trained

for specific tasks technical leave service either due to low salary incentive or lack of motivation. For example, at the Centre Medical Evangelique hospital in the Democratic Republic of Congo, two individuals who were trained to be electronic technicians for the hospital resigned due to low salaries⁴².

2.2.2.2. Medical Device Research

The World Health Assembly emphasises the importance of improving patient safety and quality of health care by strengthening the science-based systems used to assess and monitor medical equipment and technology. Simply reducing the price of medical devices or removing design features to reduce medical device costs has proven insufficient, especially as stripped-down versions or simplicity in design can be perceived as being inferior. Unfortunately, the lack of adequate technical culture in most developing countries concerning medical research and design remains an obstacle, especially as device development requires a significant amount of investment, capital and higher education.

Developing countries can develop innovative or design capabilities to build new technologies for themselves through research and development, by acquisition of operational capabilities to duplicate and adapt technology to fit local conditions. For example, Brazil has worked to counter its technology independence by building on its research capacity, through heavy investment in education and research and development opportunities⁴¹. By encouraging local innovation and increasing health equipment manufacturing by 13.8%, Brazil now meets 73% of its local demand for medical devices³¹.

Creating local markets and fostering innovation is thus fundamental as developing countries will never be able to meet their healthcare demands through medical device imports. For example, developing countries have a share of only 7% of the annual hearing aid market, even though 80% of deaf and hearing impaired people live in this region⁴³. In addition are the high costs of purchasing these hearing aids and rechargeable batteries that require electricity can be impractical in places with unreliable facilities. Godisa Technology Trust, a non-profit social enterprise in Botswana developed an affordable solar powered hearing aid battery charger, the Solar Aid for a digital behind-the-ear (BTE) hearing aid for use in developing countries (see Figure 7)⁴⁴. The company also developed a low cost (55% less expensive than industry standard), full diagnostic, portable audiometer for testing hearing thresholds of its customers, for

more customisable products. It is currently an ISO certified company, and its successful model of sustainable social enterprise has attracted interest from other countries such as Mali, Brazil, Jordan and Canada ^{44,45}.



Figure 7: Solar battery charger for hearing aids developed by Godisa⁴⁶

However, due to the current technology divide, for developing countries develop their technology capabilities, this requires a form of “technology transfer,” as most developing countries are reliant on imported equipment, knowledge, information and software⁴⁷. This can be done by either trade in goods and services, foreign direct investment or direct trade of knowledge through technology licensing⁴⁸. However, this technology transfer process is faced with many challenges, such as the asymmetric access to information, regulatory issues, patent and intellectual property issues or the lack to fully internalise the costs and benefits of a technology exchange. Implementing new technologies depend on the economic support, political cooperation, functional infrastructure and an understanding of socio-cultural issues and concerns in the context of developing countries⁴⁹.

One model of sustainable technology transfer is the establishment of long term collaborations between developing and developed countries. However, this process must be based on a concept of reciprocal exchange, with an equitable and active participation of both parties, preferable with the initiative from recipients as it enables better integration of new

concepts or technologies (see Table 3). The Sustainable Sciences Institute (SSI) in San Francisco, a non-profit organisation was founded in 1998 to effect appropriate transfer of laboratory and epidemiological technologies to developing countries. SSI helps biomedical scientists gain access to training, funding, information and equipment and supplies to help in their management of infectious diseases⁴⁹. By collaborating with the Ministry of Health in Nicaragua for over 12 years, they were able to simplify and improve on diagnostic techniques for the diagnosis and management of infectious diseases such as leishmaniasis, leptospirosis and dengue fever.

Table 3: Principles for successful research partnership ⁴⁹

<ol style="list-style-type: none">1. Decide on objectives together2. Build mutual trust3. Share information and develop networks4. Share responsibly5. Create transparency6. Monitor and evaluate collaboration7. Disseminate results8. Apply results9. Share profits equitably10. Increase research capacity11. Build on achievements

3. Health Technology Assessment

3.1. Introduction

Healthcare spending and costs have risen dramatically over the past years, making it imperative to rationalise healthcare delivery⁵⁰. With the current innovative atmosphere, the novelty of some medical procedures and devices can lead to their rapid adoption and use in clinical practice with little or no evidence as to their improvement on patient outcomes. This overload of information and technology has led many healthcare professionals to turn to evidence-based medicine in making healthcare policy decisions⁵¹. Using clinical data to provide evidence to the safety and effectiveness of medical procedures provides a more effective way of investing in beneficial and cost-effective technologies.

Health Technology Assessment (HTA) is a systematic evaluation of the properties and impact of health technology, identifying potential direct and intended consequences of technology, as well as indirect and unintended consequences. This entails a multidisciplinary assessment not only of the technical properties, safety, and efficacy of health technology, but also of their economic attributes, social, legal and ethical impacts⁵². Table 4 summarises the various steps involved in HTA. With evidence from clinical trials, case studies, published research etc, the assessment demonstrates to what extent the technology is safe, works as intended, and is cost effective.

HTA in industrialised countries is usually technology-oriented, and focuses on specific technologies such as in the consideration of coronary angioplasty over coronary bypass, MRI vs. x-ray imaging, laparoscopic surgery etc⁵³. In contrast, the HTA approach for developing countries differs significantly especially as it usually deals with healthcare systems that try to meet a majority of the populations' medical needs and that acquire most of its medical technologies through imports. Using a problem-oriented approach that focuses on managing particular problems for which alternatives exist is thus more suitable approach⁷. Crucial questions that need to be addressed include making the right choice of appropriate medical technologies, ensuring their proper use and examining the conditions of cost-effective and beneficial use. As noted earlier, the poor choice of medical devices in most developing countries

has negatively impacted healthcare systems especially as their mismanagement represents a significant waste of resources.

Table 4: Steps in Health Technology Assessment ⁵²

- | |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none">○ Identify assessment topics○ Specify the assessment problem○ Determine locus of assessment○ Retrieve evidence○ Collect new primary data (as appropriate)○ Appraise/interpret evidence○ Integrate/synthesize evidence○ Formulate findings and recommendations○ Disseminate findings and recommendations○ Monitor impact |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

3.2. Essential Medical Devices

To help in the adequate procurement, planning and management of medical devices in developing countries, the WHO has implemented a model list of Essential Medical Devices (EMD) which consists of medical devices that prioritises the healthcare needs of the population⁵⁴. In other words, the health condition of the population defines the need for medical devices as opposed to a marketing approach where availability of new devices justifies new markets or the status-quo of possessing “up-to-date” technology. This inventory of medical devices will generally assume the form of a pyramid where quantity of EMD tends to decrease with increasing device complexity²⁵.

The three criteria to guide in the development of such a list are that the devices be *necessary* in the implementation of a cost effective health intervention, be *effective* and *safe*. Focusing on the major diseases of poverty, a template list can be created by defining appropriate health interventions and listing the EMD required for these interventions. Countries can thus create and adopt a national policy within a regulatory framework to ensure the safety and quality through standards and facilitate procurement and supply of these devices. Device safety, appropriate use and effectiveness can be ensured through a life cycle approach that systematically includes maintenance, training, monitoring and vigilance reporting on medical devices in use.

3.3. Example of an Essential Medical Device: Auto-disable Syringe

Injections represent the most frequent medical procedure; an estimated 16 billion injections are administered in developing countries, 95% for therapeutic reasons, 3% for immunisation and the rest for blood and blood products, contraceptives, etc⁵⁵. Unfortunately, the WHO reports that at least 30% of vaccine injections administered in developing countries are unsafe leading to infections⁵⁶. These unsafe injection practices have resulted in 8-16 million hepatitis B, 2.3-4.7 million hepatitis C and 160,000 HIV/AIDS new cases of infection. While sterilisable syringes offer the advantage of reducing costs and producing less disposal products, the risk high of transmission of blood borne pathogens and the lack of adequate sterilisation facilities (in some areas, sterilisable syringes are just rinsed tepid water prior to reuse) has led to the preferential shift to disposable syringes^{57,58}.

However, Battersby *et al.* note that the shift to disposables has not eliminated the problems associated with injection related infections or morbidity due to abuse⁵⁸. As Figure 8 shows, although sterilisable syringes have the added burden of guaranteeing sterility during use, disposable syringes generally require more management effort during their lifecycle. The failure to provide adequate supplies can sometimes force some facilities to either cancel injections, reuse syringes or request that patients bring their own syringes, which may not always be the right type.

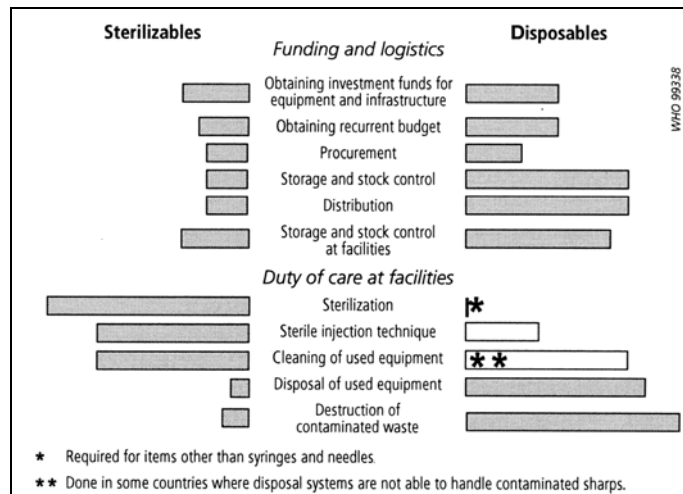


Figure 8: Level of effort and attention required by sterilisable and disposable syringe systems⁵⁸

Also, the illegal repackaging and resale of syringes still remains problematic; in a hospital in Pakistan, several blunt-needled and blood-stained syringes were found amongst opened packed syringes⁵⁸. Due to the significant volume of waste, the lack of disposal and destruction systems represent a significant risk to the population. Children are the most susceptible to needle-stick if syringes are disposed in public places where they often play. It is also important to consider that there is also the cultural conflict in the context of disposables due to the general lack of a waste culture (see Appendix C for unsafe injection practices).

To curb the problem associated with injection related injuries and infections, the WHO adopted in three part strategy to address this situation. The steps involved include:

- i. Changing the behaviour of health care workers and patients to encourage safe injection practices, especially in the wake of the HIV pandemic
- ii. Ensuring the availability of equipment and supplies, with manageable costs on health care systems.
- iii. Managing waste safely and appropriately through the availability of proper waste management systems⁵⁵.

Auto-disable (AD) syringes were thus introduced to eliminate the reuse of syringes, especially for mass immunisation campaigns. These syringes have a built in mechanism designed to give a single dose of the device, after which the syringe is permanently locked or disabled. The Soloshot™, the first commercialised AD syringe developed by The Program for Appropriate Technology in Health (PATH), has a fixed needle with a metal clip that locks the plunger after a single use⁵⁹. Another innovative product developed by PATH is the auto-disable pre-filled syringe that contains a single vaccine dose (0.25-1ml of fluid)⁶⁰. In addition to preventing syringe reuse, this technology enables the minimisation of vaccine waste and simplifies logistics by ensuring the administration of the correct dose. Drugs available through this platform include the contraceptive Oxytocin, tetanus toxoid and hepatitis B.

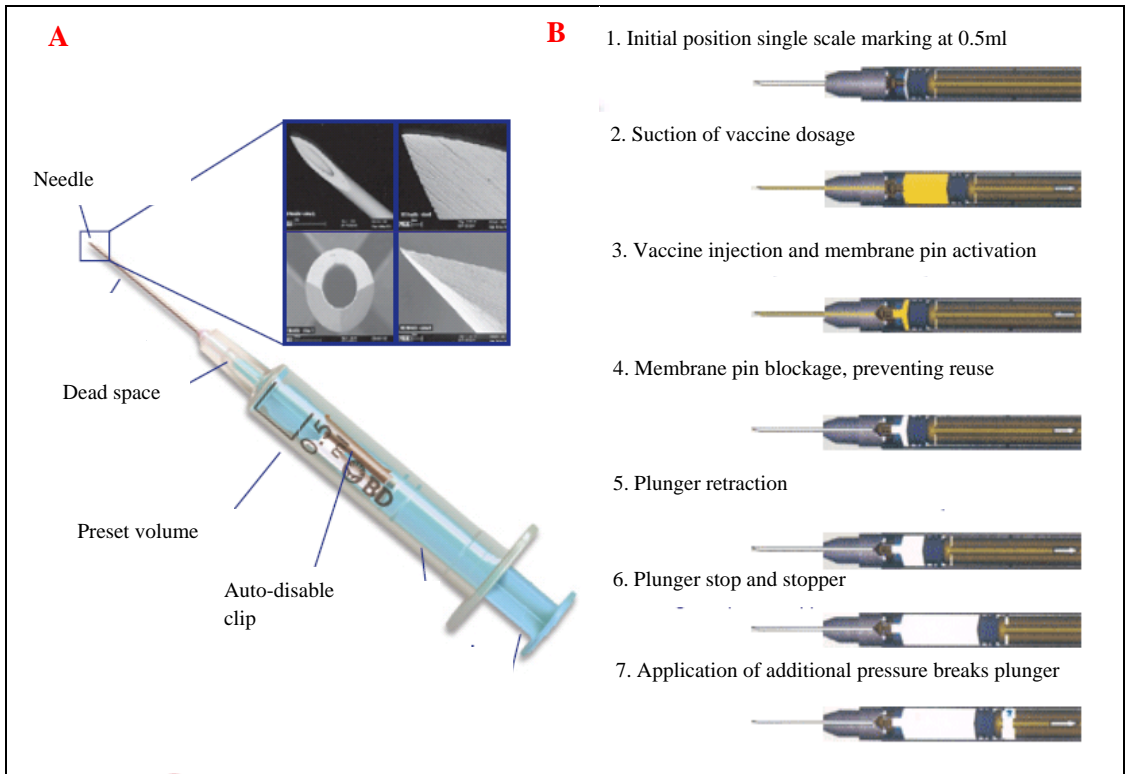


Figure 9: Auto-disable Syringe (a)⁶¹ and mechanism of action (b)⁶²

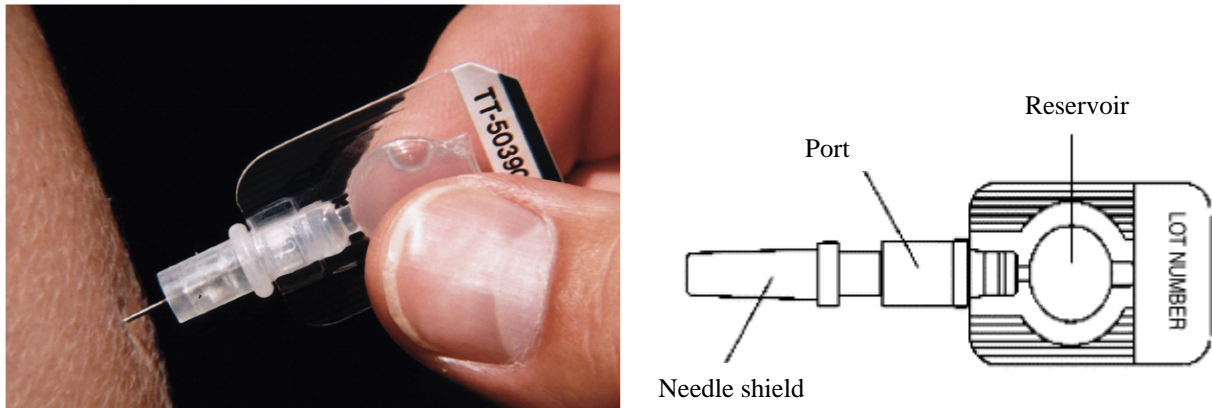


Figure 10: Pre-filled Auto-disable Syringe⁶³-Uniject™ and schematic⁶⁴

The WHO, UNICEF, United Nations Population Fund and the Federation of Red Cross and Red Crescent Societies issued a policy, with recommendations to assist policy-makers and programme managers to plan the introduction of these AD syringes. This policy is adopted as part of a comprehensive national policy and plan of action to improve injection safety, both for routine immunisation and for mass campaigns⁶⁵. The above organisations endorsed a “bundling policy” in the life cycle management of these syringes that includes the good quality vaccines, auto disable syringes and safety boxes for disposal. Each of these components is a part of this theoretical bundle and cannot be considered alone. Consequently, the WHO urges donors/lenders that finance injectable products to finance appropriate quantities as well as sharps management systems⁵⁵. The steps for successful auto-disable syringes are outlined below.

The first step requires conducting an injection safety assessment to estimate the frequency of unsafe injection practices, as well as evaluate if healthcare facilities meet the minimum requirements to support equipment supplies and waste disposal. This assessment typically takes 2-3 weeks, and costs between US \$5000-\$10,000. The information obtained will provide baseline data that will assist policy makers in defining problems and designing effective and efficient injection safety interventions⁶⁵. The next step involves developing an effective planning and management system to support the introduction of safety syringes. This includes policy statements, strategy, financing, supplies and annual work plans. In addition, health workers must be educated on the risks of unsafe injection practices and trained to administer safe injections and adequately dispose of waste products. The general public must also be educated on the need for safe injection practices and demand appropriate services.

Table 5: Planning Checklist for Injection Safety ⁶⁵

Develop an injection safety plan	Ensure vaccine delivery from delivery to vaccine administration	Manage disposal of used injection equipment
<ul style="list-style-type: none"> • Identify stake holders • Assess the situation • Include costs for safety in finance plan • Ensure injection safety through education • Manage sharps waste • Monitor and document results • Evaluate results and identify lessons learned 	<ul style="list-style-type: none"> • Use pre-qualified/national regulatory authority –approved vaccine injection materials • Bundle lyophilised vaccines with corresponding diluents, reconstitution syringes, AD syringes and sharps boxes • Communicate risks associated with unsafe injection practices to all levels • Train health care workers in proper techniques 	<ul style="list-style-type: none"> • Assess local environment regulations and options for sharps treatment and disposal • Plan storage, transportation and disposal • Identify practical, simple solutions • Monitor disposal on a regular and frequent basis

In compliance with the bundling policy, it is important to establish a reliable estimate of equipment requirements for immunisation programmes to develop an efficient stock and management system. This system should guarantee minimum stock levels for the supply and distribution of injection equipment. Table 6 shows a three year estimate of equipment supplies needed for the composite for DTP-HepB-Hib vaccine (Diphtheria, Hepatitis B and *Haemophilus influenzae* type b) based on anticipated vaccine coverage of target children. The estimates for all vaccines can be tallied, and the total costs and storage space requirements estimated. Waste disposal systems can be on-site or at a centralised location with coordinated disposal schedules, and the choice of type of equipment dictated by available resources. A budget is developed; estimating the yearly costs of injection equipment, waste disposal systems, maintenance and operation costs, personnel training, program evaluation and monitoring. Such a budget is important for the allocation of public healthcare resources as well as obtaining external funding.

Table 6: Example calculation of supplies needed for DTP-HepB-Hib vaccine⁶⁵

Calculations	2002	2003	2004
a) Total number of children under one year	871 983	894 654	917 915
b) Anticipated coverage	80%	80%	80%
c) No. of children targeted for vaccination (a x b)	697 586	715 723	734 332
d) Doses per child	3	3	3
e) Wastage factor	1.32	1.30	1.18
f) No. of doses required (c x d x e)	2 762 441	2 791 320	2 599 535
g) Doses buffer stock (f x 25%*)	690 610	7220*	*
h) Total no. of doses (f + g)	3 453 051	2 798 539	2 599 535
i) Doses per vial	2	2	2
j) Total no. vials (h + i)	1 726 525	1 399 270	1 299 768
k) AD syringes [(c x d) + 10% wastage**]	2 302 034	2 361 886	2 423 296
l) AD syringes buffer stock (k x 25%*)	575 508	14 963*	15 352*
m) Total AD syringes (k + l)	2 877 542	2 376 849	2 438 648
n) Reconstitution syringe (disposable) [†] (j + 10%)	1 899 178	1 539 197	1 429 744
o) Safety boxes [(m + n) + 100] + 10%	52 544	43 077	42 552

On a regulatory level, monitoring and supervision procedures have to be established to ensure the implementation of safe injection practices by health workers, and provide adequate supplies and disposal facilities. It is also important to establish a system to monitor adverse

events to allow for appropriate follow-up action, especially in cases of device or vaccine recall. Post immunisation evaluations are also necessary to identify areas of improvement of injection safety and results made available to healthcare personnel for feedback.

The introduction of AD syringes in immunisation programmes has had a positive impact on improving vaccination coverage rates and injection safety in developing countries^{66,67}. In most cases, health workers indicated a preference for AD syringes as they minimised vaccine wastage, and were faster, easier to use and more accurate than conventional disposable syringes. However, one major constraint has been the price of auto-disable syringes with respect to conventional disposable and sterilisable syringes; when initially introduced AD syringes were priced about three times that of standard disposables.

Fortunately, the increased demand has attracted many manufacturers and suppliers and this competition has reduced the price of AD syringes to within \$0.01 that of conventional disposables⁶⁰. The UNICEF provides only AD syringes to countries requesting syringes, and as Figure 11 shows, there has been a steep increase in the number of syringes purchased through UNICEF. Nonetheless, it is also relevant to mention cases where use of auto-disable syringes can be substituted with sterilisable syringes when the former represents a significant budgetary burden to resource-limited areas. For example, in Madagascar, a mixed programme of introducing AD syringe use on non-routine immunisation days proved to be more beneficial in reducing cost and minimising logistical complications associated with frequent sterilisation⁶⁸.

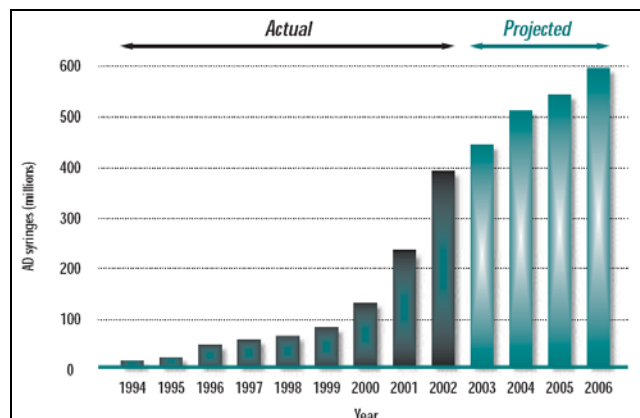


Figure 11: Actual and projected number of AD syringes purchased through UNICEF⁶⁵

4. Infectious Diseases

Infectious diseases in developing countries still pose a significant healthcare problem, these countries account for 95% of the world's disease burden⁶⁹. The leading causes of death are from lower respiratory infections, HIV/AIDS, diarrhoeal diseases, tuberculosis, malaria and tropical diseases. While most of these diseases are treatable, with improved access of drugs through drug campaigns, the lack of adequate and appropriate diagnostics often limits treatment of these diseases. Improved diagnostics are needed not only to confirm/rule out clinical diagnosis in symptomatic patients, but also to screen high risk individuals with asymptomatic diseases. For example, fetal death from congenital syphilis can be prevented if infected mothers are identified through serological antenatal screening and treated appropriately by the middle of the second trimester⁷⁰. The over treatment or over prescription of drugs through mass distribution with no confirmatory diagnosis has contributed to the increase in resistant micro-organisms, resulting in increased disease complexity and treatment costs of some diseases. For example, the overuse of the cheap anti-malarial chloroquine and increasing tuberculosis resistance has resulted in the shift towards more expensive class of compounds for treatment^{71,72}.

Identifying the testing resources and capabilities of healthcare systems is an essential step in establishing the user requirements for newly developed test methods which must be met in order to successfully implement these newly developed diagnostics. Assuming the centralised laboratory model found in developed countries is thus not applicable for test development in developing countries. Girosi *et al.* identified through literature search, three categories of resource distribution common to developing countries: no laboratory infrastructure, minimal infrastructure and moderate to advanced laboratory infrastructure⁷³. Table 7 summarises the characteristics of these three infrastructural levels based on the availability of electricity and clean water, physical infrastructure and staff.

These infrastructural characteristics impose constraints on test developers as they dictate the selection of the appropriate specimen types, biomarkers and the pathogen detection technique used. Settings with no-infrastructure thus represent the most challenging for diagnostic development, especially as rapid answer tests are desirable for immediate patient treatment. The unreliability of electricity and access to clean water and cold storage thus rules out the usage of many popular tests that would be adequate with these resources. Robust diagnostic tests that are

simple to use and require minimal expertise/training and meet the required test performance are preferable, as they can be applied to a broad range of settings.

Table 7: Health-care settings as defined by infrastructure categories⁷³

Characteristics	No Infrastructure	Minimal Infrastructure	Moderate Infrastructure	Advanced Infrastructure
Examples of actual locations	In the community or home	Health clinics (Africa), rural health clinic (Asian and Latin America)	Hospitals (Africa), urban health clinic (Asian and Latin America)	Hospitals (Latin America and Asia)
Electricity	Not available	Not reliably available	Available	Available
Clean water	Not available	Not reliably available	Available	Available
Physical Infrastructure	None	None or minimal laboratory	Poorly equipped laboratory	Well equipped laboratories
Staff	No expertise	Nurses (minimal expertise available)	Nurses, some physicians, poorly trained technicians	Nurses, physicians, well trained technicians

5. Diarrhoeal Infectious Diseases

5.1. Introduction

Diarrhoea is a manifestation of intestinal dysfunction that results in increased stool output with loss of water, electrolytes and/or nutrients. Infectious diarrhoea is due to an etiologic pathogen, often accompanied by additional symptoms such as nausea, abdominal cramps and vomiting. Infectious diarrhoeal diseases are the second leading cause of morbidity and mortality worldwide, with over 85% of cases in developing countries mainly due to areas poor environmental sanitation conditions⁷⁴. Children are the most susceptible to diarrhoeal infections, with over 1 billion diarrhoeal episodes and 2-2.5million deaths occurring in children younger than 5 years of age⁷⁵. Some common pathogens associated with infectious diarrhea are *Escherichia coli* (*E. coli*), *Shigella spp.*, *Salmonella spp* and *Vibrio cholerae*.

The major therapeutic intervention for diarrhoea consists of fluid and electrolyte therapy. The introduction of simple and cheap oral rehydration therapy solution (fluid containing of salts and glucose) in developing countries has contributed to the significant decrease in diarrhoeal associated deaths⁷⁶. In addition, is the control of diarrhoea through personal and general hygiene (e.g. washing hands), with access to clean water, clean food and appropriate sanitation facilities Antimicrobials are indicated for patients with select bacterial and protozoal pathogens⁷⁴. This is because most enteric infections are self limited and treatment might prove ineffective in some case. In addition, there is growing concern of drug resistance of major enteric pathogens like *Shigella spp* and *E. coli* due to unnecessary and excessive use of antimicrobials.

Diarrhoeal outbreaks can be controlled with proper diagnosis and rapid treatment through vaccination and syndromatic case management. Constant monitoring of pathogen susceptibility patterns is also important in selecting appropriate therapies when indicated. Assessment of stool characteristics is a key feature of identifying pathogens causing diarrhoeal. However, the standards used for diagnosis in developed countries (culture, enzyme immunoassay and PCR) are impractical, expensive and too slow for developing-world users. The need of a non-centralised, point-of-care solution that is rapid, low maintainance, easy to use and sensitive and accurate is important for management of disease. Figure 12 shows the development process of a new diagnostic from discovery research to test use.

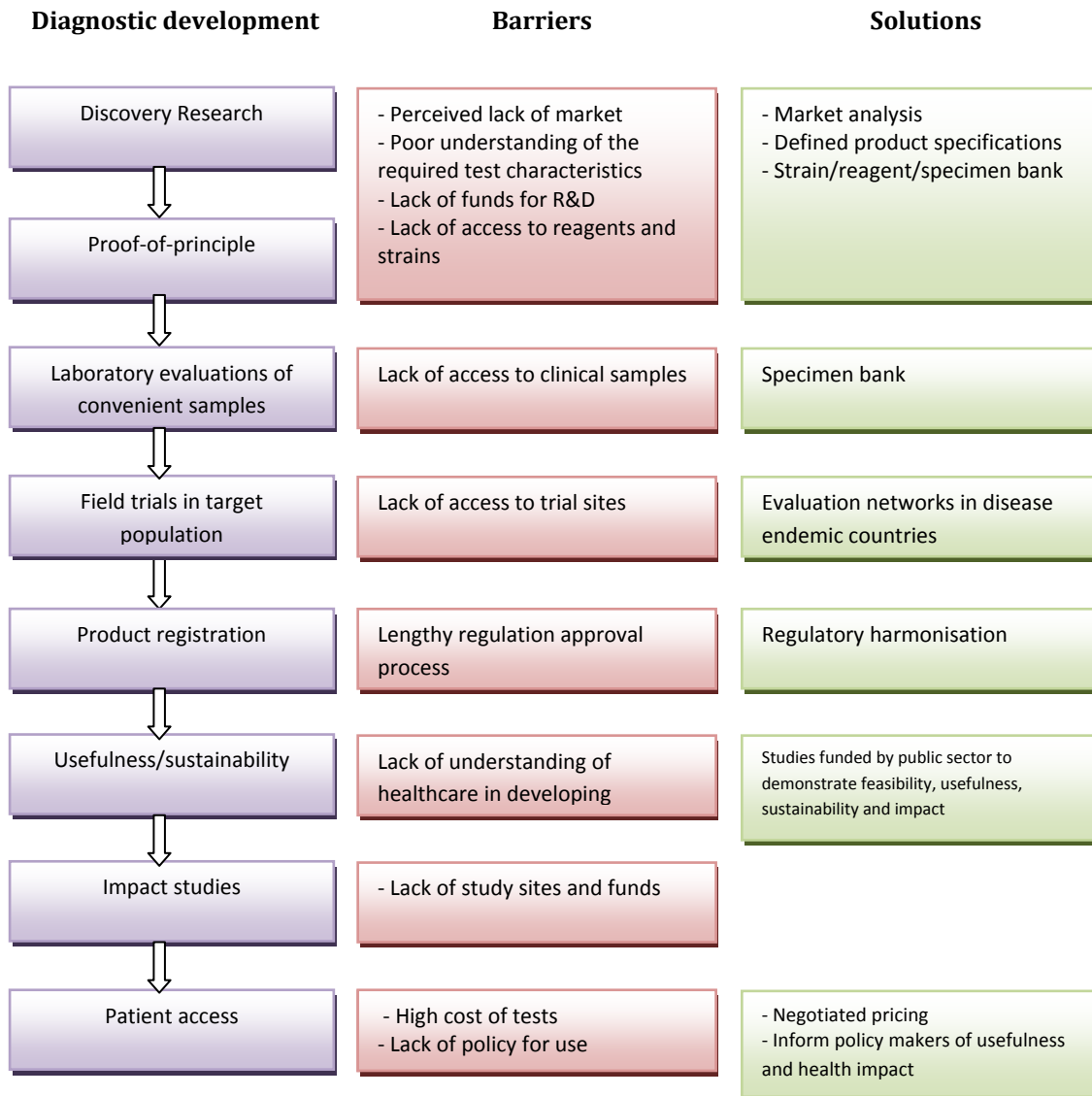


Figure 12: Diagnostic test development from research to test use: steps, barriers and solutions⁷⁷

5.2. Diagnostic Development

5.2.1. Research and Development Funding

Although the costs of diagnostic development are relatively cheaper than those for drugs, the lack of capital resources by most developing countries remains an important design constraint. Fortunately, the past few years has seen an increase in investment in designing healthcare technologies to address the specific needs and unique characteristics of the developing world. PATH HealthTech and the Lee's diagnostics development programme at the University

of Cambridge, UK are currently working on diagnostic development for developing countries market, with funding enabled through the Bill and Melinda Gates Foundation⁷⁸. Dr Paul Yager at the University of Washington is working in collaboration with PATH and other collaborators to develop in vitro diagnostics for developing countries. Funding for diagnostic development is also available through the US National Institute of Allergy and Infectious disease, though primarily motivated by biodefence concerns of the potential weaponisation of disease pathogens⁷⁸.

5.2.2. Market Analysis and User Requirements

As noted earlier, the successful implementation of diagnostics in the developing world is dependent on the ability to define and meet user requirements (see ASSURED method developed by WHO). PATH is mainly responsible for performing market analysis and evaluating user need assessments. The first task involves rationalizing the development of the diagnostic technology, by assessing the need and the health impact of the developed technology^{79,80}. This involves establishing the effect of a diagnostic tool on reducing the disease burden which requires disease-specific modeling of the status quo and changes that would occur upon introducing the new diagnostic in a certain setting. By estimating the percentage of the population that will have access to this new technology, the health impact can be determined using different health outcomes. The second task involves defining the user requirements which involves identifying their capabilities at the different levels of the healthcare systems, and estimating the patient's access these facilities.

Ricci *et al.* investigated the potential impact of a rapid diagnostic test to identify specific causes of acute diarrhea, especially in reducing stunting in children < 5years⁸¹. Recurrent diarrhoeal illnesses in these children have been shown to represent a risk in stunting, with *G. lamblia*, *C. parvum* and EAaggEC being the most implicated pathogens. Figure 13 illustrates the probability tree model they utilised for the introduction of a new diagnostic in comparison with the status quo. First, there is the probability that a child presenting with diarrhoeal symptoms will seek care, and this course of action usually depends on prevalence of the condition and severity. This individual seeking care will enter the health care system at different levels of the healthcare systems depending on accessibility. For the given test this will result in different test outcomes (true positive, false positive, false negative or true negative), with probabilities that depend on test characteristics and prevalence of the disease condition. Based on the test outcome, patient

will follow different treatment trajectories leading to one or more eventual health outcomes (see Appendix D for summary of model parameters).

In the ideal situation, children who have access to the new diagnostic and a health care provider that are tested positive for at least one pathogen receive a pathogen specific treatment and nutritional supplement. Those who test negative receive standard treatment which is typically oral rehydration therapy. Based on their analysis, Ricci *et al.* concluded that a test requiring minimal infrastructure that is 90% sensitive and 90% specific for each of the above pathogens can reduce stunting by 12.5% and save 2.8 million disability adjusted life years (DALY). This assumes a cost of treatment of \$6 and positive externalities associated with treatment equal to 0.25 DALYs.

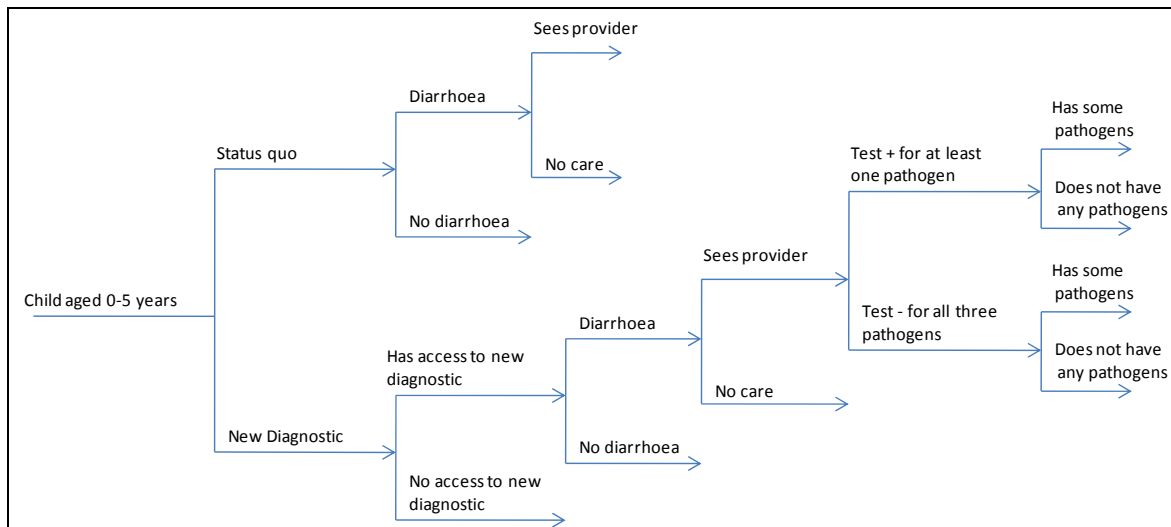


Figure 13: Probability tree for modelling diarrhoeal disease pathogens to reduce stunting in children⁸¹

The diagnostics test should be developed for use in settings with minimal infrastructure with limited staff as this allows for the flexibility of the device to be used in settings with more advanced infrastructure. The diagnostic test should be simple to operate, require little maintenance and withstand ambient temperature and dust. The non-reliability of electricity necessitates that hardware be battery-operated and the reaction procedure require minimal power. The cost of the disposable should be within a range \$1-\$5 and an inexpensive reader ranging from \$100-\$200. To reduce transportation issues, the device needs to be light-weight with little

to no fluids to add on to device bulk. Given the volatility of laboratory supplies, the reagents need to be incorporated in the device, preferably in dry form.

A qualitative test result is preferred as opposed to a quantitative one, with the availability of a print out of the results for health records. Faeces samples are preferred for the test; with biomarkers such as include organism antigen, host factor adhesion factors. There is also the promising innovative approach of using specific volatile organic compounds from vapour that emanates from the faeces in diarrhoea patients as a more user friendly approach to diagnostics. The specificity and sensitivity for the tests should both be greater than 90%. The results turnover time should be less than an hour to allow for same day treatment, as a more aggressive goal towards reducing the probability of patient leaving the testing site prior to treatment.

5.2.3. Diagnostic Methods for Diarrhoeal Infectious Diseases

5.2.3.1. Stool Analysis

Stool microscopy and culture is commonly used to identify microbial or parasitic infections. Stool can be collected in a bottle or using a rectal swab. A microscopic exam of the stool following can be done to examine its appearance or the presence of pus (e.g. increased leucocytes) or blood (e.g. red blood cells) as this can often indicate the presence of an invasive pathogen⁸². Gram stains can be used to reveal the presence of unique pathogens, where gram-positives stain blue with gram the stain. The gram negative bacteria don't retain the stain, and are thus counterstained with another colour. For example, *E. coli* (see Figure 14) and *Shigella* are both gram negative. The problem with the gram stain is that it can be inconclusive if the laboratory physician is not well trained to identify pathogens based on their morphology. The stool sample can be cultured for a few days, on differential or selective media that favour the growth of certain pathogens to isolate and identify specific pathogens.

5.2.3.2. Enzyme Immunoassay

When present in the body, microorganisms induce an immune response, whereby antibodies are produced to bind specifically to them and help in facilitating their elimination from the body. Enzyme Immunoassay (EIA) is based on antibody-antigen recognition (see Figure 15). A surface is coated with an antibody, which binds specifically to a diarrhoeal pathogen. An enzyme-labeled antibody that also binds to that same antigen is later introduced.

The enzyme attached to the second antibody catalyses the conversion of a reactant to a product, and this can be visualised by colour change. Hence, this provides a qualitative confirmation of the presence of a pathogen

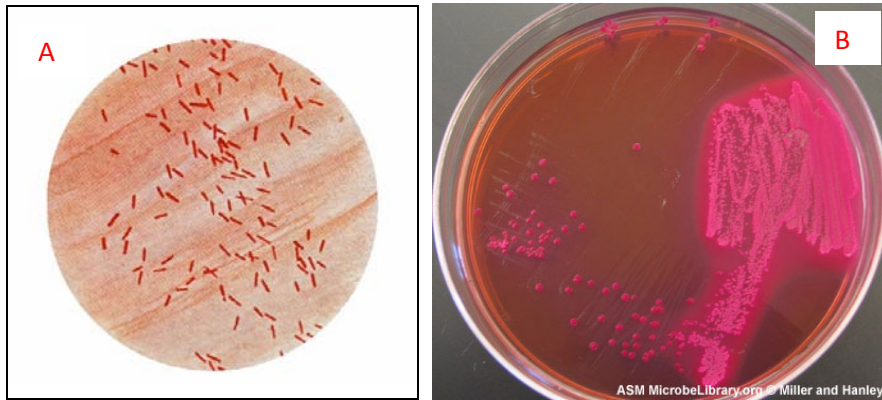


Figure 14: *E. Coli* Gram stain (a)⁸³ and culture (b)⁸⁴

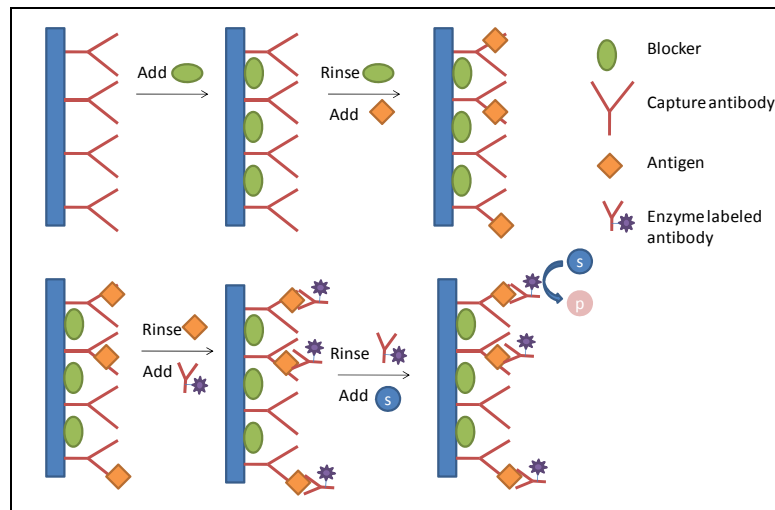


Figure 15: Enzyme Immunoassay Assay Principle⁸⁵

5.2.3.3. Polymerase Chain Reaction

The Polymerase Chain Reaction (PCR) is based on the ability of nucleic acids to bind to each other due to complementary pairing of their nucleotide sequences. The DNA or RNA of the

pathogen can be extracted, isolated and separated to single strands. Using a primer, an alternate nucleic acid strand can be synthesised in the presence of nucleotides, using a polymerase enzyme. This process requires an alternating temperature cycle, hence the need to control temperature during the reaction (e.g. using a thermocycler).

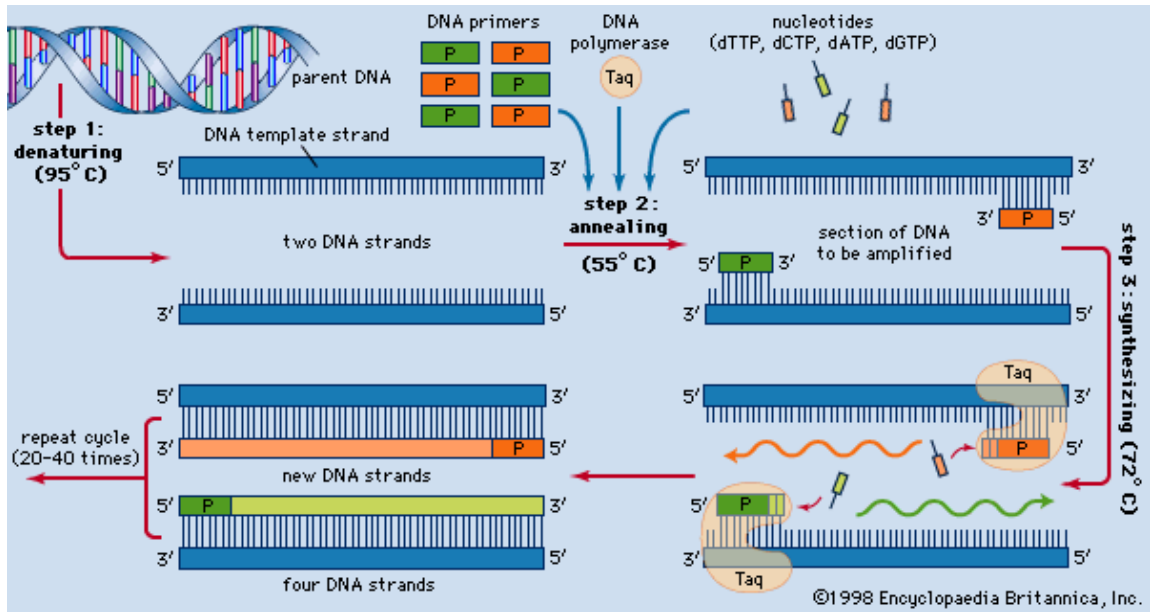


Figure 16: Polymerase Chain Reaction⁸⁶

5.2.3.4. Point of Care Diagnostics

Point-of-care (POC) diagnostics development is preferred as the short result turn over time allows for quicker patient treatment, limiting the amount of return visits by patients. POC tests offer the advantage of rapid visual results of antigen/antibody detection, cheaper production, use of minimal expertise and equipment⁸⁷. However, there is still the need for improved POC tests to meet the needs of these disease-endemic areas, due to the failure of some these tests to perform with adequate sensitivities in controlled clinical trials. The WHO developed a list of general characteristics as a framework for the development of appropriate diagnostic tests for resource-limited areas, abbreviated as ASSURED, that serves as a template for diagnostic development for developing countries (see Table 8).

Table 8: Characteristics of ideal diagnostic test for the developing world⁸⁸

- **A**ffordable by those at risk of infection
- **S**ensitive (few false negative results)
- **S**pecific (few false positive results)
- **U**ser-friendly (simple to perform by persons with little training)
- **R**apid treatment at the first visit, and robust without need for special storage
- **E**quipment-free (no large electricity dependent instrument needed to perform test, portable handheld battery operated devices acceptable)
- **D**elivered to those who need it

Nanotechnology has allowed for the miniaturisation of complex chemical reactions into small, self contained packages or lab-on-chip based platforms. Often described as the fluidic equivalent of electronic circuits, biomedical applications of micromechanical systems (BioMEMS) or microfluidics represent a promising diagnostic test platform especially as miniaturisation can offer faster response and simplification of analysis procedures. Dr. Paul Yager at the University of Washington in collaboration with PATH and other researchers are currently working on a “disposable with reader” diagnostic platform to simultaneously detect common enteric pathogens. This diagnostic assay comprises a credit-sized multiplex disposable enteric card with microfluidic circuit channels filled with chemicals/reagents needed for translating the stool/blood sample into a diagnosis. The sample is injected into the card and inserted into a hand-held instrument to control the card's temperature.

5.2.4. New Diagnostic Technology: BioMEMS

Stool culture requires the availability of well trained and supervised technologists and limited by the expenses for the supply of reagents, electricity and equipment maintenance. The time consuming nature of cultures (hours to several days) can often lead to patient impatience and the inability of the healthcare personnel to follow up treatment. Although EIA as on nucleic acid amplification techniques (NAAT) can be performed in few hours (e.g. 3-4 hours) and have more sensitivity and specificity, they generally require expensive specialised equipment. For example, PCR reactions require thermal cycling through alternative heating and cooling of samples in thermocyclers⁸⁹.

Microfluidics deals with the behavior, precise control and manipulation of fluids that are geometrically constrained to a small, diameter scale, typically < 1mm⁹⁰. One of the main

advantages of this platform is that the multiple steps of a chemical process can be integrated into a monolithic lab-on-chip disposable. The diagnostic platform thus consists of a credit-card sized disposable and an electronic instrument reader to control reaction (see Figure 17). The user inserts a swab containing the stool sample into the DEC which is placed in an instrument to control the reactions. The device can also incorporate on-chip control of thermo-pneumatic pumps, micro-heaters and temperature sensors, miniaturised fluorescence detectors, sample/analyte concentrators and filters.

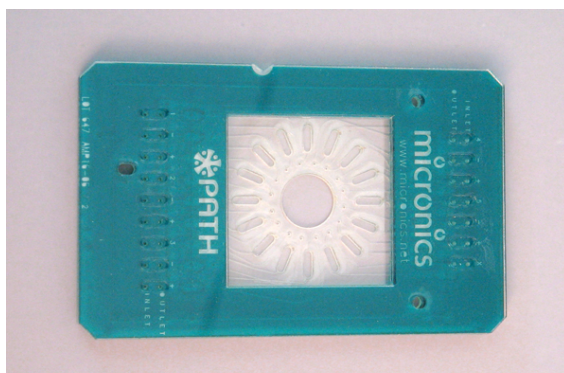


Figure 17: Disposable Enteric Card ⁹¹

The DEC is thus compatible with small sample/reagent size (50- 100 μ l) and multiple tests can be processed in parallel on a single chip, minimizing waste. This platform also provides for more precise, accurate and reproducible tests when compared to assays performed by hand as there is less liquid transfer error. This card includes four microfluidic subcircuits for organism capture and lysis from raw stool, nucleic-acid capture, multiplexed nucleic-acid amplification, and visual detection of amplified PCR products with display of results⁹². Figure 18 shows a schematic diagram of a laminated card showing the separate compartments for the reaction; the card includes silica filters and microfluidic valves to automate fluid movement in the device.

The sample is displaced via the microfluidics channels via a combination of capillary action and positive displacement pumping. Bacterial agents are identified via specific antigen capture by magnetic beads conjugated with selective antibodies from stool samples. 400 clinical samples of pathogenic stools infected with *E. coli* 0157, Shiga toxin-producing *E. coli* (STEC), *Shigella dysenteriae*, salmonella spp., and campylobacter spp. was collected by PATH and used

for product development⁹³. Information on the sample origins, how they are stored as well length of storage are important.

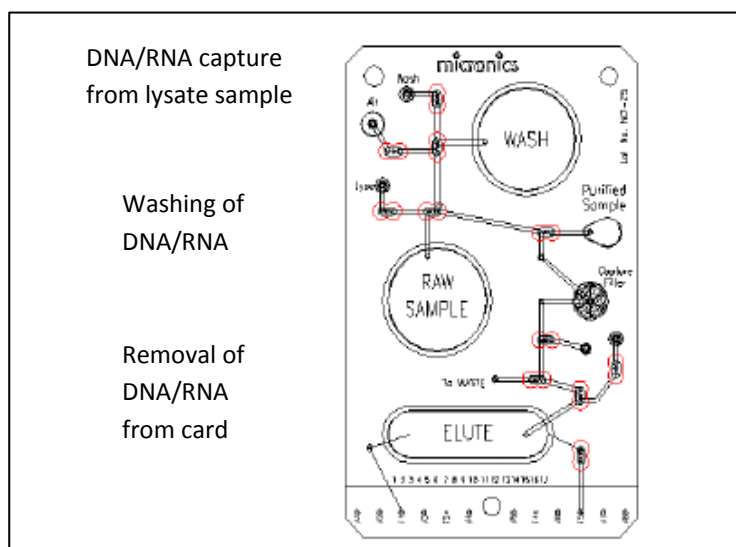


Figure 18: Schematic diagram of a disposable enteric card⁹⁴

After extracting nucleic acids from the pathogen, specific virulence genes are amplified for accurate identification. The device includes a positive and negative control to demonstrate proper sample processing and validate results. As shown in Figure 19, multiple enteric pathogens can be detected from the same stool sample using immunocapture. The complete reaction sequence will take less than 30 minutes. Early tests have shown that comparable sensitivity and specificity results to tests performed with conventional microbiological and PCR assays⁹⁵. The use of dry-reagent storage for this card has also been demonstrated whereby the activity of the reagents was retained upon re-suspension with water⁹⁴.

Another advantage of this platform is that it allows for low cost mass fabrication via rapid prototyping using CO₂ laser printing⁹⁶. The DEC's are manufactured by stacking polymeric sheets (4-12 sheets) that are individually designed via AutoCAD to create their 3-dimensionally architecture. Moving from CAD design to product can thus take less than 4 hours expedites laboratory testing

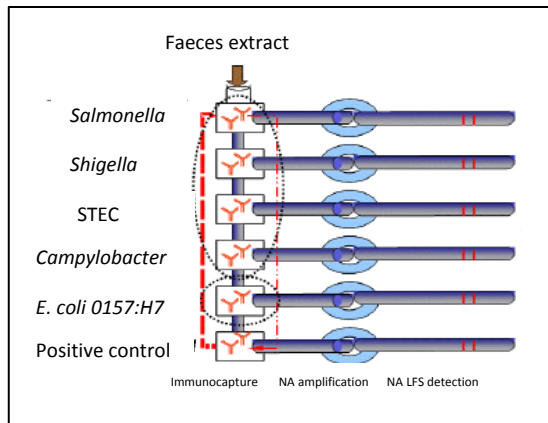


Figure 19: Parallel testing in a disposable enteric card⁹⁴

5.2.5. Evaluation Trials

5.2.5.1. Evaluation Study Design

It is not uncommon for diagnostic test to perform below their performance characteristics in clinical settings. Following laboratory proof-of-principle testing, are field trials to evaluate the performance of the developed diagnostic. This enables the diagnostic to be tested in a real-world setting, which in addition to testing specificity, sensitivity and reproducibility, also incorporates additional such as human factors (e.g. user friendliness, proper use), healthcare infrastructure and climate. These external factors can significantly affect the diagnostic test performance.

Evaluation of the diagnostics in settings generally includes two phases: a series of small case control designs with a minimum of 100 patients in each series, followed by a more large scale prospective study with a minimum of 300 subjects to validate test results. The important elements in designing an evaluation protocol include^{97,98}:

- **Defining the need for a trial and trial objectives**

The evaluation protocol should state a rationale for the evaluation and the objective of the study. This includes identifying a problem e.g. the need for a rapid screening to distinguish between infectious and non infectious diarrhoea in patient that present with symptoms to enable same day treatment of patient.

- **Study Site**
 This includes a description of the local diarrheal epidemiology (causative species, endemicity and most affected age groups), climate condition and workplace conditions at site. In addition, a description of the type of clinical setting and the type of staff available at each setting
- **Study Population**
 The target population for use of the diagnostic test should be clearly defined, taking into account the test purpose e.g. replacement for an existing test. The diagnostics test should generally be accessible and affordable to this population, if not the evaluation is deemed pointless.
- **Recruitment process**
 There are generally two circumstances under which individuals that will be recruited during the prospective studies of diagnostic evaluation: screening for individuals presenting with diarrheal symptoms patients or distinguishing between infected and non-infected individuals of the population, irrespective of visibility of symptoms. In the former, this enables the dispensation of the proper intervention by identifying the pathogen. The later is generally used for drug-resistant disease surveillance in monitoring susceptibility patterns of diarrheal pathogens. Participants must have informed consent, and consent forms have to be clear, concise, and in a language understandable to the patient. Patient information collected should include sex, age, duration of illness, previous diarrheal history and onset of symptoms.
- **Test under evaluation**
 This includes a record of details of the test being evaluated: manufacturer, batch number, date of manufacture, packaging type and inclusion of dessicant etc.
- **Reference Standard**
 Stool samples collected from consenting patients from either bulk stool or a rectal swab. A reference standard with high specificity and sensitivity is used in conjunction with newly developed diagnostic test for comparison. For diarrheal infections this is typically a stool microbiology analysis and bacteriological culture^{99, 100, 101}.
- **Test Organisation**
 The testing protocol should be developed, based on the individuals who will administer the test. This includes the necessary qualification and a description of training if required.

The characteristics of the diagnostic test evaluated are summarised in Table 9.

Table 9: Test characteristics evaluated for diagnostic testing¹⁰²

Characteristics	
Test performance	<ul style="list-style-type: none"> • Test sensitivity, specificity • Positive and negative predictive values
Ease of use	<ul style="list-style-type: none"> • Number of processing steps for device use • Need for accurate timing • Amount of user training required
Conditions of use	<ul style="list-style-type: none"> • Climate conditions
Conditions of storage	<ul style="list-style-type: none"> • Storage temperatures • Effect on test accuracy
Shelf life	<ul style="list-style-type: none"> • Shelf life length • Supply chain and expiry date

5.2.5.2. Recording, Analysing and Interpreting Evaluation Results

Results from the reference standard and new diagnostic test should be recorded separately to ensure independent interpretation of results, with double data entry to minimise error. Both results can then be compiled in a spreadsheet using information on a limited set of variables. Statistical tools are used to quantify test performance. As stated earlier, diarrheal diagnostic test for developing countries should have a specificity and sensitivity greater than 90%. A 2x2 table is used to evaluate test performance based on classification of samples results from both tests to calculate test sensitivity and specificity.

Table 10: 2x2 table to evaluate test performance¹⁰³

Test under evaluation	Reference Standard Test	
	Positive	Negative
Positive	TP	FP
Negative	FN	TN

TP= Sensitivity (Pretest Probability)
 FP= (1-Specificity) (1-Pretest Probability)
 FN= (1-Sensitivity) (Pretest Probability)
 TN= (Specify) (1-Pretest Probability)

$$\text{Sensitivity} = \frac{\frac{\text{\#of_diseased_patients}}{\text{with_with_positive_test}}}{\text{\#of_diseased_patients}} = \frac{TP}{TP + FN}$$

$$\text{Specificity} = \frac{\frac{\text{\#of_nondiseased_patients}}{\text{with_with_negative_test}}}{\text{\#of_nondiseased_patients}} = \frac{TN}{TN + FP}$$

However, it is important to note the effect of sample size on test these two characteristics as increasing sample size often reduces these estimates. Thus the inclusion of a 95% confidence interval (i.e. a 95% confidence that the interval contains true values of sensitivity and specificity) calculated using the formula below:

$$95\% \text{ confidence_interval} = p \pm 1.96 \sqrt{\frac{p(1-p)}{n}}$$

Where p=sensitivity (specificity measure) measured as a proportion, n=number or infected people (or specificity, from uninfected people)

5.2.6. Cost Analysis

The recurrent cost associated with diagnostics cannot be ignored due to their short lifecycle. It is also important to demonstrate especially to the local government and public health care sector that the impact of a newly introduced diagnostics is substantial with absorbable costs, especially if alternative already exists. This cost analysis can be calculated via three methods¹⁰⁴:

- A **cost analysis** that calculates total expenses incurred for use of the new diagnostic test including personnel, facilities, overhead, equipment, sample collection and reagents
- A **cost benefit analysis** that calculates the net cost i.e. cost of a correct diagnosis – benefits from reaching correct diagnosis. These benefits which include averted treatment costs, averted losses due to illness, and less tangible costs (e.g. reduced patient pain and suffering) are assigned a monetary value.
- A **cost-effectiveness analysis** which calculated the cost of a diagnostic and compares it to a resulting health outcome e.g. deaths or illnesses averted, DALYS

saved etc. Results from both the new diagnostic and reference standard can be compared.

5.3. Challenges to Enteric Diagnostic Test Development

5.3.1. Regulatory Standards and Guidelines

Potential diagnostic failures include incorrect medical decision and action due to inaccurate results, device malfunction, erroneous results due to environmental effects, or non-indicated use²⁵. This can be due to either to product defect, design defect, product misuse or user negligence²⁵. The lack of regulatory standards for diagnostic tests in the developing world is another major constraint in diagnostics development. As a result, developing countries are often susceptible to purchase poor performance tests especially as there is no formal evaluation of their performance and effectiveness or submission of clinical trial data. A recent 2001 global survey by WHO revealed that more than half of its 191 member countries reported no regulations for in vitro diagnostics, with most countries being from the developing world¹⁰². Even when mandated, there is the lack of national and international clinical trial guidelines for diseases prevalent in developing countries. Previous standards established by the US Food and Drugs Administration (FDA) and the European Union are not applicable for use in developing countries. Peeling *et al.* note that plans for international standards for regulatory approval of diagnostics in developing countries are still in the distant future¹⁰².

5.3.2. Accessibility to Tests

The collaboration between public healthcare sector and commercial enterprises is important in ensuring affordable costs and the sustainable supply of high quality diagnostics in developing countries. As noted earlier, suppliers will be attracted to markets where there is perceived and guaranteed demand for their products i.e. the consumers' willingness and ability to buy, despite the need of diagnostic technologies designed for developing countries. The commercial appeal of a product is also improved, if it can be applicable to both developing and developed countries.

PATH works in collaboration with companies to help them lower risk of introducing new health technology products by recognizing the capitalistic profit-making sensibilities of

diagnostic device manufactures especially in these deemed unattractive markets¹⁰⁵. The organisation also partners with public-sector organisations to guarantee product demand by conducting market studies on users' need and exploring potential manufacturing and distribution options. As such, affordable pricing can be negotiated to improve accessibility to resource-poor end users. Also, developing countries can purchase health care products through third parties such as the United Nations Population Fund which relies on technology assessments carried out by the WHO⁹¹.

6. Conclusion

6.1. Diagnostic Tests Development for Diarrheal Infections

The development of appropriate diagnostic technologies for diarrhoeal infections is important for disease case finding and management as well as for improved disease surveillance. The key attributes for the successful development of microfluidics diagnostic for diarrheal infections include:

- **Education on health issues:** A high perceived need for the test with demonstrated feasibility, usefulness, sustainability and positive health impact to the public sector
- **Cost of technology:** The cost of the disposable should be within a range \$1-\$5 and an inexpensive electronic reader ranging from \$100-\$200
- **Degree of accuracy:** Test specificity and sensitivity for the tests greater than 90%. Faeces samples, biomarkers such as organism antigen and volatile organics and dry form reagents
- **Quality control:** Reproducible chip performance using an on chip calibrator
- **User friendliness:** Developed for healthcare settings with minimal infrastructure, with a user interface that requires minimal user training and maintenance. A qualitative display of results with the availability of a print read out
- **Result turnover time:** <1 hour to allow for same day treatment
- **Test performance in various setting/ operational conditions:** The ability to withstand harsh climatic conditions with preference to preference to heat stable reagents and moist proof packaging, battery operation requiring minimal power consumption
- **Regulation:** The establishment of a regulatory body for pre-market, in-market and post market surveillance to guarantee the availability of quality products and their safe and effective use of products
- **Accessibility:** The establishment of network for adequate distribution and supply of products
- Availability of successful diarrhea therapies

6.2. Medical Device Development for Developing Countries

The reliance of developing countries on imported medical devices has had a significant negative impact on their healthcare systems, due to the inability of these devices to be properly integrated and diffused within these systems. Most medical devices assume well functional health infrastructure and supporting systems. In addition, the high costs of purchasing and maintaining medical devices can stretch the resource-limited budgets of the public sector as it tries to offer comprehensive healthcare services to a majority of the population. Making cost-effective and informed procurement decisions, based on the ability to sustain the devices in the long term is thus imperative. It has been demonstrated that one approach of introducing sustainable technologies in developing countries is for the public health sector to define the need and guarantee demand, as this offers incentive of return of investment for manufacturers. This public-private sector partnership provides the opportunity for risk-sharing especially as manufacturers enter these new markets.

Adapting or developing new technologies for developing countries requires a significant amount of investment that may be unaffordable to most developing countries. The role of external funding from private organisations, foreign governments and non-profit organisation in this development process is thus important. Donour interest in a new technology is motivated if there is clear demonstration of the need of a technology and that its introduction and diffusion will be sustainable and derive significant benefits in improving healthcare outcomes. A need-assessment of the population is thus imperative to estimate potential impact of the technology and establish and define performance characteristics based on the capabilities of their healthcare systems. As such, the device user is involved in the development process and enables testing and better refinement of the desired device characteristics. Following prototype development, are field evaluation trials to demonstrate the intended performance and adequate use of the device within the developing country setting.

Sustaining technology is not only dependent on its acceptance and mainstreaming by the public sector but also on the availability of adequate supplies through distribution networks. Third parties such as the WHO or PATH can serve as a bridge between developing countries and medical device suppliers, especially in negotiating affordable pricings. The existence of a strong regulatory body is thus necessary to guarantee the purchase of quality medical products as well as to ensure their safe and effective use through the implementation of good management

practices, user training and post-market monitoring. Ultimately, by building on their research and development capabilities, developing countries can one day be able to meet their medical device needs by acquiring of operational capabilities through proactive technology transfer, to duplicate and adapt technology to fit their local conditions.

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APPENDICES

Appendix A

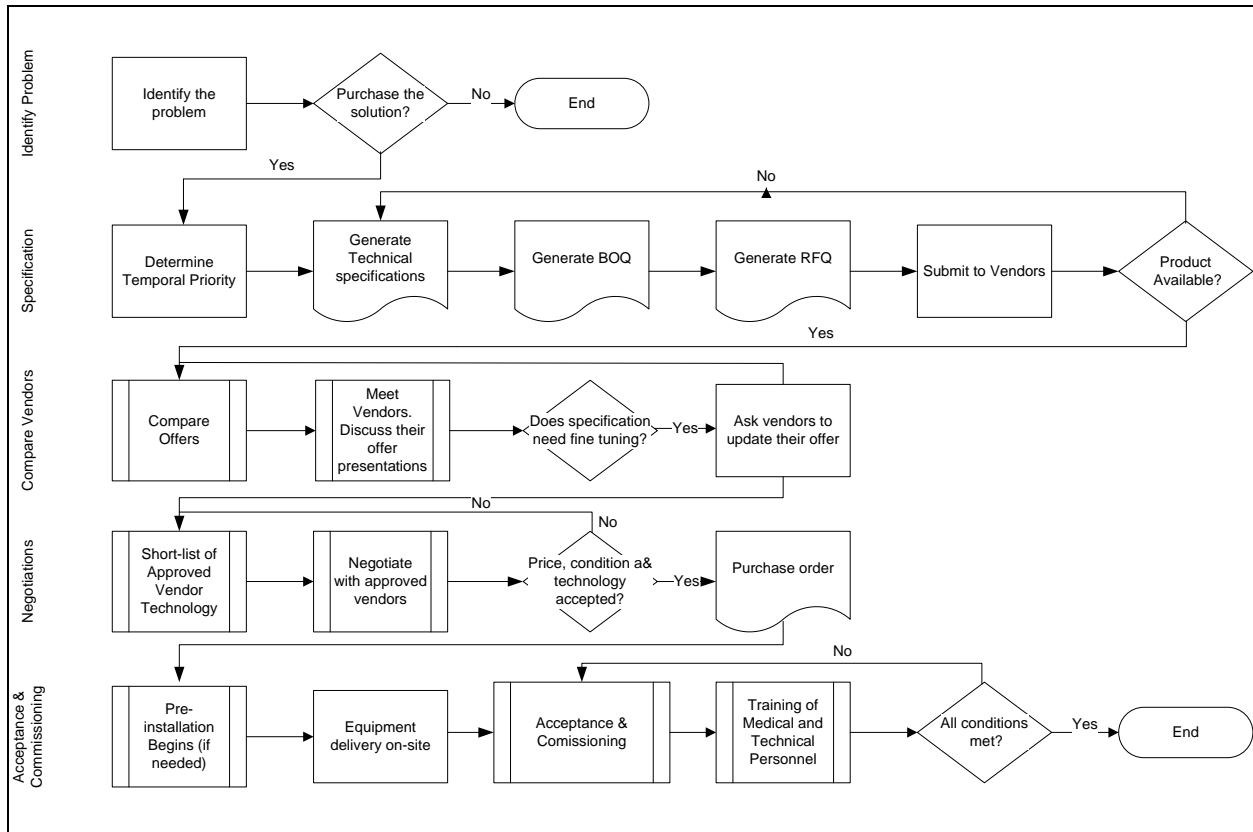


Figure 20: Medical Device Acquisition Flow Chart¹⁴

Appendix B

Table 12: Human Development Report 2007 Data

HDI rank	HDI value 2005	Life expectancy at birth, annual estimates (years) 2005 ^a	GDP per capita (PPP US\$) 2005	Public expenditure on health (% of GDP) 2004	Private expenditure on health (% of GDP) 2004	Health expenditure per capita (PPP US\$) 2004	
High Human Development							
3	Australia	0.962	80.9	31,794	6.5	3.1	3,123
11	Finland	0.952	78.9	32,153	5.7	1.7	2,203
12	United States	0.951	77.9	41,890 ^b	6.9	8.5	6,096
16	United Kingdom	0.946	79.0	33,238	7.0	1.1	2,560
17	Belgium	0.946	78.8	32,119	6.9	2.8	3,133
21	Hong Kong, China (SAR)	0.937	81.9	34,833
35	Qatar	0.875	75.0	27,664 ^{c, d}	1.8	0.6	688
46	Uruguay	0.852	75.9	9,962	3.6	4.6	784
52	Mexico	0.829	75.6	10,751	3.0	3.5	655
61	Saudi Arabia	0.812	72.2	15,711 ^e	2.5	0.8	601
65	Mauritius	0.804	72.4	12,715	2.4	1.9	516
70	Brazil	0.800	71.7	8,402	4.8	4.0	1,520
Medium Human Development							
75	Colombia	0.791	72.3	7,304 ^e	6.7	1.1	570
83	Armenia	0.775	71.7	4,945	1.4	4.0	226
86	Jordan	0.773	71.9	5,530	4.7 ^f	5.1 ^f	502
90	Philippines	0.771	71.0	5,137	1.4	2.0	203

112	Egypt	0.708	70.7	4,337	2.2	3.7	258
115	Honduras	0.700	69.4	3,430 ^e	4.0	3.2	197
118	Guatemala	0.689	69.7	4,568 ^e	2.3	3.4	256
128	India	0.619	63.7	3,452 ^e	0.9	4.1	91
130	Lao People's Democratic Republic	0.601	63.2	2,039	0.8	3.1	74
135	Ghana	0.553	59.1	2,480 ^e	2.8	3.9	95
142	Nepal	0.534	62.6	1,550	1.5	4.1	71
143	Madagascar	0.533	58.4	923	1.8	1.2	29
144	Cameroon	0.532	49.8	2,299	1.5	3.7	83
147	Sudan	0.526	57.4	2,083 ^e	1.5	2.6	54
Low Human Development							
169	Ethiopia	0.406	51.8	1,055 ^e	2.7	2.6	21
170	Chad	0.388	50.4	1,427 ^e	1.5	2.7	42
174	Niger	0.374	55.8	781 ^e	2.2	2.0	26

Notes:

a. The HDI rank is determined using HDI values to the sixth decimal point.

b. For purposes of calculating the HDI, a value of 40,000 (PPP US\$) was applied.

c. Data refer to a year other than that specified.

d. Heston, Alan, Robert Summers, and Bettina Aten. 2006. "Penn World Table Version 6.2." University of Pennsylvania, Center for International Comparisons of Production, Income and Prices, Philadelphia. [<http://pwt.econ.upenn.edu/>]. Accessed June 2007. Data differ from the standard definition.

e. World Bank estimate based on regression.

f. Data refer to a year or period other than that specified, differ from the standard definition or refer to only part of a country.

Source:

column 1: calculated on the basis of data in columns 6-8; see Technical note 1 for details.

column 2: UN (United Nations). 2007e. World Population Prospects 1950-2050: The 2006 Revision. Database. Department of Economic and Social Affairs, Population Division. New York. Accessed July 2007, unless otherwise specified.

column 3: World Bank. 2007b. World Development Indicators 2007. CD-ROM. Washington, D.C., unless otherwise specified; aggregates calculated for HDRO by the World Bank.

column 4: World Bank. 2007b. World Development Indicators 2007. CD-ROM. Washington, D.C.

column 5: World Bank. 2007b. World Development Indicators 2007. CD-ROM. Washington, D.C.

column 6: WHO (World Health Organization). 2007a. Core Health Indicators 2007 Database. Geneva. [<http://www.who.int/whosis/database/>]. Accessed July 2007.

Appendix C

Unsafe Injection Practices⁵⁷

- Inappropriate and overuse of injectable medications
- Reusing disposable needles and syringes
- Loading syringes with multiple doses and injecting in many people consecutively
- Using one syringe for many patients without changing the needle for each patient (a practice used in some childhood immunisation programs)
- Using multi-dose vials pierced with a single drawing-up needle
- Flaming needles between patients
- Re-capping needles
- Flushing needles and/or syringes with disinfectant or water to clean them after use or between patients
- Not discarding the needle immediately after use at the place of use
- Leaving contaminated sharps to be disposed of by someone other than the user
- Separating the needle from the syringe prior to disposal
- Bending the needle after use to eliminate the risk of reuse
- Placing hands into containers of used needles for cleaning and sorting
- Soaking used needles and syringes in sodium hypochlorite solutions
- Inadequately monitored needle and syringe cleaning and sterilisation practices
- Sharpening needles for reuse
- Discarding needles and syringes into general waste systems
- Collecting used needles/syringes for resale

Appendix D

Table 13: Main model parameters for diarrhoeal diagnostic development ⁸¹

Parameter	Africa		Asia		Latin America	
	Base	Range	Base	Range	Base	Range
Epidemiology and prevalence						
Population aged <5 yrs (millions)	142		357		57	
Diarrhoea prevalence (3 month period)	96%	80-100%	84%	70-95%	82%	70-95%
Prevalence of <i>C. parvum</i>	4.4%	1.7-7.2%	4.8%	1.7-8%	7.8%	2.7-12.8%
Prevalence of <i>G. lamblia</i>	10.4%	3.7-17.2%	7.7%	2.7-12.8%	16.7%	5.9-27.6%
Prevalence of <i>C. EAggEC</i>	20%	10-30%	20%	10-30%	20%	10-30%
Average stunting prevalence (aged <5yrs)	34.5%	31.7-37.4%	25.7%	22.5-28.9%	11.8%	7-17%
# of stunted children aged < 5yrs (millions)	48.5		92.4		6.5	
Healthcare access						
Proportion of children with diarrhoea visiting health facility	31%	20-40%	49%	35-65%	32%	20-40%
Healthcare outcomes						
Efficacy of treatment	50%	25-75%	50%	25-75%	50%	25-75%
Differential risk of stunting for children with diarrhoea	3	1.5-4.5	3	1.5-4.5	3	1.5-4.5

