GLOBAL HEALTH

FOOD SECURITY &

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HUMAN RIGHTS

EDUCATION

DIGITAL

INCLUSION

50 BREAKTHROUGHS

CRITICAL SCIENTIFIC AND TECHNOLOGICAL ADVANCES NEEDED FOR SUSTAINABLE GLOBAL DEVELOPMENT

WATER SECURITY

ACCESS TO

ENERGY

RESILIENCE TO

GLOBAL CHANGE

GENDER EQUITY

EMERGING

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Please cite this work as follows: “Institute for Transformative Technologies (ITT), 2019. 50 Breakthroughs: Critical Scientific and Technological Advances Needed for Sustainable Global Development.”

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GLOBAL HEALTH

OVERVIEW

More than any other aspect of human development, health has benefited from scientific and technological breakthroughs.

Unfortunately, many of these breakthroughs have not reached the people most in need at the scale and form that are required. People living in tropical countries—particularly in South Asia and sub-Saharan Africa—are exposed to a far greater array of health hazards than those living in other regions. By implication, these populations need access to the most powerful solutions. Yet, they have the least access to such solutions.

The focus of this chapter is global health, which aims to ensure adequate health care for underserved populations. While overall health outcomes in low- and middle- income countries (LMICs) have improved over the past three decades, they lag the rest of the world in virtually every single health outcome metric (**Exhibit 1**).

Life expectancy in sub-Saharan Africa is now 60 years, substantially lower than the global average of 72 years (World Bank, 2016). Life expectancy in South Asia is 69 years, and in high-income countries is 80 years.

The maternal mortality ratio in sub-Saharan Africa is 547 (out of every 100,000 women giving birth), compared with 182 in South Asia, 13 in high-income countries and a global average of 216 (World Bank, 2015). Mortality of children under 5 in sub-Saharan Africa is 76 (out of every 1,000 children born live), compared to 45 in South Asia, 5 in high-income countries and 39 around the world (World Bank, 2017).

In sub-Saharan Africa and South Asia, 34.1 percent and 35.0 percent of children, respectively, suffer from stunting, compared with 22.2 percent globally and a negligible number in high-income countries (World Bank, 2017).

Importantly, non-communicable diseases (NCDs) like diabetes, cardiovascular disease and cancer, are on the rise in LMICs. In fact, these diseases already disproportionately affect people living in LMICs, compared with high-income countries. According to the WHO, 75 percent of the global deaths from non-communicable diseases today occur in LMICs.

These countries not only have the fastest increase in diabetes prevalence, but are also where more than 75 percent of all deaths from cardiovascular disease occur. NCDs are projected to cause an even higher disease burden in low- and middle- income countries within the next decade.

Health statistics in developing regions compared to global benchmarks

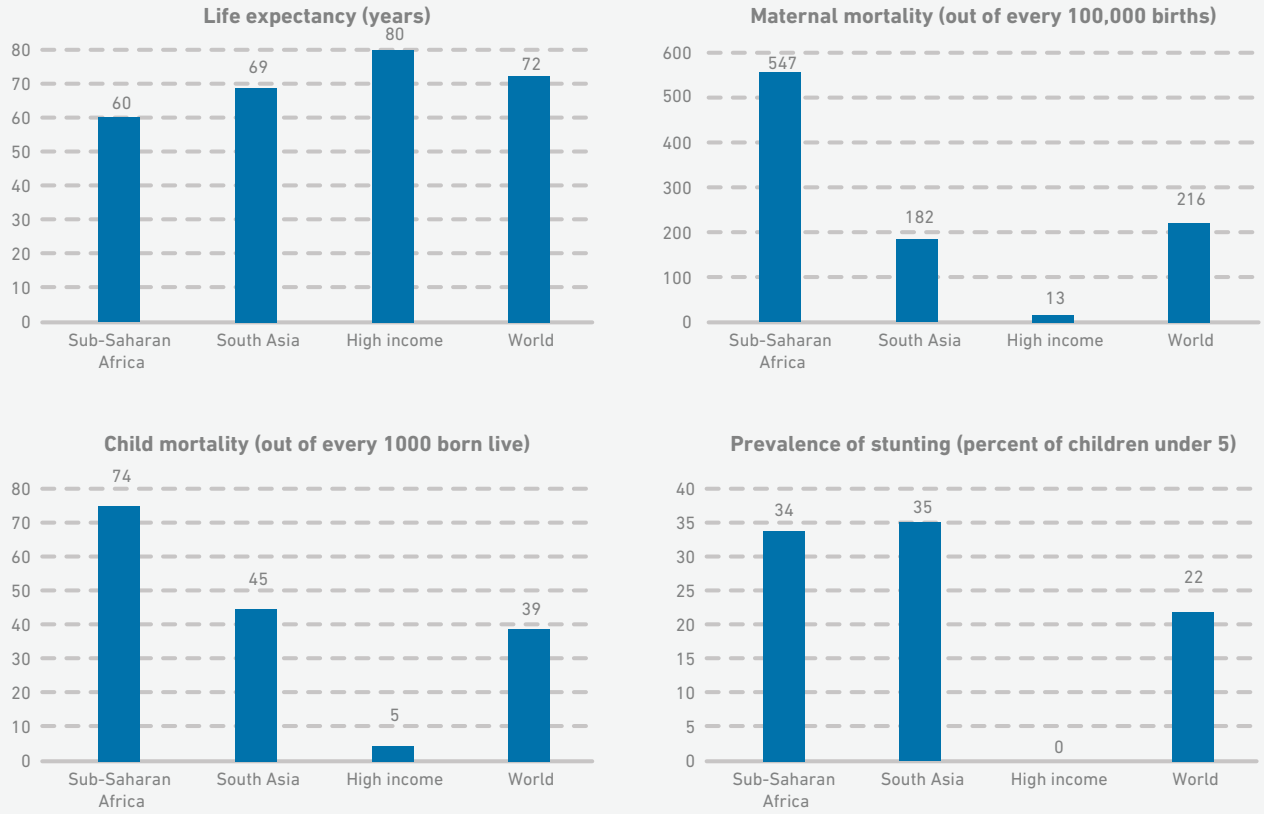

Exhibit 1: Countries in South Asia and sub-Saharan Africa have significantly worse health outcomes than their more industrialized counterparts and also fare poorly when compared with global averages. (Source: World Bank data for years 2015, 2016 and 2017)

Even as the causes of mortality vary by population segment and geography, a handful of conditions account for the majority of fatalities. As **Exhibit 2** shows, the leading causes of childhood mortality in sub-Saharan Africa are a host of neonatal conditions, malaria, diarrheal disease, and lower respiratory infections like pneumonia (IHME GBD, 2017).

In South Asia, malaria is not as significant a driver of childhood mortality; in percentage terms, neonatal conditions alone account for nearly as many deaths in South Asia as neonatal conditions and malaria deaths put together in sub-Saharan Africa.

For adult women in sub-Saharan Africa, the leading causes of mortality are HIV/AIDS, cardiovascular disease, lower respiratory infections and malaria, but in South Asia, HIV/AIDS and malaria are not as significant, instead NCDs are now the leading causes of death at an increasing rate.

Leading causes of mortality for key population segments in Sub-Saharan Africa and South Asia

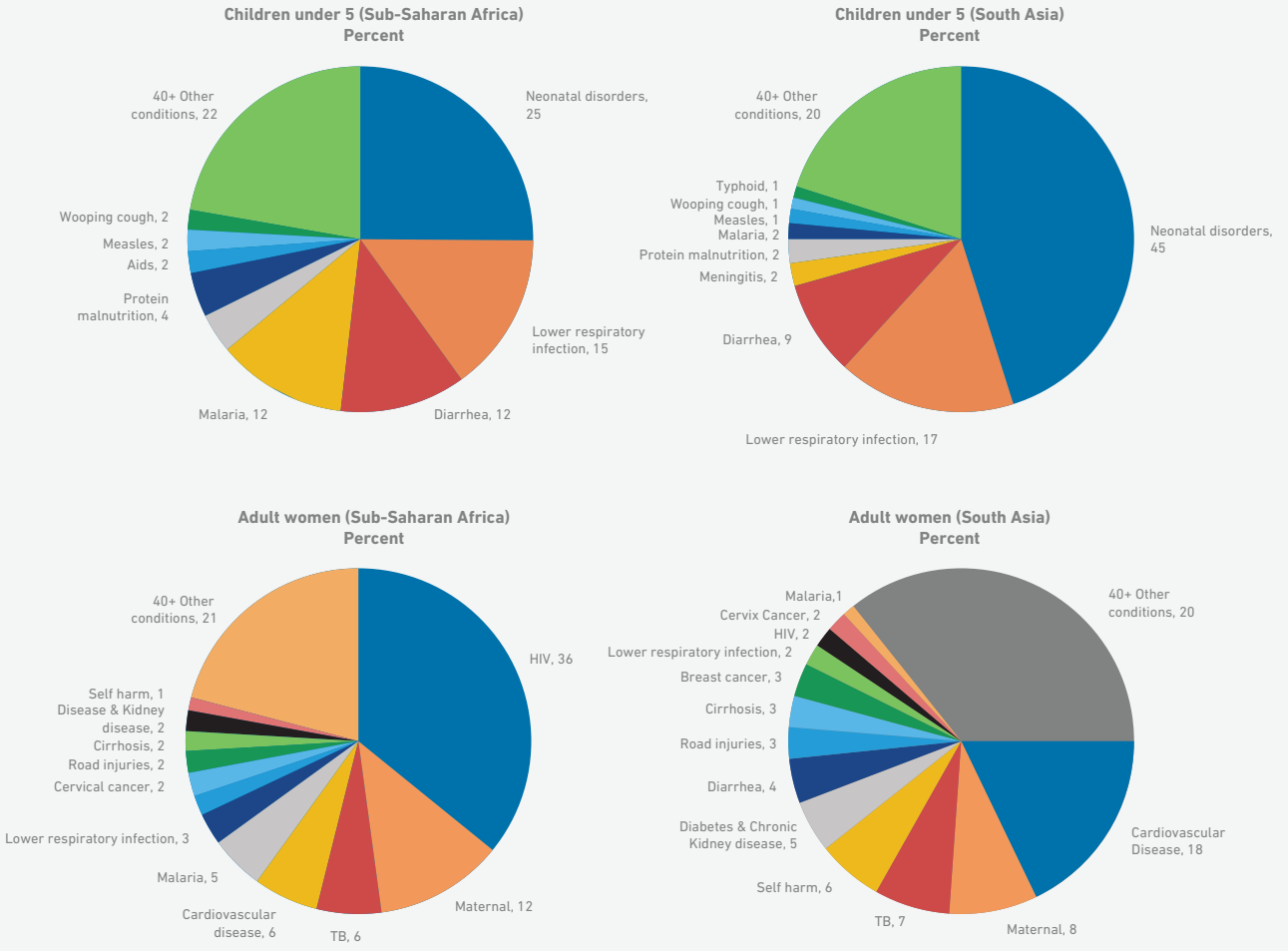

Exhibit 2: The leading causes of mortality are different for each population segment (for example, children versus women), with some differences between sub-Saharan Africa and South Asia. (Source: IHME GBD, 2017)

In addition to life expectancy and mortality, morbidity (the burden of disease on productivity and quality of life) is another valuable metric for understanding the state of health of national populations. Morbidity is measured in terms of disability-adjusted life-years (DALYs) lost.

A look at the leading causes of DALYs lost in South Asia and sub-Saharan Africa reveals that the indicators for children are not significantly different between deaths and DALYs, but the statistics for adult women show some meaningful differences.

This is primarily due to non-fatal conditions like mental/behavioral and musculoskeletal disorders, which cause a high disease burden (**Exhibit 3**).

Leading causes of DALYs lost in Sub-Saharan Africa and South Asia

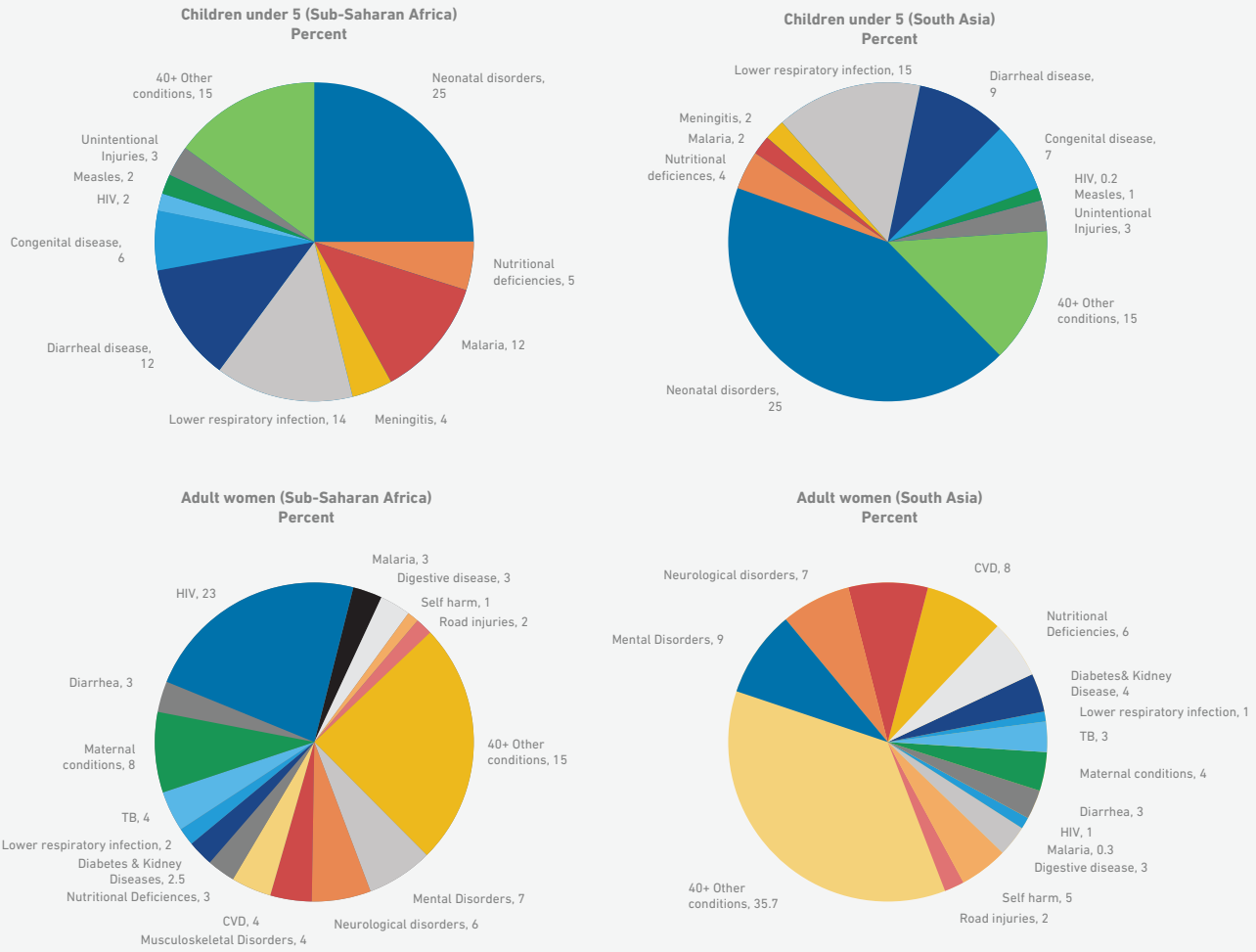

Exhibit 3: Analysis of disability-adjusted life-years (DALYs) shows that conditions like mental/behavioral and musculoskeletal disorders—while not leading to fatalities—cause a heavy disability burden among women. Among children, DALY statistics are similar to those for mortality. (Source: IHME GBD, 2017)

With these outcomes in mind, it is no surprise that indicators measuring the strength of health systems in sub-Saharan Africa and South Asia also lag behind substantially. **Exhibit 4** shows some of these indicators in South Asia and sub-Saharan Africa compared with high-income OECD countries and global averages.

Annual health expenditure per capita is $85 in sub-Saharan Africa and $58 in South Asia, compared with $4,875 in high-income countries, and an average of $1,002 globally (World Bank, 2014). As a combination of both public and private expenditure, this is a reflection how little public healthcare infrastructure there is in LMICs.

Crucially, households in LMICs—despite being considerably poorer than their high-income country counterparts—incur significantly higher per capita out-of-pocket healthcare expenditures; 36.3 percent of total healthcare expenditure in sub-Saharan Africa and 64.9 percent in South Asia is out- of-pocket, compared with less than 14 percent in high-income countries and 18.1 percent around the world.

Other signs of the sheer absence of adequate and dependable health systems is the lack of physical infrastructure and trained human resource. Across sub-Saharan Africa and South Asia, there are fewer than 0.2 physicians per 1,000 people in sub-Saharan Africa and 0.75 in South Asia.

High-income countries have 2.8 physicians for every 1,000 people, and the global average is 1.5. Similarly, there are 1.1 nurses and midwives per 1,000 people in sub-Saharan Africa, 1.7 in South Asia, 7.4 in high income countries and 3.1 around the world (World Bank, 2014).

Statistics on health systems in sub-Saharan Africa and South Asia

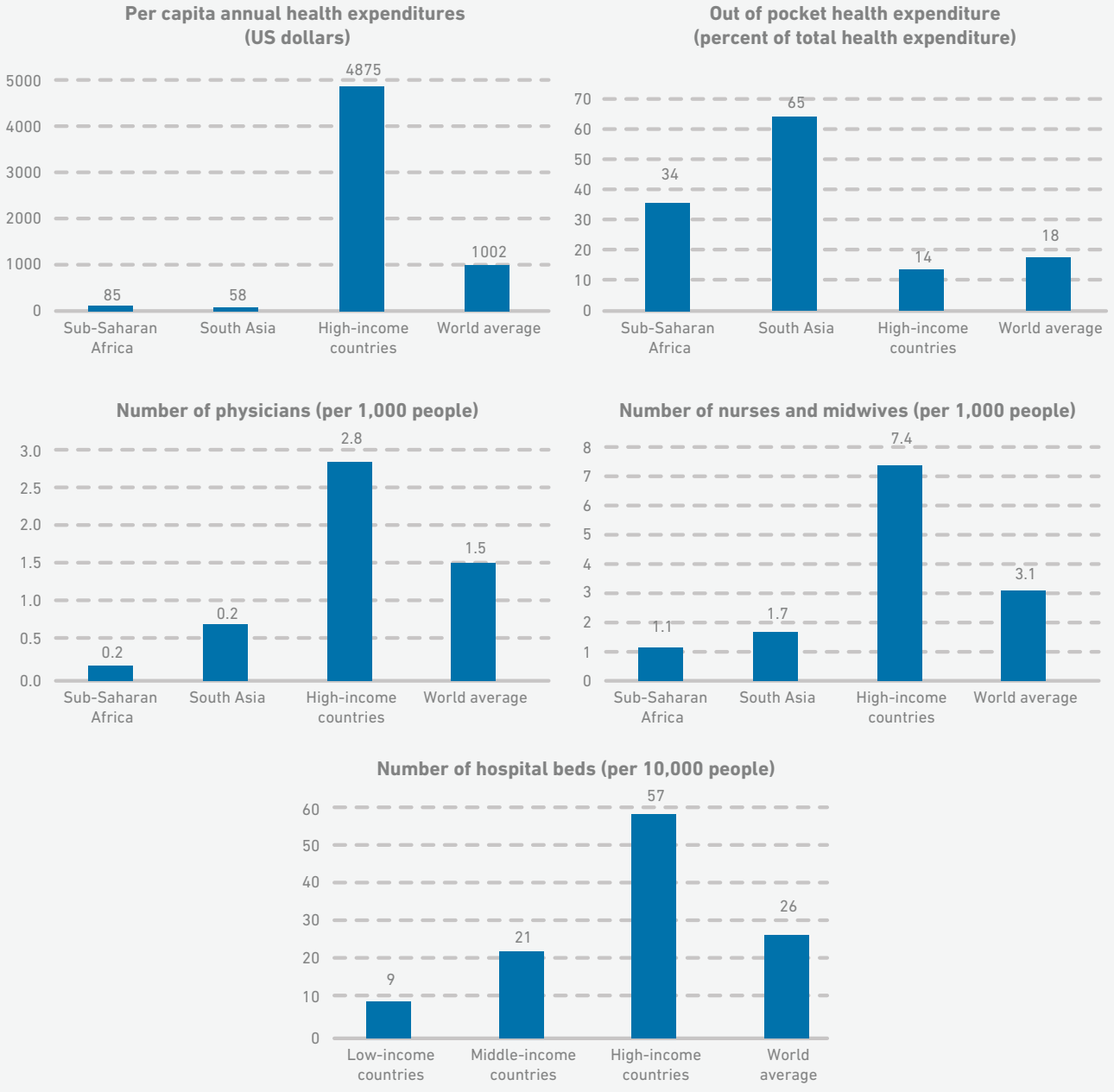

Exhibit 4: Healthcare systems in sub-Saharan Africa and South Asia, measured in terms of expenditure, human capital and access to care, lag significantly behind high income OECD countries and global averages. The challenges, deep-rooted and structural, are discussed in detail in our section on Healthcare Delivery. (Source: World Bank, 2014)

RECENT TRENDS IN GLOBAL HEALTH

As we analyze the role of technology in improving healthcare for low-income populations, the following six trends are important to consider.

Advances in diagnostic technology, Internet of Things (IoT) and data analytics are now redefining healthcare delivery systems in low-resource settings

Traditionally, healthcare delivery systems have been highly dependent on infrastructure and human resources. The past decade has seen the emergence of a new generation of low-cost medical devices which are more durable, less dependent on infrastructure, require less training to operate and are much less energy intensive.

As such, they are more appropriate for low-resource settings. Beyond diagnostics, sensors are being used to monitor cold chain supply networks to monitor and track the temperature at which vaccines are stored. Mobile-based thermal sensors record the temperatures in real time and a warning is issued to the responsible person if the temperatures exceed a threshold level.

IoT technologies are also being used to address immediate challenges in humanitarian response, such as the Ebola outbreak in West Africa. The United States Agency for International Development (USAID) has supported and employed IoT solutions via connected wearable technologies.

Sensor Technology and Analytics to Monitor, Predict and Protect Ebola Patients (or STAMP2) has been tested on Ebola patients in the United States and is being scaled up to meet the needs of government agencies, such as USAID for its Ebola treatment strategy in Liberia (ITU, 2016).

Combined with deep mobile network penetration and increasingly sophisticated data analytics, these new medical devices are laying the groundwork for effective task shifting of care delivery by local providers and for health systems to become much more decentralized. More information on other emerging technologies and their role in healthcare is in the Emerging Technologies chapter.

A number of gaps still exist in the understanding of the causes of major diseases

In recent years, science has made important advances in the understanding of diseases, particularly pertaining to issues such as the etiology of diarrheal diseases and pneumonia, the complex drivers of malnutrition and the long-term health impact of repeated exposure to diarrheal pathogens (beyond simply causing diarrheal disease).

Despite these advances, major gaps exist in the global health community's understanding of individual diseases, as well as the interaction effects of these diseases in the context of poverty. The knowledge gaps exist at a higher, epidemiological level (for example, the relative importance of various pathways to infection for diarrheal disease in rural versus urban areas), as well as at more fundamentally scientific level (such as the specific ways in which nutrition affects immunity from TB and other diseases).

Notwithstanding the gaps, these new findings already have significant implications on future research and development (like pathogen-specific vaccines for diarrheal diseases) and interventions designed to tackle major diseases, both at country and global levels.

A double burden of non-communicable (NCDs) and infectious diseases

In many LMICs, recent economic growth and the strengthening of healthcare systems have led to a reduction in the overall burden of infectious diseases. Higher life expectancy, along with demographic shifts like increasing urbanization, unhealthy diets and less physical activity, are leading to a surge in the incidence of non-communicable, chronic conditions like obesity, diabetes and cardiovascular disease. In India, for example, cardiovascular disease, followed by respiratory diseases, is now the leading killer of both men and women.

In most LMICs, healthcare systems were primarily focused on controlling infectious diseases and not NCDs. This double burden of disease (and in some countries, a changing burden of disease) seriously impacts their ability to combat the growing menace of these non-communicable diseases. In Sub-Saharan Africa, for example, for many types of cancer, the risk of getting cancer and the risk of dying from it are nearly the same, due to late stage diagnosis and lack of treatment (The Cancer Atlas, 2012).

Rising levels of antimicrobial resistance (AMR)

Antimicrobial resistance (AMR) is reaching dangerously high levels in all parts of the world, with some of the most common infections becoming difficult to treat (WHO, 2018). AMR occurs when germs, such as bacteria and fungi, develop the ability to defeat the drugs that are designed to kill them, making the drugs ineffective.

The term antibiotic resistance applies only to bacteria becoming resistant to antibiotics, while AMR is a broader term that encompasses resistance to drugs that treat infections caused by other microbes including parasites (such as malaria or helminths), viruses (such as HIV) and fungi (such as *Candida*). AMR does not mean the body becomes resistant to antimicrobials; instead, it means that microbes have become resistant to the drugs designed to kill them.

AMR is a serious and growing problem. At least 700,000 people die every year from drug-resistant strains of common bacterial infections, HIV, TB and malaria (O'Neill, et al., 2016). This number is projected to increase to 10 million lives each year by 2050 unless effective action is taken. Important examples of AMR include:

- Multidrug-resistant tuberculosis (MDR-TB) is a form of TB that is resistant to the two most powerful anti-TB drugs, and extensively drug-resistant tuberculosis (XDR-TB) is resistant to at least four of the core anti-TB drugs (see the Pulmonary Tuberculosis section for more details).
- The bacteria *E. coli* is gaining resistance to fluoroquinolone antibiotics, which are widely used to treat urinary tract infections.
- The common intestinal bacteria *Klebsiella pneumoniae* is becoming resistant to a last resort treatment, carbapenem antibiotics, in all regions of the world.
- The *P. falciparum* malaria parasite is gaining resistance to the first-line artemisinin-based combination therapies in Southeast Asia.
- Drug-resistant HIV is emerging with resistance to antiretroviral therapy (ART) in some developing countries.
- In at least 10 countries, gonorrhea is becoming resistant to the last resort medicine, third generation cephalosporin antibiotics.
- Resistance of *Staphlylococcus aureus* to first-line drugs is widespread, causing growing numbers of deaths due to MRSA (methicillin-resistant *Staphylococcus aureus*).

Emergence of AMR in microorganisms is a natural phenomenon, but has been greatly accelerated by the misuse and overuse of antimicrobials in health care and agriculture (Holmes, et al., 2016). For example, antibiotics are often taken by people with viral infections like colds and flu, for which they have no beneficial effect. Antimicrobials are one of the most commonly prescribed drugs used in human medicine, but up to half of all antimicrobials prescribed to people are considered unnecessary (CDC, 2013).

Factors contributing to AMR in low-income countries include over-the-counter availability with insufficient dosages, the use of counterfeit drugs and other less potent antibacterial agents, lack of diagnostic laboratories and poor level of sanitation, which all facilitate the spread of resistant organisms (Roca, et al., 2015).

AMR is a complex problem that is driven by many interconnected factors, and coordinated effort is required to minimize the emergence and spread of AMR. Without urgent and effective action, we risk returning to an era in which common infections and minor injuries can once again kill. A global action plan on AMR was endorsed in 2015 to ensure prevention and treatment of infectious diseases with safe and effective medicines (WHO, 2015).

The plan has five strategic objectives: improve awareness and understanding of AMR, strengthen surveillance and research, reduce the incidence of infection, optimize the use of antimicrobial medicines and ensure sustainable investment in countering AMR.

It is necessary to improve global awareness of AMR so that patients and farmers do not demand, and clinicians and veterinarians do not prescribe, antibiotics that are not needed (O'Neill, et al., 2016). It is also important to improve hygiene and sanitation conditions, because the fewer people that get infected, the less they will need to use antimicrobials and the less drug resistance will arise.

Another important step is the promotion of new, rapid diagnostics to reduce unnecessary prescription of antimicrobials and to optimize treatments. The development and use of vaccines should also be promoted, as they can prevent infections and therefore lower the need for therapeutic treatments, thus reducing the use of antimicrobials and the rise of drug resistance.

While there are some new antimicrobials in development, none of them are expected to be effective against the most dangerous forms of resistant germs. There is a need for better incentives to promote investment in new drugs, because the commercial return on R&D investment in new antibiotics is currently unattractive. Although the total market for antibiotics is relatively large, with annual sales of about $40 billion, only about $4.7 billion of this is from sales of patented antibiotics (O'Neill, et al., 2016). Between 2003 and 2013, less than 5 percent of venture capital investment in pharmaceutical R&D was for development of antimicrobials.

A greater focus on health system strengthening and affordability

Universal Health Coverage (UHC), a concept that aims to ensure that individuals and communities receive the health services they need without suffering financial hardship, is receiving more serious attention since it was adopted as a SDG in 2015. The scope goes beyond financing and includes all components essential to a well-functioning health system. Investing in improving in the delivery of primary care is essential in achieving UHC (SDG, 2015).

The focus on primary care provides a major opportunity to address many conditions like pneumonia, maternal, reproductive health, nutrition and diarrhea that are still major burdens on low and middle-income countries. But to achieve the broad goals of UHC is ambitious. Health systems need to overcome several key challenges, including attaining sustainable financing, ensuring true universalism so that poor and vulnerable are not left behind, and improving the quality and efficiency of health service delivery.

The increasing number of technology breakthroughs, if fully leveraged, will contribute greatly to improving the capabilities of providers and administrators, and better serve the needs of patients. Mobile and digital technologies, in particular, will play a key role by improving the methods and quality of data collection and turning that data into actionable information.

Disaggregated data that in an integrated system can improve the delivery of health services and products, provide timely, decision making, resource planning and increase accountability. Beyond the power of data, digital tools are also starting to play a role in the financing of healthcare, building engaging relationships between payers and beneficiaries.

Healthcare technologies are part of a complex ecosystem involving policy, behavior and economic factors

More than most other topics covered in this study, new technologies for health depend heavily on a range of required trials and approvals, policy and system reforms, behavior change on the part of users, improvement in the level of technical skills of care providers and their integration into mainstream healthcare service delivery. In this context, first it is important to remember that without an adequate number of trained healthcare workers and clinicians, as well as fundamental changes in how healthcare is sought and administered, there is a significant risk that many of these technologies will simply not have a market.

Second, conditions like diarrheal disease, pneumonia and TB, can benefit from individual technological breakthroughs. However, the underlying risk factors involved—particularly in densely populated urban settings—can only be alleviated through structural changes in how people live, especially those at the lower end of the income spectrum.

As long as the poor continue to live in squalid conditions, most medical technologies will only serve as a means to provide reactive interventions. For interventions to be proactively preventive, it is important to think beyond individual technologies and move towards a more integrated and long-term solution.

Third, not all health conditions can be battled through breakthrough technologies. This is particularly true of the rapidly escalating threat of non-communicable diseases—obesity, diabetes, cardiovascular diseases and, increasingly, cancer.

While technology can play a role in effective detection, diagnosis and treatment, incidence is primarily due to lifestyle and behavioral choices. Managing this burgeoning health challenge relies primarily on raising awareness and behavior change interventions.

In this chapter, we look at the major health conditions contributing to highest mortality and DALYs in developing countries, their clinical underpinnings, and the key challenges to overcoming them. These conditions, each a dedicated section, include:

- HIV/AIDS
- Pulmonary tuberculosis
- Malaria
- Maternal and neonatal health
- Pneumonia and lower respiratory infections
- Diarrheal diseases
- Non-communicable diseases
- Nutritional deficiencies

In addition, we examine two important systemic issues:

- Diagnostics
- Healthcare delivery

Note: In this chapter, childhood health (and related conditions) typically refers to children under 5. 'Resource-poor settings' refers to contexts in which low-income populations do not have access to clinics with basic amenities (such as reliable electricity, running water and functioning medical devices) or to adequately trained healthcare providers; this could be in rural or urban settings. 'Remote settings' usually refers to rural areas that are difficult to access due to the absence of reliable roads and/or transport. 'Peripheral clinics' refers to barely functioning healthcare facilities that serve populations in resource-poor or remote settings. Finally, 'point-of-care' describes services that are provided at or near where the patients are, rather than at laboratories or healthcare facilities which are far away from where the patients live and work.

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HIV IS A COMPLEX VIRUS
SUB-SAHARAN AFRICA IS AT CENTER OF THE PANDEMIC
70%
OF GLOBAL HIV CASES
30,000,000
PEOPLE LIVE WITH HIV/AIDS
APPROX' 2,000,000 PEOPLE TRANSMITTED HIV IN 2017
A CURE STILL ELUDES US

HIV/AIDS

INTRODUCTION

Human immunodeficiency virus (HIV) is a retrovirus that causes acquired immune deficiency syndrome (AIDS), a disease that leads to the progressive deterioration of the immune system.

Left untreated, the disease leads to death. Though it is no longer a top 10 killer globally, HIV/AIDS continues to represent a serious global pandemic in low-income countries as the fourth largest cause of mortality.

Concerted global efforts to curb transmission and the development and distribution of antiretroviral drugs have substantially reduced mortality and gradually converted HIV into a chronic disease. While the overall number of new HIV infections has fallen from 3.2 million in 2000 to 1.8 million in 2017, the pandemic is far from over. In 2017, 36.9 million people around the world were living with HIV/AIDS; about 70 percent of whom are in sub-Saharan Africa. Globally, some 940,000 people died due to AIDS-related causes in 2017 (UNAIDS, 2018).

HIV is primarily transmitted through unprotected sexual contact, contaminated needles, and from infected mother to child—in utero, at birth or through breastfeeding. There is neither a vaccine to prevent HIV infection, nor a cure for it. Consequently, targeting risk-reducing behaviors is important for preventing HIV infection and controlling the spread of the disease.

Antiretroviral treatments (ARVs) are widely available. While they do not cure the disease, they control disease progression and are able to dramatically reduce transmission. However, enabling early diagnosis and widespread access to ARVs is a significant challenge, especially in developing regions. Treatment is lifelong and very costly, and preventing patient drop off during treatment is difficult.

Given the above challenges, there are four technologies that can help reduce the burden of HIV/AIDS in developing countries.

- Breakthrough 23. Vaccines that can effectively control and eventually help eradicate the major infectious diseases of our time—HIV/AIDS, malaria, tuberculosis and pneumococcus
- Breakthrough 24. Microbicides to provide a method of protection for those who are otherwise vulnerable to HIV/AIDS infection by their partner
- Breakthrough 25. PrEP (pre-exposure prophylaxis) to reduce the risk of HIV infection
- Breakthrough 26. Improved, longer-lasting antiretroviral therapy (ART) formulations to control HIV viral replication and increase patient adherence

Though it is no longer a top 10 killer globally, HIV/AIDS continues to represent a serious global pandemic in low-income countries as the fourth largest cause of mortality. Concerted global efforts to curb transmission and the development and distribution of antiretroviral drugs have substantially reduced mortality and have gradually converted HIV into a chronic disease. While the number of deaths and new HIV infections have fallen, the pandemic is far from over. Globally each year, almost a million people die due to AIDS-related causes.

CORE FACTS AND ANALYSIS

Human immunodeficiency virus (HIV) is a retrovirus that causes Acquired Immunodeficiency Syndrome (AIDS), a disease characterized by progressive deterioration of the immune system. The diminished immune function of HIV/AIDS patients puts them at greater risk for a variety of infections, which without treatment leads to death.

In 2017, 1.8 million people contracted the virus and 940,000 people died of AIDS-related causes (UNAIDS, 2018). Particularly vulnerable, young women are twice as likely to be living with HIV than men (UNAIDS, 2018). Importantly, those living with HIV have a 20 to 37 times higher risk of developing TB (WHO, 2012).

The HIV/AIDS pandemic poses an enormous economic burden on countries with high incidence and prevalence rates, especially in light of higher prevalence in younger individuals. The resulting disability and death among workers and young parents has devastating effects on household income, and also decreases productivity and growth at the national level.

The care of children orphaned by the virus further adds to the economic burden of the worst-affected countries. Globally more than 13.4 million children are defined as AIDS orphans (UNICEF, 2016). Put together, these factors create downward spirals of poverty and social disruption in regions severely affected by HIV/AIDS.

1. Sub Saharan Africa is the center of the HIV/AIDS pandemic

Although HIV is prevalent across the world, sub-Saharan Africa is home to 25.7 million of the 36.9 million people living with HIV worldwide (UNAIDS, 2018). In sub-Saharan Africa, HIV/AIDS is the leading cause of death and third largest disease burden, representing 9.5 percent of all deaths and 8.2 percent of all DALYs (Global Burden of Disease, 2017).

It is also the single most important contributing factor in the overall disease burden among the adult population in Southern and Eastern Africa. **Table 1** illustrates the total number of people living with HIV and the number of new HIV infections and deaths in 2017 (UNAIDS, 2017)

Region	People living with HIV 2017	New HIV infections 2017			AIDS-related deaths 2017	People accessing treatment 2017
		Total	Aged 15+	Aged 0-14		
Eastern and Southern Africa	19.6 million (17.5 million-22.0 million)	800 000 (650 000-1.0 million)	710 000 (580 000-890 000)	92 000 (61 000-130 000)	380 000 (300 000-510 000)	12.9 million (11.4 million-13.4 million)
Asia and the Pacific	5.2 million (4.1 million-6.7 million)	280 000 (210 000-390 000)	280 000 (210 000-390 000)	10 000 (7 4000-14 000)	170 000 (110 000-280 000)	2.7 million (2.4 million-2.9 million)
Western and Central Africa	6.1 million (4.4 million-8.1 million)	370 000 (220 000-570 000)	310 000 (180 000-470 000)	67 000 (36 000-100 000)	280 000 (180 000-410 000)	2.4 million (2.1 million-2.5 million)
Latin America	1.8 million (1.5 million-2.3 million)	100 000 (77 000-130 000)	99 000 (75 000-130 000)	2400 (1800-3600)	37 000 (26 000-51 000)	1.1 million (992 000-1.2 million)
The Caribbean	310 000 (260 000 420 000)	15 000 (11 000-31 000)	14 000 (10 000-24 000)	1 100 (710-1 900)	10 000 (7 100-17 000)	181 000 (159 000-188 000)
Middle East and North Africa	220 000 (150 000-300 000)	18 000 (10 000-31 000)	17 000 (9 200-28 000)	1 300 (780-1 900)	9 800 (6 400-15 000)	63 200 (55 600-65 700)
Eastern Europe and Central Asia	1.4 million (1.9 million-2.4 million)	130 000 (120 000-150 000)	30 000 (120 000-150 000)	_*	34 000 (25 000-41 000)	520 000 (458 000-541 000)
Western and Central Europe and North America	2.2 million (1.9 million-2.4 million)	70 000 (57 000-84 000)	69 000 (57 000-83 000)	_*	13 000 (9 990-18 000)	1.7 million (1.5 million-1.8 million)
Global totals	36.9 million (31.1 million-43.9 million)	1.8 million (1.4 million-2.4 million)	1.6 million (1.3 million-2.1 million)	180 000 (110 000-260 000)	940 000 (670 000-1.3 million)	21.7 million (19.1 million-22.6 million)

Table 1: Global HIV/AIDS statistics show that the disease continues to be a major health problem, especially in Africa. (Source: UNAIDS, 2018)

In terms of prevalence, South and Southeast Asia are second to sub-Saharan Africa with a total of 1.9 million individuals living with HIV/AIDS (GDB 2017). However, in contrast to sub-Saharan Africa, HIV/AIDS is only the 17th largest cause of disease burden in South Asia, behind lower respiratory infections, preterm birth complications and diarrheal diseases, among others, and represents 0.54 percent of all DALYs (GDB, 2017).

2. HIV/AIDS attacks immune cells and is transmitted person to person

HIV is a member of the genus Lentivirus within the Retroviridae family. The virus infects immune cells, such as T cells, which bear the surface molecule CD4. HIV can also infect other immune cells, such as macrophages, which may serve as both a reservoir for the virus and a means of viral spread to other body tissues.

After entry into a permissive cell, a viral enzyme called reverse transcriptase converts the RNA genome into double stranded DNA. This DNA becomes integrated into the cellular genome by a second HIV enzyme, integrase.

Once integrated, the HIV provirus takes advantage of host cell enzymes to transcribe and translate its genetic material into the viral proteins, which together with its genetic copies, assemble into new viral particles and bud from the infected cell.

The body's defenses weaken when subsets of immune cells, such as T cells, are infected and destroyed. Once a patient develops AIDS, they are highly susceptible to a wide variety of opportunistic infections (BVGH, 2012).

HIV/AIDS transmission in some ways parallels the transmission patterns of other sexually transmitted diseases such as syphilis, gonorrhea and of diseases like Hepatitis B and C, which are also transmitted via blood transfusion or intravenous drug use.

HIV transmission requires unprotected and close contact with body fluids of other infected individuals, primarily through exposure to blood, semen, vaginal secretions and breast milk. As a result, the major routes of infection are through sexual contact, contaminated needles and from infected mother to child in utero, at birth or through breastfeeding.

3. Interventions have revolved around preventing transmission, and treatment with antiretroviral therapy (ART)

In addressing the HIV/AIDS pandemic, there are two key avenues for intervention: the prevention of transmission and diagnosing and treating the virus (WHO, 2013). Currently, there is neither a vaccine to prevent HIV infection nor a cure for it. Available antiretroviral drugs (ARVs) require lifelong treatment and only control viral replication and disease progression. While ARVs do dramatically reduce HIV transmission, targeting risk-reducing behaviors and preventing the spread of the disease are equally important.

In 2015, UNAIDs established the 90-90-90 targets: By 2020, 90 percent of all people living with HIV will know their HIV status; 90 percent of all people with diagnosed HIV infection will receive sustained antiretroviral therapy; and 90 percent of all people receiving antiretroviral therapy will have viral suppression. In 2017, the figures for the 90-90-90 initiative were 75 percent, 79 percent and 81 percent respectively (UNAIDS, 2018).

Interventions aimed at preventing transmission

Condoms and abstinence

Sexual transmission of HIV can be reduced by consistent and correct use of male and female condoms, limiting the number of sexual partners or abstaining from sexual activity all together. Consistent use of condoms reduces the risk of contracting or transmitting HIV by about 80 percent (Weller & Davis-Beaty, 2011).

Despite this, in 2013 only 41 percent of adults with multiple sexual partners report having used a condom during the last time they had sex. Condom use is particularly low among adolescent girls in Africa and among men who have sex with men (WHO, 2014). UNAIDS also estimated a large gap between condom availability of more than three billion condoms (UNAIDS, 2015).

Male circumcision

Medical male circumcision (the surgical removal of the penis foreskin) has been recognized since 2007 by the WHO, UNAIDS and other major health organizations as an effective component of the global strategy to end the HIV/AIDS pandemic. Clinical trials have demonstrated that male circumcision can reduce a man's risk of acquiring HIV from his female infected sexual partner by at least 60 percent (Wawer, et al., 2008).

Modeling studies show that this would also have vaccine-like efficacy, in that each man who is protected via circumcision would therefore not be capable of transmitting to a subsequent partner; thus women stand to derive some long-term benefit from circumcision due to lower probability of being exposed to, and infected by, HIV.

Voluntary male circumcision has been promoted in 14 priority countries in Africa since 2007, and by the end of 2017 nearly 18.6 million men had undergone the procedure, an almost five-fold increase from 2012. The service package now includes safer sex education, condo promotion and HIV testing as well. The number of annual circumcisions rose from 900,000 in 2011 to more than 1.7 million in 2012, and up to 4.04 million in 2017 (WHO, 2018).

Treatment as Prevention (TasP)

In 2011, an international study showed that ART can prevent the sexual transmission of HIV among heterosexual couples where one partner is HIV infected and the other is not. UNAIDS described the result as a "serious game changer" for HIV prevention (The Lancet, 2011). In 2011, a nine-country trial called HPTN 052 panning Africa, Asia and South America demonstrated that treating an HIV positive person with ART successfully decreases the amount of virus present in their bodies and reduces HIV transmission rates during sexual intercourse by 96 percent (WHO, 2012).

In 2014, the PARTNER study, in which more than 1,000 heterosexual and gay couples were enrolled, found no transmissions within mixed-status couples when the viral load of the positive partner was undetectable, and provided good evidence for the effectiveness of TasP. The WHO has embraced TasP as a key element of HIV prevention and as a major part of the solution to ending the HIV pandemic.

Pre-exposure prophylaxis (PrEP)

In November 2010, the results from a clinical trial showed promise for a new HIV prevention strategy called pre-exposure prophylaxis or PrEP. This involves the use of antiretroviral drugs by HIV negative people who are at a high risk of contracting HIV to reduce the risk of HIV infection. The trial, iPrex, demonstrated that daily use of a combination ART and Truvada (emtricitabine/tenofovir disoproxil fumarate) reduced the risk of HIV dramatically among men who have sex with men.

Since then, more than 10 clinical trials have demonstrated its effectiveness of PrEP in reducing HIV transmission among a range of populations. As of September 2015, WHO recommends that people at substantial risk of HIV infection, including HIV-negative women who are pregnant or breastfeeding, should be offered PrEP containing tenofovir as an additional prevention choice as part of comprehensive prevention (WHO, 2018).

Drug counseling, treatment and clean needles

Intravenous injection of illicit drugs is a high-risk behavior for HIV/AIDS transmission, as the virus can be passed on through contaminated needles. Prevention of drug use is targeted through counseling and treatment. Programs that have supplied drug users with clean needles have markedly reduced their risk of infection. In addition, post-exposure prophylactic treatment with ART can sometimes prevent infection if administered within 72 hours of potential exposure.

Preventing mother to child transmission of HIV/AIDS (PMTCT)

The risk of mother to child transmission (MTCT) of HIV is directly linked to maternal viral load[1]. ART use has led to the virtual elimination of perinatal HIV cases in the United States, and different regimens are being successfully used to decrease the risk of such transmission worldwide.

The 2013 WHO guidelines recommend starting all HIV-infected pregnant and breastfeeding women on lifelong ART, regardless of their CD4+ count (WHO, 2013). In 2017, 80 percent of the estimated 1.1 million pregnant women living with HIV globally received ARV treatments to prevent transmission to their children.

Substantial progress in PMTCT has been achieved in countries like Botswana where mother-to-child HIV transmission has come down from 20 to 40 percent in 2001 to less than 7 percent in 2007 (Botswana Ministry of Health, 2013). A few LMICs like Armenia, Belarus, Cuba and Thailand have eliminated MTCT as a public health problem. Such success is an indication that developed world paradigms for HIV control can be successfully implemented in developing countries.

Interventions aimed at controlling viral replication

Diagnosis of infected patients

Guidelines for HIV testing continue to evolve with changes in technology. Generally, diagnosis of infection occurs in two stages. First, a screening or first-line test is used for presumptive diagnosis. Such tests are generally immune-based enzyme-linked immunosorbent assays (ELISAs) that measure the presence of antibodies in blood or saliva.

The new generation of tests also incorporate HIV antigen detection to increase the sensitivity of the assay (WHO, 2018). As no one test can provide an absolute HIV-positive diagnosis, patients who receive a positive diagnosis from the first-line screening test then receive a higher specificity confirmatory test that verifies HIV infection and stage of disease.

Simplified, instrument-free and immune-based assays are available for rapid HIV screening in settings without access to laboratory facilities. These rapid tests have allowed many countries to implement and expand community-based and self-testing HIV diagnosis and increase HIV diagnosis.

A systematic review of studies on the reliability of self-testing showed that self-testers were able to interpret rapid test results as accurately as trained health workers (Figueroa et al., 2018). Confirmatory diagnosis can be performed using western blot, line immunoassays or for high prevalence areas by using a minimum of two to three different rapid assays. The choice of confirmatory test depends on HIV prevalence in the population, as well as by the cost and availability of laboratory services.

Treatment of infected patients

The WHO recommended treatment for HIV/AIDS is a combination of ART and management and treatment of opportunistic infections that may result from HIV-related immune suppression. The ART strategy most widely used is called Highly Active Antiretroviral Therapy (HAART) and consists of combination treatment with two nucleoside reverse transcriptase inhibitors (NRTIs), co-administered with a third drug with a different mechanism of action, such as a non-nucleoside reverse transcriptase inhibitor (NNRTI), a protease inhibitor or an integrase inhibitor.

There are currently 40 HIV products approved by the U.S. Food & Drug Administration (FDA) including individual drugs and fixed dose combinations (US FDA, 2018). The 2016 guidelines include new alternative ARV options with better tolerability, higher efficacy and lower rates of treatment discontinuation when compared with medicines being used currently: dolutegravir and low-dose efavirenz for first-line therapy and raltegravir and darunavir/ritonavir for second-line therapy.

[1]Also known as viral burden, viral titre or viral titer is a measure of the severity of a viral infection and can be calculated by estimating the amount of virus in an involve body fluid. For example, it can be given in RNA copies per milliliter of blood plasma.

Viral load testing to monitor treatment efficacy

Viral load testing is the most sensitive method to monitor patients for ART failure and determine the need to progress to second-line treatment regimens. The majority of tests today use nucleic acid amplification techniques to detect the presence of viral nucleic acid.

Treatment failure occurs when viral load either does not drop or repeatedly rises after having dropped previously, in what is called virologic failure. Though viral load monitoring capacity is being scaled up, it remains limited in low-income setting because it is cost-prohibitive and requires sophisticated laboratory equipment and highly trained personnel.

Challenges extend beyond access to the lab, from correct sampling methodologies to obtaining and transporting specimens and timely delivery of results to providers (El-Sadr et al., 2017).

Monitoring patient adherence

Treatment interruption leads to a large and quantifiable increase in viral load and dramatically increases chances of disease progression and transmission (Bangsberg, et al., 2001). Lack of treatment adherence is a leading predictor of HIV/AIDS mortality globally.

There are numerous reasons for patients falling out of treatment, described in detail further in this chapter, and include social stigma, cost of treatment and transportation constraints. Additionally, once patients begin treatment and start to feel better, they may become lax about their treatment. The support from friends and family, who have made it possible for a patient to make it to a clinic for starting treatment, may begin to wane.

Numerous approaches are being explored to increase patient adherence, including the development of long-lasting treatment formulations, mobile-health solutions, such as SMS reminders to patients to take their medicines (Siedner, et al., 2012), and real-time adherence monitoring devices that are linked to patient pill boxes and can transmit information back to a clinic about when patients have opened their medication boxes.

These approaches are superior to current adherence monitoring methods that either rely on structured patient interviews and pill counts or tracking pharmacy refill information; these methods operate on an intermittent basis and missed doses go undetected for several weeks or months. Realtime, wireless monitoring mechanisms may offer the opportunity to proactively prevent virologic rebound and treatment failure and prevent death (Haberer, et al., 2010; DeSilva, et al., 2013).

KEY CHALLENGES

While much has been done globally to tackle the HIV/AIDS pandemic, several scientific and social factors limit transmission control and finding a definite cure.

Highlighted below are some of the major challenges in the fight to reduce HIV/AIDS related mortality.

1. A highly complex virus, which makes developing vaccines difficult

HIV mutates rapidly and patients can be infected by numerous different strains of the virus. HIV is broadly classified as HIV-1 or HIV-2. The former is more virulent, causes majority of the infections and can be divided into several distinct groups; these groups are further divided into subtypes (clades) that display distinct geographic patterns of infection.

The acute diversity of HIV strains and the alacrity of the virus' spread and mutation within the human body are the principle impediments to the development of new biomedical prevention tools. Once inside the body, the virus mutates so fast that the immune system simply cannot keep pace. Indeed, it is the immune system itself that is the target of the virus.

After one week of infection, HIV is overwhelmingly found in the T cells of the gut—exactly the cells that have the capacity to defeat it. Because HIV is a retrovirus, it integrates into a person's DNA. The problem of rapid integration is particularly crucial for a vaccine. Once the virus integrates, it has the ability to hide from the immune system. Integration means that any vaccine must be able to act within the short interval between infection and before the integrated form of the virus takes over a substantial number of CD4 T cells.

An effective vaccine would be the single most transformational technology intervention to prevent HIV transmission, yet more than three decades of R&D led to scant success until 2009 and the 10 years since.

In December 2009, the first hopeful clinical trial results were published; the results of the RV144 vaccine trial in Thailand. In this study more than 16,000 HIV negative volunteers received a series of priming vaccinations with a canarypox-based viral vector vaccine (Sanofi-Pasteur), followed by boosters with a recombinant protein vaccine containing subunits of the HIV surface glycoprotein gp120 (AIDSVAX B/E, VaxGen/GSID).

The study showed approximately 31 percent protection against HIV infection as compared to the placebo control group, and the efficacy of this protective effect declined with time (Rerks-Ngarm, 2009). This study made clear that numerous basic science questions about the virus still remain unanswered.

The correlates of protection are unclear

In general, when developing a vaccine, an important input is an understanding of the natural history of a disease and the immune response it elicits. In the context of HIV, there are no examples of natural immunity in the human environment. While there are examples of a few individuals who are genetically resistant to infection and those who control the virus at low levels for a long time, there is no population of people that have actually overcome the infection.

This is a major obstacle to HIV vaccine development. The 2009 RV144 Phase III trial results gave the first supporting evidence of any vaccine being effective in lowering the risk of contracting HIV, but yielded additional questions about the immunological basis of protection in those people who received the vaccine.

In 2012, more research on this topic provided some additional but not conclusive data on correlates of protection, indicating that the immune response was antibody-based (Haynes, et al., 2012). In 2015, an experiment using 3BNC117, an antibody which blocks the first contact between the virus and the cell it is about to infect, to treat HIV-infected patients in passive immunotherapy showed that the antibody neutralized HIV and reduced the amount of virus circulating in the patients' bloodstreams. Since 3BNC117 is a type of antibody that would be generated by an ideal vaccine, the outcomes not only showed the potential of passive immunotherapy as a treatment, but also suggested that a vaccine which induced this type of antibodies would be widely protective (Caskey et al., 2015).

More research is needed to understand and elicit durable antibody response

One of the main challenges in vaccine development had been the difficulty in eliciting a timely and long-lasting immune response. During the RV 114 trial, researchers reported that vaccine efficacy seemed to peak early; cumulative vaccine efficacy was estimated to be 60.5 percent through the 12 months after initial vaccination, but declined to 31 percent after three years, a problem that is linked to waning antibody responses (Robb, et al., 2012). Much progress has been made since 2012 in developing new antigens and adjuvants capable of inducing longer-lasting antibody responses. There is also increasing understanding of factors that influence the body's immune response, such as the virus load, the diversity of the viruses, the duration of the infection, the ethnicity of the affected person and identification of special envelope proteins, etc. (University of Zurich, 2018).

2. Complex and inter-related drivers of transmission make disease control problematic

The number, complexity and interrelated nature of the drivers of HIV transmission pose enormous challenges for HIV control, and in particular, for pinpointing and implementing preventative behavioral interventions (**Exhibit 1**).

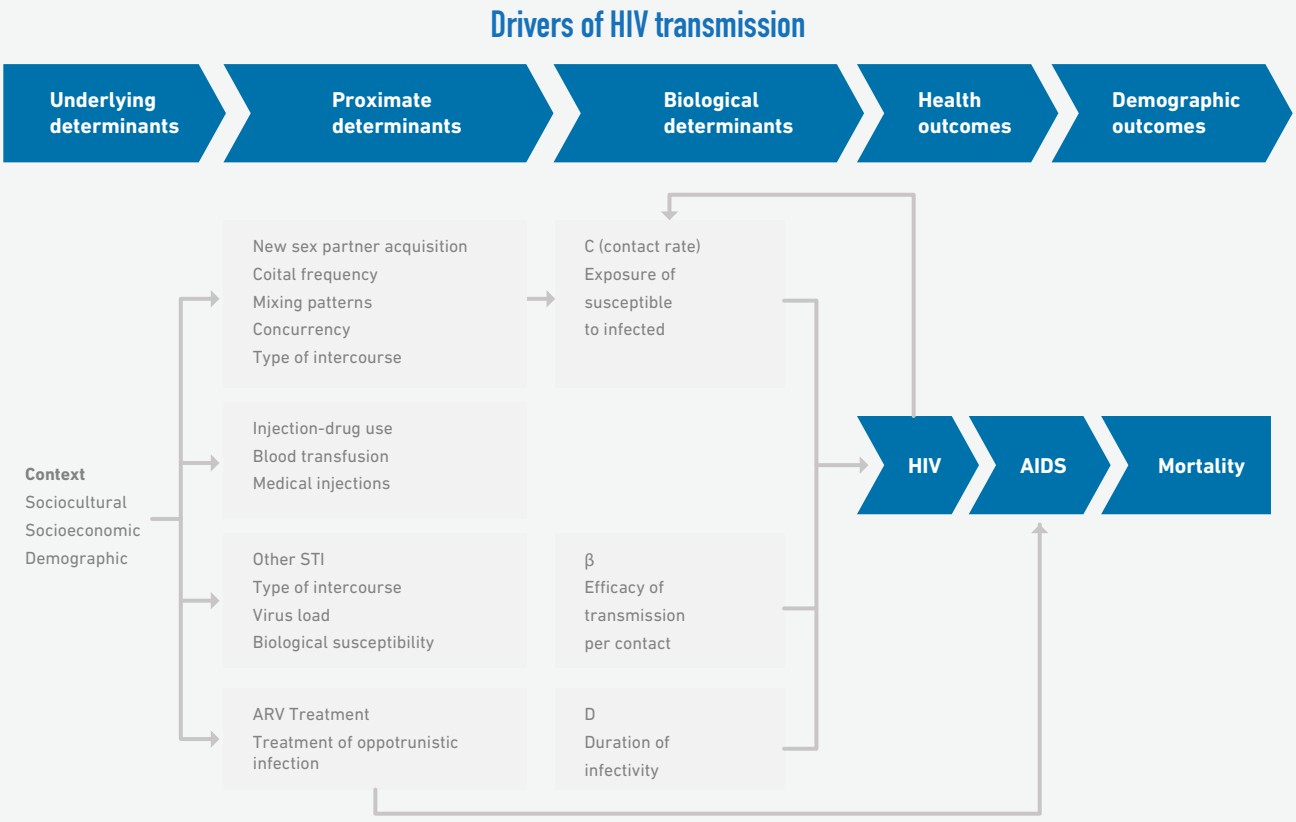


Exhibit 1: HIV/AIDS transmission is complex. The underlying sociocultural, socioeconomic and demographic determinants of HIV/AIDS transmission that drive sexual behaviors in turn shape the downstream proximate determinants of transmission. (Source: Boerma & Weire, 2005)

The key biological determinants that underlie HIV transmission include the contact rate (C), which describes the exposure of the susceptible to the infected, the efficacy of transmission per contact (B) and the duration of infectivity (D).

Those with HIV infect others in line with the contact rate, but the development of HIV into AIDS can be prevented by early detection and treatment with ART. Each of these biological determinants of infection is in turn impacted by proximate determinants (**Table 2**).

Biological and proximate determinants of HIV transmission

Biological driver	Proximate Determinants
Contact rate: Sexual Transmission	• New sex partner acquisition: the frequency of engagement in sexual activity with a new partner • Coital frequency: the frequency of sexual activity • Sexual partnership mixing patterns: the extent to which subpopulations with different prevalence of infection engage in sexual partnership mixing with others of different levels of education, involvement in illicit drug use, concurrent sex partners, and incarceration • Concurrency: the existence of more than one long-term sexual partner • Type of intercourse
Contact rate: Needle Transmission	• Use of injected drugs • Frequency of blood transfusions • Frequency of medical injections
Efficacy of transmission per contact (β)	• Prevalence of other sexually transmitted infections: STIs have been shown to increase the susceptibility of an individual to being infected, and also increase the virulence of the infection in an HIV infected person • Type of intercourse • Viral load of infected individual impacts efficacy of transmission • Biological susceptibility: individuals can have different basic levels of susceptibility to HIV infection
The duration of infectivity	• Treatment with ART. Duration of infectivity is life-long without antiretroviral therapy

Table 2: Several proximate determinants impact biological determinants of HIV transmission and infection.

The underlying sociocultural, socioeconomic and demographic determinants of HIV/AIDS transmission that drive sexual behaviors shape the downstream proximate determinants of transmission.

In recent years, increased understanding about human sexual behaviors and how they are shaped by social, economic and legal-political structures has made it indisputable that reducing HIV risk is embedded in structural change in economic opportunities, social norms, gender roles and legal freedoms (Parkhurst, 2013). HIV prevention efforts are particularly challenging in situations where power is skewed structurally along gender divisions.

Particular groups, such as commercial sex workers and women in polygamous marriages, become extremely vulnerable. Based on our current understanding of the structural determinants of HIV infection, commonly-identified high risk groups include: adolescents (in particular, underprivileged or street children), women (in particular, young women between the age of 15 and 24 years and commercial sex workers), men and transgender individuals who have sex with men, truck drivers, displaced populations and prisoners.

Such populations represent the majority of people affected by HIV outside Africa, and a significant share of new infections within Africa (WHO, 2014).

3. Difficulty of patient monitoring and adherence to treatment

The HIV/AIDS treatment cascade (**Exhibit 2**) is a way of showing the number of individuals living with HIV/AIDS who are actually receiving the full benefits of the medical care and treatment they need. Even in the United States only 1 in 4 HIV infected individuals receives the full care they need (Gardner, et al., 2011).

While little comprehensive data is available about the treatment cascade in sub-Saharan Africa and other developing countries, it is generally agreed there is a high level of drop-off that occurs between diagnosis to initiation of ART. One meta-analysis suggests a median completion rate of 17 percent for those who get from diagnosis to initiation of ART (Rosen & Fox, 2011). But gaps are closing with the most recent WHO Treat All guidelines.

United States treatment cascade

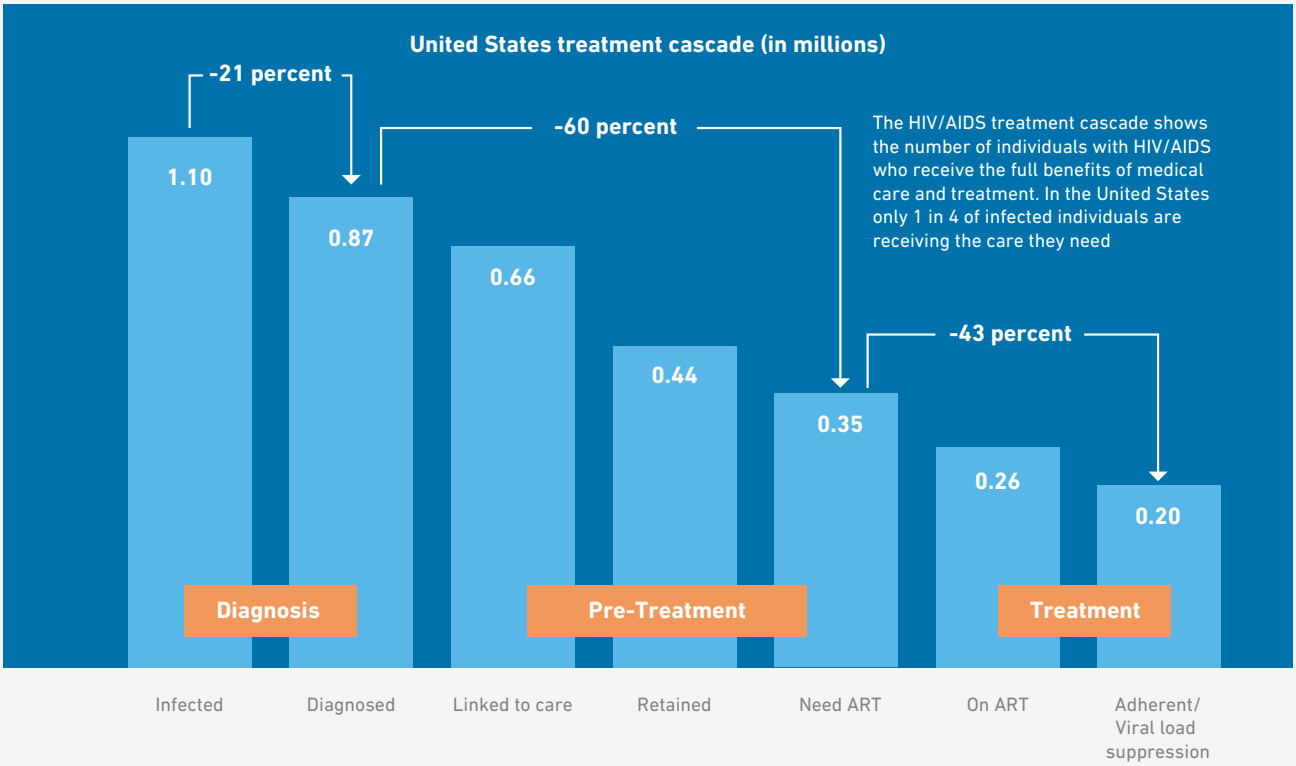


Exhibit 2: In the United States, only 1 in 4 HIV infected individuals receives the care they need. (Source: Gardner, et al., 2011)

There are a number of reasons for the rapid drop-off in the treatment cascade, as described below.

Difficulty of identifying infected individuals

Early identification of HIV infection is critical to treatment outcomes. However, HIV cannot be diagnosed through clinical symptoms. Two to four weeks after infection, patients may display flu-like symptoms accompanied by a rash and fever. Many patients are initially asymptomatic. This makes diagnosis difficult.

Although the incubation period between infection and onset of AIDS is often cited as seven to 10 years, disease course can be accelerated in LMICs due to environmental factors, co-morbidities and poor nutrition (BVGH, 2012).

Social stigma also prevents many individuals from even getting tested for HIV. HIV self-testing, as recommended in WHO's 2016 testing guidelines update, is becoming more widely available and an important new option for reaching greater numbers of people living with HIV who otherwise may not take an HIV test (WHO, 2016).

Moving from diagnosis to care and patient retention

There are now an increasing number of testing facilities offering immediate ART to those individuals they diagnose.

The CASCADE randomized control trial in 2016 and 2017 showed that offering same-day home-based ART initiation to individuals who tested positive during home-based HIV testing, compared with usual care and standard clinic referral, significantly increased linkage to care at three months and HIV viral suppression at 12 months (Labhardt et al., 2018).

Monitoring CD4+ counts generally requires expensive flow cytometry equipment and a highly trained laboratory workforce. Although simplified bench-top devices are available (for example, FACSCount, BD; Guava EasyCD4; Partec Cyflow; PointCare), most of these machines are expensive to purchase, repair and maintain and require regular electricity to operate, largely limiting their utility in developing countries to centralized laboratory facilities (WHO, 2007).

As a result, CD4+ testing means patients seeking care in one clinic may need to be referred to a separate location to provide a blood sample for diagnosis, and a follow-up visit is typically required to receive results.

Even after diagnosis and receiving care, regular monitoring to determine ART eligibility may not be perceived as medically beneficial by patients. This is especially true for those patients who do not feel sick, particularly when weighed against the out-of-pocket costs of missing work, transportation costs to access the nearest testing facility and the stigma of being identified as HIV positive within the community despite no outward symptoms.

These challenges are consistent with the results from a WHO survey of 127 member states that showed sufficient centralized laboratory capacity existed for at least four CD4+ cell count tests per HIV-infected person per year, but only 11 percent of the CD4+ testing capacity was utilized (Habiyambere et al., 2016).

There has been some recent progress towards simplifying diagnostic devices for monitoring CD4+counts, including approved and licensed devices that are inexpensive and do not require reliable power or technical prowess to operate.

Availability of ARVs and Drug Resistance

Between 2005 and 2017, the number of people who can access ARTs greatly increased from 2.1 million to 21.7 million (representing 59 percent of all persons living with HIV). Availability of ART drugs varies from country to country depending on the drug (composition, manufacturer and government approval among others), as well as health system resources.

Apart from the upfront cost of making ARTs available and accessible for everyone in need, high HIV incidence throughout sub-Saharan Africa has increased pressure on HIV clinics to rapidly expand accessibility to ART. As clinics are already overburdened and understaffed, many locations are experiencing long patient wait times and poor retention in care. As well, many countries are experiencing recurring stock outs[2] and there is increasing fear of mass drug resistance.

Patient adherence to treatment regimen

Side effects, constant necessity to be on medication (treatment is required for life) and costs involved, both medical and incidental costs to access medical care, can impact an individual's inclination and ability to stay on treatment.

Monitoring for treatment failure is extremely difficult in the low-income countries; currently prevalent diagnostics require expensive infrastructure and resources, making their widespread implementation in low resource settings very difficult. There is a particularly pressing need to develop strategies to improve adherence among young people aged 15 to 19 years, as they are more likely than adults to drop out (UNAIDS, 2018).

Adherence is generally improving with community-based or community-supported models of care (UNAIDS, 2018). Digital and mobile innovations are also found to be highly accepted and feasible and according to some evidence improving ART adherence and clinic attendance rates (Daher et al., 2017).

Pediatric challenges

The challenges outlined above are intensified for pediatric patients. Of all individuals living with HIV, children are the most vulnerable. Of the estimated 1.8 million children in need of ART in 2017, only 52 percent were receiving it (UNAIDS, 2018), lower than treatment coverage of adults.

Point-of-care early infant diagnosis (EID) reduces the waiting times for the return of test results from months to hours, improving access to early treatment for children living with HIV. However, bottlenecks remain as only half of infants who are exposed to HIV are tested before eight weeks of age. Mentor mothers are playing a big role in strengthening retention of mothers in HIV care, higher uptake of early infant diagnosis and initiation of ART for infants (USAID, 2018).

There are numerous barriers to appropriate treatment for children: Clinics are often far from home and treatment is difficult to administer, stigma prevents families from getting children diagnosed and there is a lack of training and support for families. For young children on liquid ART formulations, dosage is important.

Pediatric formulations are based on weight and the risk of measuring and administering an inadequate dose is more likely than for adults. In 2015, the United States Food and Drug Administration tentatively approved a new formulation of lopinavir/ritonavir (LPV/r), a pediatric antiretroviral for use in children 3 months or older (USAID AIDSFree).

More affordable medicines specifically adapted to the needs of children need to be developed. Nevertheless, pediatric patients are dependent on their caregivers to support adherence to treatment and for that it is essential that the caregiver is consistent and dependable.

[2]In 2017 and 2018, countries including Uganda, South Africa, DR Congo and Ghana reported worrisome ARVs stock outs.

SCIENTIFIC AND TECHNOLOGICAL BREAKTHROUGHS

There is neither a vaccine to prevent HIV infection, nor a cure for it. As things stand, the only effective methods of combating the HIV/AIDS pandemic have been the prevention of transmission and diagnosing and treating those infected.

Drawing strength from a massive global effort, these interventions, despite the complexities involved, have shown results; since 2001, the total number of new infections has fallen substantially.

Sustaining and accelerating this decline is now crucial in the fight against the virus.

There are four scientific and technological breakthroughs that are capable of significantly advancing our fight against the HIV/AIDS pandemic.

Breakthroughs:

1	2	3	4	5	6	7	8	9	10
11	12	13	14	15	16	17	18	19	20
21	22	23	24	25	26	27	28	29	30
31	32	33	34	35	36	37	38	39	40
41	42	43	44	45	46	47	48	49	50

23. Vaccines that can effectively control and eventually help eradicate the major infectious diseases of our time—HIV/AIDS, malaria, tuberculosis and pneumococcus

Collectively, HIV/AIDS, malaria, tuberculosis and pneumonia kill more than five million people a year, and represent a significant disease burden for low income populations in sub-Saharan Africa and South Asia. Effective and affordable vaccines for these diseases do not exist yet due to the intrinsic complexity of the pathogens causing them, and a lack of understanding of the specific mechanisms through which our immune systems protect against these diseases. The process of vaccine development—basic research on disease etiology, vaccine construction, pre-clinical and clinical testing—is technically challenging, expensive and time consuming.

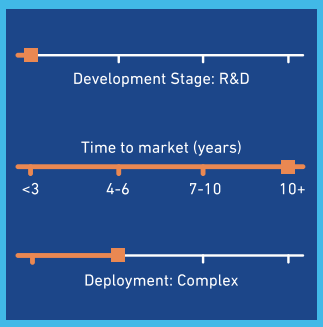
23a. A safe and efficacious HIV/AIDS vaccine

The extreme diversity of HIV strains, the rapid mutation of the virus inside the body and the fact that HIV is a retrovirus which integrates into an infected individual's DNA makes vaccine development for HIV particularly challenging. A vaccine must therefore act quickly in the short interval between infection and establishment of the integrated form in a substantial number of CD4 T cells.

After nearly three decades of HIV vaccine R&D, there are finally some promising candidates, building on some pivotal trials and better understanding of factors that influence immune responses. Current vaccine research is largely focused on understanding and developing specific or combinations of broadly neutralizing antibodies (bNABs) that have the ability to neutralize, or block, many strains of HIV and potentially prevent the virus from establishing a lasting infection. Around 1 per cent of patients have the ability to develop these bNABs that bind to structures on the surface of the pathogens. As these structures barely change and are identical among different strains, researchers are hopeful that these bNABs may help address one of the greatest challenges in HIV vaccine development—the virus's ability to mutate rapidly (AVAC, 2018).

As of 2018, there are two vaccines in large scale studies: 1) The HVTN 702 trial, also known as Uhambo, ongoing in South Africa, which is building on the RV144 trial, 2) The HVTN 705/HPX2008 trial, also known as Imbokodo, underway in multiple countries in southern Africa, which is a proof-of-concept study using a novel vaccine with mosaic immunogens. For both studies, results are expected in 2021.

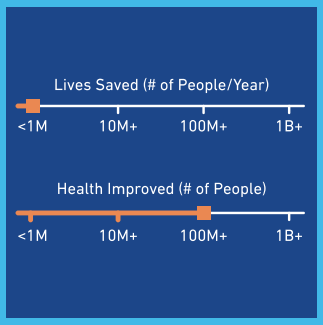
Current State



Associated 50BT Chapters

SDG Alignment

Impact



Commercial Attractiveness

Other novel strategies entering human trials include protein antigens engineered to coax the immune system down a pathway that might lead to the production of broadly neutralizing antibodies (bNAbs), as well as several trials using passive immunization, investigating whether bNAbs can prevent HIV infection (Pipeline Report, 2018).

Another potential approach is gene therapy or transfer that involves identifying high-risk individuals and turning their cells into protein factories that can create and circulate antibodies that offer long-lasting protection.

Since 2009, 19 new bNABs have been isolated and characterized[4]. However, this is an area of very early research and a viable vaccine candidate is several years away. The ultimate vaccine is likely to rely on a multi-component, prime boost strategy and will have to elicit multiple bNABs, increasing the technical difficulty of the development process. The vaccine will also need to overcome the problem of antibody durability to provide long-lasting protection so that individuals do not require frequent re-immunization.

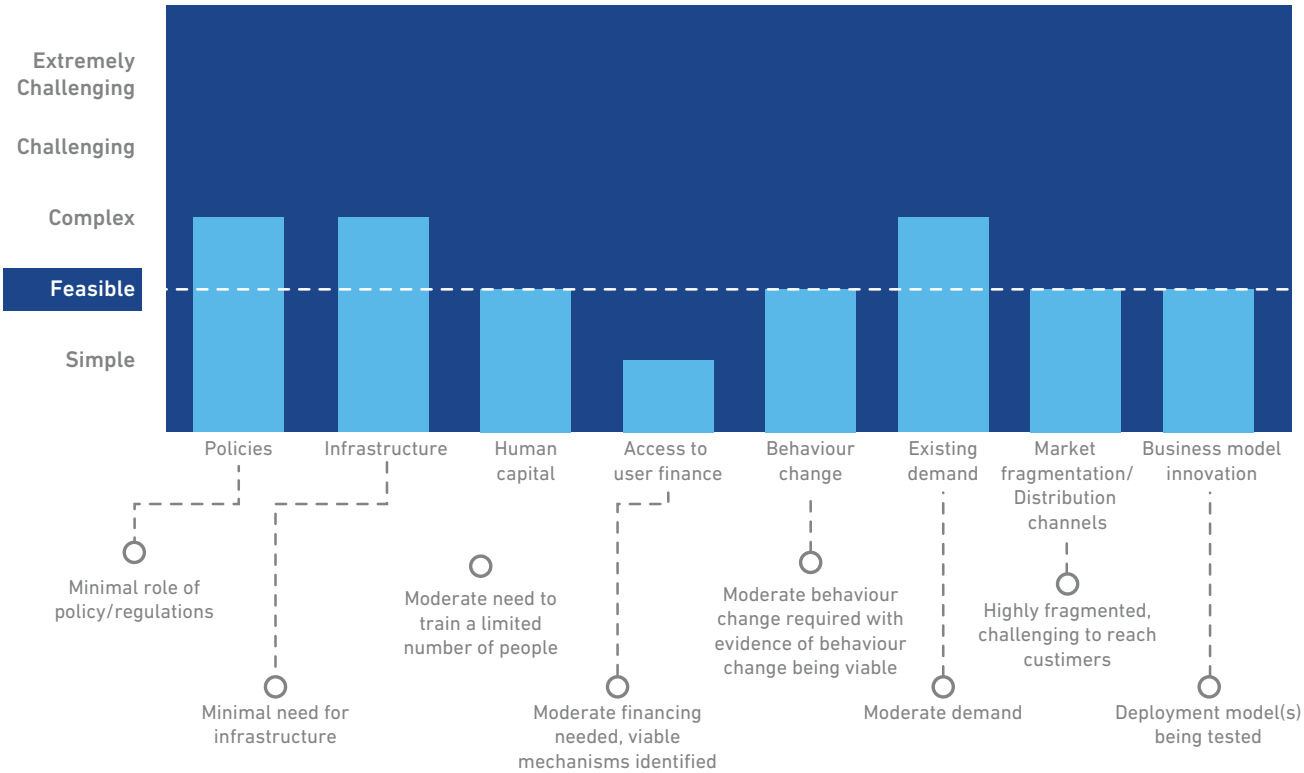
Deployment of new vaccines

Once any of these vaccines is developed, it can be deployed to children through existing, reasonably established, vaccine delivery channels. However, there are few mechanisms for delivering vaccines to adolescents and adults, and successful vaccination campaigns for these population segments would require significant government coordination, behavior change and financial investment.

Furthermore, even today vaccine delivery remains a challenge in many remote locations where supporting infrastructure like cold storage facilities are either few or non-existent. While vaccines are expected to be made available to patients at a low cost, financing for the vaccines by national governments or international donors would need to be secured in order to support widespread distribution. Policy changes would also need to support its introduction and distribution through public health systems.

Based on the above assessment, the projected time to market readiness is more than ten years, and the difficulty for deployment is FEASIBLE.

Breakthrough 23: Difficulty of deployment



[4]A large effort at research centers including International AIDS Vaccine Initiative (IAVI)'s Neutralizing Antibody Consortium (NAC), NIH's Vaccine Research Center (VRC) and Duke University's Center for HIV/AIDS Vaccine Immunology (CHAVI) have invested in this area. Since 2009, IAVI, the NAC, Theraclone and Monogram have collaborated to isolate and characterize 19 new broadly neutralizing antibodies from the Protocol G blood specimens.

2.4 Microbicides to provide a method of protection for those who are otherwise vulnerable to HIV/AIDS infection by their partner

Women, especially those living in societies and situations plagued by gender and income inequality, are often limited in their ability to ensure that their sexual partners use condoms. This risk is exacerbated in places with high rates of sexual violence and prevalence of polygamy. Specific high-risk populations, like sex workers and transgender people, also find themselves restricted in their ability to use protection during sexual contact.

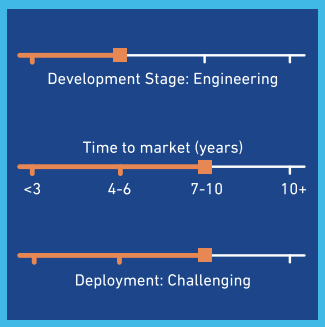
Microbicides are currently under development as vaginal or rectal products designed to protect healthy men and women from HIV/AIDS infection. These products are being tested in multiple forms—vaginal and rectal gels that can be used at the time of sexual contact and vaginal film, tablets or rings that can slowly release the microbicide drug to provide preventative coverage for up to a month.

Unlike vaccines, an effective microbicide must be made into a commodity that individuals will want to and can safely use, on a regular basis. Ideally, microbicides would be discreet, easy to use, long-lasting and easy to distribute.

There are several different microbicide candidates currently being studied. Between 2012 and 2016, two Phase III trials were conducted on the dapivirine vaginal ring and showed that ring use reduced the rate of new HIV infections by 56 percent among the women who used it as instructed (AVAC, 2018). Regulatory decisions are expected by end of 2018.

A couple of other studies are looking into how young women use the ring. Even after regulatory approval, the ring will take a few years before it becomes available for use. It will also take time to work out the best formulation and dosage, find a suitable delivery method and identify appropriate distribution channels before the product can be made available to the public.

Current State



Associated 50BT Chapters

SDG Alignment

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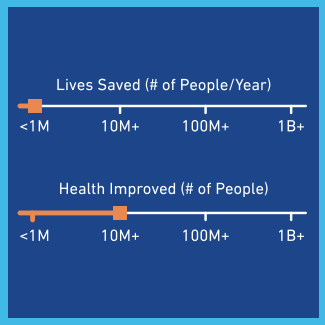


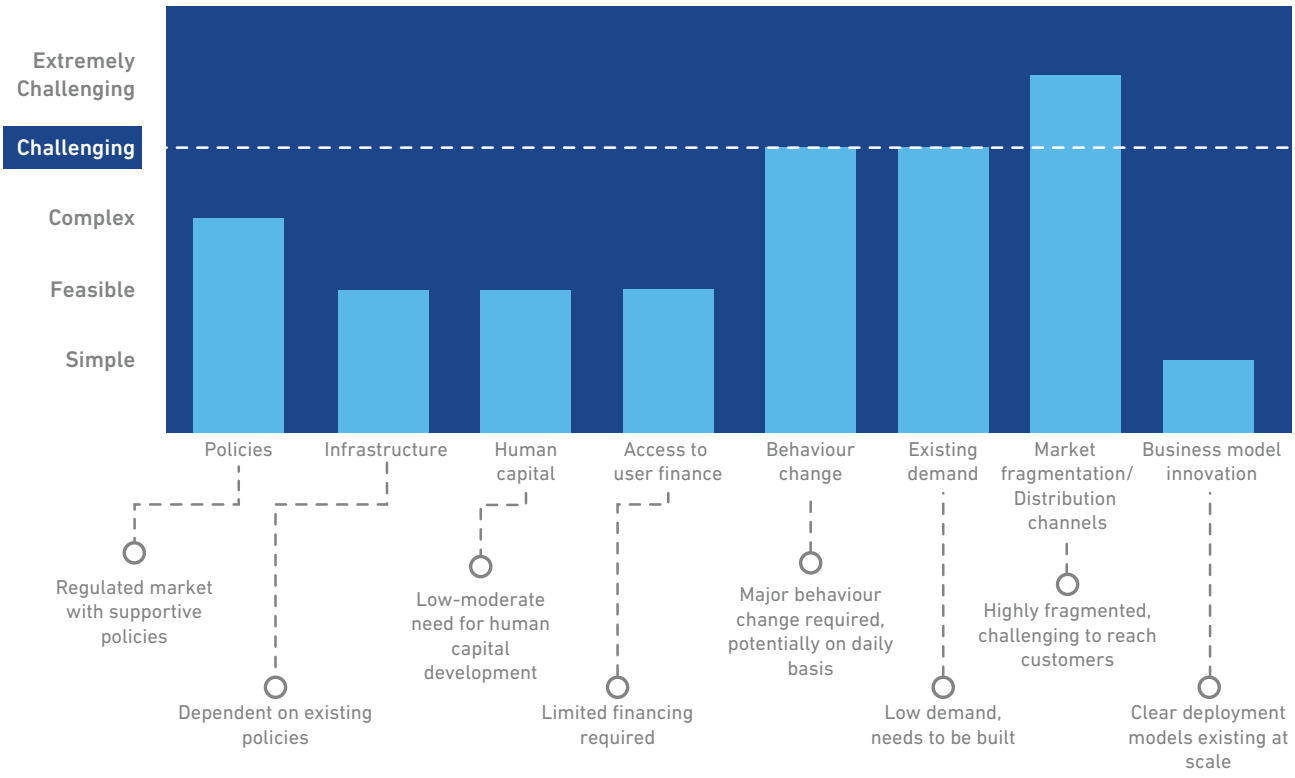
Commercial Attractiveness

Difficulty of deploying microbicides, once available, will depend on human factors, including how easy and convenient they are to use (microbicides require regular reapplication) and whether they are made available to consumers over the counter or by prescription only.

To ensure microbicides are widely available to people in LMICs, the price will have to be affordable, and this may mean that profit margins have to be kept low.

Based on the above assessment, the projected time to market readiness is one to five years and the level of difficulty for deployment is CHALLENGING.

Breakthrough 24: Difficulty of deployment



2.5 PrEP (pre-exposure prophylaxis) to reduce the risk of HIV infection

PrEP involves the use of antiretroviral therapy (ART) by those at a high risk for HIV infection to reduce the possibility of contracting the disease. It has already been included as a preventive strategy in WHO HIV prevention guidelines for high-risk populations.

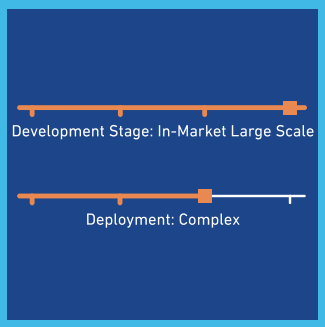
However, access to PrEP and ARVs in general is challenging, as is adherence for certain populations. Newer formulations and different delivery methods, such as a long-acting injectable PrEP or implants, can improve adherence. In addition to the currently available Truvada, a large number of ARV-based preventive products are now in the pipeline, mostly in the pre-clinical stage.

Next-generation strategies will use longer-acting drugs, focusing on delivery methods that are not widely used for HIV treatment. These include Cabotegravir, a long-acting injectable vaginal ring containing dapivirine that could be market-ready in 2019 (AVAC, 2018).

Despite these early encouraging signs, next-generation products will bring other challenges and much needs to be learned about how to enable large-scale adoption and use of PrEP, particularly among high risk populations. If the early results hold, the projected time to market readiness in developing countries is one to three years.

However, most countries facing the full impact of an HIV/AIDS epidemic do not have the infrastructure or economic resources to implement a PrEP strategy. Large scale implementation will be challenging.

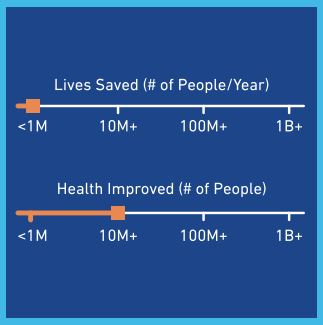
Current State



Associated 50BT Chapters

SDG Alignment

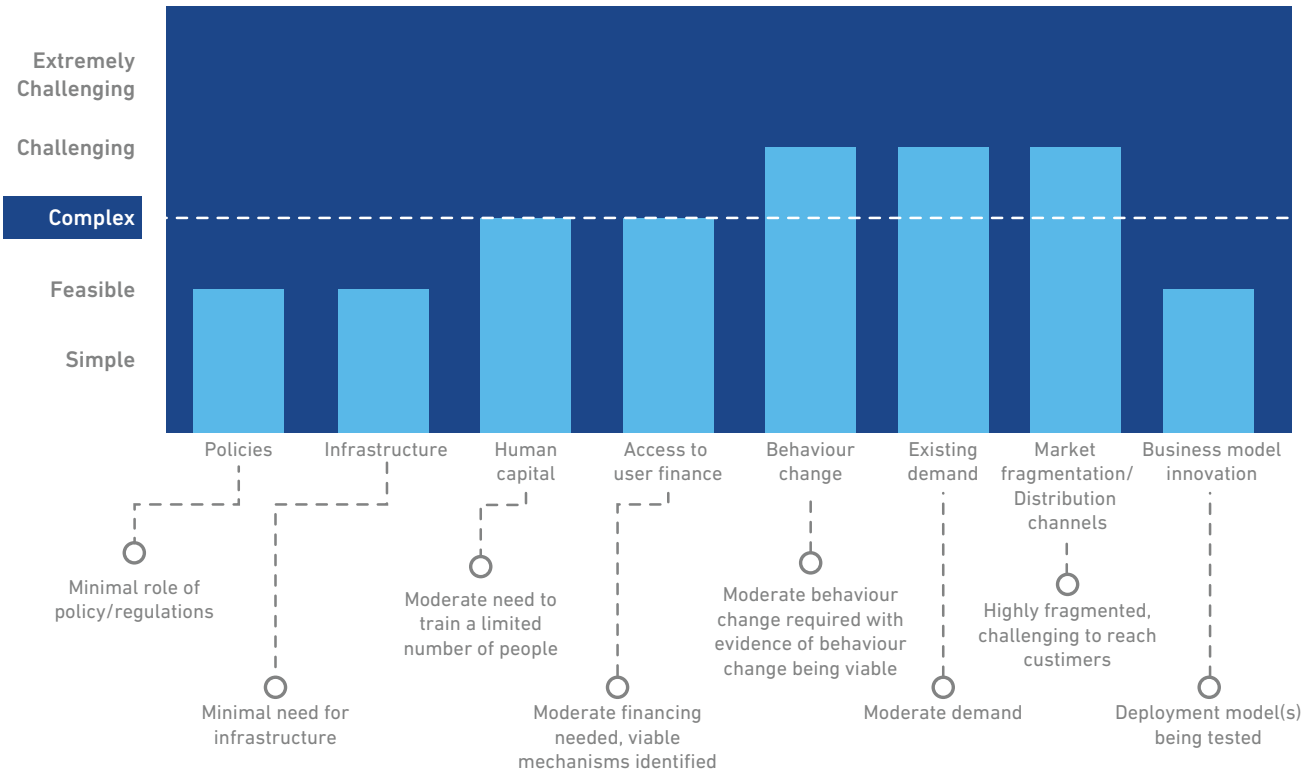
Impact



Commercial Attractiveness

Based on the above assessment, the level of difficulty for deployment is COMPLEX.

Breakthrough 25: Difficulty of deployment



26 Improved, longer-lasting antiretroviral therapy (ART) formulations to control HIV viral replication and increase patient adherence

While globally access to ART is improving, children and those living in rural areas with poor infrastructure are still particularly disadvantaged due to the demands of the treatment and associated costs and constraints. Reformulation of current ART drugs can improve ease of use, and in turn access, especially for neglected populations.

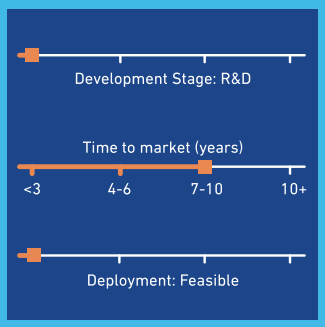
Improved and more effective drugs with simplified treatment regimens (like single fixed-dose pill or easy to administer pediatric formulations) and reduced toxicity can help prevent treatment interruption and increase patient adherence. Long-acting ARTs can go a step further by helping reduce overall treatment costs.

These improved treatments should ideally be low cost, remain stable in high heat and humidity, require few supportive technologies to deliver the treatment and offer improved safety profiles to allow use with minimal medical supervision.

There are currently a handful of long-lasting injectable ARV drugs in development. In August 2018, the Phase III study showed a monthly injectable cabotegravir and rilpivirine had similar efficacy to a standard of care, daily, oral three-drug regimen at week 48 (Viiv Healthcare, 2018).

Some of these new formulations are also being tested to see if they have a preventative effect in HIV negative individuals.

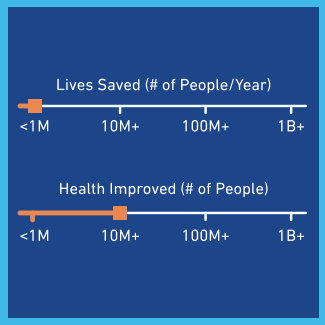
Current State



Associated 50BT Chapters

SDG Alignment

Impact



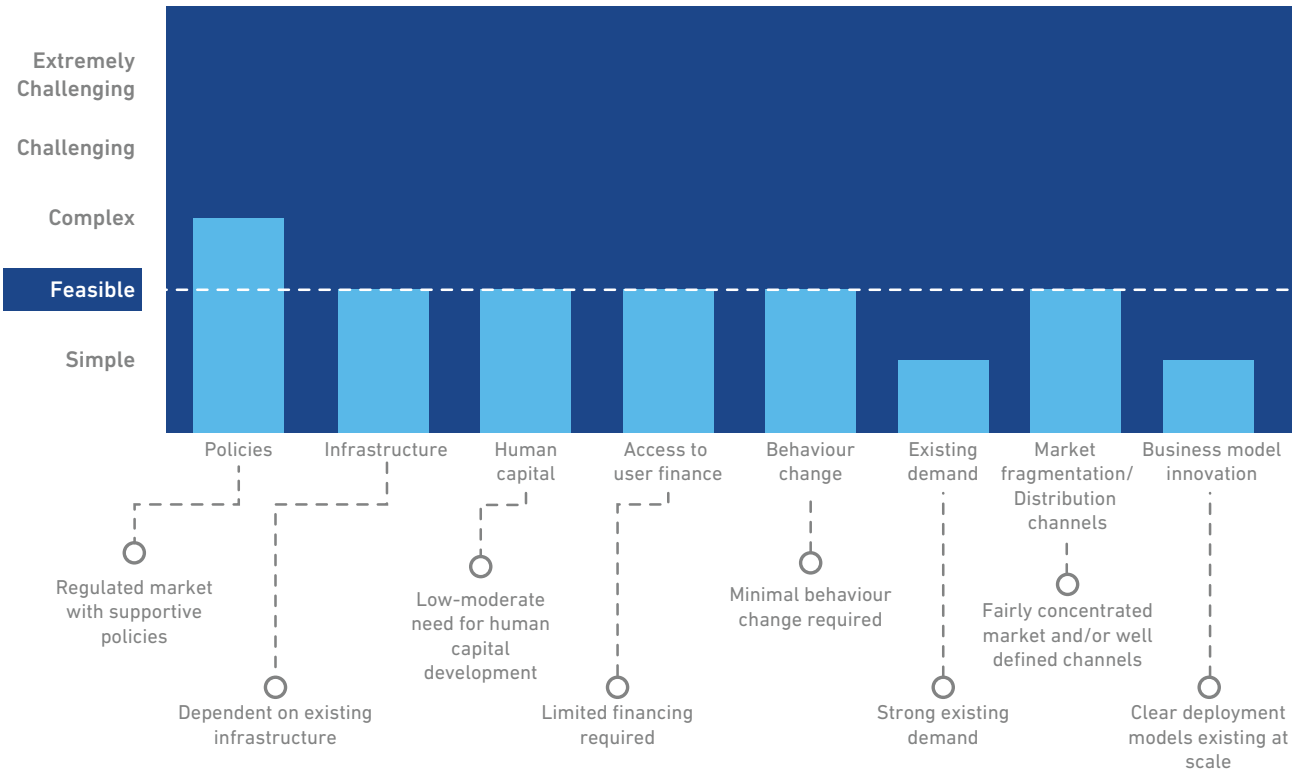
Commercial Attractiveness

Cost is the main barrier to widespread availability of new formulations and treatment. A 2010 study that modeled long-term funding needs for HIV/AIDS control in developing countries estimated that in the absence of an HIV/AIDS vaccine, global HIV control programs would cost between $400 and $700 billion for the period from 2009 to 2031 and approximately $22 billion to $24 billion annually by 2015, depending on policy choices adopted by governments and donors (Hecht, et al., 2010).

Today, in excess of $15 billion is spent on treating HIV positive people in the developing countries, and drug prices are believed to be near bottom.

The required investment to make improved therapies widely available is likely to be enormous. Based on the above assessment, the projected time to market readiness is seven to 10 years and the difficulty of deployment is FEASIBLE.

Breakthrough 26: Difficulty of deployment



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PULMONARY TUBERCULOSIS

INTRODUCTION

Pulmonary tuberculosis, commonly referred to as TB, is an airborne bacterial infection of the lungs. It is one of the most pervasive infectious diseases in the world.

In 2017, there were an estimated 10.4 million new cases and 1.2 million deaths (IHME GBD, 2017). As much as one quarter of the global population is estimated to be infected with latent TB, which occurs when someone is exposed to TB but their immune system keeps the bacteria sequestered in the body.

Most TB cases can be treated with first line antibiotics, however, a full course lasts six months, which makes compliance with treatment challenging.

Failure to complete full treatment has resulted in the emergence of TB that is resistant to first line drugs (referred to as multidrug-resistant TB or MDR-TB), which requires dramatically more expensive second line drugs taken over the course of 18 to 24 months. MDR-TB is becoming increasingly common and it is believed most cases of MDR-TB are now acquired directly, as opposed to being a result of failed treatment.

Diagnosis of TB is complex. There must be timely initial screening of patients who present with TB symptoms at the first point of care. For those patients screened as having TB, there must then be accurate diagnosis that can detect and distinguish between drug-sensitive TB and the various types of drug-resistant TB (DR-TB) including multiple drug-resistant (MDR-TB) and extensively drug-resistant TB (XDR-TB).

Current diagnostic methods possess low specificity and sensitivity and are unable to discriminate between drug-sensitive and DR-TB. The lack of a precise and accessible diagnostic for DR-TB is a critical challenge in stemming the disease's growth.

In light of the above challenges, five technologies can help reduce the burden of TB in developing countries.

- Breakthrough 23. Vaccines that can effectively control and eventually help eradicate the major infectious diseases of our time—HIV/AIDS, malaria, tuberculosis and pneumococcus
- Breakthrough 27. Shorter course treatments for both drug-sensitive TB and MDR-TB
- Breakthrough 28. New generation of antibiotics capable of treating fast-mutating bacteria like MTB and MRSA
- Breakthrough 35. Point-of-care nucleic acid test (NAT) that is simple, robust, and compatible with easily collected sample types
- Breakthrough 37. Affordable wearable technology with broader functionality for patient adherence and monitoring of health status

Pulmonary tuberculosis, also simply referred to as TB, is a bacterial infection caused by Mycobacterium tuberculosis (MTB). Affecting the lungs, it is one of the most pervasive infectious diseases in the world, with more than 10 million new cases every year and 1.2 million deaths annually.

CORE FACTS AND ANALYSIS

1. Tuberculosis is a contagious airborne disease that becomes problematic in immunocompromised people

TB is a highly contagious airborne disease that is most commonly transmitted through coughing and sneezing (WHO, 2018). It is one of the most pervasive infectious diseases in the world (**Table 1**), causing about 1.2 million deaths annually (IHME GBD, 2017).

Along with those suffering from active TB infections, an estimated one quarter of the world's population is infected with latent TB, which occurs when the MTB bacteria are sequestered by the body's immune system and remain alive but are neither an active infection or contagious. About five to 10 percent of individuals with latent TB will develop active TB in their lifetime, with the majority developing active TB within the first five years after infection (WHO, 2018).

TB Cases in 2017

Latent TB	1.9 billion total cases
Drug-sensitive TB	9.44 million new cases
Multiple drug-resistant TB (MDR-TB)	457,600 new cases
Extensively drug-resistant TB (XDR-TB)	38,900 new cases

Table 1: TB cases are often classified based on drug resistance or susceptibility. The WHO estimates that in 2017 some 9.44 million people fell ill with drug-sensitive TB that can be treated with a combination of first line drugs; 0.46 million fell ill with multidrug-resistant TB, of which 8.5 percent are considered to be extensively drug-resistant TB. (Source: WHO Global TB Report, 2018)[1]

When exposed to TB, people with healthy immune systems often only develop latent TB. However, individuals with compromised immune systems (due, for example, to malnutrition, aging or infections like HIV) are more likely to develop active TB upon initial exposure itself.

They are also more likely to develop active TB from latent TB infections. For instance, people infected with latent TB who are also HIV positive are 20 to 30 times more likely to develop active TB compared with those without HIV infection (WHO, 2018).

[1]Latent TB figures are calculated based on 25 percent of total world population of 7.6 billion in 2017.

In sub-Saharan Africa, HIV co-infection—found in 9 percent of new TB cases and 19 percent of TB-related deaths—is a major complication (WHO, 2018). Of all HIV-TB cases, 72 percent are found in the African region. Healthcare systems, especially for diagnosing and treating TB, are weaker in sub-Saharan Africa than in South Asia.

As a result, mortality rates, even for those without HIV co-infection, are higher in sub-Saharan Africa than in South Asia and Southeast Asia (WHO Global TB Report, 2018) (**Table 2**).

Regional prevalence of TB and HIV-TB co-infection

	Africa	Southeast Asia
New cases per year	2.48 million cases	4.44 million cases
Mortality (excluding TB-HIV)	413,000 deaths	638,000 deaths
Mortality rate	39 percent	26 percent
HIV prevalence in new cases	2.7 percent	3.5 percent
Percent new cases with MDR-TB	2.7 percent	2.7 percent
Percent TB re-infection cases with MDR-TB	14 percent	13 percent

Table 2: The underlying factors driving the spread of TB and the effectiveness of treatment are different in South-East Asia and Africa. (Source: WHO Global TB Report, 2018; MDR-TB includes rifampicin-resistant TB)

TB Testing, Photograph by CDC Global

KEY CHALLENGES

Although the epidemiology of TB is not fully understood, it is generally accepted that the spread of TB is facilitated by crowded, unhygienic conditions, both in homes and specific locations like public transport and hospitals. A critical role is also played by 'pump' populations, such as miners, prisoners and migrants (WHO, 2008; Stuckler, et al., 2010).

While coverage of TB services is high, in particular direct observed therapy (DOT), the slow decline in incidence rate, high number of missing TB cases, and growing concern for severe forms of drug resistant TB show that there is still a lot to be done to end the epidemic.

Most experts believe that it is feasible to end the TB epidemic, but lament that not enough funding and effort has been put into new tools to manage the disease.

In September 2018, world leaders convened for a historic UN high-level meeting on TB and endorsed a declaration to diagnose and successfully treat 40 million people with TB by end of 2022 and provide 30 million people with preventive treatment by 2022.

Member states committed to nearly doubling global levels of TB funding ($13 billion per year, with $2 billion for R&D by 2022). Nevertheless, it remains to be seen how accountability of the declaration will be ensured (Stop TB Partnership, 2018).

The most significant hurdles in the path to TB control are outlined below.

1. There is no effective vaccine for TB

The only available TB vaccine, Bacille Calmette-Guerin (BCG), was developed in the 1920s. It has so far proved effective only for preventing TB meningitis in children and severe Miliary TB, a form of the disease which tends to spread throughout the human body and cause small lesions.

The vaccine has variable efficacy in preventing pulmonary TB infections and the precise duration of the protection it affords is unknown. There is currently no TB vaccine specifically for adults. While a TB vaccine blueprint was published in 2012 by the TB vaccine community, the pace of new candidates entering pre-clinical stage and those already in the pipeline have moved slowly (Voss et al., 2018).

As well, up until 2018, there was no consensus within the community on product criteria for advancing vaccine candidates. WHO has since published two sets of preferred product characteristics (PPCs) for research and development efforts for vaccines for adults and adolescents and for improving upon BCG vaccination for infants (WHO, 2018).

The 2018 Global Report on TB Vaccines estimated that $1.25 million investment is needed to fund development of a TB vaccine (GTBVP, 2018).

2. Drug resistant TB is a growing problem

Standard treatment of active TB consists of combination treatment with four drugs (isoniazid, rifampicin, pyrazinamide, and ethambutol) daily for two months followed by two drugs (isoniazid and rifampicin) for four months.

All four drugs are generally available and relatively inexpensive. In many countries, complete treatment incurs a direct patient cost of $0 to $20, with a provider cost of $100 to $500. Costs, however, vary widely based on country and its healthcare system. Failing to complete this treatment regimen can lead to drug resistance in patients.

WHO-mandated DOTS protocol (directly observed treatment, short-course) has a patient monitoring component that ensures that patients complete the full treatment regimen.

However, 36 percent of TB patients in 2017 were not diagnosed (WHO, 2018), which can cause resistance to first line drugs, leading to multidrug-resistant TB (MDR-TB). From a negligible number in 2000, MDR-TB cases rose sharply to an estimated 558,000 total cases in 2017 (WHO, 2018).

On average, about 3.5 percent of new cases (**Exhibit 1**) and 18 percent of retreatment TB cases are now estimated to be MDR-TB. Some experts believe—although there is no supporting data—that this increase in incidence reflects an improved ability of health systems to diagnose MDR-TB, which has been widespread, and that perhaps the growth has not been as explosive as it seems.

Percentage of new TB cases that are drug-resistant

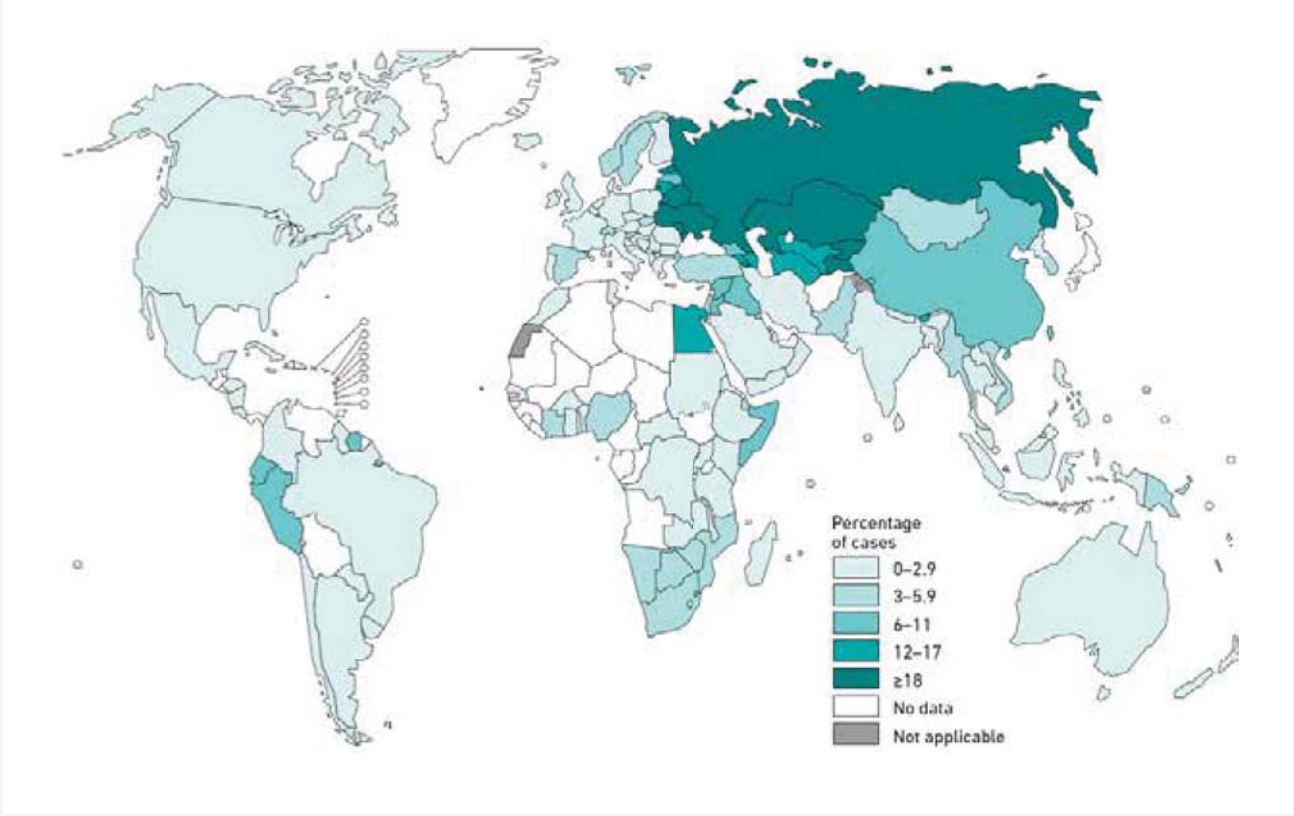


Exhibit 1: There is wide variety between countries in the percentage of new TB cases that are multidrug- or rifampicin-resistant TB (MDR/RR-TB). Countries in Eastern Europe and Central Asia have the highest rates of drug resistance, with more than 25 percent of new TB cases being MDR/RR-TB. (Source: WHO, 2018)

MDR-TB is significantly harder to treat. It requires an array of second line drugs, at a total cost of $2,600 to $4,700 to the provider, over a period of 18 to 24 months. Resistance to certain second line drugs is called extensively drug-resistant TB (XDR-TB).

This type of TB has also sharply increased in recent years, with 127 countries reporting cases of XDR-TB in 2017 (WHO, 2018). Combining these reported incidents of XDR-TB, the WHO has estimated that the proportion of MDR-TB cases that are extensively drug resistant is 8.5 percent (WHO, 2018).

Worryingly, MDR-TB appears to have transitioned from being primarily a developed condition in patients, stemming from not completing a full course of treatment, to a community-acquired disease where individuals are catching MDR-TB directly. It is believed that most cases of MDR-TB are now acquired, rather than developed due to lapses in treatment.

3. Current diagnostics are insufficient for both drug-sensitive and drug-resistant TB

Despite a variety of methods available for diagnosing TB, actual diagnosis remains suboptimal. Diagnostic challenges are further intensified in cases of HIV co-infection where existing diagnostic technologies are rendered largely ineffective.

While progress has been made in developing and introducing new diagnostic tools, such as rapid screening tests, point-of-care molecular diagnostics and next-generation sequencing for detecting drug-resistant TB, most are not only expensive but require highly trained personnel to operate.

Furthermore, there are challenges in the supply management of consumables, data storage, reporting and actionable use of diagnostic data to ensure appropriate treatments are provided.

Challenges with specific types of tests are highlighted below.

Sputum-Smear Microscopy (SSM)

The WHO DOTS protocol for TB diagnosis calls for the use of SSM where specially stained sputum is examined through a microscope for the presence of acid-fast bacilli (AFB). The protocol emphasizes the detection and treatment of sputum-smear positive cases of pulmonary TB (the most infectious cases).

However, it is now widely recognized that this approach alone is insufficient for diagnosis because:

- SSM requires extensive training for those administering the test, and delivers low-throughput results.
- SSM is not highly sensitive—roughly 70 percent sensitive in TB patients and less than 50 percent sensitive in patients with HIV co-infection.
- SSM does not identify people who have smear negative forms of TB; smear-negative pulmonary TB is especially common among people who are HIV-positive.
- SSM cannot be used to discriminate between drug-sensitive and drug-resistant forms of TB.
- SSM cannot be used to detect extra-pulmonary TB.

Bacterial Culture

To diagnose smear-negative and MDR-TB cases, sputum specimens can be cultured (grown) in laboratories, after which it is possible to diagnose or rule-out TB.

However, culture grown on solid media takes three to four weeks if not months to yield a result. This method also lacks accuracy and reproducibility. More recently, the use of liquid culture and molecular technologies has been recommended to reduce diagnostic delays (Stop TB Partnership, 2013).

Rapid Serological Tests

There are numerous rapid TB tests available on the market in developing regions. In July 2011, however, the WHO recommended against the use of these rapid serological tests for active TB, calling them "inconsistent and imprecise" and potentially leading to "misdiagnosis, mistreatment, and potential harm to public health." (WHO, 2011).

Nucleic Acid Amplification

The state-of-the-art method for TB diagnosis, recommended by the WHO since 2013, is highly precise and based on nucleic acid amplification technology (NAT), which identifies the presence of the bacterium at the DNA level.

The leading product in this space, Xpert MTB/RIF®[2], is capable of identifying rifampicin-resistant infections without bacterial culture, allowing it to accurately discriminate between drug-sensitive TB and MDR-TB. The technology is expensive. In 2015, each single-test disposable cartridge cost about $10 with concessional pricing, and the back-end reader cost approximately $17,000.

These prices, however, are changing rapidly. A number of less expensive, point of care NATs are now, or will soon be, on the market.

[2]Developed by FIND, Cepheid, Inc., and the University of Medicine and Dentistry of New Jersey with funding from NIH, and the Bill & Melinda Gates Foundation.

Next-Generation Sequencing

One of the greatest threats to global TB care and prevention efforts is the persistence of drug-resistant TB (DR-TB). Next-generation sequencing (NGS) presents an attractive option for DR-TB detection and characterization, and many NGS platform options now exist for DR-TB diagnosis (WHO & FIND, 2018).

NGS assays can provide detailed sequence information for multiple gene regions or whole genomes of interest, and assess the occurrence of rare mutations and other genomic data that molecular assays may not detect. The uptake of these technologies has been slow, due to the high cost, need for very specialized training and lack of easily actionable data outputs.

Simple rapid diagnostic tools that can replace SSM at the lower levels of healthcare systems where patient first present for care are urgently needed. These diagnostics should be effective in peripheral level health systems in diagnosing active pulmonary TB, including sputum-smear negative TB and detecting drug resistance (Stop TB Partnership, 2013)

4. Major challenges exist in the effective treatment of TB depending on whether an individual has drug-sensitive TB, MDR-TB or TB-HIV co-infection

Treatment for TB is lengthy and physically demanding. Drug-sensitive TB treatment lasts at least six months and the medication can cause significant side effects. MDR-TB treatment lasts 18 to 24 months and requires even more physically demanding medication. The length and difficulty of treatment is one of the key underlying factors influencing TB mortality and its importance as a global health issue.

Within this context, there are several important break points in the treatment process that lead to mortality.

The importance of each breakpoint varies by clinical scenario (such as whether a patient has drug-sensitive TB, MDR-TB or TB with HIV co-infection) and is outlined below.

Drug-sensitive TB

The largest drivers of mortality are patients who die in treatment and patients who are treated outside of DOTS protocol[3], as shown in **Exhibit 2** (WHO, 2013). These drivers are listed below.

- Of known TB deaths, the majority are patients who die in treatment. This reflects the fact that most individuals who develop TB do ultimately end up seeking care, but many patients do not receive treatment until the disease has become too advanced.

  This is caused by patient delays in seeking care, provider-caused delays in treatment, natural rates of treatment failure and also the effects of HIV co-infection. Delays in seeking care are driven by a lack of awareness of early TB symptoms, considerable community stigma and insufficient access to healthcare. Provider-caused delays often arise in diagnostics and referrals. TB is often diagnosed clinically or with methods that produce false negatives.

  Furthermore, diagnostics can be slow to produce results, which means some patients fall off before receiving their results and subsequently treatment, especially in rural sub-Saharan Africa where patient follow-up is particularly challenging. Patients visit an average of three clinics before receiving a positive diagnosis and care referral, creating a delay of 16 to 85 days (Nogueira et al., 2018; Virenfeldt et al., 2014). There is also a natural rate of failure with current drugs due to their interactions with the body and the disease, although most experts believe that this is a far less significant cause of mortality relative to delays in treatment.

[3]ITT analysis, based on expert interviews and literature cited throughout this report.

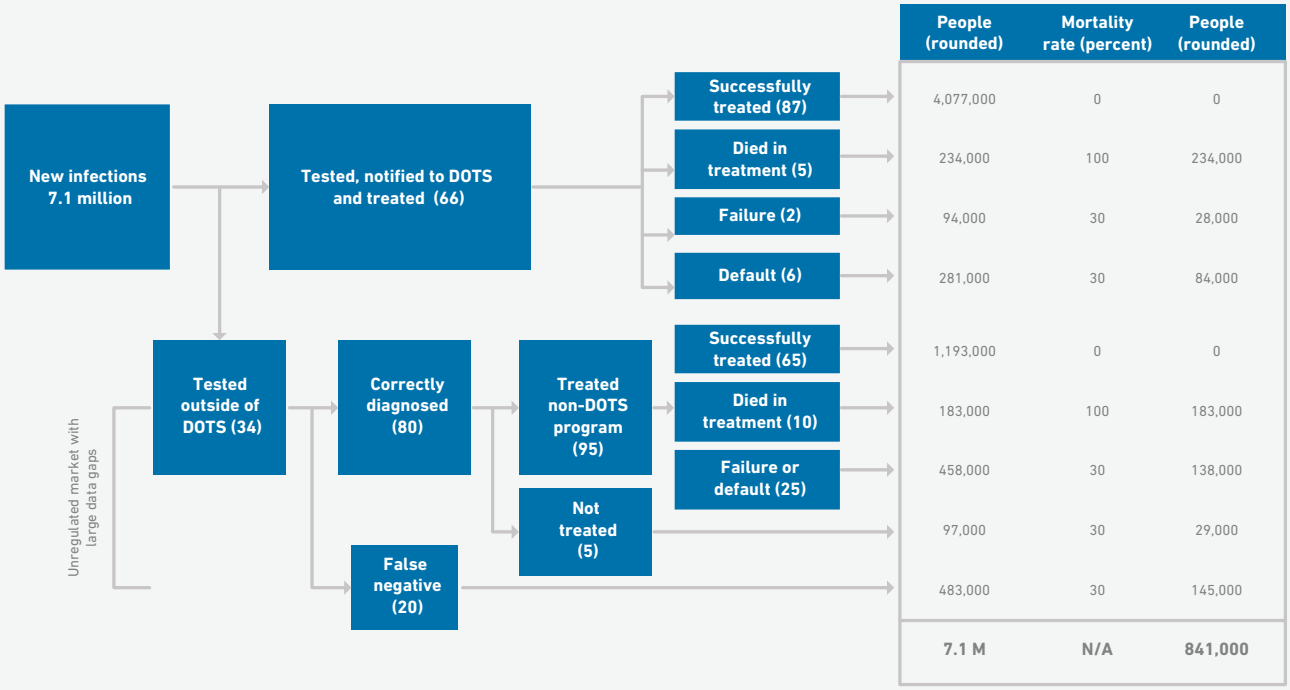
Finally, the number of patients who die in treatment is influenced by patients with TB-HIV co-infection, and while this analysis looks specifically at the 7.1 million TB patients who do not have HIV, the percentages applied in the analysis are global figures and include TB patients with HIV who have greater case fatality rates in treatment.

- Roughly a third of patients do not receive DOTS-compliant treatment because they go to private practitioners or traditional healers. These patients receive non-WHO approved treatments, which produce lower success rates.

- The latest treatment outcome data show success rates of 82 percent for TB (2016 cohort), 77 percent for HIV-associated TB (2016 cohort), 55 percent for MDR/RR-TB (2015 cohort) and 34 percent for extensively drug-resistant TB (XDR-TB) (2015 cohort) (WHO, 2018).

  Six percent of patients under DOTS coverage and 25 percent of patients outside of DOTS default due to the long treatment cycle, even if they are receiving treatment through DOTS-compliant facilities, because of insufficient compliance monitoring systems. This is a key contributor in the growth of MDR-TB, which is now driven primarily by transmission (WHO, 2013).

Drug-sensitive TB mortality drivers



People (rounded)	Mortality rate (percent)	People (rounded)
4,077,000	0	0
234,000	100	234,000
94,000	30	28,000
281,000	30	84,000
1,193,000	0	0
183,000	100	183,000
458,000	30	138,000
97,000	30	29,000
483,000	30	145,000
7.1 M	**N/A**	**841,000**

Exhibit 2: A breakpoint analysis for drug-sensitive TB. The largest breakpoints involve mortality during treatment due to delays in seeking care, provider-caused delays in treatment, and non-WHO approved treatment by private health practitioners.[4]

[4]See "Data Sources for Analysis of Mortality from Drug-Sensitive TB and MDR-TB" at the end of this section for full explanation of data and sources.

MDR-TB

- The major challenge in treating MDR-TB (**Exhibit 3**) is that it is typically misdiagnosed as drug-sensitive TB. Even if it is appropriately diagnosed, the antibiotics required for treatment are neither available nor affordable for most patients. Additionally, treatment is non-curative in almost half the patients. As a result, overall mortality rate for MDR-TB is 41.2 percent (WHO, 2018).

- The most significant driver of mortality from MDR-TB is a lack of positive diagnosis of MDR-TB, which in turn is driven by lack of diagnostics that can discriminate between MDR-TB and drug-sensitive TB. Only 24 percent of new TB cases and 70 percent of relapse cases are tested for MDR-TB, and undiagnosed cases account for over 90 percent of deaths from MDR-TB (WHO Global TB Report, 2018).

  It is worth noting that in our analysis we used calculated MDR-TB case detection rates that are much higher than global estimates. In order to reconcile global infection and mortality figures, and given the case notification rate through DOTS, and known outcomes of treatment, we calculated that 25 percent of new MDR-TB infections and 45 percent of retreatment MDR-TB cases were accurately diagnosed. These are much higher than global estimates and reflect the lack of high-quality data in MDR-TB global surveillance.

- Only 87 percent of all MDR-TB patients notified of their TB condition receive appropriate treatment (WHO, 2018). This is primarily due to low number of treatment facilities capable of administering MDR-TB and the high cost of second line drugs. Only 9 percent of TB management units have MDR-TB treatment services, while necessary drugs can cost 130 times as much as the first line drugs (Pooran, 2013). The length and technical complexity of administering proper treatment for MDR-TB is a key reason for low coverage.

- MDR-TB treatment is non-curative in more than half of patients. MDR-TB treatment has higher failure, default and death while in treatment rates than drug-sensitive TB. This is due to a number of factors including that MDR-TB patients often receive appropriate treatment at a more advanced stage of disease (after a previous round of TB treatment, or after a series of misdiagnoses for drug-sensitive TB), and longer and more physically demanding treatment regimes (WHO, 2018).

MDR-TB mortality drivers

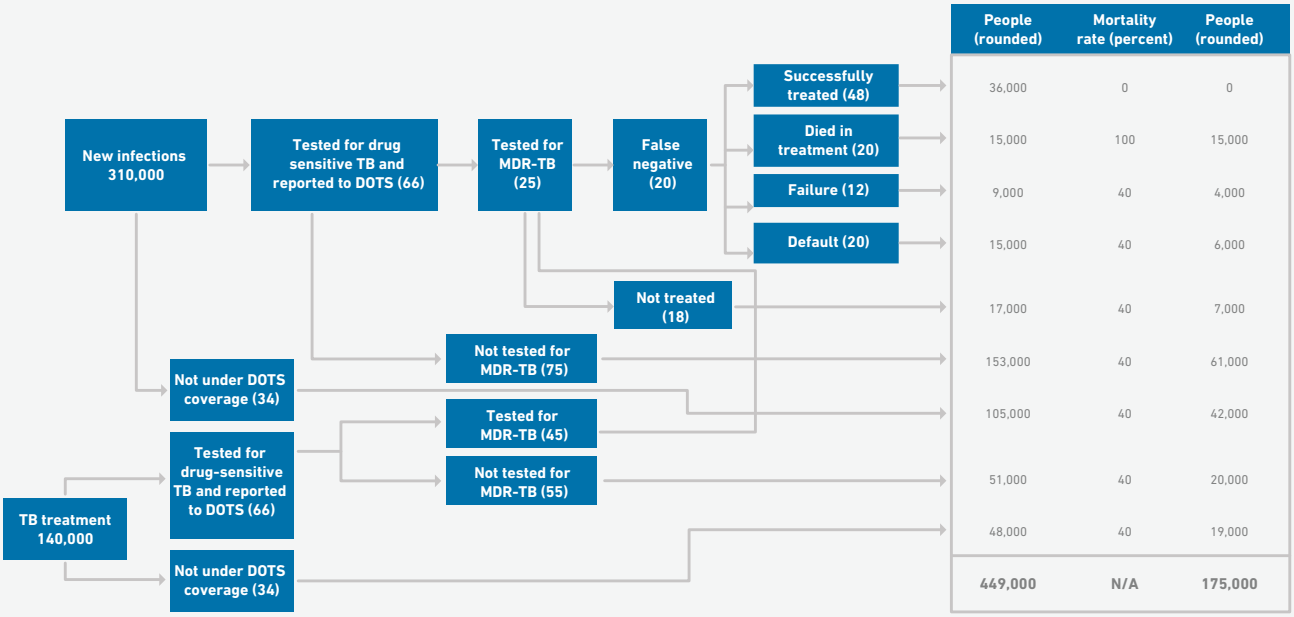


Exhibit 3: A breakpoint analysis of mortality due to MDR-TB shows that misdiagnosis of MDR-TB as drug-sensitive TB is the most significant problem. A second major concern is that even with accurate diagnosis, treatment is non-curative in more than 50 percent of patients.[5]

HIV co-infection

Nine hundred thousand people (13 percent) around the world with active TB have HIV co-infection. Of these cases, 72 percent are in Africa, where 27 percent of the 2.48 million new TB cases in 2017 had HIV co-infection (WHO Global TB Report, 2018). In most regions it is not standard practice to test for HIV when an individual is being tested for TB and vice versa.

Moreover, if an individual has HIV, diagnosing a TB co-infection using a standard sputum smear test is even harder given the high false negative rate of the test. Further complicating the challenge is that HIV-TB co-infection is often extra-pulmonary and does not show up at all in SSM tests.

For those who do receive an accurate diagnosis, drug compatibility poses a challenge. Many TB treatments are incompatible with ARVs for HIV. Rifampicin, in particular, can cause some ARVs to be metabolized too quickly, reducing their effectiveness.

[5]See "Data Sources for Analysis of Mortality from Drug-Sensitive TB and MDR-TB" at the end of this section for full explanation of data and sources.

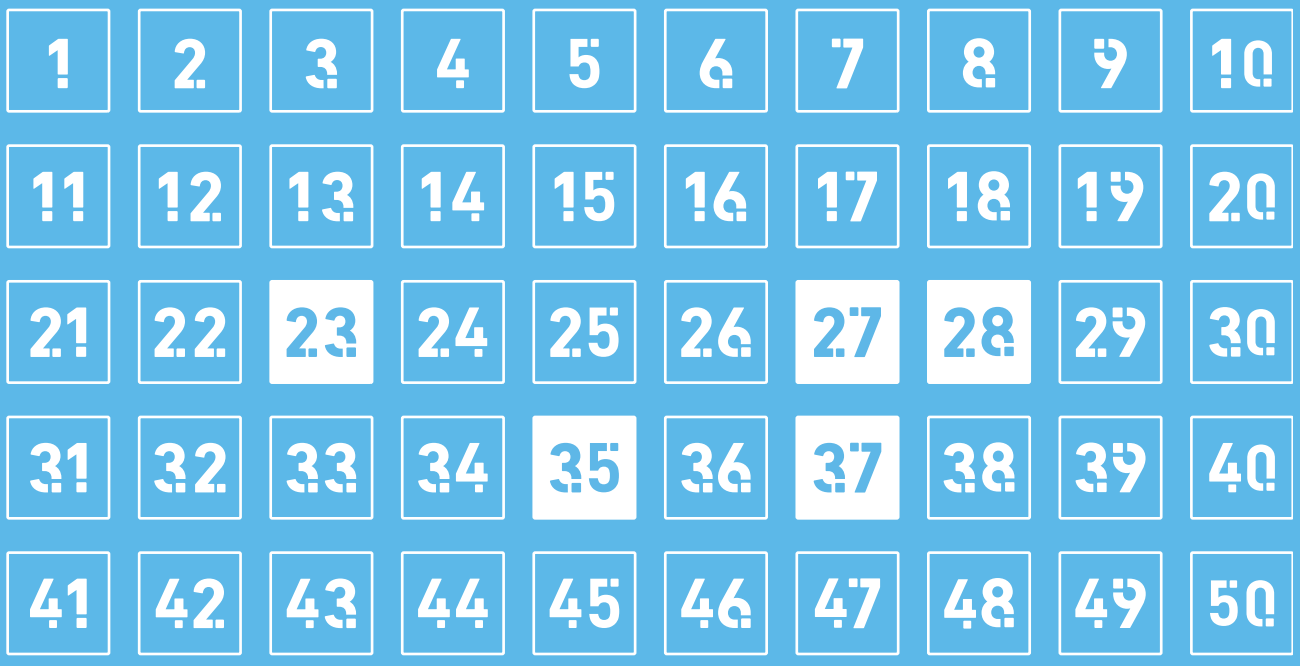
SCIENTIFIC AND TECHNOLOGICAL BREAKTHROUGHS

Many interventions have proven effective in reducing the spread and burden of TB and warrant continued attention and expansion, for example, the DOTS protocol. Additional non-technology interventions include bringing down the cost of second line drugs through market coordination interventions, similar to those used for first line drugs, and interventions to reduce care seeking and provider-caused delays. As the spread of the disease is poorly understood, there are significant opportunities in better understanding the epidemiology and transmission of the disease to design effective public health interventions.

These interventions would likely be focused on high transmission settings such as hospitals, public transportation and potentially households in urban slums. There is also a need to scale available innovations, as widespread access has still not been achieved with existing technologies and many people with TB still struggle to access an adequate initial diagnosis.

In addition to these interventions, there are five major scientific and technological opportunities to reduce TB mortality.

Breakthroughs:



23. Vaccines that can effectively control and eventually help eradicate the major infectious diseases of our time—HIV/AIDS, malaria, tuberculosis and pneumococcus

Collectively, HIV/AIDS, malaria, tuberculosis and pneumonia kill more than five million people a year, and represent a significant disease burden for low income populations in sub-Saharan Africa and South Asia. Effective and affordable vaccines for these diseases do not exist yet due to the intrinsic complexity of the pathogens causing them, and a lack of understanding of the specific mechanisms through which our immune systems protect against these diseases. The process of vaccine development—basic research on disease etiology, vaccine construction, pre-clinical and clinical testing—is technically challenging, expensive and time consuming.

23c. A vaccine for pulmonary TB

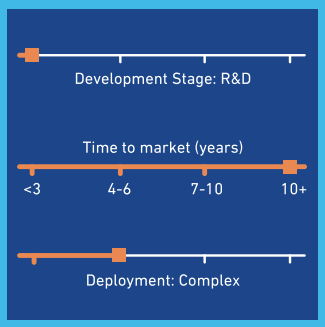
There is currently no vaccine for pulmonary TB. If available, it could be one of the most effective ways to prevent the spread of the disease. Most experts agree that without a vaccine, the ambitious SDG and End TB goals will not be met by 2035.

There are multiple potential vaccination strategies including pre-exposure vaccination to create immunity to TB, post-exposure vaccination to delay development of latent TB to active TB—particularly for HIV positive patients—or therapeutic vaccination to kill TB bacteria. The current focus is on pre-exposure vaccines for adults and adolescents as opposed to children. This is due to the higher projected impact of strategies targeting adolescents and adults over children, as well as the more advanced state of research on pre-exposure vaccines relative to post-exposure vaccines. Strategies include a pipeline of vaccine candidates that includes whole cell, adjuvanted proteins and vectored subunit vaccines.

The lack of a basic scientific understanding of protection against TB is one of the major challenges in development of a vaccine. Specifically, the correlates of protection for TB had not been well understood. However, since 2012 new information has been generated from the many preclinical and clinical test results from vaccine candidates regarding the molecular mechanisms of disease-producing activity of Mtb, immune response to a vaccine that correlate with protection from Mtb infection and basic pathogenesis of TB disease in humans and animal models.

There are now tools to manipulate the vaccine induced immune response with choice of vaccine technology, antigen and adjuvant. However, the mechanism with which the quality of immune response is affected by these choices has not been well explored (Voss, et al., 2018; GTBVC, 2018).

Current State



Associated 50BT Chapters

SDG Alignment

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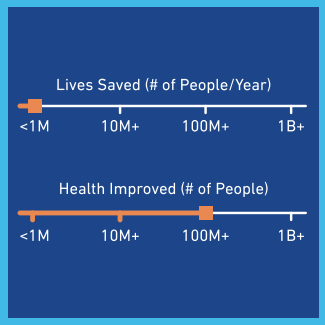


Commercial Attractiveness

As of 2018, 14 different TB vaccines are undergoing clinical trials, compared with seven in 2014 when the first edition of this report was published. All of these are either in Phase I or Phase II, with one candidate that has entered in Phase III. Seven more pre-clinical candidates also exist, with 20 novel strategies in discovery phase (GTBVC, 2018).

Two studies in particular are showing promise after a decades long quest to develop a more effective vaccine against TB.

In July 2018, a Phase II trial showed that re-vaccinating adolescents with BCG who received the vaccine as infants was 45 percent effective in preventing sustained TB infection (Nemes, et al., 2018). A Phase IIb trial conducted in September 2018 is showing promise of a vaccine candidate, M72/AS01E (GSK).

The results illustrate that the vaccine candidate was 54 percent effective at preventing active pulmonary TB disease from developing in adults with latent TB infection (Van Der Meeren, et al., 2018).

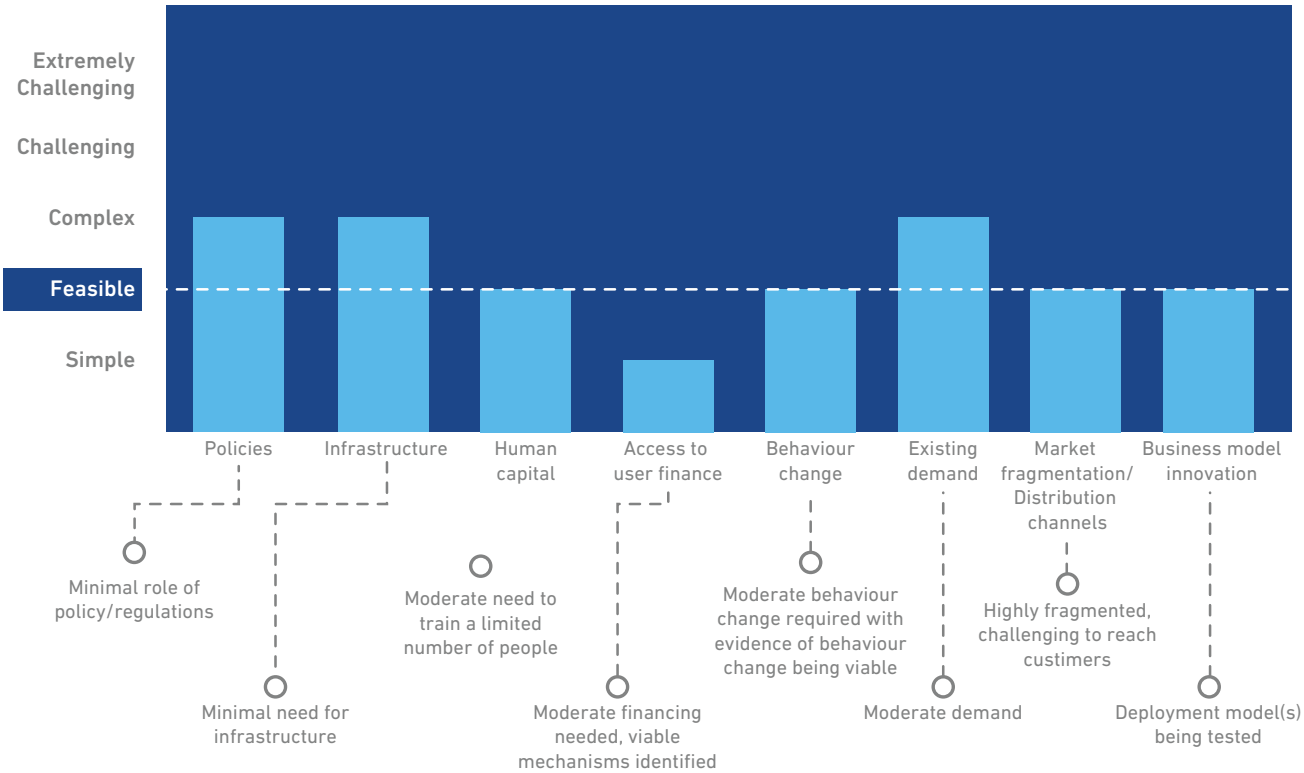
Deployment of new vaccines

Once any of these vaccines is developed, it can be deployed to children through existing, reasonably established, vaccine delivery channels. However, there are few mechanisms for delivering vaccines to adolescents and adults, and successful vaccination campaigns for these population segments would require significant government coordination, behavior change and financial investment.

Furthermore, even today vaccine delivery remains a challenge in many remote locations where supporting infrastructure like cold storage facilities are either few or non-existent. While vaccines are expected to be made available to patients at a low cost, financing for the vaccines by national governments or international donors would need to be secured in order to support widespread distribution. Policy changes would also need to support its introduction and distribution through public health systems.

Based on the above assessment, the projected time to market readiness is more than ten years, and the difficulty for deployment is FEASIBLE.

Breakthrough 23: Difficulty of deployment



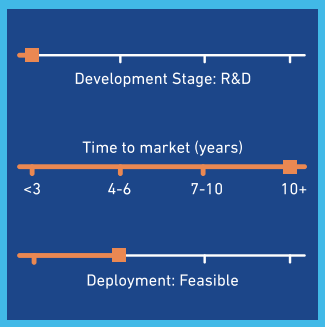
2.7 Shorter course treatments for both drug-sensitive TB and MDR-TB

Many challenges related to controlling TB are a function of long and demanding treatment regimens. Even though treatment duration of drug-sensitive TB has been brought from nine to 12 months down to six to nine months, this long time frame still creates major challenges. Second line drug regimens for MDR-TB take 18 to 24 months and are able to cure only about 50 percent of the cases. Treatment for drug-resistant TB sometimes exceeds two years. In addition, some current drugs are not easily co-administered with antiretrovirals (ARVs) for patients with TB-HIV co-infection.

These drug challenges lead to high rates of non-compliance, expensive delivery systems to provide treatment responsibly, and the growth of drug-resistant TB. New drugs that can treat drug-sensitive TB over the course of weeks as opposed to months, will dramatically alleviate many of the challenges of controlling TB. Shorter treatment for latent TB infection is already available.

The TB Alliance highlights several drugs at various stages of clinical testing for both drug-sensitive and drug-resistant TB. Three drug regimens in Phase III trials for drug-sensitive TB could be available within a few years, reducing treatment time from six to three or four months.

Current State



Associated 50BT Chapters

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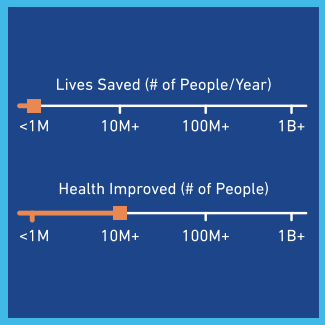
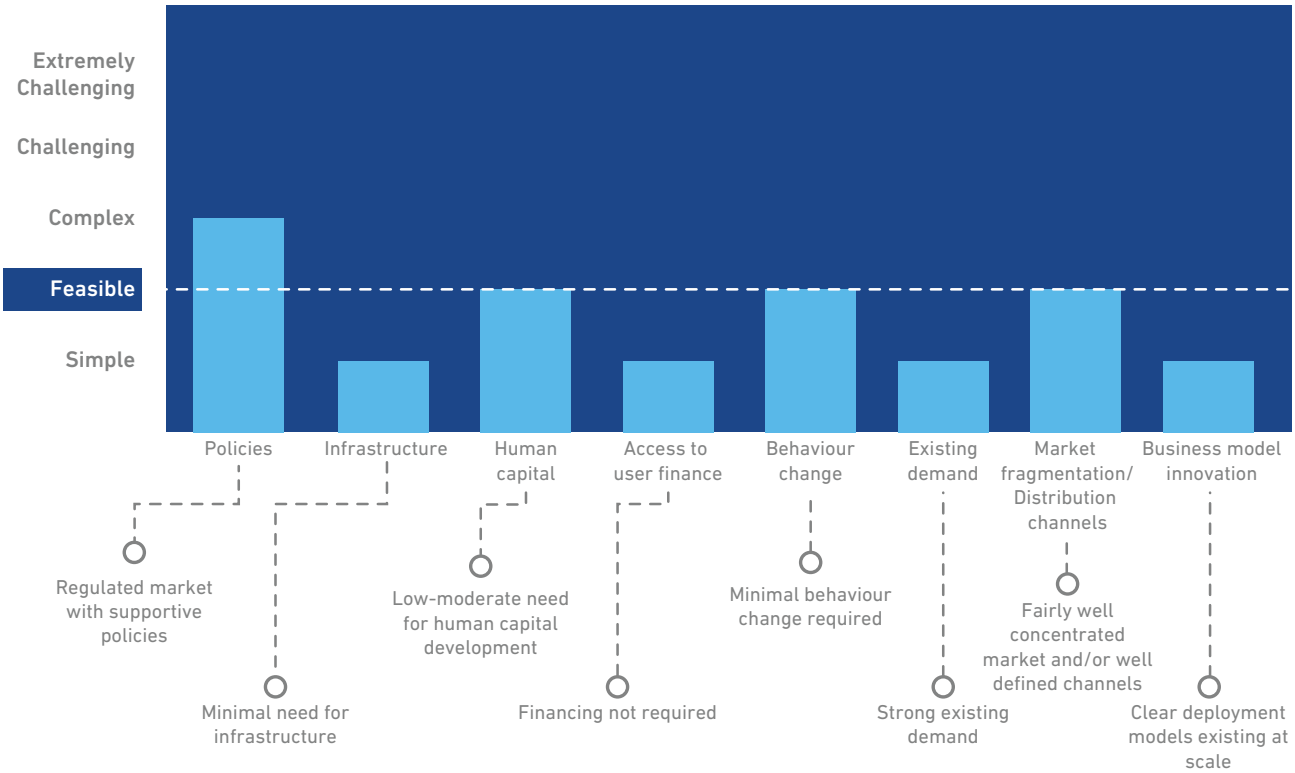


Commercial Attractiveness

The projected time to market readiness—depending on the drug—is two to four years and difficulty of deployment is FEASIBLE.

Breakthrough 27: Difficulty of deployment



28 New generation of antibiotics capable of treating fast-mutating bacteria like MTB and MRSA

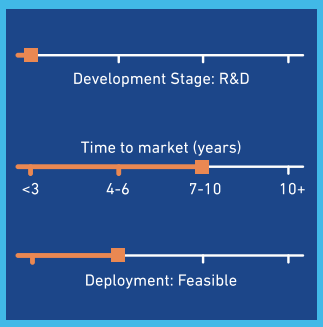
Antibiotic resistance is reaching dangerously high levels in all parts of the world, with some of the most common infections becoming difficult to treat. This occurs when bacteria develop the ability to defeat the drugs that are designed to kill them, making the drugs ineffective. Antibiotic resistance does not mean the body becomes resistant to antibiotics; instead, it means that bacteria have become resistant to the drugs designed to kill them. Each year, hundreds of thousands of people die from drug-resistant strains of common bacterial infections, and the number is increasing steadily. Important examples of resistant bacteria include:

- Multidrug-resistant tuberculosis (MDR-TB), a form of TB that is resistant to the two most powerful anti-TB drugs, and extensively drug-resistant tuberculosis (XDR-TB) that is resistant to at least four of the core anti-TB drugs.
- The bacteria *E. coli*, which is gaining resistance to fluoroquinolone antibiotics that are widely used to treat urinary tract infections.
- The common intestinal bacteria *Klebsiella pneumoniae*, which is becoming resistant to a last resort treatment, carbapenem antibiotics, in all regions of the world.
- The bacteria *Staphylococcus aureus*, which has widespread resistance to first-line drugs, causing growing numbers of deaths due to MRSA (methicillin-resistant *Staphylococcus aureus*).
- The bacteria *Neisseria gonorrhoeae*, responsible for the sexually-transmitted disease gonorrhea, is gaining resistance to the last resort medicine, third generation cephalosporin antibiotics, in at least 10 countries.

Antibiotic resistance is a complex problem that is driven by many interconnected factors, and coordinated effort is required to minimize its emergence and spread. Without urgent and effective action, there is a risk of returning to an era in which common infections and minor injuries can cause death.

Action on several fronts is needed, including improving awareness and understanding of antibiotic resistance, strengthening surveillance and research, reducing the incidence of infection through improved hygiene and sanitation, improving diagnostics to reduce unnecessary prescription of antibiotics, and optimizing the use of existing antibiotic medicines. Critically, there is also a need for a new generation of antibiotics that are effective against the bacteria that are resistant to current drugs.

Current State



Associated 50BT Chapters

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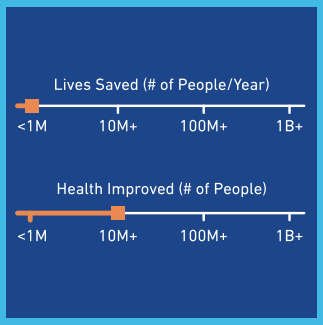


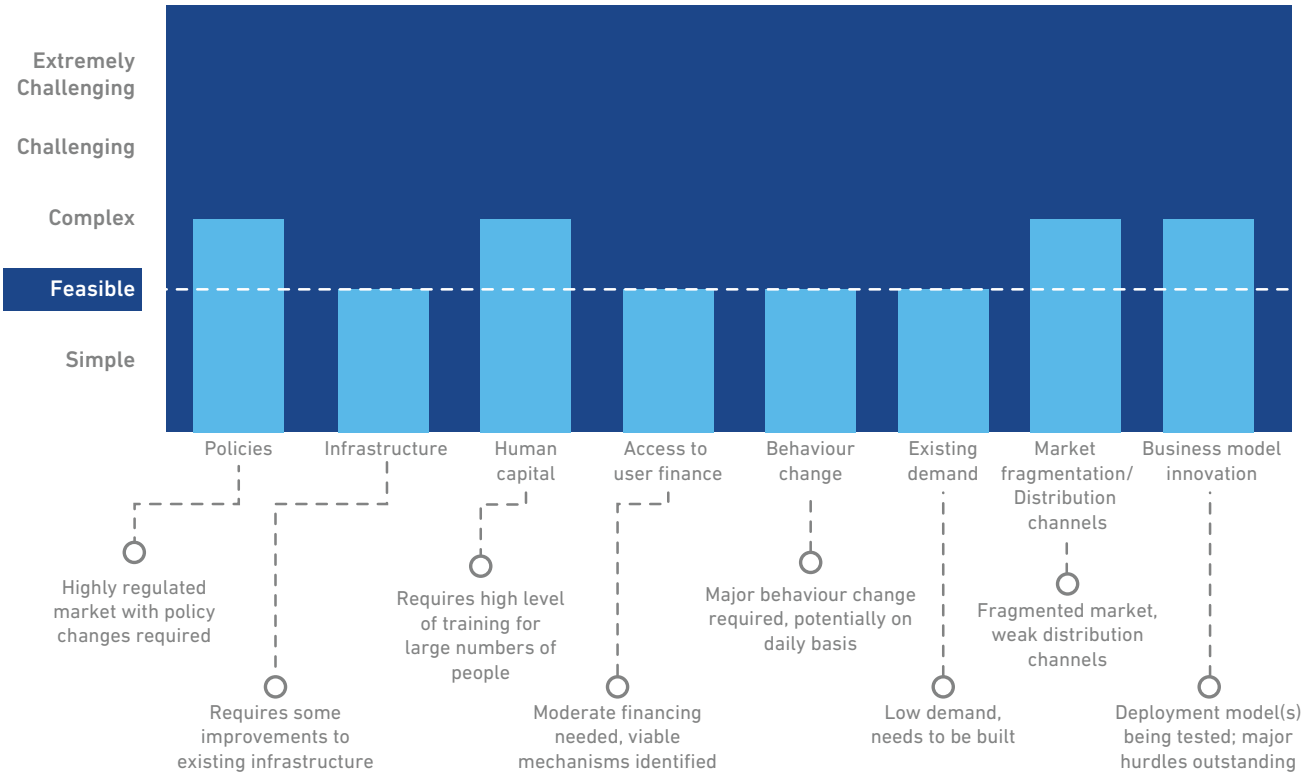
Commercial Attractiveness

While there are some new antibiotics in development, none of them are expected to be effective against the most dangerous forms of resistant bacteria. There is a need for better incentives to promote investment in new drugs, because the commercial return on R&D investment in new antibiotics is currently unattractive.

Although the total market for antibiotics is relatively large, with annual sales of about $40 billion, only about $4.7 billion of this is from sales of patented antibiotics. Between 2003 and 2013, less than 5 percent of venture capital investment in pharmaceutical R&D was for development of antimicrobials.

Even with adequate funding, the development of improved antibiotics is scientifically challenging, and we expect it will take up to 10 years for new drugs to be market ready. Once developed, the deployment of new antibiotics can use existing supply chains and is expected to be FEASIBLE.

Breakthrough 28: Difficulty of deployment



3.5 Point-of-care nucleic acid test (NAT) that is simple, robust, and compatible with easily collected sample types

A key breakthrough in disease detection is the development of point-of-care nucleic acid tests (NATs) applicable to a wide range of disease conditions. These tests should be compatible with simple sample types (such as whole blood), portable, rapid, robust despite high ambient heat and humidity, capable of being used by minimally trained technicians, and non-reliant on refrigeration, running water, and stable electricity. In addition, the technology should have a low price point to make it appropriate for use in peripheral healthcare facilities. Developing such a test poses significant technical challenges; it requires modular, instrument-free technologies for each of the NAT steps: sample processing, signal amplification and detection.

Sample preparation technologies

The manual, time-consuming and infrastructure-intensive sample collection, processing and purification associated with preparing an optimal sample for NAT must be integrated and automated so that minimally trained healthcare workers can perform testing. Non-invasive sampling technologies, simplified extraction techniques, sample concentration technologies and purification-free chemistries can help advance this goal.

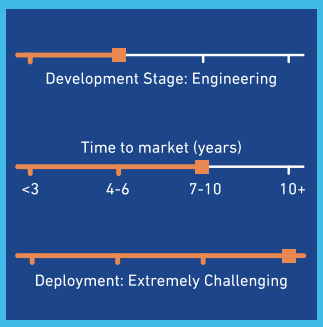
Signal amplification technologies

The thermocycler, electricity and temperature control required for polymerase chain reaction (PCR) make NAT unsuitable for point-of-care adoption in low-resource settings. New technologies that are less sensitive to sample contaminants, have simpler thermal profile mechanisms that reduce sample processing requirements, and are not dependent on grid electricity, appear to be the way forward. Also critical is reduced reliance on cold chains and refrigeration. This will come from improvements in packaging, the ability to monitor temperature history, and the use of more stable substitutes in place of heat-sensitive reagents. Additionally, NATs that do not have to rely on stable grid power may depend on improved battery technology, solar chargers or generators, or any other new technology breakthroughs that provide instrument-free heat sources.

Detection technologies

Optical detection poses a challenge because of its potential dependence on extensive equipment. There are new detection technologies that do not rely on optical detection, including measurements of mass, magnetic properties, diffraction, or electrical potential that may enable development of more robust detection systems.

Current State



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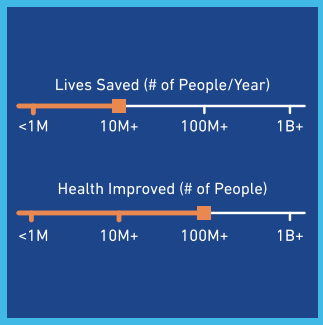


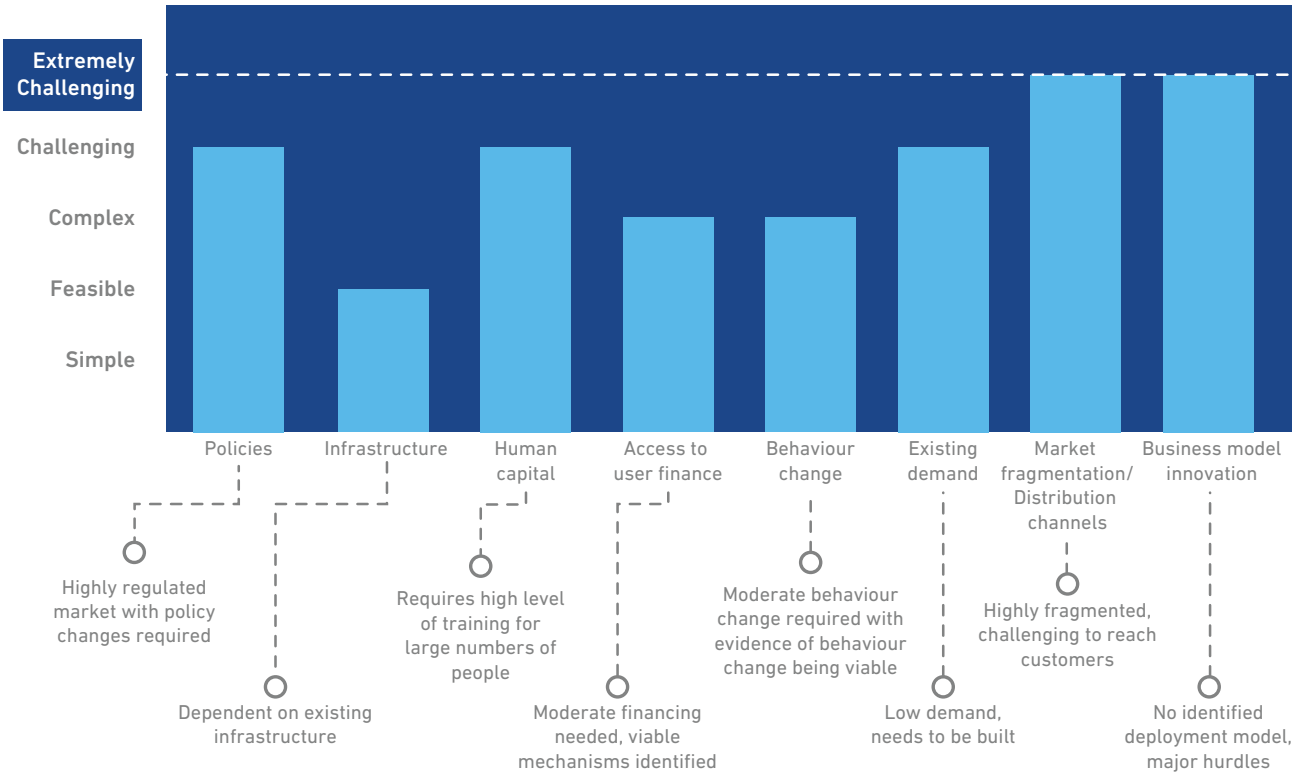
Commercial Attractiveness

Developing a point-of-care NAT will further depend on advancements in micro-fabrication and the ability to miniaturize test components that allow for multiplexing, reductions in sample size, and reduced reagent costs. Microfluidic platforms may yield a possible path forward for NATs as well, as demonstrated by the GeneXpert test for TB.

Deployment challenges include regulatory processes and WHO endorsement, as well as the large capital expenditure required of countries that may look towards adopting new diagnostics on a large scale. Regardless of how pressing a need for a new diagnostic may be, two important factors that will impact the end adoption are the costs and resources required to adequately train healthcare workers to use the new tests, and patients' willingness to pay for them.

Based on the above assessment, the projected time to market readiness is seven to ten years, and the level of difficulty is EXTREMELY CHALLENGING.

Breakthrough 35: Difficulty of deployment

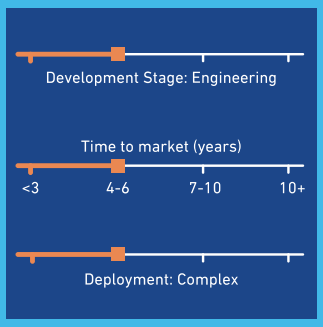


3.7 Affordable wearable technology with broader functionality for patient adherence and monitoring of health status

Wearable technology (or simply, wearables) refers to a broad category of devices that can be integrated into day-to-day clothing or other accessories to capture health data and provide information on the user's personal fitness and activity. While a typical wearable is a fitness tracker that can be worn on the wrist, today there is a much wider array of devices, including implantable devices and an ingestible pill (recently approved by the US FDA) that can track specific markers of physical and mental health and adherence to drug regimens.

Today's common wearables (such as the Fitbit) track heart rate, blood pressure, breathing patterns, physical activity and sleep levels. However, the next generation of devices (still in prototype stage) aim to collect data on blood glucose, indicators of cardiovascular disease, and even cancer. For example, Apple recently released the KardiaBand, an Apple Watch accessory with an inbuilt EKG to detect irregular heartbeat and share the information with caregivers.

Current State



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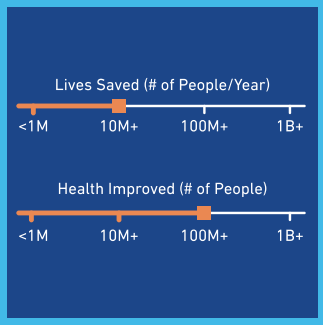
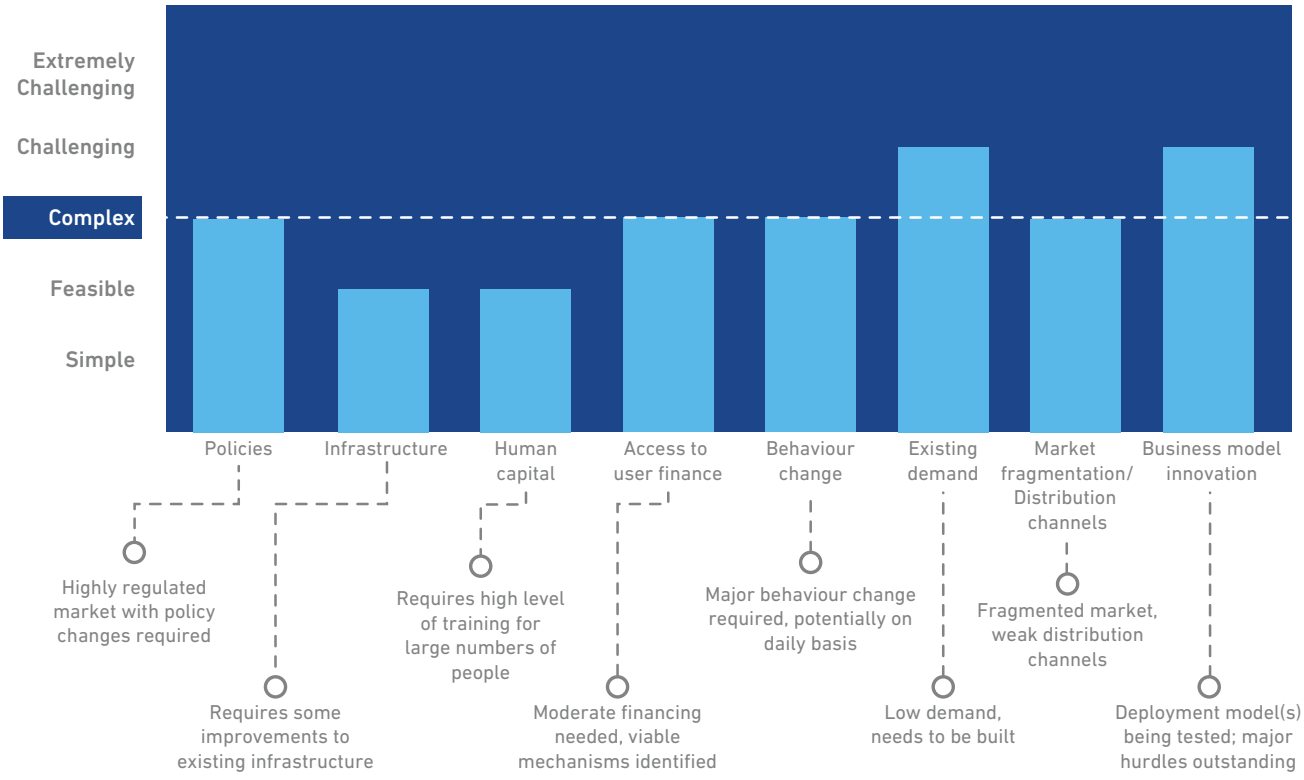


Commercial Attractiveness

Early indications are that such wearables, especially if combined with game-based incentives, can increase positive health-improving behaviors (Shmerling, 2017). While it is too early to understand the long-term impact of such technologies, an increasing number of health insurance companies and employers who provide health insurance are encouraging their use.

Breakthrough 37: Difficulty of deployment



DATA SOURCES FOR ANALYSIS OF MORTALITY FROM DRUG-SENSITIVE TB AND MDR-TB

The data available for this analysis had many shortcomings. Required figures were often unavailable, incomplete or inconsistent with other published figures. For example, The Global TB Report reports that there were 450,000 new and re-treatment cases of MDR-TB in 2010, of which only 94,000 or 21 percent were detected. However, it also states that MDR-testing rates are 5 percent for new TB infections and 9 percent for re-treated infections, significantly below 21 percent inferred from the global new case and treated case figures.

We began with data on the global number of new cases and global mortality, drawn from the Global TB Report 2013. From there we worked inwards, identifying the rate of DOTS versus non-DOTS treatment and mortality rates for various clinical scenarios.

After this stage the data became increasingly unavailable or unreliable. In some cases, we calculated figures (for example, percentage of patients outside of DOTS who are successfully treated), in order to reconcile the resulting mortality rates with the global mortality rate. Specific figures and their sources are explained below. All decimal percentage points were rounded to the nearest percent and all incidence and mortality figures were rounded to the nearest thousand.

DRUG-SENSITIVE TB

New infections (7.1 million)

The number of cases is the incidence of non-drug-resistant, non-HIV-TB co-infection cases in 2012, as reported in the Global TB Report 2013.

Tested, notified to DOTS and treated
Global case detection rate (66 percent) taken from the Global TB Report 2013. All notified patients were assumed to seek treatment.

- Successfully treated: Reported as 87 percent in the Global TB Report 2013.
- Died in treatment: Reported as 4 percent of all treated cases in the Global TB Report. The Global TB Report also states that 4 percent of treated cases were "not evaluated" and had no associated outcome. We distributed this 4 percent in a weighted manner across the Died in treatment, Failure and Default scenarios, bringing the Died in treatment rate to 5 percent of treated cases.
- Failure: Reported as 1 percent of all treated cases in the Global TB Report. The report also states that 4 percent of treated cases were "not evaluated" and had no associated outcome. We distributed this 4 percent in a weighted manner across the Died in treatment, Failure and Default scenarios, bringing the Failure rate to 2 percent of treated cases.
- Default: Reported as 4 percent of all treated cases in Global TB Report. The Global TB Report also states that 4 percent of treated cases were "not evaluated" and had no associated outcome. We distributed this 4 percent in a weighted manner across the Died in treatment, Failure and Default scenarios, bringing the Default rate to 6 percent of treated cases (this number is higher than the 5 percent in the Died in treatment scenario due to rounding).

Tested outside of DOTS
All individuals that were not among the 66 percent who were Tested, notified to DOTS and treated are assumed to have been tested outside the formal sector where DOTS is practiced. We assumed the number of patients who were never tested to be negligible.

- Correctly diagnosed/False negative: The false negative rate is assumed to be 20 percent, drawn from a literature review which highlighted very high (30 percent plus) rates of false negatives in certain high TB burden regions (parts of South Asia and Africa), and a false negative rate of around 10 percent for non-DST tests such as skin tests elsewhere in the world.

- Treated non-DOTS program/Not treated: We found limited high-quality data for patients treated outside of DOTS. We assumed 95 percent seek some form of treatment.

- Successfully treated/Died in treatment/Failure or default: We found limited high quality data for patients treated outside of DOTS. We assumed the rate of patients who died in treatment to be twice that of DOTS due to less regulated and less effective treatment outside of DOTS. We then calculated a 65 percent/25 percent split between successful treatment and failure and default rates in order to reconcile final mortality rates with global figures.

Mortality rates

Successfully treated/Died in treatment
Patients who are successfully treated by definition survive. See above for further explanation of 87 percent successful completion and 4 percent mortality in treatment figures for DOTS and 65 percent and 10 percent figures for non-DOTS coverage.

Failure/Default/Not-treated
WHO estimates 22.5 percent of untreated TB patients will die in the first 2 years (70 percent 10 year mortality rate for smear positive TB and 20 percent for smear negative TB). We assume smooth rates of infection and mortality such that while 22.5 percent of new infections will not die this year, the number who die last year and this year will be 22.5 percent. We initially ran the analysis with the figure 22.5 percent figure for treatment scenarios in which treatment fails, is not completed or is not initiated, and then increased this rate to 30 percent to reconcile mortality rates to meet global mortality figure of 840,000.

While this analysis is focused on drug-sensitive, non-HIV-TB co-infection, the figures are calculated including patients with HIV-TB co-infection.

MDR-TB

Total new infections (450,000)
The Global TB Report 2013 estimates 450,000 new cases of drug-resistant TB. This is the sum of new and relapse infections.

New infections
The Global TB Report states that 3.6 percent of all new TB cases are MDR-TB cases. With 8.6 million new TB cases per year, this implies 310,000 new MDR-TB cases.

DOTS tested
Global case detection rate is reported as 66 percent in the Global TB Report 2013. All patients not under DOTS coverage are assumed to go untreated, as MDR-TB testing is still uncommon in DOTS, and particularly outside of DOTS.

TB re-treatment

We calculated TB re-treatment cases by subtracting the number of new infections, 310,000 from the total number of estimated infections, 450,000, according to the Global TB Report.

DOTS tested
Global case detection rate is reported as 66 percent in the Global TB Report 2013. All patients not under DOTS coverage are assumed to go untreated, as MDR-TB testing is still uncommon in DOTS, and particularly outside of DOTS.

- Tested for MDR-TB: See explanation under new infections.

Treated

The Global TB Report states that 82 percent or 77,000 patients were treated for MDR-TB, of the 94,000 who were tested and eligible.

Successfully treated
Reported as 48 percent in the Global TB Report 2013.

Died in Treatment
Reported as 15 percent of all treated cases in Global TB Report. The Global TB Report also states that 14 percent of treated cases were "not evaluated" and had no associated outcome. We distributed this 14 percent in a weighted manner across the Died in treat- ment, Failure and Default scenarios, bringing the Died in treatment rate to 20 percent of treated cases.

Failure
Reported as 9 percent of all treated cases in Global TB Report. The Global TB Report also states that 14 percent of treated cases were "not evaluated" and had no associated outcome. We distributed this 14 percent in a weighted manner across the Died in treat- ment, Failure and Default scenarios, bringing the Failure rate to 12 percent of treated cases.

Default
Reported as 14 percent of all treated cases in Global TB Report. The Global TB Report also states that 14 percent of treated cases were "not evaluated" and had no associated outcome. We distributed this 14 percent in a weighted manner across the Died in treatment, Failure and Default scenarios, bringing the Default rate to 20 percent of treated cases.

Mortality rate

Successfully treated/Died in treatment
Patients who are successfully treated by definition survive. See above for further explanation of 48 percent successful completion and 20 percent mortality in treatment figures.

All other scenarios
Mortality for untreated MDR-TB is calculated to be 40 percent (compared to 30 percent for untreated drug-sensitiveTB), to fit the overall mortality figure in the Global TB Report.

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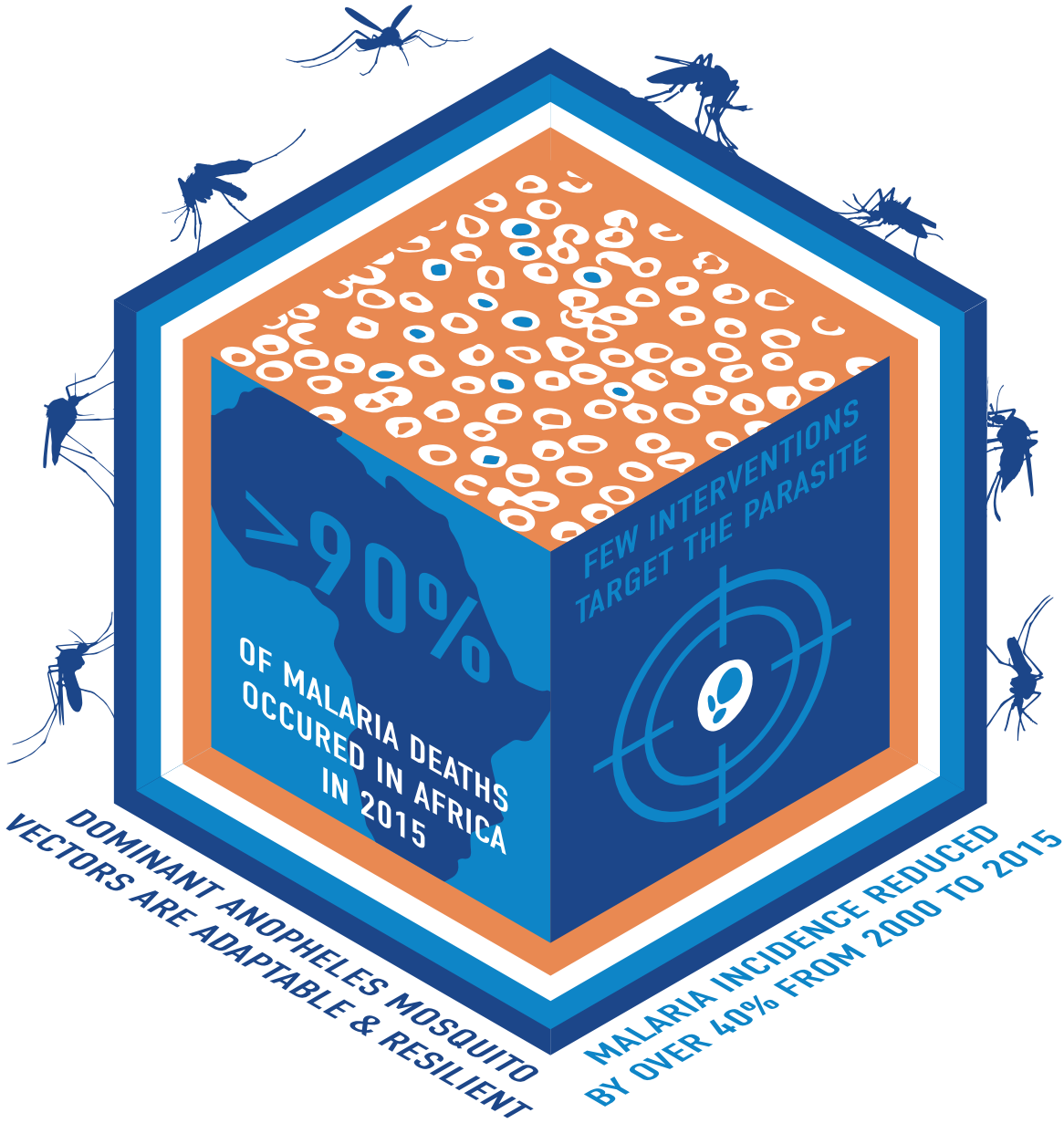

>90%
OF MALARIA DEATHS OCCURED IN AFRICA IN 2015
FEW INTERVENTIONS TARGET THE PARASITE
DOMINANT ANOPHELES MOSQUITO VECTORS ARE ADAPTABLE & RESILIENT
MALARIA INCIDENCE REDUCED BY OVER 40% FROM 2000 TO 2015

MALARIA

INTRODUCTION

Malaria has proven to be one the most persistent and lethal diseases in human history, responsible by some accounts for more deaths than any other disease.

In 2017, the global tally of malaria reached 219 million cases and 430,000 deaths (WHO, 2018). Disproportionately affecting vulnerable populations like pregnant women and children, malaria is the third leading cause of death among children under 5.

The disease is transmitted from person to person through infective bites from female *Anopheles* mosquitoes. Malaria's persistence and virulence are due to the behaviors of these mosquitoes, which are difficult to control. Furthermore, the parasites they carry (*Plasmodium falciparum* in particular) are highly complex and resilient.

The vast majority of the cases were in the WHO African Region (92 percent), followed by the WHO Southeast Asia Region and Eastern Mediterranean Region. The incidence rate of malaria is estimated to have decreased by 41 percent globally between 2000 and 2015, and by 21 percent between 2010 and 2015 (WHO, 2016).

Of 91 countries and territories with malaria transmission in 2015, 40 are estimated to have achieved a reduction in incidence rates of 40 percent or more between 2010 and 2015, and can be considered on track to achieve the GTS milestone of a 40 percent further reduction by 2020.

Despite this progress, a number of major challenges remain. These include the threat of vector resistance to insecticides and existing control methods; the development of parasite resistance to antimalarials, which results in a delayed or incomplete clearance of parasites from a patient's body; and the presence of a large, asymptomatic reservoir of parasites in successfully treated and otherwise healthy individuals, who continue to carry the parasite in their bodies for years and contribute to malaria transmission in their communities.

There are three scientific and technological advances that can help control, eliminate and eventually eradicate malaria.

- Breakthrough 23. Vaccines that can effectively control and eventually help eradicate the major infectious diseases of our time—HIV/AIDS, malaria, tuberculosis and pneumococcus
- Breakthrough 29. A single-dose complete cure for malaria
- Breakthrough 30. New long-lasting spatial mosquito repellents or attractants (chemical and non-chemical) for vector control

Malaria has proven to be one the most persistent and lethal diseases in human history, responsible (by some accounts) for more deaths than any other disease. Currently each year, there are about 220 million cases and 430,000 deaths of malaria. Disproportionately affecting vulnerable populations like pregnant women and children, malaria is the third leading cause of death among children under 5.

CORE FACTS AND ANALYSIS

Malaria is caused by protozoan parasites of the genus *Plasmodium*, belonging to the parasitic phylum Apicomplexa. Mosquitoes act as the vector, transmitting the disease from one human to another. This disease disproportionately affects vulnerable populations like pregnant women and children. It is the third leading cause of death among children under 5, who constitute more than 85 percent (more than 560,000) of total malaria-related deaths worldwide (WHO, 2013).

1. Malaria-related deaths are highly concentrated in a small number of countries and population segments

In 2015, it was estimated that there were 429,000 deaths from malaria globally. Most of those deaths are estimated to have occurred in the WHO African Region (92 percent), followed by the WHO South-East Asia Region (6 percent) and the WHO Eastern Mediterranean Region (2 percent) (**Exhibit 1**).

Of 91 countries and territories with malaria transmission in 2015, 39 are estimated to have achieved a reduction of 40 percent or more in mortality rates between 2010 and 2015. A further 10 countries had zero indigenous deaths in 2015 (WHO, 2016).

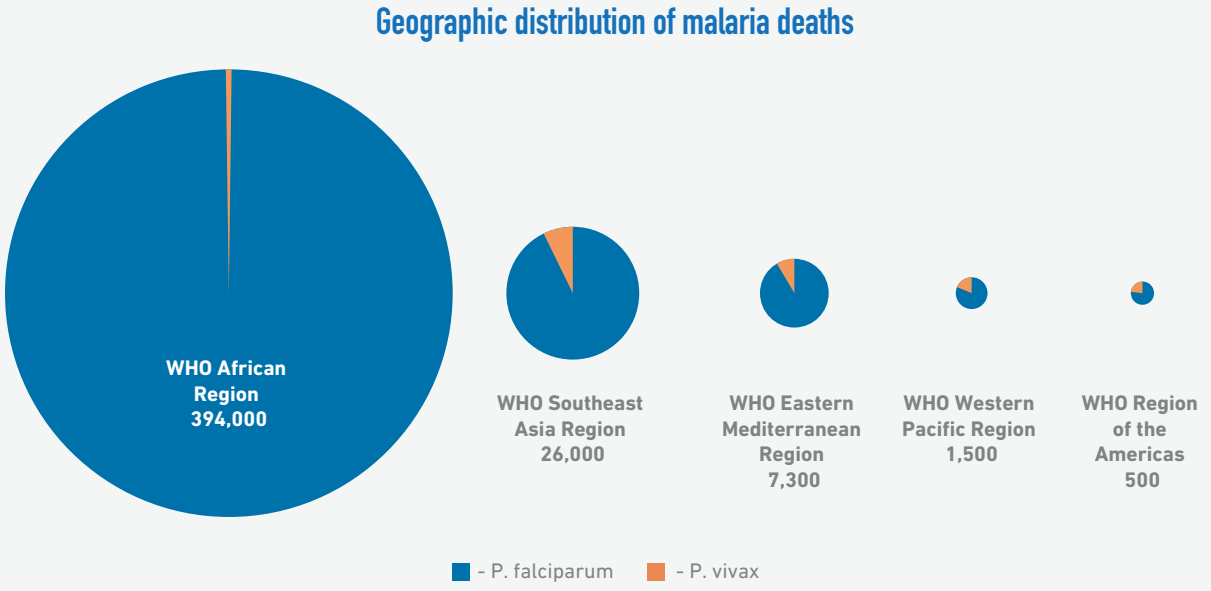


Exhibit 1: Estimated malaria deaths due to *P. falciparum* and *P. vivax* respectively, by region, in 2015. (Source: WHO, 2015).

It is estimated that 13 countries accounted for 75 percent of malaria deaths in 2015 (**Exhibit 2**). The global burden of mortality is dominated by countries in sub-Saharan Africa, with Democratic Republic of the Congo and Nigeria together accounting for more than 36 percent of the global total of estimated malaria deaths.

Four countries (Ethiopia, India, Indonesia and Pakistan) accounted for 81 percent of estimated deaths due to *P. vivax* malaria.

Estimated country share of total malaria and *P. vivax* deaths, 2015

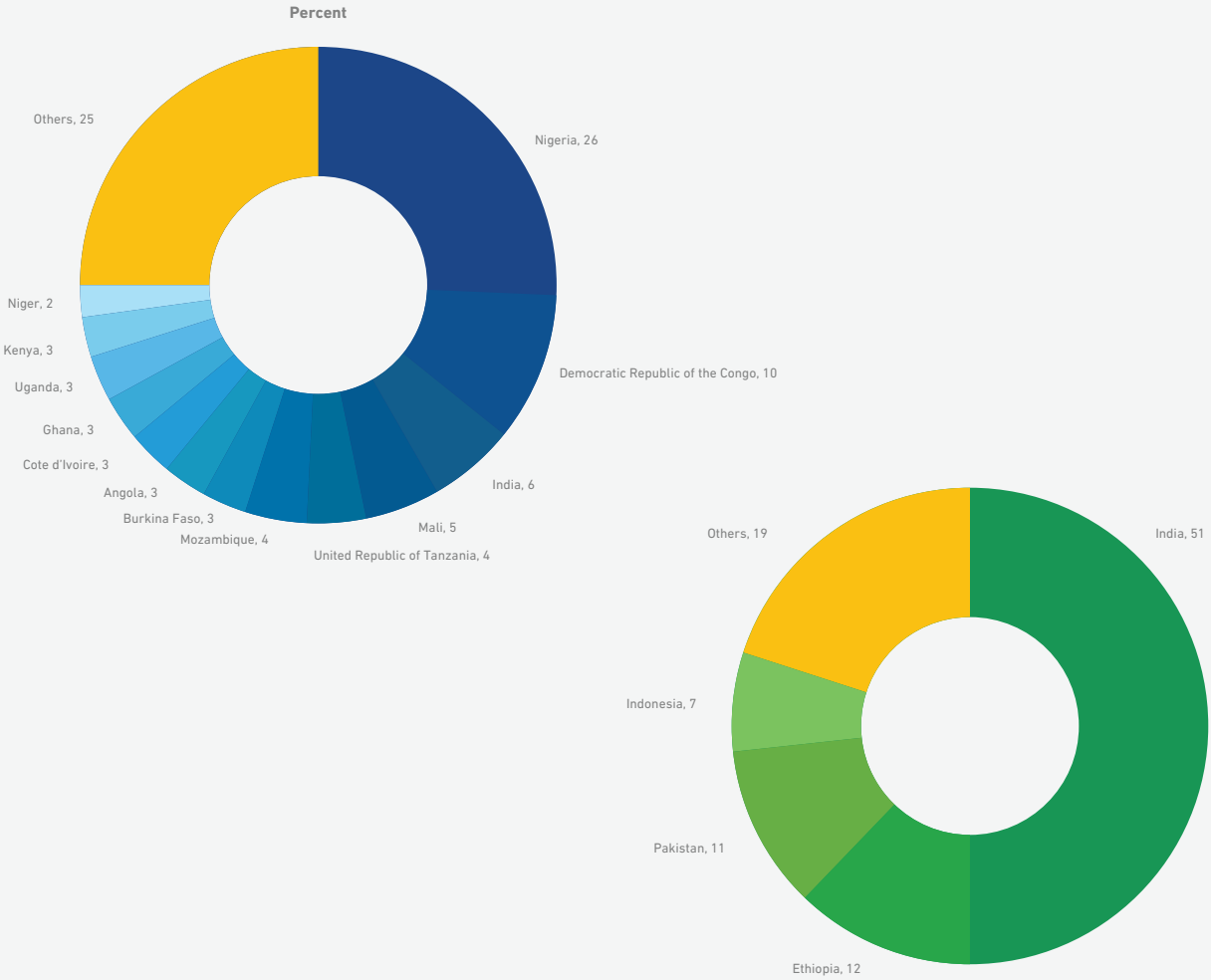


Exhibit 2: Estimated percentage of total malaria deaths by country (top), and *P. vivax* deaths by country (bottom). (Source: WHO, 2015)

If malaria-related mortality in the 10 worst-affected African countries were to be brought in line with the rest of sub-Saharan Africa, overall mortality would be reduced by almost 20 percent (WHO, 2013).

There are three major reasons for the concentration of mortality and morbidity in Africa (Feachem, et al., 2010), as outlined below.

Prevalence of *Plasmodium falciparum*, the most lethal form of the parasite

Of the more than 200 known species of *Plasmodium* parasite (Rich & Ayala, 2006), five are known to cause human malaria. These are *P. falciparum, P. vivax, P. ovale,* and *P. malariae*; in addition, a species of primate malaria, *P. knowlesi*, has recently been documented to cause human infection and fatality in many countries of Southeast Asia (Aneshvar, 2009).

Of the four common malaria species, *P. falciparum* is the most lethal and accounts for 90 percent of globally reported malaria mortality. The other species are known to usually cause sickness and significant morbidity but not death. *P. falciparum* is also far more prevalent in Africa than in other parts of the malaria-endemic world (WHO, 2013). An estimated 85 percent of malaria cases in Africa are due to *P. falciparum*, compared with around 50 percent in South and Southeast Asia, where the less fatal species, *P. vivax*, is also prevalent (WHO, 2013).

It is interesting to note that *P. falciparum* is more virulent and causes significantly higher mortality in Africa, than in comparable communities in Southeast Asia. This may be partly due to lower transmission and earlier treatment outside of Africa, but may also be explained in part by epidemiological differences and variations in the pattern of disease across the two continents (Maitland & Williams, 1998).

Dominance of resilient and highly efficient malaria vectors

There are 3,500 known species of mosquitoes, across 41 genera. Of these, females of only 30 to 40 mosquito species (from the genus *Anopheles*) transmit malaria in humans, and only seven have been found in Africa. The major malaria vectors in Africa are the *Anopheles gambiae* and *Anopheles funestus*. These vectors are particularly difficult to control because they occur in high densities in tropical climates, live in close proximity to human populations and have a strong preference for feeding on humans.

They have relatively long life spans and breed readily in water bodies of varying size, from lakes to tiny puddles (White, et al., 2013). The *Anopheles gambiae* can lay viable eggs in bodies of water as tiny as animal hoof prints, which means that there can be thousands of such water accumulations—after every rainfall—in even the smallest village. This makes larval control in Africa extremely difficult. There are also numerous secondary vector species prevalent in sub-Saharan Africa. The unique behavioral traits of these different Anopheles species, the difficulty of distinguishing between them, and the existence of multiple species in a single geography adds to the complexity of developing effective vector control strategies.

Conflict has historically been a driver of malaria

Conflict displaces entire populations (a key driver of malaria transmission), erodes health systems and thus poses significant impediments to any large-scale efforts to control the disease. With the notable exception of Burkina Faso, most of the countries with high caseloads and mortality rates in Africa (like Nigeria, the Democratic Republic of Congo, Mozambique, Cote d'Ivoire, Chad and Uganda), have witnessed very destructive civil wars in recent years.

Malaria mostly affects children

Malaria also disproportionately affects specific, vulnerable populations (WHO, 2002; WHO, 2013)[1]. More than 85 percent of malaria deaths globally were among children under 5. Children have low immunity and are particularly susceptible to the disease. Malaria during pregnancy causes as many as 10,000 maternal deaths each year. *P. falciparum* infection during pregnancy increases the chance of maternal anemia, abortion, stillbirth, prematurity, intrauterine growth retardation and low infant birth weight—the greatest risk factor for death in the first month of life. Eight to 14 percent of all low birthweight babies, and three to eight percent of all infant deaths in certain parts of Africa are the result of malaria during pregnancy.

[1]WHO defines the following high-risk groups, based on vulnerability to infection and death: pregnant women, infants and children under 5, HIV/AIDS patients and migrant or mobile populations.

2. Current and historic interventions have targeted both mosquito and parasite

WHO defines Malaria elimination as "a reduction to zero of the incidence of infection caused by human malaria parasites in a defined geographical area as a result of deliberate efforts." Malaria control is defined as "reducing malaria morbidity and mortality to a locally acceptable level through deliberate efforts using the preventive and curative tools available today." Globally, between 2000 and 2015, both malaria caseload incidence and mortality rates have decreased by 41 percent (WHO, 2016). This is largely a result of both institutional and individual interventions described below.

The most commonly used methods to prevent mosquito bites are sleeping under an insecticide-treated net (ITN) and spraying the inside walls of a house with an insecticide–indoor residual spraying (IRS). These two core vector-control interventions are considered to have made a major contribution to the reduction in malaria burden since 2000, with ITNs estimated to account for 50 percent of the decline in parasite prevalence among children aged 2 to 10 years in sub-Saharan Africa between 2001 and 2015 (World Malaria report, WHO 2016).

Interventions aimed at preventing transmission

Bed-nets, particularly long-lasting insecticide treated bed-nets (LLINs)

In such nets, particular insecticides (deltamethrin, alphacypermethrin or permethrin) are either incorporated in to the fibers of the net (during extrusion of the polymer) or coated with a binder onto the surface of the netting fabric. Currently, 13 manufacturers make WHO-recommended LLINs. These nets provide both individual and household levels of protection, especially against vector species that predominantly bite at night or rest indoors.

The netting protects the individuals sleeping underneath from mosquitoes that are either killed or repelled by the insecticide. By killing mosquitoes, the household as a whole is offered some protection. While high coverage of LLINs has been associated with some level of community-wide protection, LLINs cannot protect individuals from being bitten when they are outside the net.

Further, a key challenge with LLINs is emerging insecticide resistance. Because LLIN campaigns to date have mostly targeted children, caseloads may shift towards older individuals in the future. Still, scale-up of LLINs is credited with having made a significant contribution to the overall reduction in malaria cases and fatalities by targeting the most vulnerable section of the population, children.

Indoor residual spraying (IRS)

Small pre-defined amounts of insecticides (like dichlorodiphenyltrichloroethane, pyrethroids, carbamates or organophosphates) are sprayed indoors and on the walls of dwellings. As in the case of LLINs, IRS is only effective indoors and is a significant contributor to the reduction of caseload and fatalities.

However, its full potential is realized only if at least 80 percent of houses in the targeted areas are sprayed. One challenge with IRS is that it requires repeated applications, which may not happen. Once the sprayed insecticide weakens, mosquitoes quickly reappear. Indoor spraying is effective for three to six months, depending on the insecticide used and the type of surface on which it is sprayed. Newer formulations of pyrethroids and organophosphates can last up to nine months, and DDT can in some cases be effective for nine to 12 months.

Skin repellents

These include sprays and ointments and are used extensively for personal protection (though not malaria control) in many parts of the world, with varying levels of efficacy depending on the brand. Some of them are available at a price point that can be affordable for low-income families.

However, adoption in communities not accustomed to using such repellents will likely be difficult and efficacy will be highly dependent on education, behavior change and compliance with instructions for use. A recent randomized control trial testing the effectiveness of skin repellents in combination with LLINs found that topical repellents are not an effective incremental intervention if LLINs are already in place (Chen-Hussey, et al., 2013).

Spatial repellents

These include flammable incense and coils and are used extensively around the world with varying levels of effectiveness. Such repellents tend to give off an unpleasant smell and can increase the risk of respiratory disease.

An alternative is the use of vaporizing mats or small cardboard tablets which, when heated in a small electrically-powered device, release a pyrethroid vapor. This is more effective than coils but is significantly more expensive and can only be used where electricity is available (Pates, et al., 2002). Importantly, while skin and spatial repellents have proven effective for personal protection, neither have demonstrated community-level protection against malaria.

Large-scale draining of water bodies and swamps

This has been a key component of elimination strategies in high-income countries. However, this method only works when the vector mosquitoes primarily breed in larger bodies of water, and where potential breeding sites are easy to map and treat. Some targeted efforts to reduce large mosquito breeding grounds, like controlled irrigation of rice fields, have shown promise.

However, the *Anopheles gambiae* can lay viable eggs in very tiny pools of water, making large-scale draining irrelevant to the African context. Recently, there have been some efforts to educate populations about how to identify and eliminate small, but obvious, breeding sites[2].

Improved housing construction

This has contributed to the elimination of malaria in high-income countries, where most homes also have window screens that can keep mosquitoes out. Unfortunately, this remains a luxury the poor cannot afford.

There have been only two interventions aimed at the parasite itself

Treatment of infected patients

The WHO recommended treatment for *P. falciparum* infection is Artemisinin-based Combination Therapy (ACT).[3] Originally derived from sweet wormwood, Artemisia can now be manufactured synthetically.

In this treatment regimen, artemisinin administered in combination with another antimalarial (amodiaquine, lumefantrine, mefloquine, sulfadoxine-pyrimethamine, dihydroartemisinin-piperaquine) reduces the likelihood that the parasite will develop resistance to an individual drug, as had happened earlier with antimalarial treatments like chloroquine (now largely inefficacious in much of the malaria-endemic world).

Resistance represents an acquired (or selected) genetic difference in parasite population structure, and occurs by selecting out a subpopulation of parasites with drug pressure. Emergence of resistant parasite strains also happens when individuals with low immunity and a heavy parasite load receive small amounts of drugs, especially through monotherapy (treatment with a single drug).

The biggest challenges in malaria treatment include the continued use of poor-quality or counterfeit treatments, the use of monotherapies and lack of patient compliance to treatment regimens. All of these factors lead to the development of drug resistance and all are common in Africa, where the majority of patients with fever and other malaria symptoms seek treatment through informal channels or unregulated street vendors.

Use of malaria rapid diagnostic tests (RDTs)

Related to the treatment challenges described above, treatment with antimalarials has tended to be presumptive rather than relying on a confirmed diagnosis. A significant portion of antimalarials dispensed are used for non-malarial illnesses. A recent study conducted in Gabon found that 30 percent of children with fever received unprescribed antimalarials, and that 80 percent of these children were not actually infected with malaria (Mawili-Mboumba, et al., 2013).

These children failed to receive the treatment they required and the antimalarials were wasted on non-malarial illness. To address this challenge, the WHO has launched a new initiative called T3—test, treat, track—to ensure that all suspected malaria cases are tested and that only confirmed cases are treated with quality-assured antimalarials. This initiative is also expected to slow the emergence of drug resistance to ACTs.

[2]For example, the Student Leaders Against Malaria (SLAM) initiative.
[3]The recommended treatment regimen during pregnancy is different.

KEY CHALLENGES

There are a number of reasons why malaria has been among the most resilient and lethal diseases in human history, and why achieving a sustained reduction in disease transmission and deaths has been difficult.

The two-part lifecycle of *P. falciparum*

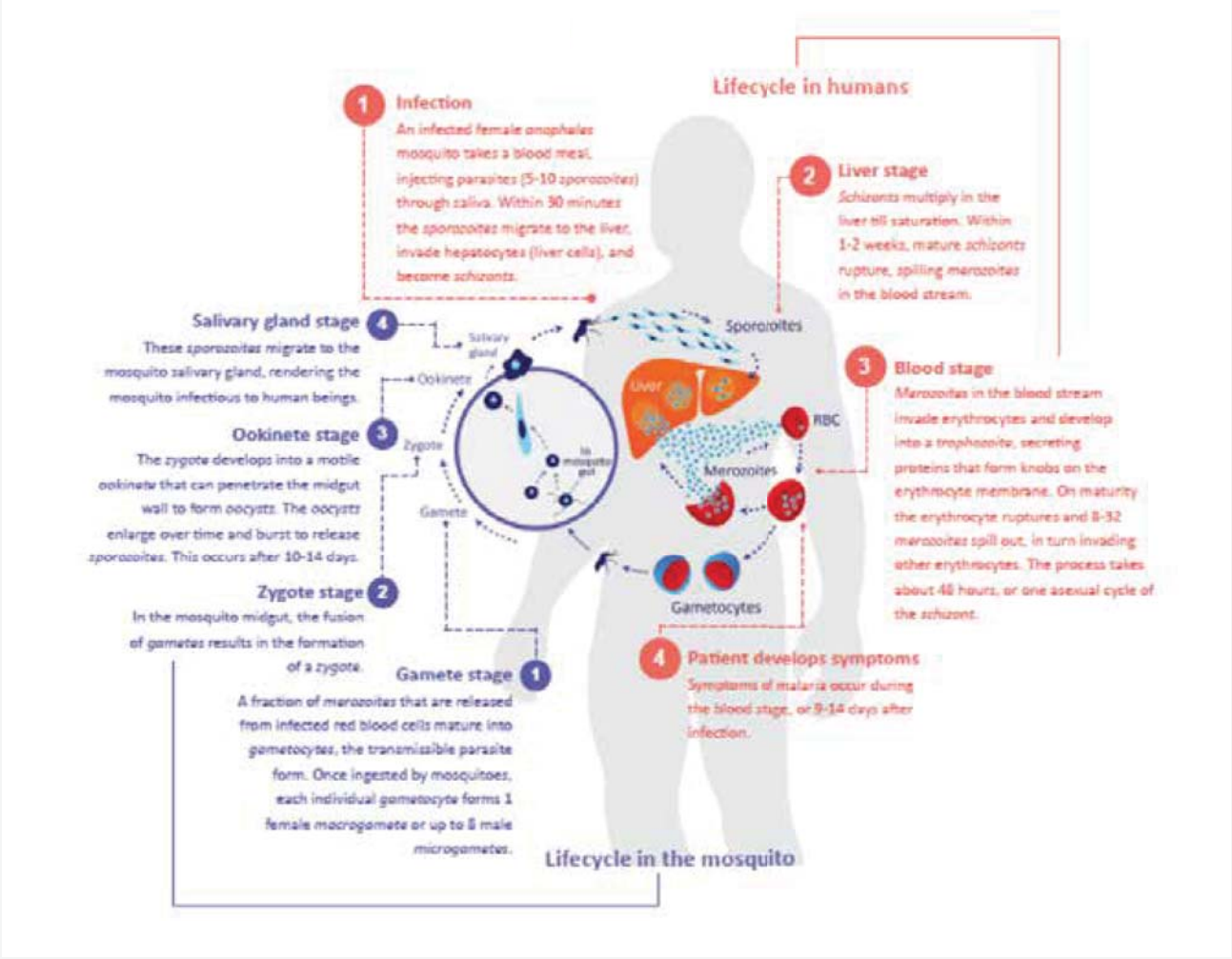


Exhibit 3: Malaria parasites have two separate life cycles: in the mosquito between the gamete and sporozoite stages, and in the human body from the time of being bitten to having the parasite fully mature into gametocyte.

1. A highly complex parasite makes developing vaccines and medications difficult

The *Plasmodium* parasite has two different lifecycles: in the mosquito and in the infected human (**Exhibit 3**). In both lifecycles, it goes through significant transformations. To this day, there are considerable gaps in the understanding of the basic immunology and host response to the disease. Among the known complexities are:

- The parasite can use antigenic switching under selective immune pressures, to evade the immune system. In other words, it changes the antigens it expresses, while maintaining the same underlying genetic composition.
- The parasite is intracellular and hence not exposed to the immune system consistently through its lifecycle.
- Infection does not automatically result in future immunity. Partial immunity against malaria builds slowly over time, is developed over years of exposure and never provides complete protection. Further, immunity can be lost in a few years if individuals move outside of endemic areas.
- Different parasitic loads can lead to dramatically different levels of sickness in different individuals. Many infected individuals remain asymptomatic and hence are not aware they have malaria, or that they are capable of transmitting it. Mosquitoes first become malaria vectors only after biting an infected human. In the long-term, if asymptomatic infection is not addressed, the reservoir of infection will continue to grow and malaria resurgence will be inevitable.

Mimicking the antigen under such complexities in order to produce a protective, artificial immune response is extremely difficult. As a result, developing an effective vaccine has proven elusive. New vaccine development programs are focused on either blocking parasite transmission from infected humans to mosquitoes or on preventing gametes from developing in the mosquito gut itself.

2. Transmission intensity is determined by a complex and variable set of factors

Malaria persistence is due to the complexity of factors underlying disease transmission and the resilient and complex nature of the parasites that are carried by mosquito vectors. Transmission factors vary across geographies and include mosquito density, longevity, propensity to bite humans, frequency of feeding, the acquisition and loss of immunity in susceptible populations, and the availability of effective treatment (WHO, 2010).

Specifically, the rate of malaria transmission depends on the human biting rate (HBR) of the mosquito, the density of mosquitoes engaged in blood feeding (which in turn is a function of overall mosquito density), propensity of prevalent vectors to bite humans, and frequency of feeding.

The product of the HBR and the percentage of infectious mosquitoes (sporozoite rate) yields what is known as the entomological inoculation rate (EIR), which represents the average number of infectious mosquito bites a person receives per unit of time. The EIR is widely considered the measure that best represents malaria transmission intensity in various geographies (White, et al., 2013; Hay, et al., 2000).

In Africa, malaria transmission intensity is variable and annual EIRs can range from less than one to more than 1,000 infective bites per person per year. While there is a linear relationship between annual EIRs and the prevalence of malaria infection (Overgaard, et al., 2012),[4] this relationship is complex and impacted by the acquisition and loss of immunity to malaria and the existence of effective drug treatment (WHO, 2010).

Malaria transmission intensity is a critical driver of prevalence of infection, incidence and symptomatic presentation of clinical disease and development of immunity and drug resistance (Kelly-Hope & McKenzie, 2009).

[4]When EIRs exceeded 15 infectious bites per year, prevalence of *P. falciparum* was never found to be less than 50 percent and annual EIRs of 200 bites or higher consistently yielded prevalence rates of greater than 80 percent.

Transmission intensity is thus central to the design and implementation of effective malaria control measures. In low transmission areas, symptomatic patients account for the vast majority of the infectious reservoir, and declines in transmission rates translate proportionally to a decline in malaria incidence and prevalence.

By contrast, in high transmission areas, much larger declines in transmission rates are needed to reduce overall malaria incidence and prevalence, and targeting symptomatic individuals alone is unlikely to achieve this (WHO, 2010). The implication is that while they may have a major impact on mortality reduction, drug strategies to reduce malaria prevalence will be effective in high transmission areas only if used in combination with other effective interventions targeting the vector.

Drug strategies increase in importance for overall malaria control only as transmission intensity declines, and the majority of patients become symptomatic. Programs then need to adapt to target the remaining parasite reservoirs, by finding and treating individual infections (Sturrock, et al., 2013).

Today, only half the countries of sub-Saharan Africa have data available on transmission intensities. What data is available suggests that EIRs and malaria transmission intensity appear to vary greatly based on the presence of different Anopheles species, the extent of urbanization, land use, population density, elevation and climate.

Improved and standardized data on EIRs and an increased understanding of the drivers of differences in transmission intensity across neighboring geographies are critical to the design and effective monitoring of malaria control interventions (Hay, et al., 2000).

3. The dominant *Anopheles* mosquito vectors are pervasive, adaptable and resilient

A mosquito's lifecycle has four stages: egg, larva, pupa and adult (**Exhibit 4**). The first three stages are aquatic and last five to 14 days. The mosquito becomes a vector only once it reaches adulthood, and only females are vectors.

Adult females feed on sugar sources for energy, but require a blood meal to develop eggs. After a full blood meal, the female rests for a few days while the blood is digested and eggs are developed. In tropical conditions, this takes two to three days. Once the eggs are fully developed, the female lays them and resumes host seeking.

Only if the mosquito has taken a blood meal from a human infected with the malaria parasite and survives the 10 to 14 days it takes the parasite to complete the incubation period and render the mosquito infectious, does the mosquito become an active malaria vector.

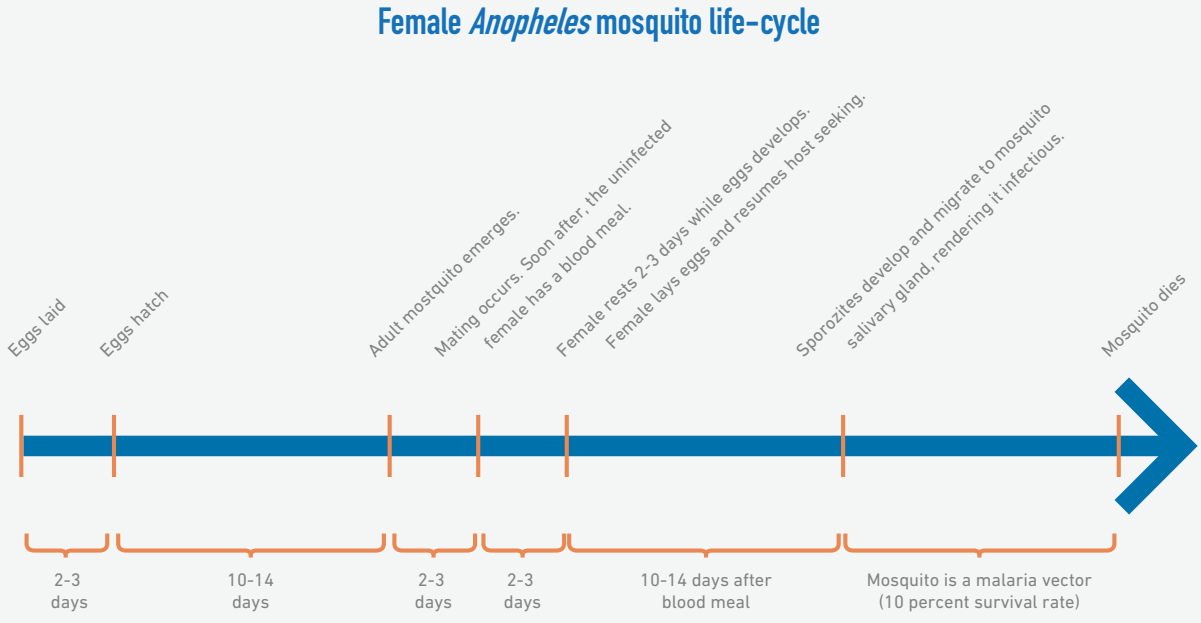


Exhibit 4: Female *Anopheles gambiae* become a vector about a month after being laid as eggs. What little data there is suggests that fewer than 10 percent survive to become vectors.

The dominant vector, *Anopheles gambiae,* has a number of characteristics that makes it an extremely efficient malaria vector.

Strong preference for human blood, combined with highly efficient feeding habits

Most *Anopheles* mosquitoes are neither strongly anthropophilic (prefer feeding on humans) nor zoophilic (prefer animal blood). However, *Anopheles gambiae* are strongly anthropophilic and, therefore, highly efficient malaria vectors. They are also endophilic (meaning they rest indoors) and nocturnal, which means that they have unfettered access to sleeping humans unless they are under appropriate bed-nets or are otherwise well-protected.

Relatively long life span

Adult *Anopheles gambiae* females tend to live one to two weeks in nature (Kileen, et al., 2000), a lifespan that is considered relatively long. Furthermore, studies in Tanzania showed *Anopheles gambiae* mosquitoes have a 77 to 84 percent daily survival rate. Extrapolating from this limited evidence, less than 10 percent of female *Anopheles gambiae* are likely to survive longer than the 14-day extrinsic incubation period it takes for them to become malaria vectors.

Thousands of breeding sites, which are very difficult to eliminate

Each adult female lays 50 to 200 eggs per oviposition, directly on water. These eggs have floats on their sides and hatch in a few days. Larvae of *Anopheles gambiae* (unlike those of most other species) can breed in very diverse habitats: fresh or salt-water marshes, mangrove swamps, rice fields, grassy ditches, edges of streams and small, temporary rain pools like tire tracks (CDC, 2014).

Without repeated and large-scale spraying, or other such expensive and environmentally destructive methods, it is extremely difficult to eliminate all these breeding sites. Recent studies have explored other methods for targeting oviposition and gravid (carrying eggs) females as a vector control strategy. Some have suggested that shiny, sticky surfaces may attract gravid females because they can be visually mistaken as aquatic habitats, and this could potentially be exploited in the development of gravid traps or novel mosquito trapping strategies (Dugassa, et al., 2012).

Mosquitoes may be capable of behavioral plasticity

Numerous anecdotal reports of mosquitoes changing their behavior and adapting feeding patterns as a result of IRS and LLINs exist. There is insufficient data to assess whether these are genetic or adaptive responses (Ranson, et al., 2011). The implication of such adaptability is that the effectiveness of LLINs may diminish over time, if, in order to minimize contact with indoor insecticides, the *Anopheles gambiae* mosquitoes begin feeding earlier in the day or do not remain exclusively endophilic. If this does happen, new control tools and strategies may be required.

4. The complex distribution of primary, secondary and tertiary *Anopheles* vector species makes design of effective vector control strategies difficult

Anopheles mosquitoes can be divided into several species complexes, which are composed of numerous morphologically indistinguishable sibling species. The *Anopheles gambiae senso stricto* is a complex of at least seven morphologically indistinguishable, but behaviorally distinct, sibling mosquito species, which include two genetically distinct species of *Anopheles gambiae senso strictu (Anopheles gambiae A.* and *Anopheles gambiae S.*) and *Anopheles arabiensis*, which are the dominant vector species in sub-Saharan Africa[5].

Anopheles funestus is also a dominant vector species, and further complication is introduced by the existence of primary, secondary and even tertiary vector species existing in sympatry within a single geography.

Effective control strategies depend on proper identification of the mosquito vector(s) and an understanding of each species' distinct feeding and biting preferences. Interventions need to be properly adapted to the local environment, taking into account the behavior and ecology of the main vector species as well as the resistance status of both parasite and vector.

[5]This species complex consists of *Anopheles arabiensis, Anopheles bwambae, Anopheles merus, Anopheles melas, Anopheles quadriannulatus* and *Anopheles gambiae senso stricto.*

The importance of this is underscored by the fact that neighboring villages can have vastly different malaria transmission intensities, depending on number of mosquito vectors present in that location. Where *Anopheles funestus* vectors are present alongside *Anopheles gambiae*, malaria transmission rates have been found to be twice as high.

In Senegal, a village only five kilometers from its neighbor was found to have transmission rates 10 times as high, due to the presence of *Anopheles funestus* (Kelly-Hope & McKenzie, 2009). Further, *Anopheles arabiensis*—also endemic in much of Africa—have become more prevalent after broad introduction of bed-nets and IRS (Bayoh, 2010), likely because they have less preference for feeding and resting indoors.

Today, large knowledge gaps exist about mosquito ecology and behavior in many highly endemic areas due to the difficulty of identifying and monitoring mosquito vectors in the field.

5. Limitations of treatment with antimalarials

Effective treatment with ACTs is a key component of reducing malaria-related mortality. The biggest challenges in malaria treatment include the continued use of poor quality or counterfeit treatments that are abundant in the marketplace, the use of monotherapies and lack of patient compliance to treatment regimens. All of these factors favor the development of drug resistance and are particularly common in Africa.

Yet another limitation of treatment strategies for broader malaria control efforts is the fact that symptomatic individuals constitute only a portion of the infectious reservoir, an important determinant of the number of infectious mosquitoes in an area and therefore the EIR. In a high transmission area, there are a large number of asymptomatic individuals due to the development of partial immunity resulting from frequent infectious bites.

Targeting symptomatic individuals alone is unlikely to achieve large declines in transmission rates or a reduction in overall malaria incidence and prevalence (WHO, 2010).

In low transmission areas, symptomatic patients account for the majority of the infectious reservoir, and declines in transmission rates are proportional to a decline in malaria incidence and prevalence. Clearly, drug strategies to reduce malaria prevalence will be effective in high transmission areas only if used in combination with other effective interventions targeting the vector.

Drug strategies increase in importance for overall malaria control only as transmission intensity declines, the majority of patients become symptomatic and programs adapt to target remaining parasite reservoirs—finding and treating asymptomatic individuals (Sturrock, et al., 2013).

6. Limitations of LLINs and IRS and increasing resistance

As described earlier, LLINs and IRS—despite their effectiveness when scaled up sufficiently—have drawbacks with respect to the breadth and longevity of the protection they offer, and carry the risk of emerging longer-term operational insecticide resistance.[6] Managing resistance is particularly challenging when an intervention is dependent on a single chemical class as in the case of LLINs.

Even in the case of IRS, which relies on four currently available insecticide classes (resistance has been reported to all four of these in some populations of *Anopheles gambiae*), managing resistance and providing sustainable vector control with existing chemicals is unlikely (Ranson, et al., 2011). In addition, there are significant portions of affected populations in remote areas, which are proving difficult to reach with these tools. New classes of insecticides and delivery tools are urgently needed to maintain the gains achieved over recent years.

[6]WHO defines insecticide resistance as the ability of an insect to withstand the effects of an insecticide by becoming resistant to its toxic effects by means of natural selection and mutations. The Insecticide Resistance Action Committee (IRAC) defines operational resistance as a heritable change in the sensitivity of a pest population that is reflected in the repeated failure of a product to achieve the expected level of control when used according to the label recommendation for that pest species.

In some malaria-endemic areas, resistance to all four classes of insecticides has been detected. Of the 73 malaria endemic countries that provided monitoring data to WHO for 2010 onwards, 60 reported resistance to at least one insecticide in one malaria vector from one collection site and 50 reported resistance to two or more insecticide classes (**Exhibit 5**).

Resistance to pyrethroids–the only class currently used in LLINs–is the most commonly reported; in 2015, more than three quarters of the countries monitoring this insecticide class reported resistance.

Evidence of geographical spread of resistance and intensification in some areas underscores the need to urgently take action to manage resistance and reduce reliance on pyrethroids (WHO, 2016).

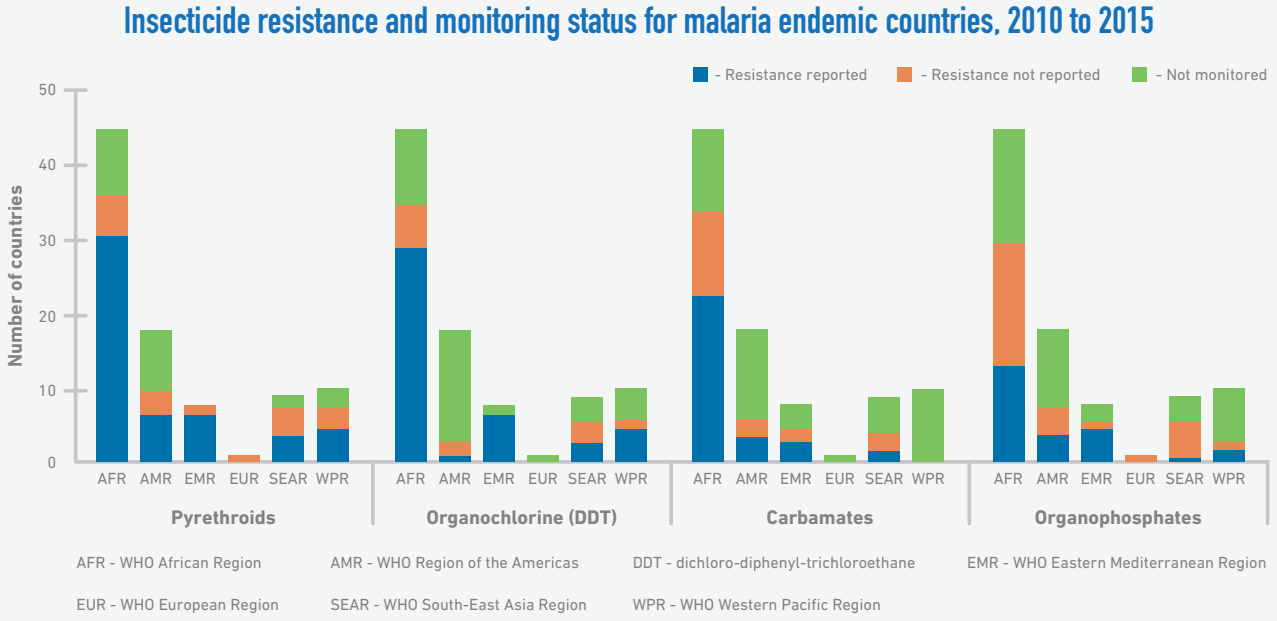


Exhibit 5: Africa is the region that faces greatest insecticide resistance among malaria endemic countries. (Source: WHO, 2015)

7. Large-scale programs to control or eliminate malaria require heavy, sustained public investment and coordination

Gains against malaria have historically relied on scale-up of successful interventions, and these gains have proven to be highly fragile. This is particularly true in high transmission settings, which have large asymptomatic reservoirs of infection (Stresman, et al., 2010).

Although malaria transmission can be dramatically reduced with effective control strategies, resurgence is inevitable in the absence of sustained interventions.

The common denominator among instances of malaria resurgence has been the weakening of malaria control programs due to reduced funding (Cohen, et al., 2012). The economic sustainability of interventions is, therefore, critical to maintaining any gains achieved in mortality reduction.

SCIENTIFIC AND TECHNOLOGICAL BREAKTHROUGHS

Global malaria efforts have necessarily had a dual focus, control in highly endemic regions and elimination on the margins. The widely accepted malaria eradication strategy is two-pronged: it relies on aggressive control strategies to reduce transmission intensity and mortality in high-burden countries and on progressive elimination of malaria from the endemic margins (Feachem, et al., 2010).

To achieve dramatic results, the dual aims of control and elimination are being considered in parallel. Short-term interventions—no matter how successful in reducing mortality—will inevitably fail to control malaria in the long run, due to the inevitability of malaria resurgence and the possibility of cross-border transmission.

Regional elimination is a long way from being a reality in much of sub-Saharan Africa, and malaria eradication will likely take several decades.

It should be recognized that as sustainable malaria control is achieved and malaria transmission intensity is reduced in highly endemic countries, the character of malaria in these countries may change. In the long-term, if *P. falciparum* incidence is controlled, the relative proportion of *P. vivax* may increase, along with the proportion of malaria affecting adult men.

New challenges will require dramatically different strategies and technologies, in order to:

- move towards elimination by targeting *P. vivax*, including addressing new populations of affected individuals.
- identify and address remaining (asymptomatic) reservoirs of malaria parasites.
- manage emerging parasite species, in particular, the simian malaria species *P. knowlesi*, which has been infecting humans in Southeast Asia.
- control cross-border malaria transmission to sustain regional elimination. Sustain funding (such as for surveillance and response) through elimination.
- better identify and monitor mosquito species in the field.

In the meantime, there continue to be large numbers of malaria-related fatalities, especially among children in African countries. As described above, the investment required to maintain and scale-up current interventions is unlikely to be sustainable in the long-term. The limitations of current interventions need to be addressed with new solutions targeted for high-burden countries and populations.

As such, this analysis focuses on identifying technologies with the highest potential to reduce malaria mortality in high transmission settings, while recognizing that these may need to evolve over time as malaria transmission rates decline in high-burden countries.

Breakthroughs:

1	2	3	4	5	6	7	8	9	10
11	12	13	14	15	16	17	18	19	20
21	22	23	24	25	26	27	28	29	30
31	32	33	34	35	36	37	38	39	40
41	42	43	44	45	46	47	48	49	50

23. Vaccines that can effectively control and eventually help eradicate the major infectious diseases of our time—HIV/AIDS, malaria, tuberculosis and pneumococcus

Collectively, HIV/AIDS, malaria, tuberculosis and pneumonia kill more than five million people a year, and represent a significant disease burden for low income populations in sub-Saharan Africa and South Asia. Effective and affordable vaccines for these diseases do not exist yet due to the intrinsic complexity of the pathogens causing them, and a lack of understanding of the specific mechanisms through which our immune systems protect against these diseases. The process of vaccine development—basic research on disease etiology, vaccine construction, pre-clinical and clinical testing—is technically challenging, expensive and time consuming.

23b. A malaria vaccine specifically for *P. falciparum*

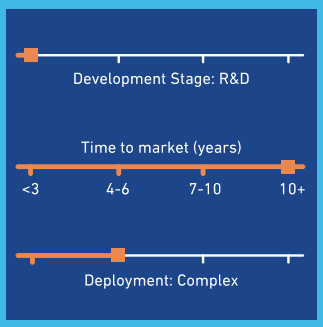
Given the difficulty in controlling *Anopheles* mosquitoes, it is clear that children will continue to be bitten and infected. Therefore, providing artificial protective immunity in the form of an anti-infective vaccine specifically for the *P. falciparum* parasite would represent a significant breakthrough in the area of malaria control.

Vaccines, in general, have a very long development lead-time; vaccines for malaria have proven particularly elusive. There are many complexities that increase the difficulty of developing a malaria vaccine that offers immunological protection. These include antigenic switching by the parasite under selective immune pressures to evade the immune system, the complex lifecycle and intracellular nature of the parasite and the lack of natural long-lasting immunity in humans against the parasite.

Consequently, mimicking the antigen to produce a protective but artificial immune response has proven extremely difficult. To account for the differential expression of antigens across the parasite lifecycle and to deepen understanding of effective or ineffective immune responses, a range of approaches to vaccine development are underway.

However, to date, only one has reached Phase III trials and 13 have had limited effectiveness. Given the current lack of a vaccine developmental candidate and the historical lack of success, experts believe it is 20 years or more away (WHO, 2018).

Current State



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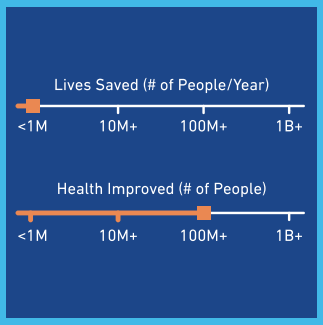


Commercial Attractiveness

A different approach currently being explored is the development of transmission-blocking vaccines. These would reduce the number of blood stage parasites and specifically limit the presence and expansion of the infectious gametocyte form of the parasite in the mosquito, thus blocking ongoing transmission.

Such vaccines will not offer protection to the immunized individual, but will prevent the individual from passing parasites onto others, which represents an important breakthrough for dramatically lowering malaria transmission rates.

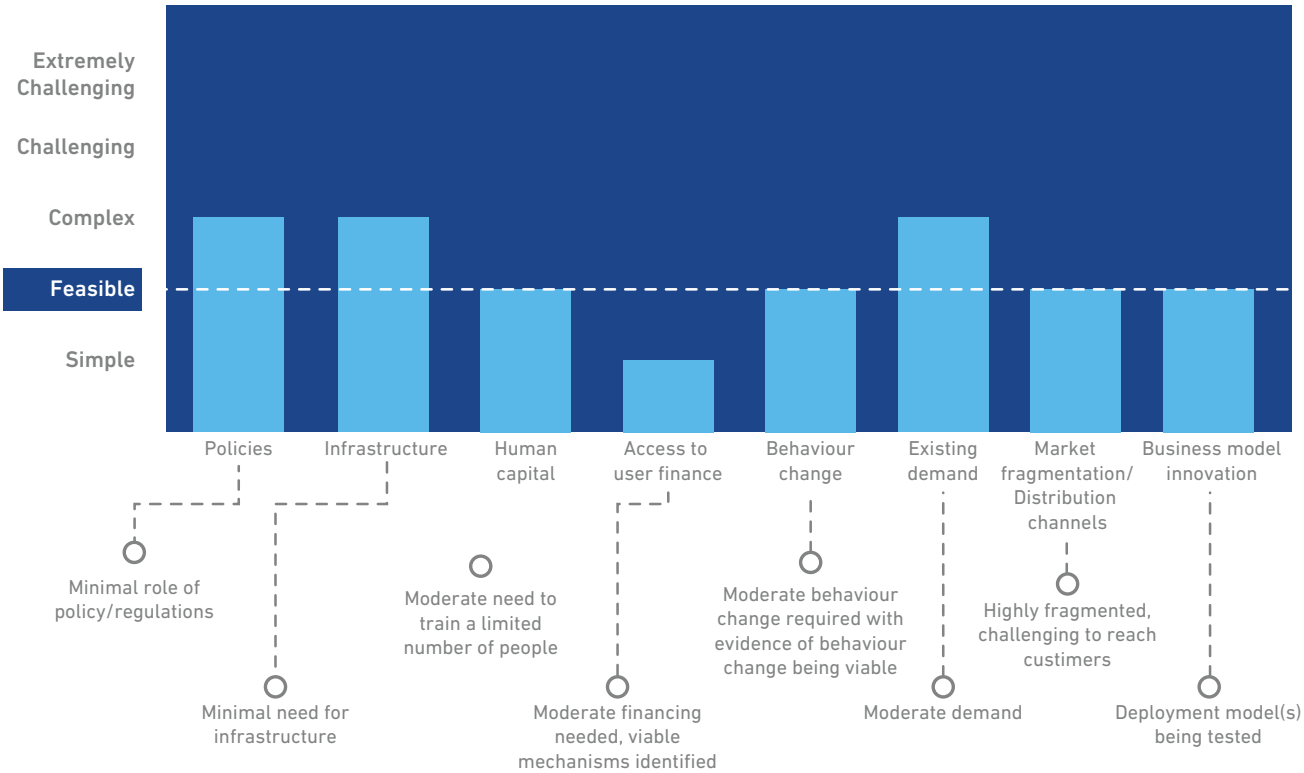
Deployment of new vaccines

Once any of these vaccines is developed, it can be deployed to children through existing, reasonably established, vaccine delivery channels. However, there are few mechanisms for delivering vaccines to adolescents and adults, and successful vaccination campaigns for these population segments would require significant government coordination, behavior change and financial investment.

Furthermore, even today vaccine delivery remains a challenge in many remote locations where supporting infrastructure like cold storage facilities are either few or non-existent. While vaccines are expected to be made available to patients at a low cost, financing for the vaccines by national governments or international donors would need to be secured in order to support widespread distribution. Policy changes would also need to support its introduction and distribution through public health systems.

Based on the above assessment, the projected time to market readiness is more than ten years, and the difficulty for deployment is FEASIBLE.

Breakthrough 23: Difficulty of deployment



29 A single-dose complete cure for malaria

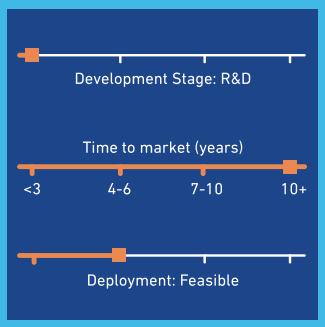
Effective treatments for malaria exist. The majority of safe medications for malaria target the blood stage of the parasite, but not stages of the parasite lifecycle, such as the gametocyte stage. The persistence of the gametocytes following treatment creates a human reservoir of parasites, which remain viable for years in an otherwise asymptomatic and healthy person.

While this does not cause disease directly, it does pose challenges for malaria control and elimination. As such, a single-dose complete cure to eliminate all malaria parasites in the human body—both blood stage and liver stage and both sexual and asexual—represents a significant breakthrough in malaria control.

There is a fairly well-developed pipeline for improved antimalarial treatments, including drugs that are targeting other stages of the parasite life-cycle. In 2018, the FDA approved tafenoquine (Krintafel) for the radical cure of Plasmodium vivax malaria in patients aged 16 or older.

This drug has been manufactured by GlaxoSmithKline. Another candidate known as OZ439 that may also be effective against artemisinin-resistant strains of malaria is in the works, with Phase IIb study scheduled to be completed in 2019 (MMV, 2018).

Current State



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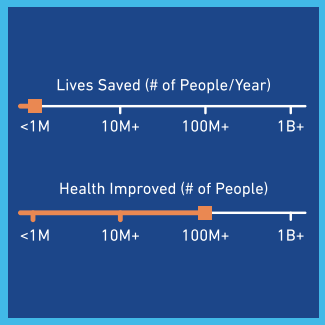
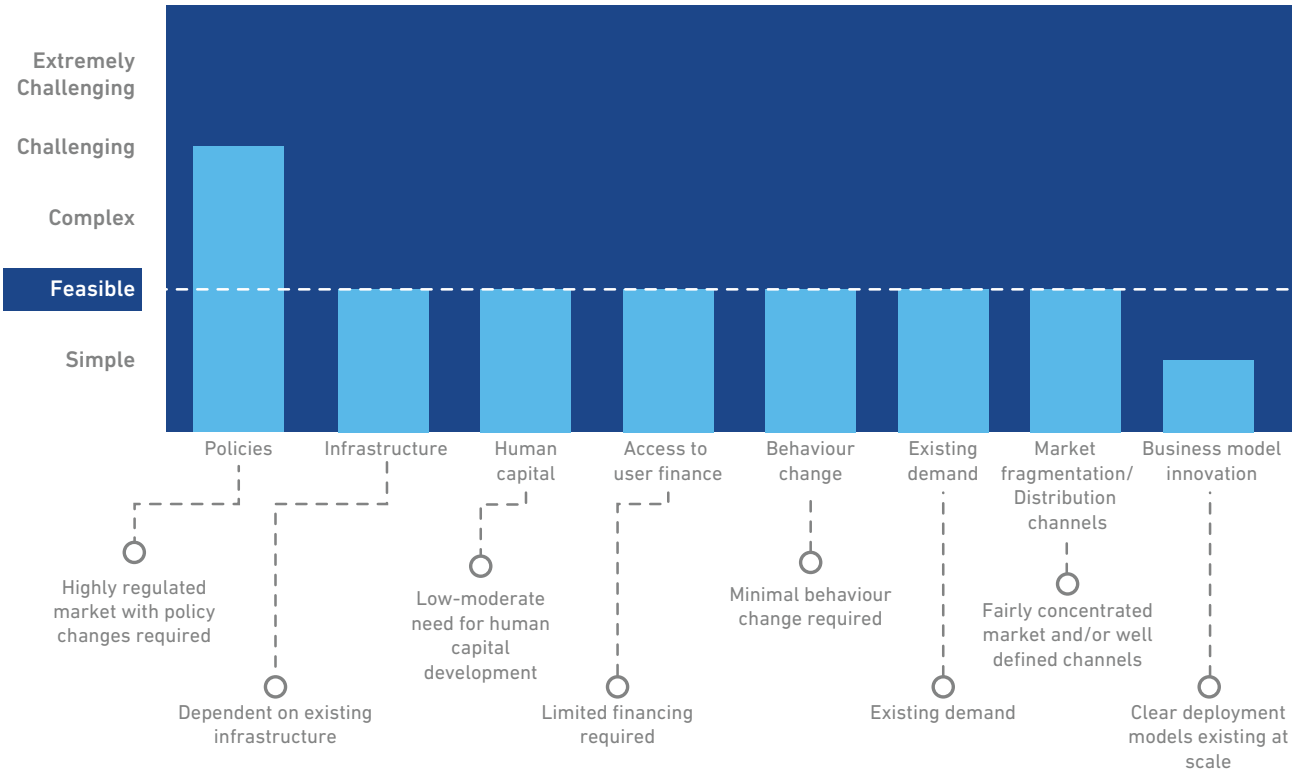


Commercial Attractiveness

Once available, these drugs will need to be approved by the WHO and incorporated into international and national level malaria treatment guidelines. As many of those who will require treatment are asymptomatic, the drugs will likely need to be introduced in combination with a highly sensitive rapid diagnostic test that can help identify these asymptomatic individuals.

Finally, sustained funding for these interventions will need to be secured. Based on the above assessment the difficulty of deployment is FEASIBLE.

Breakthrough 29: Difficulty of deployment



3.0 New long-lasting spatial mosquito repellents or attractants (chemical and non-chemical) for vector control

There are great opportunities for novel spatial mosquito repellents or attractants for vector control and improved health. Breakthroughs may be chemical-based or non-chemical, such as sound-based. It is unlikely that existing chemicals will provide sustained control while limiting the development of resistance.

New classes of long-lasting chemical repellents are required and need to be delivered through novel mechanisms that are easy to use and adopt. Delivery strategies must provide community-level protection. Control methods should be optimized for the most lethal African vectors—*Anopheles gambiae*, *Anopheles arabiensis* and *Anopheles funestus*—but will ideally be effective across all primary and secondary vector species.

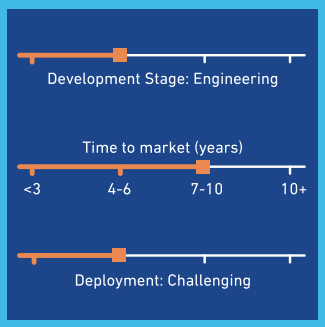
High coverage of non-chemical spatial repellents could enhance the impact of existing interventions such as LLINs and IRS, particularly in areas where mosquitoes are biting individuals outdoors. Non-chemical repellents or attractants also have the potential to overcome the challenge of insecticide resistance. Non-chemical spatial repellents (for example those based on sound) exist in the market but have not proven effective, particularly at the community-level. It is unclear whether these products are based on rigorous science.

Effective spatial repellents can be difficult to design and their benefits to individual households need to be considered in the context of benefits to the community (Achee, et al., 2012). In particular, a repellent that is very effective in a household setting may simply drive the mosquitoes to other areas and households that do not have an equally effective repellent, potentially intensifying malaria in less protected, likely poorer, areas.

Therefore, such repellents should ideally be used through a 'push-pull' mechanism (Takken, 2010), which would push mosquitoes away from at-risk households and pull them towards an area where they can easily be destroyed. Alternatively, attractants can offer the potential to easily lure and kill mosquitoes. Methods to do so by exploiting mosquito mating behaviors (like pheromones and wing beat frequency) and sensory sensitivities (odors) are being explored.

Research is progressing on chemical-based solutions, and some existing chemicals (like transfluthrin) are showing promise. Efforts aimed at providing individual-level protection include transfluthrin-treated strips (Ogoma, et al., 2012) and the under-development Kite Patch™ that relies on chemicals to disrupt a mosquito's carbon dioxide receptors. However, the potential of these devices for long-term spatial efficacy has not been demonstrated.

Current State



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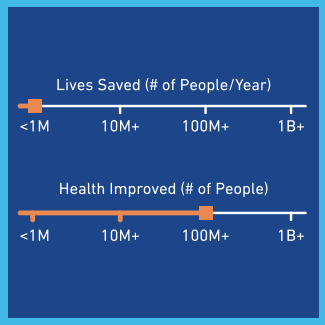


Commercial Attractiveness

As the sensory sensitivities of mosquitoes are better understood, developing repellent and attractant technologies can be more easily developed. However, to be effective, the control method will need to be considered in the broader context of the community and not just the individual household.

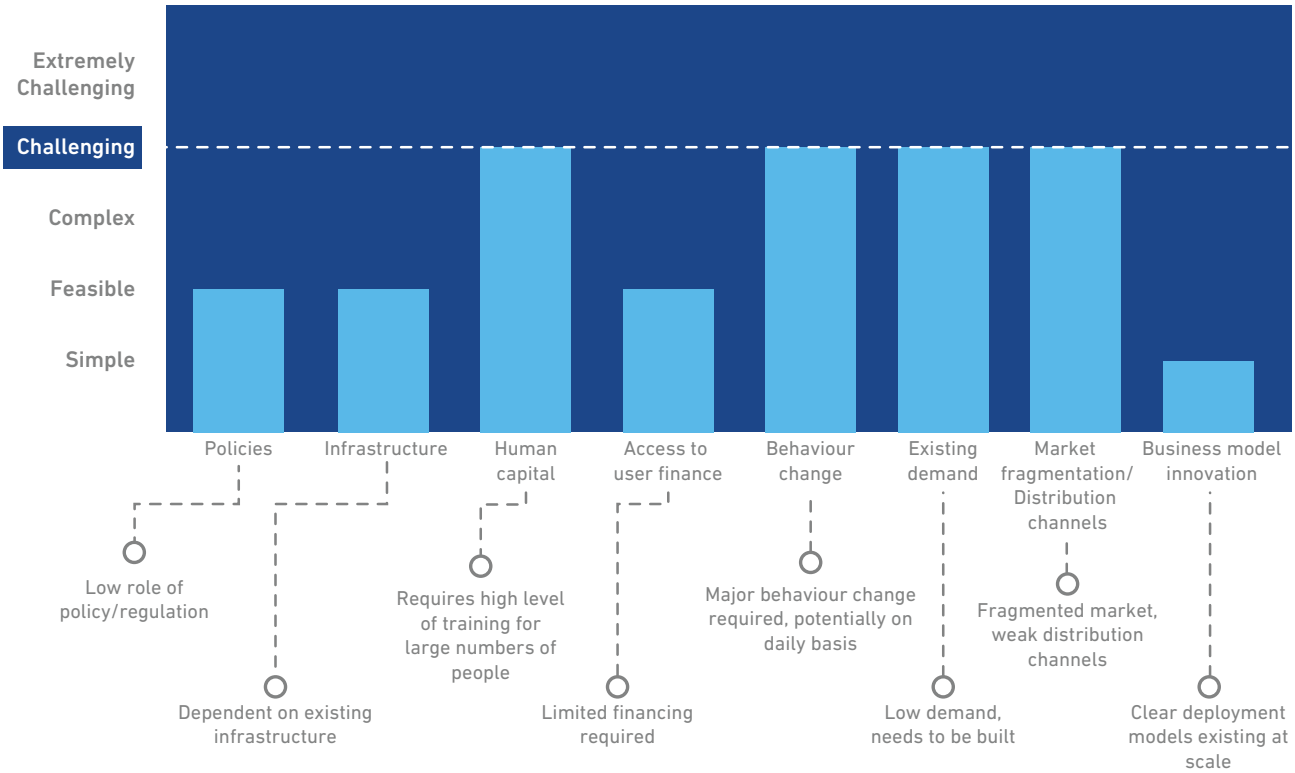
This will likely require some form of governmental coordination. Community-level protection will need to be demonstrated and this will require significant investment in operational research.

Furthermore, optimum usage may require some training (depending on the nature of the repellent or attractant) and adherence to appropriate protocol.

Importantly, non-chemical repellents should be designed such that they do not require frequent replenishment or investment in supply chain infrastructure.

Based on the above assessment, the projected time to market readiness is seven to 10 years and the difficulty of deployment is CHALLENGING.

Breakthrough 30: Difficulty of deployment



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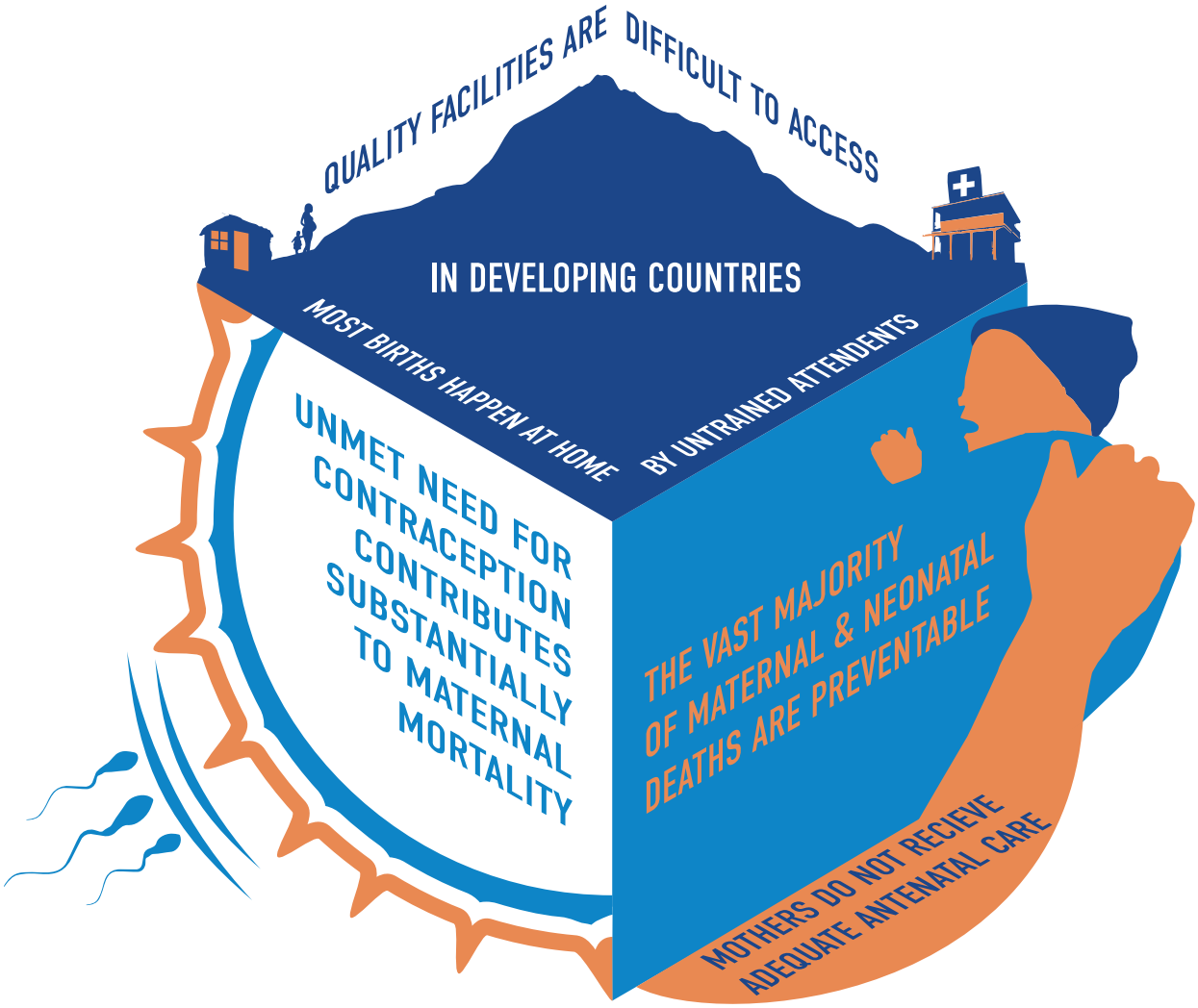


MATERNAL AND NEONATAL HEALTH

INTRODUCTION

In 2017, 308,000 women died from pregnancy or childbirth-related complications, and 2.7 million infants died in their first month of life.

The vast majority (99 percent) of these deaths occur in developing countries and most are preventable (Guttmacher, 2017).

Maternal mortality is caused by a wide range of conditions (WHO, 2018), including severe bleeding (mostly post-partum hemorrhaging), infections (usually after childbirth), hypertension during pregnancy (pre-eclampsia and eclampsia), complications from delivery, unsafe abortion, and association with diseases such as malaria and HIV/AIDs.

Of these conditions, hemorrhage and hypertensive disorders are the largest causes of mortality, accounting for 27 percent and 14 percent of mortality respectively (Say, et al., 2014). Among women who experience medical complications during pregnancy or delivery, only one in three (35 percent) receives the care they or their newborns need (Guttmacher, 2017).

Neonatal mortality is caused by three main conditions: preterm birth complications, birth asphyxia and infections, which represent 24 percent, 20 percent and 7.5 percent of mortality, respectively (IHME GBD, 2017). Underlying all of these conditions are four broad challenges:

- Approximately 43 percent of the pregnancies are unintended, with the majority due to unmet family planning needs.
- Many mothers lack skilled care during childbirth.
- Most mothers do not receive sufficient antenatal care, or care and support after childbirth.
- Many mothers are malnourished.

Interventions need to focus on reducing preventable maternal and newborn mortality. They include sexual, reproductive, maternal, newborn and adolescent health care, family planning, attention to infectious and chronic noncommunicable diseases and social determinants that contribute to maternal and neonatal mortality.

Timely management and treatment can make the difference between life and death for both the mother and the baby. Most importantly, maternal health care services have to be contextualized within the broader comprehensive primary health care approach. Action is required at all levels: individual, family and community, health systems and structural in terms of developing the requisite policies and programs.

In light of the above challenges, one technological breakthrough can help reduce maternal and neonatal mortality by strengthening primary health care in developing countries:

- Breakthrough 31. Integrated suite of digitally enabled primary care devices including point-of-care diagnostics (for basic blood, urine, and vitals tests), therapeutic devices for common conditions, and clinical operations (such as sterilization, refrigeration)

Maternal and neonatal health have been an important global health priority. As the following discussion shows, the specific conditions and root causes of mortality and morbidity are structural and systemic, and there are no 'silver bullets' that can make a substantial difference by themselves.

CORE FACTS AND ANALYSIS

Each year, maternal and neonatal medical conditions cause 308,000 and 2.7 million deaths respectively (Guttmacher, 2017), the vast majority of which—99 percent in the case of maternal deaths—occur in developing countries.

The Global Burden of Disease study estimated that neonatal conditions are the fifth largest cause of disease burden in developing countries and maternal health is the 21st highest cause of disease burden in those countries; although this seemingly lower rank does not reflect the large impact of maternal mortality on the infant or the family (IHME GBD, 2017).

Access to maternal health care is a key component of the global Universal Health Coverage (UHC) movement. WHO indicators for measuring the level of equity of UHC across countries include coverage of family planning, antenatal and delivery care, full child immunization services, and health-seeking behavior for pneumonia. There is hope that UHC reforms in many countries will help speed up equitable access to maternal health care services.

1. Most births in developing countries take place at home and are administered by untrained health workers

More than half the childbirths in developing countries take place at home with the assistance of traditional birth attendants, who, unlike skilled birth attendants, have limited or no formal training.

A 2011 study found that in sub-Saharan Africa and South Asia, 74 percent and 84 percent of women in the bottom two economic quintiles gave birth at home with the assistance of unskilled birth attendants, compared with 21 to 22 percent in the top quintile (Montagu, et al., 2011).

Since then, major progress has been made in increasing facility-based deliveries. UNICEF estimated that in 2016 the number of births that took place without the assistance of a skilled birth attendant had reduced to about one in five births (22 per cent).

Some countries, like India, have seen dramatic changes within a few years after the government started providing cash incentives to women opting for facility births.

That said, the frequency of home birth is still particularly high for the poor in these countries (**Exhibit 1**).

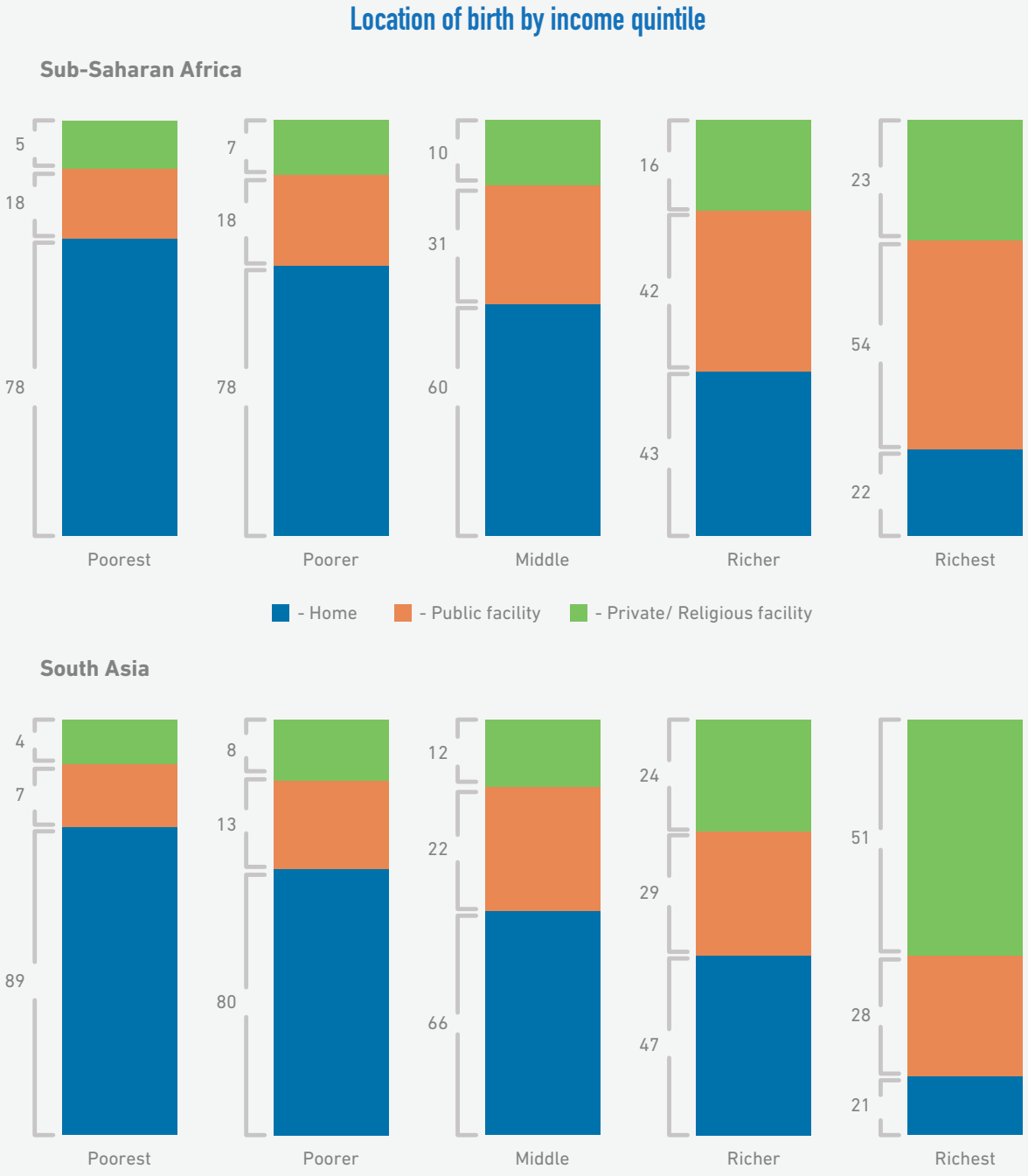


Exhibit 1: The majority of births in lower-income populations take place at home. (Source: Montagu, et al., 2011)

2. Expectant mothers do not receive antenatal care and are often malnourished

Across the largest countries in sub-Saharan Africa and South Asia, an increasing number of pregnant women are receiving antenatal care, although the numbers are still low, with the majority of women (86 percent) receiving at least one antenatal care visit, but only 62 percent receive at least four antenatal visits, the minimum number of visits recommended by WHO (UNICEF, 2016).

Rates of malnutrition among women in developing countries are high. Some 30 percent of women and 40 percent of pregnant women in the world suffer from iron-deficiency anemia (JustActions.org, 2018) and a significant number of women are stunted or undernourished, which can lead to delivery complications and preterm births.

3. Maternal mortality is driven by multiple conditions

Maternal mortality and morbidity are driven by fewer than 10 medical conditions (**Exhibit 2**). Importantly, each of these causes of maternal mortality have different clinical needs. The underlying causes and treatment needs of the two leading clinical conditions of maternal mortality are listed below.

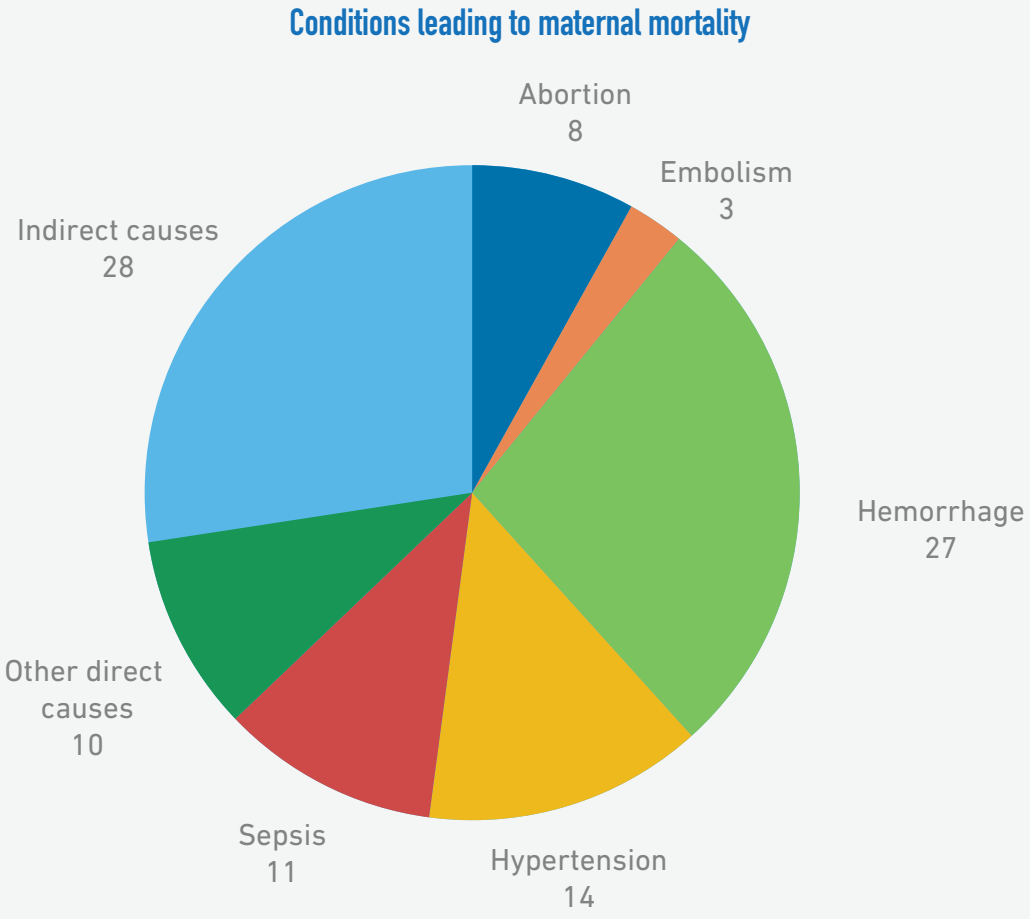


Exhibit 2: There is no single cause of maternal mortality. Several different clinical conditions, of which post-partum hemorrhage (PPH) and hypertensive diseases are the leading, are the causes. However, even these causes of mortality result from a broad range of underlying conditions and are influenced by numerous risk factors. (Source: Say, et al., 2014)

Post-partum hemorrhage

Characterized by excessive blood loss following childbirth, post-partum hemorrhage is the largest cause of maternal mortality, accounting for 27 percent of all maternal deaths. The primary cause of PPH is uterine atony, which occurs when the uterus does not contract and help stop post-partum bleeding. PPH can also be caused by abruption, retained placental tissue, coagulation abnormalities and other factors.

The WHO recommended approach to prevention of PPH is Active Management of the Third Stage of Labor (AMTSL), which includes the administration of an uterotonic that makes the uterus contract. The WHO recommends Oxytocin as the first line uterotonic, but using it at many low-resource facilities is problematic since it must be kept refrigerated.

Other thermostable uterotonics like Misoprostol are possible alternatives. However, due to its use in abortions, Misoprostol is heavily regulated or banned in several countries. Adequate community-level care, training birth attendants to administer AMTSL and sufficient distribution of uterotonics are additional challenges to reducing PPH.

It is important to note that uterotonics work in less than half of PPH cases, indicating a need for secondary treatments like balloon tamponades, anti-shock garments and hemostatic agents.

Hypertensive disorders of pregnancy

At 14 percent, hypertensive disorders of pregnancy constitute the second leading cause of maternal mortality and a range of complications linked to high blood pressure. The major hypertensive conditions are preeclampsia, when a pregnant woman develops high blood pressure and protein in the urine after the 20th week of pregnancy, and eclampsia, characterized by seizures.

The placenta is a highly vascularized organ, and while it is believed that issues in the formation of blood vessels in the placenta are what lead to hypertensive diseases of pregnancy, the specific mechanisms are poorly understood. The prevalence of hypertensive diseases in pregnancy is no different in developing countries compared to developed countries, and there is no definitive treatment even in developed countries except inducing early birth.

If diagnosed early, the mother can be prescribed hypertensive medications The WHO has recommended prevention through calcium (where calcium intake is low) and/or aspirin supplements. However, traditional birth attendants in developing countries do not have the training or equipment to detect hypertensive diseases, administer appropriate medicines or induce early birth.

In the last decade, researchers have begun to discover a number of novel biomarkers that will allow for early diagnosis of the disease and outcome prediction (Armaly, et al., 2018) and also potentially lead to new treatment.

4. Three conditions are responsible for over half of neonatal mortality

The health of newborns is affected by many of the same underlying factors that influence maternal health—malnutrition in expectant mothers, the lack skilled birth attendants with appropriate equipment and the lack of antenatal care.

As a category, neonatal conditions are the single largest cause of disease burden in LMICs, responsible for 10.9 percent of DALYs and 2.7 million global deaths per year (IHME GBD, 2017). Three conditions—preterm birth complications, birth asphyxia and infection—are responsible for 51.5 percent of neonatal mortality (IHME GBD, 2017) (**Exhibit 3**).

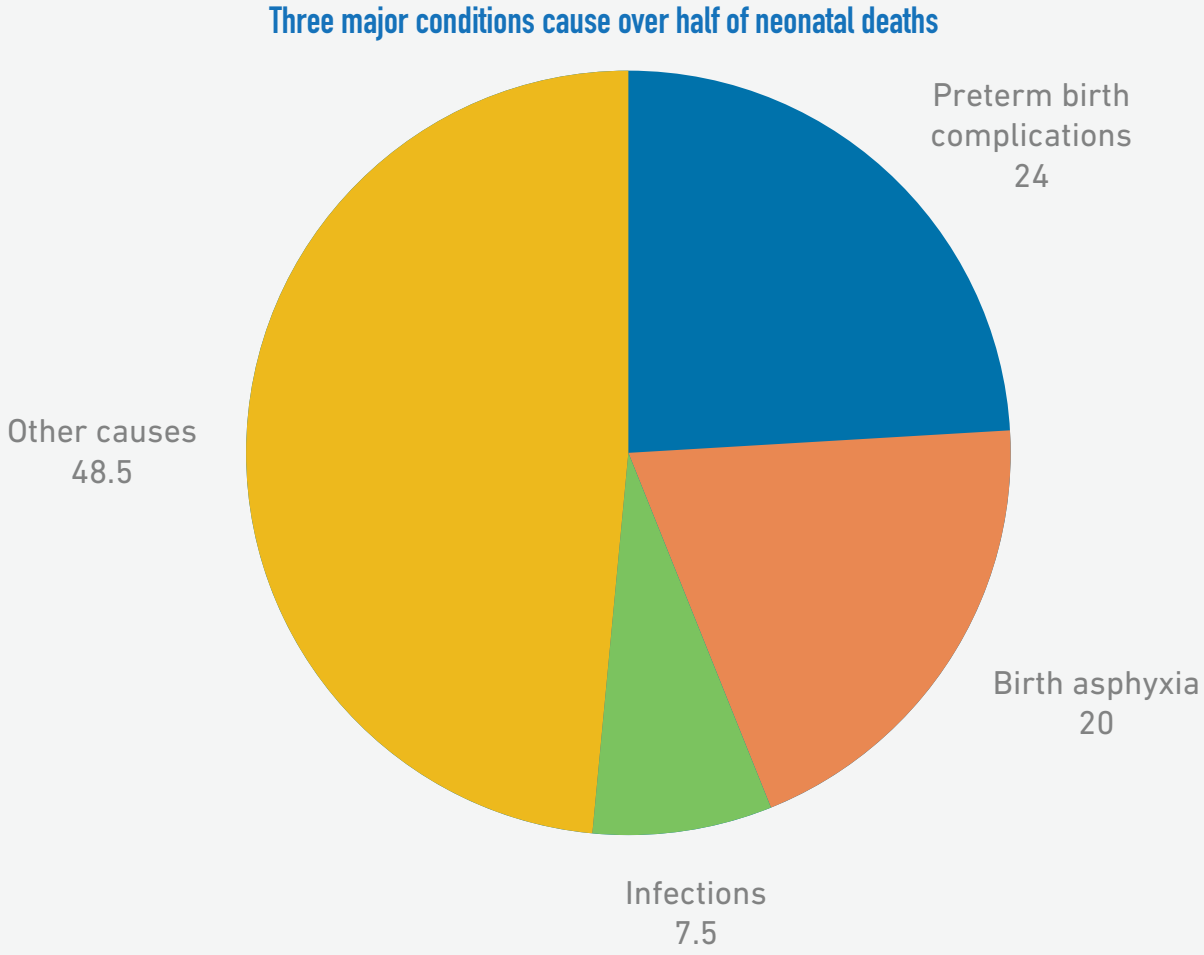


Exhibit 3: Preterm births, birth asphyxia and infections (pneumonia, sepsis and meningitis) cause more than half of all neonatal deaths. (Source: IHME GBD, 2017)

Preterm birth complications

Births are considered preterm when the infant has completed fewer than 37 weeks of gestation. In 2017, preterm birth complications caused 648,000 infant deaths (IHME GBD, 2017). Preterm infants are vulnerable to an array of conditions including respiratory distress, difficulty feeding orally, infection (most commonly sepsis and pneumonia) and hypothermia, among others. The frequency and severity of complications increase as the duration of gestation decreases (**Exhibit 4**).

Infants born very preterm (28 to 32 weeks of gestation) are particularly prone to respiratory distress syndrome (RDS), which is characterized by under-developed lungs that lack surfactant—a lipoprotein complex that helps lungs expand and contract. The weight of the infant at birth is another important indicator. Even infants who are born at or near full-term can be low birthweight and require special care.

The causes of premature birth are not well understood, even in developed countries. It is believed to be associated with multiple pregnancies, infections, genetic factors, and chronic conditions such as diabetes and high blood pressure (WHO, 2012). Though it is best to prevent preterm birth, this is difficult given the limited understanding of risk factors and the lack of antenatal care in developing countries. Since preterm birth is difficult to predict or prevent, it is more effective to focus on treating the complications at each level of prematurity

Frequency of preterm birth and major complications

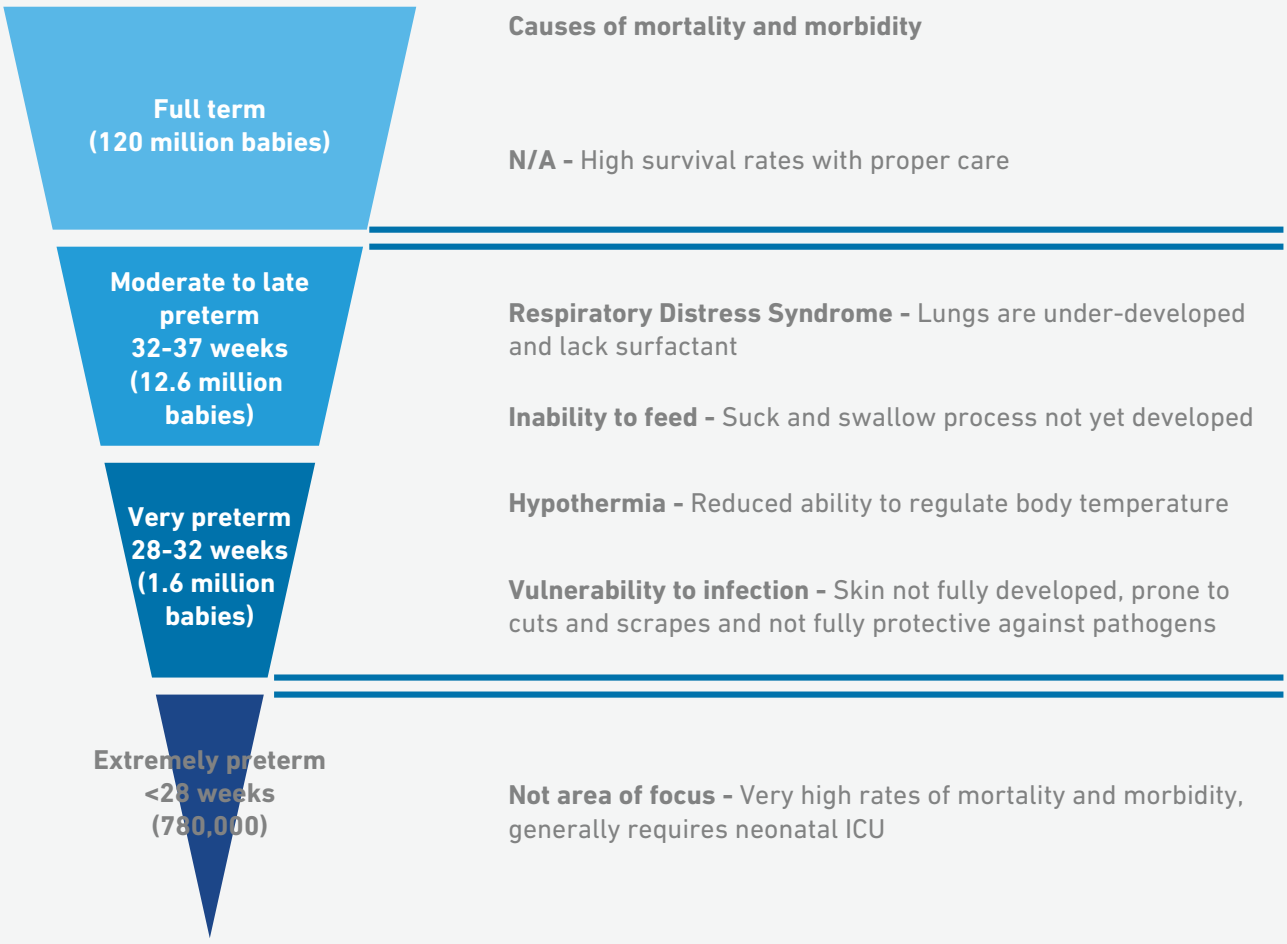


Exhibit 4: Infants born before 37 weeks experience an array of complications, which require specialized care. (Source: WHO, 2012)

Birth asphyxia

Birth asphyxia is defined as the inability to establish breathing at birth and is referred to in some studies as intrapartum-related events or complications of neonatal encephalopathy. Birth asphyxia was responsible for 540,000 deaths in 2017 (IHME GBD, 2017).

During birth, blood flow to the placenta is disrupted by contractions, which does not present a problem when the mother and fetus are healthy and labor progresses normally. Various conditions such as severe anemia and prolonged labor can exacerbate this disruption of blood and oxygen flow, however, leading to insufficient oxygen reaching the fetus and causing brain damage and death. Intrapartum complications are often addressable but require access to skilled care and equipment.

Specifically, when a fetus is deemed to be in danger of intrapartum asphyxia due to prolonged labor or another cause, asphyxia can usually be prevented through emergency cesarean section. This is often not an option in many developing countries due to lack of obstetric skills and equipment.

Newborns sometimes also need assistance in establishing breathing immediately after birth. It is estimated that 10 percent of newborns require some form of assistance in initiating breathing (Healthy Newborn Network, 2014), usually through simple resuscitation devices like self-inflating bags and masks or suction devices, to remove amniotic fluid that may be in the newborn's airway. These devices are inexpensive, but coverage is low and they require training to be properly used.

Infections

Major infections including pneumonia, sepsis and meningitis, are the third leading cause of neonatal mortality, responsible for 202,500 deaths in 2017 (IHME GBD, 2017). These major infections are often considered separately form tetanus and diarrhea, which cause another 58,000 and 50,000 deaths respectively, as they often have very different transmission pathways. Pneumonia, sepsis and meningitis are classified as early onset or late onset, depending on when the symptoms occur. Early and late onset infections are often contracted through different pathways.

The leading cause of neonatal infection is exposure to bacteria immediately before or during delivery. This occurs primarily when bacteria ascend from the birth canal during prolonged rupture of membranes and are aspirated by the infant.

Infants can also be exposed to pathogens during birth due to unhygienic delivery practices, such as use of dirty equipment, unwashed hands during delivery and improper cord care. Symptoms of early onset infection occur within seven days of birth. In late onset sepsis and pneumonia, symptoms occur 8 to 30 days after birth and can arise from community acquired infection or from bacteria contracted during birth.

5. Unmet need for family planning also contributes substantially to maternal mortality

Forty-three percent of the estimated 206 million pregnancies worldwide are unintended (Guttmacher, 2017). The majority of unintended pregnancies were caused by lack of access to, or utilization of, modern contraception—in developing regions, 214 million women of reproductive age who want to avoid pregnancy are not using a modern contraceptive method (WHO, 2018).

Unintended pregnancies due to lack of family planning increases the risk of maternal mortality in multiple ways. Contraceptive use has been shown to reduce maternal mortality rates, by decreasing the number of high-risk and high-parity births. There is evidence that women who have more than four children are at increased risk of maternal mortality (WHO, 2018). Women with unplanned pregnancies also tend to receive low-skilled care, which increases the risk of death during childbirth. Reducing unplanned pregnancies lessens the need for abortions, and in low-resourced settings that often means unsafe abortions, another leading cause of maternal mortality.

Closely spaced births also contribute to high infant mortality rates, and babies born to adolescent mothers suffer a higher rate of neonatal mortality. Adolescent mothers are also more likely to have pre-term or low birth weight-babies, which are risk factors for many early childhood health issues like pneumonia.

Fully meeting the unmet need for modern contraception would result in an estimated 25 percent, or 76,000, fewer maternal deaths each year (Guttmacher, 2017). Furthermore, family planning access and utilization is key to achieving SDG Goal 5.6, "universal access to sexual and reproductive health and reproductive rights" (UN, 2018).

KEY CHALLENGES

The challenges in maternal and neonatal health are systemic: There are too few adequately equipped clinics and adequately trained clinicians, and little regulation.

Access to quality family services, especially for adolescents, is inadequate.

Beyond the challenges of access to basic health services, it is important to note that there are also significant cultural barriers in many communities, which compel women to rely exclusively on informal, at-home care.

As a result, even when adequate clinics exist, the demand for them isn't necessarily guaranteed. This broad lack of access to basic care leads to a number of essential issues.

1. Many births in developing countries still take place at home, administered by poorly trained and poorly equipped traditional birth attendants. There is a widespread lack of skilled birth attendants.

2. Although facility birth rates are increasing, access and quality remains a concern. In low-resource settings, even where facilities are available, they tend to be overburdened and poorly equipped, lacking reliable electricity, lighting, necessary equipment, and access to clean water and sanitation.

3. Mothers do not receive adequate antenatal care. Only 62 percent of mothers in developing countries receive at least four antenatal care visits, as recommended by WHO, and this percentage is even lower in large countries in sub-Saharan Africa and South Asia.

4. Poor maternal nutrition and anemia during pregnancy make both mother and child more vulnerable to complications. Poor nutrition prior to the pregnancy itself can also affect maternal and neonatal health. Stunting in girls, occurring as early as the first two years of life, for example, increases the risk of preterm delivery and PPH later in life.

5. There is a high unmet demand for family planning. This means women who want to limit their family size, or space their pregnancies, are not able to do so, but lack of family planning also greatly increases a woman's risk of maternal death and her infant's neonatal health.

There are many barriers to ensuring that every woman has access to contraceptive methods that suit her needs. Currently, the choice of methods is limited. Many are hormonal methods that cause side effects, a major reason for discontinuation. Easier and discreet long-term methods currently require administration by health providers.

SCIENTIFIC AND TECHNOLOGICAL BREAKTHROUGHS

Maternal and neonatal mortality and morbidity is driven by fewer than 10 conditions, the majority of which are treatable by a skilled clinician with appropriate equipment. Currently, there is a shortage of both.

Medical equipment in particular needs significant technological innovation and cost reduction to reach low-income populations, especially in rural areas. With high levels of unintended pregnancies, many of which lead to maternal deaths, contraceptive technologies and administration methods require new approaches.

Many existing low-cost technologies have the potential to reduce maternal and neonatal mortality and morbidity, such as uterine balloon tamponades, low cost antiseptics and kangaroo care, among others.

Over the last decade, there has been a large increase in leveraging the ubiquity of mobile phones to reach women of reproductive age, pregnant women and providers. While there are not enough rigorous evaluations of the effect of mHealth strategies on reducing maternal and neonatal morbidities and mortalities, modest evidence suggests that such tactics can improve mothers' education, and that decision support and training applications have positive effect on providers (Chen, et al., 2018).

Proper primary health care for women and children is a vital prerequisite for maternal and neonatal success. There must be more focus on innovative approaches to improve primary care. There is one technology breakthrough that can significantly improve maternal and neonatal health by strengthening primary health care.

Breakthroughs:

1	2	3	4	5	6	7	8	9	10
11	12	13	14	15	16	17	18	19	20
21	22	23	24	25	26	27	28	29	30
31	32	33	34	35	36	37	38	39	40
41	42	43	44	45	46	47	48	49	50

31 Integrated suite of digitally enabled primary care devices including point-of-care diagnostics (for basic blood, urine, and vitals tests), therapeutic devices for common conditions, and clinical operations (such as sterilization, refrigeration)

Among the many structural challenges in healthcare delivery in developing countries is the virtual absence of adequately equipped clinics needed to support the provision of primary care. The majority of clinics, especially in rural areas serving low-income populations, lack even the basic amenities, let alone the equipment necessary to provide essential services. With the shortage of human resources, it is particularly important to expand and maximize the capabilities of locally available providers (often mid-level providers like nurses or clinical officers with varying levels of training) for patient-centered care at primary care facilities.

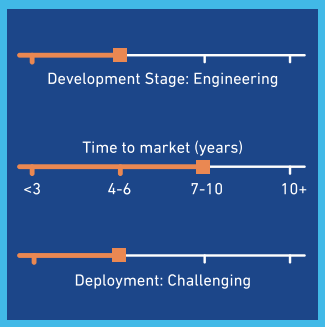
To build a clinic with the equipment necessary to provide basic primary healthcare would likely cost in excess of $100,000. This is based on preliminary research on costs of essential infrastructure (like solar panels and lighting), medical devices (like sterilizer and ultrasound) and diagnostics (such as rapid diagnostic tests and urine test analyzer) that are already available on the market, and the cost of constructing a basic building. In the absence of adequate public funding, this is too expensive for low-income populations by a factor of 10, based on our high-level assessment. In addition, the logistics of procuring the various components and assembling them into a functioning clinic require considerable effort.

A digitally-integrated suite of devices for primary care is needed, that includes point of care diagnostic devices for basic blood, urine and vitals tests. It would also include therapeutic devices for common conditions, for example, warming, phototherapy and oxygen concentration devices. It would also support clinical operations, such as sterilization devices and refrigeration for thermo-sensitive pharmaceuticals. A power management system would be integrated, including renewable energy supply where appropriate. A platform for patient and clinic management is at the core, and needs to be built using a provider- and patient-centered design approach. The focus should be on making the work of health professionals easier and better, and improving on the patient experience to ensure utilization. While maternal and neonatal intensive care devices are likely beyond the scope of this suite, health outcomes for mothers and newborns are nonetheless expected to be significantly improved, due to higher overall standards of primary care during prenatal and postnatal periods.

Such an integrated suite of devices could be a significant breakthrough if it:

- combines an integrated suite of low-cost and energy-efficient devices required to provide basic primary care:
  - Diagnostic devices and tests for relevant medical conditions including nutrition deficiencies, anemia, malaria, HIV, syphilis and hypertensive disorders

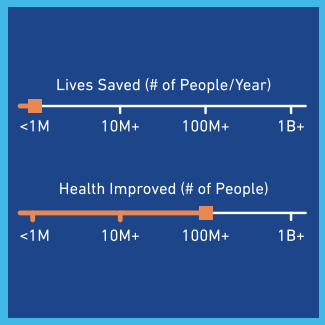
Current State



Associated 50BT Chapters

SDG Alignment

Impact



Commercial Attractiveness

- Sterilization devices for equipment
- Ultrasound devices
- Medical lighting
- Locally manufactured oxygen or oxygen concentrators
- Refrigeration to store vaccines and other thermo-sensitive pharmaceuticals;

- integrates power management, computation/ imaging, data and communication so that the various devices can function in an easy-to-install plug-and-play mode;

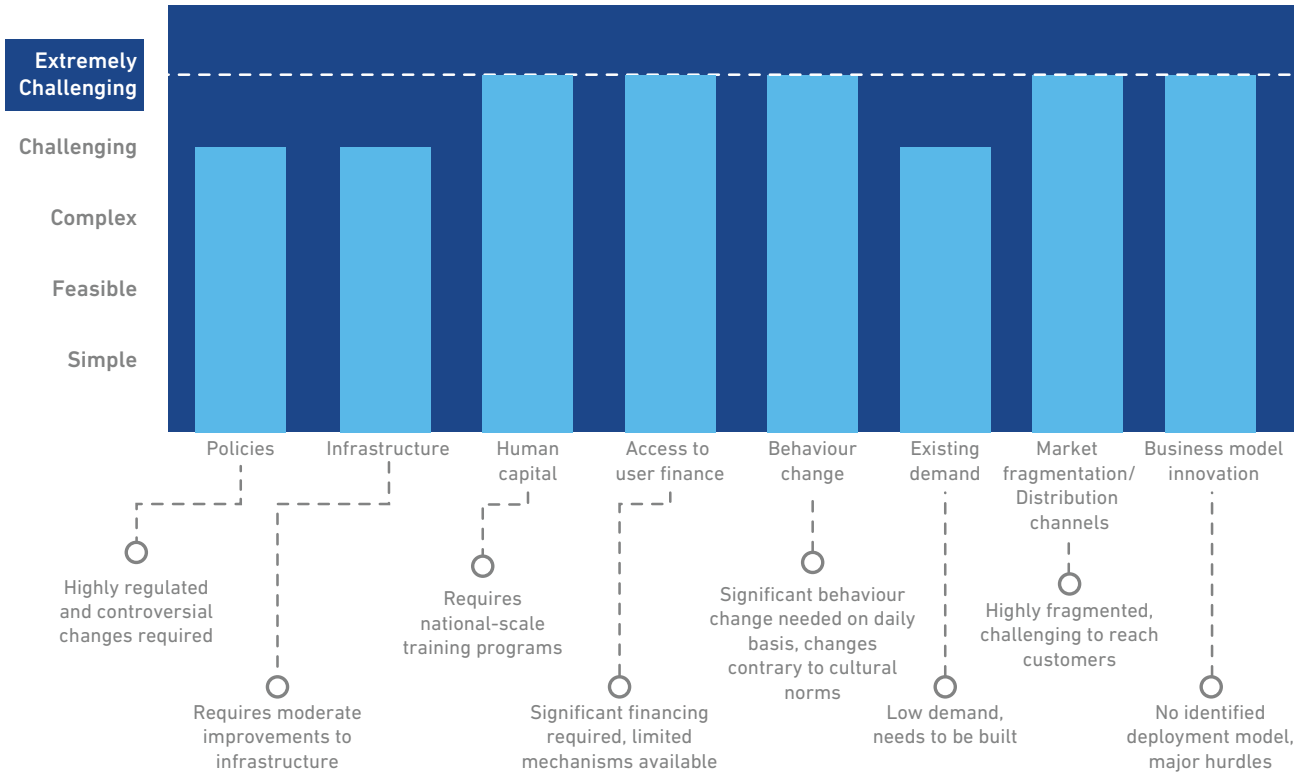
- builds on a digital platform that augments provider knowledge, experience and clinical workflows with decision support tools and diagnostic algorithms for more precise, patient-centered care; allows for remote consultation with clinicians and specialists; and enables data systems that collects and generate high-quality, timely information for decision-making and enables patient-centered care;

- costs approximately $10,000 to $15,000, based on our high-level assessment of financial feasibility, given published data on how much low-income rural families in sub-Saharan Africa and South Asia spend on healthcare.

While some of the listed devices are available at the appropriate price point, many are still priced for industrialized markets. Given the broad interest in developing individual devices, we believe enough of them are available at the right price point to begin assembling a suite of devices. There are also efforts underway to develop a digital platform to integrate the various devices. Many information and communication technology platforms exist or are in development, but most only focus on a particular area of the health delivery system or are focused around certain health conditions. It is important to note that there is no one-size-fits-all solution, particularly the design of the digital platform, across low-resource settings.

Even once such technology-enabled delivery system is developed, it will face a large number of deployment challenges. There is not enough public funding to procure a sufficient number of such clinics, the private market is underdeveloped and fragmented, and the regulatory requirements are unclear. Moreover, significant behavior change, encouraged by some form of insurance or financing to allow affordable access, is required for most low-income rural communities to seek regular and formal care. A dependable supply chain for consumables and maintenance of technologies will also be required. Hence, the difficulty of deployment will be EXTREMELY CHALLENGING.

Breakthrough 31: Difficulty of deployment



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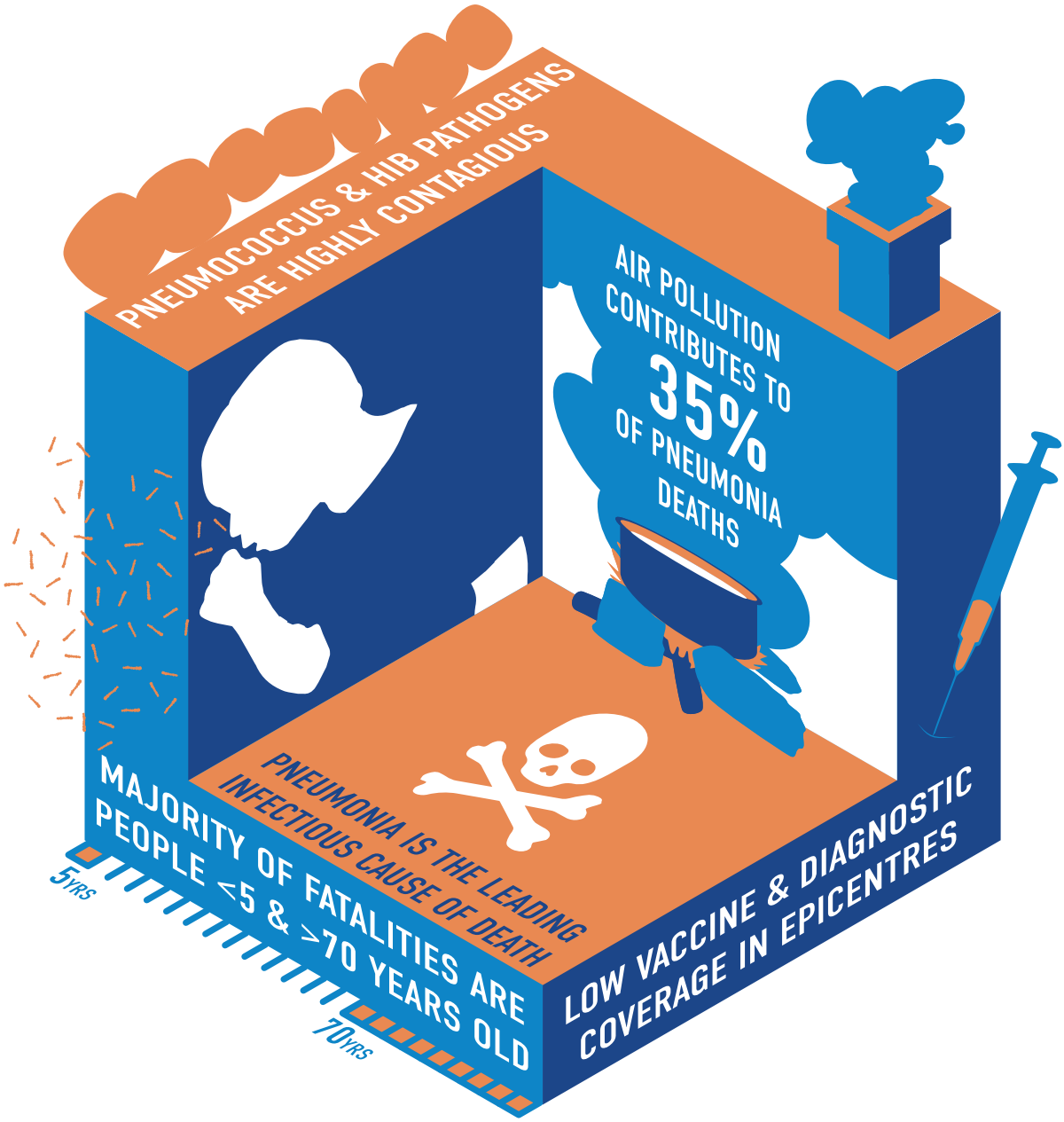


PNEUMONIA AND LOWER RESPIRATORY INFECTIONS

INTRODUCTION

Pneumonia, an infection of the lungs, is the leading cause of infectious mortality, killing an estimated 2.6 million people globally in 2017, according to the Global Burden of Disease (IHME GBD, 2017).

The burden of this disease falls heavily on two age groups: children under 5 with 809,000 deaths and adults aged over 70 years with 1.1 million deaths. In low-income countries, pneumonia is a leading cause of death among children, while in middle- and high-income countries deaths are concentrated among adults and elderly. Despite progress in reducing child pneumonia deaths, deaths among adults are increasing. Overall, pneumonia mortality rates have fallen more slowly than other major infectious diseases, by 25 percent between 1990 and 2017, compared to other top killers, such as HIV/AIDS (decreased by 47 percent) and diarrhea (decreased by 39 percent). Hence, the disease presents a major barrier to achieving at least two of the SDGs of reducing child deaths to at least 25 per 1,000 births (Goal 3.2), and to combatting the overall communicable disease burden (Goal 3.3) (Just Actions, 2018).

Streptococcus pneumoniae (pneumococcus) and *Hemophilus influenzae* type b (Hib), which are extremely common bacteria, cause the majority of pneumonia mortality. Pneumococcus, in particular, is frequently found in the nose and throats of otherwise healthy children. As a result of the ubiquity of these bacteria, risk factors that make children more susceptible to infection are critical drivers of pneumonia. Child wasting is the leading risk factor that underlies more than 50 percent of child pneumonia deaths, while air pollution (indoor and outdoor) contributes to 35 percent of total pneumonia deaths.

If pneumonia is identified early, antibiotics are an effective treatment, although only 30 percent of caretakers in low-resource settings can recognize just one of the many key symptoms and warning signs of pneumonia—a major impediment to

Moreover, just 60 percent of children under 5 years of age with symptoms of pneumonia are taken to an appropriate healthcare provider, according to UNICEF. Once infections are advanced, antibiotic therapy is less effective and oxygen therapy becomes necessary but is rarely available. Two highly effective vaccines, the Hib and pneumococcal conjugate vaccine (PCV), have been rolled out globally since 2000. Recent studies attributed the great reductions in deaths caused by these two bacteria from 2000 to 2015 to the vaccines (Wahl, et al., 2018).

In light of the above factors, eight technological breakthroughs can help reduce the disease burden from pneumonia and lower respiratory infections in low-resource settings:

- Breakthrough 23. Vaccines that can effectively control and eventually help eradicate the major infectious diseases of our time—HIV/AIDS, malaria, tuberculosis and pneumococcus
- Breakthrough 28. New generation of antibiotics capable of treating fast-mutating bacteria like MTB and MRSA
- Breakthrough 32. Low cost, novel diagnostics for pneumonia
- Breakthrough 33. Low cost, off-grid oxygen concentrators
- Breakthrough 46. Advanced biomass cookstoves that are desirable, affordable, robust and very clean
- Breakthrough 47. Novel ways of converting household or village waste products into clean cooking fuel or electricity
- Breakthrough 48. A mechanism to remove particulate emission from old trucks and other heavy-duty vehicles
- Breakthrough 49. Small-scale waste incinerators with efficient combustion and clean emissions

Pneumonia, an infection of the lungs, is the leading infectious cause of mortality globally, killing 2.68 million people in 2017. An estimated 810,000 of them are children under 5, almost all living in low- and middle-income countries. Another 1.1 million deaths are among adults aged over 70 across diverse geographies.

CORE FACTS AND ANALYSIS

1. Pneumonia is a serious lower respiratory infection that mainly affects children under 5

Pneumonia falls under the broader category of lower respiratory infections (LRIs), which can also occur in the trachea and bronchi. Upper respiratory infections (URIs), such as the common cold, occur in the nose, pharynx and larynx. LRIs are far more severe than URIs and are responsible for nearly all disease burden that results from respiratory infections.

Children under 5 are most affected by LRIs (**Exhibit 1**). The Global Burden of Disease 2010 study estimates that 65 percent of disease burden from LRIs in low- and middle-income countries (LMICs) occurs in children under 5 years, with 52 percent occurring in children less than a year old (IHME GBD, 2017). LRIs re-emerge as a major cause of mortality later in life, with pneumonia deaths rising for the elderly, even though impact on DALYs is low.

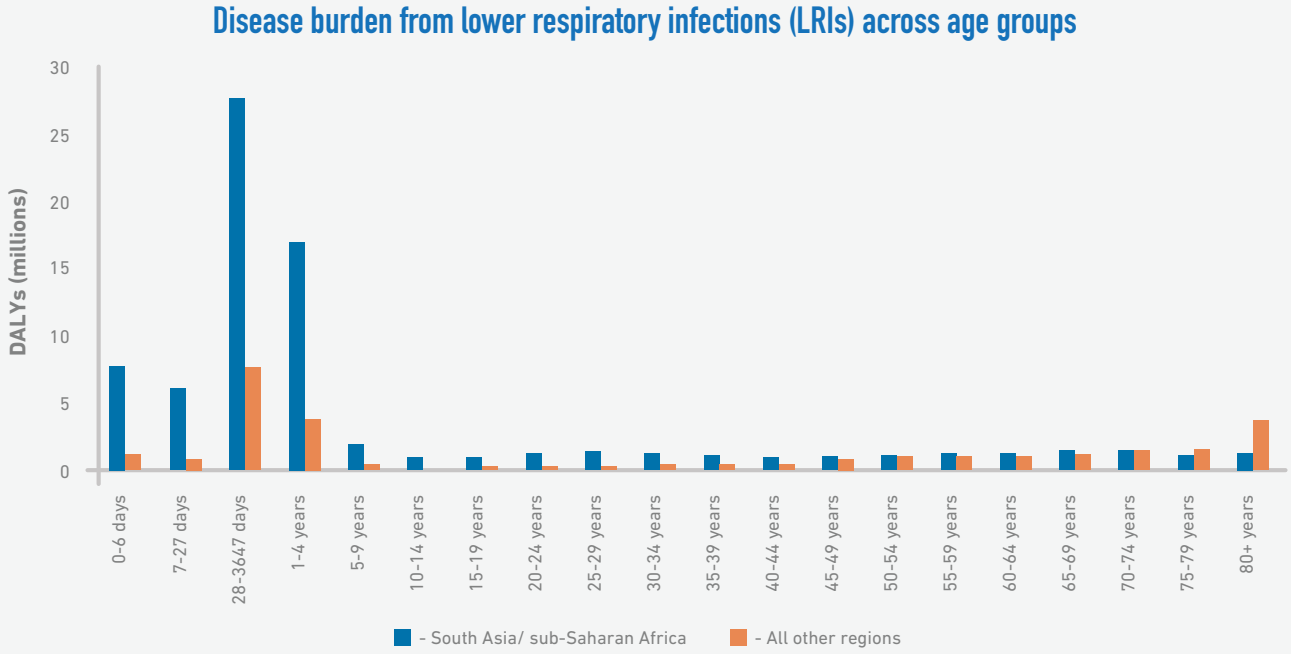


Exhibit 1: Disability adjusted life years (DALYs) for lower respiratory infection (LRIs) in South Asia and sub-Saharan Africa are highly concentrated in children under 5. (Source: IHME GBD, 2012)

Pneumonia is caused primarily by bacteria and viruses, with bacterial infections causing most severe cases, and viruses causing most non-severe cases. Often, pneumonia begins after an upper respiratory tract infection, with symptoms of pneumonia manifesting after two or three days of a cold or sore throat.

Of the two most common bacteria causing severe bacteria, the WHO and UNICEF estimate that pneumococcus may be the cause for more than half of severe cases of pneumonia and Hib could be responsible for 20 percent of the severe cases (WHO-UNICEF, 2006).

As of 2000, pneumococcus and Hib were responsible for 41 percent and 16 percent of pneumonia deaths, respectively, in children (Izadnegahdar, et al., 2013).

One vaccine study in The Gambia noted that vaccination against pneumococcus led to a 16 percent reduction in mortality from all causes (meaning, a 16 percent reduction in all childhood mortality, not just from pneumonia). The next most important pathogen is respiratory syncytial virus (RSV), which is an extremely common cause of pneumonia but generally causes less severe infections.

Prevalence of specific pathogens varies across regions, as do strains (more technically, serotypes) of pneumonia, but pneumococcus and Hib are considered to be the major drivers of mortality. The rollout of vaccines for these two bacteria will lead to the etiology of pneumonia shifting in coming years, likely toward more viral causes or toward non-vaccine strains[1].

Worldwide, pneumonia deaths occur in high-, middle- and low-income countries alike. Most pneumonia deaths in high income countries like Japan and USA occur among the elderly, while most deaths in low-income countries like Nigeria, Pakistan, DR Congo, Ethiopia, Bangladesh and Tanzania are among children under five years (Just Actions, 2018) (**Exhibit 2**).

Deaths due to pneumonia, across countries and ages

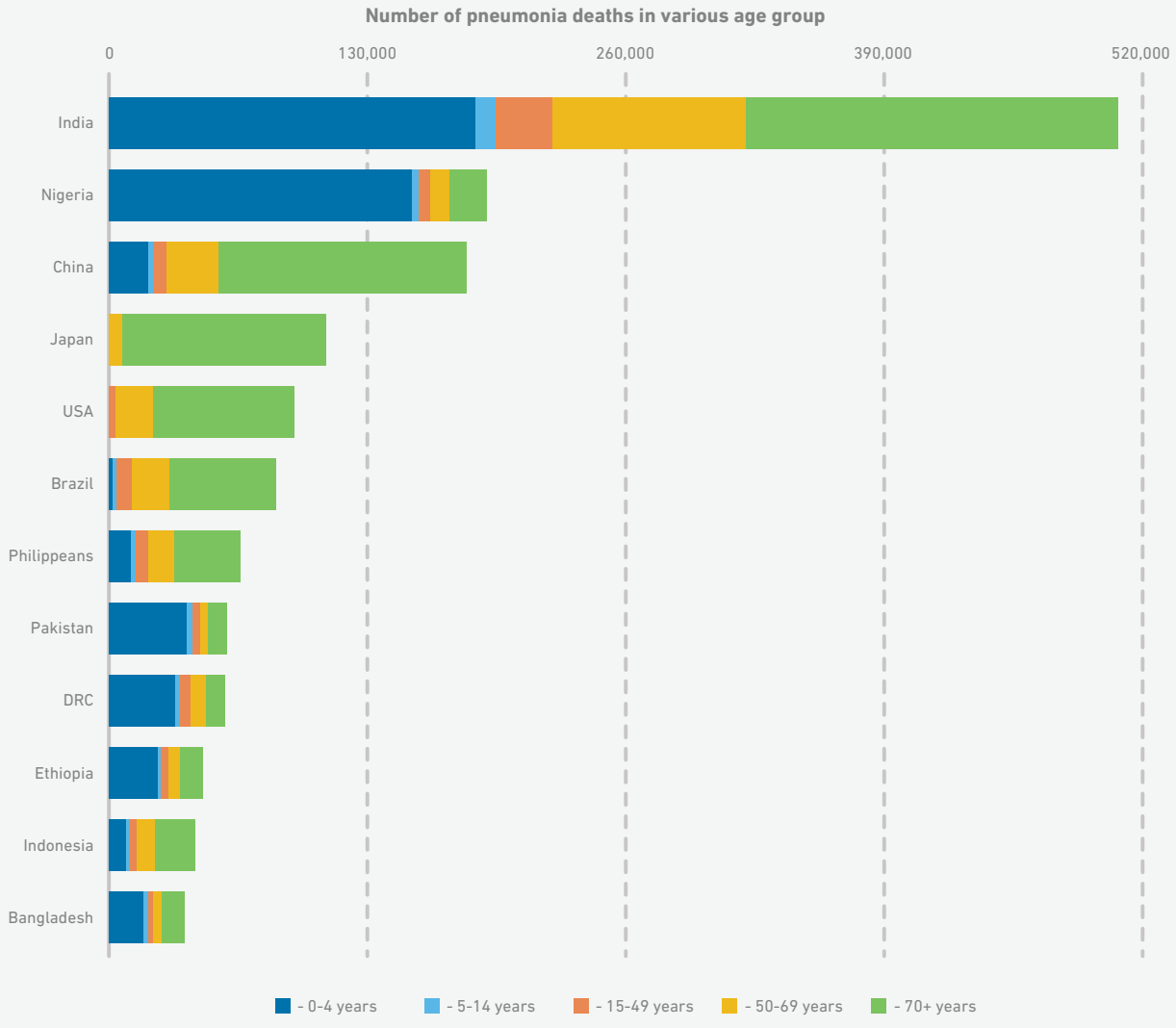


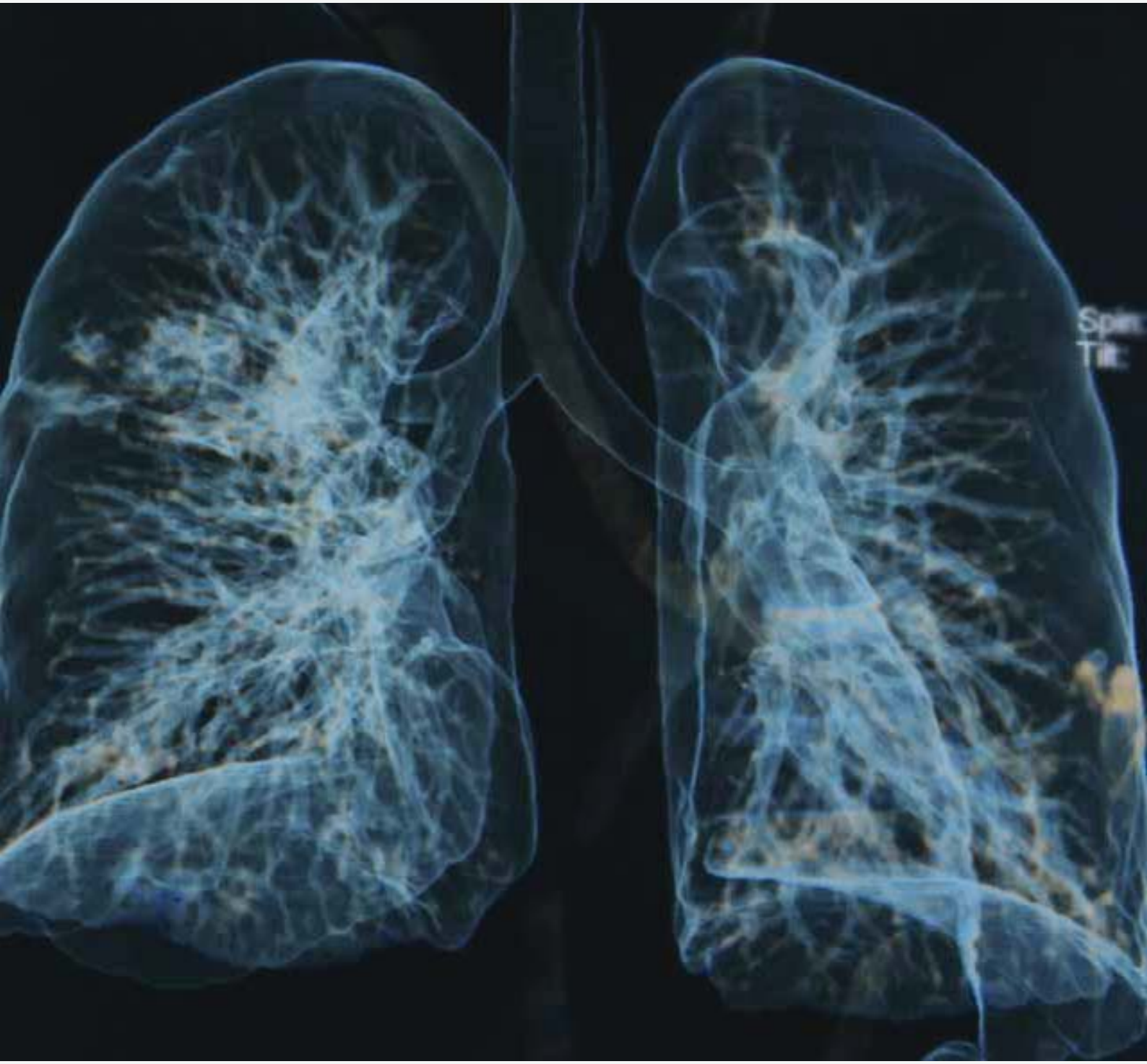
Exhibit 2: A dozen countries account for well over a half of all deaths from pneumonia. The age at deaths is typically lower in developing countries and higher in industrialized countries. (Source: Just Actions, 2018)

[1]In 2019, The Pneumonia Etiology Research for Child Health (PERCH) will release new data that aims to determine risk factors and etiology for severe and very severe pneumonia in children hospitalized in seven different countries including Bangladesh, Kenya, The Gambia, Mali, South Africa, Zambia and Thailand. Additionally, the Child Health and Mortality Prevention Surveillance (CHAMPS), aims to determine the causes of overall deaths in children and the etiology of fatal cases of pneumonia.

KEY CHALLENGES

Pneumonia is primarily driven by the ubiquity of the infecting pathogens and risk factors that increase susceptibility, especially among children and elderly adults, to these pathogens. Once children are infected, low awareness of the disease and its symptoms by caretakers and limited access to treatment are critical drivers of mortality.

Outdoor air pollution, smoking and alcohol consumption are major risk factors for adult pneumonia, and are contributing to the rapidly increasing rates of elderly deaths from pneumonia. Vaccination efforts against the two most important pneumonia-causing bacteria will markedly reduce disease burden in the coming years.



1. Many children are already carriers of pathogens that can cause pneumonia

The pathogens that cause pneumonia are highly contagious and very prevalent in the population. Pneumococci and Hib in particular colonize the nose and throat, where they reside harmlessly until the bacteria have an opportunity to penetrate the body's defense system and travel into the lungs, blood or cerebrospinal fluid. This is often spurred by another infection, usually URIs or inflammation of the lungs from smoke inhalation.

Poor populations in sub-Saharan Africa and South Asia often live in crowded and poorly ventilated conditions, which facilitates the spread of bacteria. Newborns can also become infected by exposure to microbes in the birth canal during delivery. The ubiquity of these pathogens is evident in the fact that children develop pneumonia very frequently. In LMICs, a child will develop an average of 0.29 episodes of pneumonia per year, compared with 0.05 episodes per child per year in developed countries (WHO-UNICEF, 2008).

2. Several risk factors increase vulnerability of children to respiratory infections, and worsen health outcomes

Although risk-related child pneumonia deaths are declining, major risk factors including malnutrition, preterm birth and suboptimal breastfeeding continue to contribute to childhood pneumonia deaths, with air pollution (outdoor air pollution in particular) being a growing contributor (**Exhibit 3**).

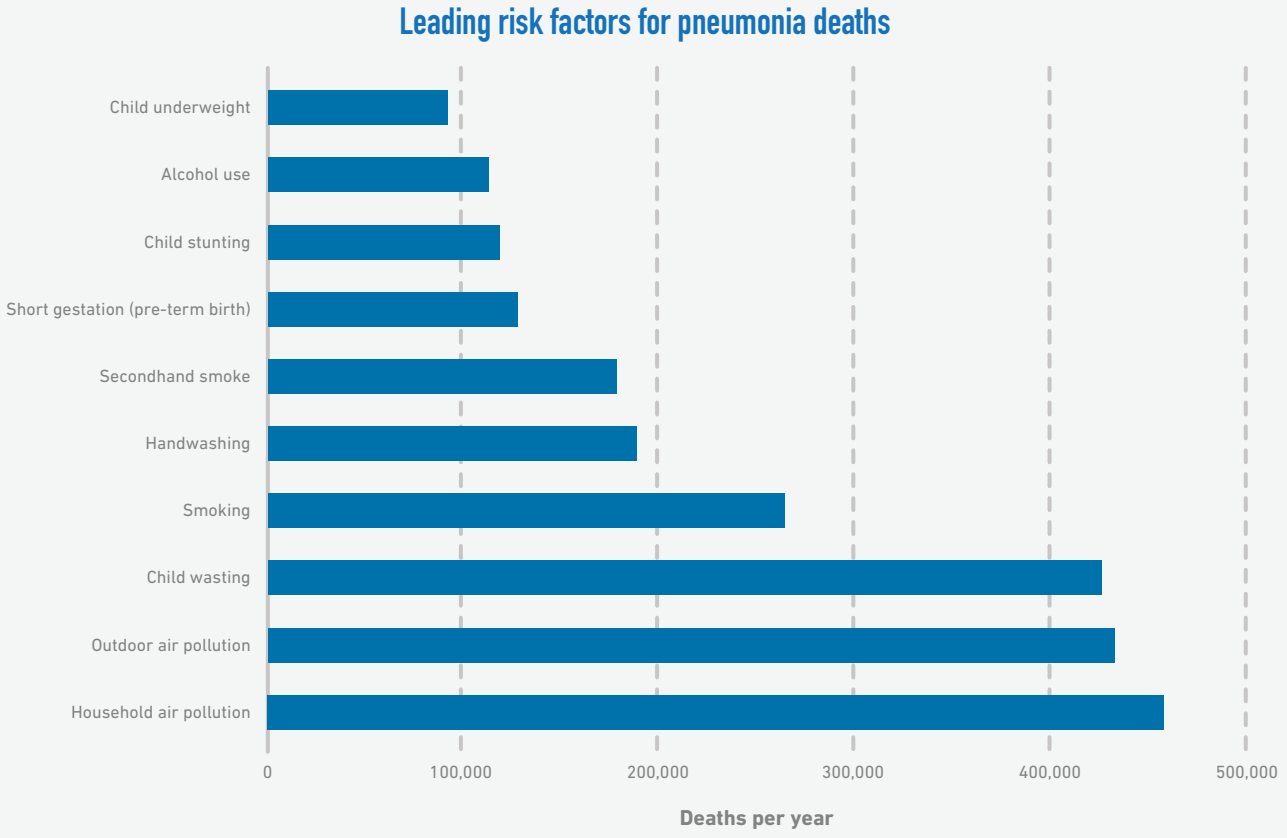


Exhibit 3: Leading risk factors for pneumonia deaths. (Source: Just Actions, 2018; IHME GBD, 2017)

Malnutrition (child wasting)

Malnutrition weakens a child's still-developing immune system, and significantly increases the risk of death from pneumonia. Studies have shown the prevalence of multiple pathogens (viral and bacterial) in children who die from pneumonia in hospital settings, but the interplay of these conditions and pathogens is not well understood. Childhood underweight, stunting, and in particular wasting, are estimated to be a factor in more than 80 percent of childhood deaths from pneumonia (Just Actions, 2018)

Second-hand smoke and household and outdoor air pollution

Outdoor air pollution, household air pollution and tobacco smoke cause inflammation of the lungs, which increases susceptibility to infections. The Global Burden of Disease study estimates that more than 28 percent of LRI burden can be attributed to indoor air pollution from solid fuels (IHME GBD, 2017).

Forty-three percent of the population in developing Asia, and almost 80 percent in sub-Saharan Africa still rely on biomass fuels for cooking (IEA, 2017), which are burned indoors without chimneys or adequate ventilation, causing high levels of particulate matter inside homes. Smoking is also highly correlated with increased rates of pneumonia. Incidence rates for pneumococcus are 1.9-4.1 times higher for active smokers and 1.9 times higher for children of smokers relative to non-smokers (van Zyl-Smit, et al., 2011).

Suboptimal breastfeeding

Breast milk provides infants with antibodies that help protect them until their immune systems develop more fully. The WHO recommends exclusively breastfeeding infants for the first six months of life, and partial breastfeeding for the following 18 months accompanied with age appropriate foods.

Infants who are not breastfed in the first six months are six times more likely to die from pneumonia as children who are even partially breastfed (Black, et al., 2013). Suboptimal breastfeeding contributes to 7.45 percent of LRI-related deaths in children under 5 (IHME GBD, 2017). Globally, only 30 percent of infants are exclusively breastfed (WHO, 2016).

HIV

Children with HIV, due to increased susceptibility to pathogens, are 40 to 50 times more likely to contract pneumonia, and three to six times more likely to die of the disease (World Lung Foundation, 2010). In sub-Saharan Africa, nearly 1.6 million children live with HIV (UNAIDS, 2017) .

3. Low vaccination coverage, particularly for pneumococcal pneumonia

Vaccines are available for both Hib and pneumococcus, the latter of which is fairly new and have only been available in low- and middle- income countries since 2009. While the rollout for the pneumococcus vaccine—pneumococcal conjugate vaccine (PCV)—has been rapid, its coverage remains low (most countries have less than 90 percent coverage) relative to the large potential benefit it can deliver.

Globally, 44 percent of children are protected with three doses of the PCV, 72 percent of children receive three doses of the Hib vaccine and 67 percent receive two doses of the measles vaccine, according to the WHO. Among the high-burden pneumonia countries, PCV coverage is below 44 percent in India, China, Nigeria, Thailand and Indonesia. Although the price of PCV has already been brought down by roughly 90 percent, it still costs $2.95 per dose, compared with other vaccines that cost between a few cents to a dollar.

According to one manufacturer, it takes nearly 2.5 years to make a dose of multi-valent conjugate vaccines from start to finish. Currently two companies supply GAVI with PCV, but total demand exceeds their production capacities. To help these companies ramp up production GAVI, in 2010, introduced an Advanced Market Commitment (AMC) pilot to provide guaranteed purchasing and create demand stability.

An evaluation of the AMC pilot in 2015 showed that collective efforts of the AMC and PneumoADIP, Gavi's Accelerated Vaccine Introduction initiative, and strong WHO recommendation for PCV, greatly accelerated PCV supply availability, coverage and Gavi country demand (The Boston Consulting Group, 2015).

4. Caretakers do not recognize early symptoms and seek treatment or medical care only when the infection is too advanced

Parents often do not recognize the most common early symptoms of pneumonia—difficult and fast breathing. A study published in 2017 found that only 30 percent of caregivers in sub-Saharan Africa recognize either one of these key early warning signs of pneumonia (Noordam, et al., 2017).

This is driven by the subtlety of these symptoms, and further compounded by the fact that often pneumonia begins as a URI, with obvious symptoms of pneumonia presenting only after a few days. Parents are more likely to react to severe symptoms, such as fever or altered mental state, at which point antibiotic therapy is less effective and children may need more supportive care like oxygen therapy.

An additional challenge is that even when a child is recognized to have pneumonia, lack of access to affordable healthcare and lack of awareness about the severity of the disease means that the child may still not be taken to receive appropriate treatment. It is estimated that only 60 percent of children under 5 in LMICs are taken to an appropriate care provider when symptoms are present (WHO-UNICEF, 2012), with rates as low as 24 percent in a high burden country like Nigeria.

Apart from costs of seeking care, studies have shown that improving mother's literacy and education levels have a direct impact on survival through childhood (Uwemedimo, et al., 2018).

5. Medical facilities do not have equipment to provide pulse oximetry or oxygen therapy

Oxygen therapy is a powerful intervention for children with severe pneumonia and has been shown to reduce case fatality rates by as much as 35 percent in LMICs (Duke, et al., 2008). However, current oxygen delivery systems are not appropriate for low-resource settings. Oxygen cylinders are difficult to transport, likely to run out and require a logistics system to ensure they are continually supplied to healthcare facilities, especially for those in remote areas.

Oxygen concentrators, the alternative, are expensive and require a reliable electricity source, training and ongoing maintenance that hospital staff are rarely able to perform.

Administering oxygen requires ongoing patient monitoring, which most clinics and hospitals in small towns and villages lack the staff for.

Either system requires a pulse oximeter to measure oxygen in the bloodstream and a splitter so oxygen can flow from a single source to multiple patients. Cheap pulse oximeters exist on the market, but are rarely found in hospitals or clinics. Splitters by contrast are expensive and can be challenging to find. Notably, oxygen therapy is rarely seen as a high priority need. This explains its scarcity in hospitals and near absence from clinics. Most concentrators, particularly in sub-Saharan Africa, have been donated with insufficient training imparted to those operating them. A 2018 study by the Clinton Health Access Initiative (CHAI, 2018) of 78 hospitals across three states in Nigeria found that only 2 percent had pulse oximeters and 25 percent of pediatric wards had functional oxygen systems. In Ethiopia, the situation was only slightly better. 45 percent of hospital pediatric wards had pulse oximeters and 64 percent had fully functional oxygen delivery devices.

6. Medical facilities lack equipment necessary to make an accurate diagnosis

Chest radiographs are considered the gold standard for diagnosing pneumonia but are not practical in low-resource settings. Instead, care providers rely on clinical diagnoses, and while this practice does not drive mortality (as clinical diagnosis is usually sufficient) it does tend to result in over-treatment. The 2018 CHAI study mentioned above also found that among the children with pneumonia who reached a health facility in Nigeria, 47 percent of non-severe pneumonia cases were missed, only 4 percent of severe pneumonia cases were correctly diagnosed and just one in 10 children received the oxygen they needed.

In particular, cases of viral pneumonia and upper respiratory infections may be prescribed antibiotics, which are ineffective and can lead to drug resistance. Recent studies have shown lung ultrasound (LUS) as a feasible alternative diagnostic to chest radiographs, some even suggest that LUS demonstrate superior sensitivity although more research is necessary to differentiate between bacterial from viral pneumonia (Balk et al., 2018). Improved diagnostics will also allow better understanding of the epidemiology of the disease and its variations across geographies.

SCIENTIFIC AND TECHNOLOGICAL BREAKTHROUGHS

As the above analysis shows, improvements in care seeking behavior can greatly reduce mortality rates for children under 5 in high burden countries. Behavioral risks can be addressed through education and awareness, including improving mother's literacy, teaching parents and caregivers to recognize and act on early symptoms of pneumonia and preventing malnutrition.

Household air pollution is driven largely by cooking activities, particularly with solid fuel sources. Among devices that can help reduce household air pollution are advanced biomass cookstoves, gas stoves, electric stoves and electric rice cookers in regions with high rice consumption. Please see more details on indoor air pollution and cookstove innovations in the Clean Cooking section of the Access to Energy chapter.

One major risk factor that is on the rise is outdoor air pollution, the negative effects of which are well-beyond pneumonia deaths alone. Reduction in ambient air pollution will be key to controlling both child and adult pneumonia. Please see more details in the Resilience to Global Change chapter.

Vaccinations are an effective solution for stemming pneumonia cases but are dependent on sustaining and increasing coverage, which is primarily a policy and supply issue. Quick gains can be made by further reducing the cost of PCV, which is driven by the complexity of the manufacturing process as well as the fact that it is proprietary.

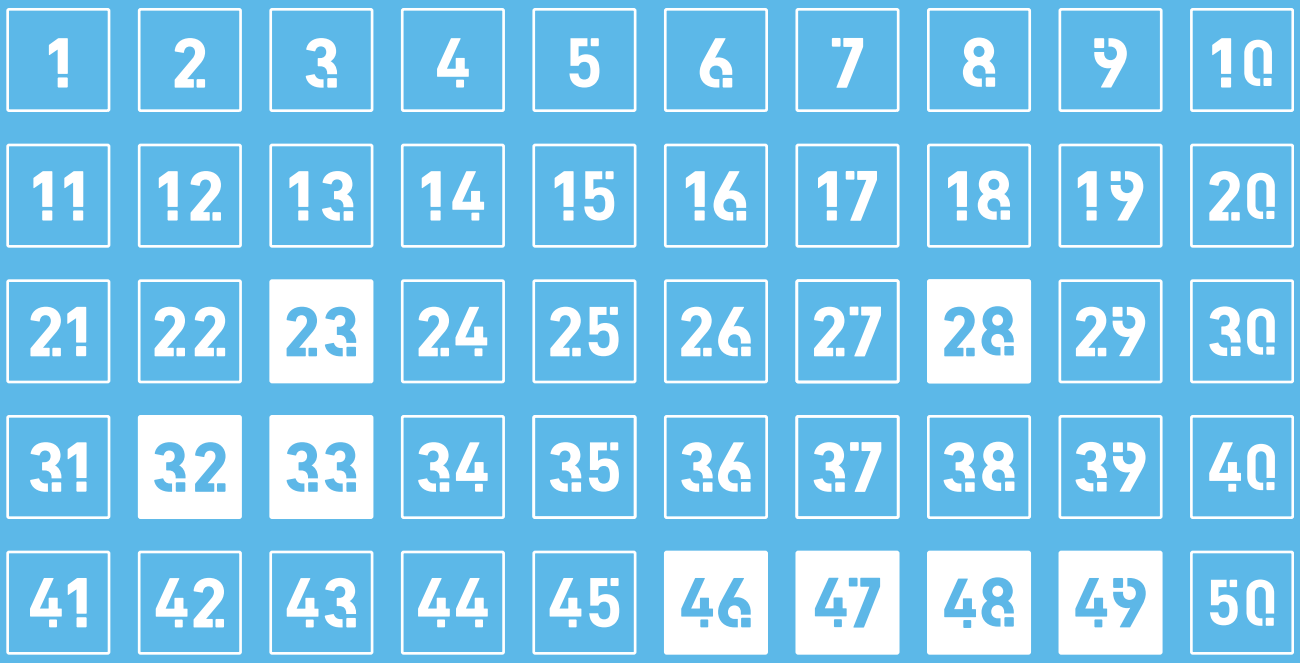
While the price of PCV has dropped dramatically, additional efforts are needed to bring it down further from its current cost of $2.95 a dose. An additional and significant challenge will soon emerge for countries that graduate out of Gavi support and must then finance the purchase of vaccines independently.

Affordability and quality of care are equally important in ensuring accurate diagnosis and effective treatment once a sick child is brought in. Increased focus on quality of care at the primary level, and current momentum in implementing Universal Health Coverage (UHC), will improve accessibility of pneumonia diagnosis and treatment, thus contributing to reducing pneumonia mortality.

Frontline providers need to be better equipped with diagnostic and curative technologies to ensure timely care. Increased R&D investments is needed for the development of rapid diagnostic tests, pulse oximetry, respiratory rate monitors and improved oxygen delivery.

There are eight scientific and technological breakthroughs that can significantly reduce the burden of pneumonia and lower respiratory infections.

Breakthroughs:



23. Vaccines that can effectively control and eventually help eradicate the major infectious diseases of our time—HIV/AIDS, malaria, tuberculosis and pneumococcus

Collectively, HIV/AIDS, malaria, tuberculosis and pneumonia kill more than five million people a year, and represent a significant disease burden for low income populations in sub-Saharan Africa and South Asia. Effective and affordable vaccines for these diseases do not exist yet due to the intrinsic complexity of the pathogens causing them, and a lack of understanding of the specific mechanisms through which our immune systems protect against these diseases. The process of vaccine development—basic research on disease etiology, vaccine construction, pre-clinical and clinical testing—is technically challenging, expensive and time consuming.

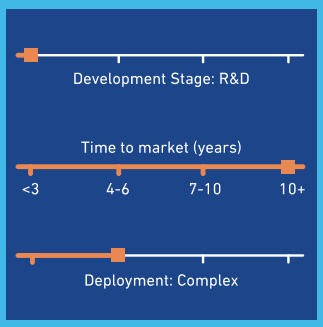
23d. An improved, lower cost vaccine for pneumococcus

UNICEF and the WHO estimate that the pneumococcus bacteria (Streptococcus pneumonia) is the pathogen causing more than half of severe cases of pneumonia. The WHO recommends that vaccination against pneumococcus should be added to all national immunization programs, and particularly in countries with high child mortality. The availability of low-cost, effective pneumonia vaccines and their rollout to low- and middle-income countries would be a significant advancement and has the opportunity to save an estimated 1.5 million lives through 2020.

The current vaccine for pneumonia—pneumococcal conjugate vaccine (PCV)—is a complex vaccine, designed to provide protection against multiple strains of pneumonia. More than 90 strains of pneumonia (referred to as serotypes) exist. Each of these present different antigens, which the immune system uses to recognize the bacteria and mount a defense. Consequently, vaccination against one strain often does not provide protection against another. To provide broader protection, PCV contains antigens for multiple strains (generally polysaccharides), which are attached to a carrier protein molecule. This conjugation process is complex and hence the vaccine is expensive relative to other types of vaccines. Currently available vaccines provide protection against as many as 13 strains depending on the manufacturer (CDC, 2016).

Deployment and adoption of improved pneumonia vaccines face two critical challenges. First, even though the price per vaccination has come down from $3.50 to $2.95 (future price is expected to reduce to $2.90), the current conjugate vaccines are still very expensive. While this is 90 percent less than the cost they are sold at in developed countries, PCV remains the single most expensive vaccine GAVI provides. Other vaccines, by contrast, can cost as little as a few pennies. This high price is due to the complexity of the conjugation process and the fact that there are only two manufacturers. (There are other manufacturers who have entered into agreement with GAVI, but do not yet have WHO-prequalified vaccines.) While the cost may be a manageable challenge for GAVI, it poses a significant problem for countries that graduate out of GAVI support, and must then procure vaccines on their own.

Current State



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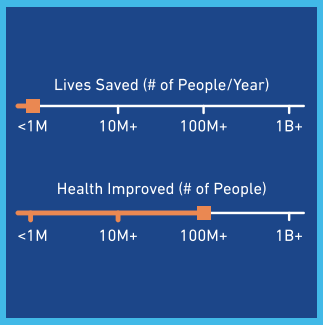


Commercial Attractiveness

Second, current vaccines do not provide protection against all strains of pneumonia. These strains, and the importance of each strain, vary by region. This means that protection against pneumonia is incomplete on an individual level, and in some regions the strain coverage is suboptimal. There is also concern about strain replacement, where strains that are currently less significant causes of mortality may become more important as a result of protection against strains that are included in the vaccine.

These challenges can be addressed in two ways. The first would be an advancement in the conjugation process. This will allow manufacturers to provide the vaccine at a lower cost, and increase the likelihood that other manufacturers will be able to offer competing vaccines. It may also allow the development of vaccines that can provide protection against a larger number of strains. Single dose vaccines that do not require refrigeration will also lower costs.

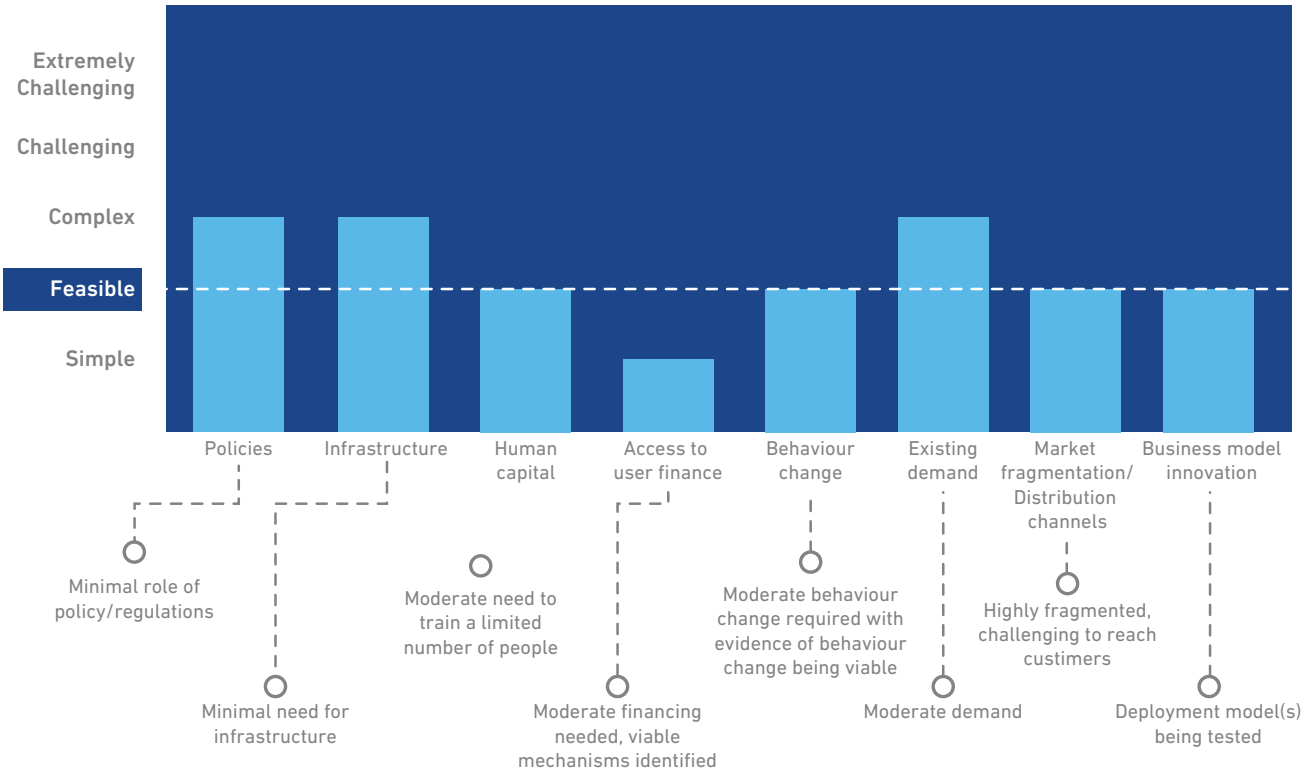
The second way is the development of an entirely new type of vaccine. This would not be a conjugate vaccine, and instead would produce immunity through another mechanism, most likely through a common protein that is present in all strains of pneumonia.

While this opportunity could be revolutionary, providing broader protection and likely a lower cost, the appropriate protein has not been identified yet. Significant primary research still needs to be conducted.

Deployment of new vaccines

Once any of these vaccines is developed, it can be deployed to children through existing, reasonably established, vaccine delivery channels. However, there are few mechanisms for delivering vaccines to adolescents and adults, and successful vaccination campaigns for these population segments would require significant government coordination, behavior change and financial investment. Furthermore, even today vaccine delivery remains a challenge in many remote locations where supporting infrastructure like cold storage facilities are either few or non-existent. While vaccines are expected to be made available to patients at a low cost, financing for the vaccines by national governments or international donors would need to be secured in order to support widespread distribution. Policy changes would also need to support its introduction and distribution through public health systems. Based on the above assessment, the projected time to market readiness is more than ten years, and the difficulty for deployment is FEASIBLE.

Breakthrough 23: Difficulty of deployment



28 New generation of antibiotics capable of treating fast-mutating bacteria like MTB and MRSA

Antibiotic resistance is reaching dangerously high levels in all parts of the world, with some of the most common infections becoming difficult to treat. This occurs when bacteria develop the ability to defeat the drugs that are designed to kill them, making the drugs ineffective.

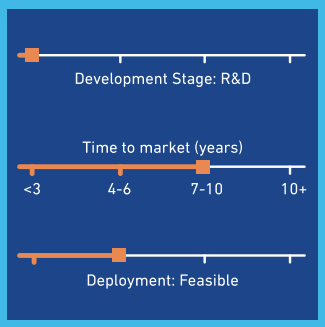
Antibiotic resistance does not mean the body becomes resistant to antibiotics; instead, it means that bacteria have become resistant to the drugs designed to kill them. Each year, hundreds of thousands of people die from drug-resistant strains of common bacterial infections, and the number is increasing steadily. Important examples of resistant bacteria include:

- Multidrug-resistant tuberculosis (MDR-TB), a form of TB that is resistant to the two most powerful anti-TB drugs, and extensively drug-resistant tuberculosis (XDR-TB) that is resistant to at least four of the core anti-TB drugs.
- The bacteria *E. coli*, which is gaining resistance to fluoroquinolone antibiotics that are widely used to treat urinary tract infections.
- The common intestinal bacteria *Klebsiella pneumoniae*, which is becoming resistant to a last resort treatment, carbapenem antibiotics, in all regions of the world.
- The bacteria *Staphylococcus aureus*, which has widespread resistance to first-line drugs, causing growing numbers of deaths due to MRSA (methicillin-resistant *Staphylococcus aureus*).
- The bacteria *Neisseria gonorrhoeae*, responsible for the sexually-transmitted disease gonorrhea, is gaining resistance to the last resort medicine, third generation cephalosporin antibiotics, in at least 10 countries.

Antibiotic resistance is a complex problem that is driven by many interconnected factors, and coordinated effort is required to minimize its emergence and spread. Without urgent and effective action, there is a risk of returning to an era in which common infections and minor injuries can cause death.

Action on several fronts is needed, including improving awareness and understanding of antibiotic resistance, strengthening surveillance and research, reducing the incidence of infection through improved hygiene and sanitation, improving diagnostics to reduce unnecessary prescription of antibiotics, and optimizing the use of existing antibiotic medicines. Critically, there is also a need for a new generation of antibiotics that are effective against the bacteria that are resistant to current drugs.

Current State



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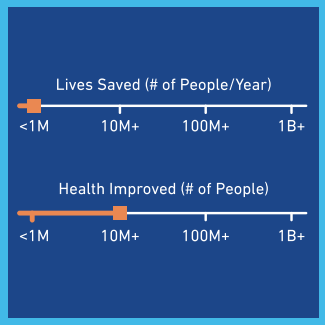


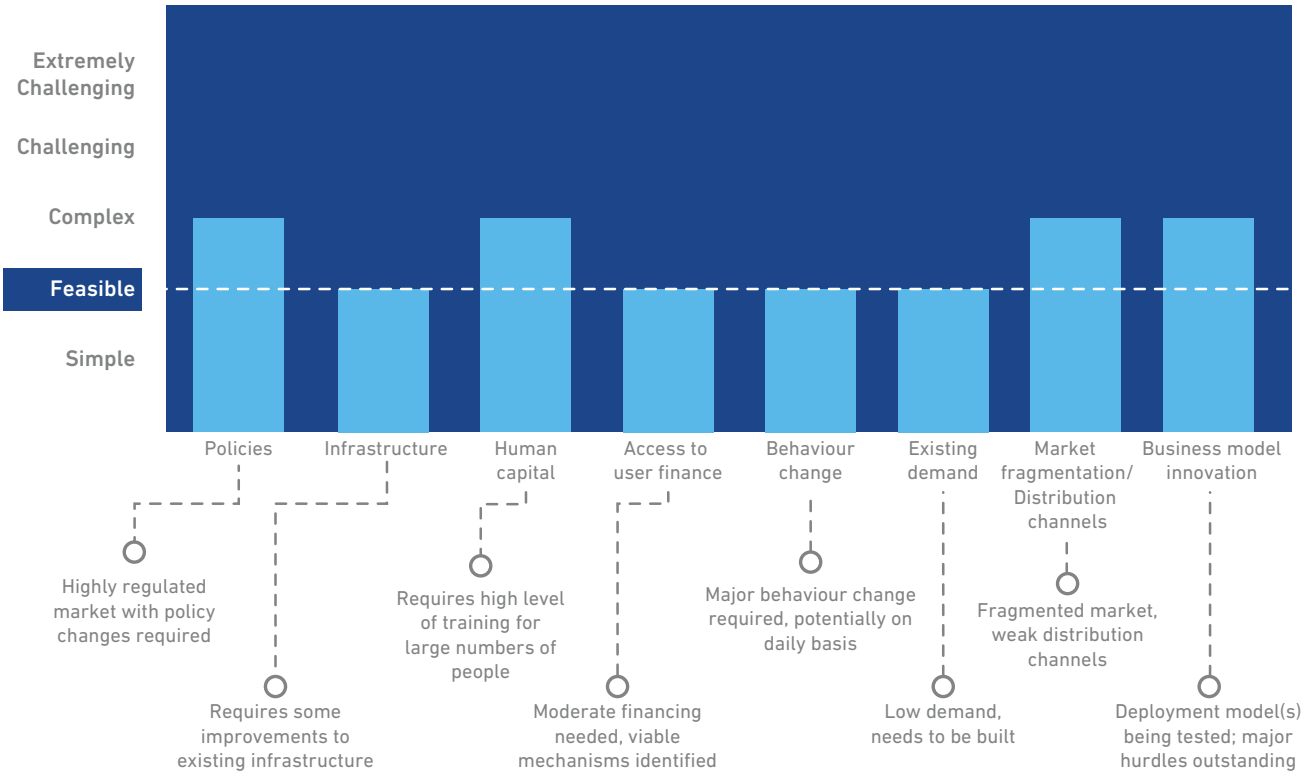
Commercial Attractiveness

While there are some new antibiotics in development, none of them are expected to be effective against the most dangerous forms of resistant bacteria. There is a need for better incentives to promote investment in new drugs, because the commercial return on R&D investment in new antibiotics is currently unattractive.

Although the total market for antibiotics is relatively large, with annual sales of about $40 billion, only about $4.7 billion of this is from sales of patented antibiotics. Between 2003 and 2013, less than 5 percent of venture capital investment in pharmaceutical R&D was for development of antimicrobials.

Even with adequate funding, the development of improved antibiotics is scientifically challenging, and we expect it will take up to 10 years for new drugs to be market ready. Once developed, the deployment of new antibiotics can use existing supply chains and is expected to be FEASIBLE.

Breakthrough 28: Difficulty of deployment



3.2. Low cost, novel diagnostics for pneumonia

Pneumonia is currently diagnosed by a clinic consultation, not by a specific diagnostic test. This makes it difficult for care providers to identify different clinical scenarios, such as whether a patient has viral or bacterial pneumonia or quickly determine the infecting pathogen, which can help indicate the potential severity of the illness. Accurate diagnostics also has the potential to reduce medicine wastage, and reduce the risk of antimicrobial resistance.

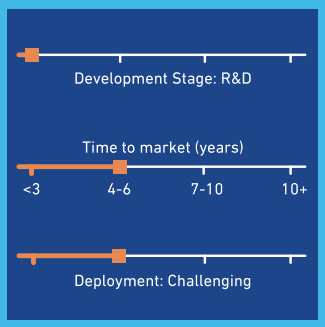
While the gold standard for diagnosis is through a chest X-ray, the imaging test is not practical for clinics in low- and middle-income countries. Most diagnoses are made based on evaluation of respiratory rate and chest in-drawing. The technological challenges and time to market for a novel pneumonia diagnostic vary depending on what the clinical goal of the diagnostic would be.

A urine-based diagnostic for pneumococcus bacteria, for example, is now available. However, a diagnostic that can discriminate between bacterial and viral pneumonia, and severe and non-severe pneumonia, is much more technologically complex; in some cases, biomarkers have not been identified yet. The primary benefit of diagnostics that provide deeper information about the infecting pathogen would likely be a better understanding of the disease and its epidemiology, as opposed to reduced mortality.

Reducing mortality from severe pneumonia would likely rely on improvements in pulse oximetry and respiratory rate timers. Both are effective technologies, and while they could be refined further, and can be incorporated into multimodal devices that also measure other vitals, the key challenge is distribution to, and adoption at, the clinics, as opposed to major improvements in either the cost or technology.

However, even the impact from better oximetry and respiratory rate timers, or any accurate rapid diagnostic tests are likely muted, as a reduction in mortality will only happen if patients seek care, are diagnosed in time and in some cases have subsequent access to oxygen therapy, which is currently rare.

Current State



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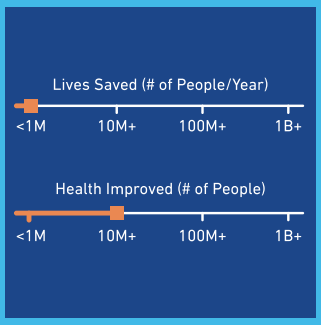


Commercial Attractiveness

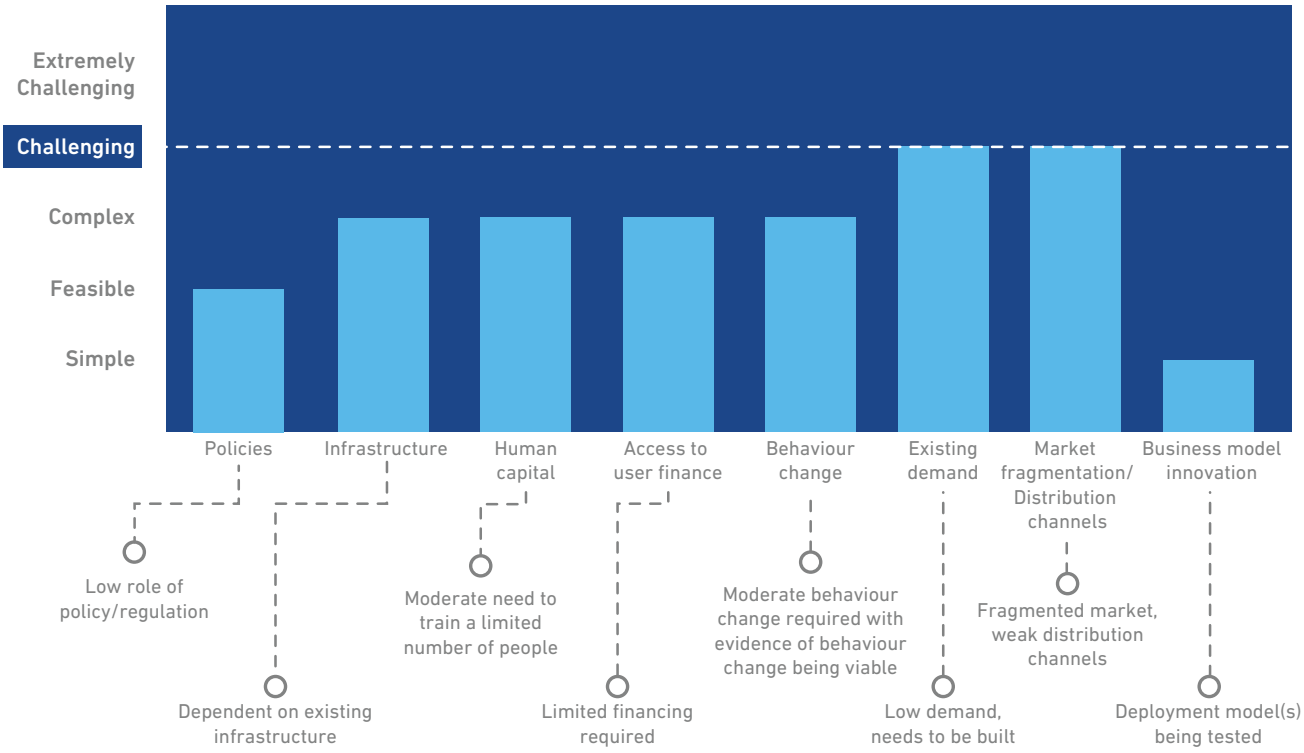
Ease of deployment varies by diagnostic type. In general, simpler devices like improved respiratory rate timers and pulse oximeters have fewer deployment barriers; they need less access to grid energy, less access to financing and less training. In each case however, lack of existing demand and market fragmentation are major hurdles in achieving scale.

There is currently no existing base for deployment of pneumonia diagnostics to rural clinics where they are most needed, so distribution of a new diagnostic would require creation of new channels as well as educating healthcare workers on the need and value of pneumonia diagnostics.

Since clinical diagnosis generally remains effective, and the downside to clinical diagnosis (like drug resistance) is neither immediate nor obvious, it will be challenging to convince healthcare funders and clinicians to devote scarce resources to purchasing and using pneumonia diagnostics.

Based on the above assessment, improved diagnostics for pneumonia are likely to be market ready in four to six years, and the difficulty of deployment is CHALLENGING.

Breakthrough 32: Difficulty of deployment



33 Low cost, off-grid oxygen concentrators

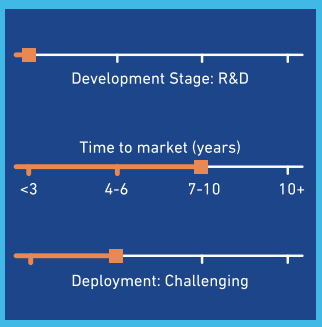
Oxygen concentrators create oxygen-enriched airflow from ambient air, and are often the most practical solution to provide critically needed oxygen therapy at hospitals, clinics and potentially even outposts (as opposed to oxygen cylinders, which require robust logistics systems). Despite the fact that oxygen therapy reduces case fatality rate of children with severe pneumonia by as much as 35 percent in low- and middle-income countries (Duke, et al., 2008), there is a noticeable lack of awareness of the opportunity that oxygen therapy could provide.

Many hospitals often do not realize that pneumonia is one of their biggest killers, or understand the sheer reduction in case fatality they could achieve with oxygen therapy.

Oxygen concentrators are an existing technology that must be redesigned to be more appropriate for low-resource settings. Concentrators usually cost several hundred to over a thousand dollars, need constant energy supply to operate and require sophisticated maintenance.

A novel oxygen concentrator would have to be dramatically cheaper, robust, and easy to maintain, or delivered in tandem with a service model. It should be able to provide oxygen in the absence of reliable grid power. This may require an oxygen storage system or a battery. Oxygen provision needs to be delivered alongside oxygen measurement. An effective oxygen concentrator should also incorporate an oximeter.

Current State



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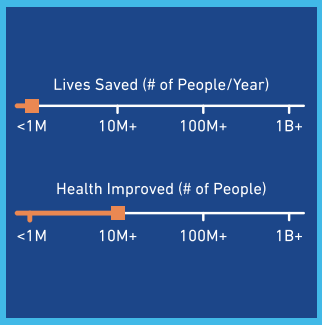


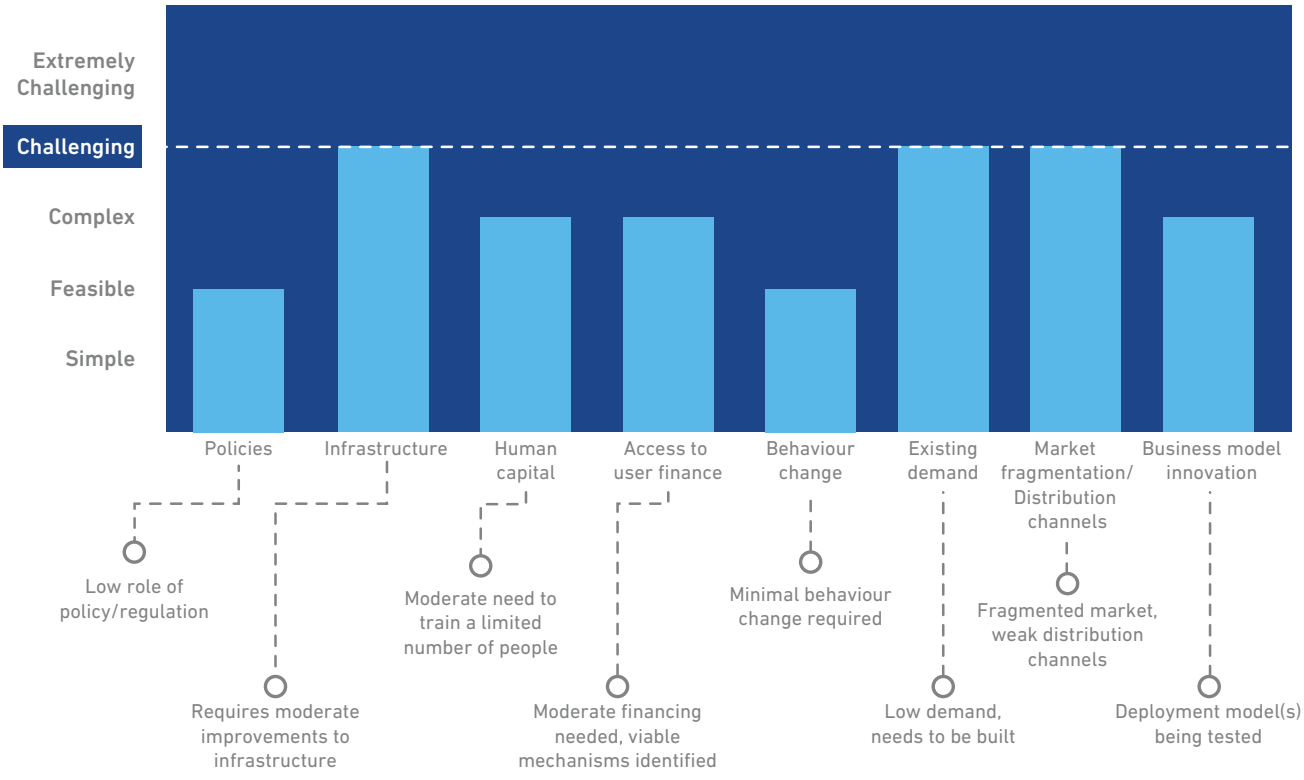
Commercial Attractiveness

While there are no major fundamental scientific or engineering challenges that need to be overcome, design must be approached from a perspective of cost, durability, ease of maintenance and minimal dependence on infrastructure. Given the lack of priority for oxygen therapy at the healthcare policy level as well as on-ground at clinics and hospitals, the current market is small, and demand will have to be built.

At the clinic level, distribution channels are not well defined, and while there is some centralization for purchasing through ministries of health, achieving wide-scale distribution is challenging. Compared with oxygen cylinders, oxygen concentrators are sophisticated and expensive devices and will require a greater element of training and financing.

The projected time to market readiness is four to six years. Based on existing and emerging technologies, the difficulty of deployment is CHALLENGING.

Breakthrough 33: Difficulty of deployment



46 Advanced biomass cookstoves that are desirable, affordable, robust and very clean

Biomass such as wood, straw and dung is the primary cooking fuel for about 2.5 billion people, or a third of the world's population. Household air pollution caused by these fuels causes millions of deaths each year, due to illnesses such as lower respiratory infection, lung cancer, ischemic heart disease, stroke and chronic obstructive pulmonary disease.

Despite major initiatives to extend access to cleaner cooking fuels like gas and electricity, more households currently use solid fuels for cooking today than at any time in human history, due to growing population size. It is likely that billions of people will continue to cook with biomass for the foreseeable future, due to economic, logistical and cultural barriers to change.

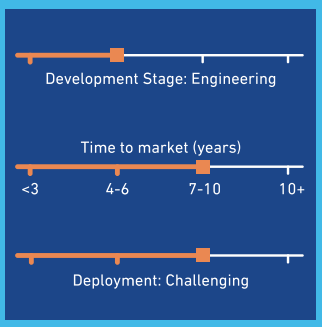
Design and deployment of improved biomass cookstoves has been an important goal of global development efforts for many decades. A wide range of biomass cookstove improvements have been proposed and trialed, with significant reduction in emissions of air pollutants like particulate matter and carbon monoxide. Some of these improved stoves have reached moderate levels of deployment in low-income countries.

However, recent research has shown that the exposure-response relationship for household air pollution is non-linear, thus the large reduction in emissions from current improved stoves brings only a modest decrease in health risk. To effectively eliminate the serious health risk of household air pollution, stove emissions must be reduced much further than is possible with current biomass stove designs.

A new generation of advanced biomass cookstoves is needed, with greatly reduced emissions so they have low health risk that is comparable to other clean cooking solutions like gas and electricity. Advanced biomass cookstoves typically use complex, multiple stage combustion methods in order to burn fuel efficiently and minimize harmful emissions.

Current versions of advanced biomass cookstoves often have high upfront costs, offer less cooking flexibility, need pre-processed fuels and require an electricity supply to power built-in fans, yet still do not reliably achieve emission levels low enough to eliminate health risk in people's kitchens.

Current State



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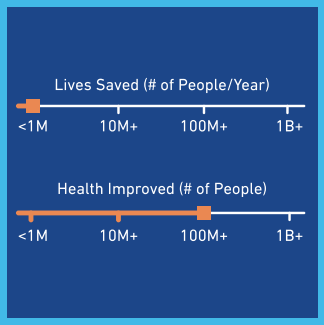


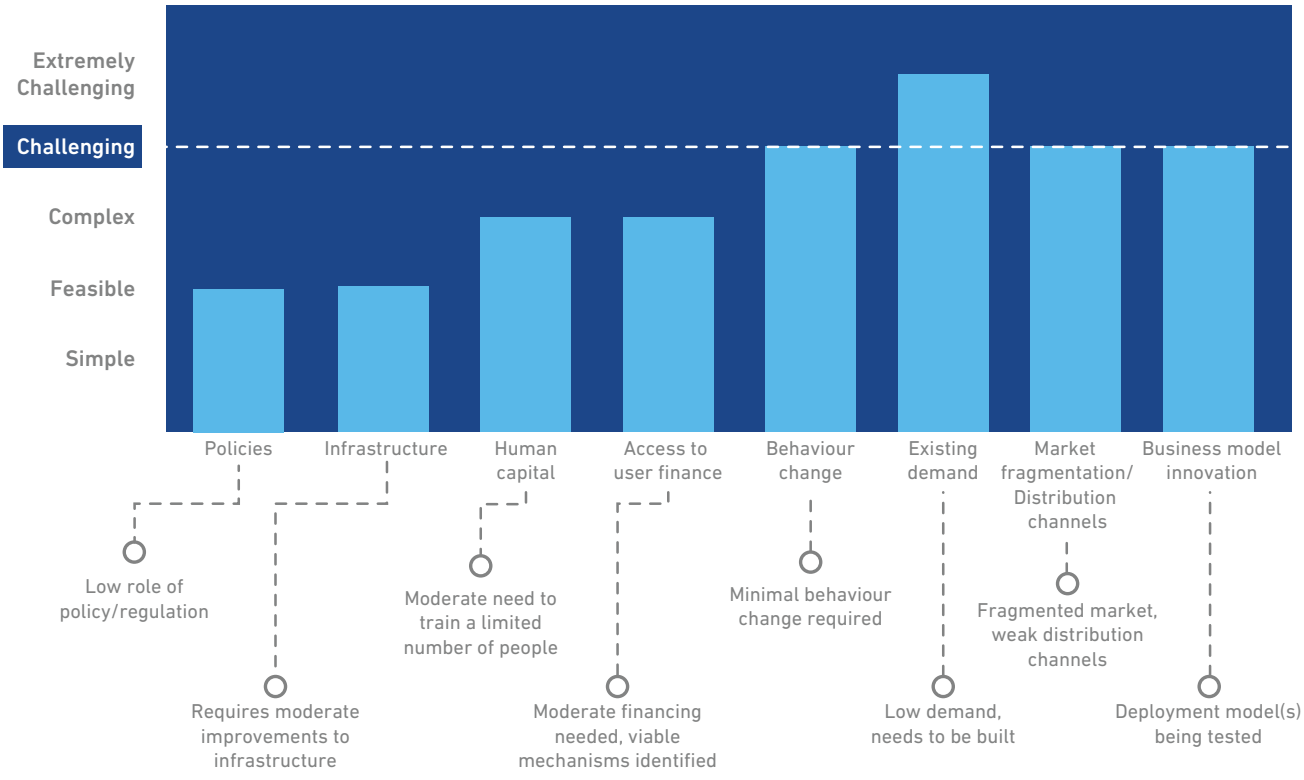
Commercial Attractiveness

An effective advanced biomass cookstove must be durable, low-cost and low maintenance. It will preferably use unprocessed fuel, or fuels that can be processed locally with available equipment. It will be compatible with traditional foods and cooking styles and not require major behavioral change by the users.

Above all, it must employ extremely efficient combustion processes and emit very low levels of dangerous pollutants. This breakthrough will require significant advances in thermodynamic and combustion sciences, as well as outstanding user-centric design.

Innovative business models will be required, and significant outreach will be needed in some regions to ensure sufficient demand. The projected time to market readiness of a breakthrough advanced biomass cookstove is five to seven years, and the difficulty of deployment is CHALLENGING.

Breakthrough 46: Difficulty of deployment



47 Novel ways of converting household or village waste products into clean cooking fuel or electricity

Gas and electricity are recognized as very clean and safe cooking fuels, yet their usage remains very low in rural areas of developing countries. This is mainly due to the high cost and logistical challenges involved in extending the required infrastructure to these areas. Liquified petroleum gas (LPG) is typically transported in cylinders, which requires an adequate road network and sufficient truck fleet that are lacking in many areas.

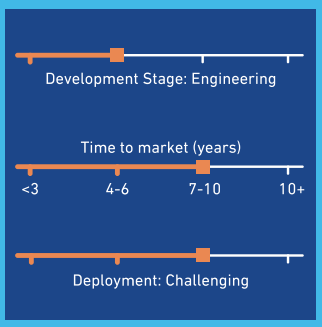
Natural gas is typically transported in pipelines, which are very expensive and therefore limits the use of natural gas in areas distant from gas wells. The price volatility of LPG and natural gas makes it difficult for low-income households to have consistent access to the fuels. Electrification of rural areas is a longstanding challenge, and even in areas that are nominally connected to the power grid, electric cooking is seldom practical due to unreliable supply and the high power requirement of electric cookers.

Decentralized production of biogas by means of anaerobic digestion of organic materials such as manure and crop waste is an established practice, but is used by only a small fraction of households, mainly in China where it is supported by government subsidies. Use of anaerobic biogas digesters requires a large upfront cost, and most biogas systems require skilled installation and maintenance which is unavailable in most developing countries.

While clean cooking fuel is lacking in rural regions, many areas have abundant organic waste materials such as human waste, animal waste, crop residue or household garbage. A breakthrough is needed in the form of an affordable, robust process to convert diverse organic waste products into clean and reliable gas or electricity for cooking. Such a process would not only provide clean cooking fuel, but would safely dispose of waste products and result in cleaner surroundings. In principle, this could be achieved by various conversion routes, such as biochemical, thermochemical or electrical.

- Biochemical processes would use living organisms to produce biogas. This could take the form of improvements to existing anaerobic digestion processes to make them less capital-intensive with easier installation and maintenance. Advances in genetic editing might be used to create microorganisms capable of digesting a wider range of input materials. If human waste were used as input material for fuel production, cultural concerns among some population segments would need to be addressed.

Current State



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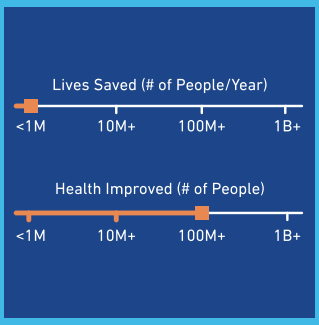


Commercial Attractiveness

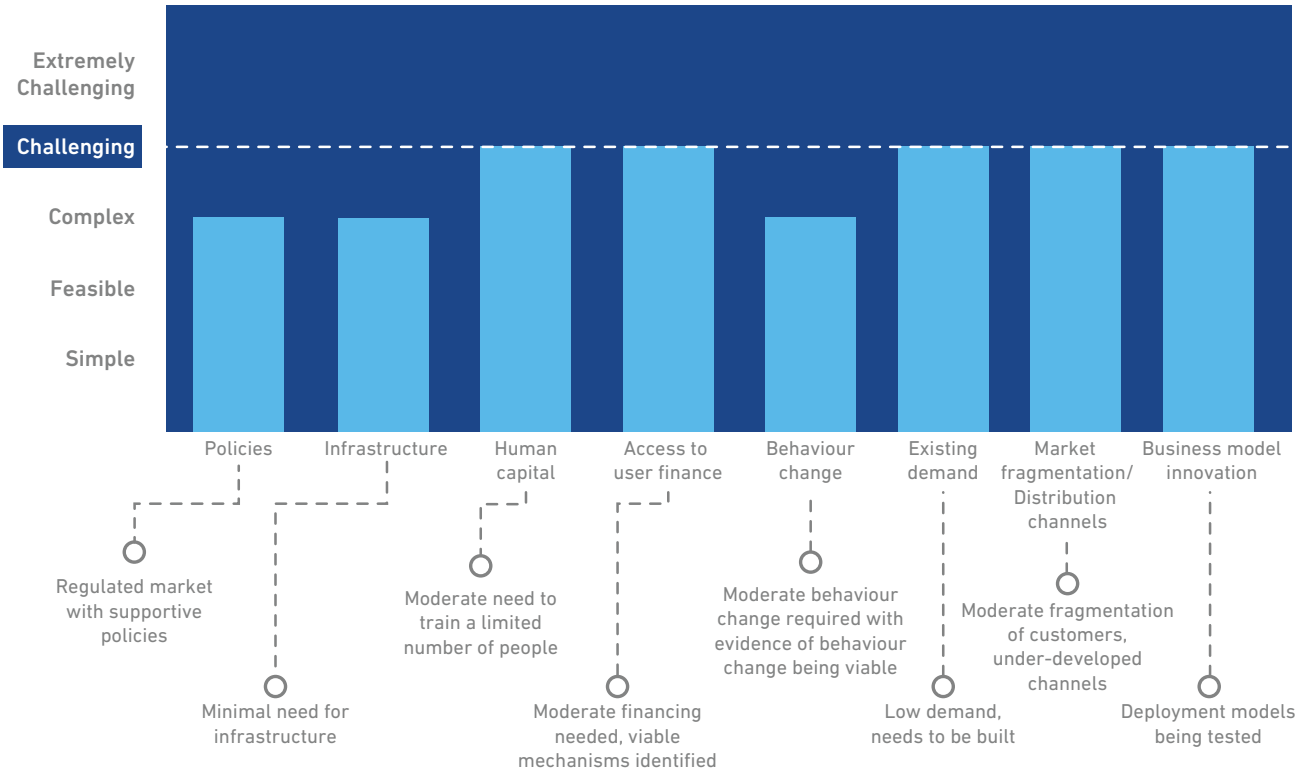
- Thermochemical methods, such as pyrolysis or gasification, use high-temperature processing to produce syngas. These methods are well established at industrial scales, but are less well developed at smaller scales suitable for villages and households. Current small-scale methods are quite polluting, and are relatively complex and require skilled operation and maintenance. In addition to cooking fuel, thermochemical processes typically produce biochar that could be used as a soil amendment.

- Electrical methods would convert the chemical energy of the waste products into electricity, which is a clean and safe form of cooking. Because cooking requires a relatively high electric current, and is typically practiced only at certain times during the day, the most suitable form of village-level electricity production for cooking may be a small-scale "peaker plant" that only operates during limited hours when meals are prepared, and would supplement a solar powered mini-grid that provides continuous power for lighting and other uses. For example, a batch-fired thermochemical gasifier could be combined with an electrical generator to provide a village with sufficient electricity for cooking during several hours in the morning and again in the evening.

There are numerous technology pathways by which this breakthrough could be realized. It will likely require advances in relevant disciplines, such as biological or mechanical engineering. It will also require a thorough understanding of the needs and wishes of the users, and innovative design and implementation to ensure satisfaction. Appropriate business models will be needed to provide economic sustainability.

The projected time to market readiness of this breakthrough is seven to 10 years, and the difficulty of deployment is CHALLENGING.

Breakthrough 47: Difficulty of deployment



48 A mechanism to remove particulate emission from old trucks and other heavy-duty vehicles

Particulate emission from heavy duty vehicles like trucks and buses are a major source of outdoor air pollution in low-income (UNEP, 2014). In Delhi, India, for example, 23 percent of all particulate emissions come from the transport sector (Sharma, et al., 2016). This is mainly due to the large number of operating older vehicles coupled with poor vehicle maintenance, inadequate infrastructure and low fuel quality.

Vehicles in developing countries are typically older than those in industrialized countries. The average age of the vehicle fleet in Tanzania is about 15 years, and in Kenya and Uganda it is about 13 years (UNEP, 2009). Some vehicles, especially diesel-powered trucks and buses, operate for more than 40 years.

These older heavy-duty vehicles are responsible for a high percentage of air pollution, despite their low fleet numbers. These vehicles continue to operate because of the high cost of new vehicles, and the existence of strong maintenance and supply lines for older technology. Due to the inherently slow turnover of vehicle fleets, and the limited economic means of many truck and bus owners to obtain cleaner replacements, existing heavy-duty fleets are likely to remain in operation for many years.

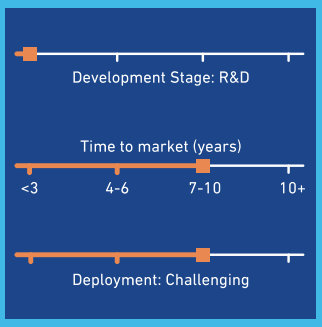
In the longer term, many improved technologies may enable cleaner urban transport systems. These include electric battery and fuel-cell vehicles and prioritized rapid urban transit with light rail or other modes. Having a cleaner transport system requires an appropriate regulatory framework and involves economic and behavioral trade-offs. Long-term policies and investments are needed to support cleaner transport as a means to reduce urban outdoor air pollution.

In the medium term, cleaner diesel fuels (with reduced sulfur and lead content) should be used, as well as incentives toward renewal of the heavy-duty vehicle fleet such as subsidies and inspection regimes. Nevertheless, many authorities are reluctant to force older heavy-duty vehicles off the road because of the national economic importance of the logistic services they provide. There is a need for an immediate alternative.

Urban air pollution could be significantly improved if these older vehicles could be easily and inexpensively retrofitted with a technology to reduce particulate matter emission. A number of retrofit emission technologies currently exist for heavy-duty diesel vehicles, such as catalyzed diesel particulate filters, which remove 95 percent of particulate matter from exhaust but cost up to $10,000 per vehicle (UNEP, 2009).

Particulate filters are mandatory on new diesel trucks in Europe, North America and other industrialized regions, costing about $3000 each. Current particulate filters impose an energy penalty on the vehicle, increasing diesel fuel consumption by about 3 percent (Reitz, 2013). Existing particulate emission controls are too expensive for widespread adoption by existing fleets in low-income countries.

Current State



Associated 50BT Chapters

SDG Alignment

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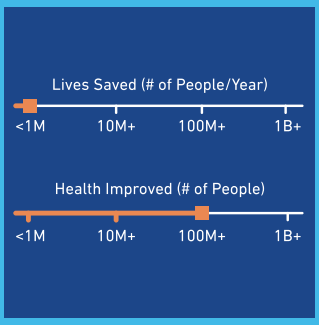


Commercial Attractiveness

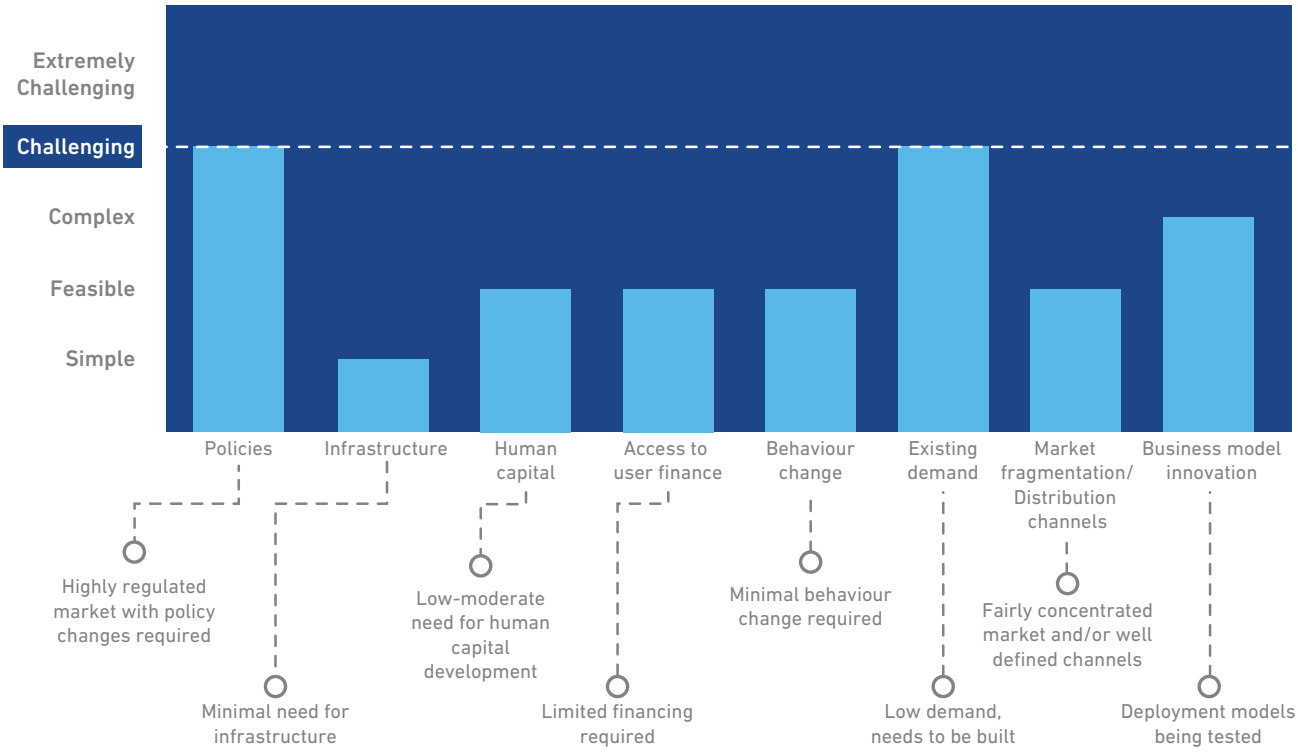
There is a need for a robust, low-cost device that can be retrofitted onto old heavy-duty diesel vehicles to reduce particulate matter exhaust. This engineered solution must be inexpensively produced—less than $1,000—with simple retrofitting onto existing fleets of trucks and buses. Operation of the device must not impose significant load on the vehicle, in terms of exhaust back pressure or electricity demand.

A successful breakthrough technology would use inexpensive and abundant materials (for example, no expensive catalysts), would require only simple installation and maintenance and would produce no harmful byproducts. A range of technical approaches may be appropriate, including filtration, electrostatic precipitation and wet scrubbing (EPA, 1979; Roy, et al., 2011).

Assuming adequate level of support to achieve this breakthrough, we expect that it would take less than five years to be market ready. A major deployment challenge is the lack of demand within the current market structure.

Some level of policy incentive must be created to encourage vehicle owners to install such a device. The difficulty of deployment in this case would be CHALLENGING.

Breakthrough 48: Difficulty of deployment



49 Small-scale waste incinerators with efficient combustion and clean emissions

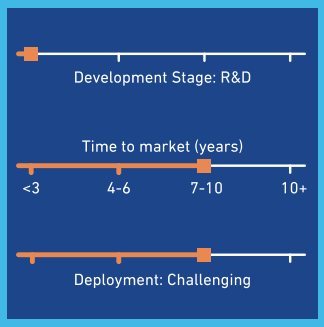
The challenge of urban waste management remains unmet in many cities in low-income countries. Mounds of household rubbish often accumulate uncollected, spreading disease vectors and increasing health risks to community residents. Fast-growing cities lack adequate truck fleets for waste collection and haulage, and existing landfills are often poorly operated and filling rapidly.

Facing the lack of centralized waste management, households and communities typically burn their garbage in uncontrolled open-air fires. This leads to the emission of particulate matter, volatile organic compounds and toxins such as dioxin, with serious adverse health impacts on residents. Refuse burning is responsible for 10 percent of all PM2.5 particulate emissions in all of India, 12 percent in the city of Delhi, and 14 percent in the state of Uttar Pradesh (Sharma, et al., 2016).

An important lever to solve the solid waste problem in low-income cities is well-engineered, appropriately-sized, incineration plants that safely combust waste materials (Silva & Lopes, 2017).

Breakthrough designs will be needed to ensure consistently safe air emission levels, even with diverse feedstock. Existing guidelines on small-scale incineration, for example of medical waste (MMIS, 2010), are unlikely to meet the necessary high standards for air emission quality. Siting of multiple small-scale incineration plants will facilitate collection of waste at local disposal centers. Mobile incinerators moved between collection points may allow higher capacity utilization and improved economics.

Current State



Associated 50BT Chapters

SDG Alignment

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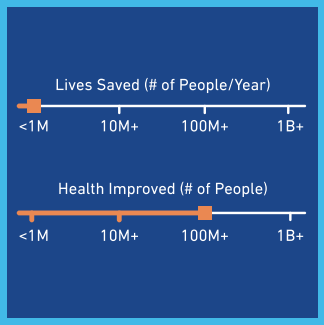
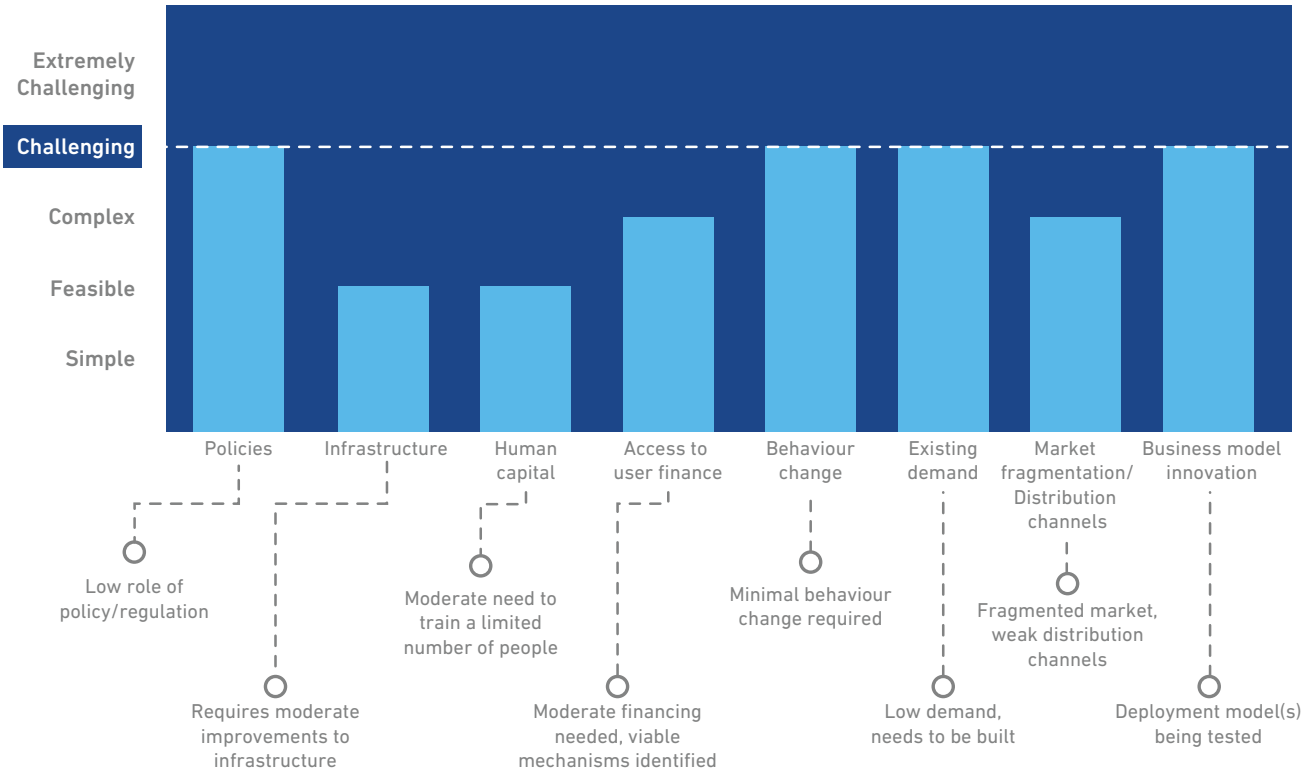


Commercial Attractiveness

With resources and dedication, this breakthrough could be market-ready in three to five years.

However, it faces strong challenges in terms of political and regulatory acceptance, and lack of demand, and business model innovation. Widespread deployment of this breakthrough is therefore CHALLENGING.

Breakthrough 49: Difficulty of deployment



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DIARRHEAL DISEASES

INTRODUCTION

Diarrheal diseases are responsible for the death of 526,000 children under 5 years of age (IHME GBD, 2017) while soil-transmitted helminths (STH) affect roughly 1.5 billion people globally (WHO, 2018).

In addition to mortality, the indirect burden of diarrheal disease and STHs is significant; they are a major contributor to malnutrition, which in turn is believed to underlie 45 percent of all childhood deaths (IHME GBD, 2017).

Diarrheal disease is transmitted through the fecal-oral pathway, traditionally addressed through interventions targeting water quality, water supply, sanitation, and hand and food hygiene. Diarrheal disease burden can also be reduced through vaccination, nutritional interventions and oral rehydration therapy.

Mortality from diarrheal disease has decreased dramatically over the past two decades. In the same time period, access to improved water, improved sanitation, vaccines and oral rehydration therapy all increased, while malnutrition decreased. However, the extent to which reduction in mortality can be attributed to specific interventions or demographic trends is a subject of debate.

Despite these gains, factors such as high population growth and constrained water supplies are expected to exacerbate diarrheal disease in the future.

Sustainability of interventions and adherence of beneficiaries (such as people consistently washing their hands) have remained major challenges in diarrheal disease prevention. Behaviors around practices like eating and defecation have deep cultural roots and can be hard to influence.

There is no shortage of failed interventions and technologies in addressing this issue. While there have been demonstrated reductions in diarrheal disease from small-scale interventions, there has been limited success in bringing these interventions to scale.

We have identified three technological breakthroughs with high potential for reducing mortality and morbidity from diarrheal disease.

- Breakthrough 3. Network of low-cost distributed monitoring sensors to measure and map air and water quality
- Breakthrough 4. Sustainable, affordable, household-level fecal waste management system
- Breakthrough 5. Medium to large-scale sewage treatment process with recovery of water (and ideally nutrients and energy)

Diarrheal disease is the third leading cause of childhood mortality worldwide, behind only neonatal conditions and lower respiratory infections. It is responsible for 526,000 childhood deaths, almost all in developing countries (IHME GBD, 2017) (Exhibit 1).

CORE FACTS AND ANALYSIS

Defined as passage of three or more loose or watery stools per day, diarrhea is usually a result of an intestinal tract infection, which can be caused by many different pathogens including bacteria, viruses and protozoa. These are generally spread through contaminated food, drinking water or person-to-person contact (WHO, 2013).

Soil-transmitted helminths (STHs) are parasitic nematodes (worms) that feed on the host tissue or compete with the host for nutrition. Many STHs are contracted when children ingest eggs that were excreted in fecal matter of infected individuals. STHs are estimated to infect some 1.5 billion people globally (WHO, 2013).

The most common and important STHs are roundworm, whipworm and hookworm. While these infections are rarely fatal, STHs can cause intestinal distress, malaise or weakness, and impaired cognitive and physical development. The severity of symptoms is directly related to the number of worms an individual harbors.

Both diarrheal disease and STHs lead to malnutrition in the host (**Table 1**). Diarrheal disease can reduce an individual's ability to absorb nutrients in the intestines and the effects of the disease last well beyond the diarrheal episode. STHs feed on host tissue, including blood, or compete with the host for nutrients. This leads to a loss of iron and protein and, similar to diarrheal disease, also causes malabsorption of nutrients.

Recently, a condition known as environmental enteropathy has been proposed to explain, in part, malnutrition that results from sustained exposure to fecal pathogens, even in the absence of diarrheal episodes. A 2008 WHO study concluded that as much as 50 percent of childhood underweight and malnutrition could be associated with repeated diarrhea or knitted helminth infections (Prüss-Üstün, et al., 2008).

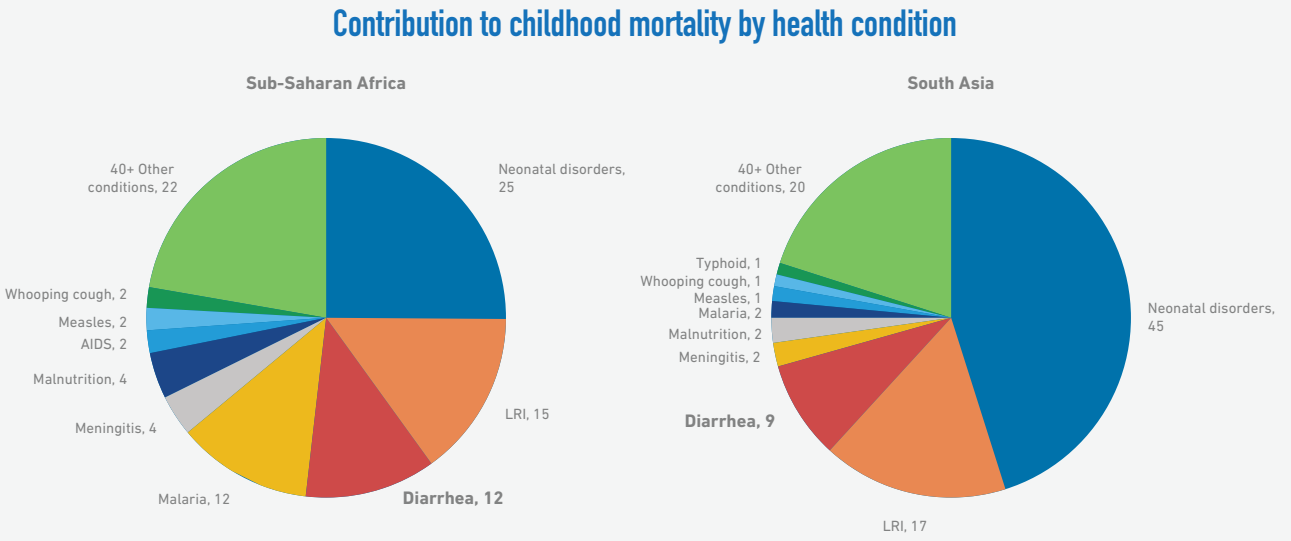


Exhibit 1: Diarrheal disease is the third leading cause of childhood mortality in sub-Saharan Africa and South Asia. (Source: IHME GBD, 2017)

Key diarrheal pathogens and soil-transmitted helminths

Pathogen Class	Important Pathogens	Effect
Diarrheal pathogen	Globally important pathogens: ***Rotavirus, Cryptosporidium parvum, Shigella, ST-enterotoxigenic E. coli (ST-ETEC)*** Additional pathogens important in some specific regions: ***Aeromonas, V. cholera, C. jejuni***	• Diarrhea, which causes dehydration and can lead to mortality • Reduction in ability to absorb nutrients (lasting beyond the diarrheal episode) • Environmental enteropathy (prolonged reduction in ability to absorb nutrients, can occur without diarrhea
Soil-transmitted Helminths	**Roundworm *(Ascaris lumbricoides)*, whipworm *(Trichuris trichiura)*, hookworm *(Necator americanus and Ancylostoma duodenale)*** and certain types of **tapeworm *(Taenia)***	• Enteric inflammation, general malaise and weakness, and impaired cognitive and physical development • Anemia (hookworm only) • Increased malabsorbtion of nutrients • Loss of appetite

Table 1: A handful of pathogens are responsible for the majority of severe diarrhea and STH infections. Rotavirus, *Cryptosporidium parvum*, *Shigella* and ST-ETEC are the four most important diarrheal pathogens globally. (Source: Kotloff, et al., 2013)

1. Diarrheal disease and malnutrition share a complex link

The relationship between diarrheal disease, soil-transmitted helminths and malnutrition is recognized but not entirely understood. Focusing specifically on diarrheal pathogens, the common belief for decades was that diarrhea itself caused a reduced ability for the body, specifically the small intestine, to absorb nutrients and that this effect could last significantly longer than the diarrheal episode itself.

One meta-analysis found that probability of stunting at age 2 increased by 2.5 percent per diarrheal episode, and 25 percent of all stunting was attributable to having five or more episodes of diarrhea (Checkley, et al., 2008).

Recently, the scientific community has begun to propose a more complex explanation, which is not related to diarrhea per se, but exposure to high levels of fecal pathogens. This condition is often referred to as 'environmental enteropathy' or 'environmental enteric dysfunction'.

Environmental enteropathy is a poorly defined condition and the underlying causal mechanisms have not yet been clearly determined (Humphrey, 2009).

One proposed model is that high enteric pathogenic bacterial exposure in the small intestines creates an immune response, which in turn causes the common characteristics of enteropathy such as atrophy of intestinal villi (small finger-like structures on the inner surface of the intestines that increase surface area for absorption of nutrients).

The effects are twofold. First, as a result of reduced surface area in the intestine, the small intestines have a reduced ability to absorb nutrients. Second, nutrients are repartitioned away from growth to support the immune system. This is an ongoing area of research.

Enteropathy could help explain why sanitation has stronger associations with achieving gains in infant and child growth, rather than reduction in diarrhea (Brown, et al., 2013). For example, a study in Peru found that diarrhea could explain 16 percent of stunting, while access to sanitation and water services could explain 40 percent (Brown, et al., 2013)[1].

[1]While many experts have come to take these positive associations between WASH interventions and health as conventional knowledge, some skeptics have noted the risk of confounding in this type of analysis, and a recent review (Dangour, et al., 2013a) did not include this particular study due to questionable methodological quality.

STHs do not trigger the same immune response as diarrheal disease. It is believed that they affect nutrition by feeding directly on intestinal contents or blood, leading to nutrient loss and anemia (WHO, 2013). STHs and their effects on nutrition and growth have increasingly become a debated topic. In 2007 and 2012,

The Cochrane Collaboration reviewed evidence for mass deworming initiatives and found that the evidence linking deworming programs to gains in nutrition and growth indicators was weak. Leaders from evaluation groups including Innovations for Poverty Action (IPA), the Center for Effective Global Action (CEGA) and the Abdul Latif Jameel Poverty Action Lab (J-PAL) have criticized these studies for excluding important randomized trials and ignoring the effect of deworming on improvements in education outcomes.

2. Diarrheal disease is primarily a childhood disease

Children under 5 represent 43 percent of the diarrheal disease burden (IHME GBD, 2017). Children are generally more susceptible to diarrheal disease, due to their developing immune systems and a high rate of malnutrition or other immune-suppressive risk factors.

Children are also at higher risk for life-threatening diarrheal disease due to the higher composition of water in a child's body relative to adults, relatively higher metabolic rates and lower capacity of their kidneys to conserve water (WHO-UNICEF, 2009).

In the past two decades there has been a large drop in childhood mortality caused by diarrheal disease (**Exhibit 2**). The WHO and UNICEF estimate that in 1990 mortality was as high as 5 million (WHO-UNICEF, 2009). Since 2000, childhood mortality from diarrhea diseases has dropped 55 percent from 1.1 million to about 0.5 million deaths per year in 2017 (IHME GBD, 2017).

While it is widely accepted that the global burden has dropped significantly over the past two decades, the specific reasons for this decline are not well understood. The primary drivers are believed to be improvements in nutrition, improved case management, particularly the widespread use of oral rehydration therapy, increased coverage of immunization for measles and rotavirus, and increased access to clean water and sanitation.

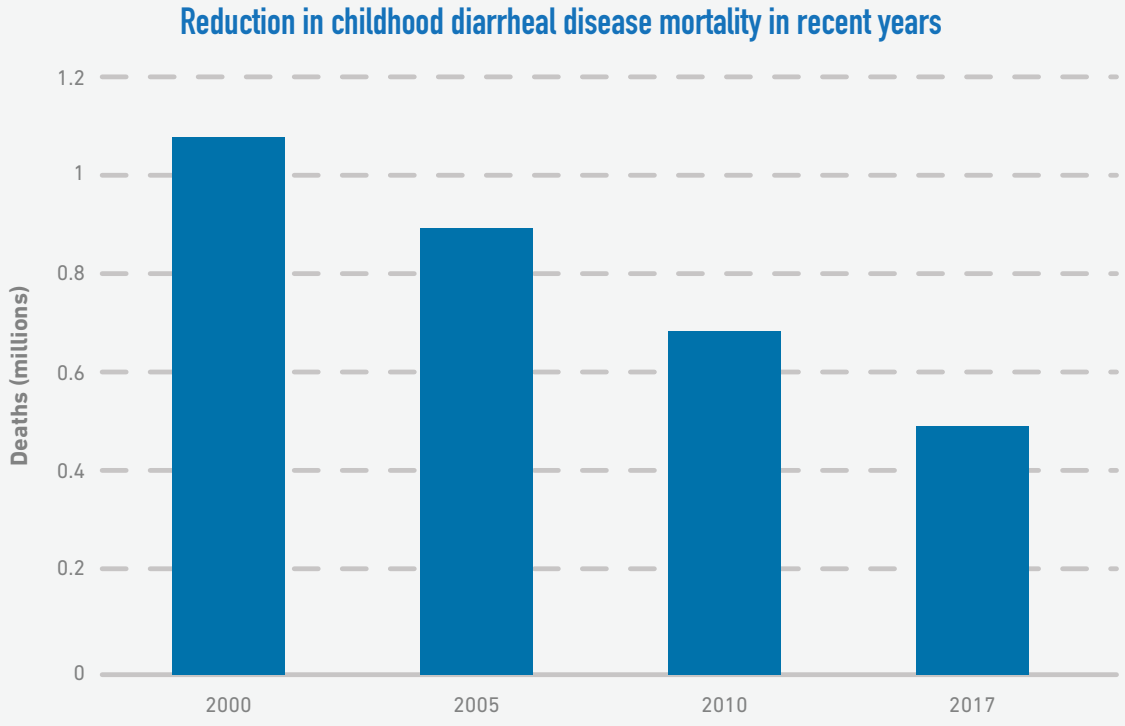


Exhibit 2: Since 2000, global mortality from diarrheal disease has decreased from nearly 1.1 million to about 0.5 million per year. The specific causes of this reduction, however, remain unclear. (Source: Liu, et al., 2012; IHME GBD, 2017)

While mortality from diarrheal disease has decreased, morbidity has remained more or less constant (Kosek, et al., 2003)[2]. This implies that the global health community has made major strides in case management and control of at least some pathogens that are responsible for moderate to severe diarrhea, but they have made relatively little progress in controlling the general transmission of diarrheal pathogens.

Diarrheal disease burden is highly concentrated in a small number of countries (**Exhibit 3**), with 10 countries representing 58 percent of deaths. Even within these countries, variability in the rate of diarrheal disease mortality is high (**Exhibit 4**).

Contribution to childhood diarrheal mortality by country

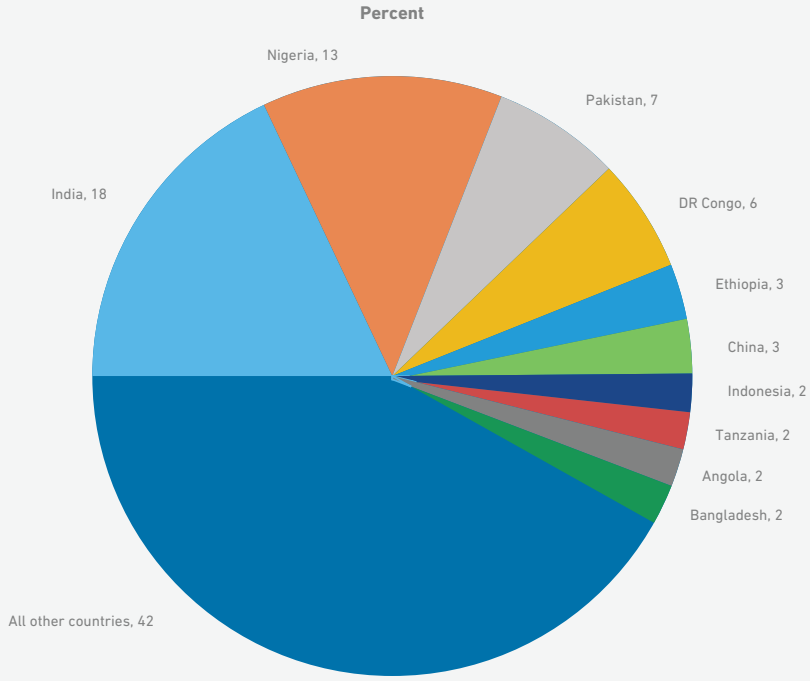


Exhibit 3: 10 countries account for 58 percent of childhood deaths from diarrheal disease. (Source: UNICEF, 2017)

Diarrhea mortality rates among children across high burden countries

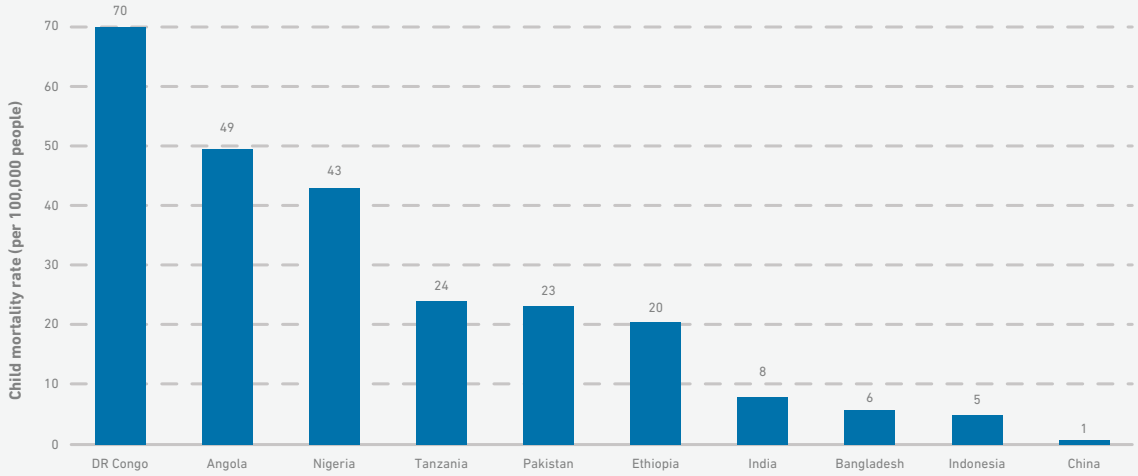


Exhibit 4: Mortality per 100,000 people varies greatly, even across high burden countries. (Source: UNICEF, 2017)

[2]This opinion is not universally held, and some experts note that cross-sectional surveys used to gather this data are unreliable (Luby, 2011).

3. Diarrheal disease and intestinal nematodes are caused by four types of pathogens

The various pathogens causing diarrheal disease and intestinal nematodes behave in different ways. Some bacteria, for example, are believed to be seasonal. There are major spikes in bacterial infections during the wet seasons, which highlights the importance of water as a transmission pathway.

In contrast, viruses, particularly rotavirus, show seasonal spikes in the drier, colder seasons. This indicates that person-to-person transmission is an equally or more important transmission pathway (Levy, et al., 2009).

Unlike viruses, bacteria can also reproduce outside of the human body (such as on food left at room temperature), thus becoming more likely to produce disease after ingestion.

STHs on the other hand must mature in soil, eliminating person-to-person transmission as a major pathway. Further description of the different types of pathogens can be found in **Table 2**.

The Global Enteric Multicenter Study (GEMS) identified four important specific pathogens that represent a disproportionate percentage of disease burden in developing countries: Rotavirus, Shigella, ST-ETEC and Cryptosporidium (Kotloff, et al., 2013).

Major classes of pathogens and their characteristics

Pathogen type	Important pathogens	Characteristics
Viruses	Rotavirus	Viruses are infectious pathogens that can only replicate after infecting other living cells. Rotavirus is the single most important pathogen associated with diarrheal disease.
Bacteria	*ST-Enterotoxigenic E. coli, Shigella, Aeromonas, V. cholera, C. jejuni*	Bacteria can grow on food and in water and sewage under the right conditions. Some bacteria are seasonal, with major spikes in the wet season.
Protozoa	*Cryptosporidium Parvum*	Protozoa are advanced organisms that are transmitted through cysts that are extremely robust, able to survive for long periods outside of the body and resistant to chlorine purification.
Soil-transmitted Helminths	Roundworm (*Ascaris lumbricoides*), whipworm (*Trichuris trichiura*), hookworm (*Necator americanus* and *Ancylostoma duodenale*) and certain types of tapeworm (*Taenia*)	Soil-transmitted helminths (STH) are parasites that do not cause diarrhea, but rather live in the body, generally the intestines, and cause enteric inflammation. Eggs must mature in soil before becoming infectious to humans, however, they are extremely persistent and can survive for weeks to months on crops and soil, and years in fecal matter.

Table 2: Each of the different types of pathogens travels along the fecal-oral pathway, but have different characteristics affecting their transmission and susceptibility to different interventions.

4. Traditionally, the flow of pathogens has been described through the F-diagram

Diarrheal disease and STHs are transmitted from person-to-person along the fecal-oral pathway, in which individuals ingest pathogens that have been excreted in fecal waste by other infected individuals and sometimes animals.

The pathway is complex and can follow many routes, which vary in importance from location to location. This pathway has historically been represented with the F-diagram that describes the flow of pathogens from fecal matter to new hosts (**Exhibit 5**).

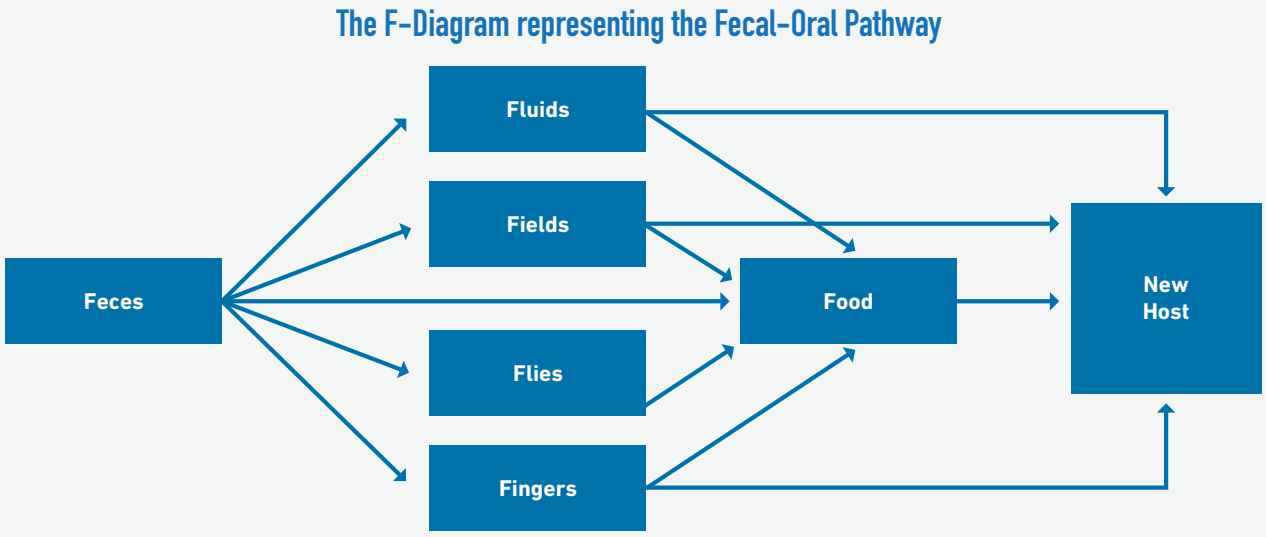


Exhibit 5: The F-diagram has historically been used to describe the fecal-oral pathway. (Brown, et al., 2013)

While this diagram is useful as a descriptive tool, it is limited in its usefulness for informing interventions. Drinking water or fluids, for example, can be contaminated in a number of ways including contamination at the source, either from flooding or direct runoff from inadequate sanitation systems, contamination in transit through water pipes with intermittent supply, or contamination in the household from poor storage practices.

5. A more nuanced fecal-oral pathogen flow model

In order to provide a more nuanced conceptual framework for problem and intervention analysis, we have developed the Pathogen Flow Model (**Exhibit 6**).

This five-stage model maps major transmission pathways, allows identification of major breakpoints and provides a view of which challenges must be solved in unison. Each stage of a pathway presents unique challenges that are responsive to different types of interventions.

Stage 1 - Pathogen hosting

The transmission of fecal pathogens begins with individuals who are carrying diarrheal disease causing pathogens in their gut. These individuals may be suffering from diarrheal disease or be asymptomatic carriers. In both cases, but particularly for individuals suffering from diarrheal disease, the disease-causing pathogens grow and replicate.

This can also occur with asymptomatic carriers of potentially disease-causing organisms who do not suffer from diarrhea. While humans can be infected by pathogens that come from animal hosts, the majority of infections responsible for the overall diarrheal and STH disease burden in children are likely acquired from other human hosts[3].

Fecal-Oral Pathogen Flow Model

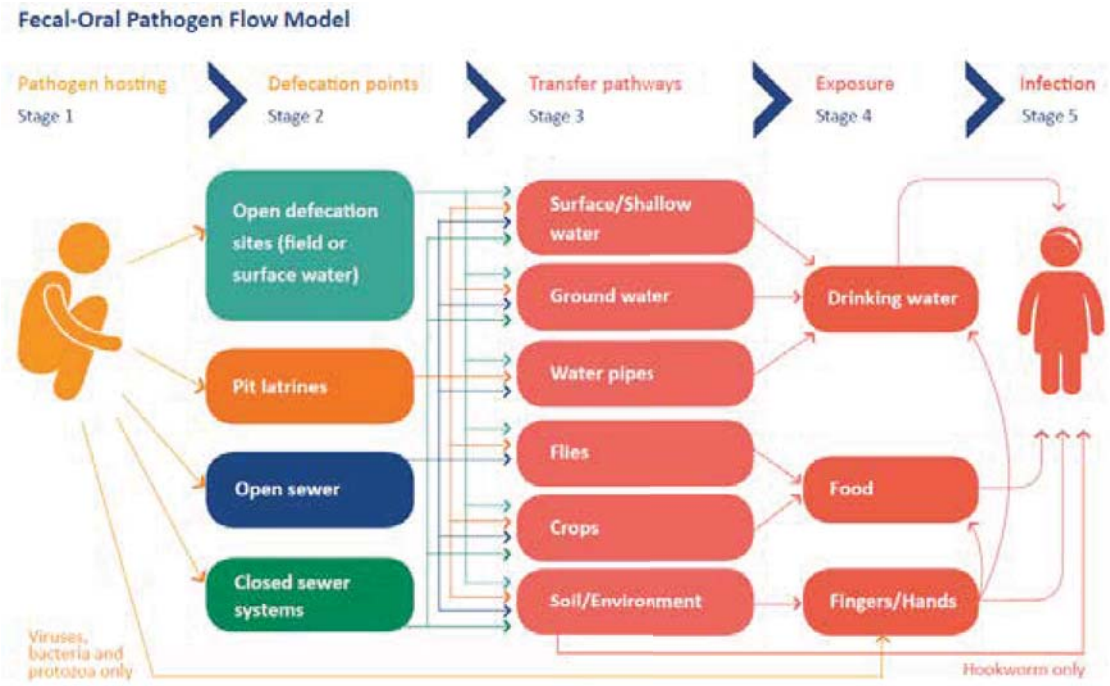


Exhibit 6: This five-stage model maps major transmission pathways for diarrheal disease and soil-transmitted helminths. It is important to note that different pathways are applicable in different contexts, for example in rural versus urban settings. (Source: ITT analysis)

[3]One notable exception is *Taenia*, which is often carried in cows or pigs.

Stage 2 - Defecation points

Following infection and the replication of pathogens in the body, pathogens are excreted into the environment at defecation points. These defecation points, such as open fields, sewers and pit latrines represent high-density sources of persistent diarrheal pathogens.

The challenges associated with defecation points vary from urban to rural locations but generally revolve around the lack of sustainable and scalable sanitation systems. It is often taken as common knowledge that sanitation interventions are positively correlated with reduction in diarrheal disease and childhood growth.

A meta analysis of sanitation interventions found an average relative risk reduction in diarrheal disease of 37 percent (Waddington, et al., 2009). A recent review, however, found there was insufficient evidence to link sanitation interventions to childhood growth (Dangour, et al., 2013b).

Stage 3 - Transmission pathways

When there are insufficient sanitation systems, diarrheal pathogens spread through transmission pathways like crops and water sources. There are many possible transmission pathways, and targeting any single pathway in isolation is unlikely to create major improvements in health.

Interventions at this stage have generally displayed less effectiveness than interventions at earlier or later points in the pathway. For example, water quality interventions at the source—a transfer point—are associated with an 11 percent reduction in diarrheal disease, while interventions at the household lead to a 35 percent reduction (Fewtrell, et al., 2005).

Stage 4 - Exposure

Pathogens enter the body in three ways: through drinking water, through food and directly from hands.

Drinking water
Drinking water is generally contaminated at three main points–at the source, in transit (such as through pipes) or in the home (through improper storage). Major interventions focusing on drinking water are generally source protection (prior to the exposure stage), water purification and safe household storage.

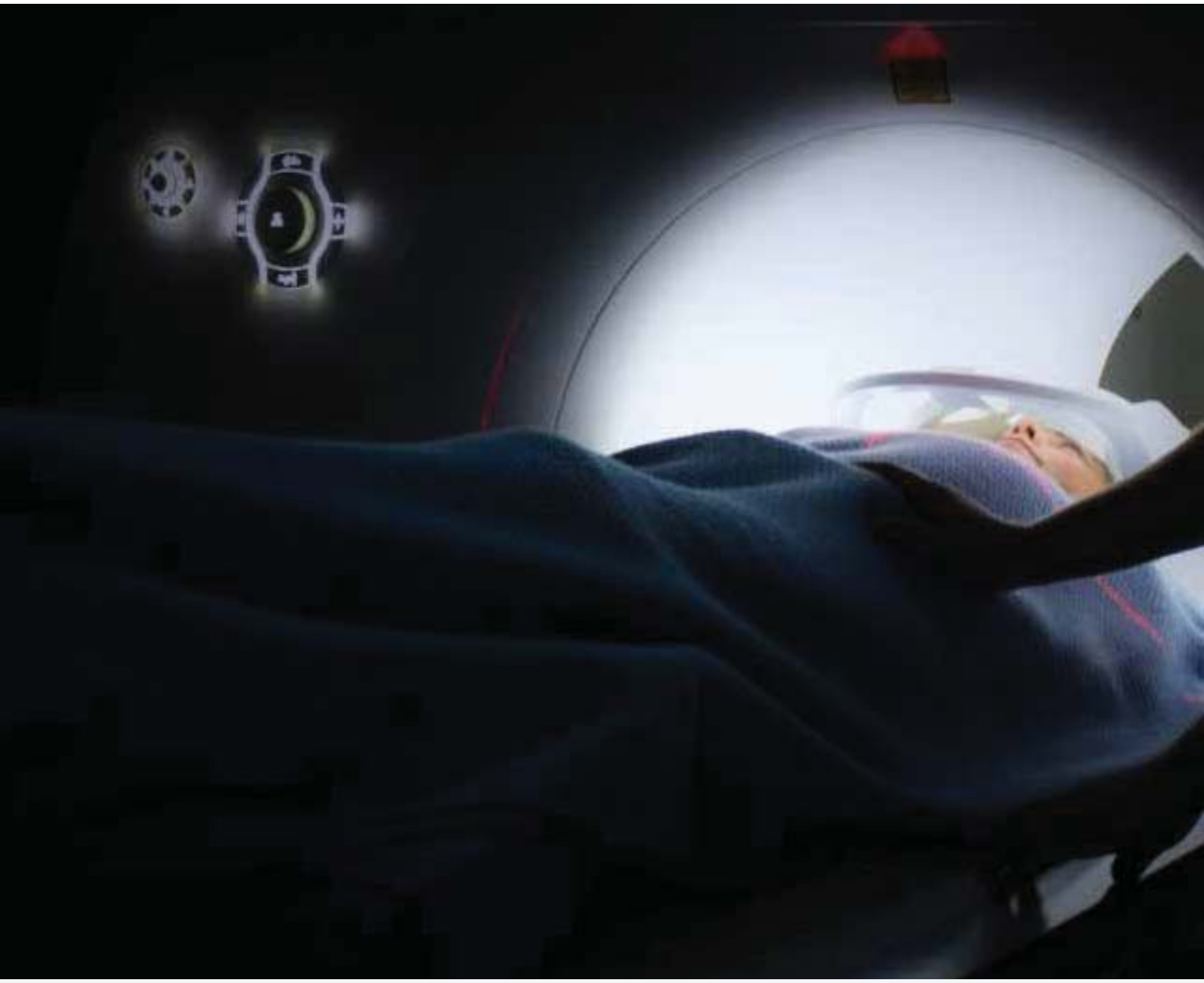
Food
Food can be contaminated in fields when farmers use wastewater for irrigation, when feces are deposited in fields due to open defecation or as fertilizer, in markets due to unhygienic conditions, or in the home through a mother's hands while preparing food, a child's hands while eating, or by flies that land on food and deposit pathogens.

The ability of bacteria to reproduce rapidly on food has led to food, and particularly complementary (weaning) food, gaining increased importance in reduction of diarrheal disease. Food hygiene generally focuses on hand washing before preparing food and eating, appropriate food preparation practices including washing or disinfecting and then properly cooking food, appropriate storage of leftover food and reheating food that had been previously prepared.

Hands and fingers
Hands and fingers can be contaminated during defecation, caring for an infant and through contact with the soil and environment. Hand hygiene is focused primarily on hand washing with soap. Interventions at the exposure stage tend to be moderately effective. Studies have found a 31 percent reduction in diarrheal disease from hygiene interventions and a 42 percent reduction from water quality interventions (Waddington, et al., 2009).

Stage 5 - Infection

Exposure does not necessarily lead to disease. Rather children who are malnourished, not optimally breastfed or are HIV positive are more likely to develop diarrhea after exposure to pathogens. Vaccination is also effective in reducing the risk of diarrhea following exposure to some pathogens.



KEY CHALLENGES

Diarrheal disease is a condition that is driven by some of the most fundamental human activities—eating, drinking, preparing food and defecating. In the absence of adequate sanitation systems, fecal pathogens contaminate the environment, food and water through environmental mechanisms and human activities.

Pathogens are then ingested, and in individuals who are susceptible, produce disease, at which point lack of adequate care becomes a major driver of mortality.

Key challenges in breaking the fecal-oral pathway, reducing susceptibility to disease through improved nutrition and health care, and improving care for those who fall sick are outlined below.

1. High rates of infection amongst the population lead to a constantly replenishing and growing supply of diarrheal pathogens and STHs in the environment

Rates of infection in many developing countries are extremely high. There are 1.7 billion cases of diarrhea globally per year, with an average of 2.9 episodes per child per year (Brown, et al., 2013). This indicates that diarrheal pathogens are constantly being excreted into the environment and in massive quantities.

2. Lack of adequate, sustainable sanitation systems enables wide-scale environmental contamination with fecal pathogens

There are a number of systemic, multifaceted problems which expose low-income populations to fecal pathogens. These include poor infrastructure, lack of public sanitation services and the absence of sustainable business models for private sanitation.

Lack of sanitation infrastructure

Sanitation infrastructure such as sewerage and treatment facilities, the most common approach to clean environments in developed countries, is severely underdeveloped in most developing countries. The gold standard of closed sewage systems where wastewater is treated before being returned to the environment is highly uncommon.

Sanitation systems generally only reach small portions of the population and are underdeveloped or in disrepair, leaving most individuals using alternative sanitation systems or practicing open defecation.

Lack of sustainable, scalable models for community or household sanitation systems

One of the key challenges with sanitation systems is maintenance—keeping the toilets at an acceptable level of cleanliness while removing waste—which is dependent on an effective business or public utility model. In most developing countries, government-funded sanitation systems have limited reach, often excluding the poor.

In the absence of public models, private or hybrid models are being developed, although none have yet been fully proven. In the absence of an effective model which generates revenue, either from usage of the toilet or through sale of the fecal sludge, sanitation systems inevitably become unsanitary and go into disuse.

Existing urban and rural systems have major shortcomings, which lead to environmental contamination

In urban areas, particularly for the poor, sanitation systems are generally pit latrines and open sewers, which have several major shortcomings. First, both are prone to flooding, which leads to widespread contamination. Second, open sewers in particular are often located in areas with high population density where they cause extensive contamination. Third, pit latrines often fill up faster than the waste decomposes, which means that they must be emptied.

Often pit latrines are emptied by private parties who dispose of the fecal sludge improperly, usually very close to urban populations, where the diarrheal pathogens can contaminate water sources or soil and come in easy contact with children. In rural areas, sanitation options are generally pit latrines or open defecation (more common in rural India, in particular).

In both cases, rains and flooding can contaminate soil and water. As with urban pit latrines, rural pit latrines need to be emptied frequently and fecal sludge is rarely disposed of properly.

3. Environmental conditions are conducive to the persistence and spread of pathogens

Bacterial pathogens can survive in water for 10 to 60 days and for many months in soil. STH eggs can survive in soil for 27 to 35 days in summers and up to six months during the winter season in temperate zones (Ensink & Fletcher, 2009). Both bacterial pathogens and STH eggs can survive significantly longer than their average lifespan in fecal waste.

4. In the absence of sanitation systems, there are a large number of ways in which food and water can become contaminated or children can be directly exposed to pathogens

When there are insufficient sanitation systems, diarrheal pathogens flow through multiple transmission pathways, which brings them in direct contact with potential human hosts. There are many possible transmission points, and therefore many breakpoints in the transmission pathway to consider.

Distributed water sources including surface water, shallow wells and boreholes

Surface and shallow water sources, especially in rural areas, can be contaminated through flooding and runoff of fecal matter and pathogens. Deeper groundwater, in both urban and rural areas, can be similarly contaminated through episodic flooding, particularly when boreholes are constructed poorly (without a concrete block at the surface to prevent fecal matter from reaching the aquifer through and around the pipe).

Centralized water sources (water pipes)

In urban settings, water distribution pipes and sewage pipes or ditches are often constructed near each other. Pipes are inherently leaky, with even well-maintained western systems losing roughly 15 percent of system water. Piping systems in developing countries are dramatically worse and often have only intermittent water supply.

When the water supply is shut off, it creates reverse pressure, and if there is fecal matter around the pipes it can leach into the water pipes. This re-contaminates water even if it has already been purified.

Crops

An estimated 10 percent of the world's food supply is irrigated with wastewater (Jimenez, 2006). Use of untreated wastewater for irrigation deposits pathogens, particularly on vegetables, which can then be ingested if the produce is not cleaned and cooked properly before eating.

Flies

Some flies are born and breed in fecal matter and carry pathogens on their exoskeleton or through their gastrointestinal system. Flies also tend to proliferate in hot and humid conditions, especially during the rainy season, when there are more pathogens in the ecosystem.

Soil and environment

Soil and the broader environment are contaminated from open defecation, disposal of fecal sludge, runoff from inadequate sanitation systems, wastewater that is used for irrigation, and episodic flooding.

Diminishing water availability leads to utilization of lower quality water sources

As water sources become over-abstracted or are replenished at slower rates due to changes in hydrological patterns, water quality tends to degrade. Individuals then have to use lower quality water sources. This exacerbates existing challenges with nearly all water sources in water-poor areas, including most of South Asia and sub-Saharan Africa. This is also expected to become increasingly critical as the global population grows and hydrological patterns continue to change.

5. Children are exposed to diarrheal pathogens, either directly from pathogens on their hands or through consumption of contaminated food or water

Exposure to diarrheal pathogens is enabled by food and personal hygiene habits as well as insufficient water purification systems.

Hand hygiene

Mothers and children do not wash hands with soap after contact with fecal matter, either through defecation or care for a child or infant who has defecated.

Food hygiene

Mothers often do not wash their hands with soap before preparing food and children do not wash their hands prior to eating. Weaning foods are prepared under unhygienic conditions and stored at room temperature. Several studies have found that the second 6 months of life are the period with the highest rate of diarrheal disease (Motarjemi, et al., 1993).

According to one study, 41 percent of weaning food items were contaminated with E. coli (Black, et al., 1982). Due to storage of foods at high ambient temperatures, weaning foods have been found to be more contaminated than food prepared for adults, (Black, et al., 1982). Apart from weaning food, previously cooked food is often not reheated before consumption later. Storage at room temperature can lead to exponential bacterial growth in cooked food. Studies have found that bacterial contamination on food greatly exceeds that found in drinking water (Black, et al., 1982).

Water quality and supply

There are several challenges in providing safe water to children. First, water delivery infrastructure is often poorly developed and in some cases absent in developing countries, particularly in rural areas. While most individuals in urban areas have access to water, access in rural areas, particularly in sub-Saharan Africa and India remains low.

In both regions, only about half of the population has access to an improved water source. When there is no national level water infrastructure, community level systems are often employed; however, these systems need ongoing maintenance models and require an adequate service model to be sustainable.

However, studies have found significant heterogeneity in results from point-of-use water treatment systems, which is likely related to compliance (Clasen, et al., 2007). In one study of the poor in urban Bangladesh, even with bi-monthly visits to educate families about the dangers of untreated drinking water, only 30 percent of families used the most popular treatment system they tested, with lower rates of compliance for other systems (Luoto, et al., 2011).

The low rate of adequate water treatment is also greatest among the poor. In Africa, the richest quintile was more than three times as likely to use adequate water treatment relative to the poorest, highlighting the fact that people who are most at risk have the least access to appropriate water treatment (Rosa & Clasen, 2010). This indicates that while there is opportunity at the household level, these technologies are unaffordable, complex and time consuming, and require daily and continuous use.

Finally, even when water is treated, recontamination of water in the household is common. A study in urban India found that 40 percent of water stores at the houses of families who boiled their water were contaminated, with 25 percent of stores exceeding the WHO threshold for safe drinking water (Clasen, et al., 2008).

This is generally believed to be due to recontamination because of unhygienic practices in storing and retrieving water (meaning, water stores are re-contaminated from placing hands in water during retrieval).

6. Lack of adequate nutrition, low access to healthcare and low coverage of vaccines

Together, these factors increase a child's susceptibility to disease after exposure.

Increased susceptibility due to poor nutrition

Diarrheal pathogens are opportunistic. Development of active infection following exposure, like with many diseases, is driven by the strength of an individual's immune system. Malnourished children, in particular, have higher susceptibility.

Children who are stunted are 1.6 times more likely to die from diarrheal disease than those who are not stunted (Black, et al., 2008); Vitamin A deficiency causes a 60 to 70 percent increase in diarrhea prevalence (el Bushra, et al., 1992), and zinc deficiency has been found to increase diarrhea prevalence by 15 to 24 percent (Bhutta, et al., 2008).

Suboptimal breastfeeding also contributes to childhood susceptibility to diarrheal pathogens. Infants under the age of 6 months who are not breastfed are more than 10 times as likely to die from a diarrheal infection as those who are breastfed (Lamberti, et al., 2011).

Low vaccine coverage for rotavirus

An effective vaccine exists for rotavirus, which is the most common cause of moderate-to-severe diarrhea in children under 2, and makes up more than 40 percent of all incidences of moderate-to-severe diarrhea in children under 1—more than double the next highest cause (Kotloff, et al., 2013).

However, childhood coverage for this vaccine is still low due to the vaccine's fairly recent introduction as a global priority and its high cost relative to other vaccines.

Lack of vaccines for Shigella, ST-ETEC, Cryptosporidium and soil-transmitted helminths

With the exception of rotavirus, there is no effective vaccine for any of the other major pathogens that cause diarrheal disease, and there are major scientific challenges to many of these pathogens (Jones, et al., 2003). There are many strains of ST-ETEC and an effective vaccine would have to produce immunity against an array of antigens.

Developing vaccines for parasitic diseases is challenging due to the increased complexity of antigen analysis of higher life forms, as is the case with cryptosporidium and helminths. The challenge of developing a vaccine against STHs is compounded by the diversity of helminth organisms (Harris, 2011). Many experts believe that the development of additional vaccines is likely a high-cost, time-consuming opportunity relative to existing interventions.

7. Children do not receive adequate care during a diarrheal episode due to the low coverage of oral rehydration therapy

ORT is a proven intervention and can reduce mortality by 69 percent but coverage remains low (Bhutta, et al., 2013). Only 39 percent of children in developing countries with diarrhea receive ORT, and there has been little improvement in this rate since 2000 (WHO-UNICEF, 2009).

This is driven by a number of factors including the misconception that diarrhea is considered a normal part of growing up, the fact that often both parents work and have limited time to pay attention to their children, weak healthcare systems and the lack of awareness that diarrhea can be a major risk to a child's life.

8. There are many fundamental scientific questions that remain unanswered

Experts noted many key scientific questions, highlighted below, that require further research to help reduce the burden of diarrheal disease and STHs.

- What is the relative importance of various pathways of transmission?
- What is the relationship between gastrointestinal pathogens and malnutrition?
- What is the burden of disease, other than mortality, that is attributable to gastrointestinal pathogens? (For example, the loss of cognitive development associated with both intestinal parasites as well as growth faltering which may be mediated through environmental enteropathy).
- What is the role of the microbiome in increasing or decreasing the susceptibility of the child to exposure to gastrointestinal pathogens? And what interventions might contribute to a healthier more protective microbiome?
- How clean does the environment need to be for thriving children and thriving communities?
- What is the underlying cause of environmental enteropathy?
- What are the pathways through which environmental contamination and malnutrition contribute to growth faltering?
- How do we scale up successful pilot projects to better protect large vulnerable populations?
- What are easier, lower cost methods for detecting and measuring the concentration and viability of pathogens in the environment?
- What are better dose-response curves to use for modeling exposure (Quantitative Microbial Risk Assessment) that describe the susceptibility of children to different organisms? Most dose-response data are from studies on healthy adults.

In summary, systemic challenges require systemic solutions. The core challenge, breaking the fecal-oral pathway, is dealt with in developed countries through large government investments in public infrastructure including sewer systems, wastewater treatment plants, water purification facilitates and ubiquitous piping into households—all of which require constant service and maintenance. This is almost certainly not practical in most of the poorest regions of the world.

SCIENTIFIC AND TECHNOLOGICAL BREAKTHROUGHS

There have been several successes in reducing diarrheal disease at a small to mid-level scale, usually in the range of thousands of households. Very few interventions, however, have been proven at a scale comparable to the problem itself—in the range of millions of households.

Amidst the successes are an abundance of failed interventions—broken water filters or toilets that were installed but never used or quickly broke, again highlighting the fact that diarrheal disease is not a challenge that can be solved just by technology, by building infrastructure or by influencing behavior or habits.

Rather, successful interventions must be holistic and consider the whole system and include business or public financing models to ensure sustainability.

Technology does, however, play an important role in a holistic solution, and there are three scientific and technological breakthroughs that can improve sanitary conditions and significantly reduce diarrheal diseases.

Breakthroughs:

1	2	3	4	5	6	7	8	9	10
11	12	13	14	15	16	17	18	19	20
21	22	23	24	25	26	27	28	29	30
31	32	33	34	35	36	37	38	39	40
41	42	43	44	45	46	47	48	49	50

3 Network of low-cost distributed monitoring sensors to measure and map air and water quality

Discharge of pollutants into the air and water is an undesirable side effect of conventional industrialization and development processes. Because many environmental pollutants are invisible, tasteless and odorless, severe cases of contamination often go undetected and unremedied. Detection of environmental pollutants currently requires costly equipment and elaborate sampling protocols, and provides only isolated snapshots of individual places, times and contaminants. To fully understand and solve the problem of environmental pollution of air and water, a more fine-grained knowledge of exposure is required.

There is an urgent need for the development and widespread deployment of sensors that detect the levels of the most significant pollutants affecting the air and water, and transmit that information to a platform where it is validated and publicly displayed. Sensors will need to identify and measure a broad range of pollutants. Key air contaminants to be measured include particulate matter, ozone and carbon monoxide, while essential water contaminants include E. coli, salinity and arsenic. Though challenging, there is an important and growing need to measure diverse chemical toxins from sources including industry, vehicles and agriculture.

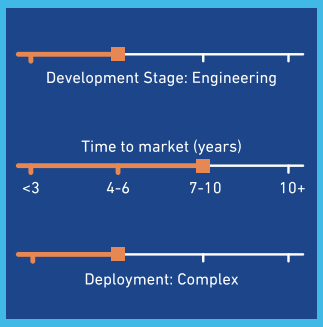
Required technological innovations include integrated sensors for the most significant contaminants that are inexpensive enough for mass deployment, as well as a platform for data collection, validation, analysis and dissemination. The sensors may be hard-wired and provide continuous monitoring of particular locations, or may be portable to conduct mobile geolocated assessments of contamination.

Fixed sensors would likely form the basis of a sensor network, transmitting (continuous or periodic) data to a mapping platform to show changes in quality parameters over time. Issues of sensor performance degradation over time will need to be addressed, to enable robust long-term monitoring. A successful sensor technology will likely not test separately for each individual contaminant, but would scan a sample of air or water and determine quickly and inexpensively its multiple constituents.

For maximum effectiveness, this sensor technology would be integrated with a web-based platform to allow collection and comparison of environmental pollution risks over time and place.

The linking of improved sensor technology with mobile communications technology would lead to a system for real-time, spatially-explicit, multi-agent exposure monitoring that would create an unprecedented understanding of global air and water pollution, and pathways toward their reduction. Once identified, areas of high risk could be assessed in more detail, and critically contaminated locations in need of remediation can be flagged.

Current State



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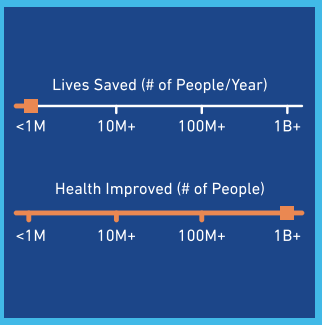


Commercial Attractiveness

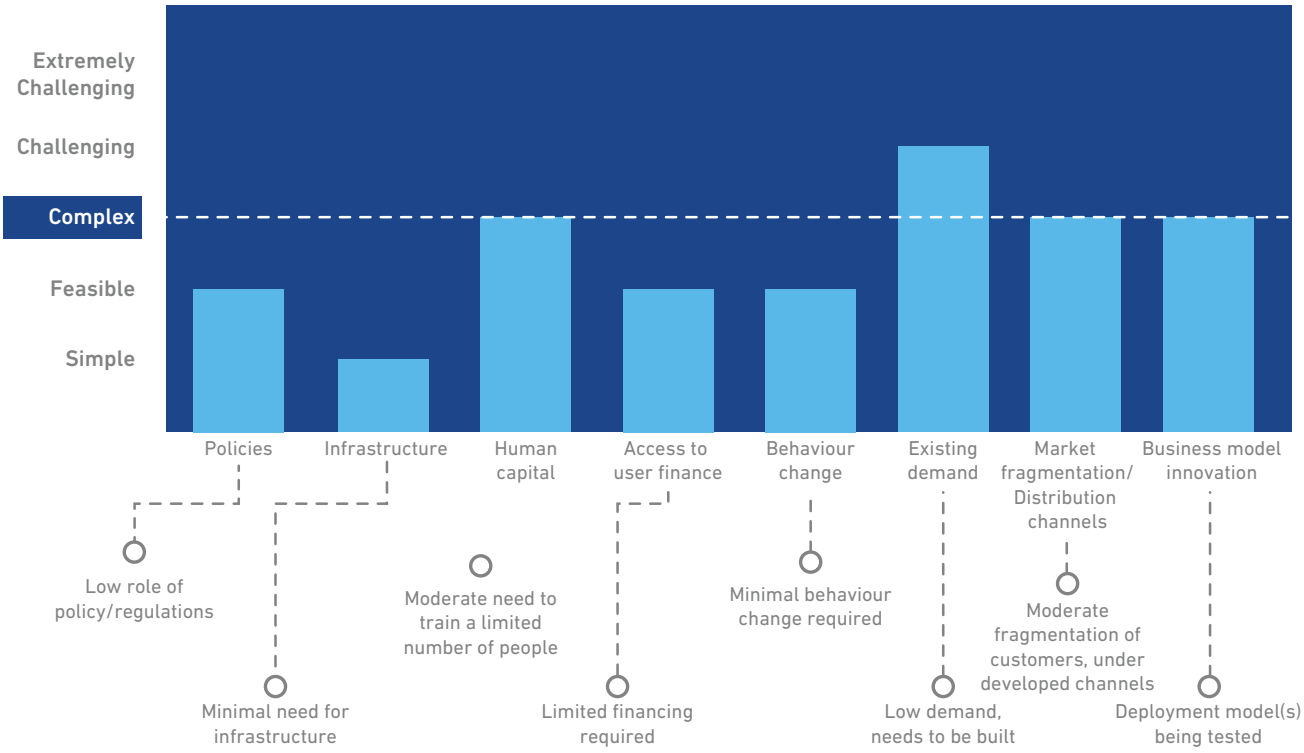
Portable sensing by trained staff using mobile devices with disposable one-time sensors could also be useful to increase the spatial density of measurements. Another approach to mobile sensing is community-based air and water quality monitoring, using low-cost portable sensors connected to smartphones that communicate results to the network.

This approach may face issues with data reliability due to incorrect sampling techniques or fraud, so would require additional validation. The initial cost of the hardware should be modest (less than $500), perhaps taking the form of a plug-in sensor that leverages the computing power of an existing mobile device. Cost of consumables should be low (less than $1 per test), allowing ubiquitous monitoring even in remote sites of low- and middle-income countries.

Progress is being made rapidly in the field of environmental monitoring, though there appears to be little focused effort towards the integrated technology we envision here. A basic form of air quality mapping using near real-time data from a global network of sensors can be found at http://aqicn.org/map/world/.

If sufficient resources were allocated to allow the necessary research and development efforts, we expect that it will take seven to ten years for this breakthrough to be ready for use. A significant deployment challenge is the lack of consumer demand for environmental monitoring. Therefore, deployment is likely to be COMPLEX.

Breakthrough 3: Difficulty of deployment



4 Sustainable, affordable, household-level fecal waste management system

A large share of the population in rural and peri-urban areas of many low-income countries lacks access to household toilets, and is habituated to open defecation. Many others have access to toilets, but of substandard type and capable of contaminating groundwater. This poses serious health risks in the form of diarrheal and other diseases. An effective household sanitation system must provide an initial hygienic separation of the fecal waste, as well as prevent opportunities for secondary exposure to the fecal pathogens such as surface and groundwater contamination. Ultimately, the fecal waste must be made harmless and definitively disposed of.

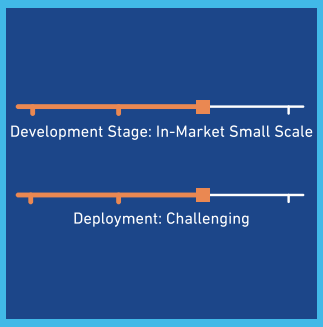
In rural and many peri-urban areas, the most appropriate sanitation system employs household-level collection and full on-site treatment of waste materials. Household-level sanitation is quite appropriate in rural areas, where extensive sewage networks would be prohibitively expensive due to low population density.

Household sanitation is also widely used in some higher density places such as peri-urban areas, where sewer networks have not reached. A wide range of on-site sanitation technologies have been developed, including pit latrines (single and twin pits), pour-flush pit toilets (with septic tanks, and single and twin leach pits), vermicomposting toilets, dry composting toilets, and anaerobic baffled reactor toilets.

However, existing on-site sanitation methods fall short is some regards. In some cases they do not safely contain fecal waste, instead letting it leak into groundwater aquifers. In other cases, the waste is safely contained in storage only temporarily, but eventually becomes full and must be emptied and can then cause broad contamination.

Despite our long experience accumulated with sanitation practices, there is a large gap for a sustainable, affordable, decentralized, on-site household sanitation solution for low-income households. Of the existing household sanitation technologies, vermicomposting toilets appear to provide relatively high performance at low cost, largely due to enhanced decomposition of fecal matter by earthworms, leading to less waste build-up and less frequent emptying and thus lower maintenance costs.

Current State



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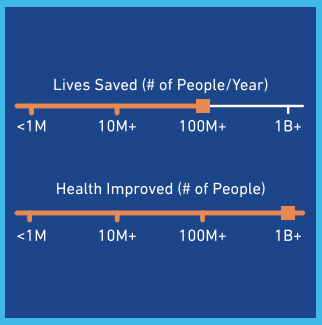


Commercial Attractiveness

The development of improved on-site household sanitation systems should be viewed as a long-term solution to rural sanitation (and possibly peri-urban sanitation) rather than an interim fix, and should be given a high priority in resource allocation.

Sanitation facilities that are merely waste storage repositories, such as pit latrines, must be coupled with mechanisms for regular emptying of fecal sludge and transporting it to appropriate sites for processing or safe disposal. Facilities that include on-site treatment, such as vermi-filtration, generate smaller quantities of residue that must be disposed of.

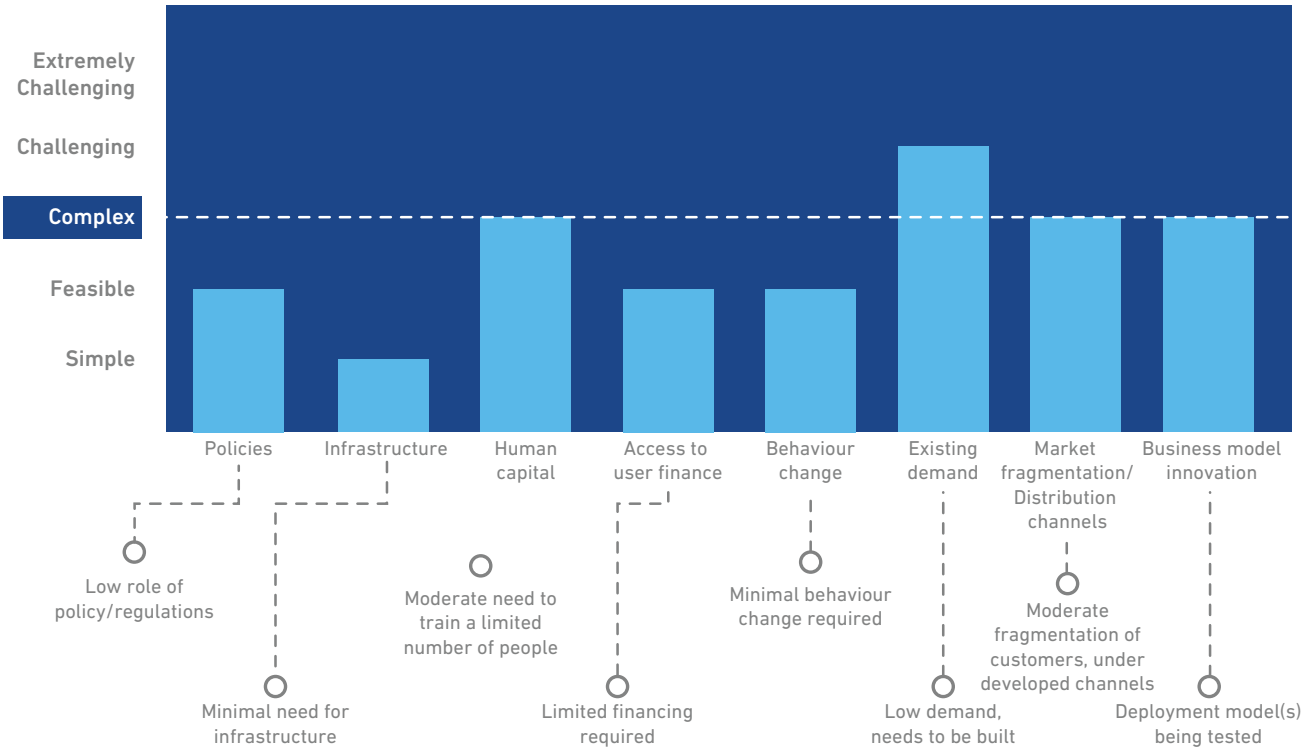
One potentially useful path may involve additives that facilitate the breakdown of fecal sludge, reducing the need to empty latrines. Researchers are currently developing and testing several options, including addition of higher organisms, microorganisms and hydrolytic enzymes.

In the longer term, opportunities could include use of fermenting organisms, development of new enzymes or facilitation of the current microorganisms involved in digestion. Regardless of the specific path, each step of the sanitation service chain is important to achieve effective waste management, from toilet siting and construction, to final treatment and disposal of waste.

Effective sanitation is challenging where there is no piped water or sewerage, as household toilets must be low-cost, have an effective method to control odor, a system for processing and disposing of waste, and occupy minimal space.

Significant experience has been gained on technical aspects of sanitation, but we lack full understanding of the important socio-cultural aspects. Initial technologies are already on the market, but the difficulty of deployment is CHALLENGING.

Breakthrough 4: Difficulty of deployment



5 Medium to large-scale sewage treatment process with recovery of water (and ideally nutrients and energy)

This imperative calls for the development and deployment of novel sewage treatment facilities that are net sources, rather than sinks, of resources. Primarily this applies to water resources, for treating and reusing the wastewater collected in sewer systems. Systems should enable reuse of the treated water for secondary purposes including industrial, recreational and agricultural applications.

A secondary focus is on energy resources, where sewage treatment facilities could operate with net zero energy inputs, and could even have the capability to produce energy for societal use. The recovery of nutrient resources from sewage, such as phosphorus or nitrogen, may also be a goal. Integrated sewage treatment can be viewed as a way to harvest clean, renewable sources of water, energy or nutrients while disposing of a waste product.

There is a great need for a low-cost, sustainable and scalable sewage management process for deployment in fast-growing cities in developing regions. In India, for example, less than 38 percent of the sewage that is generated is treated before being discharged into water bodies. The amount of resulting sewage in the environment is contributing to the country's health problems, including diarrheal outbreaks among children and lifelong stunting and wasting.

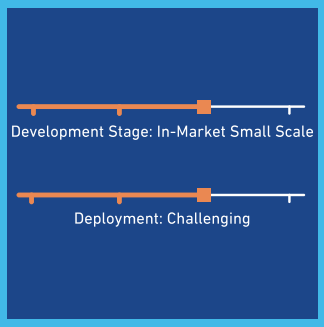
The massive organic and nutrient loading also has adverse environmental effects and leads to the destruction of ecological productivity of water bodies. Simultaneously, many growing cities have difficulty meeting the water needs of households and industries, due to physical constraints to water supply manifest as closed river basins and depleting groundwater stocks.

The quantities of wastewater generated in major cities are enormous, thus reusing this water for other purposes is a major lever for enhancing water security. For example, if 80 percent of the wastewater collected by urban sewage networks in India were reused, an additional water resource of 18 cubic kilometers per year would be obtained (ITT, 2018). What is lacking is an effective and affordable sewage treatment method that can rapidly scale up in developing regions.

Conventional wastewater treatment methods are a major resource sink, and should not be held as models for scalable sanitation methods for fast-growing cities in low-income countries. In the United States, for example, about 1.3 percent of all electricity is used for sewage treatment. This is a wasted opportunity, because raw sewage contains about six times more chemical energy than the amount of electrical energy required to treat it.

The most appropriate method of treatment for wastewater will depend largely on the intended use of the recycled wastewater and the scale of the treatment facility. Major reuse applications include agriculture (food and non-food crops), industry, and groundwater recharge, for which increasing effluent quality is required, respectively. For agricultural purposes, nutrient removal (or partial nitrogen removal) can be left out of the treatment process, whereas reuse in industrial applications or groundwater recharge requires nutrient and solids removal.

Current State



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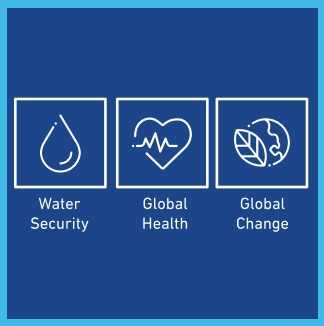

SDG Alignment

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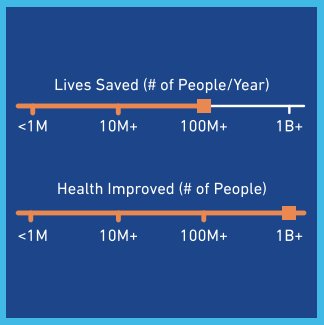


Commercial Attractiveness

Groundwater recharge applications may also require removal of micro-pollutants as well as organic carbon. In terms of costs, the higher the quality of treated effluent, the higher the total capital and operational costs are. Generally, larger treatment plants have an increased efficiency, which lowers the lifecycle costs and environmental impacts per cubic meter of treated water.

Novel sewage treatment methods followed by wastewater reuse is a potentially important lever for enhancing water security. Reusing wastewater brings two important benefits: less pollution entering water bodies, and less need for freshwater withdrawals.

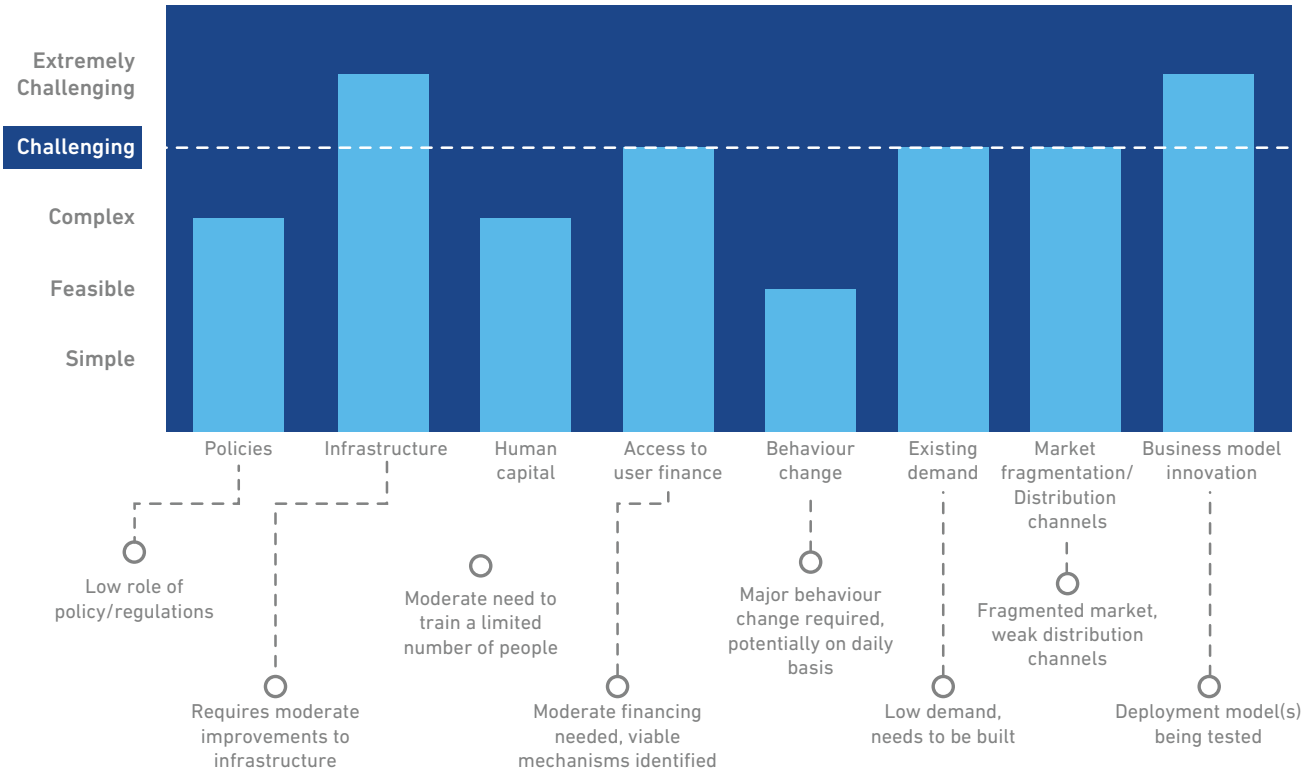
However, in the areas where it is currently practiced, wastewater reuse is typically considered as a temporary solution for acute needs, instead of implemented as a long-term solution to improve water security. Important criteria for successful treatment technologies include the extent of land area required, the economic resources needed for capital and O&M, and the quality requirements for the reused water.

Land area requirements, in particular, may be an impediment to scale-up of some technologies. Different technology solutions may be appropriate for different settings as the scale increases from household to neighborhood and metropolitan level.

There are many challenges to sanitation infrastructure deployment, and business models should not expect to extract high-value content from sewage. Sanitation systems tend to have fairly high up-front costs and require skilled labor to install and maintain. Distribution channels are also poorly defined. In addition, significant public investment is likely to be still required.

Some promising technologies have entered the market, and others should become market-ready in the coming years. Given the lack of proven models and the growing scale of the urban sanitation problem, the level of difficulty for deployment is CHALLENGING.

Breakthrough 5: Difficulty of deployment



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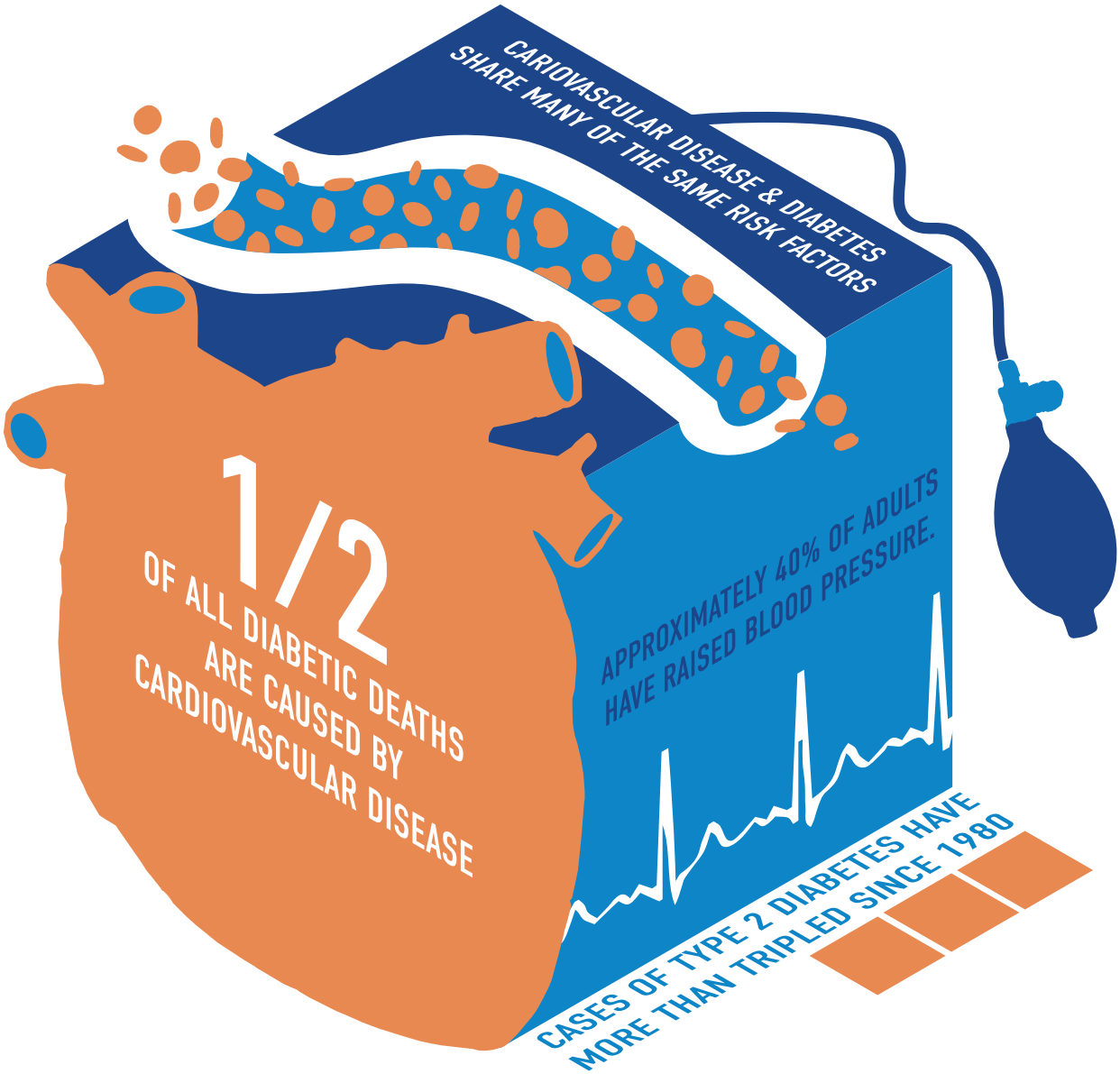


NON-COMMUNICABLE DISEASES

INTRODUCTION

In many low- and middle-income countries (LMICs), non-communicable diseases (NCDs) are becoming an increasingly important health concern, as the populations experience economic growth, increasing urbanization and declining disease burden from infectious disease.

According to WHO, out of 57 million global deaths in 2016, about 71 percent were due to noncommunicable diseases (NCDs), with cardiovascular diseases (17.9 million), cancers (9.0 million), diabetes (1.6 million) and chronic respiratory diseases (3.8 million) having the greatest burden. Earlier considered as primarily a problem of high-income countries, NCDs today disproportionately affect LMICs, with more than three quarters of NCD deaths occurring in these countries (WHO, 2016).

The leading cause of mortality amongst NCDs is cardiovascular disease (CVD), which represents 43 percent and 34 percent of NCD mortalities in South Asia and sub-Saharan Africa, respectively (IHME GBD, 2017). Contributing to this figure, and driven by many of the same risk factors, is diabetes, often considered a parallel epidemic.

Diabetes is a key risk factor for CVD; half of all diabetic deaths are caused by CVD. Other key risk factors for CVD include hypertension, smoking, raised cholesterol and being overweight. Of these, hypertension is considered the most crucial. It is estimated that between 10 and 20 million people out of the approximately 650 million people living in sub-Saharan Africa may have hypertension (Opie & Seedat, 2005).

It is estimated that 60 percent of the world's new cases of cancer are diagnosed in LMICs (Sukhun, et al., 2017), with 70 percent of cancer deaths occurring in these countries (WHO, 2018). While cancer incidence and mortality rates, in particular breast and cervical cancers, have remained stable and even lowering in many high-income countries, they are increasing rapidly in LMICs. More concerning is the particularly high age-standardized mortality rates in Africa with respect to incidence rates (Azubuike, et al., 2018).

Key drivers of NCD mortality and risk factors include demographic trends, such as increasing life expectancy, increased urbanization and inactivity, poor diets and high rates of smoking, along with genetic risk factors like predisposition to diabetes and hypertension.

In addition to these are challenges in the delivery of care. Medical systems in most developing countries were designed to treat infectious diseases rather than NCDs, and most developing countries are still early in the development of their national NCD programs. Diagnostics and treatments, in particular for cancers, are expensive and inaccessible in most LMICs.

In 2015, India became the first country to develop specific national targets and indicators aimed at reducing the number of global premature deaths from NCDs by 25 percent by 2025 in line with the WHO's global action plan for the prevention and control of NCDs.

Two technological advances show potential for tackling the growing burden of NCDs:

- Breakthrough 36. Affordable, home-use point-of-care diagnostics suite (blood, urine, vitals) for the common NCDs
- Breakthrough 37. Affordable wearable technology with broader functionality for patient adherence and monitoring of health status

Non-communicable diseases (NCDs) are becoming increasingly prevalent in low- and middle-income regions. Over the past few decades, life expectancy and incomes in developing countries have increased substantially, allowing for more prosperous and older populations.

CORE FACTS AND ANALYSIS

1. Non-communicable diseases (NCDs) are a growing health risk in developing countries

NCDs in 2017 accounted for 62 percent of total DALYs worldwide, 55 percent of DALYs in South Asia and 30 percent of DALYs in sub-Saharan Africa (IHME GBD, 2017).

NCD mortality attribution is shown in **Exhibit 1**, and demonstrates an increase in the NCD burden of disease in low-income countries and LMICs over the last decade.

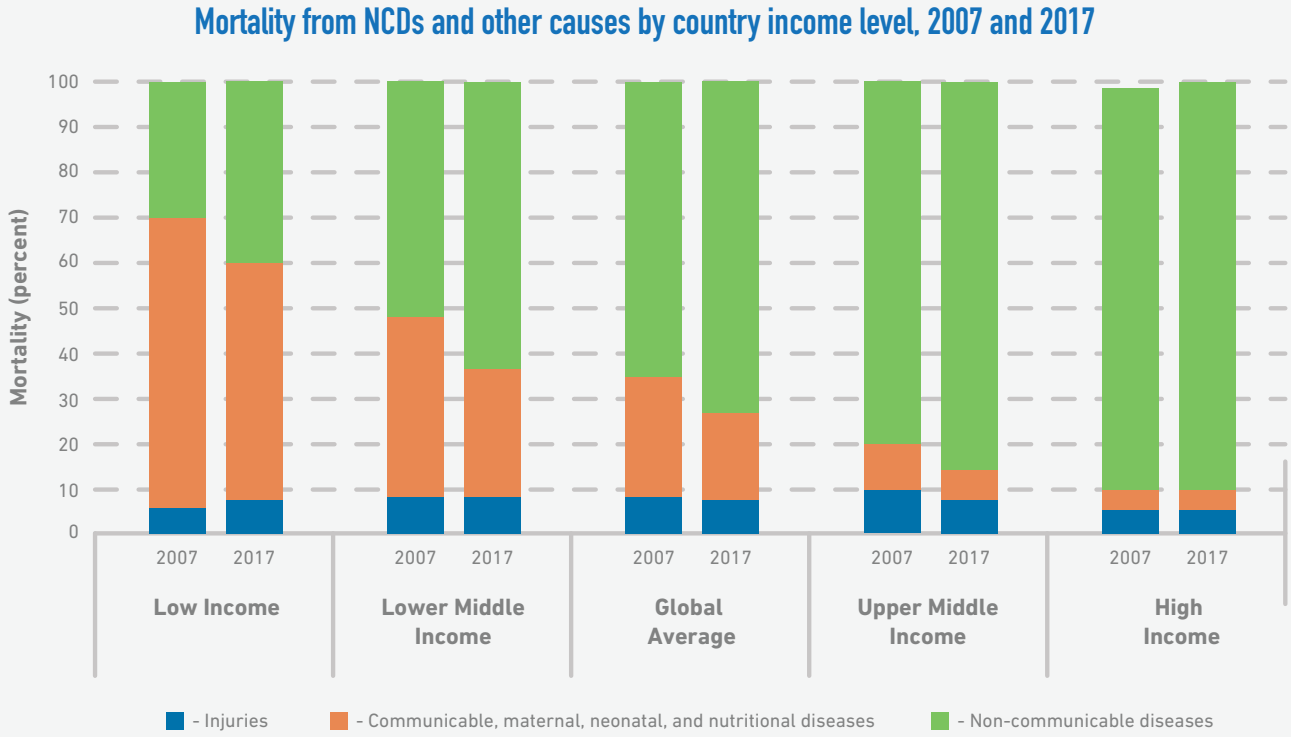


Exhibit 1: : As countries become wealthier, NCDs contribute increasingly to overall deaths. While communicable disease burden has decreased, the burden of disease from NCDs in low-income and lower-middle-income countries has increased over the past decade. (Source: IHME GBD, 2007 & 2017)

As life expectancies and incomes increase in South Asia and sub-Saharan Africa, so too has the relative importance of NCDs in public health (**Exhibit 2** and **Exhibit 3**).

As is the case with the rest of this study, this section also focuses primarily on sub-Saharan Africa and South Asia.

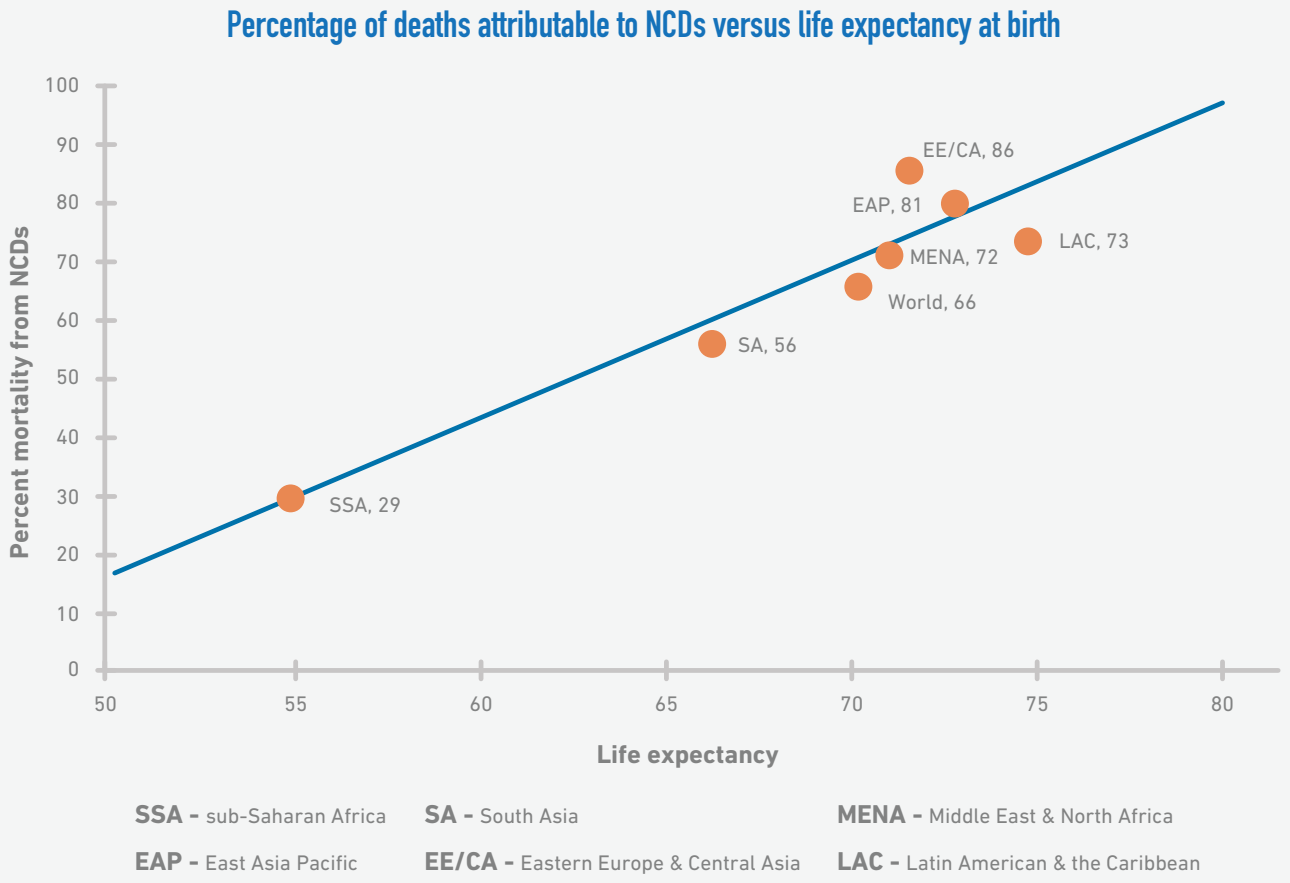


Exhibit 2: As life expectancy increases, the attributable share of mortality due to NCDs rises. Sub-Saharan Africa and South Asia's low life expectancies and young populations explain in part why NCDs are not as significant a source of mortality in these regions as in the rest of the world. As the populations in these regions age, NCDs are expected to occupy a greater share of causes of mortality. (Source: WHO, 2013; UNDP, 2013)

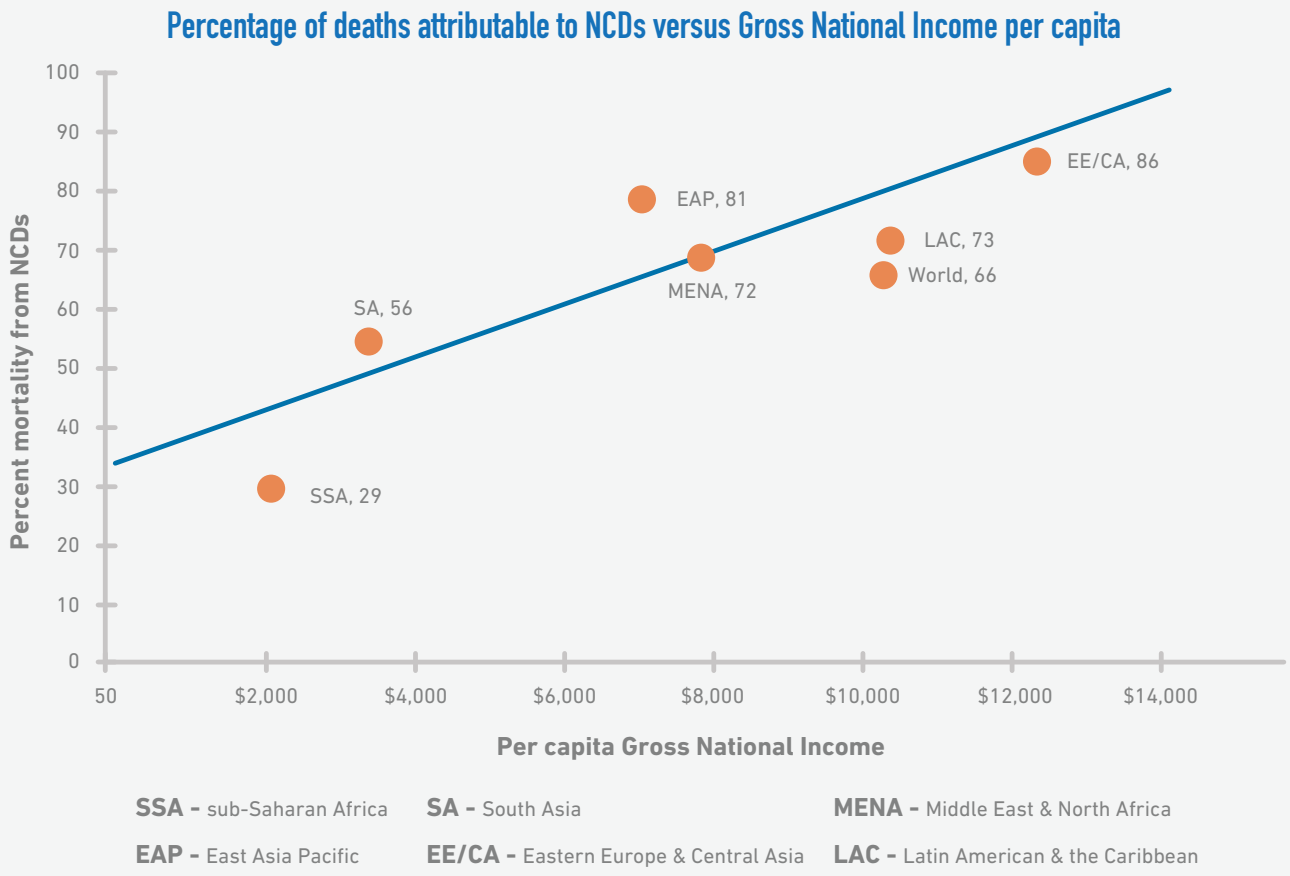


Exhibit 3: As incomes rise, the attributable share of mortality due to NCDs rises. Higher incomes accompany urbanization, richer diets and sedentary lifestyles. In addition, higher incomes enable governments to provide more resources to controlling communicable diseases, feeding into the longer life expectancies seen in Exhibit 2. (Source: WHO, 2013; UNDP, 2013)

2. Cardiovascular disease: the leading NCD killer

Among NCDs, cardiovascular disease (CVD) is the single largest cause of death (**Exhibit 4**). CVD causes nearly one-third of all NCD deaths in South Asia and sub-Saharan Africa and is more than twice as prevalent as cancers—the next largest NCD category in these regions.

While CVD prevalence rates in developing regions are low due to young populations, age-standardized mortality rates are among the highest in the world. As mentioned above, hypertension is one of the most crucial risk factors for CVD. An estimated 15 to 30 percent of people in sub-Saharan Africa have hypertension. Of greater concern, however, is the low percentage of hypertension awareness, treatment and control (Ataklte, et al., 2015).

Higher age-standardized prevalence and lack of treatment options in low-income countries indicate that the combination of younger populations, higher communicable disease burdens, and low awareness and diagnosis of key risk factors are masking a CVD problem that will manifest itself more acutely as countries successfully address other public health burdens.

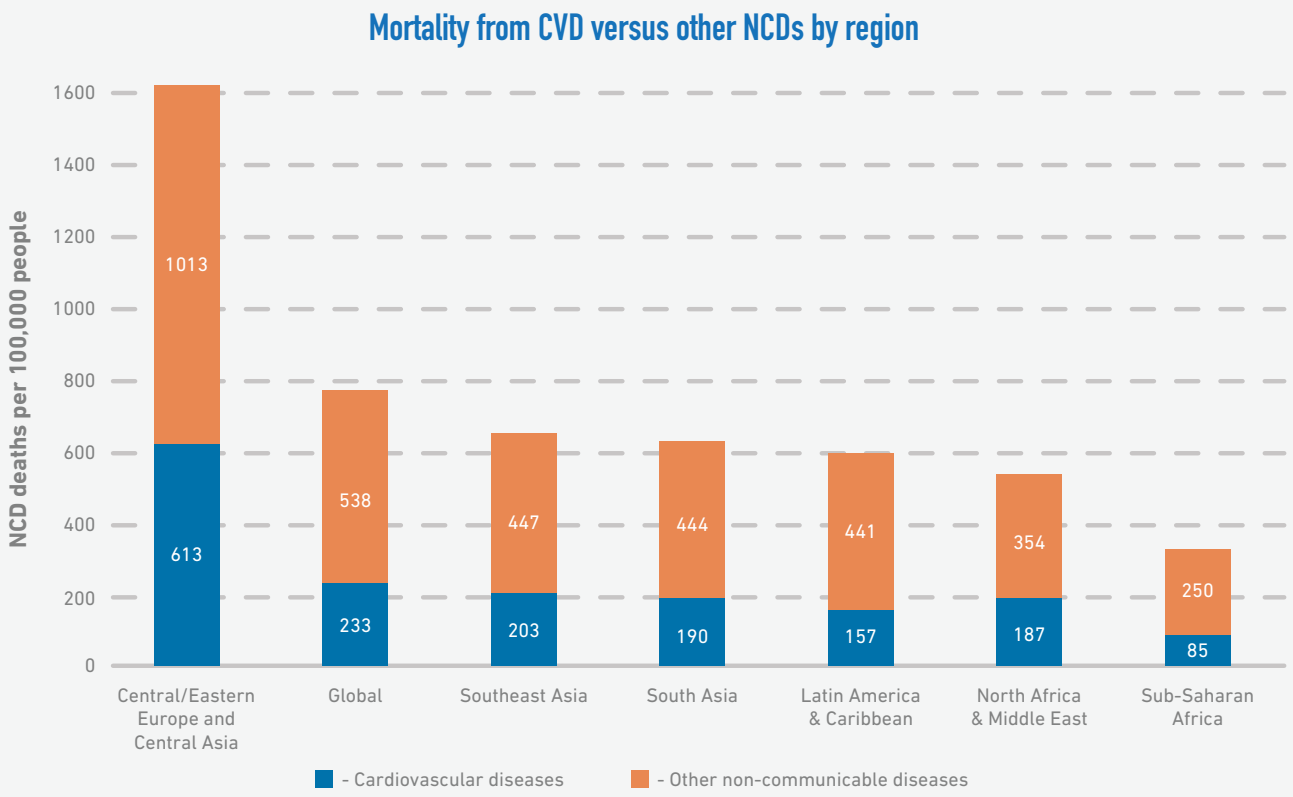


Exhibit 4: In most regions, CVD represents about a third of all deaths from NCDs. (Source: IHME GBD, 2017)

CVD encompasses a range of conditions afflicting the heart and circulatory system. Notably, two conditions in this category account for 80 percent of all NCD mortality.

Ischemic heart disease

Also known as coronary heart disease, ischemic heart disease is characterized by the reduction of blood flow to the heart, usually due to atherosclerotic build-up in arteries. This disease is the leading cause of acute myocardial infarctions (AMI) commonly referred to as 'heart attacks.'

An AMI can rapidly cause permanent heart damage or death. In 2017, ischemic heart disease was responsible for 50 percent of CVD deaths worldwide, and 57 and 42 percent of CVD deaths in South Asia and sub-Saharan Africa respectively (IHME GBD, 2017). Ischemic heart disease is the leading cause of death in South Asia, accounting for 15 percent of all deaths in the region (IHME GBD, 2017).

Cerebrovascular disease

More commonly known as a 'stroke,' cerebrovascular disease results from a disturbance in blood flow to the brain, usually either through lack of blood flow or a blockage. More than one-third of CVD victims are killed, and another third are permanently disabled, by strokes.

In 2017, strokes accounted for 30 percent and 36 percent of all CVD fatalities in South Asia and sub-Saharan Africa, respectively (IHME GBD, 2017). Cerebrovascular disease is the second most significant cause of NCD death and the fifth highest overall cause of death in sub-Saharan Africa (WHO, 2016).

3. Diabetes: a parallel epidemic

While diabetes is a separate disease, it shares many risk factors with CVD, particularly poor diet and not enough exercise. Diabetes is also one of the leading risk factors for CVD, the latter being a leading cause of death for diabetics. Half of diabetic deaths are caused by CVD. This is due both to the co-occurring risk factors with CVD as well as additional risk factors unique to diabetes, such as high fasting blood sugar. Given the close relationship between the two, including common risk factors, we consider these diseases in tandem.

Diabetes mellitus, known simply as diabetes, refers to a group of diseases in which the body is unable to metabolize sugar. In Type 1 diabetes, also known as juvenile diabetes because it disproportionally affects children, the pancreas does not produce adequate insulin to break down the sugar. In Type 2 diabetes, also known as adult-onset diabetes because it occurs later in life, the body still produces insulin, but cells lose their ability to use the insulin to metabolize sugar. The third type of the disease, gestational diabetes, occurs when pregnant women suffer from very high glucose levels because their insulin receptors are disrupted.

Of the three types of diabetes, the overwhelming share of the disease burden in developing countries (90 percent) is due to Type 2 (IDF, 2013), which is the focus of this section. Type 2 diabetes doubles the risk of CVD and can cause retinopathy and blindness, reduced blood circulation to limbs (which can lead to severe complications such as gangrene), long-term nerve damage and kidney failure.

Diabetes has grown rapidly in the past two decades. The number of people with diabetes globally has more than doubled between 1990 and 2017, from 211 million to 476 million (IHME GBD, 2017). This number is expected to increase to 592 million in 2035 (IDF, 2013).

In developing countries, 70 percent of this increase can be attributed to population growth and aging, while the remaining 30 percent is considered to be due to increasing prevalence (Danaei, et al., 2011). Prevalence of Type 2 diabetes in sub-Saharan Africa between 1960 and 1980 was lower than 1 percent but now stands at 4.8 percent and is expected to grow to 5.3 percent by 2035 (Mbanya, et al., 2010; IDF, 2013). Prevalence in South Asia is predicted to increase from 8.2 percent currently to 10.1 percent by 2035 (IDF, 2013).

4. Metabolic syndrome and key risk factors

Increase in both CVD and diabetes has been linked to growth in metabolic syndrome and the risk factors associated with it. Metabolic syndrome is a cluster of five risk factors for CVD: central (abdominal) obesity, raised triglycerides, reduced HDL cholesterol, raised blood pressure and raised fasting plasma glucose.

Individuals are considered to have metabolic syndrome when they have central obesity and at least two of the remaining four risk factors. People with metabolic syndrome are twice as likely to die from CVD, and three times as likely to have a heart attack or stroke, as people without the syndrome. They are also five times more likely to develop Type 2 diabetes (IDF, 2006).

It is estimated that 20 to 25 percent of the world's adult population has metabolic syndrome. While each of these factors independently increases the risk of CVD, the clustering that indicates metabolic syndrome appears to confer an additional cardiovascular risk beyond the sum of the individual risk factors (IDF, 2006).

The underlying causes of metabolic syndrome are still not fully understood, but insulin resistance and central obesity are believed to play key roles, in addition to genetics, physical inactivity, aging, a pro-inflammatory state and hormonal changes (IDF, 2006).

Cardiovascular disease has several additional risk factors beyond metabolic syndrome and its contributing risk factors. The Interheart and Interstroke studies focused on CVD specifically and identified nine major risk factors, which are believed to drive 90 percent of the cerebrovascular and AMI burden. These risk factors and the odds an individual will have CVD relative to those without the risk factors are shown in **Table 1** (O'Donnell, et al., 2010; Yusuf, et al., 2004).

Addressing CVD involves tackling the risk factors that drive it (**Table 1**). The most important and broad reaching risk factor is hypertension, which contributes to 45 percent of ischemic heart disease deaths and 51 percent of cerebrovascular disease deaths worldwide (WHO, 2013).

The prevalence rate of hypertension in Africa is 67 percent—the highest in the world (IHME GBD, 2017). Hypertension is primarily driven by age, genetics and certain behavioral factors like poor diet, lack of exercise, obesity, alcohol abuse and psychosocial stress.

Odds ratios[1] of various risk factors and AMI or Stroke (odds ratio greater than one indicates positive association)

Risk Factors	AMI	Stroke
Hypertension	1.9	2.6
Smoking	2.8	2.1
High cholesterol	3.3	1.9
Diabetes	2.4	1.4
Overweight	1.1	1.7
Diet*	0.7 (healthy diet)	1.4 (unhealthy diet)
Excercise*	0.9	0.7
Moderate alcohol*	0.9	0.9
Psychosocial stress	2.7	1.3

Table 1: Various risk factors increase the likelihood of a serious CVD incident. These risk factors are responsible for 90 percent of the CVD burden worldwide. (Source: O'Donnell, et al., 2010; Yusuf, et al., 2004) *These are protective factors, which protect against CVD. Diet was defined as healthy diet for the Interheart study and unhealthy diet in the Interstroke study.

[1]Odds ratio is the likelihood that someone with a particular risk factor (for example, hypertension) will have a particular outcome (such as AMI) relative to the likelihood that someone without that risk factor will have the same outcome.

5. Cancer

Cancer is the second leading cause of death globally. While the rate of new cancer cases in 2018 found in LMICs stands at 60 percent, it is estimated that this figure will increase to 75 percent by 2030 (Globocan, 2012). Much of the increasing rate comes from cancer-causing infections, such as hepatitis and human papilloma virus (HPV). These two infections are already responsible for up to 25 percent of cancer cases in LMICs (Plummer, et al., 2016).

Many cancers are now less deadly, and some are treated almost like a chronic disease. But while less than 50 percent of people diagnosed with cancer in high-income countries die from their disease, 66 percent of their counterparts in LMICs do (Al Sukhun, et al., 2017).

WHO estimates that 70 percent of all deaths from cancer occur in LMICs (WHO, 2018). Two of the biggest killers are cervical and breast cancer, with two out of three breast cancer deaths, and nine out of ten cervical cancer deaths occurring in these countries.

These two types of cancer kill almost three times as many women every year as the complications of pregnancy and childbirth, yet currently receive much less attention (The Lancet, 2016).

Around one third of deaths from cancer are due to the five leading behavioral and dietary risks: high body mass index, low fruit and vegetable intake, lack of physical activity, tobacco use, and alcohol use.

Many cases of cancers, between 30 to 50 percent, are shown to be preventable by avoiding these risk factors and using tried and tested prevention strategies. There are also cost-effective strategies, such as routine human papillomavirus (HPV) vaccination of girls and cervical screening with treatment of pre-cancers that are highly effective in preventing cervical cancer (The Lancet, 2016).

The low survival rates in less developed countries can be explained mainly by the lack of early detection programs, resulting in a high proportion of people presenting with late-stage disease, as well as by the lack of adequate or affordable diagnosis and treatment facilities.

KEY CHALLENGES

In South Asia and sub-Saharan Africa, the drivers of NCD mortality can broadly be classified into two groups (WHO, 2013):

1. Demographic, behavioral and genetic risk factors

2. Challenges in delivery of medical care

1. Demographic, behavioral and genetic risk factors

People are living longer

As mentioned earlier, life expectancy in developing countries has increased substantially over the past several decades through a combination of economic development, successes in combating infectious diseases and improved access to basic healthcare and nutrition.

These gains in life expectancy have resulted in the populations of these countries getting older. By 2025, the number of Africans over the age of 60 years is expected to double (Mbewu, 2009). Older populations are more vulnerable to NCDs like CVD and Type 2 diabetes, as shown in **Exhibit 5**.

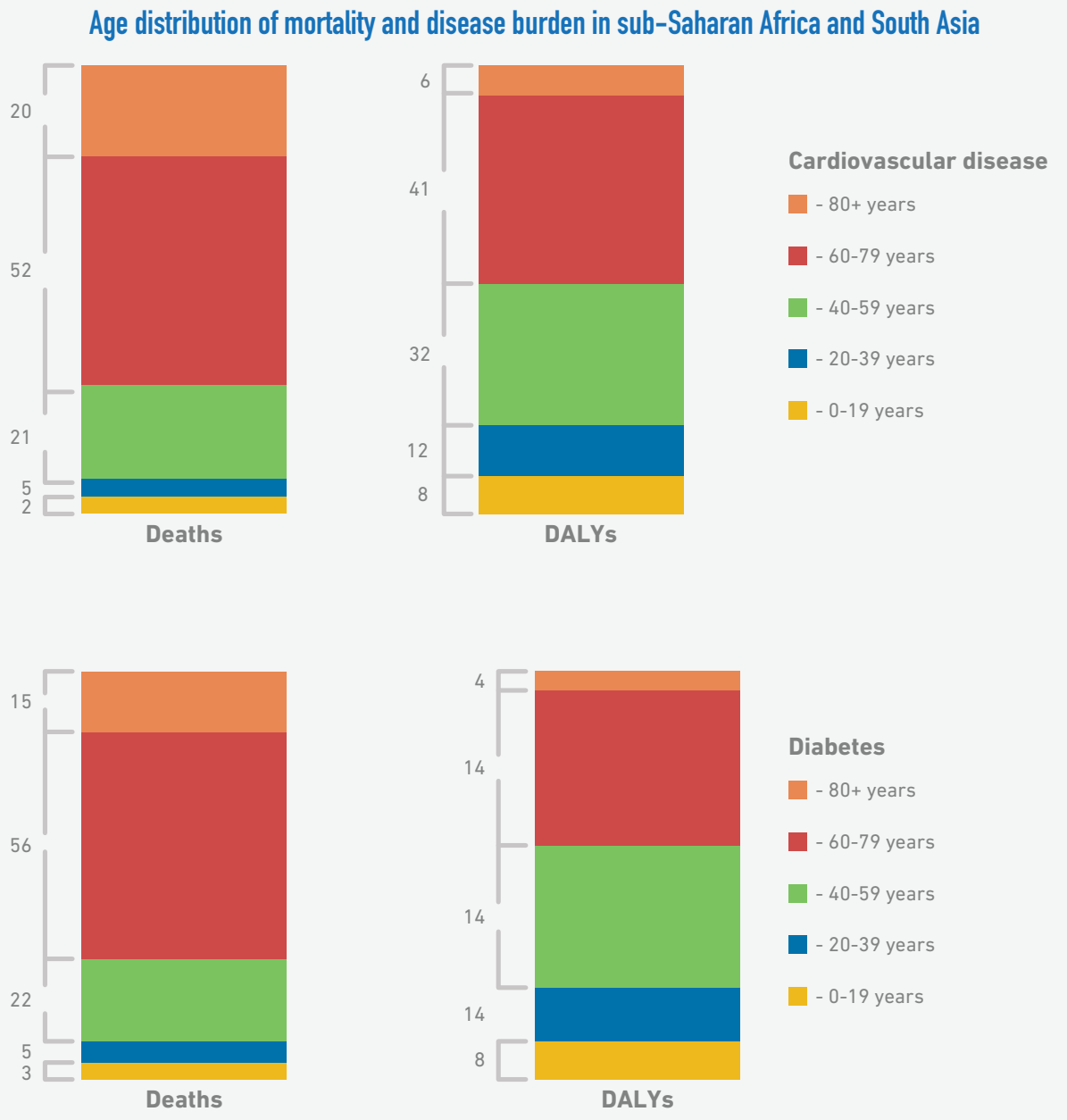


Exhibit 5: As life expectancy increases in developing countries, the population becomes susceptible to a different class of diseases, such as CVD and diabetes, which disproportionately affect older people. (Source: IHME, 2012)

Urbanization and inactivity

There has also been an increase in the rate of urbanization in developing countries, which is linked to an increase in NCDs due to reduced physical activity and less healthy diets. As **Exhibit 6** shows, urban populations tend to have higher rates of diabetes than their rural counterparts. The lower levels of physical activity are also contributing to higher rates of systolic blood pressure, a significant risk factor for CVDs in African countries.

The bulk of the increase in CVD in India occurred in urban settings (Gupta, et al., 2008) and obesity has nearly doubled in urban areas of India between 1991 and 2006 (Cecchini, et al. 2010). In Africa, the highest rates of diabetes are among urban and peri-urban communities in South Africa (Mbanya, et al., 2010).

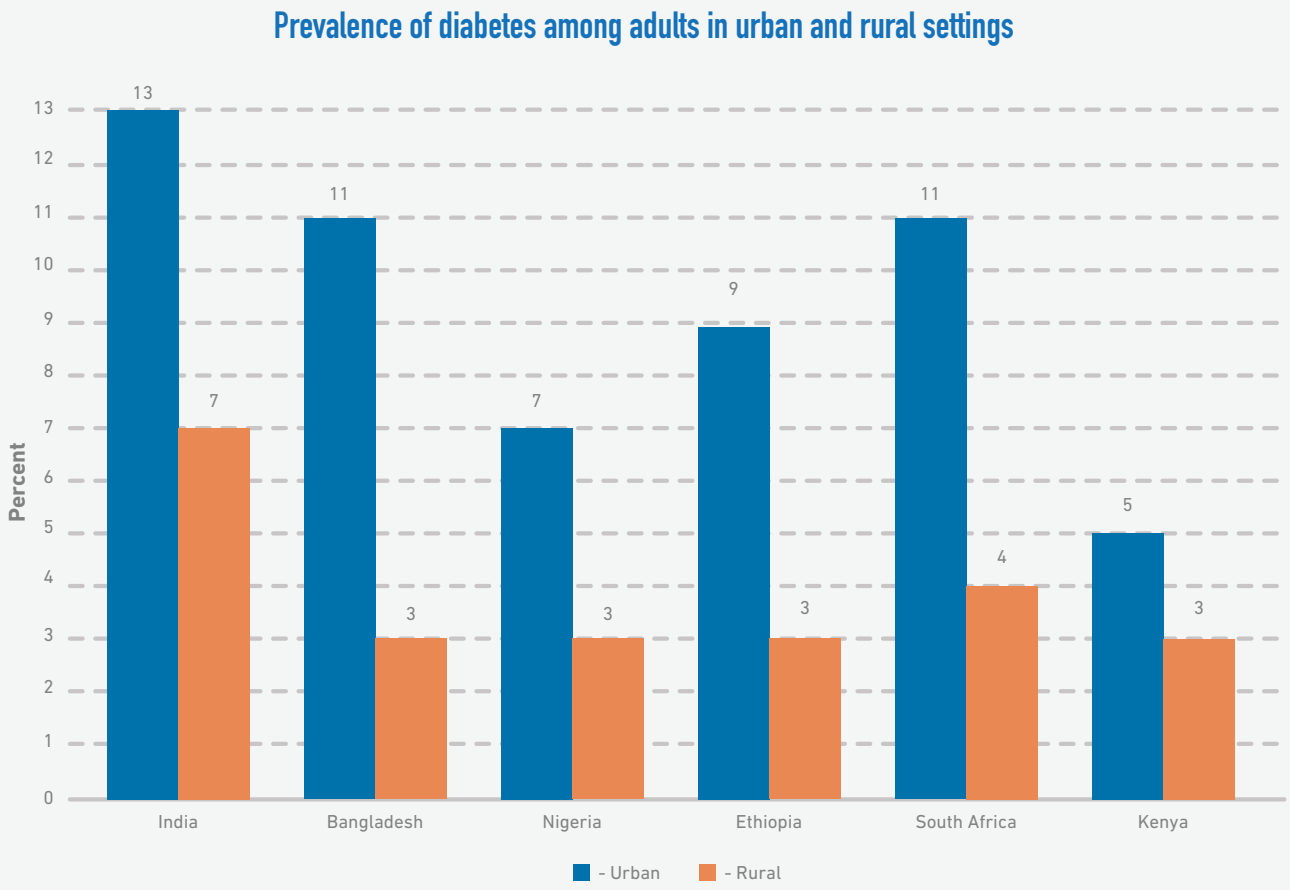


Exhibit 6: Urban populations suffer substantially higher rates of diabetes, likely due to factors such as lower levels of physical activity and higher consumption of processed foods. (Source: IDF, 2013)

Poor diets, high in processed foods

Dietary patterns in developing countries have also been changing (Pingali, 2004). Diets in low-income countries often fail to meet the criteria for healthy eating (classified by the Alternative Healthy Eating Index).

In some countries, such as in India, traditional foods have always been high in refined carbohydrates (for example, white rice), sugar, salt and tropical oils (Gupta, et al., 2011; Hu, 2011) and have been a major contributor to diabetes. Unhealthy diets also contribute to hypertension (Institute of Medicine, 2010; Hu, 2011).

High rates of smoking

Tobacco use is a significant risk factor for heart disease, diabetes and cancer. It is associated with a three-fold increase in the risk of non-fatal AMI (Teo, et al., 2006) and a 45 percent increased risk of diabetes (Hu, 2011). Tobacco use is also found to be responsible for approximately 22 percent of cancer deaths (WHO, 2018). It is estimated that 82 percent of the world's tobacco smokers live in developing countries (Teo, et al., 2006).

High blood pressure

Hypertension is caused by the previously mentioned risk factors, as well as genetics and a high intake of salt.

Globally, it is estimated than 40 percent of adults have raised blood pressure. In Africa, 46 percent of adults have raised blood pressure, higher than any other region in the world (WHO, 2013), which is particularly high considering that the demographic risk factors that generally influence hypertension are less pronounced in sub-Saharan Africa relative to other regions (meaning sub-Saharan Africa has a small middle class, is still largely rural and has lower rates of obesity).

Hypertension is diagnosed easily either through an electronic blood pressure cuff or through an inflatable pressure cuff and a stethoscope. Hypertension is treated with two inexpensive and generic drugs—captopril and nifedipine—which are generally available, although they must be taken on a daily basis.

Diabetes

As mentioned earlier, while diabetes is a condition on its own, it is also a critical risk factor for CVD, with half of all deaths of diabetic individuals being caused by CVD.

Diabetes is diagnosed using a glucometer—a blood glucose measurement device—which costs $10 to $20, although it requires single-use enzymatic strips. These strips are inexpensive to manufacture but are proprietary, which means specific strips work with specific glucometers.

This limits the availability of low-cost strips in developing countries with small existing markets. Treatment of diabetes is challenging relative to high blood pressure. Early stage Type 2 diabetes can often be managed using only oral medication. Once the disease becomes more advanced, however, injectable insulin is required, which is more expensive, challenging to administer, requires a constant supply and has some sensitivity to temperature.

Moreover, patients being treated for both early stage and late stage diabetes need access to a glucometer to monitor their blood glucose on a daily basis.

2. Challenges in diagnosis and delivery of care

Healthcare systems in developing countries were built to primarily treat infectious diseases, where treatment occurs over a fixed period of time or care is focused on certain, distinct life events like birth, early childhood or pregnancy.

Chronic diseases like CVD and diabetes require different approaches to care, particularly mechanisms for broad screening and systems that facilitate disease management and patient compliance with treatment over the course of years, rather than weeks or months. The lack of appropriate delivery systems is compounded by patients' approach to medicine in developing countries, where the concept of lifelong medication is unfamiliar.

Even in the United States, it is estimated that only about a third of individuals with hypertension are managing it effectively. For cancer, challenges range from the lack of oncology specialists, to unavailable and unaffordable diagnostics and treatment. Access to cancer prevention and screening programs and modern treatment facilities, including surgery, radiation therapy, imaging and pathology, is limited. In 2017, only 26 percent of low-income countries reported having pathology services generally available in the public sector (Al Sukhun, et al., 2017). Radiation therapy, the most common way to treat cancer, exists in less than 50 percent of African countries.

Numerous studies have concluded that the main challenge to decreasing cancer mortality has been the lack of will, effort and investment to implement cost-effective interventions.

Many common cancers, for example cervical cancer, are preventable with high-impact interventions that do not require specialist equipment or expertise. Screening programs can increase early detection and diagnosis, which can greatly improve survival rates. Moreover, only one in five LMICs have the necessary data to drive effective cancer policy (WHO, 2018).

Important emerging trends in point-of-care diagnostics involve the development of biosensors, lateral flow tests, and integrated or lab-on-a-chip technologies. A growing number of such devices for diagnosis of cancers and cardiac disease are becoming commercially available (**Table 2**), but have had limited adoption in developing economies.

Data analytics and artificial intelligence, such as image detection methods, are also showing promise in enhancing and reducing the complexity of robust diagnostic methods such as the pap smear (Lehigh University, 2017).

Diagnostics for cancer and cardiac disease

	Company	Product Name	Disease	Analyte/Antigen (Ag)	Required sample	Detection Time (Min)	Sensitivity	Specificity
Cancer	CTK Biotech	On Site PSA Rapid Test	Prostate cancer	Prostate specific antigen (PSA)	60-90 uL of S/P	10	Relative: 100%	Relative: 99%
	Alere	Alere NMP22 BladderChek	Bladder cancer	Nuclear matrix protein (NMP22)	4 drops of Urine	30	99% when combined with cystoscopy	99% NPV along with cystoscopy
	Alere	Clearview iFOBT	Colon cancer	Faecal Occult Blood	Faeces	5	93.60%	99.10%
	Arbor Vita Corp.	OncoE6 Cervical Test	Cervical cancer	E6 oncoproteins	Cervical swab	150	84.6%	98.5%
	Quicking Biotech Co. Ltd	CA125 rapid test kit	Ovarian cancer	CA125 Ag	100 uL of S	10	-	-
	Innovation Biotech	AFP Test	Hepatocellular Cancer	Alpha fetoprotein Ag	S/P	10	25 ng/mL	99%
Cardiac Diseases	LifeSign	StatusFirst CHF NT-proBNP	Congestive Heart Failure	NT-proBNP	3 drops of P	15	20 pg/mL	-
	BTNX Inc.	Rapid Response CK-MB Test	Myocardial infarction (MI)	Creatine kinase MB (CKMB)	WB/S/P	10	5 ng/mL	99.80%
	Boditech Med Inc.	ichroma™ CK-MB Test	Myocardial infarction (MI)	Creatine kinase MB (CKMB)	75 uL of WB/S/P	12	3 ng/mL	-
	Response Biomedical Corp.	RAMP MYOGLOBIN TEST	Acute myocardial infarction (AMI)	Myoglobin	WB	10	2.36 ng/mL	-
	Trinity Biotech	Meritas® Troponin I	Myocardial infarction (MI)	Troponin I	200 uL of WB/P	15	0.036 ng/mL	-
	BRNX Inc.	RAPID RESPONSE D-DIMER TEST	Venous Thromboembolism (VTE)	D-Dimer	WB/P	10	500 ng/mL	-
	American Screening Corp.	Instant-View Troponin I	Acute myocardial infarction (AMI)	Troponin I	2-- uL of WB/S	10-20	-	-

WB - Whole Blood S - Serum P - Plasma CSG - Cerebrospinal fluid

Table 2: Overview of commercially available lateral flow test strips for diagnosis of cancers and cardiac disease. (Source: Sharma, et al., 2015)

SCIENTIFIC AND TECHNOLOGICAL BREAKTHROUGHS

CVD, diabetes and cancer are major public health challenges that require systemic interventions, such as policy and healthcare system strengthening. While technology can support this, lack of technology is not the key bottleneck preventing a reduction in NCD mortality.

The decrease in CVD mortality in developed countries can be linked with three pivotal aspects: increased awareness of CVD and its risk factors, timely diagnosis and access to treatment. Reducing risk factors requires nutritional awareness and access to healthy foods, environments that enable physical activity, and actively discouraging the use of harmful substances like tobacco.

Such national level behavior change interventions rely largely on government policy and implicitly demand economic development. Developing the medical system to provide more appropriate diagnosis and care for patients is also critical. Similarly, increased awareness of risk factors, plus many cost-effective, non-technology dependent interventions, can increase early detection and diagnosis of common cancers.

Implementing these changes in developing countries will require national level awareness campaigns about the risk factors and signs of CVD and diabetes, inclusion of blood pressure and glucose level screening in routine medical care, and increased distribution of medication to treat hypertension.

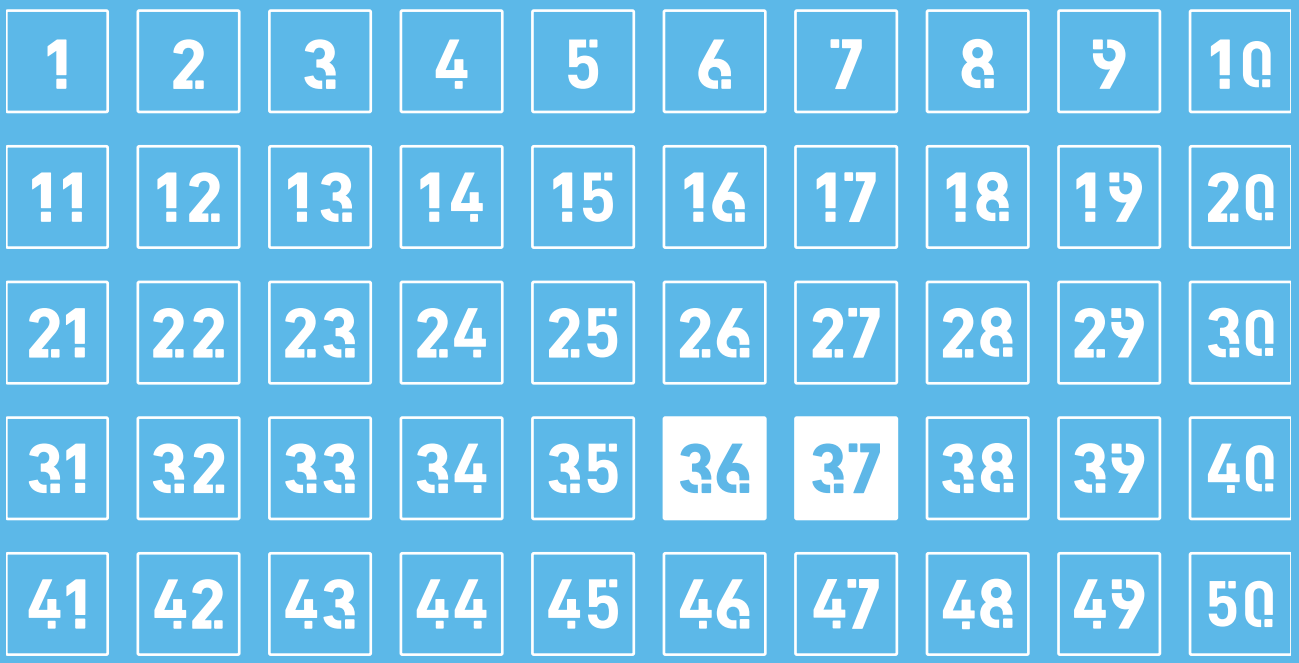
Additional interventions could include increased distribution of oral medication for those with early stage diabetes and development of simple tracking systems to ensure compliance with treatment. In the longer term, insulin should be available to all diabetics who require it, although the logistical and cost challenges around daily use of insulin make this unlikely to be a wide-scale possibility in the near future.

A few technologies can help with behavior change in areas like exercise and diet, and with the treatment of diabetes-related complications such as foot ulcers and eye disease. Treatment for foot ulcers leading to amputation is an area that appears to have some opportunity for technological innovation, particularly in devices that can help treat peripheral vascular disease.

Over the past decade, numerous scientific advancements have improved our capacity for identification, diagnosis and treatment of non-communicable diseases.

These include improved biochemical assays for rapid diagnosis, non-invasive testing methods, improved clinical hardware and software, and artificial intelligence-based therapeutics. We have identified two critical breakthroughs that build on these advances, to significantly reduce NCD burden if implemented at scale.

Breakthroughs:



36 Affordable, home-use point-of-care diagnostics suite (blood, urine, vitals) for the common NCDs

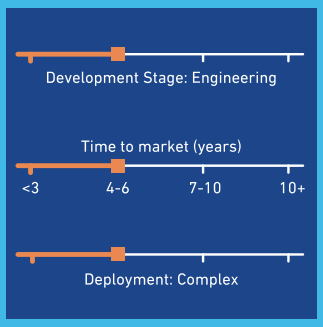
Point-of-care testing is essential for the rapid detection of diseases at the point of care, which facilitates faster disease diagnosis, reduces costs and improves outcomes. Moreover, home-use tests are increasingly designed to be simple to administer and interpret, thus overcoming the challenge of paucity of trained personnel. In the last few years, there has been a move towards integrating tests with mobile applications due to ease of data capture, better user experience and widespread adoption of smartphones. These include both standalone mobile health applications and more integrated testing applications.

The latest improvements in point-of-care diagnostics are a result of continuous developments in biosensors, lateral flow tests, as well as integrated or lab-on-a-chip technologies. These include tests for diabetes, cardiac conditions and cancer. Many of these technologies have already been developed and commercialized in developed economies but are yet to find adoption and successful commercial models for widespread adoption in developing economics.

For example, testing of EG Antigen for cervical cancer, developed by Arbor Vita is currently available only in the United States. In 2018, the US Food and Drug Administration approved the use of in-home genetic tests for breast cancer developed by genetic testing company 23andMe. Molecular diagnostics offer great promise but are less available in low-resource settings.

Data analytics and artificial intelligence, such as image detection methods, are also showing promise in enhancing and reducing the complexity of robust diagnostic methods such as the pap smear, and can help scale up proven diagnosis methods into low-resource setting. Such technologies can increasingly be deployed in home-based and point-of-care settings, due to growing capacity for data networking.

Current State



Associated 50BT Chapters

SDG Alignment

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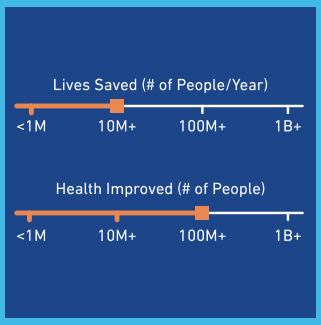
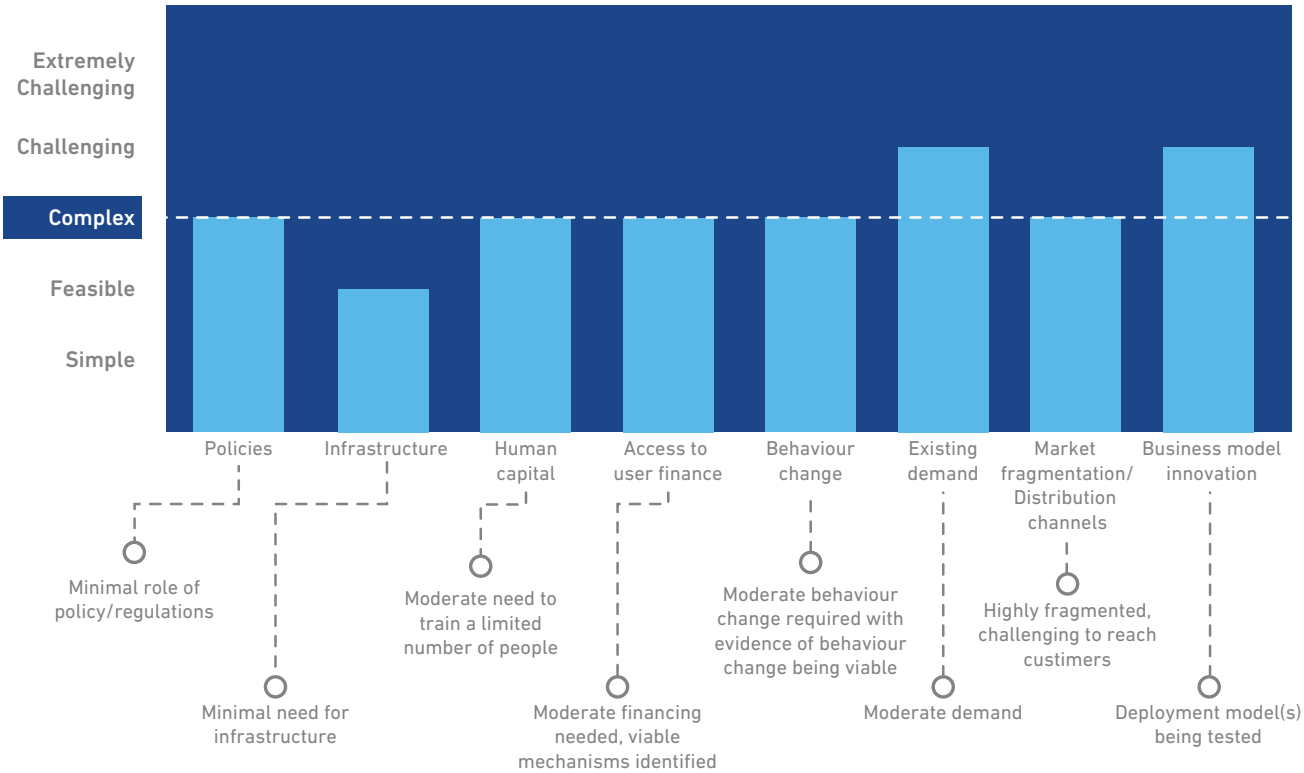


Commercial Attractiveness

Widespread deployment of home-use point-of-care diagnostics devices for common NCDs will depend particularly on consumer demand for such service. Business models will need to focus on enhancing demand for the product through motivating customer self-interest.

Initial products with limited capabilities are currently on the market, and more sophisticated devices with improved performance will likely appear in the next 5 years. The difficulty of deployment is estimated to be COMPLEX.

Breakthrough 36: Difficulty of deployment

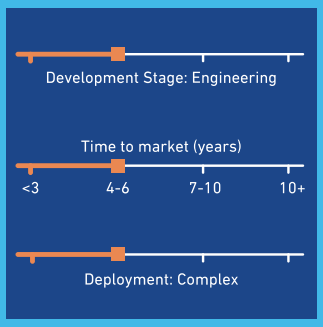


37 Affordable wearable technology with broader functionality for patient adherence and monitoring of health status

Wearable technology (or simply, wearables) refers to a broad category of devices that can be integrated into day-to-day clothing or other accessories to capture health data and provide information on the user's personal fitness and activity. While a typical wearable is a fitness tracker that can be worn on the wrist, today there is a much wider array of devices, including implantable devices and an ingestible pill (recently approved by the US FDA) that can track specific markers of physical and mental health and adherence to drug regimens.

Today's common wearables (such as the Fitbit) track heart rate, blood pressure, breathing patterns, physical activity and sleep levels. However, the next generation of devices (still in prototype stage) aim to collect data on blood glucose, indicators of cardiovascular disease, and even cancer. For example, Apple recently released the KardiaBand, an Apple Watch accessory with an inbuilt EKG to detect irregular heartbeat and share the information with caregivers.

Current State



Associated 50BT Chapters

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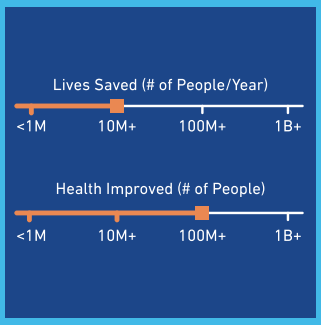
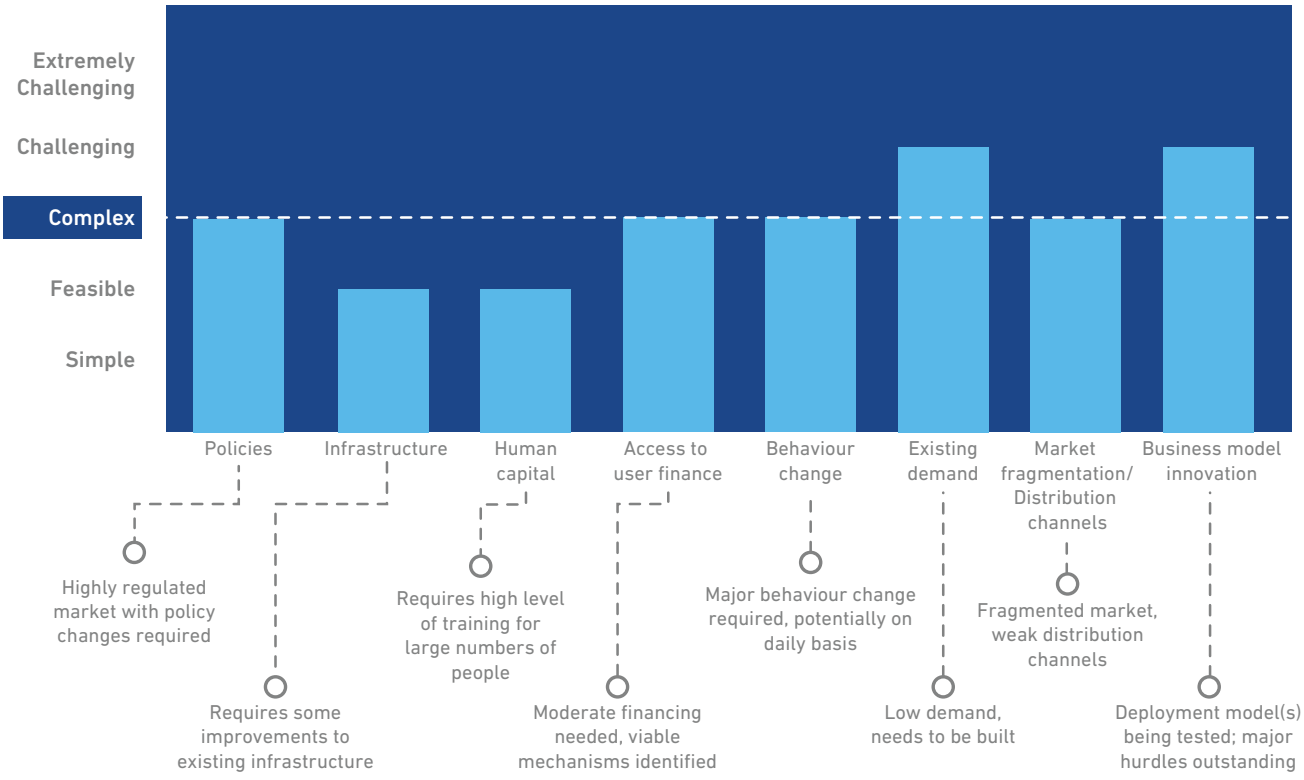


Commercial Attractiveness

Early indications are that such wearables, especially if combined with game-based incentives, can increase positive health-improving behaviors (Shmerling, 2017). While it is too early to understand the long-term impact of such technologies, an increasing number of health insurance companies and employers who provide health insurance are encouraging their use.

Breakthrough 37: Difficulty of deployment



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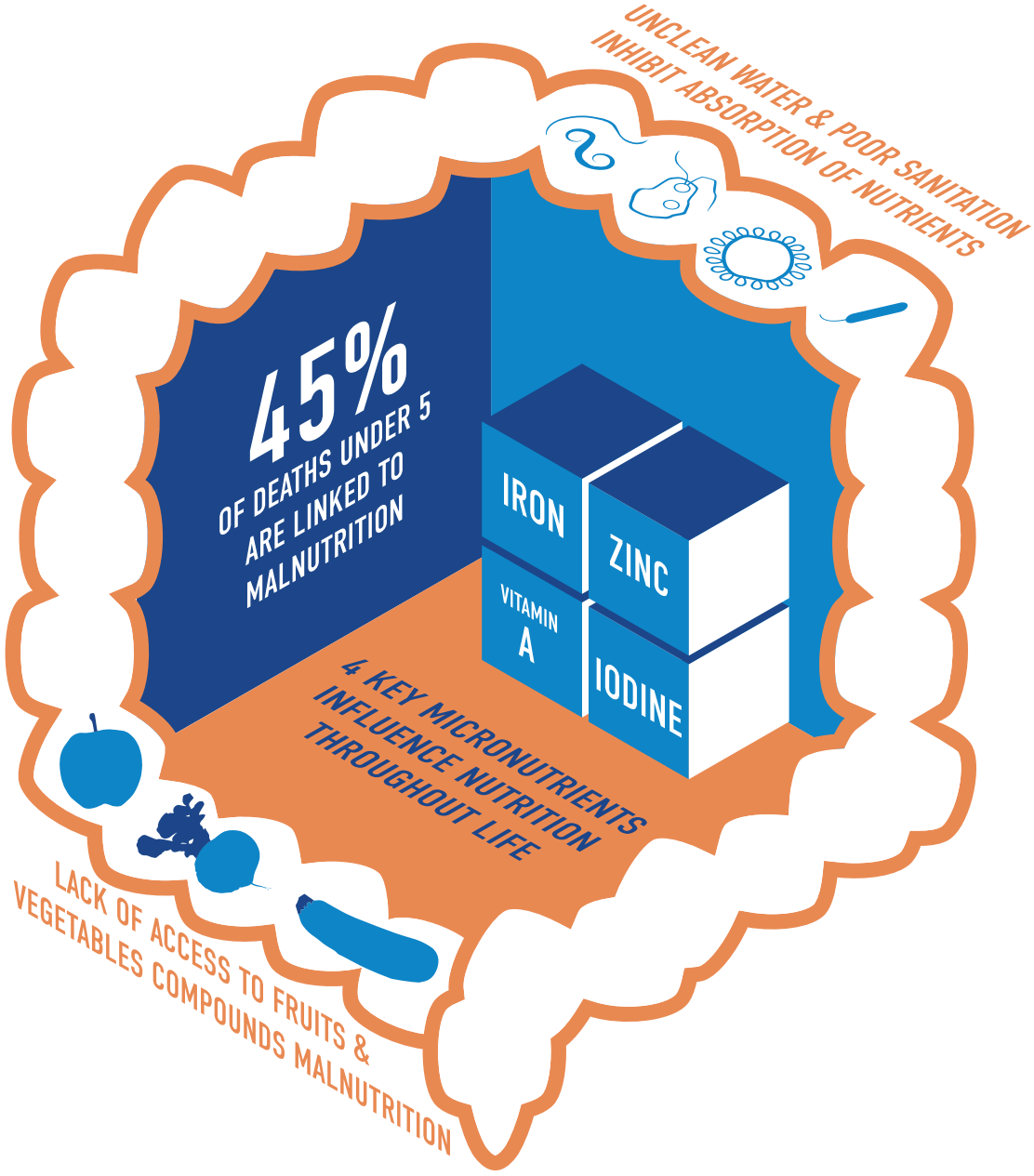


NUTRITIONAL DEFICIENCIES

INTRODUCTION

Malnutrition is linked to 45 percent of deaths among children under age 5, and is responsible for the stunting of 155 million children across the world (WHO, 2018).

Factors influencing nutrition, especially for children and women, are often complex, rooted in systemic and social issues and extend well beyond simply satisfying caloric needs.

There are two primary lenses through which nutrition is viewed. The first is physical growth in early life, specifically in the first 1,000 days, stretching from conception to a child's second birthday. Growth during this crucial period is a strong predictor of adult height, as well as learning and earning potential.

Children who are undernourished (and become stunted) are significantly more likely to experience disease. Linear growth requires a diverse diet including sufficient caloric intake, proteins, fats and micronutrients, absence of infectious disease (particularly from diarrheal pathogens) and appropriate feeding and care.

The second lens for viewing nutrition is deficiency of key micronutrients, particularly iron, vitamin A, zinc and iodine. These critical micronutrients are linked closely to cognitive development, anemia and the ability of a child to fight off infections. Micronutrients also play an important role in overall health throughout life.

We have identified two breakthrough technologies, focusing on the preservation of food, that can significantly improve nutritional outcomes for both children and adults.

- Breakthrough 12. Affordable (less than $50) off-grid refrigeration for smallholder farmers and small agribusinesses
- Breakthrough 13. Commercial scale, affordable and energy efficient refrigeration/cold-chain systems for agribusinesses and transport of food

In addition, three other supply chain innovations will also be helpful:

- Improved processing technologies to preserve food life and reduce degradation of nutritional content
- Improved storage technologies for grains and pulses to reduce development of mycotoxins
- Diagnostics to determine nutritional content and bioavailability of nutrients in foods

Nutritional deficiencies due to suboptimal intake of carbohydrates, fats, proteins and micronutrients like iron, zinc, folic acid, vitamin A and iodine, are among the most significant risk factors for death and disability in children in developing countries. Beyond supporting just health, good nutrition is vital for cognitive development and correlates with educational performance. Nutritional deficiencies underlie 45 percent of all deaths in children under 5 years of age, resulting in 2.4 million deaths annually (WHO, 2018).

CORE FACTS AND ANALYSIS

Nutrition is a broad area but is generally considered from the perspective of anthropometry or physical growth in early life, focusing on the nutritional needs to support normal and healthy growth in children. Growth is measured using physical metrics including weight for age, height for age and weight for height at birth and throughout early childhood. In the past, the global burden of undernutrition was principally measured by tracking the prevalence of underweight, which refers to children with a weight-for-age two standard deviations below a population median.

More recently, with the rapid emergence of overweight and obesity as global health concerns, the nutrition community has begun tracking prevalence of stunting—low height for age—as a superior indicator of nutrition and health. Whereas weight for age can be optimized through the provision of energy alone, through carbohydrates and fats, linear growth requires a high-quality diet with protein and growth promoting nutrients, as well as absence of inflammation, infection and disease.

In addition to supporting growth, nutrition influences susceptibility to infection in children; 57 percent of the disease burden from LRIs and 55 percent of the disease burden from diarrheal disease are attributable to malnutrition. Other infections where malnutrition is a major underlying factor include measles and neonatal disorders (Global Burden of Disease, 2017).

1. Nutrition and growth in early life

Growth in early childhood, including height attained by the age of 24 to 36 months, is a strong predictor of adult height as well as future learning and earning potential. This has led to a focus on the first 1,000 days stretching from conception to a child's second birthday. Children who are stunted at the age of 2 often remain stunted throughout life.

Globally, 155 million children under age 5 suffer from stunting and 52 million suffer from wasting (WHO, 2018). Wasting is an acute condition that requires medical intervention and is a challenge particularly in areas affected by drought, disaster and conflict. Preventing stunting in the first 1,000 days of life is considered critical for a child's health and survival.

Maternal health and nutrition during and before pregnancy

The first factor driving a child's development is the health of the mother entering, and during, pregnancy. The mother's nutrition is important for assuring healthy fetal growth, a term delivery, and for providing adequate nutrition during the even more nutritionally demanding process of lactation. Mothers who are undernourished are more likely to give birth to low birthweight and small for gestational age infants.

These infants are at higher risk of illness, poor growth or future stunting and early mortality. Furthermore, while undernourished mothers are physiologically capable of producing a sufficient quantity of milk to feed their infants (breast milk quantity is a function of suckling frequency), the nutritional quality of milk, including fat content and nutrients like vitamin A, depends on diet.

The health and nutrition of the mother before pregnancy are also important, in part because adequate nutrition is needed for early first trimester cell proliferation and brain and organ development of the fetus. Pre-conception health, however, particularly among adolescent girls, is considered challenging to address.

As a result, it has seen little focus compared with maternal health during pregnancy. That said, there are a number of straightforward interventions that can address pre-conception nutrition, especially among adolescent girls, such as screening and treatment for anemia.

Maternal health and nutrition during breastfeeding
The quality and energy density of breast milk is directly linked to a mother's diet during the breastfeeding period. When a mother's milk is low in fat (energy), the newborn must suckle more to receive sufficient nutrients to support optimal growth. This can be physically difficult for low birthweight babies, further contributing to faltering growth.

Childhood nutrition and health during breastfeeding and weaning

Exclusive breastfeeding is recommended for infants for the first six months of life. Past six months, babies should be given a combination of breast milk and complementary foods.

The caloric and nutrient density and diversity of these foods are major factors contributing to adequate early growth. Having sufficient energy is important to maintain basal metabolic function as well as to support healthy growth, but energy (calories) alone is not sufficient to ensure that bone and muscles develop and grow properly.

Healthy growth, in height and lean body mass, requires a diverse and nutritious diet and absence of disease. Any infection or inflammation either diverts nutrients away from growth to mount an immune response, or wastes them due to poor absorption and inefficient utilization.

Hygiene and sanitation are important for preventing diarrhea and subclinical inflammatory processes. There is also evidence that other environmental conditions, including stress, can interfere with nutrient use and healthy growth.

2. Four key micronutrients influence nutrition throughout life

The second lens for characterizing nutrition is 'hidden hunger' or micronutrient deficiencies. In this context, four micronutrients are particularly critical.

Iron

Anemia is a condition when the body does not have sufficient red blood cells. While it can be caused by many conditions, such as blood loss or hereditary conditions, the primary driver in developing countries is iron deficiency.

Iron is required to produce hemoglobin, the protein that carries oxygen in red blood cells. When there is insufficient intake of iron, usually found in red meat and leafy green vegetables, the body cannot produce enough red blood cells.

Globally, anemia affects 2.6 billion people and iron deficiency is the leading cause (Lopez, et al., 2015). Anemia affects 43 percent of children, 29 percent of non-pregnant women and 38 percent of pregnant women (Stevens, et al., 2013).

Vitamin A and zinc

Found in a mix of meats, fruits and vegetables, vitamin A and zinc serve a range of critical needs like fighting infections, healing wounds and tissue repair. Without an adequate intake of these nutrients, children are more susceptible to infectious diseases.

Around the world, 33 percent of preschool age children— 190 million—and 15 percent of all pregnant or lactating women suffer from vitamin A deficiency (UNICEF, 2017). One study found that Vitamin A supplementation in infants caused a 14 percent reduction in mortality within the first six months of life (Haider & Bhutta, 2011). A similar analysis showed that zinc supplementation reduced incidence of diarrhea by 13 percent and reduced pneumonia morbidity by 19 percent (Yakoob, et al., 2011).

Iodine

Almost 2 billion individuals around the world suffer from insufficient iodine intake, and 19 countries are still classified with insufficient iodine intake (Global Nutrition Report, 2018). This leads to cretinism and other forms of cognitive developmental delays. Iodine deficiency is considered the single largest preventable cause of mental retardation (UNICEF, 2008).

The Global Burden of Disease models show that iron-deficiency anemia and protein-energy malnutrition (or underweight, as it is more commonly known) together account for 85 percent of the direct disease burden from nutritional deficiencies, as well as almost 100 percent of fatalities caused by nutritional deficiency (**Exhibit 1**) (IHME GBD, 2017). **Exhibit 2** shows that malnutrition prevalence in rural communities is higher than that in urban areas in South Asia, Africa and Latin America & the Caribbean.

Between 1990 and 2010, the disease burden from being underweight has decreased significantly, but the same is not true for anemia. However, data from the 2017 Global Burden of Disease shows significant decrease in all forms of nutritional deficiencies since 2010 (**Exhibit 3**). Geospatial analysis shows that the prevalence of stunting in Africa has decreased moderately from 2000 to 2015 (Global Nutrition Report, 2018). Although the DALYs rate of anemia has decreased by 25 percent, the increase in population has kept overall DALYs essentially constant (IHME GBD, 2012).

Conditions that drive disease burden and deaths due to nutritional deficiencies

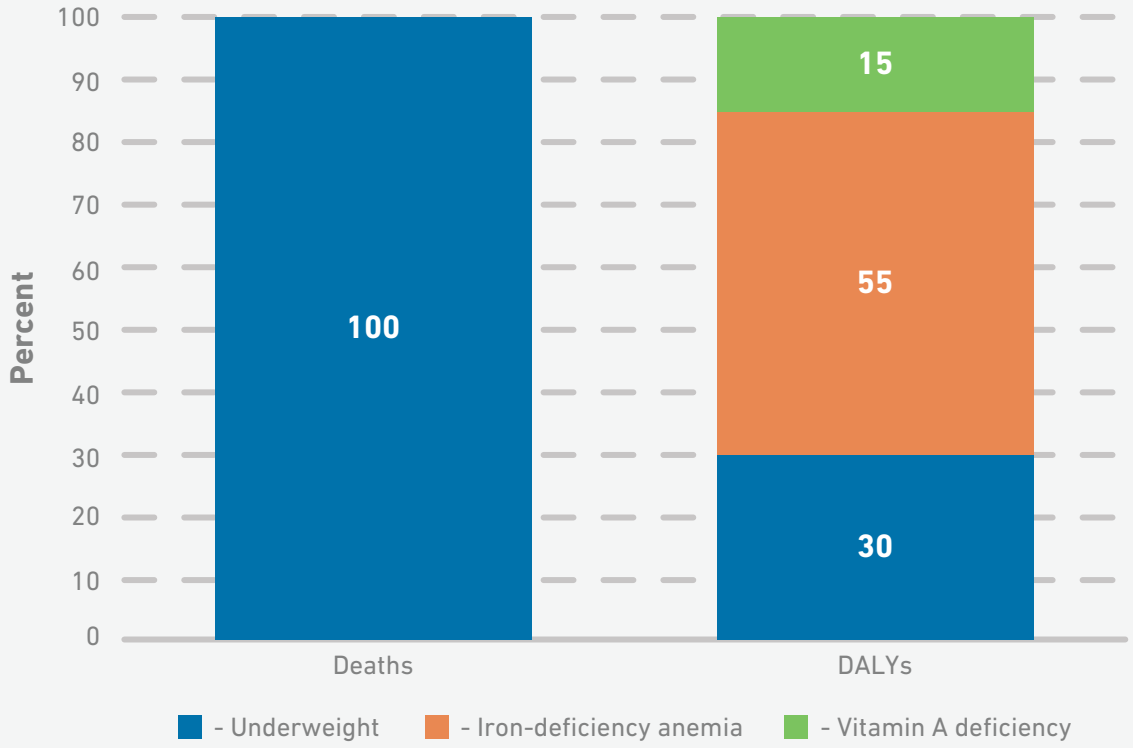


Exhibit 1: Two nutritional conditions—iron-deficiency anemia and underweight—account for the vast majority of DALYs and deaths caused by nutritional deficiency. (Source: IHME GBD, 2017)

Prevalence of stunting and wasting in developing countries

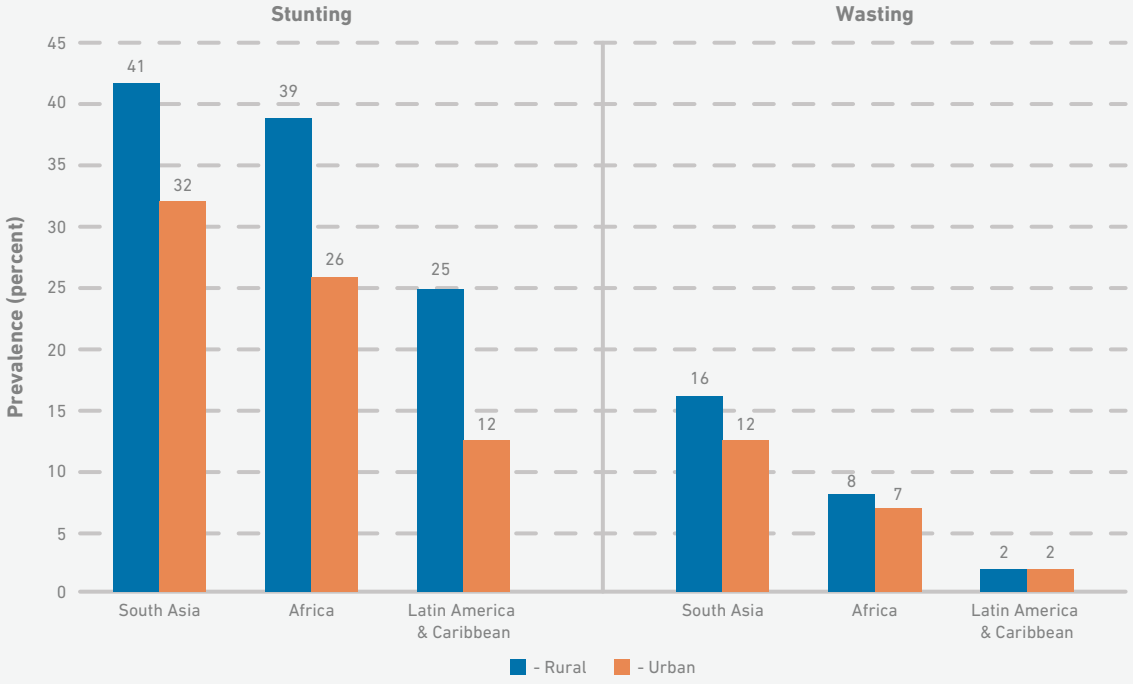


Exhibit 2: Childhood malnutrition is somewhat more prevalent in rural areas of developing countries, compared to urban areas. (Source: 2013 data from Global Nutrition Report, 2018)

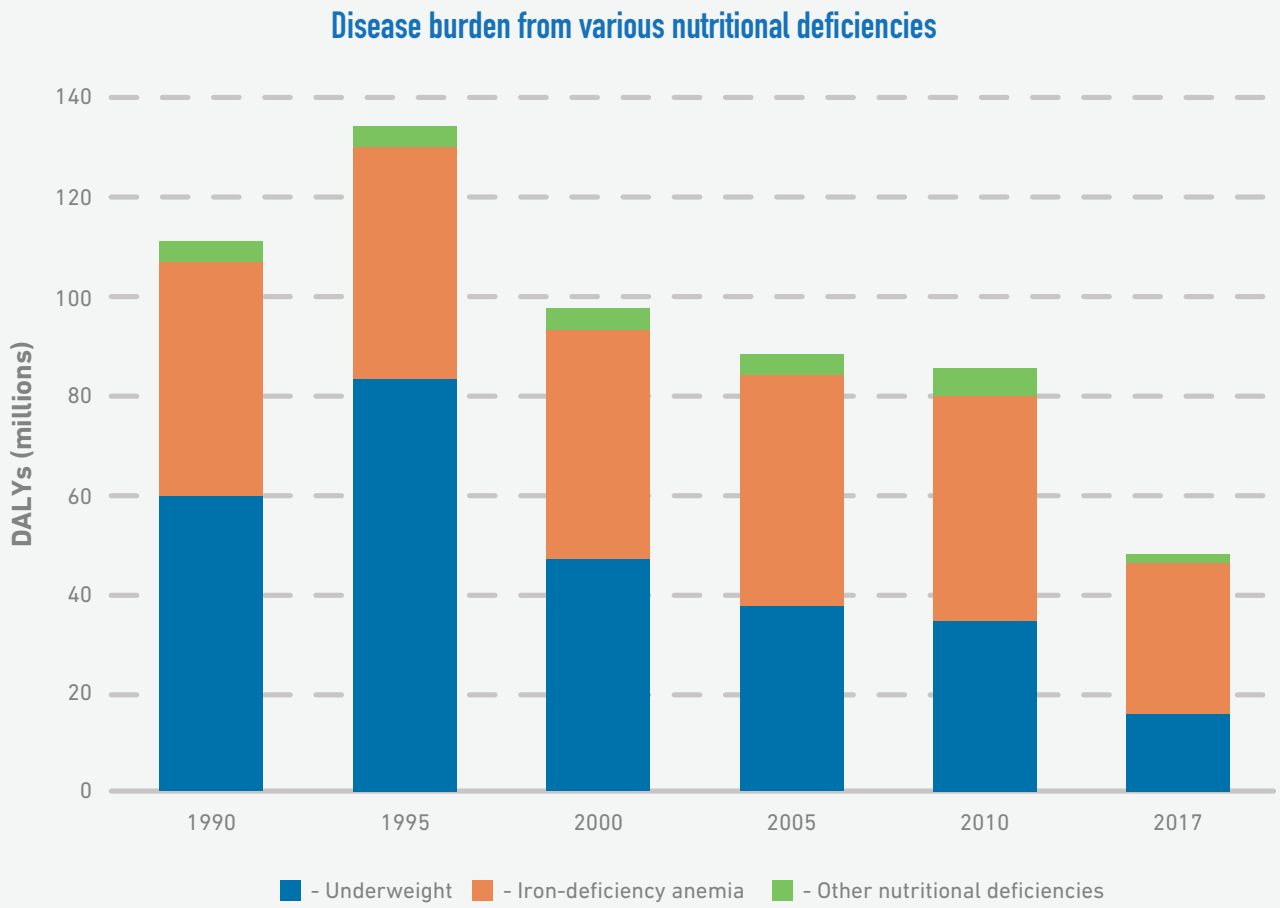


Exhibit 3: The disease burden of being underweight has decreased significantly in recent decades, while iron-deficiency anemia has been more persistent. (Source: IHME 2012; IHME GBD, 2017)

In addition to the effects of nutritional deficiencies, the risk of over-nutrition, which leads to obesity and related non-communicable diseases (NCDs) has garnered increasing attention in the last few years. Unhealthy diets comprising an excess of sugar or fat, and too few fruits and vegetables, combined with inactive lifestyles are leading to a dramatic increase in diabetes, cardiovascular disease and obesity.

These NCDs currently account for 41 million deaths globally and 32 million deaths in low- and middle-income countries (WHO, 2018; Global Nutrition Report, 2018). These figures are expected to grow. We address nutrition-related NCDs in a separate section on cardiovascular disease and diabetes, rather than this one on core nutritional deficiencies.

KEY CHALLENGES

There are four broad challenges in addressing nutritional deficiencies, three of which relate directly to early childhood growth while one pertains specifically to the problem of iron-deficiency anemia.

These challenges extend well beyond simple dietary intake (although diet is a crucial challenge), to also include the heath and care of young children.

1. Lack of rich, diverse diets, early in life

Newborns in developing countries often receive poor diets beginning with suboptimal breastfeeding and continuing through the first two years of life.

Breastfeeding

The WHO recommends, "immediate breastfeeding within the first hour of life, exclusive breastfeeding up to six months of age, with continued breastfeeding along with appropriate complementary foods up to two years of age or beyond." Breast milk provides key nutrients for infants, as well as antibodies that protect against infections like diarrhea and pneumonia (Fleming & de Silva, 2009).

On the other hand, substitutes like infant formula and other foods do not contain the antibodies found in breast milk, are expensive, and can lead to diarrheal disease when such food is prepared with unsafe water or in unsterilized feeding bottles.

Still, due to cultural factors, lack of knowledge and support, and other impediments, globally less than 40 percent of infants under the age of six months are exclusively breastfed, with only 36 percent of infants in the United States breastfed at 12 months (WHO, 2013; CDC, 2018).

Furthermore, the nutritional quality of breast milk is linked to the nutritional intake of the mother, and mothers who are undernourished or are not eating a diverse and nutritious diet produce lower nutritional quality breast milk for their babies.

Weaning

The nutritional content of complementary foods is critical as the infant weans off breast milk. Due to an infant's small stomach, it is important that complementary foods be high in nutritional value to support growth. However, in many countries infants are given thin cereal-based porridges that lack nutritional diversity.

Childhood and beyond

Nutritional deficiencies continue as a health concern well past the first 1,000 days. There are several additional diet-related challenges that affect children, adolescents and adults of all ages in developing countries.

- Lack of access to fruits and vegetables, which provide critical nutrients that are not found in sufficient quantities in cereals. Fruits and vegetables are often more challenging to grow than cereals and available easily only during harvest times; they are more sensitive to stresses and water availability, and once harvested have a limited shelf life in the absence of appropriate cooling or refrigeration. These foods are also more expensive than cereals, thus reducing access for low-income families.
- Inadequate access to, or a tradition of not feeding young children, animal source foods like meat, poultry, eggs and dairy that are rich in easily-absorbed iron, is a major driver of iron deficiency.
- Lack of awareness about the importance of dietary diversity—and what it entails—leads to infants and young children primarily being fed grain-based foods.
- The absence of agricultural cold chains and in-home refrigeration limits access to horticulture products and the ability to store perishables.
- Increasing abundance of low-priced, highly processed foods that are high in fat and sugar particularly in urban settings.
- Increasing abundance, and in turn consumption, of low priced, highly processed foods (high in fat and sugar) in place of healthier alternatives, particularly in urban areas, can lead to conditions like obesity.

2. Unclean water, poor sanitation and hygiene conditions inhibit absorption of nutrients

Diarrheal disease and intestinal nematode infections lead to reduced nutrient absorption and can cause long-term intestinal damage, inhibiting nutrient absorption long after the infection has cleared (Brown, et al., 2011).

Diarrheal disease significantly increases the risk of stunting, especially before the age of 24 months (Checkler, et al., 2008). Fecal pathogens also cause environmental enteropathy, which can lead to long-term reduction in nutrient absorption even in the absence of frequent diarrheal episodes (Brown, et al., 2013).

Young children are extremely vulnerable to diarrheal disease and gut enteropathy. Other infections and inflammation can also affect nutrition by diverting nutrients away from growth or immune response. These concerns have been discussed in greater detail in the chapter on diarrheal disease.

3. Improper care of infants

Core to the health of a child is the care he or she receives from the mother. Key behaviors related to nutrition include feeding practices and care seeking practices. The former entails knowledge of what comprises a rich and diverse diet and how to prepare and store complementary foods while the latter entails recognizing signs of sickness and seeking care when necessary.

Often, cultural practices can be at odds with what is best for the child. For instance, taboos exist in some cultures against bringing an infant out of the house and this limits access to care if the infant is sick. Proper care of the infant is increasingly being linked to a mother's education, her own self-efficacy, self-confidence and control over the family's resources. Many of these issues are believed to be more severe in urban settings where support networks are often weaker.

4. Intestinal nematode infections, and to a lesser extent, malaria infections (for anemia specifically)

Chronic blood loss resulting from parasitic infections, primarily hookworm, trematodes and whipworm are a major cause of anemia in children. Although anemia caused by blood loss is not iron-deficiency anemia explicitly, it exacerbates the effects of iron deficiency.

Both conditions, nematode infection and iron-deficiency anemia, are very common and tend to occur together. Smaller-scale studies have found that, particularly in areas with a high hookworm burden, deworming can lead to reduced anemia (Smith & Brooker, 2010).

However, the effectiveness of large-scale deworming programs is a controversial topic and the subject of significant debate. Malaria too can contribute to iron-deficiency anemia (Verhoef & West, 2003).

SCIENTIFIC AND TECHNOLOGICAL BREAKTHROUGHS

As the above discussion suggests, nutritional deficiency is driven by systemic issues tied to broader food production and food infrastructure, economic development, education, gender dynamics and the extent to which women have control over a family's resources and food.

Programs like deworming, free school lunches for low-income students and conditional cash transfers can serve as effective safety nets for vulnerable populations, but these are likely not a sustainable substitute for deeper systemic change.

We have identified two breakthrough technologies, focusing on the preservation of food, that can significantly improve nutritional outcomes for both children and adults. In addition, three other supply chain innovations will also be helpful.

Breakthroughs:

1	2	3	4	5	6	7	8	9	10
11	12	13	14	15	16	17	18	19	20
21	22	23	24	25	26	27	28	29	30
31	32	33	34	35	36	37	38	39	40
41	42	43	44	45	46	47	48	49	50

12. Affordable (less than $50) off-grid refrigeration for smallholder farmers and small agribusinesses

The absence of affordable refrigeration and electricity severely limits the ability of smallholder farmers to produce, preserve and sell perishable commodities like vegetables, fruits, meat and dairy. Such products are highly sensitive to temperature, and the lack of refrigeration dramatically reduces their shelf life, especially in tropical climates.

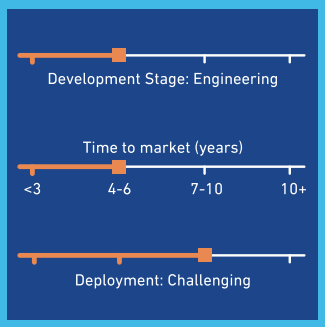
While there are some inexpensive refrigerators available in emerging markets like India and China, they still cost more than $100, need reliable electricity and are difficult to repair once damaged. A new kind of refrigerator that costs less than $50 and can run on solar power will help smallholder farmers provide better nutrition for their families, and take high-value commodities to market, thereby increasing their incomes.

There is a recent resurgence of interest of very affordable age-old traditional cooling technologies (like clay pots). While this showcases the potential demand for an affordable and durable solution, traditional options like clay are subject to biological contamination and difficult to clean.

Moreover, as agricultural systems advance, there will be greater need for commodity-specific temperature control. Furthermore, it is difficult to see traditional cooling solutions leading to modern and profitable agricultural value chains.

To serve the needs of rural, low-income farmers, refrigerators need to be operable off-grid (like solar-powered), considerably less expensive than the current $100 range and easy to repair. Such technologies appear to be on the horizon.

Current State



Associated 50BT Chapters

SDG Alignment

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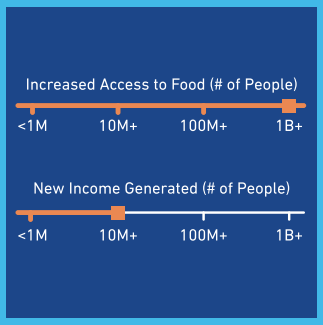


Commercial Attractiveness

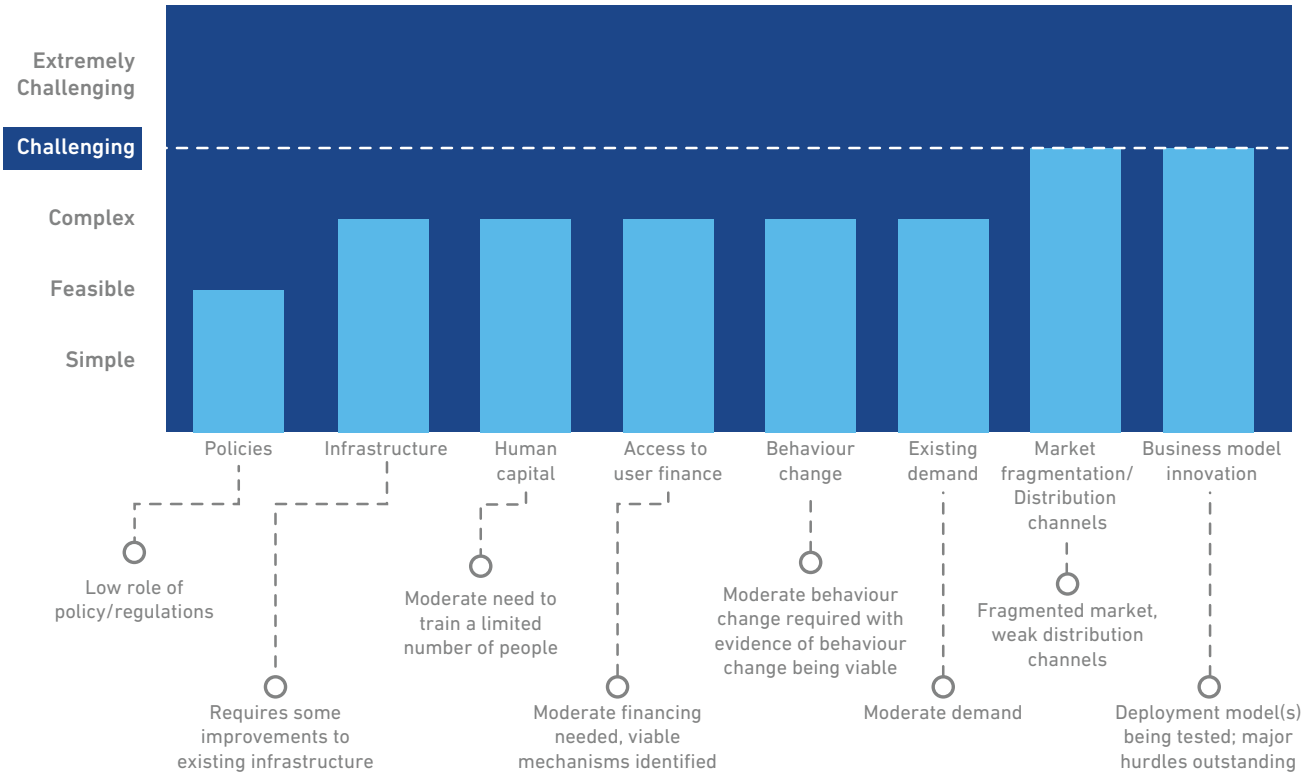
A new generation of refrigerators using thermoelectric technology is beginning to reach the market, supplementing existing vapor-compression models.

Given the broad demand for refrigeration there is reason to believe that an affordable product will gradually reach a critical mass of smallholder farmers—notwithstanding the usual problems of market fragmentation and distribution.

Based on the above, it is likely only a matter of four to six years before low cost refrigerators become practical for rural farmers.

Despite the need and expected demand, such a technology will face considerable barriers to deployment due to the fragmented nature of the market, the absence of a value chain for distribution and maintenance and the need for financing for farmers. Hence, deployment will be CHALLENGING.

Breakthrough 12: Difficulty of deployment



13 Commercial scale, affordable and energy efficient refrigeration/ cold-chain systems for agribusinesses and transport of food

The ability to transport food to markets while preserving freshness will not only reduce post-harvest losses, but also create new value propositions for smallholder farmers.

The absence of such cold chain infrastructure is one of the factors limiting access to market for higher-value produce (for example, horticulture; and as the Livestock section discusses, meat and dairy). The lack of refrigeration also reduces everyday access to a diverse base of nutrients for children and the population in general.

Refrigerated trucks available on the market today cost tens of thousands of dollars, require diesel and are built for smooth roads. To be useful to dealers and agribusiness entrepreneurs who serve smallholder farmers in remote areas, refrigerated storage chambers and transport vehicles will have to be robust and cost significantly less than $5,000.

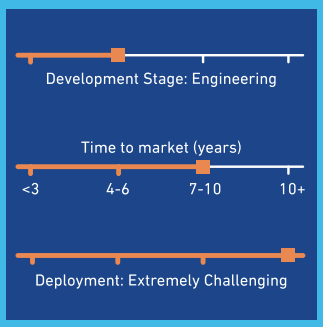
While advances in stationary refrigeration technologies can also help advance mobile refrigeration, there are a number of significant differences.

First, stationary refrigerators normally operate indoors, whereas transport refrigerators will have to operate outdoors, under much warmer ambient temperatures and harsher conditions.

Second, while a major challenge for stationary refrigeration is the absence of reliable electricity, transport refrigerators can use the fuel used to power the vehicles.

Third, refrigerated vehicles will become affordable only after general-purpose vehicles become affordable. Based on the above analysis, the projected time to market for such technologies is seven to ten years.

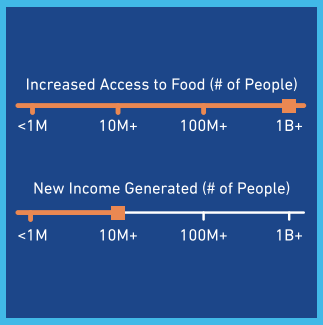
Current State



Associated 50BT Chapters

SDG Alignment

Impact

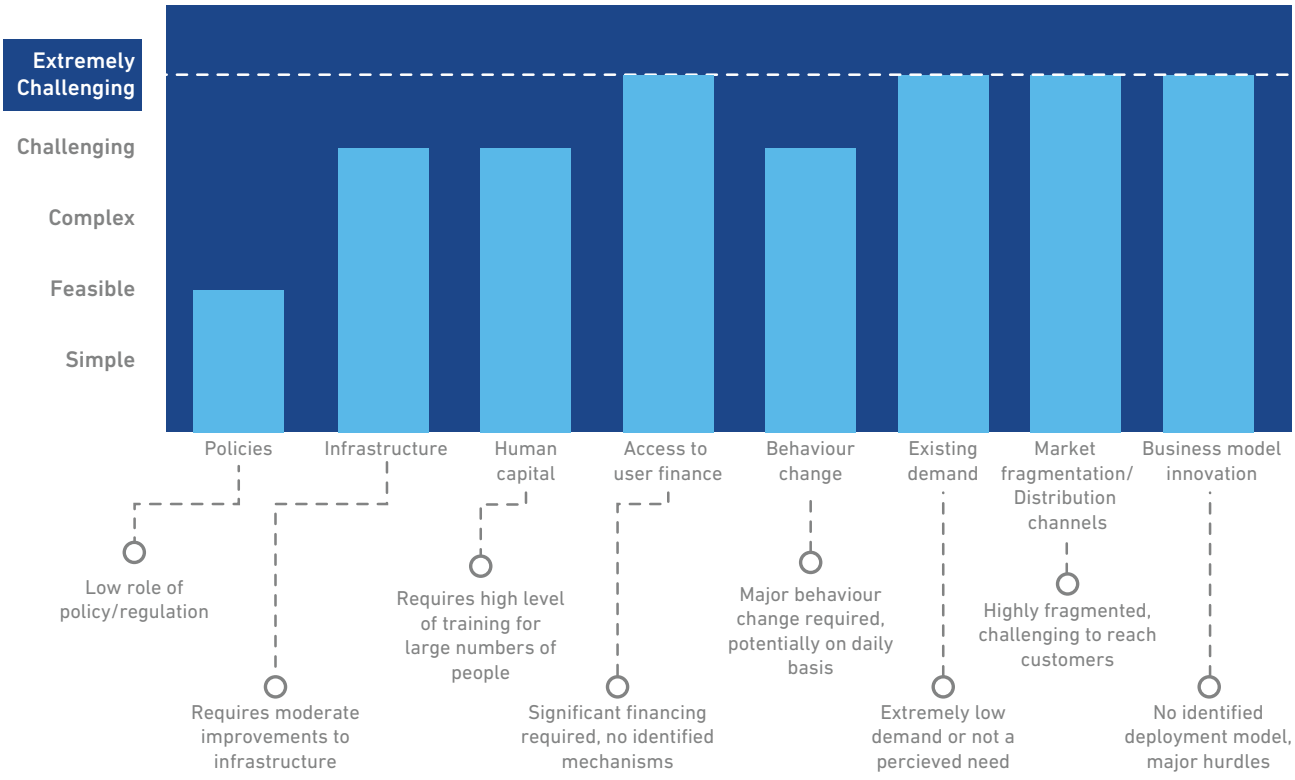


Commercial Attractiveness

Even when such a technology is developed, deployment will be difficult. The market is extremely fragmented and adoption will depend on the growth of the broader market for the relevant agricultural commodities. In addition, poor road infrastructure and the sparse presence of fueling stations will be a major hurdle in the usability of refrigerated transport.

Finally, a maintenance and repair infrastructure (currently absent) will be necessary to keep these refrigeration facilities functioning. We estimate that deployment will be EXTREMELY CHALLENGING.

Breakthrough 13: Difficulty of deployment



In addition to these two breakthroughs, three further innovations may also help in the fight against nutritional deficiencies:

Innovation: Improved processing and storage technologies to preserve food life and reduce degradation of nutritional content

Due to the seasonal nature of agriculture, farmers experience major swings in the availability of different foods. This is often most acute with fruits and vegetables, which spoil fairly rapidly after harvesting, leading to limited availability. Drying and processing preserves the life of food and often its nutritional content, thereby reducing the seasonal nature of hunger.

Specific technological needs vary depending on the food items (for example grains versus vegetables). In general, however, drying, processing and storage technologies need to be less capital intensive and should preserve as much of the nutritional content of the crop as possible. This is an area of emerging research. Milling rice, for example, often strips away nutritional content in the germ, although it also removes phytates, which bind nutrients and can prevent their absorption. The full impact of processing on nutrition requires continued research for improved understanding.

In most cases there is no fundamental technological issue to overcome. Rather, these are technologies that have traditionally received minimal attention. While there are some technologies capable of, for example, hermetic or air tight storage, none are at a cost low enough to enable large-scale deployment. When it comes to drying and processing technologies, the primary constraint is developing a technology with a low enough cost to enable a sustainable deployment model.

The projected time to market readiness varies widely. Some new products may enter the market within one to two years, while other products have received such little attention that they will likely not be introduced for seven to 10 years. The difficulty of deployment is similarly varied, but due to low margins and the need to target remote and rural areas the expected difficulty of deployment is challenging.

Innovation: Improved storage technologies for grains and pulses to reduce development of mycotoxins

Mycotoxins are poisonous compounds that are created primarily by fungi that accumulate during harvest and post-harvest storage and processing. The FAO has estimated that as much as a quarter of the world's crops could be contaminated with mycotoxins. The problem is believed to be most acute and least understood in sub-Saharan Africa, followed by South Asia.

In particular, aflatoxins are known to build up in maize and groundnuts, when crops are improperly dried and/or stored in cool, damp places in the household. Chronic exposure to mycotoxins has been linked to malnutrition, impaired immunity and various forms of cancer.

There are multiple approaches to preventing contamination from mycotoxins. Storage technologies have focused on prevention of insect infestation, which can cause exposure to fungal spores, and technologies to reduce condensation. Biological strategies include development of fungi or bacteria that can outcompete the fungi that produce mycotoxin. Chemical strategies have generally focused either on compounds that prevent insect infestation or those that prevent the growth of fungi.

Different approaches are at various stages of development. Several compounds are being tested and some are nearly market ready. However, any successful technology will face major deployment challenges. Mycotoxin poisoning is poorly understood by most smallholder farmers.

Moreover, there are few distribution channels that address smallholder farmers, where most contamination occurs. While market readiness varies by technology, some technologies could be ready within two to four years. The difficulty of deployment for any technology is extremely challenging.

Innovation: Diagnostics to determine nutritional content and bioavailability of nutrients in foods

Many nutrition interventions rely on provision of fortified foods to address nutrient gaps. While there are multiple processes to fortify staple foods, it is challenging to assure quality and control safety due to the difficulty of assessing nutritional content in food.

Assessments are usually made in laboratories, which are rarely sufficiently resourced to either accurately assess nutritional content of food or handle the sheer number of samples that need testing. Due to this lack of quality assurance, a major nutrition agency has estimated that as much as half of fortified food staples do not actually contain enough supplemental nutrients to create desired health benefits.

In order to address this issue, better diagnostics are needed that can assess the nutritional content and bioavailability of nutrients in food. The ideal device would produce rapid results and be usable in a field rather than lab setting.

Little applied research is underway in this area. Only a small number of universities or companies are developing rapid micronutrient testing devices, with at least one nearing market release. Further work related to precision, validation and local reagent production need continued research. Detecting vitamin B9, iodine and zinc deficiencies, in particular, require rapid diagnostic technologies.

The current market for such devices is concentrated. Only a small number of entities have an existing need for such a device. These institutions could benefit greatly from such a diagnostic and may be somewhat price insensitive, although cost is still expected to be a major barrier.

A dearth of commercial demand for diagnostics and a lack of willingness within local governments to enforce micronutrient testing in food remain significant hurdles. The projected time to market readiness is about one to three years, and the difficulty of deployment is complex.

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DIAGNOSTICS

INTRODUCTION

Accurate and timely diagnosis increases the likelihood of successful treatment.

Diagnostics play a particularly vital role in clinical scenarios where patients present non-specific symptoms that are common to multiple diseases, or in situations where the specific strain of the disease must be identified to determine the correct treatment regimen.

Since many infectious diseases are asymptomatic, diagnostics are necessary for screening asymptomatic patients. This helps prevent long-term complications from untreated infections and decreases the rate of disease transmission within communities. While early diagnosis and detection of communicable diseases like cervical cancer can greatly increase positive treatment outcomes, diagnostics are also essential for monitoring treatment effectiveness for chronic diseases like diabetes. Indeed, diagnostics inform and influence 60 to 70 percent of healthcare decisions.

Although simple rapid diagnostics are becoming more widely available, most are not completely reliable. Most reliable diagnostics require clinical infrastructure and need to be administered by highly trained healthcare workers. Though technologically reliable, centralized testing continue to face significant challenges in timely diagnosis and treatment due to delays from specimen transport and results reporting, among others. Accurate diagnosis and timely treatment are particularly important in the current era of drug resistance.

To meet the needs of these patients, a new generation of innovative diagnostics need to be developed. These tests must be portable and lightweight, capable of operating without grid electricity, tolerant to high ambient temperature and humidity, able to withstand physical shock while being transported, and simple enough to be used by minimally trained healthcare workers at the point-of-care. These technologies must also be built with actionable data management, effective consumables supply management and quality assurance processes. There are four technology breakthroughs that can make that possible:

- Breakthrough 32. Low cost, novel diagnostics for pneumonia
- Breakthrough 34. Automated multiplex immunoassays that can test for a broader range of diseases (compared to the current state) and are compatible with easily collected sample types
- Breakthrough 35. Point-of-care nucleic acid test (NAT) that is simple, robust, and compatible with easily collected sample types
- Breakthrough 36. Affordable, home-use point-of-care diagnostics suite (blood, urine, vitals) for the common NCDs

Around the world, clinical assessment is core to the diagnosis of disease. Diagnostic testing confirms or disproves clinical suspicion, enables early detection of disease, and allows clinicians to provide patients with the right treatment quickly, including triage to a higher level of care. Importantly, diagnostics inform and influence as much as 60 to 70 percent of healthcare decision-making (The Lewin Group, 2005) but must be used in conjunction with appropriate treatments and other interventions to have real impact on health outcomes.

CORE FACTS AND ANALYSIS

Diagnostic tests play a particularly crucial role when the patient's symptoms are non-specific (common to multiple diseases requiring different treatments) or when the treatment is sufficiently expensive that it is given only to those with confirmed cases of infection (Mabey, et al., 2004).

In such clinical scenarios, diagnostics increase the chances of successful therapy and decrease the chances of mis-treatment or over-treatment. This is critical for diseases like malaria where drug resistance threatens the long-term viability of existing treatments, or ones where different treatment protocols exist for different pathogen strains, as is the case with TB.

Even after treatment selection, diagnostics play an important role in monitoring treatment effectiveness for diseases like HIV, where treatment is long-term and its efficacy must be closely tracked.

Since many infectious diseases are asymptomatic, diagnostics also play a critical role in screening asymptomatic patients; this helps prevent long-term complications from untreated infections and decreases the rate of disease transmission within communities.

In this chapter, we focus on diagnostic challenges and needs in peripheral health centers and clinics ('Level 1' health facilities) in developing countries.

For about 60 percent of people in developing regions, point-of-care facilities are at peripheral health clinics, which are typically poorly resourced with little in the way of reliable electricity, clean running water, laboratories, laboratory equipment (like centrifuges and refrigerators) or well-trained clinicians (Nantulya, 2006; Girosi, et al., 2006).

Patients seeking care in such settings often do not have access to reliable diagnostics. The problem is particularly acute for diseases like TB, where existing diagnostic methods most commonly employed in such settings have proven lacking due to low sensitivity and specificity, and the inability to determine the drug susceptibility of the pathogen.

Diagnostic uncertainty today exacts an enormous toll in morbidity and mortality in developing countries by implicitly restricting the control of non-communicable diseases and the most fatal infectious diseases, particularly where HIV is prevalent (Perkins & Small, 2006)[1]. Innovative diagnostic tools need to be developed and deployed in low-resource settings, especially in developing countries.

[1]Convergence of infectious diseases, such as TB and HIV, exacerbates the negative impact of weak diagnostic tools. HIV in TB-endemic settings increases incidence and the population of symptomatic individuals, while co-infection decreases the sensitivity of microscopy for accurately diagnosing TB.

1. There are four main categories of analytes (indicators) of disease

Our focus is on in vitro diagnostics, the predominant method for testing for various diseases. In vitro diagnostics utilize a fluid or tissue sample from a patient to identify the presence, absence or changed quantity of specific analytes (molecular indicators of disease) through biological or chemical analysis.

The four main categories of analytes measured by in vitro diagnostic technologies are explained below.

Cells

Cell-based diagnostics are a mainstay of modern medicine and rely on the evaluation of whole cells to detect the presence of certain diseases and for hematological analysis. Information on full blood cell counts is required to diagnose and monitor conditions, such as HIV/AIDS, for which CD4+ T-lymphocyte counting (CD4 count) forms the basis of monitoring disease progression.

Most cell-based diagnostics, in their current form, are not practical for use in low-resource settings because they generally require sophisticated laboratory facilities, stable electricity and highly skilled personnel. Moreover, the success rate of these diagnostics is dependent on the skill level of the technician running the assay.

Proteins

Proteins found in patient samples, such as whole blood, serum/plasma, saliva and urine, are important for diagnosing a variety of diseases. At the point-of-care, protein detection is performed using both immunoassays and enzymatic assays. Tests are available for viral infections (anti-HIV antibodies, antibodies against influenza A/B virus, rotavirus antigens), bacterial infections (antibodies against Streptococcus A and B, Chlamydia trachomatis, Treponema pallidum), parasitic infections (histidine-rich protein 2 for P. falciparum, trichomonas antigens), and non-communicable diseases (PSA for prostate cancer, C-reactive protein for inflammation, HbA1c for plasma glucose concentration) (Chin, et al., 2013).

Nucleic acids

Nucleic acid detection is used in prenatal diagnosis of inherited disorders, diagnosis of genetic disease, identification of infection, disease staging, and measuring drug resistance. Nucleic acid testing (NAT) detects the presence of a pathogen either by directly detecting the pathogen's genetic material (DNA or RNA) in the host, or by first amplifying the pathogen DNA or RNA and then using probes that are specific to the pathogen of interest.

Advantages of NAT include high sensitivity due to amplification, and specificity because it targets unique sequences associated with the pathogen of interest. NAT can detect low-level infections when either the amount of the infecting agent is minimal or when the immune system hasn't had time to form antibodies against it.

This reduces the time between infection and diagnostic detectability of the disease (Chin, et al., 2013). This method can be used to accurately quantify the level of infection and to determine the type of strains and the drug resistance profiles, which are significant issues in diagnosing and treating diseases like TB and HIV.

Small molecules

Small molecules from a variety of bodily fluids can be used to measure health parameters. Examples include testing of iron levels to indicate anemia in pregnancy, blood glucose for diabetes monitoring, and lipid levels for cholesterol monitoring.

Such tests analyze a range of electrolytes like potassium ion and chloride, physiologically important molecules like urea, lactate, albumin and creatinine, and blood gases. These tests are based on electrochemical detection such as potentiometry, amperometry and conductance (Chin, et al., 2013).

2. Over the years, a number of point-of-care diagnostic tests and devices have been developed

In order to benefit the majority of patients in developing countries, diagnostic tests must be portable and lightweight, capable of operating without clean water or electricity, resilient to heat, humidity and transport, and simple enough to be used by minimally trained health care workers at the point-of-care. Diagnostic tests for the above analytes have not yet been fully optimized for use in low resource settings. Nevertheless, a number of relevant point-of-care diagnostic applications have been developed, which are profiled below.

Cell-based assays

Point-of-care cell-based diagnostics are becoming increasingly important in hematology, particularly for the quantification of white blood cells for diagnosing, monitoring and clinical staging of diseases like HIV/ AIDS. Such tests aim to replace resource-intensive laboratory technologies like flow cytometry, which are typically not viable in low-resource settings (Chin, et al., 2013). Most technologies being developed now are self-contained, portable, handheld, do not require extensive sample processing, and have the potential to meet the pressing need for a point-of-care CD4 count quantification method for the management of HIV/AIDS (Chin, et al., 2013).

Immunoassays

These assays utilize the binding of an antibody (naturally produced by the immune system to neutralize pathogens) to an antigen in order to diagnose a disease. Immunoassays make use of the binding interactions between antigens and antibodies to detect protein markers from either the pathogen or the host immune response. Immunoassays generally rely on either a visual read-out for the healthcare worker administering the test to show whether the antigen or antibody of interest is present, or on a fluorescent dye that can be quantified using a plate reader, microscope or other detection methods.

Immunoassays are considered the gold standard laboratory assays for diagnosing a variety of diseases that involve natural host immune responses, including infectious diseases like HIV/ AIDS and a wide variety of autoimmune diseases such as multiple sclerosis. In the developing country context, immunoassays have led to simple, low cost rapid diagnostic tests (RDTs), based on simplified ELISA (Enzyme-linked immunosorbent assay) testing techniques for a small number of important conditions: malaria, HIV/AIDS, syphilis and hepatitis B (RDTInfo, 2013), as well as proteinuria and pregnancy.

These tests have yielded significant improvement in health outcomes in developing regions, and have overcome the challenges of traditional immunoassays (namely personnel training and equipment) by including all of the reagents as part of the test and producing a visual readout that is easy to interpret.

Critically, these tests are based on patient samples like nasal swabs, urine, saliva or whole blood that can be collected using minimally invasive techniques by healthcare personnel with limited training. Currently, most RDTs are strip tests or dipsticks and rely on low cost immunochromatography (ICS) technology to detect antigens or antibodies.

Nucleic-acid testing

Nucleic acid tests are high cost, complex and require trained laboratory technicians. They are therefore mainly used in hospitals and centralized laboratories (LaBarre, et al., 2011). The difficulty of developing a self-contained, simple, robust and cost-effective NAT system for use at the point-of-care has a lot to do with the technical difficulties of integrating the steps of sample preparation, nucleic acid amplification and detection, which will be explored in more detail later in this section.

Despite these difficulties, there is increasing emphasis on bringing NAT to the point-of-care. One commercial example is Cepheid's GeneXpert® test platform for TB, which is currently available in many developing countries. However, this system requires uninterrupted and stable electrical power supply and annual validation of the system to ensure test accuracy (Chin, et al., 2013), limiting its use in low resource healthcare settings.

GeneXpert® utilizes a real-time fluorescence-based technique for polymerase chain reaction (PCR) detection. Other detection approaches being explored for NAT at the point of care include electrochemical methods, magnetic resonance and lateral flow devices for end-point detection (Chin, et al., 2013).

Clinical chemistry assays

These assays measure a variety of blood parameters including gases, electrolytes, hemoglobin, pH, enzymes, metabolites, lipids, hormones, vitamins and trace factors, inflammatory markers and cytokines, coagulation proteins, therapeutic drugs and drugs of abuse (Chin, et al., 2013).

Point-of-care testing of these clinical chemistry markers is preferable as test accuracy can decline when samples are transported to central laboratories for testing. Very few peripheral healthcare facilities in developing regions today carry out clinical chemistry testing.

Some instruments that use an electrochemical detection method for measurement of electrolytes, general chemistries, blood gases and hematocrit are not widely available yet at the point-of-care. Others are still exploring optical detection methods that have the potential to reduce the cost of clinical chemistry assays at the point-of-care (Chin, et al., 2013).

Hematology

At the point-of-care, hematology tests are widely used for measurement of hemoglobin and hematocrit to test for anemia and to measure blood coagulation. Several companies have developed point-of-care technologies to measure such parameters, including Sphere Medical, Abbott Diagnostics, Roche Diagnostics and Alere (Chin, et al., 2013).

Detection technologies

Recent technology improvements in optical detection have shown promising results. The new focus on using readily available consumer electronics, such as webcams charge-coupled device cameras and LEDs, has resulted in developing low-cost medical diagnostics in resource-poor settings. These technologies have the potential to overcome the traditional challenges faced by older optical detection technologies, which had low sensitivity and specificity (Balsam et al., 2013). A few breakthrough technology examples are:

- A webcam-based multiwavelength fluorescence plate reader and a webcam-based fluorescence microscope demonstrated for colonic mucosa tissue pathology analysis
- A lens-free optical detector used for the detection of Botulinum A neurotoxin activity
- A lab-on-a-chip, which enables the performance of enzyme-linked immunosorbent assay and other immunological or enzymatic assays without the need of dedicated laboratories and complex equipment demonstrated for the detection of the toxin staphylococcal enterotoxin B.

3. Current diagnostic technologies for major diseases have a number of shortcomings

In order to be accessible to low-income patients seeking care from peripheral healthcare facilities, diagnostic tests need to be inexpensive, portable, robust, capable of operating without heavy reliance on clean water or electricity, able to withstand ambient heat and humidity, and simple enough to be used by minimally trained healthcare workers.

A reliable supply of consumables and actionable test results are equally as important. Based on their ability to meet such requirements, diagnostic methods currently being used have a number of shortcomings, as summarized for four major disease conditions in **Table 1.**

The state of diagnostic technologies for four major diseases: Malaria, TB, HIV/AIDS and Lower Respiratory Infections

Malaria	
Diagnostic Needs	Identification of infection
Methods used in industrialized countries	N/A[2]
Methods used in developing countries	Usual diagnosis using RDT dual antigen; requires no lab intervention
Challenges with current mechanisms in developing countries	1. Rapid immunoassays can be of poor quality and cannot store data to link patients to care following a positive test result 2. They do not enable differential diagnosis between malaria and other causes of febrile illness 3. The RDTs have a poor shelf life and limited resistance to temperatures change
Promising Technologies	1. ELQ300, Anti-malarial compound and BK-SE36, Malaria vaccine 2. Non-invasive Malaria diagnostic devices
Hurdles to broad penetration	1. Healthcare delivery constraints (weak supply chain, limited quality assurance and control, inadequate guideline emphasis, staffing limitations) 2. Provider perceptions (entrenched case-management paradigms, limited preparedness for change) 3. Social dynamics of care delivery (expected norms of provider-patient interaction, test affordability) 4. Limited provider engagement in policy processes leading to fragmented implementation of health sector reform

[2]Very few patients are tested for malaria in industrialized countries, as the disease has been eliminated from these regions.

Tuberculosis	
Diagnostic Needs	1. Identification of active TB disease 2. Determination of drug susceptibility
Methods used in industrialized countries	1. PPD tuberculin test: injected just below the skin of your inside forearm 2. Bacteria bulture from sputum/sputum smear or chest radiograph 3. Blood tests: sophisticated technology to measure immune system's reaction to TB bacteria; QuantiFERON-TB Gold in-Tube test and T-Spot 4. Drug susceptibility testing (DST) via line probe assay (LPA)
Methods used in developing countries	1. DMN-Tre-upcoming technology used in Africa 2. Sputum microscopy followed by broad-spectrum antibiotics and chest radiography if smears are negative 3. Smear-negative and MDR-TB diagnosis: bacterial culture (or liquid culture) 4. Catridge-baded-NAAT test (Xpert MRB/RIF)
Challenges with current mechanisms in developing countries	1. HIV reduces the accuracy of both microscopy and radiography, so assessment of diagnostic approaches with existing methods and continuing research into new diagnostics are necessary 2. Detection of the drug resistance pattern and availability of highly active drug treatment is time consuming 3. Lack of simple, rapid triaging tests 4. High cost, implementation failures 5. Slow adoption of new tools, still highly dependent on smear tests
Promising Technologies	1. Low-cost fluorescent microscope 2. Rapid blood-based biomarker tests for quick diagnosis 3. AI powered x-ray image readers for rapid screening 4. POC molecular diagnostics 5. DNA and RNA sequencing for drug resistance testing
Hurdles to broad penetration	1. Inadequate clinical and laboratory infrastructure 2. Absent training programs for combined tuberculosis and HIV/AIDS care 3. Affordability of the tests 4. Regulatory and policy restrictions; Implementation failures

HIV/AIDS	
Diagnostic Needs	1. Identification of infection/disease screening 2. Disease staging to determine treatment initiation (CD4 count) 3. Monitor treatment efficacy/failure (viral load and drug resistance)
Methods used in industrialized countries	1. Viral load and drug resistance: Nucleic acid-based tests in central labs 2. HIV diagnostic test, FDA approved 3. Rapid Tests: a. OraQuick Advance Rapid HIV-1/2 Antibody Test (whole blood finger prick or venipuncture, plasma, oral fluid) b. Reveal Rapid HIV-1 Antibody Test (serum, plasma) c. Uni-Gold Recombigen HIV Test (whole blood finger prick or venipuncture, serum, plasma) d. Multispot HIV-1/HIV-2 Rapid Test (serum, plasma); INSTI HIV-1 Antibody Test (whole blood finger prick or venipuncture, plasma) e. Alere Determine HIV-1/2 Ag/Ab Combo Test (serum, plasma, whole blood finger prick or venipuncture) f. Clearview tests – Clearview HIV 1/2 Stat Pak g. Clearview Complete HIV 1/2 (whole blood, serum, plasma)
Methods used in developing countries	1. Screening: Rapid immunoassays that do not require lab facilities 2. Confirmatory tests: performed with a minimum of two to three different rapid assays in high prevalence areas 3. Centralized NAATs viral load, drug resistance and early infant diagnostic testing
Challenges with current mechanisms in developing countries	1. Sample collection prevents POC tests to be used widely at primary care settings 2. Significant management and operational infrastructure required for centralized testing, leading to underutilization of existing lab capacity, improper test reporting 3. Nucleic-acid tests require expensive lab equipment and trained personnel, making their widespread implementation in low-resource settings very difficult; There are currently no point-of-care viral load tests that can accept whole blood specimens
Promising Technologies	1. Mobile based diagnostic tests 2. RDTs for self-testing 3. POC technologies (Infant focused)– NAT based
Hurdles to broad penetration	1. Quality control/assurance, especially for self-testing products 2. Training and appropriate use of RDTs by healthcare providers 3. Responsible usage of HIV self-testing within the community

Lower Respiratory Infections	
Diagnostic Needs	1. Identification of pneumococcal infections and etiology • *Streptococcus pneumoniae* • *H. influenzae* • RSV • Influenza • Other pathogens
Methods used in industrialized countries	Chest x-ray and/or bacterial culture from sputum or blood
Methods used in developing countries	Syndromic management or use of diagnostic surrogates (e.g. arm circumference, chest ausculation)
Challenges with current mechanisms in developing countries	Diagnostic approach to disease management is lacking due to: • Difficulty of sample acquisition (particularly sputum from children) • Lack of pathogen identification, which relies on bacterial culture with long lead-times • Poor link to appropriate therapy • Lack of radiography
Promising Technologies	1. Rapid tests for differential diagnosis of viral vs. bacterial infection 2. Multiplex tests
Hurdles to broad penetration	1. Selection of targets for multiplex tests 2. Proving cost-effectiveness and clinical value of multiplex tests 3. Training and appropriate use of by healthcare providers

Table 1: There are several gaps in the current state of diagnostics available to low-income populations and their healthcare providers for the four major infectious diseases—HIV/AIDS, TB, Malaria and lower respiratory infections. These gaps are different for each disease[3]. (Source: ITT analysis)

[3]Diarrheal disease, caused by bacterial, viral or parasitic agents, is primarily diagnosed by clinical symptoms and has been excluded from this table. Diagnostic techniques based on immunoassay, nucleic acid amplification and culture are available for multiple specific causes of diarrhea. However, all of these diagnostics require access to sophisticated laboratory facilities. As diarrheal disease is managed by supportive rehydration therapy and non-specific medications, specific diagnosis is generally not considered essential.

4. Diagnostics for patients in developing countries need to consider several other factors

In addition to meeting operational requirements of low-resource settings, several additional technical parameters must be considered in the design of appropriate diagnostics for developing regions. Ideal diagnostic solutions will account for broader health trends and the needs of national public health systems. Three significant dimensions are listed below.

Drug resistance

A number of infectious diseases are developing drug-resistant strains, in turn complicating the already difficult task of diagnosis and treatment. For such diseases, it is critical to go beyond simple detection and recognize whether or not the strain is drug-resistant, and identify what particular treatment the infecting pathogen will be sensitive to.

With TB, in particular, the emergence of multiple drug-resistant strains is making it important to identify the specific drugs to which the pathogen or bacterium is resistant to. This means that the diagnosis needs to go beyond a 'yes or no' detection of drug-resistant TB.

In cases of co-infections (like HIV-TB co-infection) such detection becomes even more critical as combining two separate treatments may reduce the efficacy of one or more drugs being administered to a patient.

Storing and transmitting data

One of the major challenges in timely diagnosis and treatment in rural, low-resource settings is the long turnaround time. Delays occur in pre-analytical (such as specimen transport), analytical (test processing) and post-analytical (results delivery) phases. In a centralized lab, up to 50 percent of tests are not delivered at all, with the average time of 61 to 90 days from test to start of treatment (Gous et al., 2018).

While mobile connectivity has improved speed of delivering test results, current systems are not holistic in nature and data remain unactionable to address adherence. For public health systems to plan broader disease control strategies, it is very helpful to track cases as well as epidemiological and health statistics obtained during diagnoses.

Additionally, there is strong need to store and transmit patient data from point-of-care to higher-level health facilities and national-level databases. This data may be used to prevent patient dropout due to lack of follow up, enable ongoing clinical management of patients that need protracted treatment, and to enable efficient inventory management, quality assurance and need-based training for healthcare providers.

The proliferation of mobile information and telecommunications platforms makes such a capability possible (Reid, 2012).

Multiplexing capabilities

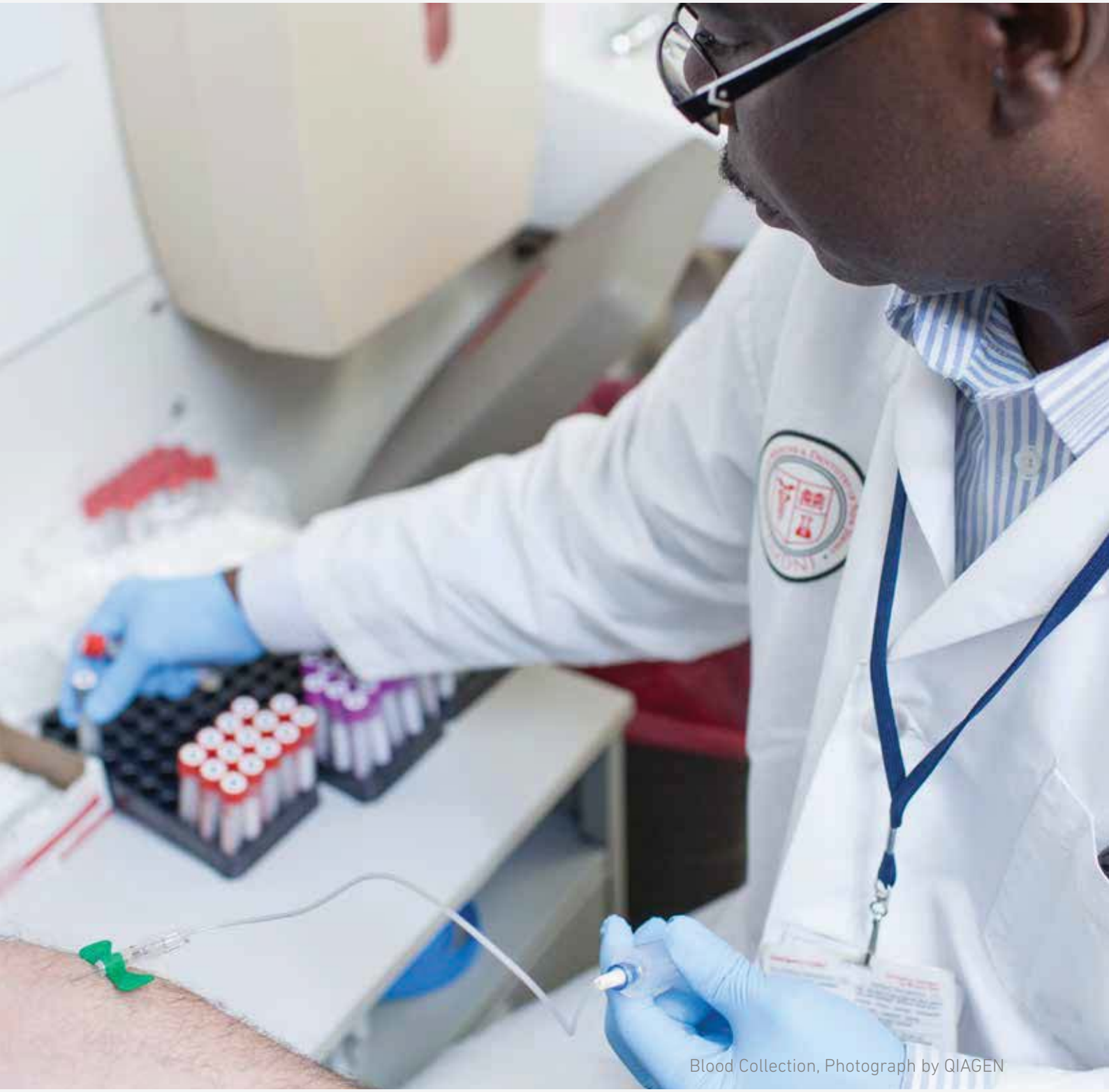
Often, poor patients are more likely to suffer from low immunity due to malnutrition, inadequate hygiene and other risk factors, and thus face a higher possibility of infection from multiple diseases or pathogens. Additionally, different diseases can present similar symptoms, such as fever. In such cases, a single device or platform capable of simultaneously diagnosing multiple diseases that present similar symptoms will be extremely valuable.

Specific examples of clinical scenarios in which multiplex testing would be desirable and examples of specific diagnostic panels are provided later in this section. The importance of multiplex testing must be carefully balanced against affordability; additional pathogen tests for a diagnostic device increases overall costs. The selection of multiplex tests should be determined based on the clinical actions that will be informed through this differential diagnosis, and the improved health outcomes that can be achieved by doing this.

KEY CHALLENGES

With the above criteria in mind, current diagnostic products and technology applications fall well short of what is required for affordable and effective diagnosis for a number of important diseases and medical conditions.

Several technical challenges play a role when it comes to developing point-of-care diagnostics for low-resource settings.



Blood Collection, Photograph by QIAGEN

1. Available immunoassay rapid diagnostic tests (RDTs) have significant limitations

Immunoassays have several limitations that restrict their suitability in low-resource settings.

First, high ambient temperatures and humidity, common to many developing countries, and the lack of refrigerated storage can cause degradation of patient samples and diagnostic reagents, which limits assay sensitivity and shelf life.

Second, antibodies can persist beyond the clearance of an infection. Immunoassays that rely on detecting antibodies in a patient can measure only the one-time existence of an infection and not whether the infection is active or has cleared (BVGH, 2012). Such tests can also result in a false negative result when there is either a low level of antigenemia or when the antigens have short life cycles (LaBarre, et al., 2011).

Third, due to inadequate regulations there is a proliferation of poor quality or counterfeit products (Mehta & Cook, 2010). Regulation of RDTs will become more and more important as the self-testing demand grows.

Finally, immunoassays cannot generally be used for identifying specific strains of pathogens or test for drug resistance. Thus, while lateral flow RDTs have represented an important advancement over diagnosis based entirely on clinical symptoms for a number of diseases, consistently high performance tests that allow for external quality control are essential.

2. NATs have proven difficult to develop for point-of-care use

NATs require the use of unstable or sensitive reagents, specific infrastructure or equipment, and highly trained staff. Integrating these essentials into portable, user friendly and affordable tools appropriate for use by minimally trained staff in low-resource settings is extremely difficult.

NAT is time-consuming and typically involves three steps: sample preparation (consisting of sample collection and processing), signal amplification and detection. Several challenges within each of these steps makes the current implementation of NAT at the point-of-care prohibitively complex (Chin, et al., 2013).

Sample preparation

An intrinsically complicated process, sample preparation involves cell or virus capture and isolation, lysis (breaking down of the cell wall or viral coat), and nucleic acid extraction and purification. This generally requires laboratory equipment such as a centrifuge or vacuum manifold.

Optimal sample preparation is critical to the outcome of the NAT assay. Post extraction, the nucleic acids are prone to degradation, which can lead to misinterpretation of results. Subsequent sequence amplification steps are highly sensitive to contaminants that result from incomplete purification. Further, the risk of cross-contamination between separate samples also poses a significant obstacle to the reproducibility and reliability of NAT assays.

Overall, the time-consuming nature of sample collection and processing and the training and infrastructure requirements associated with sample preparation limit the applicability of NAT at point-of-care in low-resource settings.

Signal amplification

Typically, NATs relies on a separate amplification step because there is insufficient nucleic acid in a raw sample for direct detection using current detection technologies. Most NATs relies on a polymerase chain reaction (PCR), a temperature-controlled and enzyme-catalyzed reaction based on thermal cycling of the sample-reagent mixture. Thermal cycling involves cycling the sample-reagent mixture through two temperature extremes, typically at relatively high rates of change. This generally requires complex equipment and stable electrical power. However, newer and simplified methods are increasingly available.

Isothermal amplification methods—which operate at a single temperature—typically require electrical power, although some technologies appear promising in addressing that hurdle (Piepenburg, et al., 2006). Reagents used for NATs typically require cold storage and technical training to be properly handled. The needs of current amplification methods—reliable power, expensive machines (like thermocyclers), high quality (reagent-grade) water, refrigeration and trained technicians—prevent deployment of NATs at the point-of-care.

Detection

Nucleic acids are typically detected through fluorescence (the most common method), phosphorescence, chemiluminescence, or through a color change resulting from a chemical or enzymatic reaction. Such optical methods usually require dyes and/or enzymes, which can degrade in high ambient temperatures typical in many developing countries, leading to higher assay background noise or reduced sensitivity.

Most biological samples contain autofluorescent compounds; when fluorescence is used as a detection technique it can also be highly sensitive to contaminants. Sample purity must be high to rely on fluorescent detection. In general, NAT detection techniques require complex optical instrumentation, stable power and trained technicians, posing challenges to implementing NAT at the point-of-care.

3. The ability to develop improved diagnostic tests is limited by the availability of disease biomarkers

In the context of diagnostics, biomarkers are measurable indicators of organisms or diseases in human tissue or bodily fluids. Known disease biomarkers are necessary to develop diagnostic tests. Ideally these samples should be easily obtainable.

Depending on the availability of biomarkers for specific diseases, multiple diagnostic technologies may be needed to analyze multiple types of samples. An expert panel organized by the American Society of Microbiology singled out the identification of novel biomarkers as "having the most potential" to contribute to the development of new point-of-care tests (Reid, 2012).

There are a range of challenges related to biomarkers for diseases prevalent in developing countries. For some diseases, relevant biomarkers have not been identified yet, while there are a number of diseases for which known biomarkers require sample types that are difficult to obtain.

For example, meningitis[4] can only be diagnosed by analyzing cerebral spinal fluid, which must be obtained through an invasive lumbar puncture. Tuberculosis, on the other hand, generally relies on sputum, which can be a difficult sample to obtain (from children) and process (for patients of all ages). Some biomarkers represent only a subset of the organisms responsible for a single disease, and other biomarkers depend on a host response that can be variable and can lack sensitivity.

Recent research has advanced our understanding of the role of biomarkers in cancer (Brenner, et al., 2014), tuberculosis (Wallis & Peppard, 2015), and Alzheimer's disease (Sheikh-Bahaei, et al., 2017).

There has been swift expansion in the potential range of biomarkers, including specific gene sequences and surface markers, ratios of expressed genes, quantitative measures of antibody or pathogen levels, and detection of specific metabolites, proteins and lipids.

New biomarkers, especially those available through easily accessible sample types, can support the development of new tests that can then run on the next generation of point-of-care diagnostic platforms.

However, discovery of novel biomarkers is scientifically unpredictable and requires significant additional investment. As biomarkers become available in accessible sample types, diagnostic test developers can easily incorporate them into new tests. Still, there will be challenges in getting clinicians to uniformly learn and adopt the new practices.

[4]Except for cryptococcal meningitis.

4. Multiplex diagnostic test panels to support clinical needs are yet to be defined

As mentioned earlier, there is increasing recognition of the value of multiplex diagnostic platforms that can diagnose multiple conditions within a single patient visit.

To perform a true differential diagnosis, a broad test menu must be available at the point-of-care. The Bill & Melinda Gates Foundation has been defining such panels of tests for a number of important conditions and clinical scenarios (**Exhibit 1**).

These represent complete panels required for treatment decisions and a departure from the historical focus on disease specific tests; except for the neglected infectious diseases category (BMGF, 2013).

Potential multiplex diagnostic platforms for point-of-care use

HIV	Maternal/ Neonatal health	Febrile	Respiratory	Enteric and diarrheal diseases	Neglected infectious diseases
HIV antibody	Preeclampsia	Malaria	Preeclampsia	Amoebiasis	Schistosomiasis
CD4	CBC	Pneumonia	Influenza	Campylobacter	Leishmaniasis
Viral load	Glucose	Dengue	RSV	E. coli	Japanese Encephalitis
CBC	Syphilis	G6 PD	TB+	Shigellosis	Trypanosomiasis
Liver function	HPV	Typhoid	MDR/XDR	Cholera	
Creatine	p24		CBC	Cryptosporidium	
TB+	HIV antibody				
MDR/XDR	Hepatitis				
	Serum iron				

Keys diagnostic platform required to perform test

Cell counting · NAT (quantitative and non) · Chemistry analysis · Immunoassay/ Lateral flow

Exhibit 1: A number of diagnostic panels are required for thorough treatment decisions. This is a departure from the historical focus on disease specific tests. (Source: BMGF, 2013)

Other tests with a potential to greatly impact healthcare and health outcomes in developing regions include (Reid, 2012):

Bacterial versus viral infection

Syndromes such as fever or upper respiratory infections can be caused by many different pathogens like viruses, bacterium, fungus or parasites. No simple test that can determine the cause of such seemingly commonplace illnesses exists yet.

Such a test should ideally be able to determine the resistance profile of the causative agent; but even a simple differentiation among causative agents will go a long way towards enabling appropriate treatment (for example antibiotics versus antimalarials). These tests could be customized further to reflect and address specific needs of a region.

For example, a 'fever panel' in a malaria endemic area could capture various causes of fever including bacterial infection, viral infection and different malaria strains.

STD panel

Sexually transmitted diseases (STDs) affect patients and their partners, and can also be transmitted to fetuses by pregnant mothers. It would be useful to have a single test to differentiate between syphilis, herpes simplex, trichomonas, chlamydia and HPV. A rapid test for HPV can also be used as a screening test for determining the risk of contracting other STDs.

Central nervous system infections

Meningitis (with the exception of cryptococcal meningitis) can only be diagnosed by examining cerebral spinal fluid that is obtained through lumbar puncture. This is an invasive procedure and requires highly trained caregivers. A simpler test that can also differentiate bacterial and viral meningitis, and the pathogens responsible for encephalitis and meningitis, would be extremely useful for enabling appropriate treatment. This depends on the discovery of new biomarkers.

State of health panel

There are opportunities to develop panels of tests outside of infectious diseases, which might measure health indicators related to chronic or non-communicable diseases (NCD), such as diabetes or heart disease.

NCDs represent 43 percent of the global burden of disease and are expected to be responsible for 60 percent of the disease burden and 73 percent of all deaths by 2020 (WHO, 2013). A rapid test that provides information such as white cell count, lipid profile and other indicators could also be of great value in enabling effective clinical case management.

SCIENTIFIC AND TECHNOLOGICAL BREAKTHROUGHS

Diagnostic tests that are robust, inexpensive and simple to use have the potential to greatly improve quality of healthcare in low-income countries. Today, approximately 60 percent of the target patient population in developing countries lacks access to advanced diagnostics tools (Nantulya, 2006). This is a result of poor infrastructure (unreliable access to power, lack of indoor climate control, poor cold chain storage conditions and lack of trained technologists), limited menu of available diagnostic tools, and cost barriers including both capital investments in equipment and per-test costs.

To improve diagnosis at the point-of-care in resource-poor settings, there is a clear need for simpler and smaller instruments. Test development should focus, in the short term, on single tests for critical disease-specific unmet diagnostic needs like point-of-care tests for HIV viral load monitoring or TB drug susceptibility.

In the medium term, platform technologies that offer broad menus of tests in a variety of sample types that previously required multiple detection technologies could be the answer. Finally, the ultimate breakthrough will be an integrated and comprehensive semi-open source diagnostic system that processes samples, performs assays and automatically reports results for a range of conditions, using components made by different manufacturers.

Breakthroughs:

1	2	3	4	5	6	7	8	9	10
11	12	13	14	15	16	17	18	19	20
21	22	23	24	25	26	27	28	29	30
31	32	33	34	35	36	37	38	39	40
41	42	43	44	45	46	47	48	49	50

3.2 Low cost, novel diagnostics for pneumonia

Pneumonia is currently diagnosed by a clinic consultation, not by a specific diagnostic test. This makes it difficult for care providers to identify different clinical scenarios, such as whether a patient has viral or bacterial pneumonia or quickly determine the infecting pathogen, which can help indicate the potential severity of the illness. Accurate diagnostics also has the potential to reduce medicine wastage, and reduce the risk of antimicrobial resistance.

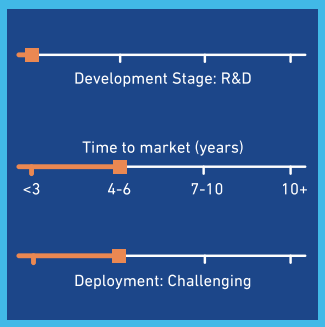
While the gold standard for diagnosis is through a chest X-ray, the imaging test is not practical for clinics in low- and middle-income countries. Most diagnoses are made based on evaluation of respiratory rate and chest in-drawing. The technological challenges and time to market for a novel pneumonia diagnostic vary depending on what the clinical goal of the diagnostic would be.

A urine-based diagnostic for pneumococcus bacteria, for example, is now available. However, a diagnostic that can discriminate between bacterial and viral pneumonia, and severe and non-severe pneumonia, is much more technologically complex; in some cases, biomarkers have not been identified yet. The primary benefit of diagnostics that provide deeper information about the infecting pathogen would likely be a better understanding of the disease and its epidemiology, as opposed to reduced mortality.

Reducing mortality from severe pneumonia would likely rely on improvements in pulse oximetry and respiratory rate timers. Both are effective technologies, and while they could be refined further, and can be incorporated into multimodal devices that also measure other vitals, the key challenge is distribution to, and adoption at, the clinics, as opposed to major improvements in either the cost or technology.

However, even the impact from better oximetry and respiratory rate timers, or any accurate rapid diagnostic tests are likely muted, as a reduction in mortality will only happen if patients seek care, are diagnosed in time and in some cases have subsequent access to oxygen therapy, which is currently rare.

Current State



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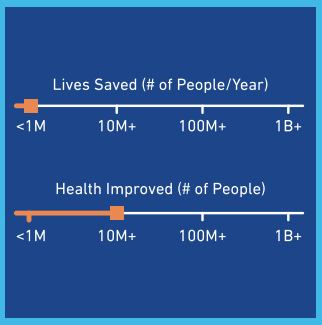


Commercial Attractiveness

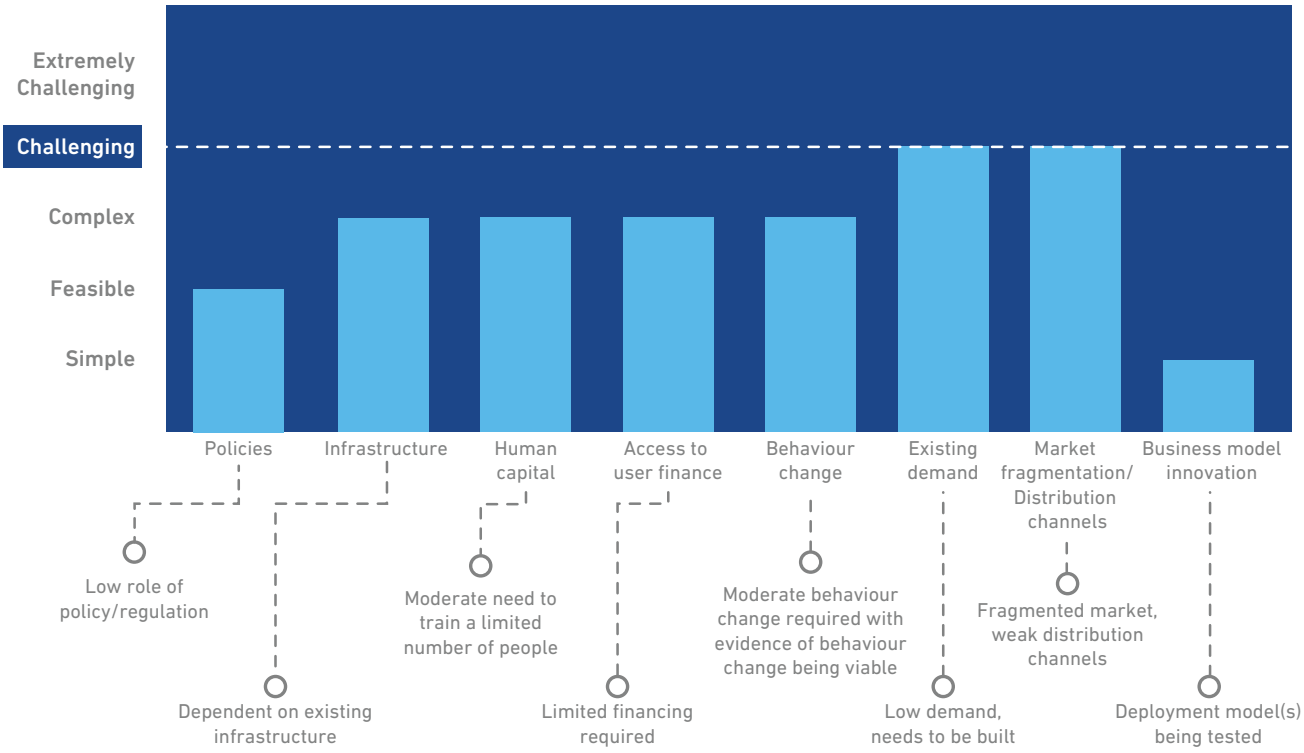
Ease of deployment varies by diagnostic type. In general, simpler devices like improved respiratory rate timers and pulse oximeters have fewer deployment barriers; they need less access to grid energy, less access to financing and less training. In each case however, lack of existing demand and market fragmentation are major hurdles in achieving scale.

There is currently no existing base for deployment of pneumonia diagnostics to rural clinics where they are most needed, so distribution of a new diagnostic would require creation of new channels as well as educating healthcare workers on the need and value of pneumonia diagnostics.

Since clinical diagnosis generally remains effective, and the downside to clinical diagnosis (like drug resistance) is neither immediate nor obvious, it will be challenging to convince healthcare funders and clinicians to devote scarce resources to purchasing and using pneumonia diagnostics.

Based on the above assessment, improved diagnostics for pneumonia are likely to be market ready in four to six years, and the difficulty of deployment is CHALLENGING.

Breakthrough 32: Difficulty of deployment



34 Automated multiplex immunoassays that can test for a broader range of diseases (compared to the current state) and are compatible with easily collected sample types

The development of point-of-care immunoassays that can use different types of samples (like blood, urine or sputum) and test for multiple biomarkers from a single patient sample represents a major breakthrough applicable to a wide range of disease conditions.

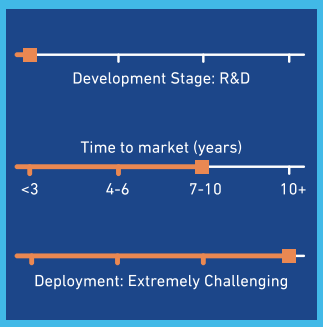
Next generation immunoassays will be multi-well, micro-scale, will integrate and automate steps from sample preparation through detection, and be appropriate for use in low-resource healthcare settings.

Several different types of point-of-care immunoassay platforms have been attempted, including antibody microarrays, immunosensors, microwell arrays and microfluidic chips, or combinations of these.

Microfluidics represents an important technology for point-of-care immunoassays, given that microfluidics offer increased surface-to-volume ratios, which can be exploited by immunoassays that capture analytes' surfaces.

However, challenges of developing such immunoassays have not yet been fully overcome, including the high sensitivity of detection required for measuring analytes in small sample volumes, the robustness and reproducibility in performing micro-scale assays, and the difficulty of manufacturing miniaturized component.

Current State



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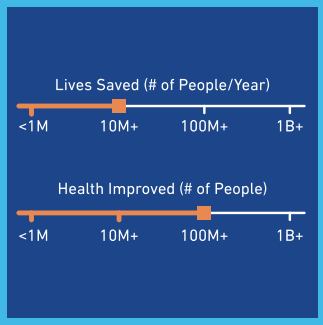


Commercial Attractiveness

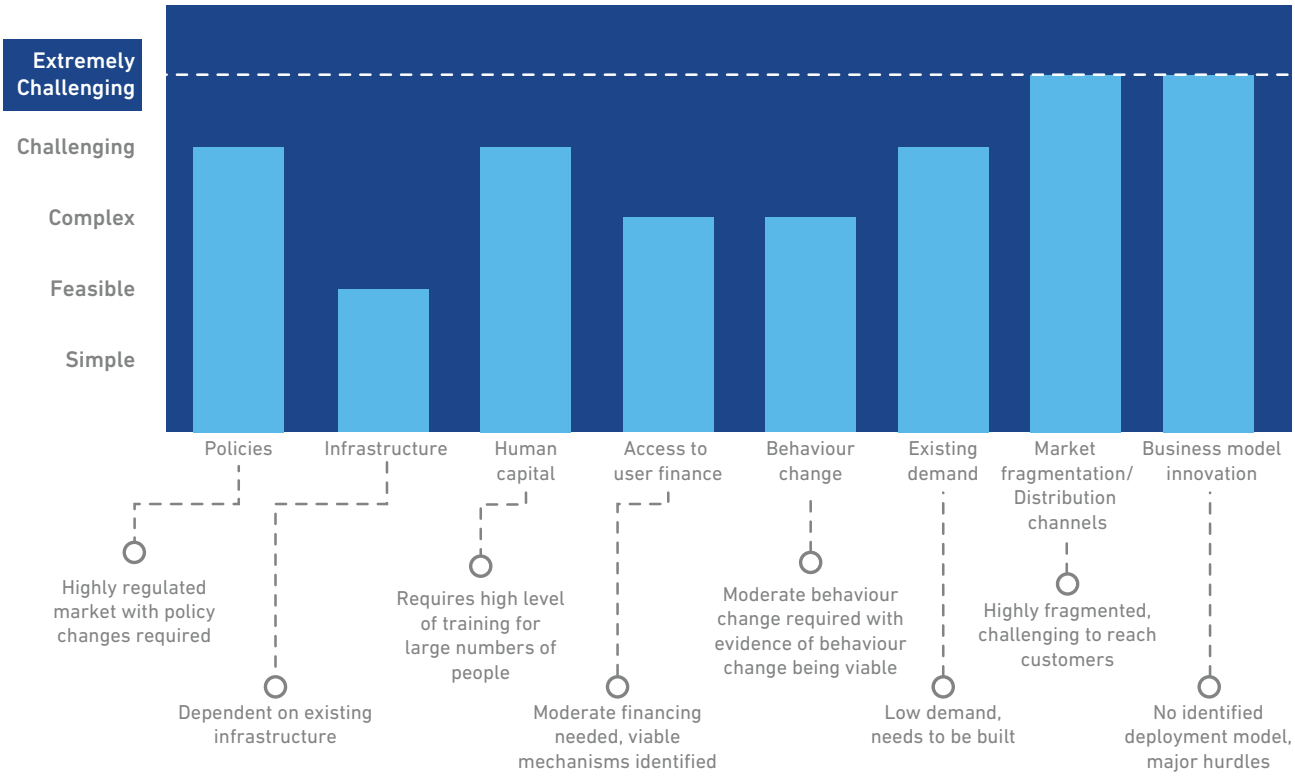
Overall, several hurdles limit the development, deployment and adoption of new diagnostic technologies. Development is hindered by the relatively small investments currently being made in developing diagnostics relative to developing new drugs and vaccines.

Deployment also rests on regulatory processes, WHO endorsement and the large capital expenditure required of countries that may look towards adopting new diagnostics on a large scale.

Regardless of how pressing a need for a new diagnostic may be, two other factors impact the end adoption: the costs and resources required to adequately train healthcare workers to use the new tests, and patients' willingness to pay for them.

Based on the above assessment, the projected time to market readiness is seven to ten years and the difficulty of deployment is EXTREMELY CHALLENGING.

Breakthrough 34: Difficulty of deployment



35 Point-of-care nucleic acid test (NAT) that is simple, robust, and compatible with easily collected sample types

A key breakthrough in disease detection is the development of point-of-care nucleic acid tests (NATs) applicable to a wide range of disease conditions. These tests should be compatible with simple sample types (such as whole blood), portable, rapid, robust despite high ambient heat and humidity, capable of being used by minimally trained technicians, and non-reliant on refrigeration, running water, and stable electricity. In addition, the technology should have a low price point to make it appropriate for use in peripheral healthcare facilities. Developing such a test poses significant technical challenges; it requires modular, instrument-free technologies for each of the NAT steps: sample processing, signal amplification and detection.

Sample preparation technologies

The manual, time-consuming and infrastructure-intensive sample collection, processing and purification associated with preparing an optimal sample for NAT must be integrated and automated so that minimally trained healthcare workers can perform testing. Non-invasive sampling technologies, simplified extraction techniques, sample concentration technologies and purification-free chemistries can help advance this goal.

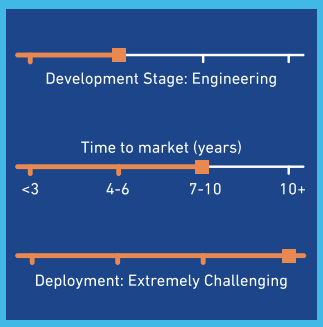
Signal amplification technologies

The thermocycler, electricity and temperature control required for polymerase chain reaction (PCR) make NAT unsuitable for point-of-care adoption in low-resource settings. New technologies that are less sensitive to sample contaminants, have simpler thermal profile mechanisms that reduce sample processing requirements, and are not dependent on grid electricity, appear to be the way forward. Also critical is reduced reliance on cold chains and refrigeration. This will come from improvements in packaging, the ability to monitor temperature history, and the use of more stable substitutes in place of heat-sensitive reagents. Additionally, NATs that do not have to rely on stable grid power may depend on improved battery technology, solar chargers or generators, or any other new technology breakthroughs that provide instrument-free heat sources.

Detection technologies

Optical detection poses a challenge because of its potential dependence on extensive equipment. There are new detection technologies that do not rely on optical detection, including measurements of mass, magnetic properties, diffraction, or electrical potential that may enable development of more robust detection systems.

Current State



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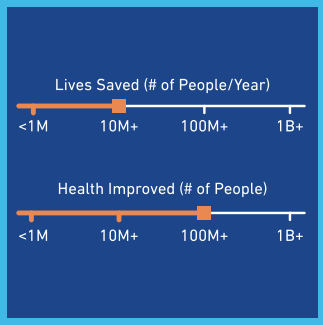


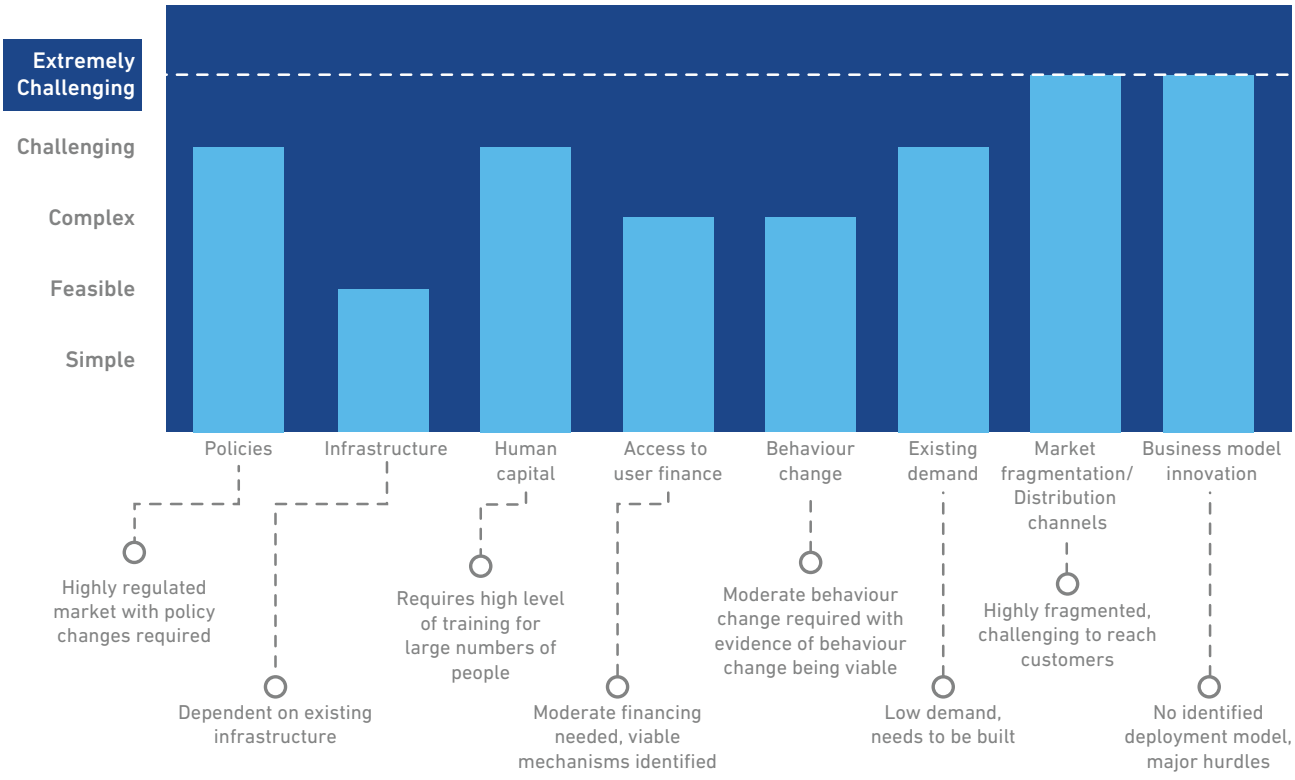
Commercial Attractiveness

Developing a point-of-care NAT will further depend on advancements in micro-fabrication and the ability to miniaturize test components that allow for multiplexing, reductions in sample size, and reduced reagent costs. Microfluidic platforms may yield a possible path forward for NATs as well, as demonstrated by the GeneXpert test for TB.

Deployment challenges include regulatory processes and WHO endorsement, as well as the large capital expenditure required of countries that may look towards adopting new diagnostics on a large scale. Regardless of how pressing a need for a new diagnostic may be, two important factors that will impact the end adoption are the costs and resources required to adequately train healthcare workers to use the new tests, and patients' willingness to pay for them.

Based on the above assessment, the projected time to market readiness is seven to ten years, and the level of difficulty is EXTREMELY CHALLENGING.

Breakthrough 35: Difficulty of deployment



36 Affordable, home-use point-of-care diagnostics suite (blood, urine, vitals) for the common NCDs

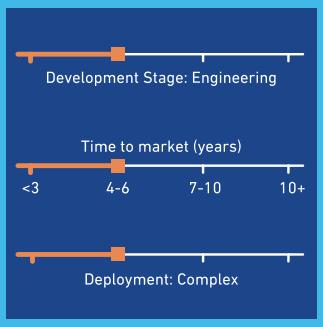
Point-of-care testing is essential for the rapid detection of diseases at the point of care, which facilitates faster disease diagnosis, reduces costs and improves outcomes. Moreover, home-use tests are increasingly designed to be simple to administer and interpret, thus overcoming the challenge of paucity of trained personnel. In the last few years, there has been a move towards integrating tests with mobile applications due to ease of data capture, better user experience and widespread adoption of smartphones. These include both standalone mobile health applications and more integrated testing applications.

The latest improvements in point-of-care diagnostics are a result of continuous developments in biosensors, lateral flow tests, as well as integrated or lab-on-a-chip technologies. These include tests for diabetes, cardiac conditions and cancer. Many of these technologies have already been developed and commercialized in developed economies but are yet to find adoption and successful commercial models for widespread adoption in developing economics.

For example, testing of EG Antigen for cervical cancer, developed by Arbor Vita is currently available only in the United States. In 2018, the US Food and Drug Administration approved the use of in-home genetic tests for breast cancer developed by genetic testing company 23andMe. Molecular diagnostics offer great promise but are less available in low-resource settings.

Data analytics and artificial intelligence, such as image detection methods, are also showing promise in enhancing and reducing the complexity of robust diagnostic methods such as the pap smear, and can help scale up proven diagnosis methods into low-resource setting. Such technologies can increasingly be deployed in home-based and point-of-care settings, due to growing capacity for data networking.

Current State



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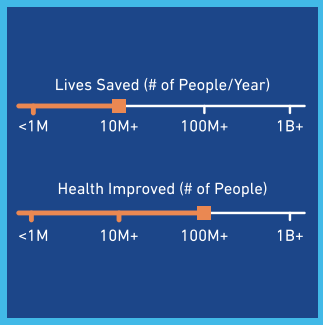
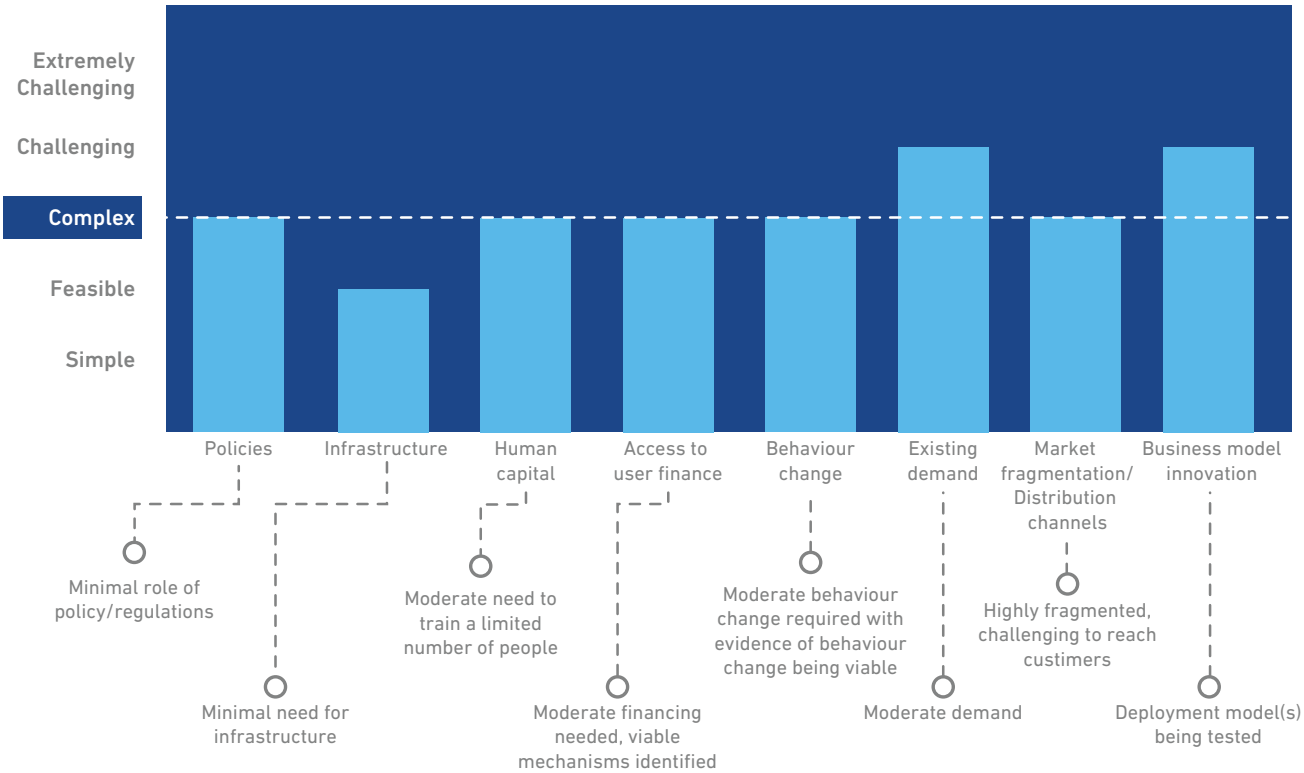


Commercial Attractiveness

Widespread deployment of home-use point-of-care diagnostics devices for common NCDs will depend particularly on consumer demand for such service. Business models will need to focus on enhancing demand for the product through motivating customer self-interest.

Initial products with limited capabilities are currently on the market, and more sophisticated devices with improved performance will likely appear in the next 5 years. The difficulty of deployment is estimated to be COMPLEX.

Breakthrough 36: Difficulty of deployment



DIAGNOSTICS GLOSSARY

Assay: A term used to describe the procedure used for conducting a diagnostic test.

Analyte: Entity or target that is being analyzed (can be an ion, a protein, a cell, a molecule, among others).

Enzyme-linked immunosorbent assay (ELISA): A biochemical technique used mainly in immunology to detect the presence of an antibody or an antigen in a sample. In ELISA, an unknown amount of antigen is affixed to a surface so that it can bind to the antigen. This antibody is linked to an enzyme, and in the final step a substance is added that the enzyme can convert to some detectable signal.

Flow cytometry: The analysis of characteristics of a particle or cell as it flows in a fluid through a beam of light.

Fluorescence: The emission of radiation (usually visible light) by a substance that has been exposed to light or other electromagnetic radiation.

Immunoassay: A biochemical test that measures the concentration of a substance in a biological liquid, typically serum or urine, using the reaction of an antibody or antibodies to its antigen.

In vitro diagnostics (IVD): Medical device products including instrument and reagents that utilize a variety of methods and formats to perform tests on human samples in order to assess disease risk, diagnose a condition or monitor a patient's health.

Lateral flow test: A simple device intended to detect the presence (or absence) of a target analyte in sample. Lateral flow tests are a form of immunoassay in which the test sample flows along a solid substrate via capillary action, and are often produced in a dipstick format.

Microfluidics: Deals with the behavior, precise control, and manipulation of fluids that are geometrically constrained to a small, typically sub-millimeter, scale.

Multiplexing: Simultaneous measurement of multiple analytes in single reaction vessel.

Nucleic acid: Macromolecule composed of chains of monomeric nucleotides. These molecules carry genetic information or form structures within cells. The most common nucleic acids are deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). Nucleic acids are universal in living things, as they are found in all cells and viruses.

Polymerase chain reaction (PCR): A technique to amplify a single or few copies of a piece of DNA across several orders of magnitude, generating thousands to millions of copies of a particular DNA sequence.

Thermal cycling: A temperature modulation process used to promote biochemical reactions.

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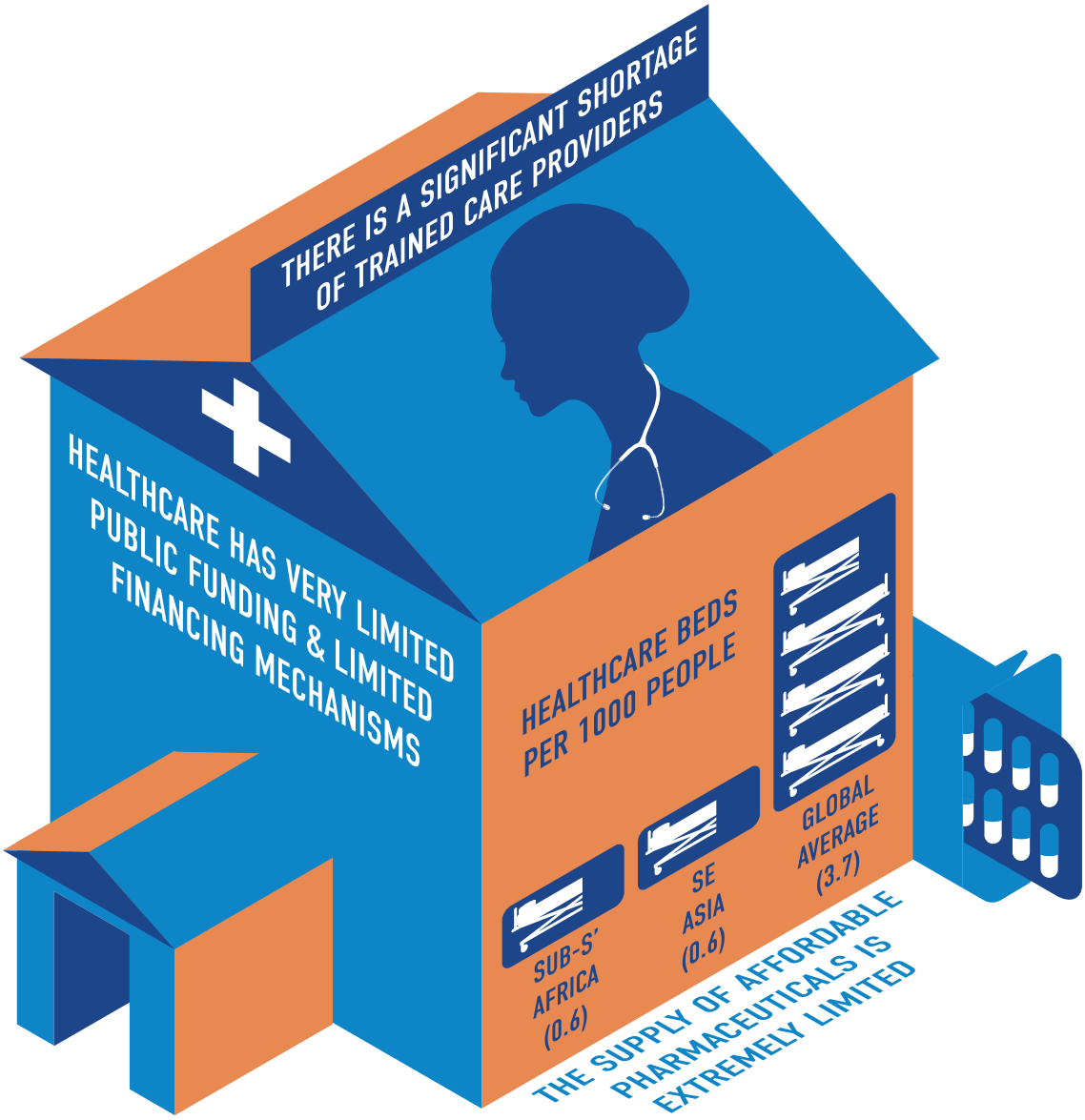


HEALTHCARE DELIVERY

INTRODUCTION

Delivery of quality, affordable healthcare for low income communities in developing countries remains a challenging and elusive goal.

More than half of the world's people have limited access to essential health services, and 400 million have no access to any health service (WHO/World Bank, 2017).

More than 800 million people (almost 12 percent of the world's population) spent at least 10 percent of their household budgets to pay for health care (WHO, 2018). Even with greater access to care, the vast gap between what providers know and what they do in practice means receiving proper treatment is an even greater challenge (Das, et al., 2018).

The problem is systemic. There are very few functioning peripheral clinics; management systems and supply chains are weak; existing medical devices are too expensive; there is a shortage of qualified providers whose incentives are not well-aligned with performance; and there is far too little funding in most developing countries to build the health system from the bottom-up.

External aid, which has historically focused on major infectious diseases, has proven neither sufficient nor sustainable for structural change. Though studies have shown that 90 percent of health conditions can be handled at the primary care level (Doherty & Govender, 2004), and 63 percent of child deaths in the 42 countries that account for 90 percent of global child mortality could be prevented each year through more effective primary care (Lancet study, 2003), primary healthcare systems in LMICs simply do not currently have the required support to deliver high quality patient-centric care, not to mention managing the changing disease burdens.

Evidently, sustainable solutions will have to be systemic. Clinicians have to be better trained and certified, policies have to be reformed in order to ensure governance and accountability, people have to be convinced to invest in preventative care, and financing mechanisms like affordable health insurance have to become widely available. In addition, the absence of affordable medical devices and the lack of access to electricity and clean water pose significant barriers to building functional low-cost peripheral clinics. Importantly, health outcomes are not just a function of the strength of the health system, but also of broader living conditions that this report covers in chapters on water security and sanitation, among others.

The good news is these issues are getting the attention they need. Universal Health Coverage (UHC), adopted as a SDG in 2015, aims to ensure individuals and communities receive the health services they need without suffering financial hardship. The scope goes beyond financing and includes all components essential to a well-functioning health system. Investing in improving in the delivery of primary care is essential in achieving UHC (SDG, 2015).

There are three breakthroughs that can improve the delivery of healthcare:

- Breakthrough 31. Integrated suite of digitally enabled primary care devices including point-of-care diagnostics, therapeutic devices and clinical operations
- Breakthrough 38. Low cost off-grid refrigerators for preserving vaccines (and other temperature sensitive pharmaceuticals) in remote settings
- Breakthrough 39. A thermo-stabilizing mechanism for vaccines and other temperature sensitive pharmaceuticals

Major investments in global health since the announcement of the Millennium Development Goals (MDGs)—from initiatives and organizations like PEPFAR, GAVI, and the Global Fund to Fight AIDS, TB and Malaria—have led to significant progress and improvements in a number of health conditions. However, these initiatives have largely been vertical programs aimed at combating specific communicable diseases, with limited investment in system-strengthening (Travis, et al., 2004). Consequently, there is now recognition of the value of diagonal approaches in which effective disease-specific programs also build elements of sustainable delivery systems (Kim, et al., 2013). Efficient and effective health service delivery, in particular for primary care, has a central role in achieving SDG 3 to "ensure healthy lives and promote wellbeing for all at all ages."

CORE FACTS AND ANALYSIS

1. There are numerous challenges that impede the delivery of effective healthcare in low-resource settings

The historical lack of investment in development of healthcare infrastructure and delivery systems remains a fundamental hurdle to improving overall national health outcomes. One important contextual factor to consider, however, is that some of the basic constraints of the past few decades may no longer be as difficult to overcome today.

Proliferation of technologies like solar-power, mobile networks and low-cost ICT devices like smartphones and tablets have made efficient and effective healthcare delivery a much more viable prospect now. Delivery can evolve from a hub-and-outreach model to a hub-and-spoke model in which brick-and-mortar clinics can be constructed in tandem with larger, better-equipped facilities. System innovations using digital technologies are increasing at a rapid rate.

Solutions that aim to influence behavior change and increase demand for services and products; strengthen the capacity of health care workforce for more effective task-shifting; and improve the quality of data collected, the way data is managed and used can all help the growth of such hub-and-spoke facilities and improve quality and efficiency of care, especially at the primary level.

While the previous chapters discussed the context and challenges associated with various health conditions that disproportionately affect low-income populations, this chapter focuses on the actual delivery of care. Delivering healthcare requires six structural elements:

1. Funds and financing mechanisms at multiple levels: Funding for public health systems; business financing for entrepreneurs interested in building clinics and providing care; and financial services like health insurance, for low income populations so that patients can afford services

2. Infrastructure: Networks of easily accessible clinics for routine care, with adequate facilities for escalation in the event of emergencies and special needs with reliable supply chain and transport

3. Human capital: Adequate numbers of trained and licensed physicians, nurses, midwives and health workers, with minimal reliance on untrained or unlicensed health practitioners

4. Pharmaceuticals: A reliable supply of effective and affordable medications for prevention and treatment of conditions common to the population

5. Equipment and medical devices: To ensure the clinics are well provisioned and functioning regularly, preserve vaccines and other sensitive materials like blood, conduct lab tests and help clinicians perform routine as well as emergency operations

6. Information and governance: Data on patient history, population-level trends and performance of clinics, clinicians and the health system as a whole in terms of access to care and quality of care, which can be utilized to develop standards, monitor compliance to those standards and hold providers and administrators accountable

All available data about health systems in low-income countries show that there are significant gaps along each of the above structural elements. The most important of these gaps are discussed further in this chapter.

KEY CHALLENGES

The hurdles to healthcare delivery, especially in rural areas, are structural and multi-faceted. The absence of a robust tax base leads to a lack of public funding, which then leads to a lack of investment in infrastructure, human capital and oversight.

1. There is very limited public funding of healthcare, with even more limited financing mechanisms

Per capita annual health expenditure in Africa and Southeast Asia, respectively, are $116 and $169; this is 4 to 5 percent of the expenditure in European countries ($2,507), and about 10 to15 percent of the global average of $840 (WHO, 2016).

In Africa and South-East Asia, the bulk of health expenditure is on private systems; a reflection of both the poor quality of public health systems as well as the higher cost of private systems.

In addition, the lack of affordable and appropriate insurance schemes or other financing mechanisms results in much higher out-of-pocket health expenditures in Africa and South Asia; 35 percent of health spending in Africa and 43 percent in South East Asia is out-of-pocket (WHO, 2015) (**Exhibit 1**).

Distribution of healthcare expenditure

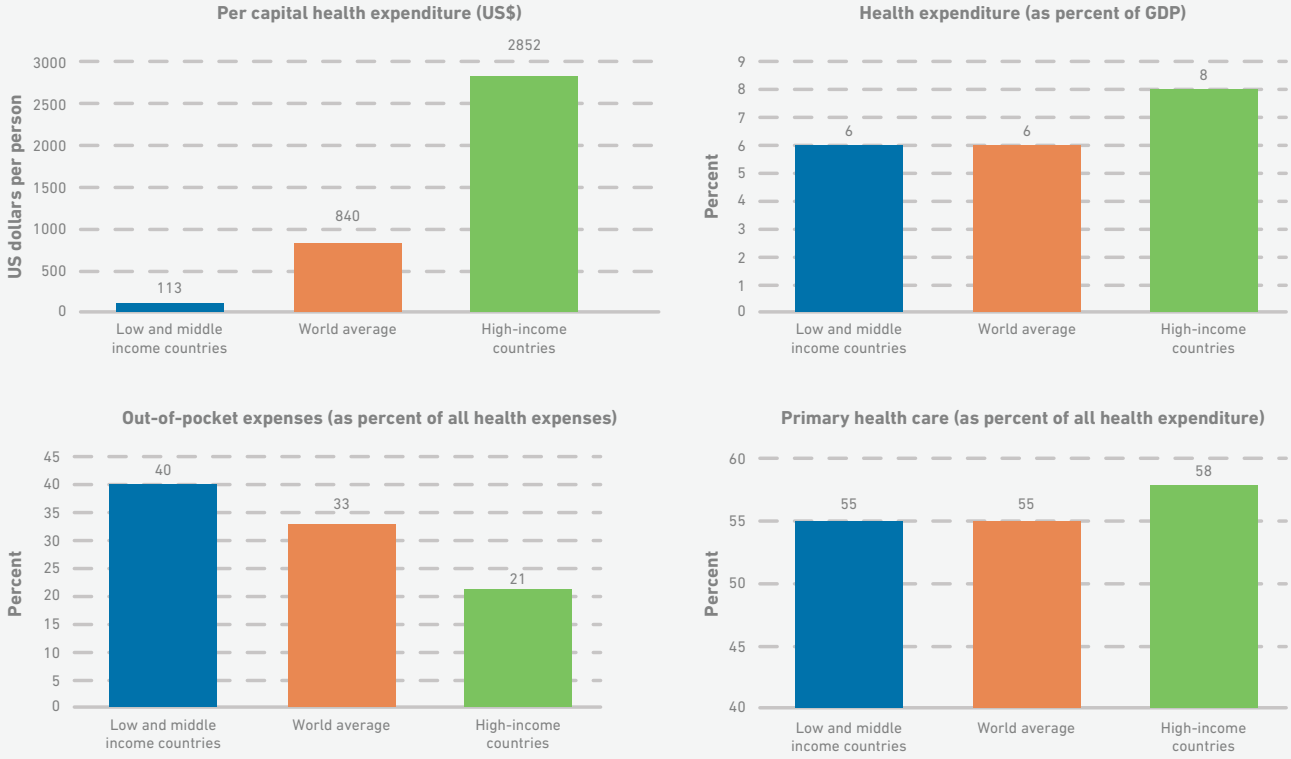


Exhibit 1: Healthcare spending per capita in low- and middle-income countries lags significantly behind world averages and high-income countries. As a result of lower public investment in health, citizens of countries in these regions incur much higher out-of-pocket expenditure. (Source: WHO, 2016)

2. Healthcare infrastructure—hospitals and clinics—is very sparse

One measure of healthcare infrastructure availability is the number of healthcare beds—across urban hospitals, rural clinics and remote outposts—available to the population. In low-income countries, there are approximately 9 healthcare beds for every 10,000 people[1], compared with 57 in high income countries (Peters, et al., 2008) (**Exhibit 2**).

Beyond these quantitative measures, several studies (Gawande, 2003; WHO, 2006; Dastur, 2008) have shown that even available clinical facilities tend of be of very low quality; few clinics have reliable electricity, lighting, running water, clean sanitation facilities and general hygiene.

As a result, patients are often treated at facilities that are not equipped to address many conditions, and clinicians have limited scope of escalating care to better-equipped facilities. Supply chain and transportation is also a big challenge and affects everything from procurement and supply of essential medicines, consumables for diagnostics, delivery of test results, emergency transport, among others.

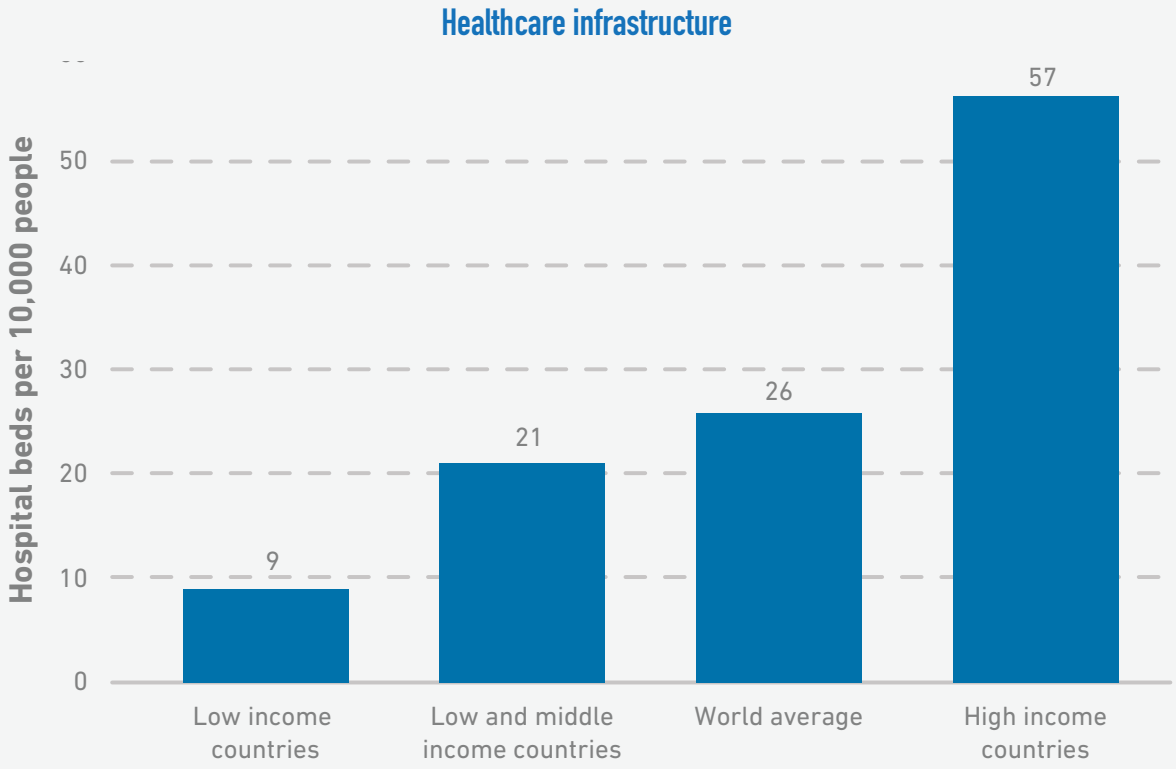


Exhibit 2: One of the most significant challenges to delivering adequate healthcare in low- and middle-income countries is the lack of hospitals and clinics, often measured as the number of beds per 10,000 people. (Source: Peters, et al., 2008)

[1]Data on the number of healthcare beds is very sparse, and these estimates represent averages from a small number of countries.

3. There is a significant shortage of human capital in the form of physicians, nurses and other trained care providers

In addition to the severe dearth of optimally functioning clinics, there is also a significant shortage of trained clinicians in developing countries (**Exhibit 3**). In sub-Saharan Africa, for example, there are fewer than 0.2 physicians and 1.1 nurses or midwives per 1,000 people.

In South Asia, there are only 0.75 physicians and 1.7 nurses or midwives per 1,000 people. In comparison, high income OECD countries have 2.8 physicians and 7.4 nurses or midwives for every 1,000 people, while the global average is 1.5 physicians and 3.1 nurses or midwives for every 1,000 people (World Bank, 2013).

This shortage of trained personnel has serious consequences for those in need of care. The majority of births in sub-Saharan Africa and South Asia take place at home and are administered by untrained health workers.

Hence, most patients at all stages of life often end up relying on unlicensed, untrained 'quacks' (Economist, 2008; Monitor, 2013) who frequently misdiagnose conditions and prescribe wrong medications.

However, the quality of care by trained providers is not necessarily superior. Researchers have found that the quality of care provided in the public sector is similar to that by informal providers in rural India (Das, et al., 2016). They also found that training improved the ability of informal providers in India to correctly manage the kind of conditions they may see in their clinics, though it did not decrease their overuse of unnecessary medicines or antibiotics (Das, et al., 2016).

These studies help pave the way to better understand the levers for improving quality of care.

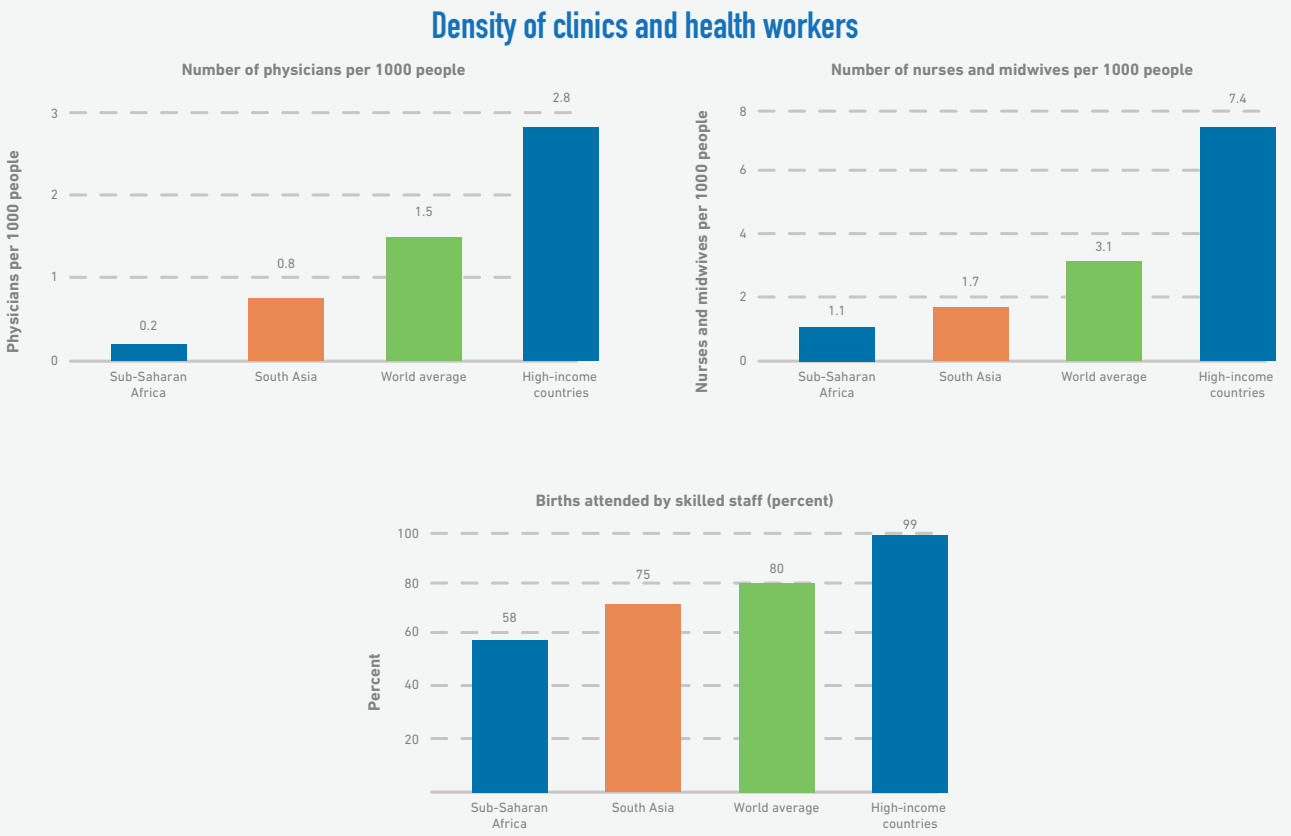


Exhibit 3: There is a major shortage of trained clinicians (physicians, nurses and midwives) to administer healthcare in developing countries. One consequence is that the majority of births are administered by untrained health workers. (Source: World Bank, 2013 & 2014)

4. The supply of affordable pharmaceuticals is extremely limited

The problem of inappropriate prescription only exacerbates the more widespread problem of inadequate access to affordable medicines. There is very little systematically collected data on the availability and affordability of medications.

In a survey of 27 developing countries, an average of only 35 percent of selected medicines were available in public sector health facilities (UN, 2008) (**Exhibit 4**). Availability was higher (63 percent) in private health facilities.

When medicines are not available in the public sector, patients will either have to purchase them from the higher-priced private sector or forgo treatment altogether (WHO, 2007). When drugs are available, even the lowest cost generics tend to be highly unaffordable.

Drugs sold in East Africa tend to cost 290 to 360 percent of benchmark international prices; hence, a month's worth of generic reference medications for a household costs between five and seven days' wages for the lowest wage rung of government employees in those countries.

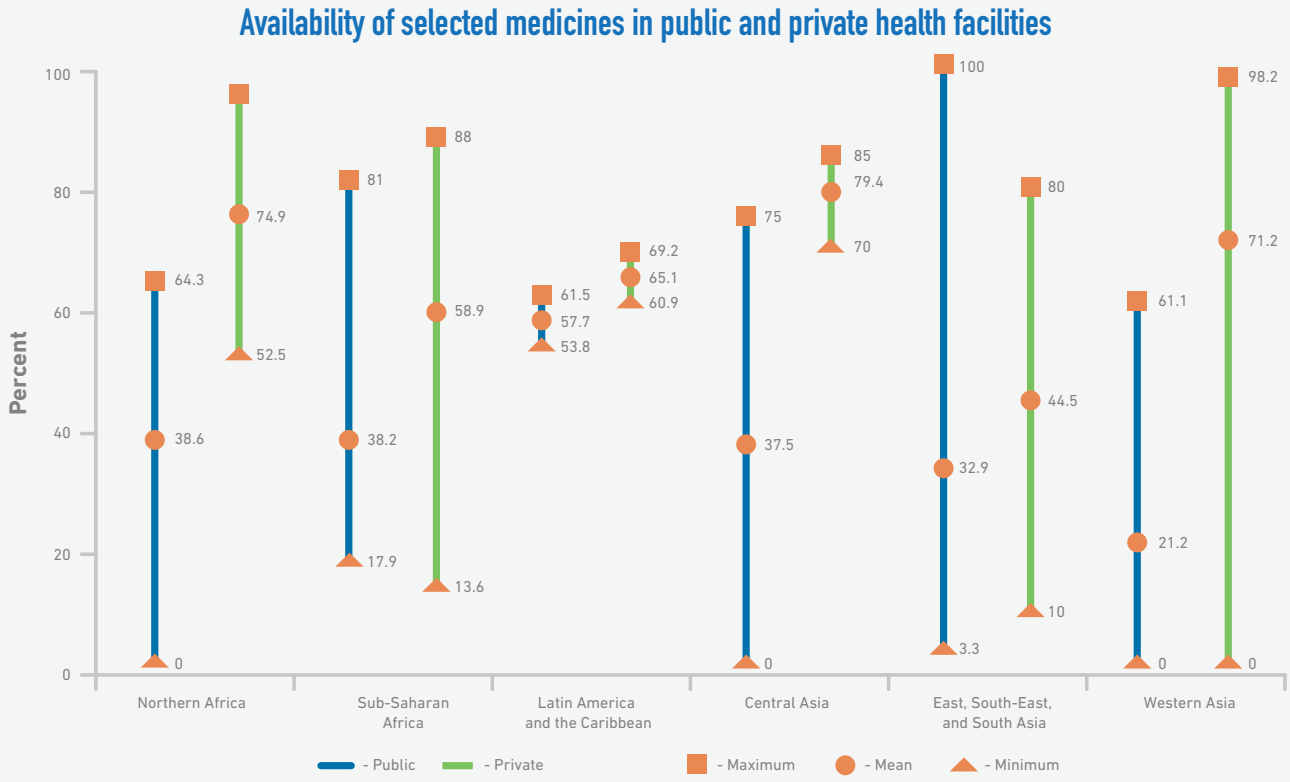


Exhibit 4: Essential drugs are typically more available in private health facilities than in public ones. (Source: UN, 2008; survey of 27 developing countries)

[27]Data on the number of healthcare beds is very sparse, and these estimates represent averages from a small number of countries.

5. Most essential medical devices on the market are far too expensive for low-income populations, and those made for developing country settings are not robust or functional enough

Many clinics, especially those in rural areas, lack basic amenities such as electricity, lighting, running water and sanitation. Urban clinics, on the other hand, tend to have access to some of these core amenities.

However, sophisticated equipment like radiology machines, centrifuges, autoclaves, medical refrigerators for vaccines and other sensitive pharmaceuticals, and diagnostic devices (beyond RDTs and basic microscopes) tend to be available only in a fraction of the medical facilities (**Exhibit 5**).

For example, for every 1 million people in sub-Saharan Africa, there are only 0.1 MRI scanners, 0.4 CT scanners and 3.6 mammography scanners, whereas OECD countries have 20.2 MRI scanners, 36.1 CT scanners and 123.3 mammography scanners per 1 million people (WHO, 2010).

According to a 2013 study in several countries in sub-Saharan Africa and South Asia by the Bill and Melinda Gates Foundation, as many as 85 percent of primary health centers, responsible for national vaccine delivery do not have any vaccine refrigerators.

In those that do have a refrigerator, between 15 percent and 50 percent of equipment are older than the recommended 10 years, after which time they are more susceptible to breakdown and poor temperature control (Ashok, et al., 2016).

As a result of the lack of functioning vaccine refrigerators, a large number of children remain adequately immunized, and approximately 1.5 million children under 5 years old die each year from vaccine-preventable diseases (WHO, 2016). Also, irrespective of the country's wealth, about one third of vaccine-storage units, which range from small refrigerators to huge cold rooms, are colder than is safe (The Economist, 2017).

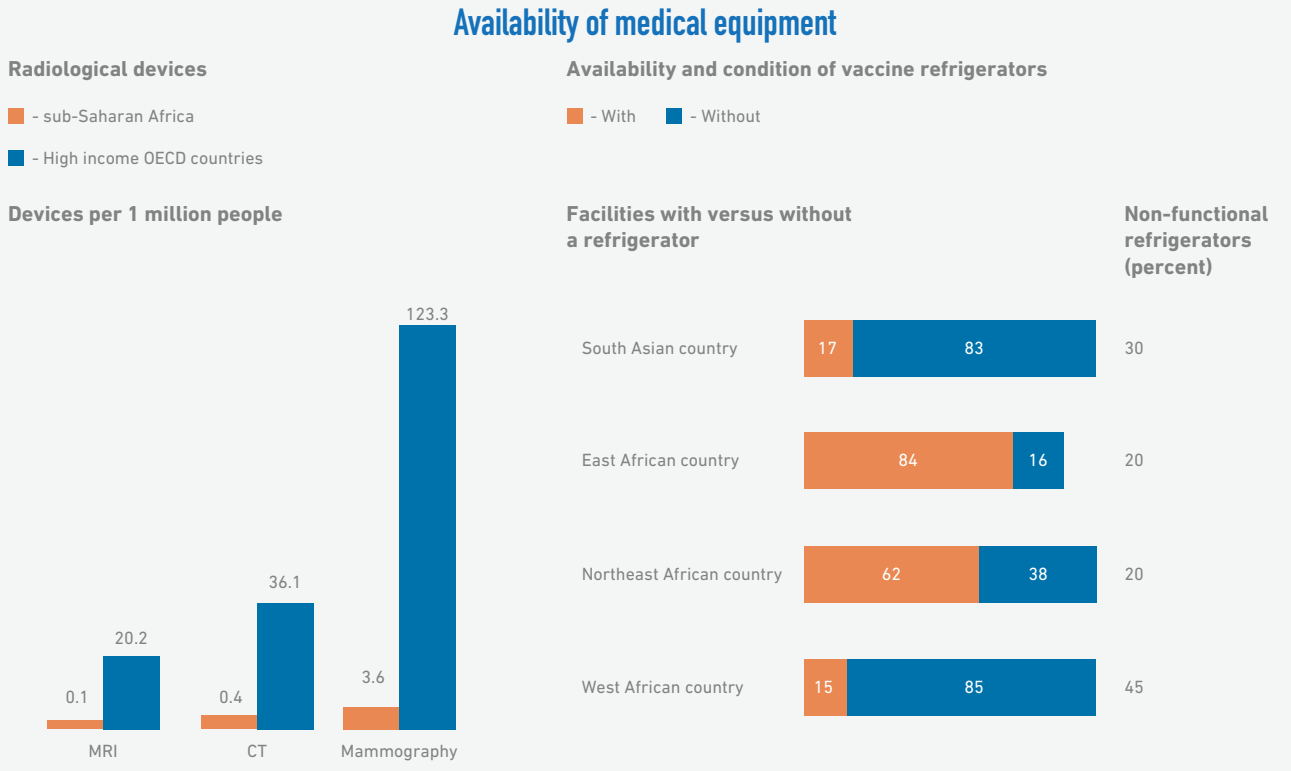


Exhibit 5: Clinics in sub-Saharan Africa and South Asia generally lack basic equipment such as refrigerators and radiology machines. The lack of vaccine refrigeration leads to large gaps in immunization. (Source: WHO, 2010; Gates Foundation, 2013)

6. There is inadequate information collected on patients or populations, leading to a lack of transparency

Most healthcare record keeping in developing countries is done on paper, if at all. This lends itself to significant problems with governance, which in turn, impacts quality of care.

There are leakages in budget and resource management; jobs are 'purchased'; there is limited meritocratic performance management of individuals, facilities, or systems; and there is significant bribery and corruption (Lewis & Pettersson, 2009).

Fortunately, the recent emergence of mHealth technologies has shown tremendous promise in remote data collection, monitoring, communication and procedural support, training of health workers, diagnosis and telemedicine (UN Foundation and Vodafone Foundation, 2009).

While the collection of data has now become more widespread, challenges remain—on effective management, long term behavior change of providers and integration of data for efficient decision-making.

As per the most recent report on Universal Health Coverage by the WHO (2015) there are major data gaps in almost every area affecting planning, targeted implementation, performance improvement, and accountability to civil society, parliament and development partners, among others.

For instance, most low- and lower- middle-income countries lack civil registration and vital statistics (CRVS) systems, well-functioning health facilities and community information systems, disease surveillance systems, health workforce and health financing accounts.

SCIENTIFIC AND TECHNOLOGICAL BREAKTHROUGHS

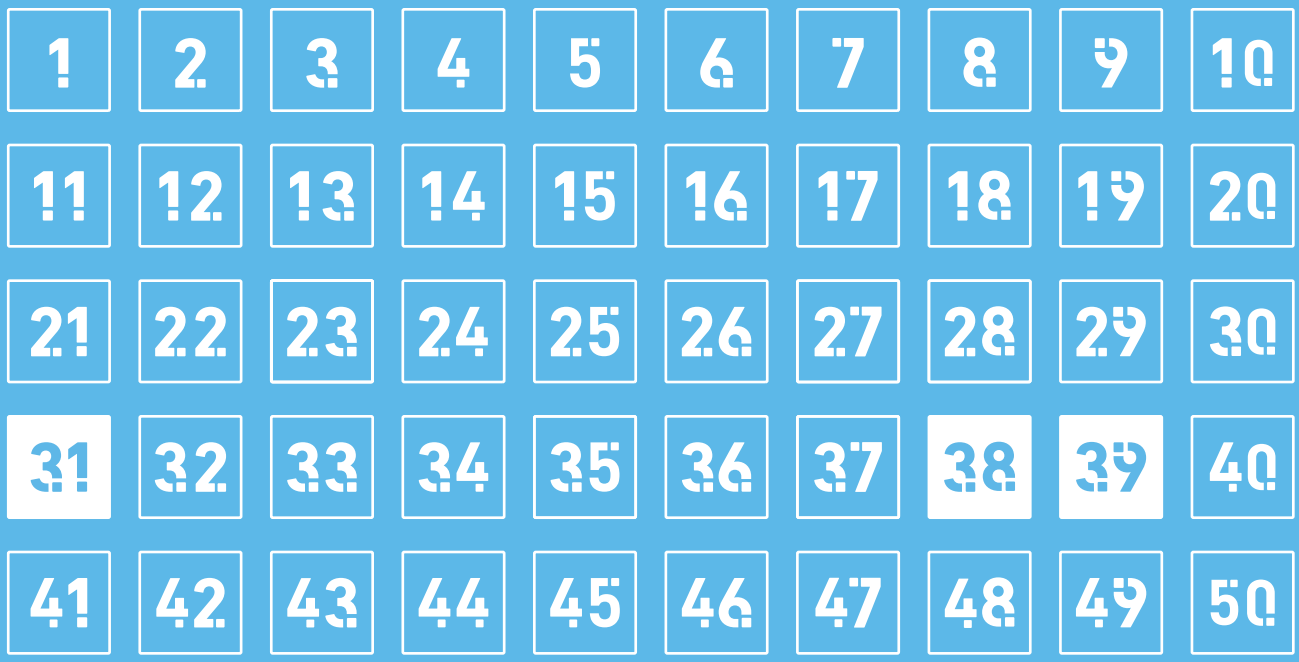
Clearly, the development of sustainable, large-scale health systems and delivery structures requires substantial funding, ideally through a local tax base powered by a robust economy.

Still, targeted gains can be achieved in the absence of substantial funding or economic development—an interim state until low-income countries reach a point where they have high-caliber institutions to train large numbers of clinicians, dense networks of facilities, adequate equipment, a functioning supply chain of medicines and consumables, and robust information management systems.

Efforts such as vaccine and blood delivery by unmanned air vehicles (UAVs), AI-powered diagnostic algorithms, and decentralized health information systems have been trialed in recent years to address the challenges in healthcare delivery.

The potential of these technologies is discussed further in the Emerging Technologies chapter of this report. Beyond these potential innovations, we believe there are three scientific and technological breakthroughs that can significantly improve delivery of healthcare.

Breakthroughs:



31 Integrated suite of digitally enabled primary care devices including point-of-care diagnostics (for basic blood, urine, and vitals tests), therapeutic devices for common conditions, and clinical operations (such as sterilization, refrigeration)

Among the many structural challenges in healthcare delivery in developing countries is the virtual absence of adequately equipped clinics needed to support the provision of primary care. The majority of clinics, especially in rural areas serving low-income populations, lack even the basic amenities, let alone the equipment necessary to provide essential services. With the shortage of human resources, it is particularly important to expand and maximize the capabilities of locally available providers (often mid-level providers like nurses or clinical officers with varying levels of training) for patient-centered care at primary care facilities.

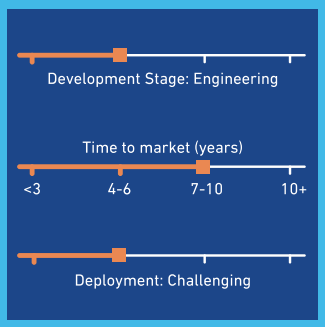
To build a clinic with the equipment necessary to provide basic primary healthcare would likely cost in excess of $100,000. This is based on preliminary research on costs of essential infrastructure (like solar panels and lighting), medical devices (like sterilizer and ultrasound) and diagnostics (such as rapid diagnostic tests and urine test analyzer) that are already available on the market, and the cost of constructing a basic building. In the absence of adequate public funding, this is too expensive for low-income populations by a factor of 10, based on our high-level assessment. In addition, the logistics of procuring the various components and assembling them into a functioning clinic require considerable effort.

A digitally-integrated suite of devices for primary care is needed, that includes point of care diagnostic devices for basic blood, urine and vitals tests. It would also include therapeutic devices for common conditions, for example, warming, phototherapy and oxygen concentration devices. It would also support clinical operations, such as sterilization devices and refrigeration for thermo-sensitive pharmaceuticals. A power management system would be integrated, including renewable energy supply where appropriate. A platform for patient and clinic management is at the core, and needs to be built using a provider- and patient-centered design approach. The focus should be on making the work of health professionals easier and better, and improving on the patient experience to ensure utilization. While maternal and neonatal intensive care devices are likely beyond the scope of this suite, health outcomes for mothers and newborns are nonetheless expected to be significantly improved, due to higher overall standards of primary care during prenatal and postnatal periods.

Such an integrated suite of devices could be a significant breakthrough if it:

- combines an integrated suite of low-cost and energy-efficient devices required to provide basic primary care:
  - Diagnostic devices and tests for relevant medical conditions including nutrition deficiencies, anemia, malaria, HIV, syphilis and hypertensive disorders

Current State



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SDG Alignment

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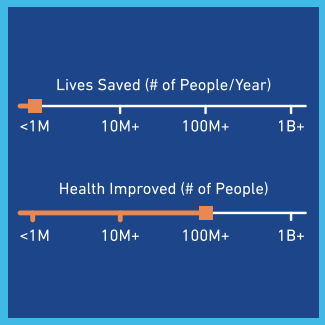


Commercial Attractiveness

- Sterilization devices for equipment
- Ultrasound devices
- Medical lighting
- Locally manufactured oxygen or oxygen concentrators
- Refrigeration to store vaccines and other thermo-sensitive pharmaceuticals;

- integrates power management, computation/ imaging, data and communication so that the various devices can function in an easy-to-install plug-and-play mode;

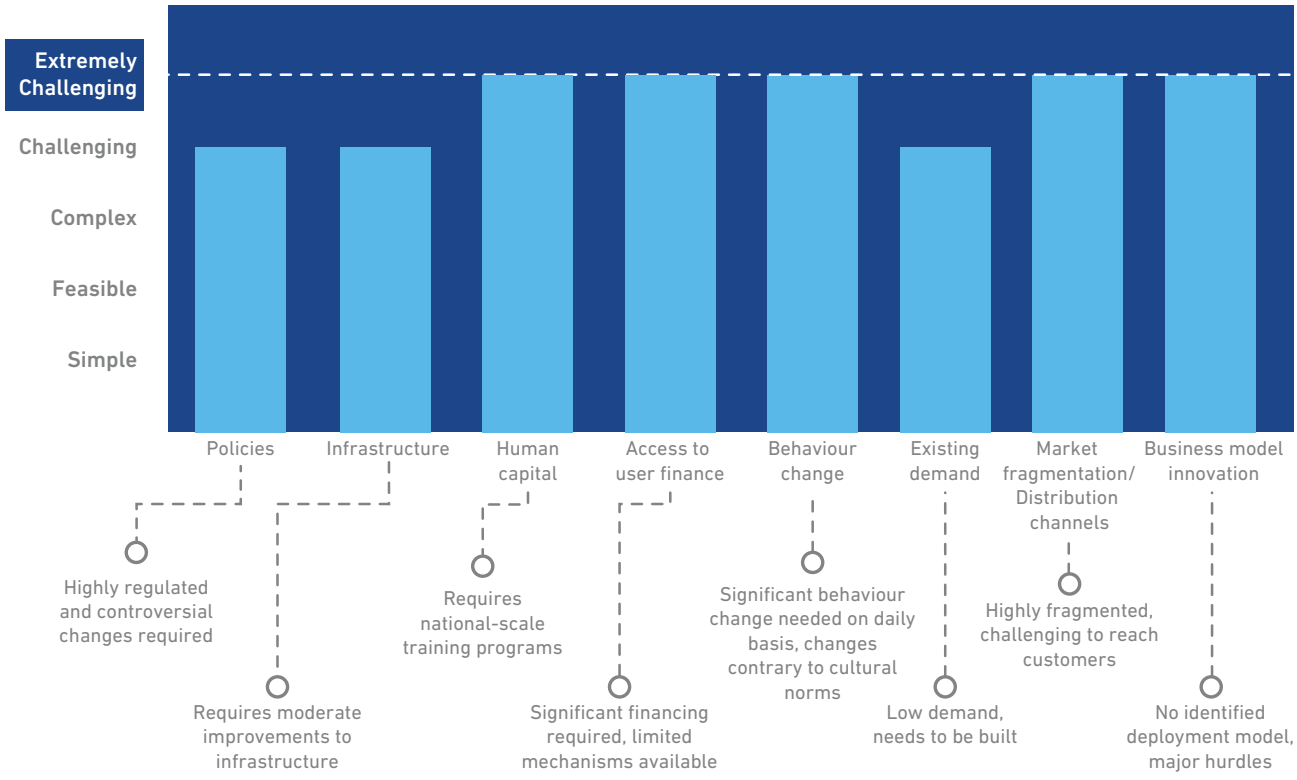
- builds on a digital platform that augments provider knowledge, experience and clinical workflows with decision support tools and diagnostic algorithms for more precise, patient-centered care; allows for remote consultation with clinicians and specialists; and enables data systems that collects and generate high-quality, timely information for decision-making and enables patient-centered care;

- costs approximately $10,000 to $15,000, based on our high-level assessment of financial feasibility, given published data on how much low-income rural families in sub-Saharan Africa and South Asia spend on healthcare.

While some of the listed devices are available at the appropriate price point, many are still priced for industrialized markets. Given the broad interest in developing individual devices, we believe enough of them are available at the right price point to begin assembling a suite of devices. There are also efforts underway to develop a digital platform to integrate the various devices. Many information and communication technology platforms exist or are in development, but most only focus on a particular area of the health delivery system or are focused around certain health conditions. It is important to note that there is no one-size-fits-all solution, particularly the design of the digital platform, across low-resource settings.

Even once such technology-enabled delivery system is developed, it will face a large number of deployment challenges. There is not enough public funding to procure a sufficient number of such clinics, the private market is underdeveloped and fragmented, and the regulatory requirements are unclear. Moreover, significant behavior change, encouraged by some form of insurance or financing to allow affordable access, is required for most low-income rural communities to seek regular and formal care. A dependable supply chain for consumables and maintenance of technologies will also be required. Hence, the difficulty of deployment will be EXTREMELY CHALLENGING.

Breakthrough 31: Difficulty of deployment



38 Low cost off-grid refrigerators for preserving vaccines (and other temperature sensitive pharmaceuticals) in remote settings

Vaccines and a number of other pharmaceuticals are highly temperature sensitive. Thermostable mechanisms likely represent the long-term solution for deploying these life-saving pharmaceuticals to remote parts of the world. In the meantime, refrigeration will continue to play a critical role in preserving and delivering them to those in need.

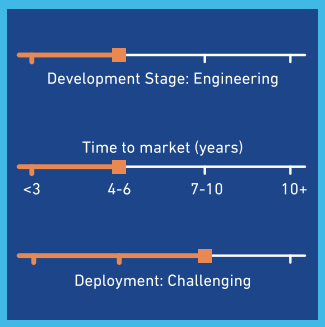
Larger storage and health facilities tend to have access to reliable refrigerators powered by grid electricity or diesel-powered generators. Smaller, rural facilities, however, have neither the necessary funding, nor access to reliable power sources.

Existing refrigeration technologies have proven unreliable or unaffordable for small, remote health centers, and for last-mile outreach. Currently, most remote health centers use mechanical compression (requiring high levels of energy, environmentally questionably coolants, and/or batteries) or absorption (requiring kerosene or gas as the fuel); these technologies are energy-intensive, heavy, and difficult to maintain.

As a result, a large number of such refrigerators are non-functioning. While there are reliable technologies for larger-scale clinics, these refrigerators are too large and too expensive for small health centers; and they still do not address the problem of last-mile outreach. Outreach campaigns have no access to active refrigerators, and have to use ice-lined cooler boxes which often lead to freezing and keep the vaccines cold only as long as the ice does not melt. As such, an affordable, portable, solar-powered refrigerator will be crucial, especially for outreach campaigns to remote areas.

In recent years new refrigeration technologies like smaller-scale vapor compressors and solid-state thermoelectric cooling mechanisms have been introduced, and are beginning to be used for small refrigerators. One such technology is a vaccine storage device called Arktek™ that can keep vaccines at appropriate temperatures for a month or more. The super-insulated device uses only ice—no propane, batteries, electricity, solar panels or other power sources are necessary at the point of use.

Current State



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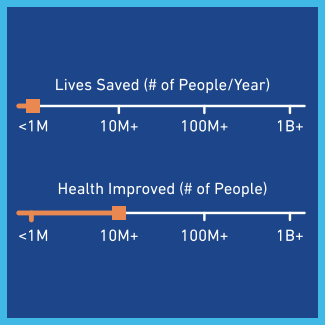


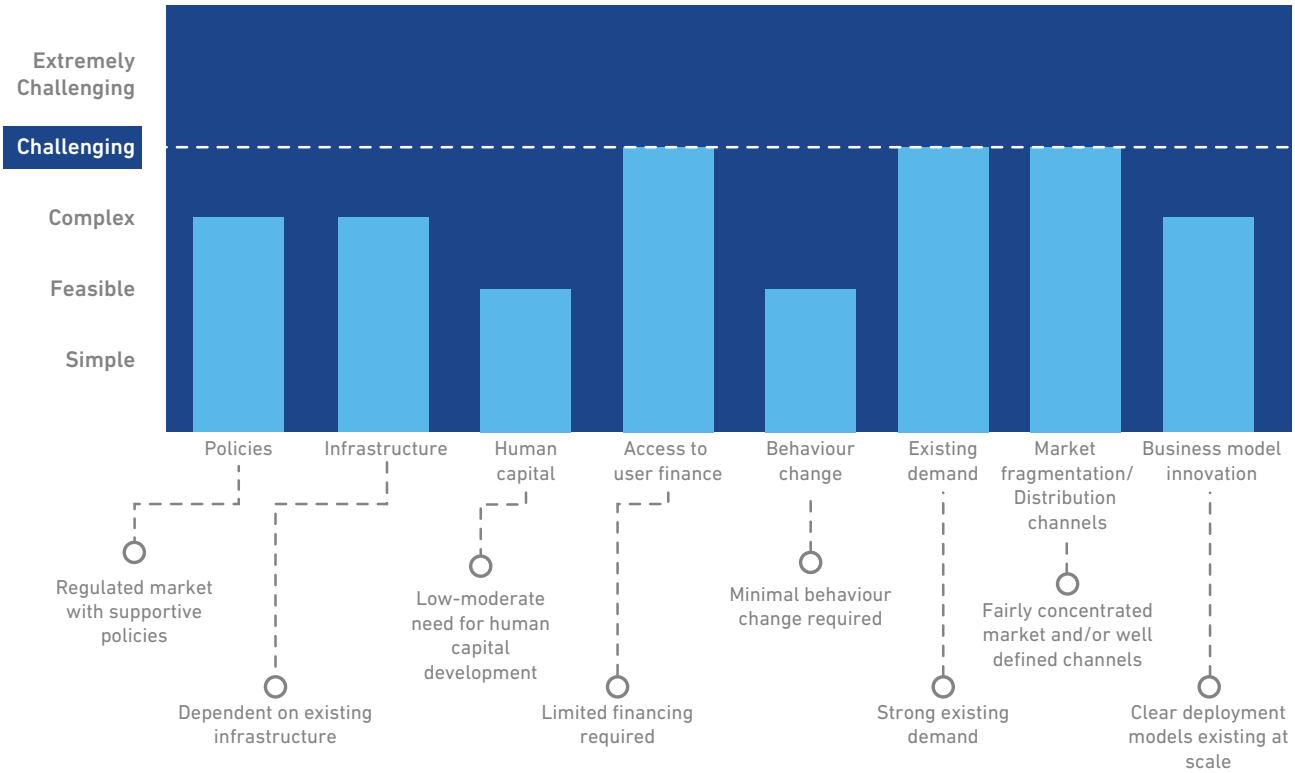
Commercial Attractiveness

Arktek™ can handle travel over rough roads and use in harsh environments, making it ideal for rural areas and for outreach work, or as a stationary device at rural health posts. Clinical trials of Arktek™ have been conducted in Senegal and Ethiopia, and the device has received positive feedback from users. In another initiative, the UNICEF is conducting drone delivery trials of vaccines in Vanuatu. Although this is innovative, viability of a scale up plan is yet to be proven.

While this is positive news, there is still no affordable market-ready technology available, nor proven refrigeration method at the scale needed for sustained outreach campaigns. A number of emerging approaches have been validated and the technology is being actively developed in research institutions and industrial facilities.

Once developed, the deployment challenges for these technologies will include a highly fragmented market with limited access to finance, sparse distribution channels, limited technical capacity along the value chain and a difficult path to creating demand. Hence, deployment will be CHALLENGING.

Breakthrough 38: Difficulty of deployment



39 A thermo-stabilizing mechanism for vaccines and other temperature sensitive pharmaceuticals

Many vaccines are thermosensitive, and need to stay between 2 and 8 degrees Celsius continuously, from the point of manufacture to the point of administration. Other life-saving pharmaceuticals like Oxytocin—used to treat postpartum hemorrhage after women give birth—are also equally reliant on refrigeration (although the requisite temperature range can vary for different types of pharmaceuticals).

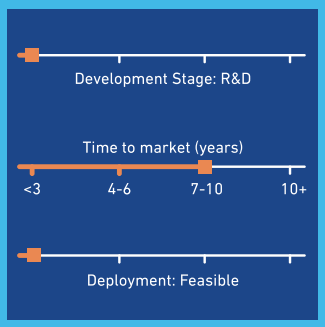
While a new generation of low-cost refrigeration technologies can make progress on vaccine preservation, the long-term solution is to obviate the need for refrigeration altogether.

The main reason these pharmaceuticals are temperature sensitive is the vulnerability of the pathogens in typical live-attenuated vaccines and the intrinsic instability of protein structures in pharmaceuticals. Therefore, the lack of electricity and refrigeration in remote areas means that many millions of individuals do not have access to critical vaccines and medications. A mechanism (such as stabilizing additives) to thermally stabilize these pharmaceuticals can substantially increase their viability and availability.

While a number of efforts are underway to develop stabilizing formulations for vaccines (like nanostructured polymers, viscous liquids like propylene glycol and novel drying sprays), virtually all of them are in early stages and none have proven applicable to the range of vaccines, especially in field tests.

Given the complexity of the R&D required, the need for rigorous clinical trials and the required approvals by various regulatory agencies, it is unlikely that a proven solution becomes market ready within the next 10 years.

Current State



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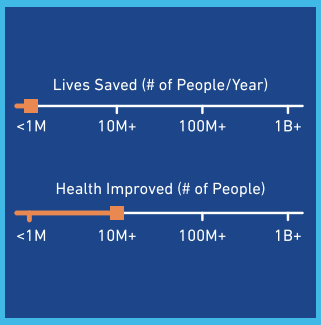
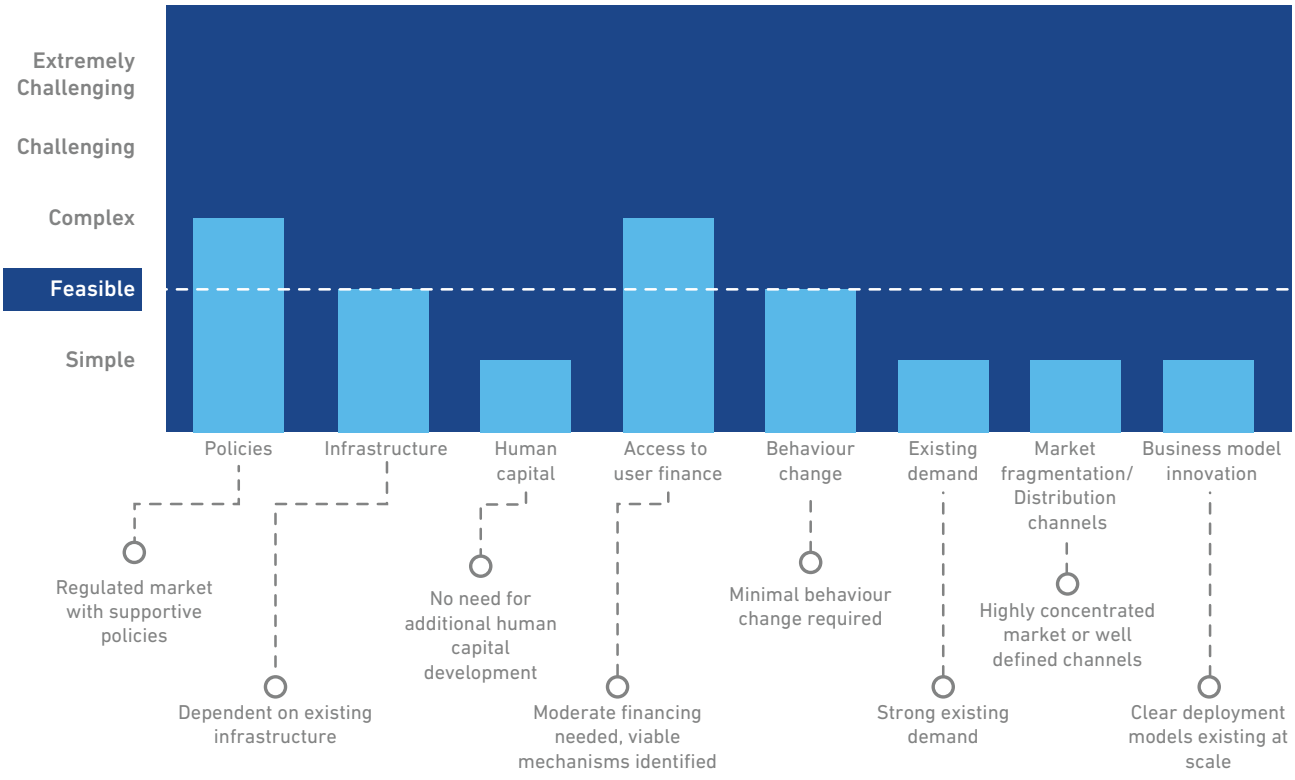


Commercial Attractiveness

Once such a technology becomes viable, the established channels for vaccine procurement and distribution, relatively strong coordination of the market for vaccines (for example through the major institutions responsible for global immunization like the WHO, GAVI and UNICEF) and the demand for such a breakthrough from these institutions will make deployment relatively FEASIBLE.

Breakthrough 39: Difficulty of deployment



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