BIOENGINEERING

Translating diagnostics and drug delivery technologies to low-resource settings

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Diagnostics and drug delivery technologies engineered for low-resource settings aim to meet their technical design specifications using strategies that are compatible with limited equipment, infrastructure, and operator training. Despite many preclinical successes, very few of these devices have been translated to the clinic. Here, we identify factors that contribute to the clinical success of diagnostics and drug delivery systems for low-resource settings, including the need to engage key stakeholders at an early stage, and provide recommendations for the clinical translation of future medical technologies.

INTRODUCTION

The Sustainable Development Goals set by the World Health Organization (WHO) seek to provide universal access to a basic catalog of "essential" diagnostics and medicines (*1*). Although this list is considered the minimum necessary for rudimentary health care, a 2008 study showed that a sampling of 15 essential medicines were available at less than 45% of medicine outlets in public health systems in low- and middle-income countries (LMICs) (*2*). Defined by the World Bank as countries with a gross national income per capita of less than U.S. $12,696 in 2021, LMICs are home to 6.5 billion people—84% of the global population (*3*). With the development of most diagnostics and drugs occurring in high-income countries (HICs) for use in HICs, many recent health care innovations are impractical to deploy in LMICs.

Health care systems in LMICs often vary greatly from those in HICs because of underlying factors ranging from limited financial resources and unreliable electricity to challenges in patient access and the limited availability of trained workers. A lack of reliable roads or public transportation can make it difficult for patients to reach quality medical care for regular checkups. For health providers, the lack of temperature-controlled transportation en route to remote clinics can disrupt the cold chain, which negatively affects the performance of diagnostic reagents, drugs, and vaccines that require refrigeration. There is also a dearth of health care professionals in LMICs, which average just 1.3 physicians and 2.5 nurses/midwives for every 1000 people compared to 3.0 physicians and 10.9 nurses/midwives per 1000 people in HICs (*4*).

In addition, environmental factors affect the type of prophylactics, diagnostics, and therapeutics needed in many LMICs. For example, preventing and treating infectious diseases is a primary concern in LMICs, but typically not the highest priority in HICs [an exception being the current coronavirus disease 2019 (COVID-19) pandemic]. About 85% of all premature deaths from communicable diseases will occur in LMICs by 2030 (*5*). Vaccines, diagnostics, and treatments for neglected tropical diseases (NTDs) receive limited industry interest because of their lack of profitability, contributing to a cycle of poverty in which chronic illness reduces worker productivity and economic influence (*6*–*8*).

Although the infrastructural needs for improved health care in LMICs must be met by other industries, there has been a substantial global effort to engineer diagnostics, drugs, and drug delivery systems that circumvent current limitations. Diagnostic devices have been developed to run on mobile battery power rather than wall outlets, which might be unreliable or completely unavailable. Similarly, vaccines that are stable at temperatures up to 40°C have been developed to reach patients and clinics outside the range of cold chains. However, most innovations intended for LMICs have not been successfully translated from the laboratory to the clinic. Although there are a variety of factors that have contributed to this lack of success, the most frequent include product cost, usability, and the complexity of conducting clinical trials in relevant low-resource communities. Gaining an improved understanding of the constraints in low-resource settings is vital to the development of health care innovations intended for those areas (Fig. 1).

It is important to note that LMICs are not monolithic environments and that there are individuals and regions within LMICs with more resources, just as there are communities within HICs that have fewer resources. Nevertheless, because many LMICs face similar challenges and because health care policy is typically governed at the national level, it is useful to refer to LMICs as a whole in regard to their resource limitations and unmet clinical needs as addressed by innovations discussed here. Communities in HICs with limited health care access not only likely stand to benefit from much of the research reviewed here but also have challenges and needs that differ from those in LMICs. Here, we highlight successes and failures in translating health care innovations to LMICs, identify common pitfalls, and propose potential solutions to advance the WHO's goal of universal health coverage, with a focus on diagnostics and drug delivery.

DIAGNOSTICS

Traditionally, medical diagnostic tests have been performed away from the patient by highly trained personnel working in centralized laboratories. In the past few decades, the need for shorter turnaround times (TATs) along with technological advances in microfluidics and sensors has produced an alternative strategy referred to as point-of-care testing (POCT), which provides results closer to

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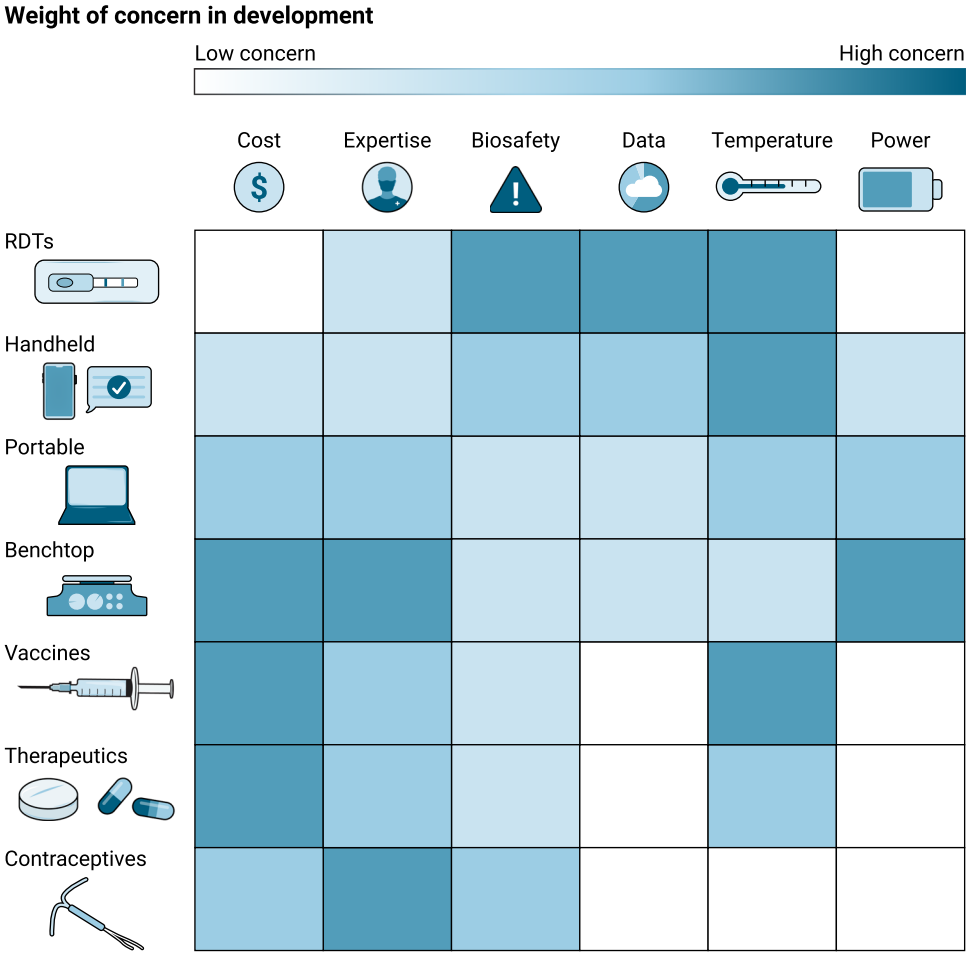

Fig. 1. Barriers to success in LMICs. Color intensity correlates to weight of concern in development. (**Top** to **bottom**) Rapid diagnostic tests (RDTs) are cost-effective and have minimal power requirements. In addition, little expertise is required to operate the test and interpret the result. On the other hand, RDTs suffer from fluctuations in temperature and poor data management and pose a high biosafety risk for both the user and the environment because their simple design does not provide for safe use and disposal. Handheld devices come at an increased cost over the RDTs; however, the cartridge design provides more protection to the user from the biological sample, and most new systems also come with some data management capabilities. Portable instruments overcome most of the drawbacks of the previous systems, but their cost is higher, and these systems tend to require more power. Benchtop instruments are the most well-equipped systems with more features for temperature and biosafety control. However, the cost and the power requirements of such systems tend to be the highest among all the diagnostic devices. Most vaccines require refrigeration and are intended for use in the entire population, increasing their cost. They are also administered by health care workers and typically produce biohazardous sharps as waste. Therapeutics are frequently expensive to develop and are often administered by health care workers; they also occasionally need refrigeration and may involve biohazardous sharps. Contraceptives can require extensive personnel training to administer, accompanying moderate to substantial financial cost and producing biohazardous waste.

the patient. POCTs have become ubiquitous in settings that require rapid TATs such as emergency rooms (e.g., the Abbott i-STAT) and in niche consumer-driven markets for use at home (e.g., glucose monitors and pregnancy tests) (*9*). Despite the advantages of small size, portability, and rapid TATs, POCT systems also come with trade-offs such as reduced accuracy and higher cost per test.

Historically, the POCT industry has focused on measuring high-abundance analytes that are important in clinical chemistry applications, including hemoglobin, hematocrit, blood gases, metabolites, electrolytes, and coagulation factors. These tests are often enabled using sensors and assays with high selectivity that can be run with minimal sample processing. Immunochromatographic methods in the form of the lateral flow assay (LFA) are also common and have emerged as one of the fastest-growing analyte detection methods in the industry. A third common type of POCT, the nucleic acid amplification test (NAAT), has also recently been realized in LFA format.

Challenges limit the use of POCTs in LMICs, underscoring the need for additional innovation. As a step toward bridging this divide, the WHO published the essential diagnostics list (EDL) in 2019, including 55 tests for "priority" infections such as malaria, tuberculosis (TB), HIV, and syphilis, as well as 58 tests targeting other common infections and nontransmissible diseases (*10*). After publishing the EDL, the WHO assembled the Strategic Advisory Group on In Vitro Diagnostics for NTDs and, in 2020, published an ambitious "Road Map" to eradicate and eliminate 20 NTDs by 2030 (*11*, *12*). NTDs are commonly found in LMICs that face social and economic struggles, which put additional constraints on NTD

diagnosis and treatment (*13*). Although POCTs are urgently needed in such settings, tests with poor performance and/or inexpert implementation can lead to misdiagnosis and subsequent problems. Thus, more sophisticated POCT technologies relying on microfluidics or bespoke sensing technologies could both improve access to health care and enable the collection of valuable epidemiological data on the prevalence of NTDs for more efficient resource allocation in these low-resource settings (*14*, *15*).

In the interest of guiding the development of portable medical diagnostics for use in LMICs, the WHO developed a set of criteria to assess whether a diagnostic test addresses the needs of the targeted population: affordable, sensitive, specific, user-friendly, rapid and robust, equipment-free, and deliverable to end users, or ASSURED in short (*16*). Despite recent efforts, ASSURED remains largely out of reach for today's POCTs (*17*); a more realistic minimum set of criteria for POCT destined for LMIC settings is small, portable, and affordable (SPA) (*18*). Although SPA is a more achievable goal, demonstrating proof of concept in a laboratory with stable electric supply, controlled temperature and humidity, and the convenience of powered cold storage does not demonstrate usability in LMICs, where unpredictable environmental factors can compromise even the most innovative of methods and detectors (*19*). In 2015, the Whitesides group (*20*) described a framework for the development of low-cost diagnostic devices required to move from the laboratory to the field, which constitutes a useful guide for any research group that plans to challenge their system in a real low-resource setting.

Clinical chemistry

Clinical chemistry has long been an attractive target for POCT development. Tests that fall in this category include assays for host analytes and those from infectious species. These tests are important in near-patient situations, especially in emergency scenarios to guide split-second decisions, and therefore, there have been many attempts to bring these tests to the bedside in LMICs (*21*, *22*). The tests in this category take diverse forms; here, we focus on those that do not require antibody-antigen interactions or nucleic acid amplification, which are covered in subsequent sections.

In 1991, Gong and Backenstose (*23*) reported the validation of Hb-Quick, a portable, battery-powered hemoglobinometer. With good precision, accuracy, and linearity, their hemoglobinometer was designed to be used by clinicians, and successful deployment of the Hb-Quick in physician's offices proved that these devices were compatible with operation by untrained personnel. Similarly, an LFA-like test for the determination of hemoglobin in blood was developed in 2013 (*24*). Using only prepatterned paper and a portable scanner, the test was able to measure the concentration of hemoglobin in blood that had been premixed with the Drabkin reagent, yielding results highly consistent with an expensive hematology analyzer comparator (R^2 = 0.9598). The test was further adapted and optimized to detect sickle cell disease and was validated in Angola with 94% sensitivity and 97% specificity at an estimated U.S. $0.07 per test (*25*, *26*).

A paper-based test was developed to monitor liver function by the semiquantitative determination of aspartate aminotransferase and alanine aminotransferase, intended for use in LMIC settings (*27*). The standard test in HICs requires highly trained technicians and expensive instruments, and testing in LMICs has been limited to centralized laboratories with long TATs. In this paper-based test, the user loads whole blood on one side of the device, which comprises a plasma separation membrane, two layers of patterned paper, and lamination for environmental protection. Each patterned zone contains all the reagents required for each assay, producing a visible result on the other side of the device within 15 min. The authors validated the device performance in 233 clinical samples, showing >90% accuracy compared to the clinical gold-standard technique. This success was followed by evaluation at the Hospital for Tropical Diseases in Ho Chi Minh City on 598 patient samples in which they saw 96.3% agreement with the clinical laboratory standard (*28*).

A low-cost POCT for sickle cell disease using aqueous multiphase systems, called SCD-AMPS, was evaluated at the University Teaching Hospital in Lusaka, Zambia (*29*). This test uses a capillary to separate erythrocytes based on their density (Fig. 2, A and B) (*30*). The authors identified some uncontrolled variables not accounted for in a standard laboratory setting, including the storage and shipping conditions of the reagents and variability among the device batches. Because the assay required a centrifuge, the authors deployed a small centrifuge powered by a car battery (Fig. 2C) to evaluate the potential portability of their system for testing at rural health centers in Zambia. A further study of an updated SCD-AMPS paired with a multiphase analyzer in Zambia demonstrated 98% diagnostic accuracy compared to high-performance liquid chromatography, a gold-standard test that requires funding and infrastructure not feasible in low-resource settings (*31*).

Last, the so-called diagnostic fidget spinner (Dx-FS) was recently reported to diagnose bacterial urinary tract infections (Fig. 2, D to F) (*32*). The user filters a urine sample by spinning the device, such that the centrifugal forces cause the sample to flow through a membrane that retains any bacteria present for subsequent analysis. Upon exposure to the detection solution and additional spinning, bacterium-containing samples developed a yellow color distinguishable by eye after incubation at 37°C for 45 min. To demonstrate the applicability of their device, the authors performed a validation study at the Kauvery Hospital in Tiruchirappalli, India, finding similar sensitivity and specificity to conventional diagnosis by culture, which requires a microbiology laboratory. A Dx-FS kit, capable of testing two samples, costs U.S. $0.48; if coupled with a portable heater for the incubation step, then this method has potential to be a useful system for a wide range of applications in LMIC settings.

Immunoassays

Immunoassays rely on antibody-antigen interactions, in which the detection of a reporter molecule indicates the presence or absence of the target analyte. Depending on the source of the sample (whole blood, plasma, serum, urine, and saliva) and the steps required, immunoassays can be completed within seconds to hours. Microfluidic technologies have been a primary driver of the translation of immunoassays to POCTs. Several advances such as multidimensional paper networks (*33*) and devices bearing arrays of microchannels (*34*) have paved the way; however, multiple microfluidic modalities may be integrated to allow performance of a complete immunoassay at the POC (*35*). Challenges including chip fabrication cost, reagent storage and delivery, signal detection, and ease of use must be overcome. Immunoassay POCTs are intended to go far beyond typical clinical settings and are emerging as a powerful tool both for doctors in assessing an individual's health status and for epidemiologists in surveying population-level immunity and illness (*36*).

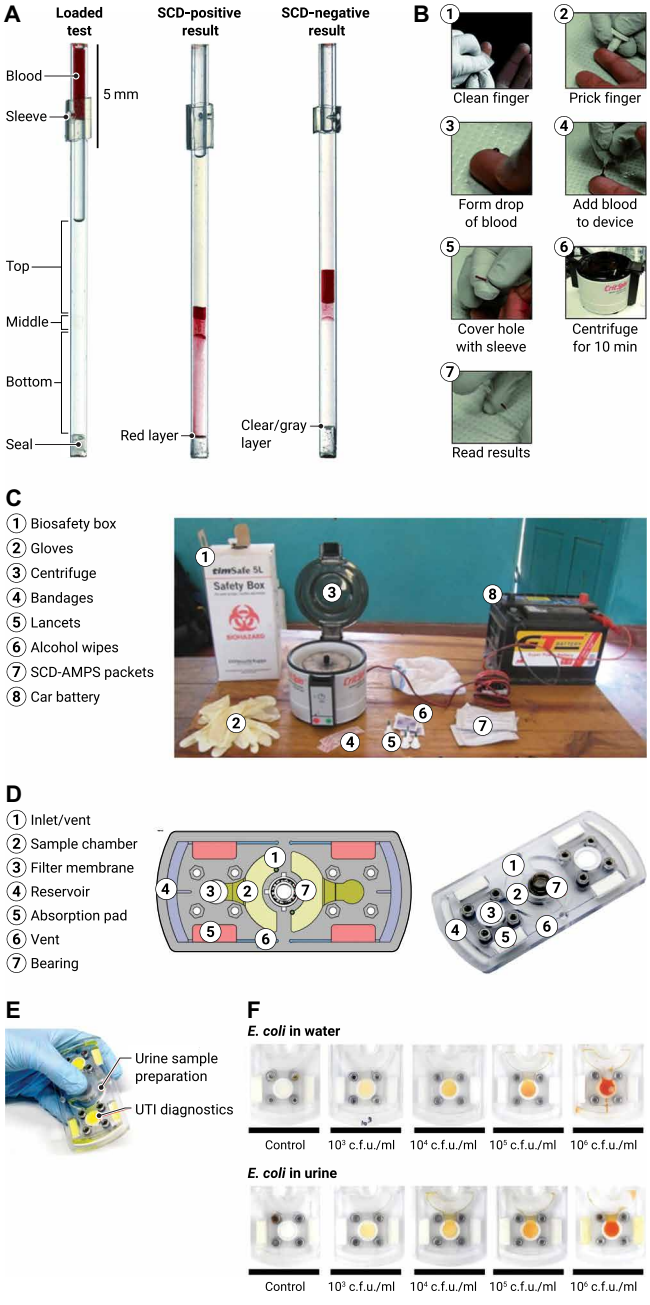

Fig. 2. Diagnostic prototype devices tested in LMIC settings—part 1. (**A**) Photographs of the point-of-care testing (POCT) for sickle cell disease based on aqueous multiphase systems (SCD-AMPS). Left: Blood wicks into the top of a capillary containing an aqueous two-phase system, which is then centrifuged to separate cells from plasma. Middle: Cells that enter the bottom phase indicate sickle cell disease. Right: Cells that remain in the top phase are normal. (**B**) Series of photographs illustrating the SCD-AMPS procedure. (**C**) Photograph of the equipment used to perform the SCD-AMPS assay in Lusaka, Zambia. Figures in (A) to (C) were reproduced from (*20*) and (*29*), with permission from Wiley-VCH and the Public Library of Science, respectively. (**D**) Two-dimensional (2D) rendering of the diagnostic fidget spinner (Dx-FS) (left) and 3D rendering of the Dx-FS with labeled parts. (**E**) Photograph of the Dx-FS indicating the sample loading chamber and detection zone, as used in Tiruchirappalli, India. (**F**) Pictures of the Dx-FS detection zone after exposure to water (top) and urine (bottom) samples containing different densities of *Escherichia coli*. Figures in (D) to (F) were reprinted with permission from Michael *et al.* (*32*). UTI, urinary tract infection; c.f.u., colony-forming units.

Immunoassays implemented in LFA format are likely the most popular for translation to LMIC settings. These systems use a porous support (or pad) to spontaneously transport the liquid sample using capillary action. As the fluid flows through the pad, the target analyte reacts with reagents on the pad, leading to the development of a readable signal (*37*). Most LFAs are designed to provide a result that is easily distinguishable by eye, with the pregnancy test being the most common example. As a result, LFA-based immunoassays tend to be low cost and easy to use, making them great candidates for POCTs, and are often called rapid diagnostic tests (RDTs). Nevertheless, because the result relies on the user's handling and interpretation, most LFAs have poorer clinical performance in the field when compared to similar immunoassays implemented in the laboratory (*38*). This drawback has led the POCT industry to design auxiliary instruments that can read the result of LFAs using optical techniques (*39*) and ubiquitous technologies (e.g., smartphones) (*40*), standardizing the assessment of the result.

The mChip, a mass-scalable microfluidic immunoassay device that performs a miniaturized enzyme-linked immunosorbent assay (ELISA), was developed for the diagnosis of HIV and syphilis in whole blood collected from pinpricks (*41*). The microfluidic cassette is injection molded from transparent polystyrene and a cyclic olefin copolymer, which facilitates production of thousands of mChip devices for less than U.S. $0.10 per chip. The cartridge stores reagents sequentially in tubing separated by air spacers and drawn out by syringe, automating reagent delivery and eliminating the need for pumps or any other external instrumentation (*42*). The mChip can process seven samples in parallel using a sandwich immunoassay based on the reduction of silver ions onto gold nanoparticles, and the signal generated is quantified using an inexpensive light-emitting diode (LED) and photodetector within about 15 min. The performance of the mChip HIV test was evaluated at the Muhima Hospital in Kigali, Rwanda, using 70 whole blood samples and 101 archived samples, where it showed a sensitivity of 100% and a specificity of 94%; the duplex mChip HIV-syphilis test was evaluated at Projet Ubuzima in Rwanda using 67 serum and plasma samples, with similarly high sensitivity and specificity for both tests compared to commercial benchtop ELISA kits.

In 2015, the mChip was updated in the form of a dongle that could interface with a smartphone (Fig. 3) (*43*). The chip was used to perform three immunoassays in parallel: an HIV test and two syphilis tests. The dongle included a chamber with a flexible lid that, when pressed, generated vacuum to move liquid within the microfluidic channels of the chip. The electronic components of the dongle were powered and controlled using an audio jack, which eliminated the need for external power supply. The microfluidic chip was deployed in three health centers in Kigali, Rwanda, where five laboratory technicians tested a total of 96 patients, finding comparable results to the gold standard with 92 to 100% sensitivity and 79 to 100% specificity. In addition, 97% of patients reported that they would recommend the dongle test to others. This technology has since been tested for acceptability in New York City as an HIV and syphilis self-testing kit accompanied by a smartphone app, with all participants reviewing the device favorably (*44*).

The Measles-Rubella Box (MR-Box) was developed to perform laboratory-quality ELISAs for the assessment of immunity against measles and rubella virus with a portable footprint (*45*). The system uses digital microfluidics, a liquid processing technology distinct from the microfluidic devices described above, which enables the

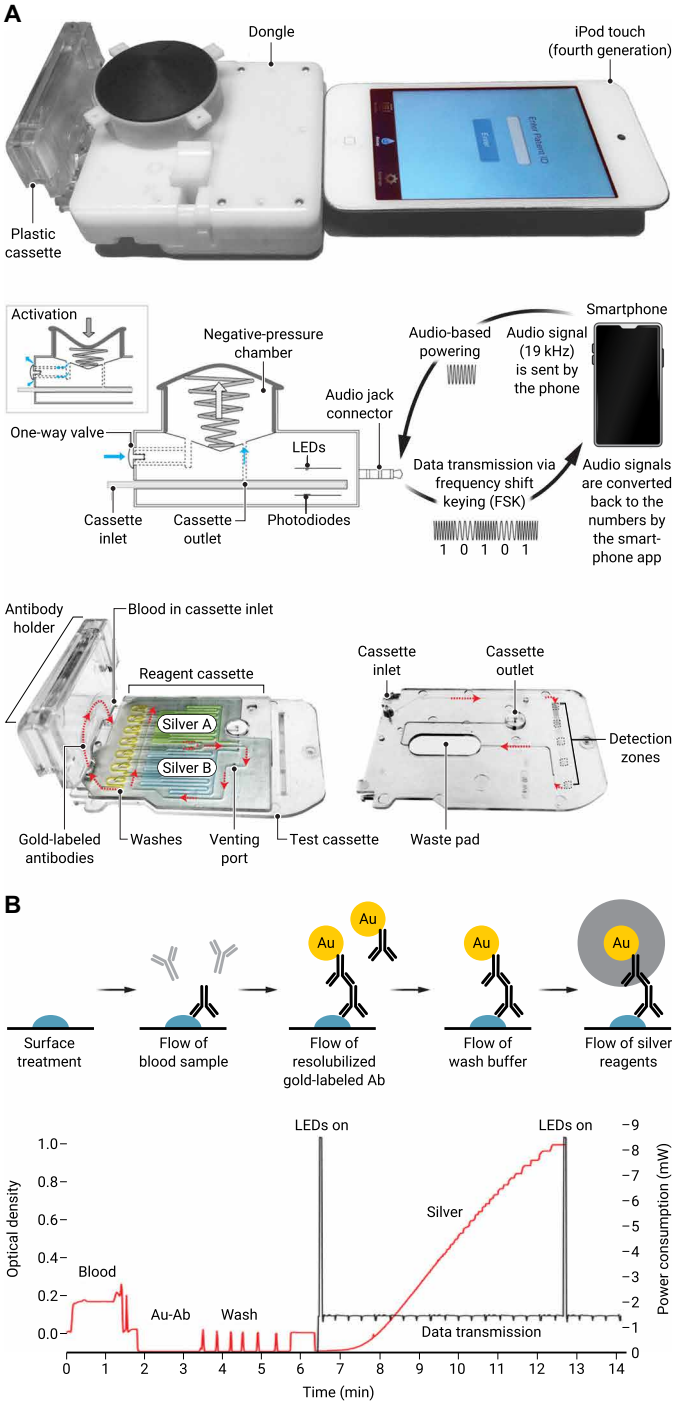

Fig. 3. Diagnostic prototype devices tested in LMIC settings—part 2. (**A**) Photograph of assembled mChip/dongle (top), drawings of dongle (middle), and photographs of the mChip cartridge (bottom) used for portable immunoassays for diagnosis of HIV and syphilis in Rwanda. (**B**) Detection scheme (left) and representative time traces (right) of power consumption (black) and optical density (red) generated from the mChip/dongle. Ab, antibody. Figures in (A) and (B) were reproduced from Laksanasopin *et al.* (*43*), with permission from AAAS.

manipulation of nanoliter to microliter droplets by applying potentials to arrays of electrodes. Building on previous reports (*46*, *47*), the MR-Box featured all the components required for a bead-based ELISA with a chemiluminescence readout, including a magnet for the separation of magnetic particles, a photomultiplier tube, and the electronics required to operate the assay cartridges (Fig. 4, A and B); the fully assembled instrument costs less than U.S. $2500, with each cartridge costing U.S. $6.00. The system was deployed in the Kakuma refugee camp in northwest Kenya where it was used to serosurvey 140 residents of the camp for measles and rubella immunoglobulin G (IgG), with both tests showing sensitivities and specificities >80% compared to laboratory-run reference tests.

In 2020, with the outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the microfluidics community turned its attention to the diagnosis of COVID-19, an application of global importance. A comprehensive summary of these efforts is beyond to scope of this report; however, a few notable examples include the works of Lin *et al.* (*48*), who introduced a portable microfluidic immunoassay system for the simultaneous detection of IgG, IgM, and antigen of SARS-CoV-2 in pharyngeal swabs, and Zhang *et al.* (*49*), who described a smartphone dongle for the rapid serological detection of SARS-CoV-2 infection (antinucleocapsid IgG) using a quantum dot barcode assay. As the pandemic has raged on, commercial LFAs for COVID-19 have become ubiquitous in HICs and LMICs alike. For example, the Foundation for Innovative New Diagnostics (FIND) database (*50*) breaks out COVID-19 diagnostics by region, country, type, and other criteria. This proliferation of tests has had mixed effects. On one hand, WHO-qualified tests have played an important role in global public health response, whereas on the other hand, the use of unqualified tests (with dubious efficacies) may have caused more harm than good. As has been the case for other tests, the translation of COVID-19 diagnostics to remote settings and LMICs has not been trivial (*51*, *52*). The performance of the Centres for Disease Control and Prevention of the African Union (*53*) has been admirable in procuring COVID-19 LFAs for the continent and providing guidance about their use and interpretation, but challenges are abundant. Some relief from these challenges may be found from local development and production of tests, as highlighted in the "Perspectives" section below.

Nucleic acid amplification tests

In contrast to clinical chemistry or immunoassays, NAATs amplify the analyte in question, typically through a series of temperature-controlled enzymatic steps, forming many copies of a given sequence for the detection of low amounts found in small samples. However, it is challenging to miniaturize and ruggedize the temperature control required, and the sensitivities of these techniques make them particularly prone to false positives outside of highly controlled environments. Low-temperature and isothermal amplification methods such as recombinase polymerase amplification (RPA) (*54*), nucleic acid sequence–based amplification (NASBA) (*55*), and loop-mediated isothermal amplification (LAMP) (*56*) show some promise for reducing the complexity of NAAT instrumentation (*57*) and for increasing accessibility in low-resource settings.

Multiple research groups have developed methods to try to overcome the inherent challenges in forming distributed NAATs for disease diagnostics. For example, a LAMP assay for the diagnosis of malaria in blood was developed to allow identification of positive samples either by eye or using a turbidimeter (*58*, *59*). Blood samples collected and tested using this assay in northwestern Thailand demonstrated 98% sensitivity and 100% specificity when verified by a microscopy standard, which requires trained technicians to interpret.

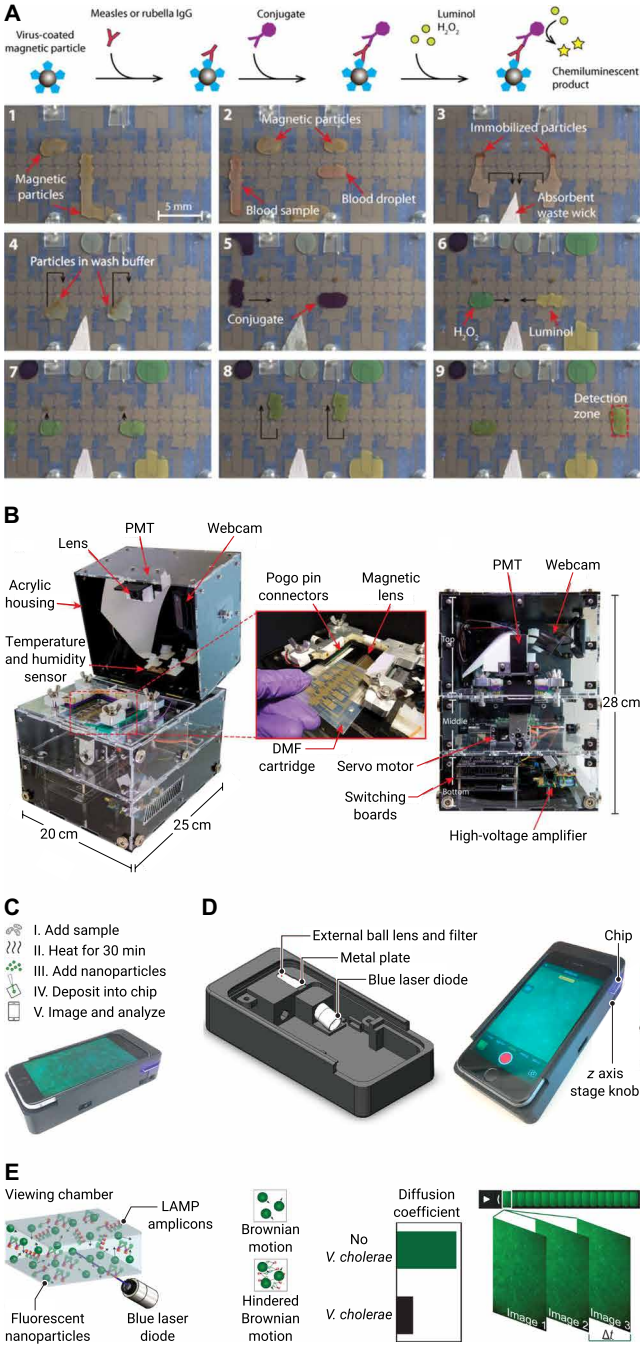

Fig. 4. Diagnostic prototype devices tested in LMIC settings—part 3. (**A**) Schematic diagram of the assay steps performed on the Measles-Rubella Box (MR-Box) (top) and photographs of the digital microfluidic chip demonstrating the nine-step process (with droplets containing colored dyes to aid in visualization) for detection measles or rubella IgG in Kakuma refugee camp in Kenya. (**B**) Photographs of the MR-Box (left, front view; inset, device; right, back view) including all the electronic components required to perform the assay. Figures in (A) and (B) were reproduced from Ng *et al.* (*45*), with permission from AAAS. PMT, photomultiplier tube. (**C**) Photograph of OmniVis instrument (left) and schematic illustrating the process (right) for analysis of cholera [used in a field trial in Bangladesh (*69*)]. (**D**) 3D rendering of the OmniVis device components. (**E**) Schematic illustrating the assay principle (left), representative renderings (middle) of data and analytes for sample with and without *Vibrio cholerae*, and stack of representative images from an assay (right). Figures in (C) to (E) were reprinted from Moehling *et al.* (*68*), with permission from Elsevier.

Although this test has yet to be integrated into a portable device, this study demonstrated the robustness of the assay and provides motivation for the continued development of more integrated systems.

More recently, a multilayer paper network for the diagnosis of malaria species combined paper origami and particles for DNA extraction, dedicated LAMP amplification sites, and LFA strips for visualizing the result (*60*). Lysis buffer and magnetic beads followed by binding buffer are used to extract DNA from the blood sample, which is then added to the paper test; folding of the paper allowed the DNA to interact with LAMP reagents. The device was tested on 67 patients in two primary schools in rural Uganda, yielding 98% sensitivity and demonstrating that paper-based devices can deliver precision diagnostics for malaria in low-resource settings.

A rapid test for the extraction, amplification, and detection of Zika virus RNA was developed to use NASBA and visualize a signal on paper using cell-free expression assays. In these systems, DNA "toehold switches" are designed to bind to a specific RNA sequence, which triggers the expression of a colorimetric enzyme. By freeze-drying the toehold switches and protein synthesis components onto paper, the reagents remain stable and ready to use at room temperature for more than 1 year. When rehydrated with a sample of RNA, the cell-free production of the LacZ enzyme catalyzes a colorimetric change from yellow to purple if the target RNA is present (*61*). The authors also assembled a portable optical reader that enabled them to monitor the color change of the substrate. In a field trial in Latin America, an adapted assay testing for Zika and chikungunya infections had a diagnostic accuracy of 98.5% across 268 patient samples (*62*).

A prototype platform, the multiplexable autonomous disposable (MAD) NAAT, was capable of performing nucleic acid extraction, amplification, and detection in the LFA format with no permanent instrument or manual sample processing required (*34*). The platform detected methicillin-resistant *Staphylococcus aureus* in nasal swab samples. All necessary heating elements and batteries to perform iSDA (isothermal strand displacement amplification) were integrated into the MAD NAAT instrument but yielded a test success rate on 33 clinical samples of only 62% (*63*). The device is currently being adapted in the laboratory for better performance and multiplexed detection of chlamydia, gonorrhea, and an array of respiratory pathogens (*64*). This is an area of intense research interest, which has led to a number of innovations, including the microfluidic rapid and autonomous analytical device (microRAAD) (*65*) and the portable, rapid on-cartridge magnetofluidic purification and testing platform (PROMPT) (*66*). PROMPT was developed for the simultaneous detection of *Neisseria gonorrhoeae* and the pathogen's resistance to ciprofloxacin in penile swab samples using magnetic beads. This platform was successfully deployed in sexual health clinics in Baltimore, MD, USA ($n = 66$) and Kampala, Uganda ($n = 151$) with >97% sensitivity and specificity for *N. gonorrhoeae* and was in 100% agreement with culture results for ciprofloxacin resistance.

OmniVis LLC, a start-up founded by researchers from Purdue University, develops diagnostics using particle diffusometry (*67*). The technology was combined with LAMP to test for cholera in water. In this test, an environmental water sample is added to a sample well that is then both amplified and imaged by the same small iPhone-enabled hardware (*68*, *69*). Water quality workers trained to test for cholera in Bangladesh (Fig. 4, C to E) showed that the device performed well, reducing the average TAT from 3 days with the previous standard technique to just 47 min. The same OmniVis technology was also used to detect malaria parasites in whole blood

without DNA extraction (*70*). The system detected quantities of the parasite that are too low to detect by microscopy, as seen in asymptomatic infections. The smartphone-based hardware was again used to amplify and detect parasite load and was sixfold more sensitive than current "ultrasensitive" RDTs.

Because we have entered the COVID-19 era, NAAT-based diagnostics have attracted unprecedented attention (*71*–*77*). Despite the short period available for method development, researchers have developed multiple viral RNA sensors. One example of note is the use of reverse transcription LAMP (RT-LAMP), which has been extensively used as an alternative to polymerase chain reaction, preferred for the absence of thermocycling and the associated instrumentation. A modification of the WarmStart RT-LAMP kit (New England Biolabs) allowed for amplification of the SARS-CoV-2 RNA, which showed 97% sensitivity and 99% specificity using 768 pharyngeal swabs (*78*). Several other groups worldwide have developed RT-LAMP assays for detection of COVID-19, tested with high sensitivity and specificity but on fewer clinical samples, with the urgency of the pandemic providing great motivation to quickly translate diagnostics into clinical use (*79*–*81*).

Portable NAATs have had substantial commercial success. For example, Cepheid (GeneXpert) (*82*), DRW (Samba) (*83*), Abbott (m-PIMA; formerly known as Alere) (*84*), and Roche (cobas Liat) (*85*) offer portable POCT NAAT solutions that the WHO has approved for early infant diagnosis (EID) of HIV (*86*). In addition, the EID Consortium (after pooling data from Kenya, Malawi, Mozambique, Tanzania, South Africa, and Zimbabwe) reported that the first two devices performed well when used in the field and operated by trained personnel (*87*, *88*). Of these systems, the GeneXpert appears to be the most broadly used system in LMICs with uses that also include the detection of other diseases such as TB (*89*). Note that there are myriad criteria related to markets, investment, intellectual property, manufacturing scalability, and supply chains that determine which technologies are adopted at wide scale. These influences are critically important but are not a focus of this Review.

DRUG DELIVERY

In 2016, there were 15.6 million more deaths in LMICs than would be expected for a population of equivalent size in HICs; of these deaths, 8.6 million were attributed to a lack of access to health care or improper implementation of good health care practices (*90*). Along with improvements to medical training and public health education, enhancing access to vital drugs is essential to closing this gap. Engineering delivery systems is one promising approach to overcoming health care challenges that LMICs are facing. These technologies can make it easier to administer therapeutics outside of medical facilities, enhance efficacy, decrease side effects, and improve patient compliance. Here, we focus on three areas in which delivery technology has, or can have, a major impact on health in LMICs: sexual and reproductive health, therapeutics, and vaccines.

Although there have been global health successes, major problems remain. For example, treatable sexually transmitted infections (STIs) are still a substantial problem in LMICs despite increased contraceptive use. In addition, therapeutics for diseases unique to LMICs are often associated with poor efficacy or debilitating side effects; vaccination is hampered by the need for repeated access to patients, cold chain deficiencies, and the lack of effective vaccines against many LMIC-endemic pathogens. These clinical needs have spurred the development of innovative delivery solutions, but many of these technologies have not progressed beyond the preclinical stage. It is therefore clear that advancing delivery technologies similar to these will require engineering solutions that meet the unique needs of LMICs.

Sexual and reproductive health

The past few decades have seen a rise in the use of modern contraceptive practices in LMICs (*91*). Access to contraception and other family planning resources reduces the incidence of miscarriages, unsafe abortions, and many high-risk pregnancies, thereby reducing maternal mortality (*92*). There is also an economic benefit, as women gain more freedom to participate in the workforce (*93*). Although public health initiatives are needed to overcome societal factors and stigma preventing greater contraceptive use (*94*–*96*), engineering more effective and easier-to-use contraceptive technologies will also help to enhance adoption.

Subdermal implants are very effective long-acting reversible contraceptives. Nexplanon (called Implanon NXT outside of the United States, produced by Merck & Co.), for example, is a 40-mm by 2-mm rod consisting of a core filled with etonogestrel (ENG) and a rate-limiting ethylene vinyl acetate membrane that facilitates the slow diffusion of ENG, a progesterone receptor agonist, out of the device (*97*, *98*). Inserted subdermally into the upper arm, the rod releases ENG at effective concentrations for up to 5 years. Implants are given access pricing for LMICs provided by the manufacturers, making them cost effective with no compliance requirement and an exceptionally low failure rate (*93*). The requirement of both insertion and removal in a clinical setting, however, inhibits their widespread uptake (*99*–*101*). Nexplanon's applicator was specifically redesigned in 2012 to improve ease of administration, reducing a major potential barrier to use (*100*). Several years after the rollout of the new applicator, a study in the Democratic Republic of Congo in 2020 showed that medical and nursing students could readily be trained to use Nexplanon's updated applicator; 95% of trainees were satisfied with their experience and 99% of patients receiving the device from these students said that they would recommend the contraceptive method to a friend (*102*).

Implantable, injectable, and oral methods of contraception have demonstrated great value but have resulted in the decreased use of physical barrier contraceptives such as condoms, thereby contributing to the increasing transmission of STIs (*103*, *104*). In 2016, the WHO estimated that 376 million new infections of the four curable STIs (chlamydia, gonorrhea, syphilis, and trichomoniasis) occur each year, with the highest prevalence in the African region (*105*). *N. gonorrhoeae* has acquired resistance to become a "super-bug" with no single reliable treatment, requiring dual therapy to treat and with very few new drugs in the experimental pipeline if existing combination therapy were to fail (*106*, *107*).

Multipurpose prevention technologies (MPTs), also called dual protection technologies, attempt to prevent both pregnancy and STI transmission and are currently in development at several research institutions. An intravaginal ring designed to provide extended dosing of levonorgestrel (LNG; a contraceptive) and tenofovir (an antiretroviral drug used against HIV) was shown in phase 1 clinical trials to maintain effective drug concentrations for at least 15 days (*108*). Given the extreme differences in both aqueous solubility and desired release rate between the two drugs, the group engineered a

hybrid reservoir system. A polyurethane sheath with a semisolid core of tenofovir, glycerol, and water made up about 90% of the ring circumference, whereas a small solid polyurethane reservoir segment containing dissolved LNG was incorporated for LNG release (Fig. 5, A to D) (*109*). A phase 2a trial was performed in Western Kenya in 2019 and 2020 (ClinicalTrials.gov identifier: NCT03762382), but the results have yet to be released.

A similar bifunctional multidrug elastomeric intravaginal ring was developed using a matrix of ethylene vinyl acetate (EVA) to store its hydrophobic drug constituents—contraceptive LNG and an anti-HIV drug—and a hollow partial core containing its hydrophilic drugs against HIV, human papillomavirus (HPV), and herpes simplex virus (HSV) (*110*). Although still in preclinical testing, a study using this device in rhesus macaques demonstrated full protection against repeated simian-HIV reverse transcriptase (a chimeric HIV model in primates) and HSV-2 challenges, prevented hormonal cycling, and showed sufficient vaginal fluid drug concentrations to suggest anti-HPV activity (*111*).

Polyphenylene carboxymethylene (PPCM), which acts as both a contraceptive and a microbicide, is another promising candidate for MPTs. Active against HIV, HSV, HPV, gonorrhea, and chlamydia, PPCM also induces a premature change to sperm to prevent successful fertilization of an oocyte (*112*). Under development by Yaso Therapeutics Inc., Yaso-GEL is a vaginal gel containing PPCM that has shown promise in vitro but is still at the preclinical testing stage (*112*, *113*).

Vaccines

Despite the great success of the WHO's Expanded Programme on Immunization, each year, an estimated 19.4 million children remain undervaccinated, leading to 1.5 million vaccine-preventable deaths (*114*, *115*). Most unvaccinated and undervaccinated children live in LMICs and often have limited access to health care (*114*). Many areas have low vaccination rates due to poor vaccine distribution; researchers found that children living more than 1 hour away from a health center were 2.8-fold less likely to complete the recommended vaccination schedule on time compared to children living less than 1 hour away (*116*). In addition, NTDs, for the most part, lack successful vaccine candidates, further increasing the infectious disease burden in LMICs.

Polio vaccination is largely seen as a success story, with polio nearly eradicated worldwide, but this outcome was not achieved quickly nor without substantial difficulty. Two effective vaccines, the Salk inactivated polio vaccine (IPV) and the Sabin live-attenuated oral polio vaccine (OPV), have been, and still are, used both separately and together to combat the three serotypes of poliovirus (*117*). OPV was preferred for its ease of administration (oral drops instead of intramuscular injection), superior immunogenicity, lower cost, and potential to immunize other individuals through vaccine strain community spread. However, the ability of the attenuated vaccine strain to mutate to a more virulent strain and cause vaccine-associated paralytic poliomyelitis has impeded eradication efforts (*118*, *119*).

To preempt reversion, one group edited the OPV genome to stabilize the virus (*120*). They made several modifications, one of which involved eliminating G-U base pairs in one segment of the viral genome to prevent the formation of a point mutation known to increase temperature tolerance and virulence. They also made a substitution in the viral RNA-dependent RNA polymerase to reduce recombination frequency and mutation rate. In early clinical

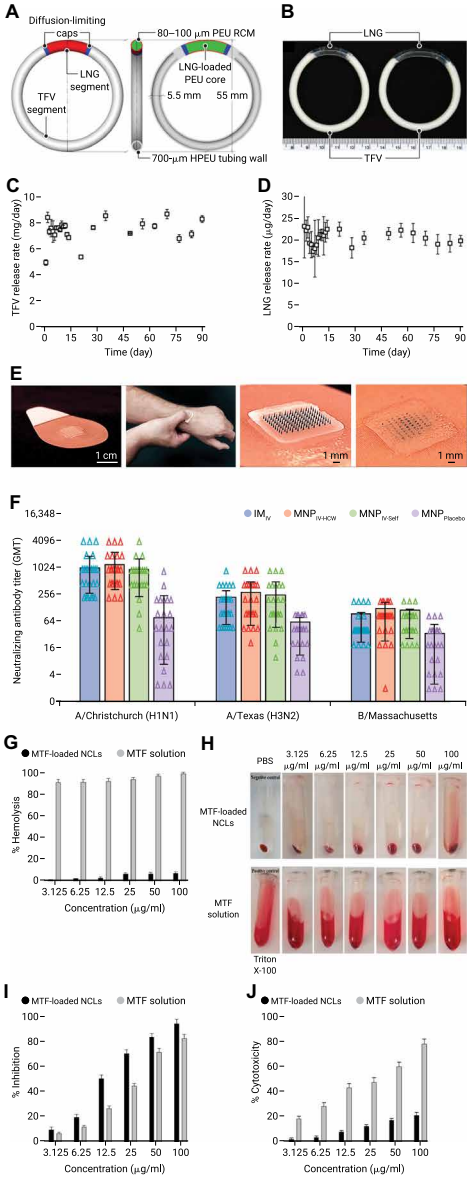

Fig. 5. Drug delivery techniques. (**A** to **D**) An intravaginal ring with two polymer phases allows different release rates for LNG (a contraceptive) and tenofovir (TFV), an antiretroviral. (A) Schematic showing external and cross-sectional views of the components of the ring. (B) Image of rings with 10-mm (left) and 20-mm (right) LNG segments. (C and D) In vitro release of TFV and LNG for 90 days from the 20-mm LNG ring. Figures in (A) to (D) were reproduced from (*109*), with permission from the Public Library of Science. (**E** and **F**) Microneedle patches provide equivalent influenza vaccination to intramuscular injection. (E) Images of the microneedle patch in use. (F) Measure of neutralizing antibody titers against three influenza strains by hemagglutination inhibition for intramuscular injections (IM_{IV}), microneedle patches administered by a health care worker ($MNP_{IV\text{-}HCW}$), microneedle patches administered by the patient ($MNP_{IV\text{-}Self}$), and placebo microneedle patches ($MNP_{Placebo}$). Figures in (E) and (F) were reprinted from Rouphael *et al.* (*140*), with permission from Elsevier. (**G** to **J**) Miltefosine (MTF)–loaded nanostructured lipid carriers (NLCs) produce fewer side effects and improved antileishmania activity to free MFT solution. (G) Quantitative and (H) qualitative measures of hemolysis by MTF-NLCs and MTF solution. PBS, phosphate-buffered saline. Graphs showing (I) increased efficacy in vitro against *Leishmania* parasite and (J) decreased cytotoxicity of the NLC formulation. Figures in (G) to (J) were reproduced from Khan *et al.* (*162*), with permission from Elsevier. polyether urethane, PEU; hydrophilic polyether urethane, HPEU.

trials, these modifications successfully caused the vaccine to remain attenuated (i.e., not regain virulence) with a striking decrease from the original vaccine form. In a clinical trial, the edited "OPV2" strain induced neutralizing antibody titers, and viruses recovered from the stool of individuals who received the vaccine retained the attenuated phenotype (*120*). Final results were posted in early 2021 (ClinicalTrials.gov identifier: NCT03430349), providing promise for future implementation.

As the Global Polio Eradication Initiative reaches what is hopefully its final stages, innovations will aid the last-stage efforts to eradicate polio from the three countries where it remains endemic. To reduce reliance on wild-type polio strains in the production of Salk IPV, a formalin-inactivated Sabin vaccine strain was developed and was found in a phase 2/3 trial to be noninferior to conventional Salk IPV (ClinicalTrials.gov identifier: NCT03169725) (*121*, *122*). Biological Mimetics Inc. developed a gamma radiation–inactivated version of the Sabin strain with the intention of improving immunogenicity by avoiding exposure to formalin; their vaccine was shown to be more immunogenic than the inactivated Salk strain (IPV), although it has not yet moved into clinical trials (*123*).

Technological advances may also help overcome vaccine cold chain storage requirements, which complicate transportation in vaccination campaign settings in LMICs. In 2012, the meningitis A vaccine MenAfriVac became the first vaccine approved by the WHO for use in a controlled temperature chain (CTC; as opposed to the full cold chain logistics approach) (*124*). MenAfriVac was developed with stability in mind, using the stable tetanus toxoid protein as a carrier, stabilizing excipients, and lyophilization (freeze drying) for long-term storage (*125*). The CTC method allows the vaccine to be stored at temperatures up to 40°C for 4 days before administration, which can both reduce cost and expand access (*124*, *126*). A 2017 analysis of MenAfriVac's impact on the African meningitis belt found a 57% decrease in meningitis cases after a vaccination campaign, with a 99% decrease in cases in fully vaccinated populations (*127*). A study of MenAfriVac administrators in Benin found that 100% of vaccinators would prefer to conduct their next campaign using CTC methods (*128*). The HPV vaccine Gardasil (Merck & Co.) has subsequently also been approved for CTC use, and the WHO is actively pursuing additional CTC-viable vaccines to further their vaccination efforts (*129*).

Accessing patients in rural areas of LMICs can be logistically burdensome, especially in the case of vaccines that require multiple doses administered over several months to achieve full effect. A method that delivers all doses of a vaccine, or multiple vaccines, in a single clinical visit would enable full protection from many infectious diseases for children after just one-time access to health care. Because 5.8 million of the 19.4 million infants that remain undervaccinated each year receive at least one dose of a vaccine, this technology could directly reduce undervaccination by almost one-third (*130*, *131*). Controlled-release delivery systems are one appealing option for accomplishing this goal. Controlled-release vaccines have traditionally exhibited continuous release (*132*), which has been shown to be as effective as multiple soluble injections in some preclinical studies. However, concerns about the propensity of excess and prolonged antigen presentation to induce immune tolerance have been expressed, and although there are minimal recent studies to support them, they may lead to increased regulatory scrutiny (*133*–*135*). One study attempted to overcome this potential challenge by creating a controlled-release platform capable of releasing antigens in discrete pulses after a material-dependent delay (*136*). This microfabrication-based stamped assembly of polymer layers (SEAL) process produces particles with a distinct antigen-filled core surrounded by a poly(lactic-*co*-glycolic acid) (PLGA) shell. By changing the PLGA used and, thus, the degradation rate of the shell, pulsatile release could be achieved from days to months (*136*). This platform was noninferior to multiple soluble injections and produced a twofold dose sparing effect in a mouse model using a model antigen. This technology could potentially be used as a delivery system for the recently developed malaria vaccine (RTS,S/AS01; brand name Mosquirix). Although this vaccine has shown some success in clinical trials, the recommended dosing regimen requires four doses administered on an unusual schedule and shows very limited long-term efficacy. A feasibility study by the WHO began in 2019 in Malawi, Ghana, and Kenya and is currently underway (ClinicalTrials.gov identifier: NCT03806465) to examine the real-world implementation and benefit of this vaccine (*137*, *138*). Preliminary results from the ongoing study motivated the WHO to formally recommend Mosquirix for children in high-transmission areas in October 2021 (*139*). Regardless of the delivery platform, delayed-release vaccine devices must provide long-term thermostability in the 37°C body, protect from possible acidification of the microparticle interior due to polymer degradation, and allow for scale-up.

Microneedle arrays provide another promising vaccination method, which have the potential to be self-administered, to eliminate the need for cold storage, and to enhance immunogenicity (*140*, *141*). Intradermal delivery of vaccine enables these systems to deliver antigen in the proximity of a high concentration of skin-resident dendritic cells, possibly allowing dose sparing and showing great promise in preclinical trials and feasibility studies (*142*–*144*). A phase 1 study using microneedle patches to deliver an influenza vaccine demonstrated both the patch's immunological noninferiority to intramuscular injections and a patient preference for the patches (*140*), supporting the prospect of self-administration in both LMICs and HICs (Fig. 5, E and F). This microneedle patch has since been adapted to the measles-rubella vaccine and is currently being studied in a phase 1/2 clinical trial that was initiated in 2020 (ClinicalTrials.gov identifier: NCT04394689). Another recent study developed a patch that delivers core-shell particles produced using a process similar to the SEAL method. By combining controlled release and the benefits of microneedle administration, this platform achieved immunological noninferiority after a single application (*145*). These microneedles provided effective vaccination against *Streptococcus pneumoniae* in a challenge model, exhibiting an immune response that was equivalent to dose-matched injections.

Immunoengineering may also improve the efficacy of low-potency vaccines. Methods to enhance the immune response to vaccines could allow poorly immunogenic antigens to confer protective immunity. Many vaccine vehicles have been developed to serve this purpose, most of which use nanoparticles to preferentially deliver antigens with or without adjuvants to the lymph nodes (*146*). Depending on their size and properties, nanoparticles can passively drain to the lymphatics, where they can enhance presentation to different types of immune cells (*147*, *148*). The low efficacy of Mosquirix prompted several groups to develop particle-based systems that have improved its immunogenicity in animal models (*149*–*151*). A recently published chemoattenuated malaria vaccine showed great promise in early clinical trials, with 87 and 78% of participants showing protection from homologous and heterologous controlled

human malaria infection, respectively, albeit with a more complex dosing regimen (*152*). For further reading, Soni *et al.* (*153*) performed a comprehensive review of immunoengineering and its role in pediatric vaccinology.

Unfortunately, the benefits of biomedical advances are not equitably distributed, and the health care gap between HICs and LMICs may be growing. The recent development of mRNA vaccines by Pfizer-BioNTech and Moderna against COVID-19 marks a new era in vaccinology, but their necessity to be stored frozen (−20°C) presents delivery challenges in LMICs, where cold chain infrastructure is not well developed. The increased cost of production necessitates a large-scale manufacturing system to become affordable, although the potentially higher flexibility in mRNA design and subsequent success rate may ultimately result in a reduction in development costs that shifts the cost-benefit ratio in favor of expanded development of vaccines for LMIC-endemic diseases. However, at present, it is likely that more traditional vaccine designs are needed to access more remote and low-income populations. An SARS-CoV-2 receptor binding domain protein vaccine, now called Corbevax, was developed as a collaboration between researchers at the Baylor College of Medicine and Biological E. Limited with the express goal to make a COVID-19 vaccine accessible for LMICs (*154*). Although still in a phase 3 clinical trial in India (Clinical Trials Registry - India number 2021/06/034014), results from a recent phase 2 trial show a low incidence of adverse events and persistent antibody titers up to 6 months after the second vaccine dose (*155*). The developers conducted scale-up optimization to minimize cost and can market their promising vaccine for $^{1}/_{10}$ of the cost of the Pfizer mRNA vaccine (*156*–*158*).

Therapeutics

Although NTDs make up 11% of the global disease burden, from 2012 to 2018, only 3.1% of therapeutic products reaching the market were indicated for their treatment, likely because of the lower financial incentives associated with developing these therapies (*159*). Some of these drugs were new, such as fexinidazole, the first oral therapeutic for African trypanosomiasis and a notable step toward decreasing the burden of this fatal disease (*160*). Others are repurposed from other applications, such as miltefosine, a cancer drug approved as the first oral treatment for leishmaniasis.

Oral miltefosine can be toxic to epithelial cells in the gastrointestinal tract, and intravenous miltefosine can cause hemolysis, producing substantial side effects and limiting its use (*161*). Given that the *Leishmania* parasite lives in the lysosomal vacuoles of macrophages and the known tendency of macrophages to uptake nanostructured lipid carriers (NLCs), miltefosine has been formulated in these nanocarriers to target the parasitic source while limiting hemolytic and cytotoxic behavior elsewhere (*162*). Miltefosine-loaded NLCs formed using a microemulsion technique reduced hemolysis 11-fold compared to the control miltefosine solution (91 to <8%) and completely eliminated gastrointestinal toxicity when dosed orally (Fig. 5, G to J). In a murine infection model, NLC treatment decreased both lesion size and parasite density to a mild infection, whereas the control drug only prevented infection from increasing (*162*). Although this formulation shows considerable promise, it remains in preclinical trials.

Often used in combination with miltefosine, amphotericin B (AmB) is a powerful antifungal therapeutic that targets ergosterol, the cholesterol equivalent unique to fungi and protozoa (*163*, *164*). Although AmB preferentially binds ergosterol, it retains some ability to interact with cholesterol, contributing to substantial adverse events including vomiting, hypoxia, and nephrotoxicity (*165*–*167*). Multiple liposomal formulations of AmB have been approved by the U.S. Food and Drug Administration (FDA) to retain the drug response while reducing toxicity. For example, AmB colloidal dispersion uses cholesteryl sulfate to form a stable colloidal complex that uses competitive binding to prevent low-affinity interactions between AmB and cholesterol but permit high-affinity binding to ergosterol (*168*). Similarly, AmB lipid complex uses two lipids to retain AmB in a complex unless it is in the presence of fungal cells (*169*). In a review of 25 trials, no significant differences were found in the cure rates between conventional and lipid formulations of AmB, but all lipid formulations were significantly less nephrotoxic than the conventional formulation (*170*).

Several nanoscale drug delivery systems have also been developed for the treatment of TB—the conventional therapy for which requires long-term adherence to a strict and often multidrug daily or weekly dosing schedule (*171*). One group has developed an inhalable TB treatment that can directly deliver drugs to alveolar macrophages, the cellular reservoirs of *Mycobacterium tuberculosis* (*172*). Dry powder inhalers (DPIs) are appealing for their independence from the cold chain, but aminoglycoside TB drugs are hygroscopic and are prone to forming soft agglomerates that can stick to the device's classifier walls and block outflow. The Cyclops disposable DPI was developed to alter the particle impaction angle to change the contact and adhesion force of drug to the classifier wall and to increase the number of air supply channels that reduce the powder contact area (*173*). Aminoglycosides were dissolved in water and spray-dried to form a powder with 1- to 5-μm particulates, which allowed doses up to 50 mg to be inhaled through the Cyclops. A phase 1 clinical trial using the Cyclops device to deliver dry powder amikacin to patients with multidrug-resistant TB began in 2020 (ClinicalTrials.gov identifier: NCT04249531).

VIGNETTE: THE MENAFRIVAC VACCINE

The development of MenAfriVac provides an illustrative example of how engaging key stakeholders early and often can play a critical role in the successful translation of drug delivery technologies to the clinic in LMICs (Fig. 6). After an epidemic of group A *Neisseria meningitidis* (Men A) in Africa killed 25,000 people in 1996–1997, the WHO commissioned a team of experts to review existing epidemiological studies of the disease in sub-Saharan Africa, data from trials of different meningococcal vaccines, and the projected cost of vaccine production (*174*). An expert panel concluded that a Men A conjugate vaccine was the most feasible, and in 2001, the Bill and Melinda Gates Foundation awarded a grant of U.S. $70 million to the WHO and the Program for Appropriate Technology in Health (PATH) to help establish the Meningitis Vaccine Project (MVP) (*175*). Later that year, the newly appointed director of MVP met with public health officials from affected countries in Africa, an important move to determine what conditions must be met for the sustainable implementation in the countries it aimed to reach. The most important request was that each dose must cost less than U.S. $0.50; an official from Niger asked of the MVP, "please don't give us a vaccine that we can't afford. That's worse than no vaccine" (*176*).

With this cost target, no industrialized vaccine manufacturer was willing to partner with the MVP for the project, even after

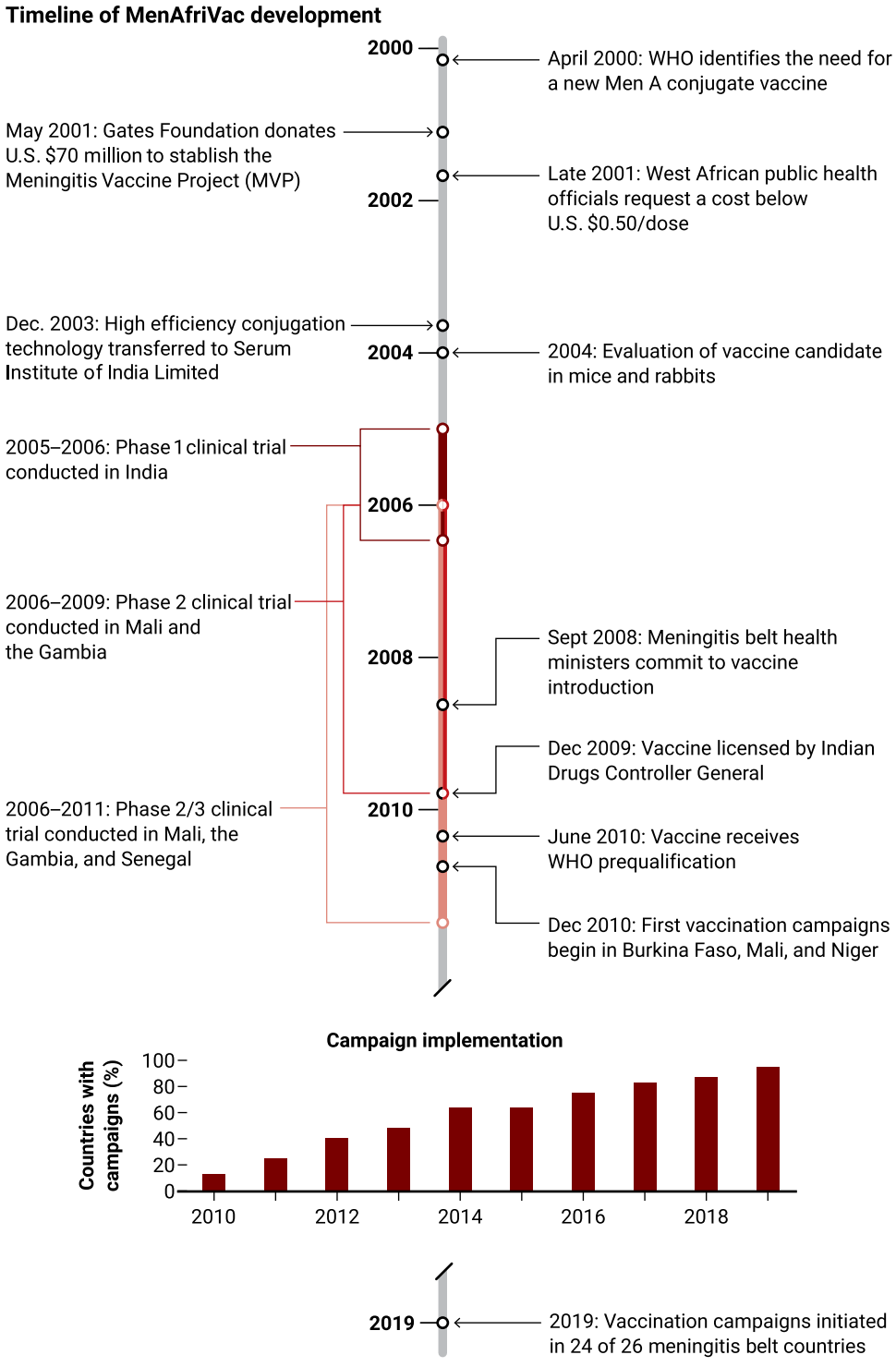

Fig. 6. Timeline of MenAfriVac development.

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additional subsidies and incentives were offered (*177*). The MVP then shifted their strategy to instead identify a manufacturing partner in an LMIC, coordinating production and establishing contracts for the most important components of the project themselves. SynCo Bio Partners in The Netherlands supplied the Men A polysaccharide, the Center for Biologics Evaluation and Research of the U.S. FDA provided the adjuvant-antigen conjugation technology needed, and the Serum Institute of India Limited supplied the tetanus toxoid and manufactured the vaccine for U.S. $0.40 per dose (*174*). By 2004, the vaccine candidate had shown efficacy and immunogenicity in mice and rabbits; a phase 1 clinical trial began in 2005 in India (*178*). Between 2006 and 2013, the MVP conducted seven phase 2 and/or 3 clinical trials in India, Mali, Gambia, Senegal, and Ghana with more than 11,000 participants in age groups ranging from 14 weeks to 29 years (*174*). In September 2008, a group of health ministers in the meningitis belt signed the Yaoundé Declaration, committing to introducing the vaccine using a prevention and control strategy endorsed by the WHO and the Global Alliance for Vaccines and Immunization—today called Gavi, the Vaccine Alliance (*179*). A dossier of clinical data through 2009 was compiled and submitted to the Drugs Controller General of India (DCGI) and the WHO; the vaccine was licensed by DCGI in December 2009 and received WHO prequalification in June 2010 (*180*). In December 2010, countrywide vaccination campaigns began in Burkina Faso, Mali, and Niger (*176*).

Over the next decade, more meningitis belt governments began MenAfriVac campaigns according to their designated risk by the WHO. By 2018, an estimated 330 million people aged 1 to 29 years had received the vaccine in 22 of 26 meningitis belt countries (*181*). In 2019, two of the remaining countries, Kenya and Eritrea, began campaigns (*182*, *183*); the final two, Rwanda and Tanzania, are conducting risk assessments to determine appropriate rollout strategies (*181*). Studies demonstrate that completed campaigns produce a 57% decrease in meningitis cases, with fully vaccinated populations experiencing a 99% decrease in cases (*127*). By fully assessing the needs and limitations of the target population at the onset of the project, the WHO, PATH, and MVP were able to adjust every step of their development process, including forgoing a vaccine candidate that was more immunologically promising but also more expensive and logistically challenging (*178*), to ensure that their vaccine would provide a real-world benefit to the people of the meningitis belt.

PERSPECTIVES

The development of new diagnostic and drug delivery technologies for detecting and treating LMIC-relevant diseases is necessary, but simply meeting the technical criteria is not sufficient. These technologies must also be engineered to function within their intended environment, which includes the careful consideration of economic, cultural, and infrastructural characteristics that may be unique to LMICs. Many innovations have been technical successes but failed to achieve widespread adoption because of unanticipated logistical factors. For example, deuterium oxide (D_2O; "heavy water") has long been known to be an excellent thermostabilizer for the OPV, but its potential for nefarious use in the manufacturing of nuclear weapons has created geopolitical pressure that prevents its use in something as widely distributed as OPV (*184*–*186*). The Cepheid GeneXpert molecular diagnostic device has been successfully rolled out through subsidization by Cepheid's High Burden Developing Country program, but studies of several instrument sites in both 2014 and 2019 showed failure rates of almost 10% due to factors such as high ambient temperatures, erratic power supplies, and dust entering the system (*187*, *188*). An assessment in Brazil in 2021 also found that the GeneXpert was cost-effective only with the subsidy from the Foundation for Innovative New Diagnostics, demonstrating vulnerability to future funding changes (*189*). Furthermore, several concerns have been voiced over the years on the robustness of the enzymes used in NAATs, because they tend to underperform or even fail as a result of fluctuations in temperature during shipping and storage at nonrecommended temperatures (*190*, *191*). Although the use of internal amplification controls has been avoided during the development of such tests, we propose that this position should be revisited for portable applications, because amplification controls could likely improve the performance of these tests in the field.

Despite the limited number of devices that have reached the clinic, those that have can serve as blueprints for the clinical translation of future technologies in LMICs. Similarly, much can also be learned from systems that failed, especially those that appeared promising until late-stage clinical trials. With a growing wealth of field experience that researchers can draw upon, there is reason to be optimistic about the future prospects of clinical translation in this area. Many technologies and methods have been reported that show great promise for LMIC deployment, but only a fraction of those have been validated in field trials and fewer still have achieved widespread implementation. The barriers to evaluating diagnostics in human trials are typically much lower than drug delivery studies involving humans, especially when the study requires only a common sample such as blood or urine and the device never directly interacts with the trial participant. In addition, trials for new drug delivery technologies often require complex biological readouts that necessitate close monitoring and follow-ups, which can be extensive and expensive. For these reasons, there have been many more reports of field testing of diagnostics to date. The ASSURED criteria for diagnostics set the bar very high, and the process of planning, preparing for, and implementing a diagnostic field trial in an unfamiliar setting is a major additional undertaking that can challenge academic scientists. These trials are quite expensive and can come with elements of risk to personal safety, and there are no guarantees that they will produce publishable data. If a trial is successful, researchers must then assemble a team to assess the overall health benefit of the innovation, often including an estimation of disability-adjusted life years saved per dollar, to make a compelling argument for adoption. Even in cases in which assays do not achieve success in LMIC field trials, they can be tremendously useful as training tools that enable scientists to better understand the environment in which their innovations will be used. This knowledge is crucial for the development of successful technologies, such as those espoused by Hall *et al.* (*192*, *193*) and Pardee *et al.* (*194*), in which reagents and materials for diagnostics are purpose-built to be inexpensive and manufacturable directly in the settings where they are needed.

Medical infrastructure is often limited in LMICs, with highly trained personnel frequently localized to cities and hospitals and with inadequate transportation options from rural areas (*195*). Therefore, innovations that minimize the need for extensive training will improve usability and accessibility. For example, a recent revision to the Nexplanon insertion device reduced the complexity of the procedure, enabling nursing students to administer it on-site rather than requiring implantation at a health care facility (*102*). Easy-to-use diagnostic devices paired with smartphone apps such as the mChip allow widespread use with minimal training required (*44*). POC and user-administered innovations in contraception and STI prevention through the PPCM gel (*112*) and in vaccination through microneedle patches (*140*, *141*, *144*) can further reduce administration burdens that exist currently because of shortage of qualified personnel. The engagement of stakeholders (e.g., medical staff, government officials, and patients) is an important step toward ensuring that administrative burdens are minimized and technologies are feasible for rollout and uptake; the early communication with health ministries in the development of MenAfriVac (Vignette) is an excellent example. Several models and frameworks exist to promote the importance of such input and to advise on their implementation, including those by Aranda-Jan *et al.* (*196*) and Fisher and Johansen (*197*).

Price minimization should be a substantial consideration in all bioengineering developments for LMICs. POC diagnostics are often developed to undercut the cost of the current clinical standard, resulting in a financially favorable value proposition. Meanwhile, open-source and do-it-yourself tools can help make diagnostics even more affordable and ubiquitous (*198*). However, the case for drug delivery systems is not as straightforward. Although incorporating a new technology to deliver an existing drug or vaccine inevitably increases its cost, the net cost of administering these technologies could actually decrease because of a variety of factors that include dose-sparing effects, improved bioavailability, reduced cold chain requirements, reduced reliance on trained health care workers for administration, or reduced transportation costs due to fewer required visits. However, even a minimal cost increase—for example, to purchase a fortified food product—may inhibit adoption if not accompanied by consumer education, perhaps making national health ministries a better target for implementation campaigns. Prophylactics and other preventative measures have the potential to offer not only clear health benefits but also clear economic benefits in the long term. Unfortunately, the indirect nature of these economic benefits (e.g., gains in future productivity) may make this a more difficult ask. Therefore, the benefits of these delivery technologies will need to be precisely studied and quantitatively demonstrated before widespread adoption.

For both diagnostics and therapeutics, organizations such as the WHO can negotiate preferential prices from manufacturers, as they

did with lipid formulations of AmB. These prices are often not universal, however. The preferential price of lipid AmB is only honored for visceral leishmaniasis treatment, although AmB is useful against many other infections (*199*). Similarly, the funds that provide GeneXpert TB test cartridges at reduced cost in many LMICs often are not provided in perpetuity; the cost increase can be up to eightfold and may markedly reduce the capabilities of extensive testing programs (*200*). Furthermore, these deals may, unfortunately, create a financial disincentive for companies to create diagnostics, prophylactics, and therapeutics intended for diseases that are unique to LMICs. In parallel, there have been efforts such as the reagent collaboration network Reclone.org (*201*) that helps scientists around the globe to gain access to reagents for research and diagnostics, both through sharing among laboratories and partnerships. In addition, the AfriDx (*202*) with the Open Bioeconomy Lab (*203*) in collaboration with the Hall laboratory at the University of Cambridge aims to supply the required infrastructure for diagnostic tests for tropical diseases to clinics within several LMICs. Drug delivery techniques may be effective at improving efficacy and reducing the side effects of therapeutics, but increasing cost may be untenable. Instead, it may be possible to use local delivery and controlled release to reduce the total amount of an expensive drug needed and thereby reduce net cost. Similar techniques provide potential for improved vaccine immunogenicity and reduced vaccine administration appointments, with the same demand for an equivalent or reduced net cost.

CONCLUSION

Although there are many barriers to the development and deployment of biomedical technologies in low-resource settings, scientists in several different fields have overcome these challenges to produce clinically impactful innovations. It goes without saying that new technologies must provide adequate function to be adopted; however, unlike in HICs, where technologies are often optimized exclusively for performance, affordability is also weighed heavily in LMICs. In an ideal world, national health ministries would not have to prioritize anything other than performance, but with limited resources, difficult cost-benefit calculations must be made. Affordability incorporates not only the unit cost of the diagnostic or drug but also the cost to develop and obtain approval for the technology, transport the components, provide training for personnel, and run the test or administer the drug. The confluence of factors necessary for success of diagnostics in LMICs is well summarized by the SPA criteria that highlight accuracy, accessibility, and affordability. Improving one of these characteristics at the expense of another (e.g., increasing specificity by decreasing rapidity) may be readily justified for diagnostics but may be more tenuous for therapeutics when cold chain limitations or prohibitive cost may preclude the use of some of the most effective drugs. Although the criteria for successful drug delivery are less well defined, technologies that have the clearest value proposition and therefore the most potential for immediate adoption are those that provide superior performance at a lower cost than the present standard of care. Optimally, delivery technologies should be thermostable, scalable, easy to administer, safe, affordable, and noninferior to the standard of care. At minimum, these engineered developments for LMICs must be both accessible and at a price acceptable to the patients or health ministries for whom it is intended. In the unfortunate but common instance where there simply are no options for diagnosis or treatment, technology that can satisfy an otherwise unmet need can provide a substantial benefit even without meeting the gold standard in laboratory or hospital care.

Despite the challenges, there is great potential to improve health care in LMICs. Because of the large addressable population, small improvements in performance or cost can have major health and affordability ramifications. For example, even a per-test price decrease of U.S. $0.10, when applied to the 2.7 billion RDTs sold for malaria from 2010 to 2019, would have saved U.S. $270 million (*204*). Vaccines against COVID-19 also provide a considerable opportunity for price reduction and cost saving; the United States is currently paying U.S. $5 to $7 per dose for the Pfizer mRNA vaccine, whereas the Indian government purchased 300 million doses of the Corbevax subunit vaccine candidate at U.S. $0.685 per dose, resulting in relative cost savings of U.S. $1.6 billion (*157*, *158*). These examples highlight the potential health and economic value that can be unlocked through additional investment in biomedical technology development specifically focused on LMICs, because an investment of millions of dollars could potentially prevent millions of deaths or lead to long-term savings in billions of dollars. Funding through the Bill and Melinda Gates Foundation, Fogarty International Center, Gavi, Tata Trusts, and others is catalyzing LMIC medical technology development that, with anticipation of LMIC-specific limitations, will improve health care equitability and ensure a healthier society for all.

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