

DISCOVERY

STRATEGY OVERVIEW

OUR MISSION

Guided by the belief that all lives have equal value, the Bill & Melinda Gates Foundation works to help all people lead healthy, productive lives. Our Global Health Program supports this mission by harnessing advances in science and technology to save lives in developing countries.

We focus on problems that have a major impact on people in the developing world but get too little attention and funding. Where proven tools exist, we support sustainable ways to improve their delivery. Where they don't, we invest in research and development of new interventions, such as vaccines, drugs, and diagnostics.

Our financial resources, while significant, represent a very small fraction of the overall funding needed to improve global health on a large scale. We therefore advocate for the policies and resources needed to provide people with greater access to health solutions. Strong partnerships are also essential to our success in making a difference and saving lives.

THE OPPORTUNITY

Innovation drives the creation of new health solutions in the developed world. Vaccines prevent devastating infections and illnesses, drugs help manage and treat disease, and medical devices enable care providers to diagnose ailments and improve overall health. Increasingly, lifesaving vaccines and other tools are reaching poor people in the developing world as well. For example, vaccines supported by the GAVI Alliance (formerly the Global Alliance for Vaccines and Immunisations) have reached more than 213 million children since 2000.

Despite a decade of progress, many health conditions in the developing world lack appropriate solutions. It is estimated that only 10 percent of all medical research addresses conditions accounting for 90 percent of the global disease burden.¹ This lack of investment results in substantial shortcomings in the prevention, treatment, and measurement of diseases and health conditions that primarily affect the world's poor.

There are still substantial gaps in scientific knowledge related not just to the diseases and health conditions of developing countries but to the tools we can use to diagnose and deliver lifesaving treatments. There are no vaccines or cures for some widespread and life-threatening diseases, such as HIV. Many diagnostic tools are either obsolete or inaccessible. Treatments for diseases such as tuberculosis (TB) and malaria are becoming less effective due to drug resistance. Moreover, due to limited support for research that addresses some of the most neglected diseases and populations, the world's best and brightest scientists are not sufficiently engaged.

OUR STRATEGY

We aim to create and improve preventative, diagnostic, and therapeutic interventions for infectious diseases and conditions affecting maternal, neonatal, and child health and nutrition. We do this in three primary ways: 1) by identifying and filling gaps in knowledge that limit our progress on the critical path to health solutions; 2) by creating new technology platforms that can accelerate research in support of our goals or enable products suited to resource-poor settings; and 3) by investing in transformative ideas to help solve tough global health challenges. The need to develop and apply solutions that can be deployed, accepted, and sustained in the developing world drives all our investments.

Our work builds on the investments of others in the fundamental sciences. We use research innovations from different fields to accelerate progress toward our strategic health priorities. We seek ideas and solutions from creative minds across the globe.

INTERVENTION AREAS

Identify and Close Knowledge Gaps in Science

A critical understanding of the scientific basis of the nature, course, and effect of the leading diseases and health conditions in the developing world is essential to creating effective health solutions. However, many

scientific questions lack answers. For example, despite years of effort, we do not fully understand how HIV, TB and malaria evade the immune response to establish chronic or latent infections. We also do not understand the relationship between the nutritional state of the host, the host environment (both immune and microbial), and the pathogen. In-depth knowledge is particularly lacking in the context of chronically malnourished individuals, who suffer from recurrent or persistent diarrhea and other infections, along with impeded growth and development. We need a holistic understanding of this pathological network to ensure the optimal performance of vaccines and development of effective interventions.

We support projects to clarify the potential role of genes, transcripts, proteins, or pathways, as well as fundamental studies of the etiology and pathology of the disease or condition. These projects aim to yield new conceptual knowledge required to identify critical leads in the development of health solutions. Some of these efforts include:

- our work with **The Scripps Research Institute** to identify molecular pathways to adjuvant vaccines through genetic processes
- studies at **Oxford University in partnership with investigators in Africa** who are addressing human, insect and pathogen genes that may serve as targets for the prevention and treatment of malaria
- efforts at **Harvard University** to identify host factors that can be targeted to control HIV infections
- exploring the contribution of the gut microbiome to nutritional health and immunologic response with partners at **Washington University**

Establish Critical Platform Technologies

Create New Vaccines

Major breakthroughs are occurring worldwide in the development of new vaccines. Vaccines against meningitis, pneumococcal pneumonia, and rotavirus have recently been licensed. Although there have been some promising new results from clinical studies, it will be a long time before we have fully effective vaccines for HIV, malaria, and TB.

In current vaccine discovery approaches, antigens are combined with adjuvants and formulated to stimulate the desired immune response. The ability to identify the best combination of antigen, adjuvant, and formulation early in the process, before more expensive and lengthy clinical studies are conducted, is critical to progress.

Our goal is to generate new vaccine leads by developing technologies that prioritize and refine vaccine candidates before costly and time-consuming clinical trials. We aim to learn about the other factors unique to the health of our target populations, such as malnutrition, enteropathy (diseases impacting the intestinal track), and co-infections, which shape the likelihood of lifelong protection against disease. We are currently supporting efforts at multiple institutions in Africa, Asia, Europe, and North America to:

- identify the specific types of immune responses that effective vaccines must elicit
- design antigens for effective, protective immunity
- improve the reliability of laboratory and animal tests used to evaluate potential vaccines prior to human trials
- identify biomarkers that are accurate surrogates of protection that might help vaccine discovery and development

Improve Vaccines for Use in Resource-poor Settings

Even after the discovery of effective vaccines, many factors must be considered before using them in the developing world. Vaccines requiring multiple doses can be problematic for families that need to travel long distances to the nearest health clinic to receive them. Refrigeration of vaccines requires continuous electricity, which is often unreliable in resource-poor settings. Vaccines delivered by injection currently require a trained professional to administer. Injectable vaccines also increase the risk of transmitting HIV, hepatitis, and other infections through unsterile or reused syringes and needles.

Our goal is to improve approaches and tools for vaccine delivery. We are currently funding efforts to:

- develop vaccines that induce long-lasting protection with a single dose
- create ways of improving or eliminating the vaccine cold chain
- devise needle-free delivery of vaccines

Create More Effective Drugs

Antimicrobials have been the cornerstone of infectious disease treatment, control programs, and elimination campaigns for many diseases. However, relatively few treatment options are available for the diseases that have the greatest impact in the developing world, and those that are available have suboptimal curative properties and often generate side effects that limit their usefulness. The recent rise in drug-resistant cases of tuberculosis and the newly observed artemisinin-tolerant malaria parasite highlight

another growing problem: The evolution of drug-resistant pathogens is increasingly compromising the effectiveness of existing treatments.

Our goal is to create a new generation of drug candidates for the treatment of malaria, TB, visceral leishmaniasis, human African trypanosomiasis, onchocerciasis, and lymphatic filariasis. We aim to develop drugs with greater potency, improved pharmacokinetics, and less toxicity than current agents. We also aim to identify agents that control diarrhea by targeting host functions (e.g., anti-secretory agents). We hope to improve substantially the outcome of treatment for diseases such as TB, eventually reducing the duration of treatment from a minimum of six months to only a few weeks.

Our strategy also emphasizes the identification of new technologies and approaches to slow the evolution and spread of drug resistance. This includes alternative-formulation and drug-delivery technologies. It also includes identifying drugs targeting mechanisms that are less likely to lead to resistance under drug pressure, such as controlling the disease rather than the infection and modulating targets in the host.

Diagnose and Measure Health Status

In the developing world, a large proportion of people with health problems make decisions about the next steps for their medical care without an accurate diagnosis. This is because they don't have ready access to institutions with the infrastructure and trained personnel to provide clinical diagnostics. Even most clinicians lack the tools to diagnose diseases and conditions quickly, accurately, and inexpensively. Sophisticated medical tests that can help improve care are often unaffordable. Furthermore, they may require extensive laboratory facilities that take days to deliver results—a hardship for people who may live many hours from the nearest health clinic.

We aim to create a new class of point-of-care (POC) diagnostics that will be easy to use, low cost, and otherwise appropriate so they can achieve a significant impact and rapid uptake in resource-poor settings. This will entail creating diagnostic technologies that don't require reliable electricity or clean water and can be provided in village settings by minimally trained healthcare providers.

We also aim to create a platform of common use, development, and integration standards. The platform would enable researchers to assess multiple pathogens and health conditions using a common set of technical, logistical, and medical decision-making approaches.

The combination of a POC test and common platform will ultimately result in better health outcomes. We will support projects investigating the creation of new components, such as signal amplification, as well as the integration of components into new end-to-end systems.

Control Transmission of Disease

Insects spread many serious diseases, including malaria and dengue, that infect millions of people annually and inflict enormous tolls on the health and productivity of individuals, communities, and entire nations. A primary strategy for fighting these diseases is the use of insecticides to kill disease-transmitting insects, or vectors. Though insecticides have been instrumental in reducing infectious diseases, they are not always successful. Mosquitoes have grown increasingly resistant to available insecticides, and some insecticides are too toxic to use on a large scale.

Our strategy supports creating and rolling out new, effective, sustainable vector-control tools to manage resistance and reduce and eventually interrupt the transmission of vector-borne diseases. We are currently making investments in the development of nontraditional biologic and genetic approaches as well as in new chemical interventions aimed at depleting or incapacitating a disease-transmitting insect population.

Improve Nutrition

Simple nutrients such as vitamin A, iodine, iron, zinc, and folic acid are vital components of human health. One study in 2008 found that deficiencies of vitamin A and zinc were estimated to be responsible for a million deaths, and a combined 9 percent of global childhood DALYs (Disability Adjusted Life Years).² The effects on children of being underweight and having vitamin and mineral (micronutrient) deficiencies are staggering: permanent disability, irreversible physical and cognitive damage, and lowered disease resistance, which increases the severity of illnesses such as pneumonia, diarrhea, and malaria.

The importance of creating reliable and affordable sources of nutritious food has taken on new meaning with unstable food prices and the added impact of an economic crisis. In times of crisis, the poor eat less of the most nutritious foods such as meat, fruits, and vegetables, and switch to lower-cost staple foods. Enhancing the levels of micronutrients and protein in staple foods consumed by the poor can reduce malnutrition.

Our strategic approach prioritizes the use of transgenesis, biochemistry, selective plant breeding, and other technologies to provide combinations of micronutrients and essential amino acids in local crops such as rice,

sorghum, cassava, and bananas. Through a number of investments, we are working toward enhancing the protein in such foods in a socially and culturally acceptable way.

Invest in Transformative Ideas

It is critical that we increase the number and diversity of intellectual resources targeted at solving the world's greatest health challenges. In addition to working with infectious disease specialists, we attempt to collaborate with the broader scientific community, engaging new minds from wide-ranging fields, including chemistry, physics, cancer biology, bioengineering, electronics, and computer science. A critical part of this is ensuring the involvement of scientists from countries affected by our priority disease areas. We invest in organizations, such as **Keystone Symposia**, that can help us foster collaborations, because we believe solutions from scientists in the developing world will ultimately be more appropriate and have the greatest chance of broad use.

Grand Challenges in Global Health (GCGH) is the primary vehicle we use to stimulate innovation and transform the way we approach problems in global health. In 2005, in partnership with **the Foundation for the National Institutes of Health, the Wellcome Trust, and the Canadian Institutes for Health Research**, we funded 45 innovative projects to meet seven identified health goals. Many of the projects are well on their way to overcoming some of the most pressing scientific and technological barriers we face in our efforts to improve the health of the world's poor.

Recognizing that great ideas can come from anywhere and anyone, in 2008 we expanded the GCGH initiative to include **Grand Challenges Explorations (GCE)**. GCE uses a simple online grantmaking process. Applications are two pages and require no preliminary data from applicants. Innovators champion proposals and award grants based on the quality of the idea and its potential for impact rather than the experience or affiliation of the applicant.

Through GCE, we are receiving creative new ideas from across the globe that may change the ways we tackle the hardest health problems. For example, Udantha Abeyratne at the **University of Queensland in Australia** is developing ways to equip mobile phones and MP3 players with microphones to record cough and sleep sounds for use in diagnosing pneumonia.

Through three rounds of GCE proposal reviews, we have awarded grants to 262 researchers from 30 countries. We have funded all levels of scientists—from young post-graduate investigators to veteran researchers—at universities, research institutes, nonprofit organizations, and private companies.

PROGRESS

Innovation can come from anywhere, yet it takes continued focus on the problem at hand to translate an idea into a usable solution. Our approach has been to define the need and reach out to the world's scientists to meet the scientific and technical challenges that stand in the way of a solution. Although most scientific discoveries typically take years, even decades, we have already seen some of our early grants yield potential real-world applications. Below are some examples of these applications.

- A group at the **University of Michigan** has achieved preclinical proof-of-principle for a nasally administered vaccine.
- The mapping of the complete malaria parasite genome has allowed **Seattle Biomedical Research Institute** to create a new vaccine candidate for malaria, based on altering critical genes needed for malaria to propagate and cause disease. The new vaccine based on the genetically attenuated parasite is entering clinical testing.
- Building on the Nobel Prize-winning work of Richard Axel on the fundamental biology of smell receptors in insects, **Columbia University** has created an assay to screen for chemicals that can block the female mosquito's ability to locate human targets. It is now actively screening compound libraries.
- A consortium of nine partners, co-led by an African organization (**Africa Harvest**) and an organization in the private sector (**Pioneer DuPont**), has achieved proof-of-principle for multiple nutritional enhancements in sorghum, a staple crop. The consortium has stacked multiple genes into a single line of sorghum to enhance iron and zinc availability and improve protein quality and digestibility.
- A program called the **TB Drug Accelerator** provides grants to organizations working to advance knowledge of the persistence of TB. It helps identify new ways to target the pathogen, develops new tools for drug discovery, and discovers new leads. This comprehensive discovery effort will lay the groundwork for the development of new TB drugs for ultra-short treatment regimens.

CHALLENGES

While discovery research can enhance the likelihood that we will achieve our health impact goals, challenges still remain. Transformative innovations may require rethinking the path through development and delivery. Questions such as how to test a tool or technology, how to introduce it, and who will use it must be considered from the start. Ideas outside the current paradigms already face high barriers.

In times of economic constraint, tolerance for risk and innovation, as well as willingness to invest in long-term solutions, usually declines. We need governments to make long-term commitments to fund and support research and development to ensure that we can dramatically change the landscape of available health solutions in years to come.

We know that great ideas with the potential to yield huge gains in health outcomes can come from anywhere. It is difficult and time-intensive to reach the people who have those ideas and convince them to focus on global health, so we have to continue to explore new ways to engage others in pursuing critical global health goals.

WHAT WE'RE LEARNING

Our investments in discovery are modest relative to the resources available from governments and the private sector. We've learned that we need to focus diligently on the problems directly on the path to the health solutions needed in our priority areas. Defining the goal in the context of the problem and the target population is essential. A clear set of objectives and a documented research plan with defined decision points and milestones help identify and resolve questions in direction and management as they arise, focusing teams on issues critical to success. We must also be willing to create new paths where the potential health impact outweighs the challenge of creating them.

Our work has highlighted the need to address ethical, social, and cultural issues early. These issues can influence the likelihood of success of a research project and shape the path to acceptance and uptake of the final product.

Scientific inquiry and technological innovation are not always linear and predictable, so flexibility is important. The ability to shift course, change project structure, and rebalance the relative effort devoted to various aspects of a project over time is essential to resolving unexpected problems and capturing opportunity.

We have learned that we can facilitate success through collaboration. Sharing results of early findings can catalyze the discovery of solutions to technical challenges. We also have an important role to play in bringing partners to the table that can provide additional funding and/or amplify our potential for impact.

THE WAY FORWARD

We are working intensely to discover new low-cost tools that can be used to prevent, diagnose, and treat a host of diseases and to improve the health of the world's poor. Given the magnitude of this goal, we look toward our government, academic, business, foundation, donor, and community partners for their continued collaboration and commitment to this work.

The private sector is an essential partner in turning concepts into real products for people. Whether for the discovery of vaccines, fortified foods, or insecticide-treated bed nets, we rely on the participation of the pharmaceutical, food, and other industries for facilitating development and delivering innovations to those who need them. Without their involvement, the discovery of new technology-based health solutions would be greatly compromised and their translation into accessible products would not occur.

Given the substantial scientific and technical challenges that remain, we look to scientists from across disciplines, sectors and geographies to turn their attention to these compelling health issues. It is their ideas that will transform the health of the poor.

TO LEARN MORE

About the Global Health Program:
www.gatesfoundation.org/global-health

About Discovery:
www.gatesfoundation.org/healthscienceandtechnology

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Guided by the belief that every life has equal value, the Bill & Melinda Gates Foundation works to help all people lead healthy, productive lives. In developing countries, it focuses on improving people's health and giving them the chance to lift themselves out of hunger and extreme poverty. In the United States, it seeks to ensure that all people—especially those with the fewest resources—have access to the opportunities they need to succeed in school and life. Based in Seattle, Washington, the foundation is led by CEO Jeff Raikes and Co-chair William H. Gates Sr., under the direction of Bill and Melinda Gates and Warren Buffett.

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