An array of well-heeled new players has dramatically reshaped how wealthy countries tackle infectious diseases of the poor. But increasingly, these ambitious efforts are confronting their own limitations.

The New World of Global Health

A REVOLUTION IS UNDER WAY THAT IS fundamentally altering the way the haves of the world assist the have-nots. Over the past 7 years, a cadre of deep-pocketed, impassioned players has committed more than $35 billion to fight the diseases of the world’s poor. At the forefront of these efforts is the Bill and Melinda Gates Foundation, which since 1999 has pledged $6 billion—roughly the budget of the World Health Organization (WHO) during the same time—to battling HIV/AIDS, malaria, tuberculosis, and other long-underfunded diseases.

Close on the foundation’s heels are a half-dozen other massive new efforts, including the Global Fund to Fight AIDS, Tuberculosis, and Malaria, which has promised $4.8 billion to 128 countries, and the President’s Emergency Plan for HIV/AIDS Relief (PEPFAR) from the Bush Administration that has pledged $15 billion to help selected countries. The Global Alliance for Vaccines and Immunization (GAVI), with half of the $3 billion in its coffers supplied by the Gates Foundation, is helping 72 countries fortify the immune systems of their children. And thanks in part to a star-studded cast that is championing the cause—including the rocker Bono, matinee idols Angelina Jolie and Richard Gere, former U.S. presidents Jimmy Carter and Bill Clinton, U.K. Prime Minister Tony Blair, U.N. Secretary-General Kofi Annan, and economist-cum-firebrand Jeffrey Sachs—stories on global health now routinely grace the covers of news magazines.

But amid all the heartfelt praise, the organizations at the forefront of the global health movement are now undergoing both increasing outside scrutiny and internal soul-searching about what they are actually accomplishing. Their goals are huge, some would say impossibly ambitious—for instance, upping childhood immunization rates to 90%, or providing “universal access” to anti-HIV drugs. And achieving these grand objectives is proving tougher than many anticipated. Many countries, for instance, face cumbersome procurement policies that make it difficult to translate dollars into drugs. Shortages of trained health-care workers mean that those drugs that are available may not be used properly. Corruption has bedeviled a few large grants, whereas many other aid recipients have found themselves drowning in the required paperwork.

The organizations leading the charge are also beset with growing pains, struggling with issues of accountability, credit, and even fundamental direction. There is also considerable confusion about how all these new entities fit together, as well as how they mesh with old-timers such as WHO, the United Nations Children’s Fund (UNICEF), and the World Bank. “There’ve been lots of creative ideas and lots of new people,” says Barry Bloom, dean of Harvard University’s School of Public Health. “But there’s one missing piece. There’s no architecture of global health.”

Seeds of change

No single event triggered the outpouring of funds for global health, says Columbia University’s Sachs, who cites everything from an obscure 1978 health conference in the USSR to a 1993 report by the World Bank. Bill Gates has called the report, Investing in Health, a profound influence. In it the authors made the case that increasing funding for battling diseases in poor countries (then estimated at a mere $41 per person each year—1/30th what was spent in rich countries) would not only reduce the burden of disease but also dramatically improve the economies of poor nations.
Critical care. A counselor in South Africa explains the HIV test to children of an infected mother.

Until then, says Seth Berkley, who helped write the report and now heads the International AIDS Vaccine Initiative, health problems were seen “as a drain on the system”—not as a fundamental cause of poverty.

The exploding AIDS epidemic helped underscore the report’s dire message about the link between poor health and poverty. AIDS also spawned a powerful activist community that highlighted the slow pace of drug development—and the vast inequities between rich countries and those too poor to afford powerful anti-HIV drug cocktails.

Even before the Gateses jumped in, Cable News Network mogul Ted Turner in 1997 pledged $1 billion, much of it for fighting disease, to the United Nations to help the world’s poor. Two years later, Bill and Melinda Gates began donating billions of dollars’ worth of Microsoft stock to their foundation, which by 2001 had $21 billion in assets and a strong focus on global health. The size and boldness of their initial grants—including $750 million to kick-start GAVI—jolted public health veterans. “Everyone started dreaming,” says Jim Yong Kim, who recently left the head job at WHO’s HIV/AIDS program to return to Harvard University. “It was the first time we thought that way. Before, it was scraping for the pennies that would fall off the table.”

Boosting vaccination

Because few interventions provide as much bang for the buck as vaccinating children, immunization programs have long been a cornerstone of public health efforts. Since the 1970s, WHO, UNICEF, and Rotary International together have started massive campaigns that have substantially raised vaccination rates against many childhood diseases. In 1990, for instance, an estimated 75% of the world’s children received the combined diphtheria-pertussis-tetanus (DPT) vaccine—a jump from 20% a decade earlier. But soon those efforts began to falter. DPT vaccination rates never climbed again throughout the 1990s. In addition, several years typically passed before developing countries received the benefits of new vaccines introduced into wealthy countries, and even then, vaccines often didn’t reach the poorest of the poor.

Launched in 2000 as a public-private partnership outside the U.N. umbrella, GAVI set out to do things differently. Rather than stage pilot projects and then attempt to expand them from the “top down,” it took a “bottom-up” approach, asking countries how they would use the money to increase coverage with existing and new vaccines. By hiring UNICEF to do bulk purchasing and distribution, GAVI hoped to drive down vaccine prices and prevent corruption simultaneously. Grants would be canceled if countries did not properly audit their own efforts. Leaders in the global health movement repeatedly refer to the “catalytic” and “galvanizing” impact that GAVI has had on how other organizations operate.

As of September 2005, GAVI had made 5-year commitments to 72 countries for $1.6 billion worth of support. This has led to the vaccination of some 100 million children, sparing more than 1 million from premature death due to Haemophilus influenzae B, pertussis, hepatitis B, measles, and other diseases, GAVI claims.

In many ways, GAVI’s task is easier than those facing programs designed to treat HIV-infected people or to prevent the spread of malaria. Vaccines are, relatively speaking, a simple tool to use. “GAVI is pushing more money through systems that generally were working pretty well,” says Roy Widdus, who led a now-defunct GAVI predecessor called the Children’s Vaccine Initiative.

Hands on. Bill Gates drops the polio vaccine into the mouth of a boy in New Delhi.

New Global Health Efforts

<table>
<thead>
<tr>
<th>ORGANIZATION</th>
<th>FOCUS</th>
<th>YEAR LAUNCHED</th>
<th>DONORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bill and Melinda Gates Foundation</td>
<td>Global health</td>
<td>2000</td>
<td>Bill and Melinda Gates</td>
</tr>
<tr>
<td>The Global Fund to Fight AIDS, Tuberculosis and Malaria</td>
<td>Financing treatment and prevention</td>
<td>2002</td>
<td>Governments, foundations, corporations</td>
</tr>
<tr>
<td>International Finance Facility for Immunization</td>
<td>Financing vaccine delivery/GAVI</td>
<td>2005</td>
<td>U.K., France, Italy, Spain, Sweden</td>
</tr>
<tr>
<td>Multi-Country HIV/AIDS Program</td>
<td>Financing scale-up of existing government and community prevention and treatment efforts</td>
<td>2000</td>
<td>World Bank</td>
</tr>
<tr>
<td>Global Alliance for Vaccines and Immunization (GAVI)</td>
<td>Financing and delivery of childhood vaccines</td>
<td>1999</td>
<td>Gates Foundation, governments</td>
</tr>
<tr>
<td>Public-Private Partnerships</td>
<td>Drugs, vaccines, microbicides, diagnostics</td>
<td>n/a</td>
<td>Philanthropists, governments, industry</td>
</tr>
<tr>
<td>Anti-Malaria Initiative in Africa</td>
<td>Cut malaria incidence in half by 2010 in 15 countries</td>
<td>2005 (proposed)</td>
<td>U.S. government</td>
</tr>
<tr>
<td>United Nations Foundation</td>
<td>Children’s and women’s Health</td>
<td>1998</td>
<td>Ted Turner</td>
</tr>
</tbody>
</table>

*Overlap exists between organizations (e.g., PEPFAR money supports the Global Fund).*
Even so, underimmunization of children remains a major concern. As UNICEF recently pointed out, more than 2 million children a year still die from vaccine-preventable diseases. GAVI has also had to reassess its own overly optimistic projections. GAVI initially envisioned that after 5 years of “bridge” funding, countries would have figured out how to finance and provide the increased immunizations themselves. But that’s not happening, says Tore Godal, who headed GAVI from its inception until last January and now works as an independent health adviser in Geneva. Poor countries simply did not get the increase in health budgets that GAVI had anticipated, says Godal. As a result, GAVI recently decided to offer bridge funding for 10 years. Even so, it remains unclear whether countries can take over as initially envisioned.

William Muraskin, a history professor at The City University of New York, Queens College, criticizes GAVI for several “fundamental flaws.” In an article published in the November 2004 American Journal of Public Health, he asserts that GAVI’s bottom-up philosophy is illusory. He also contends that countries “had to be wooed” and “financially enticed” to accept GAVI’s goals and “financed” also contends that countries “had to be wined and dined” to accept GAVI’s goals and “financially enticed” to accept GAVI’s goals and “financed”

Godal counters that no one forces countries to submit proposals. “It is up to the countries to decide what they want to apply for within the remit of GAVI,” he says, adding that the hepatitis B vaccine indeed was a priority for many. GAVI Executive Secretary Julian Lob-Levyt says its most sobering challenge will be finding the money to purchase expensive new vaccines now on the horizon, such as those in the pipeline for pneumococcal disease, rotavirus, and human papillomavirus.

**Gates fate?**
In December 2004, officials at the Bill and Melinda Gates Foundation invited a power-packed group of outsiders to the Carter Center in Atlanta, Georgia, to discuss the direction of what had recently become the world’s largest philanthropy. Former U.S. President Jimmy Carter attended the small gathering, as did a select group of leaders from academia and nonprofits, the prime minister of Mozambique, WHO’s Jim Kim, the director of the Wellcome Trust, and the president of the U.S. National Academy of Sciences. The group lavished praise on the Gateses, but a few participants voiced misgivings that the young foundation’s global health program was starting to head off course. Carter in particular gave a blunt speech criticizing the program for having become too enamored with basic research at the expense of delivering drugs and preventives today. Patty Stonesifer, who co-runs the foundation with Bill Gates Sr., recalls the essence of Carter’s message this way: “I’m an impatient man—I want to save some people now.”

By and large, the global health community has appreciation that borders on reverence for the way the Gates Foundation has reinvigorated their efforts. And from the outset of its global health program, the foundation has attempted to fund projects like GAVI that deliver existing medicines as well as riskier basic research.
endeavors. Yet several people *Science* interviewed, who requested anonymity, complained that the foundation over the past 3 years has tilted too far toward duplicative, fundamental research that often fails and has also lost its nimble derring-do, becoming more like the U.S. National Institutes of Health (NIH). “How can Bill Gates have his name attached to an organization that’s slower than the U.S. government?” asks one. “They’ve gone from being an easy foundation with which to deal to one that’s very complicated and bureaucratic,” says another.

Several critics attribute the shift to Richard Klausner, the former director of the U.S. National Cancer Institute (NCI), who ran the foundation’s global health program from 2002 until announcing his resignation last September (*Science*, 16 September 2005, p. 1801). In particular, they point to two programs that started under Klausner’s tenure.

One is Grand Challenges in Global Health, a bold effort to fund research that could lead to breakthroughs deemed most likely to improve health in poor countries. The foundation has won plaudits from both inside and outside the research community for aggressively seeking ideas from more than 1000 scientists around the world. But the process took too long, say critics—more than 2 years. And some are unhappy with the 43 final selections, most of which focus on fundamental, long-term, high-risk research. Critics say the Grand Challenges are diverting $436 million of foundation money to support the kinds of research that NIH should fund. Although several of the winning proposals are unusually inventive and provocative, there is also a distinctly developed-world flavor to these labs: All but three projects are headed by researchers with the wishes of Bill and Melinda Gates. “It’s a complicated set of tradeoffs,” says Klausner, who also had strong outside support during his tenure.

Another project that has received substantial Gates funding—and raised some eyebrows—is the Global HIV/AIDS Vaccine Enterprise, a multi-institutional effort to draw a blueprint for the field and then create consortia of researchers to address the most critical questions. NIH, a partner in the enterprise, has already committed more than $300 million to what’s called the Center for HIV/AIDS Vaccine Immunology (CHAVI), and Gates has pledged another $360 million to form similar groups. Some AIDS vaccine investigators fear that a small group of elite, well-funded researchers will receive the lion’s share of the money to explore questions that they would have pursued without the extra help.

Although it has yet to be announced publicly, the Gates Foundation indeed plans to award part of its $360 million Enterprise money to at least two members of the CHAVI team. And another CHAVI team member won a $16.3 million Grand Challenges award from Gates to do related work.

Foundation officials defend their choices. Helene Gayle, who heads the HIV/AIDS program for the foundation, says, “There’s a logic to going with success” and that they didn’t want to exclude “the usual suspects” just because they were already well funded. Gayle adds that Gates is specifically working with NIH to make sure that they do not fund researchers for the same work twice. And she says the foundation made an effort to select lesser known people, too, in an attempt to create a network of researchers who might not otherwise collaborate. “So maybe some of the same players,” says Gayle, “but we hope a different game.”

**AIDS aid**

Funding on HIV/AIDS dwarfs that of any other infectious disease. Between 1996 and 2005, annual spending on AIDS programs in developing countries shot from $300 million to more than $8 billion, according to UNAIDS estimates, with most of this astonishing jump coming from the Global Fund, the World Bank’s Multi-Country AIDS Program (MAP), and PEPFAR. In contrast, WHO says the next largest killers, malaria and tuberculosis,
Leading the way. The global health movement received a huge boost from AIDS activists, shown here staging a protest march in Thailand.

together receive less than $2 billion each year.

But people are questioning how much improvement this investment in HIV/AIDS is buying on the ground. A related concern is the amount of time grant recipients are spending simply sorting out the massive amounts of red tape created by the various programs and their overlapping agendas.

The biggest AIDS donor is the Global Fund. Unlike GAVI, the fund has rigorously avoided the top-down approach; it prides itself on being “country owned” and inclusive. Transparency and accountability are the buzzwords. The fund, which supports everything from providing antimalarial bed nets to anti-HIV drugs, has no staff permanently in countries and channels money through local financial institutions, as opposed to the World Bank. Rather than offering central drug procurement, the fund encourages countries to strengthen their own supply-and-distribution systems.

But critics say the goal of giving countries complete autonomy has come at too steep a price. The fund disburses money to countries only when they hit specific milestones, and since January 2004, they have been falling behind, according to AidsSpan, a New York City–based watchdog of the Global Fund. The gaps in disbursement suggest that “deliverables” such as drugs and bed nets aren’t reaching populations as quickly as hoped. “The thing I really want to know about is not dollars disbursed but pills in mouths,” says Bernard Rivers, who heads AidsSpan.

The fund is “a very good thing, but there are huge problems in terms of operating it,” agrees Winstone Zulu, an AIDS and TB activist in Zambia. Zulu says other longtime donors closed their pocketbooks when the fund arrived, but that the new money has become ensnared in bureaucratic tangles, and some critical programs in Zambia had to shut down.

Global Fund Director Richard Feachem agrees that it’s a “mixed portfolio” when it comes to countries “turning the money into products.” Procurement is a “key bottleneck,” he says, as some countries have “sclerotic” procedures. “They were designed to prevent corruption, and they actually prevent procurement,” says Feachem. “We’re doing a lot of changing in thinking.”

In two countries, Ukraine and Uganda, the fund suspended grants because of serious country mismanagement and outright corruption. A handful of other countries have almost had their grants canceled for failing to reach milestones.

On top of these problems, the fund has never had as much money as its creators envisioned. “The Global Fund is chronically begging for money from the rich countries,” says Sachs, one of its key proponents. “And this has meant that the Global Fund has not been as clear or inviting as it should have been to poor countries to put up very bold strategies.” In the latest financing round this September, donors committed $3.7 billion for 2006–’07—far short of the projected $7 billion the fund says it needs.

The World Bank’s much smaller MAP, which provides more flexible aid both to deliver medicines and to build health systems, faces similar concerns. A review of six MAP projects in 2004 found that the bank did not offer enough technical guidance, nongovernmental organizations (NGOs) were often included more in name than in practice, and none conducted adequate monitoring and evaluation.

The Bush initiative PEPFAR is the most recent entry into AIDS aid. It got off to a fast start in delivering drugs to people largely because of its top-down strategy that includes staff on the ground and central procurement. Salim Abdool Karim of the University of KwaZulu-Natal in South Africa says PEPFAR has been “amazingly successful” in his country and has had “much better politically sensitive management on the ground” than the Global Fund.

Yet Karim and many others take exception to some of PEPFAR’s requirements, which are tightly tied to the Bush Administration’s conservative agenda. For instance, those who receive PEPFAR grants must have a policy “explicitly opposing prostitution,” which Karim and others say has threatened their research and prevention efforts with sex workers. “This is reprehensible,” says Karim. PEPFAR has also been criticized for devoting one-third of its prevention budget to abstinence programs, downplaying the value of condoms in the general population, and limiting the use of generic drugs by insisting that they first be approved by the U.S. Food and Drug Administration. (A U.S. Institute of Medicine panel is reviewing PEPFAR and plans to release its findings by this spring.)

A report issued in November 2005 by 600 treatment activists, Missing the Target, sharply rebuked the Global Fund, PEPFAR, the World Bank, and others for failing to work together as effectively as possible in delivering anti-HIV drugs. “A much more systematic approach to setting goals, measuring progress, and assessing and addressing barriers is needed.”

Architectural indigestion

UNAIDS issued a report in May 2005 that had telling cartoons about the tangle of various stakeholders working on HIV/AIDS in Tanzania
Public-Private Partnerships Proliferate

The label “neglected diseases” packs a rhetorical wallop, as it conjures up needy causes that the world callously has ignored. But the phrase is losing some of its punch when it comes to malaria, tuberculosis, Chagas, dengue, visceral leishmaniasis, and African trypanosomiasis. Although profit-minded pharmaceutical companies have long shied away from research and development on drugs against maladies that mainly afflict the poor, 63 drug projects now under way are targeting these very diseases. As Mary Moran wrote in the September 2005 issue of PLoS Medicine, “The landscape of neglected-disease drug development has changed dramatically during the past five years.”

Moran heads the Pharmaceutical R&D Project at the London School of Economics and Political Science. In its recent analysis of drug-development projects for neglected diseases (it did not analyze vaccines or diagnostics), Moran’s team credited a raft of new “public-private partnerships” (PPPs)—80% of which are funded through philanthropies—for the surge in new efforts.

Pioneered by the Rockefeller Foundation and later by the Bill and Melinda Gates Foundation, PPPs link big pharmaceutical companies or smaller biotechs with academics, nongovernmental organizations, and multilateral groups such as the World Health Organization. Ten years ago, not a single PPP for global health existed. Today, there are nearly 100 of them, in the most liberal definition, with a combined war chest of more than $1 billion. “It’s a seismic change,” says Seth Berkley, head of the International AIDS Vaccine Initiative, which, at 10 years of age, is the granddaddy of PPPs for global health. Moran and her co-workers predict that as many as nine products now in development will come to market in the next 5 years. In each case, the companies have agreed to sell any resultant drugs to poor governments at deep discounts or no profit. Moran’s group further notes that between 1975 and 2000, the pharmaceutical industry developed a meager 13 new drugs for neglected diseases—and because of their high prices, only one was widely used.

Companies that enter into PPPs have little prospect of making money on the drugs they develop, but Moran notes that they face relatively limited financial risk because their partners typically pay for the most expensive part of the process: staging large, clinical trials. This “no profit–no loss” business model does offer big pharma benefits: a good public image and an introduction to developing-country markets and researchers who might help them elsewhere.

Although the entry of big pharma into this field is welcome—and, some say, long overdue—the problem is by no means solved, cautions Peter Hotez of George Washington University in Washington, D.C. In an article in the November 2005 issue of PLoS Medicine, he and his co-authors point out that many diseases remain neglected. “When people speak of global health, the first thing you hear about is HIV/AIDS, malaria, TB, and you’re liable to think that’s all there is,” says Hotez, who works on hookworm vaccines. Hookworm, schistosomiasis, leprosy, and 10 other neglected tropical diseases “affect at least as many poor people as the big three,” they write. And they contend that for a mere 40 cents per person a year, four existing drugs could be used to quickly reduce the harm caused by seven of these scourges. —J.C.