

A real shot

With massive injections of cash and reinvigorated will, new partnerships are set to boost vaccination rates worldwide. Bruce Diamond examines the hurdles that remain.

In the tiny west African country of Gambia, 17,000 infants in December 2004 completed a 30-month phase 3 trial of a new vaccine that could prevent pneumococcal diseases such as pneumonia, meningitis and septicemia. Thousands of Gambian children under the age of five die of such illnesses. But until recently, they had little hope of access to such new, costly vaccines.

The US Food and Drug Administration in 2000 licensed the first vaccine to prevent pneumococcal infections, which claimed more than 1.6 million lives in 2001. The vaccine, Wyeth's Prevnar, has since been administered to more than 20 million children in 37 countries.

In the first two years alone, Prevnar virtually obliterated a glaring disparity in the prevalence of infections between white and black children in the US. Last year, its fourth-quarter sales were \$340 million, an increase of 62% over those in 2003, garnering it the distinction of being the world's first 'blockbuster' vaccine. At \$250 for a four-dose course, however, Prevnar is out of the reach of most children in the developing world.

In poor countries such as Gambia—where most people live on less than a dollar a day—its cost is no small obstacle. Products such as Prevnar have historically taken 20 years or longer to reach the countries with the greatest need.

The World Health Organization (WHO) estimates that more than 2.7 million children died from vaccine-preventable illnesses in 2001; that total fell to 1.4 million in 2002, but more than 27 million infants born in 2003 still failed to receive immunizations by their first birthday.

Recognition of immunization's impact is nothing new, but the push to vaccinate has only seen sporadic success. But with billions in new aid, global partnerships between governments and the private sector have over the past five years laid the groundwork for the most ambitious effort yet.

Opening the windows

For decades, international agencies such as the United Nations Children's Fund (UNICEF) tried to galvanize governments and private donors to boost immunization rates. But by the late 1990s, vaccination for diphtheria, tetanus and polio (DTP) had fallen below 75% in 22 countries, and below 50% in 19 countries, primarily in Africa.

At the same time, complex market forces stifled the development of new vaccines and forced all but a handful of manufacturers to shutter their vaccine divisions. With research and development costs approaching \$1 billion for a single candidate vaccine, manufacturers just couldn't afford to pour resources into products for countries with miniscule healthcare budgets.

It became increasingly clear that a new strategy was needed to develop and deliver vaccines where they are most needed. Finally in 2000, the year Prevnar was released, a \$750 million seed fund from the Seattle-based Bill and Melinda Gates Foundation launched a new international partnership.

The Global Alliance for Vaccines and Immunization (GAVI)—administered by a partnership of national governments, the United Nations, the WHO, the World Bank and representatives from the pharmaceutical industry—was up and running in less than a year.

GAVI and its financing body, the Vaccine Fund, in 2001 began disbursing awards—with five-year commitments totaling more than \$1.2 billion—to 71 of the 75 countries whose annual per capita gross domestic product is less than \$1,000. By the end of 2003, four million children had received basic immunizations in countries with GAVI-funded programs. More than 42 million children in 50 of those countries have

also received hepatitis B immunizations, and nearly five million children have been protected against *Haemophilus influenzae* type b (Hib).

"We are now in a place that none of us ever could have dreamed about," says Scott Halstead, a founder of the moribund Children's Vaccine Initiative.

At the end of its first five years, the alliance has more than matched the initial grant with government and private donations. In January, a second \$750 million donation—this one over a ten-year period—to the alliance settled any lingering doubts about its longevity.

GAVI is using that grant, combined with its early track record, to secure long-term commitments from a wider swath of nations. Norway has made a five-year pledge of \$290 million and the UK has begun mustering the support of the European Union and the G8 nations. UK Chancellor Gordon Brown has pledged £960 million over 15 years to an immunization subunit of the newly created International Finance Facility, a capital investment plan that could harness billions in development assistance.

"In our deepest, darkest psyches, nobody ever dreamed that some rich guy in the Pacific Northwest was going to write a check for \$750 million," says Orin Levine of Johns Hopkins University, who runs GAVI's program to accelerate pneumococcal vaccines. "Maybe the biggest impediment in the past was that we were not dreaming big enough."

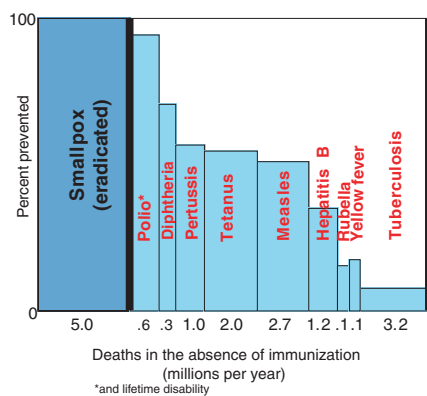
Mastering the markets

As richer nations open up their coffers, however, some still worry that the poorest countries will remain dependent on philanthropy as the primary means of sustaining those gains. "Without Bill Gates' donations, I think some of these advances and successes would not have occurred," says Stanley Plotkin, an executive advisor at Sanofi Pasteur, and a renowned vaccinologist. "Beyond the next 10 years I think one has to be somewhat skeptical, because Bill Gates is not immortal."

Indeed, countries will have to begin footing more of the costs of the expanded immunization programs. As new vaccines arrive, health ministers will have to abandon hopes of pennies-per-dose fixes. The challenge, Levine says, is to help countries assign a value to vaccines, then offer companies the guarantee of profitable markets.

"If we really want vaccines against AIDS, tuberculosis, malaria and pneumococcal disease, it's not going to be 20 cents a dose," Levine says. "Companies need to get into this not through philanthropic interest, but through financial self-interest as well."

Deaths (global) from vaccine-preventable diseases



Urgent need: Vaccine-preventable diseases kill millions of children each year.

Levine and others are using mathematical models to show these governments the economic benefits of spending on immunization. A dollar spent to vaccinate a child, Levine says, is empirically equivalent to a dollar toward that child's education.

Developing countries like Gambia could begin using Prevnar as early as next year, but its cost will almost certainly need to be subsidized. In its 2001 application for GAVI funds, the Gambian government said it would begin assuming the costs of hepatitis B and Hib vaccines when its grant expires in 2007. According to a WHO analysis, however, in the years after Gambia's Vaccine Fund assistance expires the country could face a \$1.6 million annual shortfall to keep its immunization program afloat.

Gambia is not the only country finding it difficult to countenance the long-term budgetary impact of adding the hepatitis B and Hib vaccines; dozens of others have already told GAVI that they'll need more time to begin shouldering even a portion of those costs.

"I always assumed that you just show [countries] the disease burden and everything else would follow," Levine says. But in the past 15 years, he says, he began to understand that a country's theoretical need for a vaccine may not come close to matching the real demand, defined by its own recognition of need, and its resources to purchase and administer the vaccine.

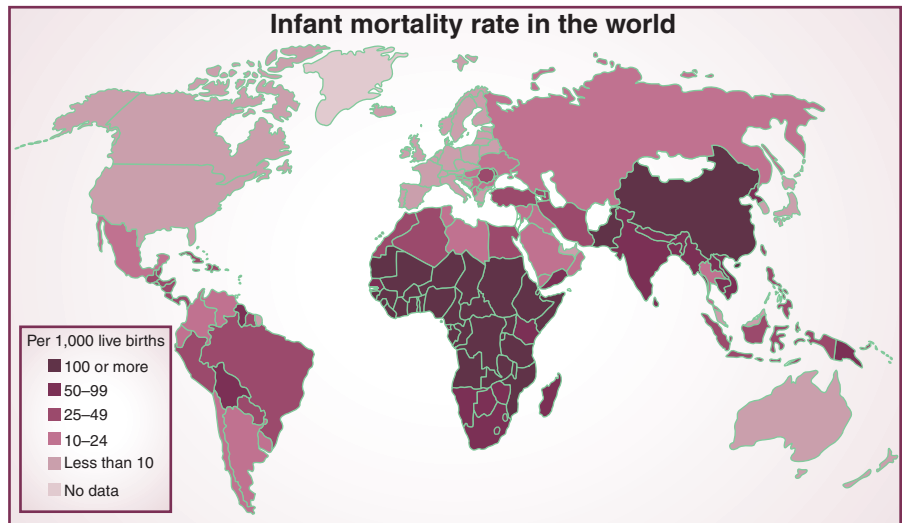
"Unless we develop a step-by-step program to understanding the disease burdens and the benefits of vaccination programs, we're going to get less-than-optimal results," says Adel Mahmoud, president of Merck & Co.'s vaccine division.

More information could help fix the perpetually fractured cycle of supply and demand, which has long stymied the availability of new vaccines. For decades, UNICEF and others estimated need simply by counting the number of children who could be immunized. But that practice could inflate the demand by more than 50% and, if the medicine went unused, leave manufacturers with sizable losses. This inability to accurately predict global demand prompted producers to vastly limit their production quantities. Curtailed supply then kept prices inflated, which further discouraged the countries from committing to the vaccines.

"You may talk about demand—but if there's no assurance that the product will be purchased, then that demand is only theoretical," says Mahmoud. "The difficulty has always been, how can a company like Merck assist the demand of the global marketplace and be assured of getting a fair return on our investment?"

Local producers

Many pieces must be put in place in order to redefine the paradigm. GAVI has created models for



Heavy burden: Countries that most need vaccines are the least able to afford them.

expanding vaccine markets and accurately projecting their long-term rates of growth. It has also launched programs to accelerate countries' access to vaccines currently being developed against rotavirus and pneumococcal infections.

Including private-sector representatives among its leaders has enabled GAVI to pursue programs that take both sides of the supply-demand equation into account, says Sanofi Pasteur's Shawn Gilchrist, an industry representative at GAVI.

The Vaccine Fund has also enabled UNICEF, which buys 80% of the vaccines for developing countries, to make purchasing agreements for three to five years. That makes it easier for suppliers to step up production, because they can spread their costs over several years' time and act with the assurance that the vaccines will be bought.

Others point to the emergence of manufacturers in India, Brazil, Indonesia and Korea, which are filling a key role and supplying a growing proportion of worldwide demand.

"The biggest thing now is that more local suppliers are needed," says Patrick Lydon, who analyzes the sustainability of immunization programs for the WHO. "We need more competition in order to affect prices; it doesn't seem that we're going to be able to drive pricing down just by increasing demand and uptake."

The Serum Institute of India, for example, is now the world's largest producer of measles and DTP vaccines. The Pune-based company supplies more than half of those products purchased by UNICEF, and is expected to launch a tetravalent vaccine in March, adding hepatitis B to the DTP combination. About 60% of UNICEF's total vaccine purchases, not including polio, are supplied by companies in the developing world.

More collaboration will be needed to help local manufacturers perfect the technology for

newer combination-antigen vaccines, but their growing contribution is considered crucial.

But even with all the pieces in place, it is difficult to predict how long it will take for vaccine prices to fall. The hepatitis B vaccine, for example, is now being used in nearly 50 of the 71 Vaccine Fund-eligible countries, up from only 7 in the year 2000, and its cost is expected to drop below the dollar-per-dose threshold within ten years.

But the Hib vaccine still costs more than \$3.50 per dose, and prices have actually increased for the GlaxoSmithKline vaccine that combines hepatitis B and Hib with DPT. That unpredictability has restricted its use to only 14 new countries and prevented others from considering its use.

Public- and private-sector representatives have been working to develop new interventions that could lower vaccine prices. The Vaccine Fund might soon be able to negotiate legally binding advanced purchase contracts, through which manufacturers would provide new vaccines at a fixed cost per dose. That price might be higher in the period after the products' release, enabling companies to recoup some of their costs. Companies would promise to reduce the prices after a fixed number of years, however.

Advanced purchasing arrangements have long been touted as a sound strategy to provide companies guaranteed demand in return for a promise of enough supply. But Merck's Mahmoud remains skeptical that the legal technicalities of such contracts can ever be solved.

"I'm not being overly optimistic or overly critical—what is important is to see some of these mechanisms get put to their application," Mahmoud says. "The more you see of this translation of theory to practice, the better off we are—all of us."

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