Influx of New Funds Puts Global Health Goals Back On Track

Set in 2000, the Millennium Development Goals (MDGs) have become a widely shared framework for combating poverty, inequality, and major infectious diseases, primarily HIV/AIDS, tuberculosis, and malaria. This past September, Tedros Adhanom, the Health Minister of Ethiopia, and the heads of four leading global health organizations—the GAVI alliance, the Global Fund, UNICEF, and UNAIDS—convened a special summit as part of the United Nations General Assembly in New York to assess progress toward meeting these goals.

Despite a number of key gains, among which being that large-scale campaigns against malaria and AIDS are benefiting from new partnerships and technologies, stable long-term donor support, and better coordination among diverse health organizations, the panelists warn that effective strategies designed to reach inaccessible, marginalized, and vulnerable populations are still lacking.

Adhanom expressed his government’s strong commitment to achieving the MDGs. Ethiopia, he says, plans to have 25,000 free health care centers in operation by the year 2010. Strikingly, because a strong cultural bias in his country keeps women from accessing health care services from men, their plans call for staffing the centers exclusively with women. To date 24,000 female health care workers, of an anticipated 30,000, have been trained and deployed. Getting women into health care centers is particularly important because mothers bring their children who can be immunized during the same visit.

Raising immunization rates is considered essential to achieving another millennium development target, namely reducing child mortality by two-thirds before the MDGs end date of 2015. Notably, polio now teeters on the edge of eradication and the incidence of measles, even in the poorest countries, is being dramatically reduced. Moreover, the vaccine that protects against Haemophilus influenzae b has virtually eliminated this source of meningitis in parts of Africa.

GAVI, an alliance of global health organizations, plays an important role in delivering childhood vaccines throughout the developing world. Since its formation in 2000, GAVI programs and support have helped protect 36.8 million children with vaccines that are, in turn, expected to prevent an estimated 2.9 million deaths from childhood diseases. In many countries vaccination rates now reach 70%. “However successful we’ve been so far, greater challenges lie ahead,” says GAVI Alliance Executive Secretary Julian Lob-Levyt. “It’s becoming harder; we have to travel greater distances to ensure that vaccines reach the most vulnerable children; and health systems are the weakest in areas we urgently need to reach.”

“Equity is at the forefront of our development agenda,” says Michel Kazatchkine, Executive Director of the Global Fund to Fight AIDS, TB, and Malaria, which has financed $11.4 billion worth of programs since its creation in 2002. UNICEF Executive Director Ann Veneman adds that “Inequality in society breeds disease, and reaching the MDGs requires an equitable distribution of public health access across social, gender, ethnic, and geographic levels.” She also points out the importance of preventing violence against women because so many are infected with HIV through rape.

“Even though many more HIV-infected patients are now living longer and healthier lives thanks to increased access to treatments, the challenge now is to sustain these gains and ensure more equitable access for marginalized people,” says Peter Piot, Executive Director of UNAIDS. He, like other speakers, underlines the need for equity saying that it, not cost containment, is the only acceptable approach to improving global health. Piot also argues for increased accountability, emphasizing the need for “watchdogs.”

At this, the halfway mark for the MDGs, it appears a great deal of work remains undone. The UN Secretary-General Ban Ki-moon agrees, telling world leaders: “While we are moving in the right direction, we are not moving quickly enough,” calling on them to step up efforts to “inject new energy into the global partnership for development.” And inject they did. By the end of the September meeting, participants from governments, the private sector, and other nongovernment organizations pledged a record $16 billion to the MDGs, including $3 billion specifically to combat malaria. “A response,” according to General Assembly President Miguel D’Escoto Brockman, “that exceeded our most optimistic expectations.”

Marcia Stone
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Uproar Lasts Long after Pittsburgh VA Destroyed Pathogen Collection

Administrators at the Veterans Affairs (VA) Pittsburgh Healthcare System (VAPHS) in Pittsburgh, Pa., arranged for an estimated 8,000 specimens in the VAPHS Special Pathogens Laboratory to be destroyed abruptly in December 2006—giving rise to acrimony and recriminations that are yet to subside. The collection, developed by microbiologists Victor Yu, Janet Stout, and their collaborators, consisted mainly of *Legionella* and other pneumonia-causing bacterial pathogens, many of them resistant to antibiotics. An outside group of microbiologists and infectious disease experts earlier this year described the destruction of that collection as “an affront to science and scientific study.”

Clamor over loss of the collection struck a chord with several members of Congress, particularly Rep. Brad Miller (D-NC), who chairs the Investigation and Oversight subcommittee of the House of Representatives Committee on Science and Technology. Miller not only convened a hearing, “Biobanking: How the Lack of a Coherent Policy Allowed the Veterans Administration to Destroy an Irreplaceable Collection of *Legionella* Samples,” last September, he also had his staff investigate the matter and has pledged to introduce legislation that will safeguard other such collections. Full testimony from the hearing is available at http://www.legionella.org/vaspl.asp.

It is an understatement that there are profound disagreements between Yu, Stout, and their immediate collaborators on one side and VA administrators on the other.

“Initially, I was not concerned about the transfer of the collection from the VA,” Stout testified. With the Special Laboratory closed, she and Yu were working at the University of Pittsburgh, where they planned to transfer their collection. “I knew that other VA investigators had left the VA and taken their collections of specimens with them,” she says. Further, several VA administrators assured her that they would “facilitate” that planned transfer. The 8,000 specimens collected between 1979 and 2006 included strains of *Legionella*, staphylococci, *Pseudomonas*, *Klebsiella*, enterococci, streptococci, and *Candida*.

Despite those assurances, however, the collection was not saved. “The attack and destruction of our work is justified with bureaucratic jargon,” Yu says. “Nowhere in the testimony of the VA bureaucrats was there any regret or compunction of the gravity of their offense. In contrast, the Congressmen were easily able to comprehend the fact that the public and the scientists themselves were egregiously harmed.”

The subcommittee report recom-

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Nobel Prizes and Special Lasker Award 2008

Several of the 2008 Nobel Prizes touch either specifically or indirectly on microbiology, while the 2008 Lasker Special Achievement Award in Medical Science went to a microbiologist:

- The Nobel Prize in Medicine or Physiology is shared by Harald zur Hausen, of the German Cancer Research Centre, Heidelberg, Germany; Françoise Barré-Sinoussi of Institut Pasteur, Paris, France; and Luc Montagnier of University of Paris and Director, World Foundation for AIDS Research and Prevention, both in Paris, France. Among his efforts, zur Hausen determined that the human papilloma virus (HPV) causes cervical cancer, the second most common cancer among women. Barré-Sinoussi and Montagnier are recognized for discovering the human immunodeficiency virus (HIV). More information can be found online at http://nobelprize.org/nobel_prizes/medicine/laureates/2008/

- The Nobel Prize in Chemistry is being shared by Osamu Shimomura at the Marine Biological Laboratory (MBL), Woods Hole, Mass., and Boston University Medical School, Mass.; Martin Chalfie of Columbia University, New York, N.Y., and Roger Y. Tsien at the University of California, San Diego, La Jolla, Calif. Shimomura isolated the green fluorescence protein (GFP) from the jellyfish *Aequorea victoria*, while Chalfie first used GFP as a visual tag for analyzing various biological phenomena, and Tsien contributed toward understanding how GFP fluoresces and also extended its palette beyond green, enabling other researchers to tag proteins and cells with different colors. More information can be found online at http://nobelprize.org/nobel_prizes/chemistry/laureates/2008/

- The Lasker Special Achievement Award went to Stanley Falkow of Stanford University in Stanford, Calif., for many achievements, including his development of our understanding pathogenesis, new molecular tools for studying it, and his role in founding the discipline of molecular epidemiology. More information can be found online at http://www.laskerfoundation.org/awards/2008special.htm
Combining Antibiotics Enhances Activities, Raises Questions

Three antibiotics—myxopyronin, corallopyronin, and ripostatin—inhibit bacterial RNA polymerase (RNAP) through interactions with the RNAP “switch region,” a hinge-like structure that opens and closes around the active-center of this enzyme, according to Richard Ebright and Eddy Arnold of Rutgers University in New Brunswick, N.J., and their collaborators. Together these three antimicrobial agents potently inhibit both gram-positive and -negative bacterial growth, while showing no cross-resistance with other antibacterial agents. Further, by targeting RNAP, this trio of compounds can effectively target both growing and dormant pathogens, including Mycobacterium tuberculosis. Another plus is that they bind to the hinge region of that key enzyme, a site that is distant from where other antibiotics, notably rifamycin which is used in treating tuberculosis, bind this molecule. Details appear in the October 17 issue of Cell.

How Infection Status Affects Subsequent Infections and Immune Responses

Chronic underlying infections sometimes modulate host responses to superimposed and acute, albeit self-limiting, bacterial infections, according to David Schauer of Massachusetts Institute of Technology (MIT), Cambridge, Mass., and his collaborators, whose report appears in the November Infection and Immunity (76: 4851–4858). Their research “is the first to study the interaction between a chronic bacterial infection and a superimposed acute bacterial infection,” says Vincent Young of the University of Michigan (UM), Ann Arbor, who did not collaborate in the MIT-led research. That research thus “supports the hypothesis that prior exposure to one pathogen may influence the clinical course due to” another.

As part of the study, Schauer and his collaborators exposed mice to Helicobacter hepaticus, which colonizes the gut but causes no clinical symptoms. About two months later, the researchers exposed those mice to Citrobacter rodentium, which infects mice and causes symptoms such as diarrhea similar to those caused by enteropathogenic Escherichia coli in humans.

Typically, such infections—in mice and humans—are self-limiting. However, in these experiments with mice, the initial subclinical infection with H. hepaticus not only lengthened the course of the subsequent C. rodentium infection, but it also altered the host immune response by suppressing expression of interferon-γ and boosting expression of interleukin-17. Altogether, these changes led the mice to develop colitis. These findings suggest that “an individual’s infection status . . . is important in determining the outcome of infection, immune-mediated disease, or even immunization,” Schauer says.

The germ of this research was the hygiene hypothesis, Schauer continues. It holds that childhood exposure to unclean conditions harboring various microorganisms and parasites “can lead to immune responses that influence outcomes of infectious and immune-mediated diseases,” he says. “We wanted to provide proof of principle and begin to define the mechanism for such interactions.” They chose H. hepaticus because it behaves much like H. pylori in humans, giving rise mainly to subclinical infections in situations where hygiene practices are suboptimal.

In more general terms, the multiply infected mice “reflect a more realistic situation for what humanity faces in terms of the body’s constant fight

mends that the President’s Office of Science and Technology Policy “develop a focused policy for biospecimen collection management” and asserts that “Biobanking cannot succeed if its basic policy structure is honored more in the breach than in the observance.”

While destroying the collection irreparably damaged the careers of these microbiologists, Stout and Yu draw specific lessons from their experience that could prove instructive for other microbiologists when called on to protect similarly valuable collections. In other words, some simple steps could help in protecting important biological materials, according to Stout. Thus, she recommends that microbiologists and other researchers (i) keep duplicates of all research, including records from institutional review boards (IRBs) and other research and development (R&D) files; (ii) become familiar with and adhere to rules governing IRBs and with other R&D practices because, even if they are not being strictly observed, they may be invoked later; (iii) check consent forms to ensure that they cover future uses of retained specimens; and (iv) make sure commitments from administrators are in writing, and pester for such assurances whenever necessary.

Jeffrey L. Fox
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Several Recent Developments Involving Anthrax Vaccines

Recent developments involving vaccines to protect against anthrax include:

- The National Institute of Allergy and Infectious Diseases and the Biomedical Advanced Research and Development Authority provisionally awarded $29.7 million to Emergent BioSolutions of Rockville, Md., and $83.9 million to PharmAthene of Annapolis, Md., to produce up to 25 million doses of anthrax vaccines for the national strategic stockpile.
- Citing the Public Readiness and Emergency Preparedness Act, Health and Human Services Secretary Mike Leavitt in October declared that, because the country is faced with an anthrax emergency, companies that prepare vaccines or other products to protect against anthrax would be protected against lawsuits, at least until 2015.
- Reducing the dose schedule and injecting the anthrax vaccine intramuscularly reduced the numbers of localized adverse events but provided immune responses that are comparable to the currently approved means for administering the vaccine by subcutaneous injection, according to Conrad P. Quinn and collaborators at the Centers for Disease Control and Prevention in Atlanta, Ga., and at other institutions. Details are reported in the October 1 Journal of the American Medical Association.

Lager Yeasts Unexpectedly Fall into Two Camps

Although many view lager beer simply as a means for refreshment, some scientists are distilling that refreshment into a means for tracing the evolutionary history of specialized brewing yeasts. “Lager yeast provided us with a unique opportunity to study a microorganism that arose 600 years ago by a hybridization of two different strains,” says Gavin Sherlock of Stanford University in Stanford, Calif. He and Barbara Dunn identified two genetically distinct groups of lager yeast, casting doubt on a widely held belief that all economically important lager strains derived from a common source.

Commercial brewers make lagers with Saccharomyces pastorianus, a yeast that is a hybrid of S. bayanus and S. cerevisiae. S. pastorianus actively ferments at much colder temperatures than those needed for making ales, which typically are brewed with S. cerevisiae.

Sherlock and Dunn analyzed 17 strains of S. pastorianus that are in commercial use worldwide to produce lagers. When those strains were subjected to customized, two-species microarray analysis, they fell into two groups. Strains in group 1 are missing a substantial portion of the S. cerevisiae genes but retain the entire S. bayanus genome. Strains falling into group 2 retain about an equal mix of genes from both genomes.

Membership in the two groups correlates with brewery locations. Group 1 includes strains used to brew Saaz-type beers produced typically in what is now the Czech Republic, whereas strains falling into Group 2 are being used to brew Frohberg-like beers in the Netherlands, North America, and the Carlsberg breweries of Denmark.

The experiments by Schauer and his collaborators address another issue that widely affects but rarely is accounted for in studies that rely on animals such as mice to model human diseases. Although such animals are likely to carry subclinical infections and thus might well alter the results, this variable is seldom taken into account, points out Young from UM. The MIT “paper shows that a difference in even one organism amongst the many thousands that compose the indigenous microbiota can significantly alter the response to experimental infection,” Young says. He urges other investigators to consider this issue more carefully.

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Researchers find that yeasts used in producing lager belong to two genetically distinct groups. This casts doubt on a widely held belief that lager strains derived from a common source, providing insights into the evolution of these organisms and helping brewers who seek to fine tune their products. (Image © Getty images/Mitch Tobias.)

says, the analysis showing them dividing into two distinct groups “led us to suspect that two hybridization events had occurred.”

Portions of the S. pastorianus sequences also closely match those of a S. cerevisiae yeast used to brew ale. “That’s not surprising,” says Sherlock, “but it’s a nice confirmation of our methods.” He and Dunn reported their findings in the October 2008 issue of Genome Research (18:1610–1632).

Beers are classified as either lagers or ales, based on the type of yeast used in brewing them and the temperature at which they are fermented. Ales are brewed at warmer temperatures, and trace to ancient times, whereas lagers were first brewed in Bavaria a mere 600 years ago. Lagers became popular in the late 1880s when refrigeration made continuous low-temperature fermentation possible at virtually any location.

Studying S. pastorianus provides an “opportunity to look at a relatively recently arisen species just a few centuries old, compared to things separated by millions of years,” Sherlock says. Although his focus is on evolution, understanding genetic differences between yeast strains could prove useful to brewers who seek to fine tune the flavor, color, and aroma of their products. For example, certain genes critical to brewing, such as those controlling maltose metabolism, are present at increased copy numbers, he notes. Others, such as genes that determine whether yeast cells flocculate, are missing. Breweries could use the techniques developed by the Stanford researchers to monitor how their own yeast strains change over time, according to Sherlock.

Such molecular biology methods may particularly suit quality control at modern breweries, where mergers find large companies brewing different brands of beer. “You want to maintain the integrity of the yeast strains and keep them separate,” says microbiologist Greg Casey, manager of applied brewing technology at MillerCoors in Littleton, Colo. Since World War II, Americans have come to prefer lighter and lighter lagers, making the yeast contribution to flavor increasingly important. While working at the Carlsberg brewery in Copenhagen, Denmark, in the mid-1980s, Casey characterized yeast strains by labor-intensive karyotype analysis of chromosomes, and he came to rely on differences between chromosomes 1 and 10 as telltale markers for brewing qualities. What Sherlock and Dunn find at the molecular level “parallels the differences found by old-fashioned karyotyping,” Casey says.

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S. aureus Extracellular Polysaccharide Eyed for Broad-Spectrum Vaccine

Chemical tinkering with poly N-acetyl glucosamine (PNAG)—a sugar polymer that is part of the sticky extracellular layer of Staphylococcus aureus—can enhance its reactivity with mammalian immune systems, opening a door for potential vaccine development, according to Gerald Pier of Harvard Medical School in Boston, Mass. He spoke in September at the meeting of the U.K. Society for General Microbiology in Dublin, Ireland. Because other pathogens, including gram-negative bacteria, also produce PNAG, working with this signature polymer might lead to development of a vaccine with broad-spectrum activity, he suggests. “We now have a way to tip the balance for resistance to infection back towards humans by vaccination.”

Removing many of the acetyl side chains that ordinarily are linked to amino groups in the PNAG polymer enhances its ability to generate an immune response, according to Pier and his collaborators. Further, the modified polymer elicits antibodies that are much better at depositing complement opsonins onto the PNAG,” thus
enhancing phagocyte-mediated ingestion and killing of the bacterial pathogens, he says. These changes markedly improve the response compared to that generated by the unmodified PNAG polymer, which he describes as “rather poor” at binding complement and then inducing phagocytes to kill bacteria.

“The chemical form [of PNAG] that stimulates the immune response does not exist in vivo, hence the natural human immune response to PNAG is composed mostly of the ‘bad’ antibodies—those that do not promote bacterial killing,” Pier says. “But it is important to emphasize that the ‘good’ antibodies that we induce by chemically modifying the PNAG for vaccination bind quite well to the native form of PNAG produced in vivo. Obviously, if the antibodies we induced by the chemical modification only bound to the chemically modified PNAG, they would be no good in vivo.”

*S. aureus* cells adhere to natural and implanted surfaces mainly through extracellular sugars such as PNAG. When such cells form biofilms, they more effectively ward off host immune responses as well as the action of antibiotics. Biofilms are not the target of the vaccine that Pier plans to develop. Instead, his focus is on the planktonic bacteria that might enter particular anatomic sites or bodily fluids—notably, blood, lungs, the urinary tract, and skin. “Implanted devices colonized with a biofilm likely will still have to be treated by either antibiotic therapy or removal from the body,” he says.

The first formulation of such a vaccine is a human monoclonal antibody that binds PNAG, and such a product is being readied for clinical trials, according to Pier. “Assuming no unexpected toxicology, then we anticipate producing antibody for infusion into humans in a phase 1 trial in the spring or early summer of 2009,” he says. Although this first product targets *S. aureus*, its capacity to quell bacterial pathogens might be wider, according to Pier. “Vaccination against this antigen has the potential to target a range of pathogenic bacteria,” he says. For example, gram-negative bacteria such as *Escherichia coli*, *Bordetella pertussis*, and *Yersinia pestis* also make PNAG. Moreover, the alginate antigen of *Pseudomonas aeruginosa* is “highly analogous” to PNAG, and thus might also be recognized by antibodies that are directed to PNAG.

Exploiting the immunogenicity of deacetylated PNAG and its stimulation of protective immunity against *S. aureus* makes sense to Saïd Jabbouri of the Université du Littoral-Côte d’Opale in Boulogne-sur-Mer, France. His research on *S. aureus* supports the potential of PNAG as the basis of a “broadly protective” vaccine. However, he cautions, it would be helpful to know if patients with elevated levels of anti-PNAG antibodies are better protected from infection than those who do not, and, conversely, if those who contract an infection have diminished levels of such antibodies.

**Deep Underground Is Lonely Habitat for *D. audaxviator***

The microorganism *Desulforudis audaxviator* is apparently the sole inhabitant of the Mooning gold mine near Johannesburg, South Africa, making it the first ecosystem known for having only a single biological species. Within that underground site, 2.8 kilometers or 1.74 miles beneath the surface of the earth, this rod-shaped bacterium exists in darkness, without oxygen, and a moderate 60°C, according to Adam Arkin and Terry Hazen of the Department of Energy (DOE) Lawrence Berkeley National Laboratory and their collaborators at the DOE Joint Genome Institute and Pacific Northwest National Laboratory as well as at several universities. The bacterium derives energy from hydrogen and sulfate produced through radioactive decay of uranium, while it builds organic molecules from water and inorganic carbon, and nitrogen from ammonia in the surrounding rocks, the researchers report. Details appear in the 10 October *Science.*