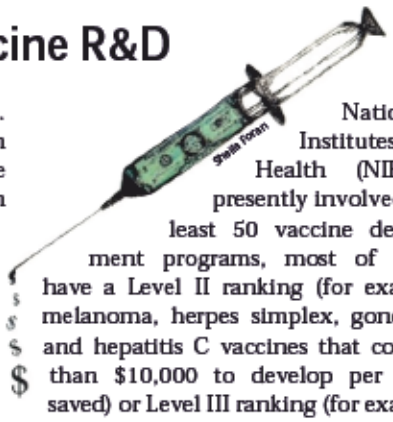
Report calculates value for money of US vaccine R&D



Almost four years after it was commissioned by the National Institute of Allergy and Infectious Diseases (NIAID), the Institute of Medicine (IOM), a branch of the National Academy of Sciences, has released a report analyzing which vaccines give the best return per R&D investment dollar. It concludes that vaccines for cytomegalovirus, influenza, insulin-dependent diabetes, multiple sclerosis, rheumatoid arthritis, group B streptococcus and *Streptococcus pneumoniae*—classified as Level I vaccines—have the best all-round R&D investment value.

"NIAID asked us to look into the future of where science will lead us, and to estimate costs of vaccine development, implementation and cost savings of premature morbidity and mortality," explains chair of the IOM Committee to Study Priorities for Vaccine Development, Robert Lawrence, Johns Hopkins School of Hygiene and Public Health.

The report, "Vaccines for the 21st Century: A Tool for Decisionmaking," stratifies 26 vaccines into four levels based on development cost versus the quality-adjusted life years (QALY) saved. This quantitative model operates within a computer spreadsheet and can be adapted to any candidate vaccine. It can be obtained free of charge from the IOM in Washington D.C.

Under its congressional mandate, the committee was restricted to evaluating vaccines of importance to the US rather than those that are beneficial on a worldwide scale: "We would have liked to examine disease burden in the developing world as well, but diseases such as schistosomiasis and malaria were off limits," says Lawrence.

Also off limits was an assessment of the value of developing an HIV/AIDS vaccine. Apparently the panel was not to appraise this type of vaccine because NIAID has already made substantial commitment to HIV vaccine research. However, Lawrence expects somebody outside the committee will quickly determine its cost-effectiveness now that the software for the model is in the public domain.

According to Adis International's R&D Insight drug development database, the National Institutes of Health (NIH) is presently involved in at least 50 vaccine development programs, most of which have a Level II ranking (for example, melanoma, herpes simplex, gonorrhea and hepatitis C vaccines that cost less than $10,000 to develop per QALY saved) or Level III ranking (for example, rotavirus and streptococcal A vaccines that cost between $10,000 and $100,000 per QALY saved). As a rule of thumb, explains Lawrence, "a therapy under $100,000 is usually a good buy in the US healthcare environment, so commitment to vaccines in all three of the first levels is justified."

The NIH is also working on at least three of the less favorable Level IV vaccines, which cost more than $100,000 per QALY saved. These include shigella and *Escherichia coli* vaccines. A summary of the report is available at http://www2.nas.edu/hpdp

KAREN BIRMINGHAM, LONDON

The sun sets on the CVI

Many delegates attending a mid-March closed meeting led by the World Bank in Bellagio, Italy expressed emotions from disgust to amazement at what seemed to be the destruction of, rather than the transformation of, the Children's Vaccine Initiative (CVI). The meeting sounded the termination of the CVI, along with the contracts of its 14 staff by year's end and its replacement, at least in the short-term, by a much smaller secretariat acting purely as a clearinghouse of information between its partners—the World Bank, the World Health Organization (WHO), the Rockefeller Foundation and UNICEF.

The CVI, a nine-year-old multi-agency program, had been working towards the addition of new vaccines, such as hepatitis B, haemophylus influenzae B, rotavirus and the potentially new pneumococcal vaccines, to the existing world vaccination schedule (*Nature Med.* 4, 136; 1998). If delivered to 80 percent of the world's children, these four 'new' vaccines could save four million young lives each year.

Although many believe that shutting down this organization would be detrimental to global immunization programs, the Dean of Public Health at the University of Harvard, Barry Bloom—a passionate advocate for children's vaccines—says he is "thrilled" at the outcome. The Bill and Melinda Gates Children's Vaccine Program, founded in December last year with $100 million from the William Gates Foundation, is also clearly satisfied with the arrangement and has promised "a lot of program money" to develop a new initiative for improving the existing vaccination system.

Bloom's upbeat position is based on the argument that CVI has achieved its goal, and that its continued existence actually discourages its member organizations and associates from getting involved first-hand in new vaccine development and distribution. According to fans of the new deal, these organizations are now ready to make real commitments to buying and distributing new vaccines. The partners, including representatives from the pharmaceutical industry and donors but notably lacking delegates from countries needing the vaccines most, left Bellagio to forge a strategic plan to be ready by September. The goal is to achieve what they are calling "sunrise"—finally vaccinating the world's children with the new vaccines. A commitment to this objective is what thrilled Bloom.

However, some insiders believe that the dissolution of the CVI is a purely political maneuver. Under its new confident and technocratic leader, Grö Harlem Brundtland, the WHO is actively re-taking control of areas such as vaccine distribution, where its power had been slipping. "This is because WHO's capacity in immunization has grown tremendously in the time since CVI has been established," explains Bruce Ayleward, head of the WHO's polio eradication initiative, adding that "under the re-organization of WHO's activity here in Geneva, things have been changed."

And it seems that things are still changing at WHO headquarters, with internal rumblings over which cluster will gain ultimate control over vaccine programs: either the Health Technology and Drugs cluster, headed by Michael Scholtz,

which currently oversees 90 percent of vaccine work, will retain control, or this will be passed to the Communicable Diseases cluster, headed by David Heymann. Likewise, it is also uncertain whether the new secretariat will be housed within the WHO or UNESCO.

WHO maintains that three objectives were agreed at the Bellagio meeting: to underpin the existing expanded program of immunization (EPI), which reached 80 percent of the world's children with six older vaccines in 1990; to finally eradicate polio, and use that and EPI as models of how to get new vaccines delivered; and for a group led by the World Bank to work on new financing mechanisms to raise the $2 billion budget needed for the program.

According to recent CVI estimates, $1–2 billion per annum is needed for the poorest countries. This breaks down into $100-200 million for immediate new vaccine purchases, an equal sum for infrastructure and rebuilding of a rotting cold-chain from airport to village; $500 million a year to purchase rotavirus and pneumococcal vaccines; plus a margin for unforeseen contingencies.

One major obstacle, however, is convincing partners such as industry that eliminating the neutral CVI is the right step. Alan Shaw, chair of the biologicals committee of the International Federation of Pharmaceutical Manufacturers Associations and head of vaccine research at Merck, admits that he was surprised by the outcome of the Bellagio meeting. "For the last 2–3 years the CVI had become a useful forum for discussions about vaccine policy and how to implement newer vaccines into the global immunization schedules. In a sense we were sorry to see that dismantled, but hope that we can build another means of doing the same thing," Shaw told *Nature Medicine*. Shaw is currently drafting a letter to be sent to Brundtland on industry's perceptions of the Bellagio meeting.

The pharmaceutical industry is particularly worried about the lack of independence of the new secretariat. Tom Vernon of Merck Vaccines wants to see some form of oversight group. "CVI not only advocated, it analyzed and criticized. Who will analyze and criticize "sunrise" and call partners to account if they fail in their commitments?" he asks.

KAREN BIRMINGHAM, LONDON

NIAID to begin clinical transplant tolerance trials

A substantial new federal grant to be issued by the National Institute of Allergy and Infectious Diseases (NIAID) looks certain to 'push the envelope' of academic transplantation research by focusing on clinical tolerance trials for organ transplants and autoimmune diseases. Apparently, the impetus for the new funding was the scientific advances in animal models of tolerance and induction, and the fact that the pharmaceutical industry has already begun to investigate this approach in clinical trials. The grant coincides with a new report warning that the US is in danger of losing its lead position in immunology research (see page 471).

The request for proposals (RFP) for the "Collaborative network for clinical research on immune tolerance," which is co-sponsored by National Institute of Diabetes and Digestive and Kidney Diseases and the Juvenile Diabetes Foundation, states that up to $120 million will be awarded in grants over the next seven years. Applications close on May 14th.

Although one-year kidney graft survival approaches 90 percent using standard immunosuppressive therapy, chronic rejection is a major problem, with only around 45 percent of kidney grafts surviving ten-years after transplant. This survival rate has not improved since the early 1980s, and survival percentages of other organs, such as heart and pancreas, is even lower. The induction of tolerance—teaching the host immune system to accept a donor graft as 'self'—is preferable to current immunosuppressive therapies, which are associated with many side effects. "Immunosuppressed patients are more susceptible to infections and cancer, and immunosuppressants promote vascular changes and may actually underlie chronic rejection," says Daniel Rotrosen, chief of the Asthma, Allergy and Inflammation Branch of NIAID.

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Transplant immunologists have made rapid progress in learning how to induce donor-specific immune tolerance to achieve long-term graft survival, and several tolerogenic agents, such as the T cell co-stimulatory blockers, CTLA4-Ig, anti-CD40 ligand or anti-B7, can induce donor-specific tolerance in rodent and non-human primate transplant models. The Massachusetts-based biotechnology company, Biogen, is currently in Phase II trials with an antibody against CD40 ligand (Antova) for idiopathic thrombocytopenic purpura and lupus nephritis. Renal transplant trails were scheduled to start early this year. Bristol-Myers Squibb is testing CTLA4-Ig in Phase II trials for psoriasis and Phase I trials for rheumatoid arthiritis.

But whether tolerance research is ready for human studies is a matter of debate among academic transplant scientists and was the hot topic at the recent keystone conference "Molecular and Cellular Biology of Transplantation," in Nevada. NIAID director, Tony Fauci, feels "the time is right to put resources toward tolerance clinical trials for immune-mediated diseases such as autoimmune and allergic disease, and transplant rejection," and many scientists concur with this opinion and want to push ahead. However, others believe the science is too premature to be tested on humans.

All researchers agree that immune tolerance to transplantation is the future of the field. "A number of us feel that we've had the most mileage we were going to get out of immunosuppressive drugs and we're ready for a new paradigm," says Laurence Turka, University of Pennsylvania, a member of the expert panel that made RFP recommendations to NIAID. "Tolerance induction is the next big leap," says Turka.

Nevertheless, some transplant clinicians feel that there will be an ethical dilemma in placing a kidney transplant patient in a tolerance clinical trial when immunosuppressive therapy has such high initial graft acceptance potential. Turka says that applicants for the funding will have to explain how they will choose patients, and that part of the goal of the RFP is to spur new ideas from the clinical community about the best way to handle these issues.