

THE WHITE HOUSE
WASHINGTON

ROUTING SLIP

TO:

~~BRUCE REED~~

CHRIS J.

KARIN

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FROM:

SIDNEY BLUMENTHAL
ASSISTANT TO THE PRESIDENT

SUBJECT:

FOR YOUR INFORMATION

CC- TOM FREEDMAN

PR NCETON PROJECT 55 NC.

Tuberculosis Initiative

FACSIMILE

To: Sydney Blumenthal Fax: 202-456-1213 Date: 9/22/99 # of Pages: 7 (including this page)	From: Dana Deaton Project Manager Tuberculosis Initiative Fax: (202) 588-7798 Phone: (202) 588-7715 email: ddeaton@essential.org
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Message:

To Sydney Blumenthal,

I am writing from Ralph Nader in reference to an invitation from the American Society of Tropical Medicine and Hygiene (ASTMH) for Bill Clinton to speak at the upcoming ASTMH Meeting (Nov 28-Dec 2, 1999). This letter was sent many months ago at a time when the President's availability could not be confirmed. Ralph would again request the President's attendance and to urge his prompt confirmation.

In light of President Clinton's recent U.N. address, in which he highlights his commitment to fighting malaria and tuberculosis as an important resolution for the new millennium, his participation at the ASTMH Mtg. is critical and timely.

In this fax, I have included Clinton's U.N. address (as printed in the NY Times), correspondence between Clinton and the ASTMH about the Meeting, and a recent letter from Clinton to our organization about his commitment to fighting tuberculosis.

Please be in touch with me or Ralph Nader (202-387-8050) about Clinton's participation at the ASTMH Meeting.

1600 20th Street N.W.

Washington, D.C. 20009

Thank you very much.

Dana Deaton, TBI Project Manager

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September 22, 1999, Wednesday, Late Edition - Final

SECTION: Section A; Page 18; Column 1; Foreign Desk

LENGTH: 1106 words

HEADLINE: Words of Clinton: 'Three Resolutions for the New Millennium'

BODY:

Following are excerpts from President Clinton's address yesterday to the United Nations General Assembly, as recorded by The New York Times:

For all our intellectual and material advances, the 20th century has been deeply scarred by enduring human failures, by greed and lust for power, by hot-blooded hatreds and stone-cold hearts.

At century's end, modern developments magnify greatly the dangers of these timeless flaws. Powerful forces still resist reasonable efforts to put a human face on the global economy, to lift the poor, to heal the earth's environment. Primitive claims of racial, ethnic or religious superiority, when married to advanced weaponry and terrorism, threaten to destroy the greatest potential for human development in history, even as they make a wasteland of the soul.

Therefore we look to the future with hope but with unanswered questions:

In the new millennium, will nations be divided by ethnic and religious conflicts? Will the nation-state itself be imperiled by them or by terrorism? . . .

Will we be free of the fear of weapons of mass destruction or forced to teach our grandchildren how to survive a nuclear, chemical or biological attack? Will globalism bring shared prosperity, or make the desperate of the world even more desperate? . . .

The truth is that the 20th century's amazing progress has not resolved these questions. But it has given us the tools to make the answers come out right, the knowledge, the resources, the institutions. . . . With that in mind, I offer three resolutions for the new millennium.

First, let us resolve to wage an unrelenting battle against poverty and for shared prosperity, so that no part of humanity is left behind in the global economy.

Globalism is not inherently divisive. While infant mortality in developing countries has been cut nearly in half since 1970, life expectancy has increased by 10 years. According to the U.N.'s Human Development Index, measuring a decent standard of living, a good education, a long and healthy life, the gap between rich and poor countries on this measure has actually declined.

Open trade and new technologies have been engines of this progress. . . . But this promising future is far from inevitable. We are still squandering the potential of far too many: 1.3 billion people still live on less than a dollar a day. More than half the population in many countries have no access to safe water. . . .

We must refuse to accept a future in which one part of humanity lives on the cutting edge of a new economy while the other lives at the knife edge of survival.

What must we do? Well, we can start by remembering that open markets advance the blessings and breakthroughs we want to spread.

That's why we in the United States have worked to keep our markets open during the recent global financial crisis, though it has brought us record trade deficits.

It is why we want to launch a new global trade round when the W.T.O. World Trade Organization meets in Seattle this fall, why we are working to build a trading system that strengthens the well-being of workers and consumers, protects the environment and makes competition a race to the top, not the bottom. . . .

The challenge and opportunity for developing countries is to skip the cost of the industrial age by using technologies that improve the economy and the environment at the same time.

Finally, to win the fight against poverty we must improve health care for all people. Over the next 10 years in Africa, AIDS is expected to kill more people and orphan more children than all the wars of the 20th century combined. Each year diseases like malaria, tuberculosis, pneumonia, leave millions of children without parents, millions of parents without children.

Yet for all these diseases vaccine research is advancing too slowly, in part because the potential customers in need are too poor. Only 2 percent of all global biomedical research is devoted to the major killers in the developing world. No country can break poverty's bonds if its people are disabled by disease and its government overwhelmed by the needs of the ill. . . .

The second resolution I hope we will make today is to strengthen the capacity of the international community to prevent and, whenever possible, to stop outbreaks of mass killing and displacement.

This requires, as we all know, shared responsibility, like the one West African nations accepted when they acted to restore peace in Sierra Leone, the one 19 democracies in NATO embraced to stop ethnic cleansing in Bosnia and Kosovo, the one Asian and Pacific nations have now assumed in East Timor, with the strong support from the entire United Nations, including the United States. . . .

Finally, as we enter this new era, let our third resolution be to protect our children against the possibility that nuclear, chemical and biological weapons will ever be used again. The last millennium has seen constant advances in the destructive power of weaponry. In the coming millennium this trend can continue. Or if we choose, we can reverse it with global standards, universally respected. . . .

We must work to deny weapons of mass destruction to those who would use them. For almost a decade, nations have stood together to keep the Iraqi regime from threatening its people and the world with such weapons. Despite all the obstacles Saddam Hussein has placed in our path, we must continue to ease the suffering of the people of Iraq. At the same time, we cannot allow the Government of Iraq to flout 40, and I say 40, successive U.N. Security Council resolutions and to rebuild his arsenal. . . .

There are many other challenges. . . . In meeting them, the United Nations is indispensable. It is precisely because we are committed to the U.N. that we have worked hard to support the management -- effective management -- of this body.

But the United States also has a responsibility to equip the U.N. with the resources it needs to be effective. As I think most of you know, I have strongly supported the United States meeting all its financial obligations to the United Nations and I will continue to do so. We will do our very best to succeed this year. . . .

Not long ago I went to a refugee camp in Macedonia. The people I met there, children and adults alike, had suffered horrible, horrible abuses. But they had never given up hope because they believe that there is an international community that stood for their dignity and their freedom. I want to make sure that 20 or 50 or 100 years from now, people everywhere will still believe that about our United Nations. . . .

LANGUAGE: ENGLISH

LOAD-DATE: September 22, 1999



Search: General News; tuberculosis

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AMERICAN SOCIETY OF TROPICAL MEDICINE AND HYGIENE

ASTMH Headquarters • 60 Revere Drive • Suite 500 • Northbrook, IL 60062 • 847/480-9592 • FAX 847/480-9282

October 2, 1998

The Honorable William J. Clinton
President
The White House
Washington, DC 20500

Dear President Clinton:

It is with great regret that I write to inform you that the American Society of Tropical Medicine and Hygiene (ASTMH) has had to cancel its upcoming Annual Meeting in San Juan, Puerto Rico October 18th through 22nd. Unfortunately, the damage sustained as a result of Hurricane Georges has made it impossible for San Juan hotels to accommodate our meeting. I had hoped that you would be able to participate as a speaker at this meeting.

Because we will not be rescheduling the meeting, I would like to invite you to speak at the Society's next meeting which will take place in Washington, D.C. from November 28th through December 2nd, 1999. Many of the speakers who had planned to attend the Puerto Rico meeting, including Ralph Nader and Dr. Anthony Fauci, will be invited to speak at next year's Washington, DC meeting.

ASTMH members are actively involved in advancing global health and disease research efforts, and look forward to the opportunity to work with you to raise awareness about the need for a strong commitment by the United States to global disease eradication efforts, especially the control of malaria - a major cause of death in Africa. Your support for these efforts is critical to ensuring continued U.S. involvement. The Society stands ready to assist you in making sure that adequate funds are directed to global infectious disease programs such as the World Health Organization's "Roll Back Malaria" plan and research efforts supported by the National Institutes of Health, the Agency for International Development, and the Department of Defense.

Again, I apologize for having to inform you of this cancellation, but I hope you will consider my invitation to speak at next year's meeting. Please feel free to contact me at (617) 432-1563 or dfwirth@hsph.harvard.edu if you have any questions.

Sincerely,

Dyann Wirth, Ph.D.
President-elect

THE WHITE HOUSE
WASHINGTON

OCT 14 1998

October 7, 1998

Dyann Wirth, Ph.D.
President-elect
American Society
of Tropical Medicine and Hygiene
Suite 500
60 Revere Drive
Northbrook, Illinois 60062

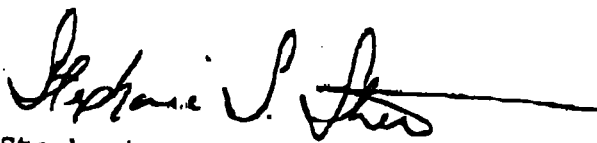
Dear Dr. Wirth:

On behalf of President Clinton, thank you for inviting the President to attend the 1999 Annual Meeting of the American Society of Tropical Medicine and Hygiene in Washington, DC.

The White House is presently unable to confirm the President's availability on November 28-December 2, 1999. You will be contacted when further information becomes available.

Please know that President Clinton appreciates your interest and that your request will continue to receive careful consideration. Should you need further scheduling assistance, please feel free to contact my office.

Sincerely,



Stephanie S. Streett
Assistant to the President
Director of Presidential Scheduling

SSS/twe

THE WHITE HOUSE
WASHINGTON

September 16, 1999

The PP55 Tuberculosis Initiative
1600 20th Street, N.W.
Washington, D.C. 20009

Dear Friends:

Thank you for your letter regarding tuberculosis research. I was glad to learn your thoughts, and I am sorry I was unable to respond sooner.

As you may know, supporting biomedical research remains a top priority of my Administration. In last year's budget, I made a commitment to increase funding for the National Institutes of Health by nearly 50 percent over five years, as well as to increase funding for other programs within the Department of Health and Human Services, including the TB program at the Centers for Disease Control and Prevention. Moreover, my proposed budget for fiscal year 2000 requests \$75 million in funds specifically for tuberculosis research at NIH, which represents a 14 percent increase over 1998 funding levels. Please know that I will keep your recommendations in mind as we continue to work with Congress to protect funding for medical programs.

As we prepare to enter the new millennium, the struggle against tuberculosis will continue to challenge our nation and the world. I am deeply grateful for your work, and I welcome your continued involvement in the fight for a cure.

Sincerely,

Bill Clinton

**CENTER FOR STUDY OF RESPONSIVE LAW
P.O. BOX 19367
WASHINGTON, D.C. 20036**

*Mail with
-Gaw*

**Fax to Tom Friedman
From Amir Attaran**

One page to follow this one

If this fax is not properly received, please phone (604) 222-1256

PRESS RELEASE

EMBARGOED UNTIL [Date/time?]

RE: President Clinton announces American involvement in African malaria campaign

Today in Senegal, President Bill Clinton announced that the United States would contribute \$1 million toward building the Multilateral Initiative on Malaria (MIM) – an American-initiated collaboration of the USA, eleven European countries, twenty one African countries, the Burroughs Wellcome Fund, the Malaria Foundation, the Organization of African Unity, the Wellcome Trust, the World Bank, and the World Health Organization – that is aimed at coordinating new research to control a rising global epidemic of the disease. The \$1 million contribution will go toward supporting MIM conferences, and providing Internet access to malaria research laboratories in Africa.

The malaria problem is worse than ever. Since the failure of malaria eradication efforts in the 1960s, the disease has regained the upper hand. Sri Lanka, which had only eighteen malaria cases in 1963, today has over *one million*. In Senegal, where the President made his address, French scientists reported a *seven-fold increase in malaria deaths over the last five years*. Today, every year about *half a billion* people are diagnosed with malaria, and 2.7 million human beings lose their lives to the disease. In Africa, as many people die of malaria in one year as have died of AIDS in the last dozen years. One million African children die of this scourge annually – the equivalent of seven jumbo jets of children crashing *every day*. Americans who travel to malarious areas are also at risk: about 1500 Americans a year are hospitalized with malaria on returning home, after spending as little one day abroad.

What is worse, resistance to antimalarial drugs, and the absence of an effective malaria vaccine, are threatening to make the disease incurable for the first time since the 17th century. Researchers in South East Asia recently discovered strains of malaria that cannot be treated by any drug now on the market. The spread of these strains to Africa within the next decade, where 90% of malaria cases occur, is "a looming crisis", in the words of researchers at Harvard University and the WHO. Yet very little is being done to prevent this. As the National Academy of Sciences reported in 1996, "not a single major Western pharmaceutical company is now developing new drugs for the disease."

A research audit published by the London-based Wellcome Trust in 1996 found the malaria research budgets of all nations, charities, drug companies, and the WHO totals under \$90 million annually, which is comparable to the budget of a single, modestly-sized hospital in the United States. Ralph Nader, who is campaigning for increased research, calls this, "a pittance of a sum, a shame on the conscience of nations; and an affront to Africans, whose collective loss of life is treated to a research budget that is less than 1/20th the cost of a single B-2 bomber."

President Clinton's announcement of \$1m toward bootstrapping the MIM is a welcome first step towards a reinvigorated American malaria effort. We are encouraged by the Clinton Administration's growing recognition of the malaria problem. Yet, very much more needs to be done. We therefore call on the Administration to seek new, significantly increased appropriations for malaria research and control in its 1999 budget.

XXX

FOR FURTHER INFORMATION please contact:
Dr. Amir Attaran
Malaria Project Director
Center for Study of Responsive Law
Ph: (202) 387-8030 or (604) 222-1256

P.O. Box 19312
Washington, DC 20036

President William Jefferson Clinton
The White House
1600 Pennsylvania Avenue NW
Washington, DC 20500

February 3, 1998

Dear President Clinton:

During your recent State of the Union address, you called for a substantial increase in Federal spending for basic biomedical research in the forthcoming budget. As you are aware, enhancing biomedical research funding and the budget of the National Institutes of Health has bipartisan support in Congress.

While the United States prepares to invest more heavily in research and technologies for public health, I am writing to ask that the needs of the world's poor, who suffer greatly from infectious diseases, be given special attention in the funding process. As Vice-President Gore, speaking before the National Council for International Health in 1996, recognized, emerging infectious diseases are among "the most significant health and security challenges facing the global community". Yet, despite the importance of this challenge to America, our commitment, both before and after Mr. Gore's onetime priority call, to researching the vicious, re-emergent scourges of the developing world remains embarrassingly low.

In this letter, I focus on the example of malaria: a disease which is an everyday fact of life in the developing world, but for which there is very little research funding. Although last year was the centenary of the discovery of the cause of malaria (it is caused by a parasite transmitted by the bite of an infected mosquito), the disease remains an epidemic of undiminished force at the end of the millennium. In the words of the World Health Organization:

Malaria is endemic in 91 countries, with about 40% of the world's population at risk. Each year there are 300-500 million clinical cases of malaria, 90% of them in Africa, and between 1.5 million and 2.7 million deaths. Among all infectious diseases, malaria continues to be one of the biggest contributors to disease burdens in terms of deaths and suffering. By undermining the health and capacity to work of hundreds of millions of people, it is closely linked to poverty and contributes significantly to stunting social and economic development...[And] in many parts of the world, malaria is becoming an even greater problem than before.

Numbers like these are so alien to American experience that they are hard to comprehend. To envision the number of children killed by malaria annually,

imagine seven jumbo jets, full of children, crashing *every day*. To get a sense of malaria's ubiquity in the tropical world, consider that if Americans, rather than Africans, were malaria's victims, every American would be hospitalized on average once a year. Many would be hospitalized twice.

As if this were not enough, malaria kills the weak and rends the fabric of families. Children under five years old are much more likely to die of malaria than adults: about a million African children are killed by the disease each year² -- or one child in twenty³. Women, too, are especially vulnerable. By the simple act of pregnancy, a woman increases her risk of serious or lethal malaria by four-fold⁴. If she is lucky enough to survive, malaria will frequently cause reduced birthweight in her infant. The parasite can even infect her fetus, condemning her newborn to begin life with malaria⁵.

Yet no matter how compelling these humanitarian arguments may be, scientists have been given little opportunity to bring malaria under control. There is as yet no proven vaccine against malaria; and only a handful of drugs, most of which have been overused and are now ineffective. In Southeast Asia, scientists have even discovered strains of "multidrug-resistant malaria with no safe, effective alternative for treatment" -- i.e. malaria virtually without a cure -- which they expect will spread to other continents within a decade⁶. Such developments should worry us, because our global pharmacopeia is already sparse, and existing drugs are losing efficacy by the day. As scientists bemoaned in the *Journal of the American Medical Association* last year, "few new drugs will be available in the future because of reduced funding for antimalarial drug research and development."⁷

Indeed, malaria scientists are correct to complain about a scarcity of research funding. In FY1993, the world spent about \$84 million on malaria research⁸. The Federal Government contributed about half that amount, or \$42 million. By contrast, the Government presently spends about \$2.3 billion on cancer research, and \$1.5 billion on HIV/AIDS research. To put it another way, in an era when the United States spent as much as \$36,000 on research for each fatal case of AIDS within its borders, it spent only about \$21 on research for each fatal case of malaria abroad⁹.

The AIDS problem deserves the funding it receives, but it must not be forgotten that malaria is no less of a scourge, and as the overall federal biomedical research budget grows, malaria surely deserves better than neglect. Indeed, malaria kills almost as many people, per annum, as have died of AIDS in the last 15 years¹⁰.

Malaria's neglect has roots in the policies of past Administrations, and has continued into your own term of office. For example, in 1994 USAID's malaria vaccine development program was cut by more than half¹¹. It is because of brutal cuts such as this that one science reporter today calls America's malaria effort "a pittance"¹².

What is to be done? Government must take the lead. The pharmaceutical industry is economically unwilling or unable to recoup an investment in malaria research, for the simple reason that the prospective market for antimalaria products is not sufficiently affluent¹³. The Institute of Medicine of the National Academy of Sciences notes that "not a single major Western pharmaceutical company is now developing new drugs for malaria"¹⁴, and the number of companies working on malaria vaccine technologies can be counted on a single hand. But as with other areas of technology where Federal funding led the way, to the benefit of America as a whole, malaria research too promotes our national self interest. There are at least four reasons for this.

First, although malaria is no longer endemic to the United States (it was very common in the early part of this century), the disease still afflicts Americans. *Every* business traveler, soldier or vacationer returning home from a malarious area is at risk of the disease, no matter how brief their sojourn abroad. About 1500 American travellers each year are hospitalized in the US with this sort of "imported" malaria¹⁵. And as international travel grows, especially business travel to newly-industrializing countries, some of which harbour multidrug-resistance, the incidence of malaria among Americans is certain to rise.

These dangers are illustrated by the experience of American troops abroad. In Vietnam, malaria was the most frequent cause of hospitalization after combat wounds, affecting nearly 10% of soldiers at a given time¹⁶. Troops deployed to Somalia for Operation Restore Hope were no more fortunate. Despite military training and discipline in the use of antimalarial drugs, soldiers got 48 cases of malaria while in Somalia¹⁷. On returning home, the soldiers got another 112 "imported" cases, all requiring hospital treatment¹⁸. Many of the soldiers' cases were drug-resistant, and up to 43% of soldiers who were treated suffered one or several relapses later¹⁹. In all, malaria was the number one cause of hospitalization for troops who saw service in Somalia²⁰.

The lesson for civilian travelers could not be clearer: traveling in a malarious area, no matter how prudent one may be, is dangerous. No antimalarial drug is perfect; no exposure is without risk; and no person is immune. Suffice it to say that scientists have even recorded cases of malaria among travelers who were simply on board an aircraft that made a brief refuelling stop in West Africa²¹.

Second, the global burden of malaria has serious economic implications for developing countries, and by extension, implications for American foreign policy. Malaria is a perennial plague, and works like a "disease tax" in Africa: limiting inward capital investment, squelching development, damping trade in goods and services, and generally depressing the standard of living.

Third, research in malaria has the potential to enhance American activity in core, commercially valuable technologies. As I mentioned, nobody has succeeded in vaccinating humans effectively against malaria, or for that matter, any other parasitic disease. But it is precisely because malaria vaccine development is so technically challenging that the knowledge gleaned in research is so valuable. As the Institute of Medicine of the National Academy of Sciences observed:

The inherent complexity of the malaria parasite and the resulting immune response make it a natural target for cutting-edge fundamental and applied research. As a result, malaria vaccine research has historically been a leader in the development of new technologies with broad applicability to human health. For example, the world's first recombinant vaccine produced in bacteria and the first synthetic peptide vaccine to be tested in humans were malaria vaccines. The most complex vaccine yet devised...is a malaria vaccine now undergoing testing in humans...In addition, some of the most advanced adjuvant work has been driven by malaria vaccine research, and these agents are likely to be important components of vaccines against HIV/AIDS, herpes, cancer, and other diseases.²²

Just as public support for space science in the 1960s, or particle physics today, are seen as valuable to the cultivation of American scientific advances, malaria vaccine research presents an unequalled opportunity to give rise to technologies that would help us combat other diseases endemic to America. These could be parasitic diseases, such as cryptosporidiosis, which caused 400,000 illnesses in Milwaukee in 1994²³; or they could be terrible scourges such as AIDS. Needless to say, the commercial significance of these technologies for American industry is certain to be enduring.

Lastly, malaria research can help promote America's stature in the developing world, which is wise foreign policy, while at the same time promoting Americans' traditional values of helping the weakest help themselves. Last year, at the instigation of Dr. Harold Varmus, Director of the National Institutes of Health, the malaria research community met in Dakar to create the Multilateral Initiative on Malaria (MIM). The objective of the MIM is to create networks of American, European and African laboratories to work in collaboration on malaria research²⁴. For a modest investment in the MIM, the United States can build scientific capacity in Africa, promote contacts between American researchers and their European colleagues, and work toward conquering a devastating disease -- all of which makes for excellent scientific diplomacy.

I cannot stress enough, Mr. President, that biomedical research on malaria is not about traditional, third-world aid: it is about basic science, done largely in American laboratories, that has the potential to help the least fortunate countries of the world throw off the yoke of disease that stifles their life expectancy and material progress. There is no "cycle of dependency" in funding malaria research. There is only Americans' goodwill to stop the pointless death of children; to support the health of women; and to foster economic security for all people of the globe.

Malaria deserves serious attention from your Administration. I would recommend that the White House become involved by convening the best experts the field has to offer, to design and steer a renewed American research effort, backed by a funding commitment equal to the scientific challenge. An early, initiatory gathering of these knowledgeable persons with you at the White House would demonstrate the priority given this scourge by your Presidency.

Sincerely,

A handwritten signature in black ink, appearing to read "Ralph Nader". The signature is stylized with a large, looping "R" and a cursive "Nader".

Ralph Nader

¹ World Health Organisation, The World Health Report 1996 (WHO, Geneva, 1996), p. 47 [hereinafter *World Health Report*].

² For percentage, see World Bank, World Development Report 1993: Investing in Health (Oxford University Press, Oxford, 1993), at 208-9 [hereinafter *World Development Report*].

³ J. Anderson *et al*, Malaria Research: An Audit of International Activity (The Wellcome Trust, London, 1996), at 12 [hereinafter *Wellcome Malaria Report*].

⁴ N. Diagne *et al*, (1997) "Incidence of clinical malaria in pregnant women exposed to intense perennial transmission", *Transactions of the Royal Society of Tropical Medicine and Hygiene* 91(2):166-70.

⁵ P. Fischer (1997) "Congenital malaria: an African survey", *Clinical Pediatrics* 36(7):411-13; H. Silver, "Malarial infection during pregnancy", *Infect Dis Clin North Am* 11(1):99-107.

⁶ D. Wirth and J. Cattani (1997) "Winning the war against malaria", *MIT Technology Review*, August/September 1997.

⁷ H. Lobel and P. Kozarsky (1997) "Update on prevention of malaria for travelers", *Journal of the American Medical Association* 278(21):1767-1771.

⁸ The numbers are even less (about \$67 million) if one excludes non-State funded research, e.g. foundation grants and other charitable funding. See M. MacLean *et al*. (1997) "Making malaria research bite", *Nature Medicine* 3(1):14; and Wellcome Malaria Report, *supra*, at 17.

⁹ AIDS figure from Rep. Robert Livingston, Chairman, House Appropriations Committee, cited in M. Pines, "Can AIDS be Tamed?", in A Report from the Howard Hughes Medical Institute: The Race Against Lethal Microbes (Howard Hughes Medical Institute, Chevy Chase, Maryland, 1996), p. 49-50; Malaria figure calculated by taking US funding contribution (\$42 m) from Wellcome Malaria Report, *supra*, and dividing by WHO's estimate of about 2 million malaria deaths annually, from World Health Report, *supra*.

¹⁰ The Malaria Foundation Factpack (October 1997), <http://www.malaria.org/factpack.htm>.

¹¹ Wellcome Malaria Report, *supra*, at 16-7.

¹² Daniel S. Greenberg, "A Pittance to Fight Malaria", *Washington Post*, January 4, 1998.

¹³ Institute of Medicine, National Academy of Sciences, America's Vital Interest in Global Health (National Academy Press, Washington, 1997), p. 36-7.

¹⁴ *Ibid*.

¹⁵ Centers for Disease Control, *MMWR* (Jun 13, 1997) 46(23):536-539.

¹⁶ S. Neel (1973) "Vietnam Studies: Medical Support, 1965-1970" Washington, D.C.: US Department of the Army.

¹⁷ Wallace MR *et al*. (1996) "Malaria among United States troops in Somalia", *Am J Med* 100(1):49-55.

¹⁸ Newton, *supra*.

¹⁹ Smoak BL *et al*. (1997) "*Plasmodium vivax* infections in U.S. Army troops: failure of primaquine to prevent relapse in studies from Somalia", *American Journal of Tropical Medicine and Hygiene* 56(2): 231-234.

²⁰ Dr. R. De Fraites, Preventative Medicine Staff Officer, Office of the Army Surgeon General, January 1998 (personal communication to Dr. A. Attaran of my office).

²¹ M. Isaacson (1989) "Airport malaria: a review", *Bulletin of the World Health Organization* 87:737-43; H. Lobel *et al* "Long-term malaria prophylaxis with weekly mefloquine", *Lancet* 341:848-51. Both cited in Institute of Medicine, National Academy of Sciences, Vaccines Against Malaria: Hope in a Gathering Storm (National Academy Press, Washington, 1996), p. 7.

²² Institute of Medicine, National Academy of Sciences, Vaccines Against Malaria: Hope in a Gathering Storm (National Academy Press, Washington, 1996), p. 13-4.

²³ M. Kramer *et al* (1996) "Surveillance for waterborne disease outbreaks - United States 1993-1994" *MMWR CDC Surveillance Summary* 45(1):1-33.

²⁴ B. Mons *et al* "Partnership between South and North crystallizes around malaria", *Science* 279:498-99.

Time to put malaria on the global agenda

Growing international awareness of the impact of malaria, and in particular the prospect of an imminent catastrophe in Africa, is generating an unprecedented groundswell for a bold new effort in control.

Exactly 100 years after Ronald Ross discovered the role of the mosquito in the life cycle of the malaria parasite, efforts to control the disease stand at what could prove to be a historic watershed. Over the past year, a number of research organizations, led by the US National Institutes of Health (NIH) and France's Institut Pasteur, have been meeting with malaria researchers, research charities and development agencies, to draw up a coordinated international strategy for malaria research.

The outcome of these discussions is being fed into talks between the World Bank and the African office of the World Health Organization (WHO), which are exploring the feasibility of setting up a multi-agency, 50-year control programme — the African Malaria Initiative. All of these players are in turn talking with the pharmaceutical industry to find ways to reverse its unprecedented withdrawal from vaccine research and development of antimalarial drugs. Testifying to this movement, this week's *Nature* carries an appeal calling on the international community to mobilize in the fight against malaria (see page 541).

Africa's cry for help

The impending crisis in Africa has triggered this resurgence of interest. The parasite's resistance to chloroquine, the main means of prophylaxis and treatment on the continent, is growing alarmingly. Fansidar, the only cheap alternative, seems doomed to the same fate. "It's going to be pretty shocking," predicts Louis Miller, head of the Laboratory of Parasitic Diseases at the US National Institute of Allergy and Infectious Diseases.

A recent seven-fold increase in malaria deaths over five years in parts of Senegal has been linked to emergence of chloroquine resistance, according to Jean-Francois Trape, a Dakar-based researcher from ORSTOM, the

French development research agency. And chloroquine resistance in Senegal is much less intense than in other parts of Africa.

Malaria is already estimated to kill between 1.5 and 2.7 million people every year — several times as many as died in the recent genocide in Rwanda. Another 5 to 100 million people have the disease, and one-third of humanity lives in zones where it is endemic, catching it. Malaria kills one person — a child under five — every 12 seconds.

Nine out of ten cases occur in sub-Saharan Africa, and two-thirds of the rest are concentrated in just six countries. There are decreasing orders of prevalence in India, Brazil, Sri Lanka, Vietnam, Colombia and the Solomon Islands.

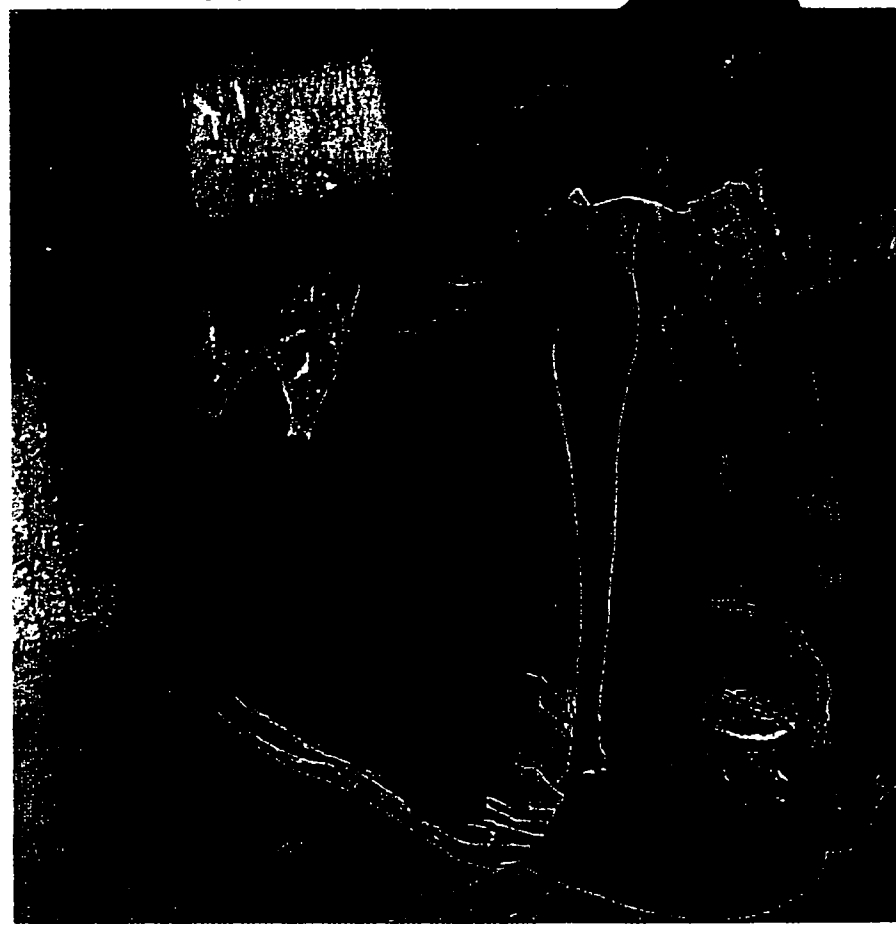
Malaria is resurging in many countries

where it had been eliminated or sharply reduced during the 1950s by a WHO-coordinated campaign to eradicate the vector, *Anopheles* mosquitoes, using pesticides such as DDT.

Malaria research and control slipped off the international agenda in the two subsequent decades, says Anatoli Kondrachine, head of malaria control at WHO. The relative success of the campaign lulled many countries into a false sense of security, he says. "Now we are paying a very heavy price for that gap."

Research is helping to fill that gap. New control measures and treatments are most needed in sub-Saharan Africa, where transmission rates are so high that levels of reduction that would bring the disease to a dead end in India or Brazil have little impact on malaria. The region was in fact left out of the earlier eradication campaigns precisely for this reason.

Some control action can be done using existing control techniques given adequate commitment (see page 541). But research is needed to develop other measures more effective in the long term, and the new tools needed to improve malaria control. Mosquitoes have become resistant to pesticides, and the harmful effects of spraying the environment has prompted new control patterns. New drugs, and new diagnostic techniques, are also needed to all malarious



REUTERS

This Briefing has been written by Declan Butler, European correspondent for *Nature*, with additional reporting by John Maurice and Claire O'Brien.

On other pages | India: p536 | Research: p537 | Vaccines: p537 | Vectors: p538 | Money p539 | Industry p540

countries, not to mention the tourists and other travellers who visit them.

Thirty-year offensive proposed

Faced with this situation, Ebrahim Samba, African regional director of WHO and Richard Feachem, director for health, nutrition and population at the World Bank — and former dean of the London School of Hygiene and Tropical Medicine — last year began exploring the idea of creating a multi-agency, 30-year programme to control malaria.

Discussions have since been broadened to include the US Agency for International Development (USAID), US Centers for Disease Control, European Commission, the Organization of African Unity and other agencies. "There should be no delusion that this is a five- or ten-year programme," says Feachem. "We are thinking of a 30-year effort, and everyone would need to buy in for durations of that order."

Over the past decade, countless international and national strategies to "end malaria" have been devised. But many have gathered dust in government drawers, and few have been properly or fully implemented. "The problem is what people are doing in the field, which is not a lot and not very effectively," complains Feachem.

The thrust of the new initiative is on building the infrastructure needed for

malaria control in Africa. Back this with a coordinated and adequately funded international effort, and you have the makings of a situation where existing control and therapeutic tools could be used more effectively, says Feachem.

But research would also be an essential component, and the world's major research bodies would therefore need to be "formal partners". Harold Varmus, director of the US



Feachem: backs 30-year effort.

National Institutes of Health, says that joining forces would be "very, very healthy for malaria research in Africa".

The possibility that the programme would fund research directly has not been excluded, says Feachem. "Everything is on the drawing board. The initiative will be an umbrella for many things, and one will need to be a well-directed, adequately funded programme of research; it could be inside or outside, but strongly linked."

None of the agencies discussing the proposed African Malaria Initiative is yet talking dollars. But many of those involved are convinced that the programme will provide a vehicle for better use of existing funds, and act as a magnet to attract new money from the international community.

India plans \$200 million attack on malaria

When India launched a major malaria eradication programme in the early 1950s, 75 million people in the country were catching the disease annually, and 800,000 were dying. Twelve years, and much DDT, later, malaria had gone from 90 per cent of the territory; new cases had dropped to 100,000 annually, and deaths to 100,000.

But a decade later, the disease had climbed to 10 million annually, and over the past two decades the government has spent up to a quarter of its national budget on malaria control. In the past three years, there have been four major epidemics, with 2.85 million cases, 250,000 deaths, and 100,000 deaths, and under-reported deaths tolls were around 500,000.

Shri Lal, director of the National Malaria Eradication Programme, says that in the early 1980s, the programme was almost completely broken down. It was restarted in 1981 as the NMEP, and today efforts are being hampered by increasing resistance to chloroquine, the diminishing efficacy and increasing cost of DDT, and the spread of mosquito resistance. In addition, *Plasmodium falciparum*, which was prevalent in India in the past, has been succeeded by its more deadly relative *P.*

falciparum, which has been less susceptible to chloroquine.

The situation is "bad," admits Vulumiri Ramalingaswami, former chief of the Indian Council of Medical Research, who partly attributes the resurgence of the disease to poorly planned irrigation and urbanization programmes.

India will spend US\$40 million on malaria control this year — up from US\$20 million last year. It is also planning a five-year programme targeting 240 million people in 100 high-risk districts that account for 90 per cent of all *P. falciparum* cases in the country, says Lal. The programme will introduce new tools such as pesticides and improved bednets. This initiative will be funded by a loan from the World Bank. The NMEP is to be strengthened and will cost around \$200 million over the next 10 years, officials estimate.

Some argue that bureaucracy and too much money is the main obstacle to control. Operations are run by the states which have jurisdiction over health matters, and that has relegated the national programme to the supplier of drugs and pesticides, claims an observer. The national programme "looks good on paper but does not function at the grass roots," he says. **K. S. Jayaraman**

The initiative has only become possible because of a recent shift in policy at the World Bank. Its support for health projects has leapt from negligible levels in the 1980s to \$2 billion annually — about 10 per cent of the bank's current spending — and is growing. There is said to be consensus within the bank that, among the problems that Africa faces, malaria is near the top.

Political commitment crucial

A decision on whether to launch the African Malaria Initiative is expected later this year, although it would probably not begin until around 2000. "We are in no hurry, we want to get it right," says Feachem.

Political and financial commitment from African leaders is acknowledged to be a prerequisite for the success of the initiative. Its supporters argue that there is no point in external agencies putting money into a sector to which the government of the country is not giving priority.

In practice, health, and malaria in particular, comes near the bottom of the spending priorities of most African countries, and far behind items such as arms, which often eat as much as half of state spending. But change is in the air. When the Organization of African Unity (OAU), meets for its annual summit later this year, malaria will be on the agenda of the 53 heads of state for the first time.

Political commitment is also needed to reverse widespread 'fatalism' about malaria in Africa. "Countries seem to accept that living with malaria is inevitable, that there will always be dead children," says Déogratias Barakamfityé, director of malaria control at the African regional office of WHO. Infant mortality from malaria is so high that in some cultures parents wait a few years before christening their children.

Robert Mshana, executive secretary of the OAU, says that the aim of the summit is to persuade African heads of state to "accept that the [success of the] fight against malaria will be largely dependent on African countries themselves". He adds: "African leaders need to say: 'Malaria is killing our children, we must be determined to do something about it'."

Winning a political commitment would strengthen the hands of health ministers in negotiations with their finance ministries. "We want them to persuade politicians that there are tools which could reduce mortality, that there are considerable economic losses, and that they must allocate the human and financial resources needed," says Barakamfityé.

But Mshana also warns that political will is by itself insufficient. "We have had these slogans for the last 50 years and nothing has moved." Governments could help immediately simply by reducing taxes on products used in research, control or therapy, he says: "In some places the import taxes on mosquito nets are so high that nobody can afford them."

Research 'essential' for control strategy

Two main research goals are most likely to lead in the long term to large strides in malaria control. One is a vaccine, and the second is likely to be the genetic engineering of mosquitoes to confer resistance to the parasite. And there is growing awareness that a more science-based approach is needed in general if malaria control techniques are to be implemented effectively.

One glaring need is better understanding of the complex interaction between malaria transmission rates, acquired immunity, and the clinical forms and incidence of the disease. In regions such as sub-Saharan Africa, where an individual may receive up to 1,000 infectious bites a year, many people slowly acquire a natural immunity that allows them to tolerate a parasite load without developing severe symptoms.

When such populations experience prolonged periods of low transmission, individuals can quickly lose their immunity and risk developing severe malaria if transmission rates increase again. This fact has enormous implications for both the success of control measures, and the understanding of the frequent epidemics triggered by fluctuations in climate.

Some scientists argue that control methods such as insecticide-impregnated bed-nets — which have been shown to cut

mortality and morbidity by 15 to 33 per cent in short-term trials — may in the long term only make populations more vulnerable to severe disease by reducing natural immunity. If they are correct, methods such as bed-nets and genetically engineered mosquitoes would have little impact on the control of the disease, and indeed could even make matters worse.

This complex debate seems to be going the way of those who feel that the lives saved immediately justifies taking the risk. But it has revealed the overriding need to accompany vector control programmes with rigorous long-term epidemiological studies of their impact on immunity, morbidity and mortality.

The same need applies to urban malaria, where transmission seems to be reduced, but severe and fatal disease more frequent. This may have important public health significance, given that migration from rural to urban areas is expected to be the biggest social change in Africa in the coming decades.

The need to understand the complex dynamics of malaria is also acute in other sectors. There is growing awareness that proper testing of candidate vaccines, and successful introduction of any working vaccine, will require much more research on epidemiology, parasite polymorphism, and mechanisms of immunity and transmission,

and knowledge of how these vary from region to region.

More broadly, there is growing awareness that control needs to be more science-based. Richard Feachem of the World Bank says that a comprehensive and integrated approach is needed, not what he describes as "a thoughtless grabbing of the latest attractive idea and just putting it into the field without adequate care".

Harold Varmus, director of the US National Institutes of Health, describes moves to develop control programmes without a strong emphasis on research as "penny wise and pound foolish. I don't think you can do malaria control without a research component, because we don't really know the best way to do control."

Indeed, many believe that what is now needed is an integrated approach, stretching from better diagnosis and treatment of sick children in the home to rational drug use to limit the spread of resistance, monitoring and evaluating control measures, and developing tools such as drugs and vaccines through basic research. The simplistic notion "that a magic bullet developed in a laboratory in London or Washington would bring an end to malaria is now obsolete", says Luiz Pereira da Silva, a vaccine researcher at the Institut Pasteur in Paris.

Vaccines: a roller-coaster of hopes

After many years of frustration, malaria researchers are excited at the prospects raised by a preliminary evaluation of a vaccine developed by SmithKline Beecham Biologicals and the US Army, which protected six out of seven volunteers subjected to repeated bites by infected mosquitoes.

The vaccine is based on the the major surface protein of sporozoites, the circumsporozoite protein, which helps them infect hepatocytes. Previous vaccines using this protein had failed in trials because they did not elicit a sufficient immune response. But the new study suggests that this obstacle might be overcome using adjuvants, compounds which stimulate the immune system. "It's a tremendously exciting development", says Ripley Ballou, head of immunology at Walter Reed.

The study tested not just the vaccine but also three different adjuvants. Three groups of subjects were assigned to groups differing only in the adjuvant used. The six out of seven protected were all given a proprietary adjuvant codenamed QS21 (all six control volunteers became infected). This underlines the important role that adjuvants have in protection, not just in vaccines for malaria, but for many other diseases.



Current trials will be watched carefully for signs of progress in the hunt for a vaccine.

The early quest for a vaccine built on the observation that people repeatedly bitten by infectious mosquitoes gradually acquire immunity over a period of many years. Moreover, in the 1960s the British scientists Sydney Cohen and Sir Ian Mc Gregor discovered that antibodies from such individuals could reduce

the parasite load in people lacking immunity and clear disease symptoms.

Around the same time, researchers at New York University (NYU) achieved full protection for the first time, using animal models — by injecting small numbers of sporozoites derived from mosquitoes that had previously been irradiated. Later, researchers at the University of Maryland, NYU and the Walter Reed Army Institute showed that 90 per cent of a group of human volunteers challenged with sporozoites from irradiated mosquitoes later resisted exposure to virulent sporozoites.

Search for 'sporozoite' vaccines

But this was hardly a practical field strategy; inducing resistance required exposing volunteers to several hundred bites by irradiated mosquitoes over several months. The more practical alternative of culturing millions of sporozoites, irradiating them directly, and formulating a vaccine, was also precluded, as sporozoites were impossible to culture (as they still are).

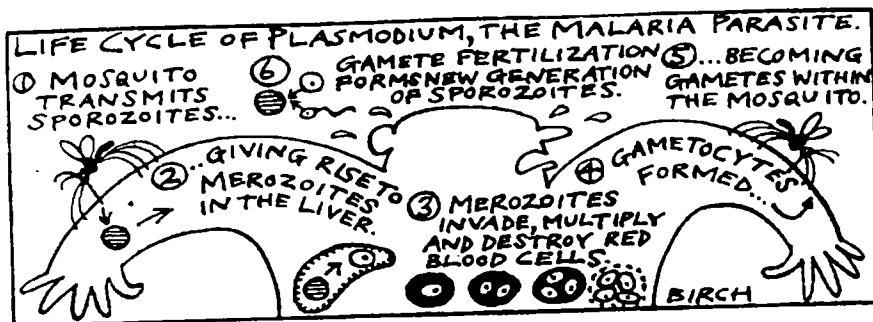
But the successes sent researchers scurrying to their laboratories to find sporozoite proteins that would reproduce the effect of whole

irradiated sporozoites. In the 1980s, a group at New York University, showed that monoclonal antibodies against the circumsporozoite protein of rodent and human malaria protected against infection. They later cloned the gene coding for a CS protein, although vaccines based on this failed in trials because they did not elicit high titres of antibody.

Such 'sporozoite' (or pre-erythrocytic) vaccines are just one of three broad vaccine approaches each targeted at one of the three main phases of the parasite's lifecycle. Sporozoites, the form of the parasite injected by the feeding female mosquito, migrate through the bloodstream to the liver within half an hour. In the hepatocytes, they pass through several intermediate stages, and multiply, before emerging around a week later as tens of thousands of 'merozoites' (events up to this point are known as the pre-erythrocytic phase, which is also asymptomatic).

These merozoites invade red blood cells where they complete their cycle, and later rupture the cells and invade new red blood cells (the asexual erythrocyte phase). The 'sexual phase' begins when some of these then form gametocytes — these are sucked up by feeding mosquitos, inside which they combine to form new sporozoites.

Pre-erythrocytic vaccines target the sporozoites themselves or the forms inside liver cells (although the parasites are inside the cell they express epitopes on its surface which can be detected by T-cells that kill the cells directly or by releasing lethal cytokines such as gamma interferon). The liver stages are in principle ideal targets because they remain in the cells for several days. The main difficulty is



that there is as yet no way of making a vaccine which elicits a T-cell immune response.

'Anti-asexual blood stage' vaccines target the phase where merozoites infect blood cells — the phase that causes disease symptoms. One of the most studied vaccines is based on a surface protein of merozoites (MSP1), which gives protection in rodents and primate models — this protein is particularly promising because the regions involved in protection shows no variation. In contrast, another target, EMP-1 (or erythrocyte membrane protein) a parasite protein expressed on the surface of the red blood cell — and which is involved in cerebral malaria — shows high antigenic variation and is not suitable for vaccine development.

Attack on parasite inside mosquito

'Transmission blocking vaccines' interrupt fusion and development of parasite gametes in the mosquito itself. They do not protect individuals directly, but are aimed at reducing transmission, which is why they are sometimes called 'altruistic' vaccines. A fourth approach is therapeutic vaccines targeted against toxins released by the parasites

themselves or during red cell rupture.

Hopes for an anti-asexual blood stage vaccine were raised with a report by Colombian biochemist Manuel Patarroyo of a promising small trial of the controversial synthetic SPf66 vaccine (see *Nature* 332, 158; 1988). Early trials have been described as giving efficacies as high as 80 per cent, but their design has been criticized, and subsequent trials gave efficacies of just 31 and 8 per cent. One last year showed the vaccine had no effect. Patarroyo plans to test his SPf66 vaccine in 50 volunteers using the QS21 adjuvant in Colombia this summer.

In the 1990s, trials of three pre-erythrocytic vaccines in Africa and Asia have also yielded poor results, again because they were poorly immunogenic. A multistage vaccine, NYVAC-Pf7 developed by Virogenetics and Connaught, which showed promise in animal studies, has also given disappointing results. Such multistage vaccines make a concerted attack on several stages of the parasite within the body.

DNA vaccines are another novel approach. Stephen Hoffman, head of malaria research at the US Naval Research Institute in Bethesda, Maryland, plans to test a single-gene vaccine in volunteers this summer. If all goes well, the institute will then test a more sophisticated vaccine devised by Vical, a biotechnology company based in San Diego. The Italian subsidiary of the US company Chiron Vaccines is also working on a multi-stage DNA vaccine.

Apart from the promise of adjuvants, optimism is also high about CS-based vaccines because of the fact that insecticide-impregnated bednets have recently been shown to bring about large reductions in mortality. This suggests that the number of incoming sporozoites is a critical factor in mortality and that even a CS vaccine which did not give complete protection could have a big impact on deaths.

But one caveat in the study by SmithKline Beecham and the Walter Reed Army Institute is that the cut-off point used to define protection was 60 days, and a question remains whether protection will be sustained. A vaccine giving a short-lived effect might protect travellers but not people living in endemic regions. Another question is whether the adjuvants would be toxic in young children. Answers to these and other questions should come from vaccine trials under way in the Gambia.

Transgenic mosquitoes: a new solution?

Many scientists believe the time has come for a serious research effort to develop new techniques of vector control. In particular, rather than focussing on eradicating the mosquito, which is notoriously difficult to control, they are now focusing on creating transgenic insects incapable of transmitting malaria, and finding ways to spread the genes involved in natural resistance throughout wild populations.

Such genes are currently being mapped by genetic linkage studies of malaria-resistant strains of mosquitoes. For example, several such genes have been identified in the refractory strain *Anopheles gambiae* by Frank Collins, a vector biologist at the Centers for Disease Control and Prevention and his collaborators Liangbiao Zheng and Fotis Kafatos at the European Molecular Biology Laboratory in Heidelberg.

Collins and Kafatos have collaborated in a multilaboratory effort to map the mosquito genome, which began in the late 1980s with support from the US MacArthur Foundation and Britain's Wellcome Trust.

Another approach is to engineer mosquitoes carrying foreign genes that confer protection against infection. John Gubrun and his colleagues at the Liverpool School of Tropical Medicine in Britain have introduced a mammalian gene for an antibody that acts as an antigen on the ookinete phase of the parasite in the mosquito.

The bigger challenge is to introduce such engineered traits into the wild population. Workers in the field believe that engineered mobile particles, such as plasmids or transposons — can integrate and be replicated in the mosquito genome, and spread quickly among the population. Releasing of a small number of transgenic mosquitoes should result in the desired genes spreading throughout the wild population.

No one has transformed mosquitoes in a stable fashion using transposons. But researchers are optimistic that they are close to reaching this goal, while remaining aware that many safety issues need to be resolved before genetically engineered mosquitoes can be safely released into the environment.

Global agencies hold the financial key

The David now challenging the Goliath of malaria is particularly diminutive. Global spending on malaria research by the public and non-profit sector is estimated at just US\$84 million annually¹ and, even after adding industrial spending, the total would probably be no more than twice that. Spending on cancer research in the United Kingdom alone is double that spent of malaria research worldwide.

Furthermore the funding curve over the past decade has been downwards. The US Agency for International Development, the biggest single funder of malaria research, reduced its support from \$49 million in 1985 to \$9.7 million in 1994 (see Figure). Competing demands for funds have spiralled since the end of the Cold War, claims Carter Diggs, a USAID official, in particular support for the newly independent states of the former Soviet Union.

Some of this funding gap has been plugged by increases at Britain's Wellcome Trust and the US National Institute of Allergy and Infectious Diseases. And many are now confident that the nadir has been reached and that an upturn is about to take place, given the renewed interest in the disease; WHO will this year inject an extra \$10 million into malaria research and control, for example, a sum equivalent to one-third of its annual spending in this area.

Scientists' hopes are also being boosted by the prominent lead being taken by Harold Varmus, director of the US National Institutes of Health (NIH), in promoting malaria



Varmus: seeks role for NIH in Africa.

research. Varmus says he is keen for NIH to "play a bigger role in health in Africa. I find it very easy to make the case that the Departments of State and Defense and development organizations need to think about the rewards of medical research and better healthcare and its impact on promoting stability in Africa."

Greater US involvement in Africa would "really help", says Keith McAdam from the UK Medical Research Council's (MRC) centre in the Gambia, arguing that in the past the United States has not been prominent in setting up long-term commitments on the continent.

Varmus's aspirations are backed by a report released last month by the US Institute of Medicine's Board on International Health, which calls on the United States to take a stronger lead in global health issues by coordinating work among academics, non-governmental organizations, industry and international agencies. It is in "America's enlightened self interest to more fully engage in global health", the report concludes.

The report reveals that US support for international health projects is lower now as a proportion of gross domestic product than at any time since 1950. Its overseas assistance lags behind that of several other industrialized countries. In 1995 the United States spent \$7.3 billion on overseas health projects, compared with Japan's \$14.5 billion, France's \$8.4 billion and Germany's \$7.5 billion.

The spirit of Dakar

The international scientific community is now making a new effort to coordinate malaria research and control and attract new funding. Its efforts crystallized at a meeting, 'Malaria in Africa: Challenges for Cooperation', held in Dakar, Senegal, in January. There, for the first time, the world's research agencies, charities and major donors — such as the World Bank — sat around the same table to explore ways forward. Varmus and Maxime Schwartz, his counterpart at France's Institut Pasteur, were the driving forces behind the meeting.

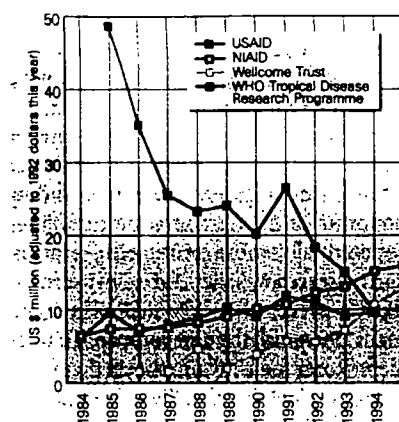
The meeting debated ways to reinforce and coordinate research needed to develop or improve tools for malaria control. One consensus reached was the overriding need to build sustainable research capacity in Africa. This emphasis on African science was reflected in the unprecedented number of African researchers participating.

"If this meeting had been held in 1980 you would have had much fewer scientists from Africa; it would have been driven from the North," says Tom Nchinda, who recently retired as head of research and capacity building in Africa at WHO's Tropical Disease Research programme. "Now we have a very substantial crop of well-trained African scientists."

Research agencies in the North have closed many field stations in developing countries over the past two decades, and the immediate need is to preserve established centres of excellence in Africa, argues McAdam. "It is easy to obtain three-year grants but that doesn't create the infrastructure to make a place work," he says. Stable funding from the MRC has been essential to the survival of the Gambia centre, he says, given that the \$4 million annual grant accounts for almost three-quarters of its budget. But such sustainable support is "difficult to find" at present, he says. The centre has about 500 scientists, 430 of them African.

The Dakar meeting also identified Internet access and other communications infrastructure in Africa as an immediate priority, as this would help scientists to work together more quickly and efficiently, and to share data using common protocols. Varmus pledged an immediate \$1 million and the help of NIH's technical expertise.

"A small amount can go very far here,"



Ups and downs: increased support from research bodies has, until now, not compensated for a fall in USAID funds.

says Varmus. McAdam agrees: "It would be an enormous boost if the US National Library of Medicine could be on-line here. Communications at field stations are poor."

Another small-scale initiative that could have an important impact is the Malaria Foundation — the brainchild of a small group of scientists who aim to coordinate research and to raise funds from the public. The foundation, now being set up, will use the Internet (<http://www.malaria.org>), set up working groups covering all areas of research and compile a global directory of those involved in the fight against malaria.

The organizers of the Dakar meeting are keen that it should not be a one-hit wonder, and have therefore issued a call for concrete ideas on how further progress can be made. These will be reviewed by an international group of working parties at a follow-up meeting in The Netherlands in July. Scientists whose applications are approved will be invited to submit full proposals.

What will happen next remains unclear. The movement behind the Dakar meeting has no name, and some scientists are hesitant to give it an administrative structure. Varmus says one possibility would be simply to "look at proposals and assign them to different agencies for support". But he says that he is also willing to consider a more formal international structure to pool funds.

Varmus and others have their eyes on attracting funding from new and much larger sources than those already available: development agencies such as the World Bank, whose budgets for development are an order of magnitude higher than those for research. Tapping even a small proportion of the enormous sums available for development would be a major boost to the pitiful sums currently available.

1. Malaria research: An audit of international activity. Wellcome Trust Unit for Policy Research in Science and Medicine.

Can industry be wooed back into the act?

There is a cruel irony in the fact that, just as the explosion of parasite resistance to drugs makes it more pressing than ever to find new drugs and vaccines, the pharmaceutical industry is abandoning malaria research.

Tropical disease research has been a major casualty of the consolidation of the industry over the past decade, with companies tending to concentrate their resources on fewer — and potentially more profitable — areas. Malaria research was shed, for example, in the merger between Rhône-Poulenc Santé and Rorer in 1990, with the new company Rhône-Poulenc Rorer focusing on just six therapeutic areas.

The number of companies carrying out research on malaria vaccines can now be counted on the fingers of one hand. And industry has virtually abandoned drug discovery — the only company still pursuing such research, Hoffmann-La Roche, says that it too has now decided to stop.

Companies are restricting their activity to the clinical development of those compounds that are known to work. "It's cheaper; we start with a molecule that works," says one industrialist. "It's development, not research."

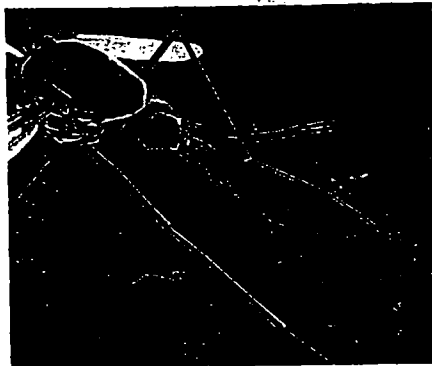
Many companies have had their fingers burned. Over the past few decades, for example, several of them screened hundreds of thousands of compounds without much success. But Pierre Druihle, a researcher at the Institut Pasteur in Paris, argues that it is ironic that companies should abandon drug discovery just when assays for screening for active drug compounds are much more sensitive than in the past, and when genome research and molecular studies are yielding new targets for rational drug design.

A fund has now been created to support a proposed collaborative programme to sequence the 30-megabase genome of *P. falciparum*. The US Department of Defense has given \$15 million to the fund, with another \$4 million coming from the US Burroughs-Wellcome Fund, the UK Wellcome Trust and NIH. Pilot studies are being carried out by the Institute for Genome Research in Rockville, Maryland, Britain's Sanger centre, and NIAID.

It is urgent to relaunch drug discovery, says Dyann Wirth, a molecular parasitologist at Harvard School of Public Health, and chair of WHO's committee on malaria drugs. But without industry, drug development is a lost cause, says Druihle, as only it has the capacity to synthesise and test the hundreds of analogues needed to convert a promising molecule into a drug lead.

Vaccines await 'breakthrough'

The picture for vaccine scientists is less bleak, but only marginally so. The large vaccine manufacturers, SmithKline Beecham and



Once bitten: most companies have abandoned their attempts at drug discovery.

Pasteur Merieux Connaught, still work on malaria vaccines, but many others, such as Merck, Sanofi, and Behringwerke, have given up.

Companies are traditionally reluctant to invest in vaccine development, which carries high costs, low profits and big risks of liability claims. But many companies say that whereas basic research is now producing interesting leads, it has not progressed sufficiently, and that investing now would therefore be a costly and risky business.

The relative lack of industrial interest means that vaccine scientists often cannot produce the large quantities of good manufacturing-practice (GMP) grade antigens needed for clinical trials. "We have six or seven interesting molecules, but have to synthesize them ourselves, while we don't have the competence to work with adjuvants [compounds included in vaccine formulations, which boost the immune system]," says Luiz Pereira da Silva, a vaccine researcher at the Institut Pasteur. "We are forced to improvise, and we can't advance unless we can do trials."

Relaunching industrial research

Faced with the reality of industrial withdrawal from the field, scientists and international organizations are engaged in a flurry of discussions with industrialists to try to encourage them to change their mind.

Research agencies are contemplating strategies to fill the gap left by the retreat of companies, by going beyond their traditional role of funding basic research, and also carrying out development work to bring malaria vaccines to a stage where companies might regain interest.

The idea of creating a broad multi-disease programme to develop vaccine concepts is "under consideration" at the US National Institutes of Health, according to its director Harold Varmus. "We need to try to go as far as possible by ourselves," says Maxime Schwartz, director of the Institut Pasteur. He adds that a "major problem" in doing so in

Europe is the lack of a plant to produce GMP-grade vaccines for research. "This is too expensive for Pasteur alone."

Another idea being floated is for the World Bank and other agencies to subsidize the early stages of drug and vaccine discovery to spread the financial risk. Another is to create consortiums between drug companies, donors and public research agencies. The introduction in Europe of legislation similar to the US Orphan Drugs Tax Credits would also help, says Walter Van Der Smissen, head of government affairs at SmithKline Beecham Biologicals.

Many industrialists say they are open to the idea of taking part in consortia. But they point out that such schemes may not be feasible, given that they are fraught with problems such as sharing of intellectual property, and are likely to fall foul of legislation banning cartels. "I have difficulty seeing how it could happen," says Van Der Smissen, "but perhaps it's time to change the model of thinking."

A more market-driven approach is to guarantee companies sales for their products. There is a precedent. The enormous size of the vaccine market in the developing world — about 3.5 billion doses annually — has allowed organizations such as the United Nations children's fund, UNICEF, to purchase vaccines at cost price. Manufacturers benefit because the huge volume of orders allows them to cut their costs.

Taking the idea further, some suggest that international organizations could specify in advance the characteristics of a specific vaccine or drug which, if met, would qualify it for worldwide use. This would entice companies to invest in the development of such products, say industrialists.

But companies themselves also "need to reassess their markets", argues Richard Feachem of the World Bank. He points out that many countries in Asia and Latin America are relatively well off, while India, and even many poor African countries, have burgeoning middle classes with money to spend on healthcare.

Drug companies are beginning to acknowledge that most of their sales growth over the next ten to twenty years will come from developing countries. "Glaxo-Wellcome and others will put greater emphasis on developing countries and this will lead to renewed interest in meeting local country needs," says one company official.

Growth in these markets will eventually stimulate drug companies to reinvest in tropical disease research. But, until such market forces come into play, companies are unlikely to restart tropical disease research unless the international community provides them with the incentives to do so. □

The spirit of Dakar: a call for action on malaria

Sir— Malaria has been a problem for too long. More than a million people still die from it every year, most of them young children. Nine out of ten of these deaths occur in Africa, where resistance to chloroquine is spreading, diminishing the impact of a drug which in the past has helped to limit the damage wreaked by the disease. Resistance is also increasing to Fansidar, the only other drug affordable for widespread use in Africa. This grim situation prompted an unprecedented meeting earlier this year in Dakar, Senegal, where, for the first time, scientists from both French- and English-speaking parts of Africa and scientists from the North came together to confront malaria.

The challenge is enormous. New approaches are needed to control malaria and its mosquito vectors. New drugs must be found to prevent and treat the disease, and vaccines need to be developed. This requires research at every level; these efforts benefit from cooperation. One example of an international cooperative effort is the sequencing of the *Plasmodium falciparum* genome which will accelerate drug and vaccine discovery and may encourage bright young minds into the field.

The urgent need is to put malaria on the scientific, media and political agenda, and in particular to identify it as a priority for research, both in the developed North and in those areas of the South where the disease is endemic. At the same time, the resources to pursue these goals will remain restricted.

Research is critical for the development of tools for disease control and for their effective deployment. In smallpox, for example, even with the vaccine, the critical insight that it was necessary to vaccinate people only in the vicinity of cases, not the entire population, resulted in cost-effective deployment of staff and resources. In malaria, where the biology of the adversary is more complex, and the existing tools less effective, the interplay between research and control strategies is even more crucial.

The Dakar meeting endorsed the principle that sustained research on malaria in Africa should be a key component of any strategy for tackling the disease. More opportunities for training African scientists as well as for strengthening the research infrastructure will be crucial for building collaborations between African scientists and their partners in the North. Trained African scientists will also be critical for future field trials and interventions.

One unprecedented opportunity to boost

research in Africa at a relatively modest cost is offered by the Internet. An immediate challenge is to identify the systems and resources needed to provide research centres in Africa with access to e-mail and other Internet services. This would allow African scientists to access the scientific information they need, and to communicate quickly and cheaply with colleagues elsewhere.

Electronic networks are an essential aid in building collaborative research networks, for which the need is absolutely compelling if we are to tackle malaria — a disease characterized by highly variable patterns of transmission, pathology and drug resistance in different parts of Africa.

It is only by creating joint repositories of materials — such as strains, reagents and insects — and by common protocols that observations made at various locations and laboratories can be compared. Multi-centre clinical research is also needed to develop or improve therapies for complications of malaria, such as anaemia and cerebral malaria.

Recognizing these needs, the Dakar meeting proposed that sponsoring agencies should promote collaborative research efforts both among African scientists and between scientists in the North and South. An announcement has been made about letters of interest¹ for collaborative research projects. These will be reviewed in July.

A few examples of priorities² for long-term research are provided here.

- Vaccines could be the most cost-effective way to control malaria, but we need both research in the North and collaboration with African scientists to develop candidate vaccines which can be tested in centres in Africa. Studies on epidemiology, parasite polymorphism and mechanisms of immunity in Africa are also a prerequisite for any trials.

- Antimalarial drugs must be developed to replace those becoming obsolete. This will require incentives to attract participation by the pharmaceutical industry and novel approaches to drug development, including production and testing of drugs in Africa.

- The recent development of pyrethrum-impregnated bed nets holds great promise for controlling malaria, but the social and economic factors for their introduction need to be studied in detail. And bed nets cannot be simply introduced, but need to be accompanied by long-term studies to assess their impact on mortality and mosquito resistance to pyrethrum.

- Similarly, case management — recognizing

that a sick child has malaria and providing effective treatment in the home — requires contributions from both the social and biological sciences.

The coming months offer what seems to be a window of opportunity for boosting international cooperation in malaria research as a component of overall control. The African regional office of the World Health Organization with support from the World Bank is considering the conclusions reached at Dakar as part of the development of a long-term, African-developed and African-led malaria control strategy. The Organization of African Unity (OAU) will hold its annual meeting in June, and malaria will be on the agenda. The same month, the G-7 countries will discuss emerging and re-emerging infectious diseases, including malaria.

In the spirit of the Dakar meeting, we recognize that control of malaria in Africa will require a long-term collaboration between scientists in the North and South and the involvement of many more countries than the initial group which took part in the Dakar meeting. It will require commitments from the industrialized countries to funding, and from African leaders to support scientists and health and research infrastructure in their countries.

The fact that the Dakar meeting was opened by the President of Senegal and closed by its Minister of Health seems to symbolize the growing awareness by leaders in Africa of the need to support research efforts by both indigenous scientists and their colleagues abroad. The international community has a responsibility to recognize malaria, like the AIDS pandemic, as a major challenge and to commit itself to do more to prevent the disaster that looms over Africa.

Jean-Marie Bruno (French Ministry of Cooperation); Richard Feachem (World Bank); Tore Godal (TDR, WHO); Thomas Nchinda (elected representative of African scientists for post-Dakar efforts); Bridget Ogilvie (Wellcome Trust); Barend Mons (Netherlands Organization for Scientific Research); Robert Mshana (Organization of African Unity); George Radda (Medical Research Council, UK); Ebrahim Samba (WHO, Brazzaville); Maxime Schwartz (Institut Pasteur); Harold Varmus (National Institutes of Health, USA); The Dakar Scientific Advisory Committee: Samba Diallo (Senegal), Ogobara Doumbo (Mali), Brian Greenwood (United Kingdom), Wenceslaus Kilama (Tanzania), Louis H. Miller (USA), Luiz Pereira da Silva (France)

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1. Request for letters of interest.

http://www.niaid.nih.gov/dmid/mal_itr_en.htm

2. Priorities from the Dakar meeting can be obtained at:

<http://www.niaid.nih.gov/dmid/malair/>

a brief index of malaria facts

[extent of the disease]

Number of countries where malaria is endemic:
90

Percentage of world population at risk of malaria:
40%

Number of cases of malaria per annum, globally:
500,000,000

Percentage of global population who get sick with malaria, per annum:
10%

Number of fatal cases of malaria, per annum:
2,700,000

Most common age at death:
4 years

Percentage of African children killed by malaria:
5%

Number of African children who die of malaria, per day:
2800

[impact on women and infants]

Multiple by which pregnancy increases mothers' risk of malaria:
4.2

Percentage of African infants who are born with malaria parasite:
up to 23%

Frequency that malaria is responsible for low birthweight in African babies:
40%

[scarcity of research funding]

American funding for biomedical research on malaria (FY1993):
\$42 million

American funding for biomedical research on cancer (FY1993):
\$2.3 billion

Ratio of cancer research funding to malaria research funding:
54 to 1

Federal subsidy to McDonald's to promote marketing of Chicken McNuggets in third world:
\$2 million

[military]

Percentage of American soldiers deployed in Vietnam War who got malaria (1965):
about 10%

Rank of malaria among causes of hospital admissions of troops who served in Vietnam:
2

Percentage of American soldiers deployed in Jilib, Somalia who got malaria (1993):
about 29%

Rank of malaria among causes of hospital admissions of troops who served in Somalia:
1

[civilian]

Number of American travelers hospitalized in USA for malaria contracted abroad (1995):
1419

Minimum number of days one must spend in a malarious area to risk infection:
under 1

Date the WHO announced the malaria problem had been "licked":
May 1975

Date the WHO's Deputy General was hospitalized for suspected malaria:
May 1975

[drug resistance]

Number of drugs commercially available for the treatment of malaria:

8

Number of drugs that scientists know are resisted by some strains of malaria:

8

Number of drugs which are consistently effective against the malaria parasite:

0

Number of major Western pharmaceutical companies now researching new malaria drugs:

0

Number of countries reporting malaria resistant to all known drugs:

1

Estimated number of years before multidrug-resistant malaria reaches other endemic areas:
about 10

[economic impacts]

Estimated direct and indirect cost of malaria in Sub-Saharan Africa (1995):

\$1.8 billion

Percentage of GDP, Sub-Saharan Africa:

0.6%

Cost to very low income African family for malaria treatment, per annum:

\$19

Total household revenue of very low income African family, per annum:

\$68

Percentage of household revenue spent to treat malaria alone:

28%

[sources]

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Malaria Foundation	13
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US Department of the Army	16, 17
Wellcome Trust	7, 12
World Bank	31
World Health Organization	1, 2, 3, 4, 5, 21, 30, 31

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...quotable malaria quotes...

On the disease:

"Malaria which had been eliminated or effectively suppressed in many parts of the world, is undergoing a resurgence. It is a public health problem today in more than 90 countries inhabited by some 2,400 million people -- 40 percent of the world's population. Malaria is estimated to cause up to 500 million clinical cases and 2.7 million deaths each year. Every 30 seconds, a child somewhere dies of malaria. The global effects of the disease threaten public health and productivity on a broad scale and impede the progress of many countries toward democracy and prosperity."

*Institute of Medicine of the National Academy of Sciences
(1996)*

On research funding:

"Global investment in malaria research over the past ten years has been very low compared with other disease areas, and appears to be declining further. Expressed as investment in research per death, malaria research -- at approximately \$42 per fatal case -- receives less funding, by one or two orders of magnitude, than other diseases such as cancer, HIV/AIDS or asthma."

*The Wellcome Trust
(1996)*

"The trend in worldwide funding over the last decade has been downward, largely reflecting decreasing investment from the USA, especially USAID."

*The Wellcome Trust
(1997)*

On the third world:

"In Africa alone...in 1990, malaria was responsible for the loss of 31.7 million Disability Adjusted Life Years."

*World Health Organization
(1997)*

"A single bout of malaria is estimated to cost a sum equivalent to 10-20 working days in India and Africa."

The Malaria Foundation
(1997)

"When a substantial proportion of a country's population is ill with malaria for five or six months each year, sustained economic development is very difficult to achieve. Countries thus compromised cannot easily become active trading partners with the United States, nor are they positioned to decrease their dependence on foreign aid."

Institute of Medicine of the National Academy of Sciences
(1996)

On Africans:

"The disease has its major impact in sub-Saharan Africa, where over 90 percent of the worldwide cases are reported. Approximately 10 percent of hospital admissions and 20-30 percent of outpatient consultations in Africa are due to malaria...Children are particularly at risk in rural Africa where the disease is one the major childhood killers and responsible for the death of one in 20 children before the age of five years. It is also the most common disease among school children and young adults in Africa where it tends to strike at harvest time, affecting productivity. The disease causes anaemia in children and pregnant women, and increases their vulnerability to other diseases."

The Wellcome Trust
(1996)

On Americans abroad:

"The importance of malaria for the US military is enormous. In Vietnam, for example, nearly 10 percent of soldiers had the disease in late 1965, and attack rates for some units were as high as 60 per 100 soldiers each year. Overall, malaria was the most important cause of hospitalization other than combat wounds. During the late 1980s, drug-resistant [malaria] infection caused serious illnesses in approximately 1,600 Peace Corps workers in West Africa alone. Finally, tourists are at increasing risk, even with short-term exposure, as demonstrated by recent reports of transit passengers being infected with malaria while waiting on planes that were being refuelled in West Africa. Over 1,000 cases of malaria are known to occur each year in tourists returning to the United States."

Institute of Medicine of the National Academy of Sciences
(1996)

"[Malaria is the] cause of more military casualties than bullets in every 20th century war in malarious regions."

The Malaria Foundation
(1997)

"[World War II] will be a long war, if for every division I have facing the enemy, I must count on a second division in the hospital with malaria, and a third division convalescing from this debilitating disease."

General Douglas MacArthur
(1943)

On women:

"Pregnant women are at high risk of becoming infected [with malaria], as well as children in their first years of life. In pregnant women, malaria can cause anemia which can be the major cause of maternal mortality, especially during the first pregnancy."

International Journal of Gynaecology and Obstetrics
(1997)

On drug resistance:

"The outlook for malaria control in the face of this deteriorating situation [of drug resistance] is grim. The continuing emergence of drug resistance in the malaria parasite and the widespread insecticide resistance of the mosquitoes responsible for transmitting the disease have reduced the selection of tools to control malaria -- there are fewer options available now than there were 20 years ago."

Institute of Medicine of the National Academy of Sciences
(1996)

"Today, resistance is emerging and spreading faster than new drugs can be developed...Given the speed with which parasites are becoming resistant and the length of time required to develop new drugs (even accelerated development takes 5 to 10 years from discovery to clinic), we face a looming crisis: multidrug-resistant malaria with no safe, effective alternatives for treatment. This problem exists today in Southeast Asia and will occur in most other malaria-endemic areas within the next decade."

MIT Technology Review
(1997)

On drug development:

"The diseases that currently dominate the needs of developing countries...remain relatively neglected by the pharmaceuticals industry. For example, in the world today, there are 225 million new cases of malaria each year and the death toll among children is approaching one million. Yet, it is the board's understanding that not a single major Western pharmaceutical company is now developing new drugs for the disease."

*Institute of Medicine of the National Academy of Sciences
(1996)*

On vaccine research:

"There is widespread agreement...that vaccines against malaria would be a cost effective public health tool to reduce the burden of disease and will be an essential component of successful control of the global threat. The impressive strides made in the field of malaria research in the past 15 years provide compelling reasons to believe that a malaria vaccine is a biotechnological and immunological possibility. In spite of growing scientific optimism, however, the pace of vaccine development appears to be slowing because of diminishing public funds, fragmented public sector efforts, and limited interest within the vaccine industry."

"Workshop participants agreed that the successful development and widespread application of a vaccine that can prevent illness and death of malaria could be **one of the most important advances in medicine, with the potential for improving the lives of hundreds of millions of people.**"

*Institute of Medicine of the National Academy of Sciences
(1996)*

On new technologies:

"The inherent complexity of the malaria parasite and the resulting immune response make it a natural target for cutting-edge fundamental and applied research. As a result, malaria vaccine research has historically been a leader in the development of new technologies with broad applicability to human health. For example, the world's first recombinant vaccine produced in bacteria and the first synthetic peptide vaccine to be tested in humans were malaria vaccines. The most complex vaccine yet devised...is a malaria vaccine now undergoing testing in humans...In addition, some of the most advanced adjuvant work has been driven by malaria vaccine research, and these agents are likely to be important components of vaccines against HIV/AIDS, herpes, cancer, and other diseases."

*Institute of Medicine of the National Academy of Sciences
(1996)*

Winning the War Against Malaria

By Dyann F. Wirth and Jacqueline Cattani

Dyann F. Wirth is professor of molecular parasitology in the Department of Tropical Public Health at the Harvard School of Public Health. She also chairs the Committee on the Chemotherapy of Malaria for the U.N. Development Programme/World Health Organization/World Bank Special Programme for Research and Training in Tropical Diseases. Jacqueline Cattani is manager of the Task Force on Insecticide-Impregnated Bednets and Other Materials, and the Task Force on Integrated Management of the Sick Child, for the same organization.



[Links related to this article](#)

***In the 1950s, we had two of the best weapons
against malaria -- chloroquine and DDT -- yet
we failed to defeat it. Now, as the threat
of untreatable disease looms,
we have a second chance.***



Every 12 seconds, a child dies of malaria. New initiatives to prevent and treat malaria could save the lives of one-fourth of these children by the turn of the century.

When Americans think of childhood diseases, we rarely think of malaria. Yet it is a leading cause of death among the world's children. More than 2.5 million die of malaria each year, most of them in Africa. And those who survive chronic infection suffer a combination of anemia and immune suppression that leaves them vulnerable to other fatal illnesses.

Among adults living in areas of high transmission, malaria is best thought of as a chronic, debilitating illness that robs its victims of years of productivity. A single mosquito bite can transmit one of the four parasites that cause malaria, setting in motion bouts of fever, chills, and nausea that can recur for weeks. And in some areas, people receive as many as 300 infective bites per year. According to a 1993 World Bank report, malaria represents a global public health burden second only to tuberculosis among infectious diseases. In sub-Saharan Africa, where most cases of malaria and nearly all malaria-related deaths occur, more years of life are lost to malaria than to any other disease.

Despite massive efforts to eradicate the disease in the 1950s and early 1960s, there is more human malaria in the world today than at any other time in history. More than 500 million people are infected with malaria worldwide; one fourth of the world's population is at risk for infection. And the risk is rising as environmental changes and large-scale migration bring people and mosquitoes together and as parasites develop resistance to successive generations of drugs.

Malaria has confounded some of the best minds of this century. A hundred years after the discovery that mosquitoes transmit malaria, we still do not know enough about the disease to defeat it permanently. But we do have the tools to limit its spread and dramatically reduce the rate at which children are dying. Our goals should be to reduce childhood mortality from malaria by at least one fourth before the turn of the century, by half in its first decade, and by more than 90 percent in its second decade. By reexamining both the successes and the failures of the past, we can develop a more effective, comprehensive public health strategy to contain and control this lethal opponent.

Learning from Failure

Renewed interest in malaria at home and abroad makes this a politically opportune time for new initiatives. Articles in both the popular press and scientific journals have called attention to the looming crisis posed by the disease. In January 1997, malaria experts from 35 countries and representatives from the major agencies that fund malaria research convened at an international conference to address the

spread of the disease in Africa. And the World Health Assembly, the governing body of the World Health Organization (WHO), passed a resolution calling on member states to renew their political commitment to malaria control and to guarantee sufficient funding, staff, and other resources to sustain this effort.

This is not the first time that public and private agencies have geared up to assault the disease. In the 1950s, WHO, the United Nations International Children's Emergency Fund (UNICEF), and the U.N. Food and Agriculture Organization enthusiastically declared that the time was right to eliminate malaria as a public health problem throughout the world. The malaria eradication programs they sponsored relied on a combination of prevention -- spraying with the insecticide DDT -- and early identification and treatment of infected individuals, deploying an arsenal of new antimalarial drugs, the best known of which was chloroquine. (Although WHO described this effort as a global eradication campaign, sub-Saharan Africa was not included in the early phases, probably because high transmission rates, the lack of administrative and financial resources, and the logistical problems of reaching rural areas were so daunting. Presumably, the plan was to include Africa after success had been demonstrated elsewhere.)

Despite its initial promise, the DDT campaign backfired. Programs in many malaria-endemic countries were unable to sustain the level of thoroughness and efficiency required to make residual insecticide spraying effective. The result was inadequate or erratic coverage. Mosquitoes that survived low doses of insecticide reproduced, creating populations of insecticide-resistant, malaria-carrying pests. In response to erratic spraying, mosquitoes simply changed their behavior -- for instance, they stopped settling on the walls of houses that had been sprayed and moved to nearby vegetation that hadn't.

Where the malaria eradication program worked, it soon became a victim of its own success. As the incidence of malaria became negligible in these areas, international organizations downgraded the disease as a priority health issue; at the national level, politicians and government agencies withdrew their support. The result was a dramatic resurgence of infection. In Sri Lanka, for instance, the incidence of malaria reached its lowest point in 1963, when 17 cases were reported. But by 1969, the number of registered cases had shot back up to more than half a million. Today Sri Lanka, like most other malarious countries, is still struggling to control the disease and has abandoned the goal of eradication. Overall, the eradication campaign showed little result outside the United States, Europe, and some parts of northern Africa.

Compounding the political failure of these early efforts was the emergence of drug resistance. As early as 1960, chloroquine-resistant strains of *Plasmodium falciparum*, the parasite that causes the most deadly form of malaria in humans, began to spread in Southeast Asia and South America. In Southeast Asia, resistance to second-generation drugs such as Fansidar emerged rapidly after their introduction for treatment of chloroquine-resistant infections. Resistance to both chloroquine and Fansidar has now spread to Africa and infections with multidrug-resistant *P. falciparum* are now common in many areas where the parasite is endemic.

To the extent that the parasite represents a moving target for drugs and insecticides, no single chemical compound is likely to defeat it. In the 1950s, we had the best weapons against malaria that we've ever had, yet we failed to control the disease. The failure of these early eradication campaigns teaches that multiple strategies -- and a sustained commitment of significant resources -- are required to solve the problem.

Over the past two decades, however, we have failed to apply that lesson. Indeed, past interventions have done more to eradicate funding for malaria research than they have to eliminate disease. In the initial years of the eradication effort, DDT appeared so promising that international agencies saw little need to study the disease further. Only in 1965, 15 years after the eradication program began, did WHO finally begin to encourage malaria research. The de-emphasis on science combined with a decline in the number of malariologists left countries ill prepared to deal with the crisis we face today.

Research on malaria remains severely underfunded. According to a 1996 report released by the Unit for Policy Research in Science and Medicine (PRISM) of the Wellcome Trust, a private charity that is one of the major sponsors of biomedical research, expenditures for malaria research equal about \$42 per death, while expenditures for research on diseases like AIDS, cancer, or asthma are 100 to 1,000 times higher. According to the PRISM report, in 1993 only \$84 million was spent on malaria research worldwide. The largest share -- more than one-quarter -- was devoted solely to vaccine development. Indeed, for decades, the hope of defeating malaria has rested largely on the belief that a vaccine for the disease is just around the corner.

The Puzzle of Partial Immunity

For 40 years, scientists have labored to create a vaccine against malaria, inspired by the success of this approach against smallpox, yellow fever, and polio. However, unlike these other types of infections, malaria induces only partial immunity in those who contract the disease. After multiple bouts of the disease, a person develops enough immunity to prevent severe infection and mortality, but can still become ill. Moreover, even this limited immunity can be maintained only by frequent reinfection. Thus the ideal vaccine -- one that could provide full and permanent protection from illness -- would have to perform better than natural immunity, an ambitious goal for which there is no precedent. If researchers were to succeed in developing a vaccine that mimics naturally occurring immunity, it could save millions of children's lives. It would not, however, eradicate malaria the way vaccines have eradicated smallpox.

No one knows the mechanism by which people eventually become partially immune to malaria. It may be related to the complexity of the parasite. Recent work has demonstrated that the malaria parasite expresses a repertoire of thousands of surface molecules, or antigens, which change constantly in the course of a single infection. The parasite therefore presents a moving target for the host immune system: by the time the host forms antibodies in response to one antigen, the parasite has already switched to a new one.

Despite these difficulties, scientists have come very close to developing vaccines that work. Their efforts have focused on the three

uses of the parasite life cycle. The first type of vaccine targets the sporozoite, the form in which the parasite enters the host's body to prevent it from establishing infection. A second, known as the Spf66 vaccine, seeks to destroy the parasite only after it has invaded the host's red blood cells -- an approach that could establish partial but not full immunity. And the third type of vaccine targets the oocyst, a stage in the life cycle of the parasite that occurs only in the mosquito. The aim of this so-called altruistic vaccine is to prevent transmission from human to human via the mosquito. When a mosquito feeds on the blood of a vaccinated human, she ingests not only the parasite but also the antibodies specific to the target antigens. These antibodies will prevent the parasite from reproducing and multiplying in the mosquito and subsequently being passed on to other humans. This kind of vaccine would not protect the vaccinated person from contracting malaria, but vaccinating enough people in a given area could substantially reduce the number of infective bites residents receive.

These vaccines have shown promising results in animals, but none have worked well in humans. No one knows why the parasite operates differently in humans than in animals, and it is not clear when or how we will bridge this gap in our knowledge. A report on malaria prevention and control by the Institute of Medicine (IOM) summarized the results of the malaria vaccine trials with cautious optimism. What we have learned from these initial studies may help in designing the next generation of vaccines, but despite the talents, hopes, and funds devoted to this solution, an effective vaccine for malaria remains exactly where it has been for the past 40 years: tantalizingly out of reach.

Getting an effective vaccine is years if not decades away, and that the best vaccine is likely to have only limited impact in the long run. In the meantime, to keep the illness from getting worse, we need to step back and reemphasize both prevention and control. One very promising way to prevent malaria is the use of mosquito nets treated with a safe, biodegradable pyrethroid insecticide to protect sleeping children. In the early 1990s, four large, randomized, controlled community trials were conducted in four African countries representing different malaria risks -- Burkina Faso, Ghana, Kenya, and the Gambia -- to determine the impact of using treated nets on mortality rates of children younger than 10. The three-year trials, conducted under the auspices of the U.N. Development Programme (UNDP), WHO, and the World Bank, involved nearly half a million people and 20 research institutes and donors. The results were dramatic: children's deaths from malaria dropped 15 percent in Burkina Faso, 17 percent in Ghana, 33 percent in Kenya, and 25 percent in the Gambia. (An earlier study in the Gambia cut child mortality 63 percent, but that study was based on 100 percent compliance. The larger studies evaluated the nets under real-life conditions, in which compliance ranged from 20 percent to 90 percent.) The magnitude of the reduction in deaths indicates either that malaria is the most important cause of death in the age groups included in the trials or that preventing malaria in young children somehow helps reduce their likelihood of dying from other diseases. These results suggest that if bed nets were widely available, they could save the lives of up to 500,000 African children each year.

Bed nets are not yet widely available in Africa, and those that are cost between \$25 and \$30 each -- well beyond the reach of the average family. However, locally manufactured nets could cost as little as \$5; a year's supply of insecticide costs between 50 cents and \$1. Although this sum is still high relative to annual cash income (between \$300 and \$400 in some regions), there is reason to believe that at most African families could afford it. According to WHO, African families spend up to \$65 (or one-fifth of their income) annually on antimalarial drugs, mosquito coils, and insect repellents to protect themselves from malaria, with limited effect. If these expenditures could be redirected to reasonably priced insecticide-impregnated bed nets, overall family expenditures would actually decrease.

Studying ways to promote and distribute insecticide-impregnated bed nets. Like insecticide spraying, distributing bed nets is a long-term commitment, so the key is to ensure that this intervention is sustainable. Rather than simply donating nets, international agencies should support local initiatives or otherwise work with local manufacturers to ensure that bed nets are available to all children in their families can afford. WHO and other international agencies should also fund the research and development of new insecticides that can safely be used on bed nets, since sooner or later vector mosquitoes are likely to become resistant to the pyrethroid insecticides.

Headache to Coma

Improvements in prevention are promising, diagnosis and drug treatment remain the mainstay of malaria control worldwide. The key to effective disease management are rapid diagnosis and proper treatment. A patient with malaria who comes to a clinic in the morning complaining of a headache may, if untreated, fall into a coma by midafternoon. The longer an episode of malaria goes untreated or ineffectively treated, the higher the mortality rate.

In much of the developing world, however, primary health care systems are unable to provide early diagnosis and treatment. Diagnosing malaria is difficult because the symptoms of infection, particularly early on, are nonspecific -- fever, chills, headache. In many areas, both diagnosis and treatment are often delayed because of the long distances patients must travel to reach a health facility. In addition, effective antimalarial drugs may not be available in areas of drug resistance.

At primary health care clinics, where most children with malaria are likely to seek treatment, must be trained to differentiate illnesses with overlapping symptoms, including pneumonia, measles, malaria, diarrhea, and malnutrition, all of which are leading causes of death in children under five in developing countries. Right now, health workers receive training through a variety of self-administered programs, each of which focuses on the diagnosis and treatment of a single disease. Health workers are left to their own methods for differentiating among diseases and setting priorities for treatment. Focusing on the most apparent symptoms may cause health workers to overlook an associated, potentially life-threatening condition. A health worker might prescribe a fever-reducer for a child with a high fever and rapid breathing in the belief that the child has pneumonia, for instance, without realizing the child is severely ill with malaria, which shares the same complex of symptoms.

To address this problem, WHO and UNICEF have developed a new approach to diagnosis and treatment called Integrated Management of Childhood Illnesses, which they are implementing on an experimental basis in clinics and health posts in selected districts in Uganda, Tanzania, the Philippines, Vietnam, and Indonesia. The goal is to shift resources and responsibility for training primary health care workers from the national disease-specific programs to the district level and to help health care providers accurately assess the overall needs of the sick child. Health workers are also trained to communicate key information to mothers, thus helping them ensure the health of their children. So far, it appears to be working: preliminary evaluation shows that clinic staff trained under the new approach make more accurate diagnoses and more appropriate referrals for sick children.

Beyond improving diagnosis and referral, we need to ensure the availability of effective treatment. Antimalarial drugs are among the most commonly prescribed drugs in the world, and not only because the disease is so widespread; health workers in endemic areas often overprescribe antimalarials as a result of improper diagnoses. What's more, the few drugs we have are closely related to one another, increasing problems with drug resistance.

Today, resistance is emerging and spreading faster than new drugs can be developed. The newest antimalarials-Malerone, developed by Glaxo-Wellcome, and drugs based on the ancient Chinese herbal remedy artemisinin -- are the only drugs that remain effective in areas most plagued by drug resistance, such as Thailand. Parasites resistant to these compounds have already emerged in the laboratory, and health agencies are closely monitoring their emergence in the field.

Given the speed with which parasites are becoming resistant and the length of time required to develop new drugs (even accelerated development takes 5 to 10 years from discovery to clinic), we face a looming crisis: multidrug-resistant malaria with no safe, effective alternatives for treatment. This problem exists today in Southeast Asia and will occur in most other malaria-endemic areas within the next decade.

Despite the obvious urgency of the situation, pharmaceutical companies are not developing new drugs. Over the past decade, the few major pharmaceutical companies that had antimalarial drug discovery and development programs have discontinued or downsized these programs, which were both costly and unprofitable. Today, only a few academic centers and government agencies are working on the discovery of antimalarial drugs: only a few new drugs in the late stages of clinical development remain in the pipeline. (Malerone still awaits final approval in some countries and new formulations of artemisinin are still being tested.)

There is an urgent need to develop novel compounds or compounds that focus on novel pathways -- processes essential to the growth and development of the parasite -- that are not the target of current antimalarial drugs. Moreover, researchers must address the problem of drug resistance from the earliest stages of drug development. One strategy to prevent resistant organisms from emerging is to use multiple drugs targeted at different pathways, or at different steps in a single pathway. Another is to identify ways to interfere with the mechanisms that spur mutation or regulate gene expression. A third important target is a protein in the membrane of the parasite that allows the organism to recognize and pump out drugs. Once the protein is expressed, the parasite can resist multiple, unrelated drugs, even those to which it had not previously been exposed. Preventing the expression of this protein or blocking its pumping action is another way to prevent or even reverse resistance.

While previous efforts to develop new drugs and vaccines have been based on empirical observations, new drug development techniques are likely to provide the basis for the next leaps in our knowledge. Techniques such as combinatorial chemistry (creating new compounds by systematically combining sets of chemical groups) and computer-aided drug design (using x-ray crystallography and computer modeling to analyze protein-drug interactions) have accelerated the process of finding new drugs and vaccines for other diseases. We need to apply these tools to malaria before we face the widespread threat of untreatable disease. Since expertise in drug development is concentrated in the private sector, the participation of the pharmaceutical industry -- perhaps supported by government funding -- is essential to the success of this effort.

Back to Basics

Unfortunately, knowledge of the fundamental biology of the malaria parasite has lagged behind that of many other organisms, largely because of a lack of funding for basic research in this area. Computer-aided drug design or combinatorial chemistry cannot be applied in a vacuum: researchers need to identify the biological processes or specific enzymes that can serve as targets for new drugs or vaccines. To take advantage of these techniques, we need to learn more about the genetic makeup of the organism, its growth and development, and its relationships with the mosquitoes that carry it, the human host, and the environment. For example, we now know that the malaria parasite digests hemoglobin as its source of amino acids. Studying ways to prevent the digestion of hemoglobin could lead to new drugs.

Genetics research promises new insight into mechanisms by which the malaria parasite operates and might be defeated. For instance, techniques for producing parasites that contain a specific modification in a single gene will allow scientists to determine whether specific genes are associated with virulence, drug resistance, or enhanced transmission. This promises to usher in a period of rapid growth in our knowledge of the fundamental processes in the parasite.

A powerful new tool is the Malaria Genome Sequencing Project, a cooperative effort to sequence the genome of *P. falciparum*, sponsored by the Wellcome Trust, the Burroughs Wellcome Fund, the National Institutes for Health, and the U.S. Department of Defense. The goal of this project is to define every gene in the organism by 2000 and, armed with this information, to identify new targets for drug and vaccine development. By comparing gene sequences in the parasite with those of other microorganisms, for instance, we can determine whether enzymes that are used as drug targets in other microorganisms are present in the malaria parasite; if so, they could serve as targets for new antimalarial drugs. Genome scanning techniques, in which scientists study the impact of

specific stimuli on the whole array of genes simultaneously, will help scientists discover how different genes interact as the organism responds to new vectors, drugs, or the host's immune system. The ability to dissect these kinds of complex responses is likely to bring a whole new dimension to our understanding of the parasite.

Information from the genome project may also help scientists develop new DNA-based vaccines. The principle is similar to the approach used in gene therapy: researchers inject into human tissue genes that code for one or more of the parasite's surface proteins. Following the genes' instructions, the human cells manufacture the protein, using the same machinery they use to make human proteins. The immune system recognizes the vaccine-induced protein as foreign and develops protective antibodies. Since DNA-based vaccines can incorporate several genes, they could stimulate the production of antibodies to several antigens at once, thereby strengthening the immune system's defenses as the parasite switches from one antigen to another. However, this alone will not solve the problem of immune evasion: there are simply more variant antigens than a single vaccine can deliver.

Because they are inexpensive and require no refrigeration (a major consideration in the rural areas where malaria is prevalent), DNA-based vaccines provide a promising alternative to traditional vaccines. Using the same surface proteins as those targeted by existing malaria vaccines, scientists are now testing DNA-based vaccines on animals. These trials show promise, but the real test will come in people. The FDA should speed its preliminary approval of DNA-based malaria vaccines so that they can be tested for safety and efficacy in humans.

Today, we have the tools we need to achieve dramatic improvements in prevention, early diagnosis and treatment and, in the long run, to develop new drugs and effective vaccines. But applying them will require a dramatic increase in financial and political support. In endemic countries, governments from the national to the community level must guarantee sustained and stable support for malaria control. At the same time, they will have to exert political pressure on international agencies and the private sector to commit funding and expertise to this disease over the long run. The participation of the private sector is essential and will have to be achieved through some combination of moral pressure and financial incentives. More than money, what it will take to defeat malaria is the political and moral determination to save the lives of millions of children.

Sidebar:

The War at Home

One of the few victories in the war against malaria occurred in the United States under the direction of the Tennessee Valley Authority (TVA), the regional development agency created in 1933. At that time, malaria was endemic in the southeastern United States, sapping the health and productivity of the region's residents. To protect its workers as well as ensure the success of its economic development projects, the TVA stepped in to tackle the problem.

The agency's first step was to reduce the population of parasite-carrying mosquitoes in endemic areas. After conducting intensive research on the environmental conditions that foster breeding, the TVA initiated a comprehensive environmental management program. Because mosquitoes lay eggs in or near water -- the eggs cannot survive dry -- the agency built and maintained an extensive network of drainage ditches to keep water levels in reservoirs low, thereby reducing the area in which mosquitoes could breed. The agency also cleared vegetation from reservoir and river shorelines every summer. (Vegetation contributes to the survival of mosquito larvae by keeping them from being swept away by wind or water currents.)

To limit transmission of the disease, the agency installed window screens in houses and encouraged cattle grazing near reservoirs in order to divert mosquitoes from biting humans. In addition, the TVA initiated an active surveillance program to track and treat suspected cases of malaria, an effort that ultimately led to the establishment of the Centers for Disease Control. The cost of the campaign thus went far beyond the initial high capital investment in preparing the reservoirs. Expenditures on malaria control remained high even as the rate of infection went down. Between 1942 and 1950 the United States spent more than \$50 million (about \$317 million in 1995 dollars) to control malaria in the South.

What lessons can the TVA campaign provide for malaria control in developing countries? Although malaria eradication is possible under certain circumstances, the approach that worked so well in the American South is not readily transferable to malaria-endemic areas today. In the Tennessee Valley, less than a third of the population was at risk of contracting malaria -- and then only during the summer months. Yet enormous financial, human, technical, and infrastructural resources were needed to eliminate malaria in this region. In most of Africa, by contrast, the entire population suffers from malaria, and year-round transmission occurs in many areas. The mosquito species in Africa are the most efficient vectors of all the malaria-carrying mosquitoes, and ecological conditions allow them to thrive. The goal of eradicating malaria through a sustained, comprehensive environmental management and disease surveillance program in these countries is far beyond their financial and institutional reach.

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CENTER FOR STUDY OF RESPONSIVE LAW
P.O. BOX 19367
WASHINGTON, D.C. 20036

19 February 1998

Tom Friedman
Room 213, Old Exec. Office Bldg.
Washington, DC 20502

Dear Tom,

Further to our phone call today, I am writing to give you an overview of what contacts Ralph and I have had in the last several weeks on the malaria issue. We have met with nothing but enthusiasm, and agreement that current levels of malaria research funding must be seriously augmented to become commensurate with the scope of the problem.

As you read this, please keep in mind the caveat that we have concentrated our lobbying efforts on increasing funding for malaria within the HHS agencies (NIH and CDC). Limited resources led us to choose this focus. Yet, there are also malaria research programs at USAID and DoD, both of which are also underfunded. They ought not to be overlooked in the development of a larger malaria strategy.

What follows is a précis of the meetings we have had to date. I also commend to you, for a sense of the malaria problem and the dearth of research funding, to read the short documents entitled "Malaria Facts" and "Malaria Quotes", as well as Ralph's letter on malaria to the President, which are found in the enclosed packet.

• **Health and Human Services**

We met with Secretary Shalala on February 3, to discuss both the malaria lobbying project and the Princeton tuberculosis project. Present at the meeting were both representatives of NIH and CDC.

The Secretary unhesitatingly agrees that malaria research must be enhanced -- indeed, she preempted our presentation on the need for research and jumped right to the question of how best to involve HHS in foreign research projects. The Secretary is correct that malaria research, by its nature, must be done largely overseas, in endemic areas; however, she is concerned that if HHS agencies extend their reach overseas, they tempt a turf war with USAID, which also has malaria projects abroad. This she sees this as powerfully counterproductive: she adamantly believes there should be a single, central authority to oversee and coordinate all the government's malaria research (a belief we concur in). Therefore, to avoid jurisdictional conflict with USAID, she's planning new legislation to expand the mandate of HHS agencies to operate overseas.

The Secretary's concerns over turf conflicts are well founded, but in our view there is no jurisdictional constraint posed by the present legislation, a view concurred in by general counsel for the CDC. Existing law provides that, "The Secretary may conduct biomedical research, directly or through grants or contracts, for the identification control, treatment and prevention of diseases (including tropical diseases) which do not occur to a significant extent in the United

States.¹" She may also, "make grants or loans of equipment and materials, for use by public or nonprofit institutions or agencies, or by individuals, in participating foreign countries"². Indeed, these powers have proven sufficient to support the existence of NIH and CDC labs abroad, as well as NIH's underwriting of overseas labs owned and operated by foreign governments.

• NIH and the National Institute of Allergy & Infectious Disease

Ralph and I met with Dr. Harold Varmus (head NIH) and Dr. Tony Fauci (head NIAID) on February 6 to discuss both the malaria and TB projects. Both believe that government must take the lead in malaria research, because of a market failure in which pharmaceutical companies have abandoned their vaccine and antimalarial drug research programs. What is more, both are convinced that if government shirks this role, the catastrophe of global, multi-drug resistant malaria is on the horizon. To put it shortly, both want to be doing very much more malaria research than is presently the case. They are opposed to earmarking funds at the appropriations process; but they are very glad for language from Congress encouraging them to proceed with certain projects, so long as the language is not just exhortatory but is backed by additional money to carry out those projects.

At present, NIAID (where all of NIH's malaria research is done) is spending about \$25 m per year on malaria research, divided about 80% to 20% among extramural and intramural research, respectively. While this amount has increased modestly (having doubled in the last ten years), it remains far from sufficient to intensively undertake what NIAID believes are two leading priorities: the development of new drugs and vaccines, respectively. Thus, NIH contemplates two new major research programs, each of which deserves a decade of support in the first instance, to design, produce and field-test candidate drugs and vaccines. The cost of such programs is notoriously hard to estimate, but NIAID suggests that vaccine development would cost about \$350 m over 10 years; and it is my guess that a similar amount again would be required for drug development. NIAID could estimate the actual cost, and the lead time necessary to ease into these major programs, more precisely.

Dr. Varmus is also keen to involve NIH more deeply in international malaria research. To this end, he has been the prime mover behind what is called the Multilateral Initiative on Malaria (MIM). On Dr. Varmus' own motion, a conference of American, European and African scientists was held in January 1997 at Dakar, Senegal, to forge a consensus on goals for malaria research, and the means to attain these goals. This group has convened three times subsequently in Europe to refine the *raison d'être* of the MIM itself: to build multinational scientific "networks", in which American, European and African researchers work in collaboration with one another; to exploit synergies in the combination of Western nations' technical facilities, with African nations' ability to facilitate clinical investigations and field studies; to furnish basic scientific infrastructure, such as Internet connectivity, to African laboratories; and to promote human capacity for science in Africa, through the training of researchers and African leadership in research networks.

The selling point of the MIM is that it is a vehicle both for attaining necessary research objectives, and for promoting a benevolent foreign policy based on scientific diplomacy. Present NIAID expenditure consistent with the MIM is very little: about \$1 m / year to the Tropical Disease Research program of the World Health Organization for scientific education and capacity building in Africa; and about \$ 2.5 m /year for Internet connectivity at the NIH field research stations in Mali, and annual scientific meetings in Africa. Once the first MIM research networks get underway (research proposals are presently being fielded), then naturally additional resources for MIM will be required.

¹ 42 USC §241

² 42 USC §242[1]

- **CDC**

We met with Dr. Helene Gayle, Dr. Trent Ruebush and Bill Gimson of the CDC February 18. Again, the sentiment was that the CDC malaria research effort, which is presently about \$7.3 m / year, is well short of what the agency should be doing.

Considering the pittance that CDC receives for malaria, the diversity and importance of the research they perform is astonishing: new drug testing; stretching the useful life of existing drugs; mosquito control; and malaria prevention by bednets are all in the research portfolio. Future activities will likely include vaccine development and statistical epidemiology of the disease.

CDC is very clear that no more projects can be taken on without augmenting funding. As with NIH, the agency does not want an earmark, but will be glad for language from Congress directing them to proceed with certain projects. CDC has a list of several new projects that are waiting in the wings and ready to implement at once, and for which the collective cost is about \$10 m / year. These include projects to reduce the incidence of malaria among American travelers, immunology studies for vaccine development, and contributions toward capacity building in Africa and the MIM.

- **House Health Appropriations Subcommittee**

The minority side of the health appropriations subcommittee appears to be strong. Discussions with aides for Representatives Obey, Pelosi and Stokes have gone well. All are waiting for us to draft and submit language on malaria funding, which they will consider for inclusion in the subcommittee's report. We are presently consulting widely in the malaria research community, in preparation for drafting this language.

The offices of Reps. Pelosi and Stokes are also considering organizing a malaria "brownbagger". Our aim for this would be to cultivate the interest of members on the health appropriations subcommittee, the Black Caucus (relevant, since malaria is such a scourge of Africa), and the proponents of the Africa Trade Act (wherein US-Africa cooperation on health is explicitly mentioned).

Aides for Rep. Porter (Chairman) are interested in the issue, but are concerned that because NIH and CDC did not explicitly request for funding for malaria in their budgets, it will be difficult to augment the FY99 budget unless representatives of NIH and CDC speak to the need for enhanced funding in testimony before the subcommittee. Aides from the offices of Reps. Pelosi and Stokes have agreed to accept questions from us, and to ask them in testimony, that we may work around this problem.

- **Senate Health Appropriations Subcommittee**

On the minority side, the office of Senator Harkin (Ranking Member) has instructed the subcommittee staff to receive from us draft language for the subcommittee's report. As mentioned above, we are now in consultations aimed at preparing this language. Also, aides in Senator Bumpers' office have been enthusiastic, notably because Mrs. Bumpers, who is interested in childhood diseases, shall visit a children's hospital in Africa next month. We expect to brief her for that trip.

On the majority side, the office of Senator Specter (Chairman) has similarly instructed the subcommittee staff to receive report language from us.

• **DESIRED ACTION FROM THE WHITE HOUSE:**

There are several ways that the White House could work to move this issue forward. These range from promoting the issue publicly, to taking administrative steps.

To begin with, a Presidential speech on malaria research would charge the issue before the appropriations subcommittees. The topic is timely in light of the President's upcoming trip to Africa, where malaria has taken its place on the political radar screen. Last year, the heads of state of the OAU nations issued the *Harare Declaration on Malaria Prevention and Control*-- the first time ever that African leaders or the OAU expressed a collective will on a disease. Considering the intractability of Africa's political problems, a foreign policy based increasingly on health and capacity building (as with the MIM) is both uncontroversial and popular on the continent. A speech now would help set the foundation for NIH and CDC to make substantially larger requests for malaria research in FY2000, enough so that the major projects such as vaccine and drug development could get underway.

Second, an Administration-wide strategy for malaria research and control is long overdue. On the face of it, dividing malaria research among four agencies (NIH, CDC, USAID, DoD) without central coordination is both inefficient and invites turf battles. For example, all four agencies are, or soon will be, involved in malaria vaccine development, but no vaccine "master plan" or authority for the rational division of research effort exists -- an omission that the Institute of Medicine decried in its 1996 report, *Vaccines Against Malaria: Hope in a Gathering Storm*. Secretary Shalala, as mentioned above, is of the view that the malaria research effort needs centralization. Proposals for centralization are beyond the compass of this briefing, but the question should be taken up along with funding increases.

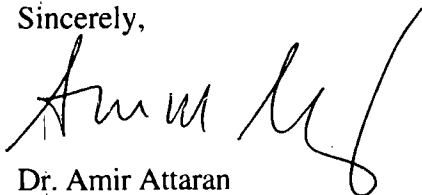
Third, to the extent that the Administration is seeking a supplemental appropriations bill for FY99, extra money for malaria research could be included, notwithstanding that special funding for malaria was not requested by NIH and CDC in the FY99 budget. This option permits a speedy legislative response to be taken to any initiative that is mooted in connection with the President's Africa trip.

Fourth, if there is an flexibility left in the President African itinerary, a visit to NIH or CDC research facilities in Africa could be arranged. The flagship NIH facility is in Mali, and that of the CDC in Kenya. The CDC Kenya lab is especially photogenic, and was a filming site for the popular TBS documentary on infectious diseases entitled "The Coming Plague".

I think that gives you a fair idea of where we have progressed in the last several weeks. Do not hesitate to call if I can be of help in answering your questions. I will be on the West Coast by the time you read this: (604) 222-1256. I'll be returning to Washington later in March (387-8030), or sooner if required, and can meet with you then if you wish.

Thanks, above all, for your interest in this.

Sincerely,



Dr. Amir Attaran

...quotable malaria quotes...

On the disease:

"Malaria which had been eliminated or effectively suppressed in many parts of the world, is undergoing a resurgence. It is a public health problem today in more than 90 countries inhabited by some 2,400 million people -- 40 percent of the world's population. Malaria is estimated to cause up to 500 million clinical cases and 2.7 million deaths each year. Every 30 seconds, a child somewhere dies of malaria. The global effects of the disease threaten public health and productivity on a broad scale and impede the progress of many countries toward democracy and prosperity."

*Institute of Medicine of the National Academy of Sciences
(1996)*

On research funding:

"Global investment in malaria research over the past ten years has been very low compared with other disease areas, and appears to be declining further. Expressed as investment in research per death, malaria research -- at approximately \$42 per fatal case -- receives less funding, by one or two orders of magnitude, than other diseases such as cancer, HIV/AIDS or asthma."

*The Wellcome Trust
(1996)*

"The trend in worldwide funding over the last decade has been downward, largely reflecting decreasing investment from the USA, especially USAID."

*The Wellcome Trust
(1997)*

On the third world:

"In Africa alone...in 1990, malaria was responsible for the loss of 31.7 million Disability Adjusted Life Years."

*World Health Organization
(1997)*

"A single bout of malaria is estimated to cost a sum equivalent to 10-20 working days in India and Africa."

The Malaria Foundation
(1997)

"When a substantial proportion of a country's population is ill with malaria for five or six months each year, sustained economic development is very difficult to achieve. Countries thus compromised cannot easily become active trading partners with the United States, nor are they positioned to decrease their dependence on foreign aid."

Institute of Medicine of the National Academy of Sciences
(1996)

On Africans:

"The disease has its major impact in sub-Saharan Africa, where over 90 percent of the worldwide cases are reported. Approximately 10 percent of hospital admissions and 20-30 percent of outpatient consultations in Africa are due to malaria...Children are particularly at risk in rural Africa where the disease is one the major childhood killers and responsible for the death of one in 20 children before the age of five years. It is also the most common disease among school children and young adults in Africa where it tends to strike at harvest time, affecting productivity. The disease causes anaemia in children and pregnant women, and increases their vulnerability to other diseases."

The Wellcome Trust
(1996)

On Americans abroad:

"The importance of malaria for the US military is enormous. In Vietnam, for example, nearly 10 percent of soldiers had the disease in late 1965, and attack rates for some units were as high as 60 per 100 soldiers each year. Overall, malaria was the most important cause of hospitalization other than combat wounds. During the late 1980s, drug-resistant [malaria] infection caused serious illnesses in approximately 1,600 Peace Corps workers in West Africa alone. Finally, tourists are at increasing risk, even with short-term exposure, as demonstrated by recent reports of transit passengers being infected with malaria while waiting on planes that were being refuelled in West Africa. Over 1,000 cases of malaria are known to occur each year in tourists returning to the United States."

Institute of Medicine of the National Academy of Sciences
(1996)

"[Malaria is the] cause of more military casualties than bullets in every 20th century war in malarious regions."

The Malaria Foundation
(1997)

"[World War II] will be a long war, if for every division I have facing the enemy, I must count on a second division in the hospital with malaria, and a third division convalescing from this debilitating disease."

General Douglas MacArthur
(1943)

On women:

"Pregnant women are at high risk of becoming infected [with malaria], as well as children in their first years of life. In pregnant women, malaria can cause anemia which can be the major cause of maternal mortality, especially during the first pregnancy."

International Journal of Gynaecology and Obstetrics
(1997)

On drug resistance:

"The outlook for malaria control in the face of this deteriorating situation [of drug resistance] is grim. The continuing emergence of drug resistance in the malaria parasite and the widespread insecticide resistance of the mosquitoes responsible for transmitting the disease have reduced the selection of tools to control malaria -- there are fewer options available now than there were 20 years ago."

Institute of Medicine of the National Academy of Sciences
(1996)

"Today, resistance is emerging and spreading faster than new drugs can be developed...Given the speed with which parasites are becoming resistant and the length of time required to develop new drugs (even accelerated development takes 5 to 10 years from discovery to clinic), we face a looming crisis: multidrug-resistant malaria with no safe, effective alternatives for treatment. This problem exists today in Southeast Asia and will occur in most other malaria-endemic areas within the next decade."

MIT Technology Review
(1997)

On drug development:

"The diseases that currently dominate the needs of developing countries...remain relatively neglected by the pharmaceuticals industry. For example, in the world today, there are 225 million new cases of malaria each year and the death toll among children is approaching one million. Yet, it is the board's understanding that not a single major Western pharmaceutical company is now developing new drugs for the disease."

*Institute of Medicine of the National Academy of Sciences
(1996)*

On vaccine research:

"There is widespread agreement...that vaccines against malaria would be a cost effective public health tool to reduce the burden of disease and will be an essential component of successful control of the global threat. The impressive strides made in the field of malaria research in the past 15 years provide compelling reasons to believe that a malaria vaccine is a biotechnological and immunological possibility. In spite of growing scientific optimism, however, the pace of vaccine development appears to be slowing because of diminishing public funds, fragmented public sector efforts, and limited interest within the vaccine industry."

"Workshop participants agreed that the successful development and widespread application of a vaccine that can prevent illness and death of malaria could be **one of the most important advances in medicine, with the potential for improving the lives of hundreds of millions of people.**"

*Institute of Medicine of the National Academy of Sciences
(1996)*

On new technologies:

"The inherent complexity of the malaria parasite and the resulting immune response make it a natural target for cutting-edge fundamental and applied research. As a result, malaria vaccine research has historically been a leader in the development of new technologies with broad applicability to human health. For example, the world's first recombinant vaccine produced in bacteria and the first synthetic peptide vaccine to be tested in humans were malaria vaccines. The most complex vaccine yet devised...is a malaria vaccine now undergoing testing in humans...In addition, some of the most advanced adjuvant work has been driven by malaria vaccine research, and these agents are likely to be important components of vaccines against HIV/AIDS, herpes, cancer, and other diseases."

*Institute of Medicine of the National Academy of Sciences
(1996)*

Winning the War Against Malaria

By Dyann F. Wirth and Jacqueline Cattani

Dyann F. Wirth is professor of molecular parasitology in the Department of Tropical Public Health at the Harvard School of Public Health. She also chairs the Committee on the Chemotherapy of Malaria for the U.N. Development Programme/World Health Organization/World Bank Special Programme for Research and Training in Tropical Diseases. Jacqueline Cattani is manager of the Task Force on Insecticide-Impregnated Bednets and Other Materials, and the Task Force on Integrated Management of the Sick Child, for the same organization.



[Links related to this article](#)

*In the 1950s, we had two of the best weapons
against malaria -- chloroquine and DDT -- yet
we failed to defeat it. Now, as the threat
of untreatable disease looms,
we have a second chance.*



Every 12 seconds, a child dies of malaria. New initiatives to prevent and treat malaria could save the lives of one-fourth of these children by the turn of the century.

When Americans think of childhood diseases, we rarely think of malaria. Yet it is a leading cause of death among the world's children. More than 2.5 million die of malaria each year, most of them in Africa. And those who survive chronic infection suffer a combination of anemia and immune suppression that leaves them vulnerable to other fatal illnesses.

Among adults living in areas of high transmission, malaria is best thought of as a chronic, debilitating illness that robs its victims of years of productivity. A single mosquito bite can transmit one of the four parasites that cause malaria, setting in motion bouts of fever, chills, and nausea that can recur for weeks. And in some areas, people receive as many as 300 infective bites per year. According to a 1993 World Bank report, malaria represents a global public health burden second only to tuberculosis among infectious diseases. In sub-Saharan Africa, where most cases of malaria and nearly all malaria-related deaths occur, more years of life are lost to malaria than to any other disease.

Despite massive efforts to eradicate the disease in the 1950s and early 1960s, there is more human malaria in the world today than at any other time in history. More than 500 million people are infected with malaria worldwide; one fourth of the world's population is at risk for infection. And the risk is rising as environmental changes and large-scale migration bring people and mosquitoes together and as parasites develop resistance to successive generations of drugs.

Malaria has confounded some of the best minds of this century. A hundred years after the discovery that mosquitoes transmit malaria, we still do not know enough about the disease to defeat it permanently. But we do have the tools to limit its spread and dramatically reduce the rate at which children are dying. Our goals should be to reduce childhood mortality from malaria by at least one fourth before the turn of the century, by half in its first decade, and by more than 90 percent in its second decade. By reexamining both the successes and the failures of the past, we can develop a more effective, comprehensive public health strategy to contain and control this lethal opponent.

Learning from Failure

Renewed interest in malaria at home and abroad makes this a politically opportune time for new initiatives. Articles in both the popular press and scientific journals have called attention to the looming crisis posed by the disease. In January 1997, malaria experts from 35 countries and representatives from the major agencies that fund malaria research convened at an international conference to address the

spread of the disease in Africa. And the World Health Assembly, the governing body of the World Health Organization (WHO), passed a resolution calling on member states to renew their political commitment to malaria control and to guarantee sufficient funding, staff, and other resources to sustain this effort.

This is not the first time that public and private agencies have geared up to assault the disease. In the 1950s, WHO, the United Nations International Children's Emergency Fund (UNICEF), and the U.N. Food and Agriculture Organization enthusiastically declared that the time was right to eliminate malaria as a public health problem throughout the world. The malaria eradication programs they sponsored relied on a combination of prevention -- spraying with the insecticide DDT -- and early identification and treatment of infected individuals, deploying an arsenal of new antimalarial drugs, the best known of which was chloroquine. (Although WHO described this effort as a global eradication campaign, sub-Saharan Africa was not included in the early phases, probably because high transmission rates, the lack of administrative and financial resources, and the logistical problems of reaching rural areas were so daunting. Presumably, the plan was to include Africa after success had been demonstrated elsewhere.)

Despite its initial promise, the DDT campaign backfired. Programs in many malaria-endemic countries were unable to sustain the level of thoroughness and efficiency required to make residual insecticide spraying effective. The result was inadequate or erratic coverage. Mosquitoes that survived low doses of insecticide reproduced, creating populations of insecticide-resistant, malaria-carrying pests. In response to erratic spraying, mosquitoes simply changed their behavior -- for instance, they stopped settling on the walls of houses that had been sprayed and moved to nearby vegetation that hadn't.

Where the malaria eradication program worked, it soon became a victim of its own success. As the incidence of malaria became negligible in these areas, international organizations downgraded the disease as a priority health issue; at the national level, politicians and government agencies withdrew their support. The result was a dramatic resurgence of infection. In Sri Lanka, for instance, the incidence of malaria reached its lowest point in 1963, when 17 cases were reported. But by 1969, the number of registered cases had shot back up to more than half a million. Today Sri Lanka, like most other malarious countries, is still struggling to control the disease and has abandoned the goal of eradication. Overall, the eradication campaign showed little result outside the United States, Europe, and some parts of northern Africa.

Compounding the political failure of these early efforts was the emergence of drug resistance. As early as 1960, chloroquine-resistant strains of *Plasmodium falciparum*, the parasite that causes the most deadly form of malaria in humans, began to spread in Southeast Asia and South America. In Southeast Asia, resistance to second-generation drugs such as Fansidar emerged rapidly after their introduction for treatment of chloroquine-resistant infections. Resistance to both chloroquine and Fansidar has now spread to Africa and infections with multidrug-resistant *P. falciparum* are now common in many areas where the parasite is endemic.

To the extent that the parasite represents a moving target for drugs and insecticides, no single chemical compound is likely to defeat it. In the 1950s, we had the best weapons against malaria that we've ever had, yet we failed to control the disease. The failure of these early eradication campaigns teaches that multiple strategies -- and a sustained commitment of significant resources -- are required to solve the problem.

Over the past two decades, however, we have failed to apply that lesson. Indeed, past interventions have done more to eradicate funding for malaria research than they have to eliminate disease. In the initial years of the eradication effort, DDT appeared so promising that international agencies saw little need to study the disease further. Only in 1965, 15 years after the eradication program began, did WHO finally begin to encourage malaria research. The de-emphasis on science combined with a decline in the number of malariologists left countries ill prepared to deal with the crisis we face today.

Research on malaria remains severely underfunded. According to a 1996 report released by the Unit for Policy Research in Science and Medicine (PRISM) of the Wellcome Trust, a private charity that is one of the major sponsors of biomedical research, expenditures for malaria research equal about \$42 per death, while expenditures for research on diseases like AIDS, cancer, or asthma are 100 to 1,000 times higher. According to the PRISM report, in 1993 only \$84 million was spent on malaria research worldwide. The largest share -- more than one-quarter -- was devoted solely to vaccine development. Indeed, for decades, the hope of defeating malaria has rested largely on the belief that a vaccine for the disease is just around the corner.

The Puzzle of Partial Immunity

For 40 years, scientists have labored to create a vaccine against malaria, inspired by the success of this approach against smallpox, yellow fever, and polio. However, unlike these other types of infections, malaria induces only partial immunity in those who contract the disease. After multiple bouts of the disease, a person develops enough immunity to prevent severe infection and mortality, but can still become ill. Moreover, even this limited immunity can be maintained only by frequent reinfection. Thus the ideal vaccine -- one that could provide full and permanent protection from illness -- would have to perform better than natural immunity, an ambitious goal for which there is no precedent. If researchers were to succeed in developing a vaccine that mimics naturally occurring immunity, it could save millions of children's lives. It would not, however, eradicate malaria the way vaccines have eradicated smallpox.

No one knows the mechanism by which people eventually become partially immune to malaria. It may be related to the complexity of the parasite. Recent work has demonstrated that the malaria parasite expresses a repertoire of thousands of surface molecules, or antigens, which change constantly in the course of a single infection. The parasite therefore presents a moving target for the host immune system: by the time the host forms antibodies in response to one antigen, the parasite has already switched to a new one.

Despite these difficulties, scientists have come very close to developing vaccines that work. Their efforts have focused on the three

ses of the parasite life cycle. The first type of vaccine targets the sporozoite, the form in which the parasite enters the host's body to prevent it from establishing infection. A second, known as the Spf66 vaccine, seeks to destroy the parasite only after it has invaded the host's red blood cells -- an approach that could establish partial but not full immunity. And the third type targets the oocyst, a stage in the life cycle of the parasite that occurs only in the mosquito. The aim of this so-called altruistic vaccine is to prevent transmission from human to human via the mosquito. When a mosquito feeds on the blood of a vaccinated human, she ingests not only the parasite but also the antibodies specific to the target antigens. These antibodies will prevent the parasite from surviving and multiplying in the mosquito and subsequently being passed on to other humans. This kind of vaccine would not protect a vaccinated person from contracting malaria, but vaccinating enough people in a given area could substantially reduce the number of infective bites residents receive.

These vaccines have shown promising results in animals, but none have worked well in humans. No one knows why they work differently in humans than in animals, and it is not clear when or how we will bridge this gap in our knowledge. A report on malaria prevention and control by the Institute of Medicine (IOM) summarized the results of the malaria vaccine trials with cautious optimism. What we have learned from these initial studies may help in designing the next generation of vaccines. But despite the talents, hopes, and funds devoted to this solution, an effective vaccine for malaria remains exactly where it has been for the past 40 years: tantalizingly out of reach.

Even if an effective vaccine is years if not decades away, and that the best vaccine is likely to have only limited impact in reducing malaria illness, we need to step back and reemphasize both prevention and control. One very promising way to prevent malaria is the use of mosquito nets treated with a safe, biodegradable pyrethroid insecticide to protect sleeping children. In the early 1990s, four large, randomized, controlled community trials were conducted in four African countries representing different malaria risks -- Burkina Faso, Ghana, Kenya, and the Gambia -- to determine the impact of using treated nets on mortality rates of children younger than 5. The three-year trials, conducted under the auspices of the U.N. Development Programme (UNDP), WHO, and the World Bank, involved nearly half a million people and 20 research institutes and donors. The results were dramatic: children's deaths from malaria dropped 15 percent in Burkina Faso, 17 percent in Ghana, 33 percent in Kenya, and 25 percent in the Gambia. (An earlier trial in the Gambia cut child mortality 63 percent, but that study was based on 100 percent compliance. The larger studies evaluated compliance under real-life conditions, in which compliance ranged from 20 percent to 90 percent.) The magnitude of the reduction in deaths indicates either that malaria is the most important cause of death in the age groups included in the trials or that preventing malaria in young children somehow helps reduce their likelihood of dying from other diseases. These results suggest that if bed nets were widely available, they could save the lives of up to 500,000 African children each year.

Bed nets are not yet widely available in Africa, and those that are cost between \$25 and \$30 each -- well beyond the reach of the average family. However, locally manufactured nets could cost as little as \$5; a year's supply of insecticide costs between 50 cents and \$1, though this sum is still high relative to annual cash income (between \$300 and \$400 in some regions), there is reason to believe that most African families could afford it. According to WHO, African families spend up to \$65 (or one-fifth of their income) annually on antimalarial drugs, mosquito coils, and insect repellents to protect themselves from malaria, with limited effect. If these expenditures could be redirected to reasonably priced insecticide-impregnated bed nets, overall family expenditures would actually decrease.

Studying ways to promote and distribute insecticide-impregnated bed nets. Like insecticide spraying, distributing bed nets is a long-term commitment, so the key is to ensure that this intervention is sustainable. Rather than simply donating nets, international agencies should support local initiatives or otherwise work with local manufacturers to ensure that bed nets are available to all children in their families can afford. WHO and other international agencies should also fund the research and development of new insecticides that can safely be used on bed nets, since sooner or later vector mosquitoes are likely to become resistant to the pyrethroid insecticides.

Headache to Coma

While improvements in prevention are promising, diagnosis and drug treatment remain the mainstay of malaria control worldwide. Two effective disease management strategies are rapid diagnosis and proper treatment. A patient with malaria who comes to a clinic in the morning complaining of a headache may, if untreated, fall into a coma by midafternoon. The longer an episode of malaria goes untreated or is ineffectively treated, the higher the mortality rate.

In the developing world, however, primary health care systems are unable to provide early diagnosis and treatment. Diagnosing malaria is difficult because the symptoms of infection, particularly early on, are nonspecific -- fever, chills, headache. In many regions, both diagnosis and treatment are often delayed because of the long distances patients must travel to reach a health facility. In addition, effective antimalarial drugs may not be available in areas of drug resistance.

At primary health care clinics, where most children with malaria are likely to seek treatment, must be trained to differentiate illnesses with overlapping symptoms, including pneumonia, measles, malaria, diarrhea, and malnutrition, all of which are leading causes of death in children under five in developing countries. Right now, health workers receive training through a variety of self-administered programs, each of which focuses on the diagnosis and treatment of a single disease. Health workers are left to use their own methods for differentiating among diseases and setting priorities for treatment. Focusing on the most apparent symptoms may cause health workers to overlook an associated, potentially life-threatening condition. A health worker might prescribe paracetamol for a child with a high fever and rapid breathing in the belief that the child has pneumonia, for instance, without realizing the child is severely ill with malaria, which shares the same complex of symptoms.

To address this problem, WHO and UNICEF have developed a new approach to diagnosis and treatment called Integrated Management of Childhood Illnesses, which they are implementing on an experimental basis in clinics and health posts in selected districts in Uganda, Tanzania, the Philippines, Vietnam, and Indonesia. The goal is to shift resources and responsibility for training primary health care workers from the national disease-specific programs to the district level and to help health care providers accurately assess the overall needs of the sick child. Health workers are also trained to communicate key information to mothers, thus helping them ensure the health of their children. So far, it appears to be working: preliminary evaluation shows that clinic staff trained under the new approach make more accurate diagnoses and more appropriate referrals for sick children.

Beyond improving diagnosis and referral, we need to ensure the availability of effective treatment. Antimalarial drugs are among the most commonly prescribed drugs in the world, and not only because the disease is so widespread; health workers in endemic areas often overprescribe antimalarials as a result of improper diagnoses. What's more, the few drugs we have are closely related to one another, increasing problems with drug resistance.

Today, resistance is emerging and spreading faster than new drugs can be developed. The newest antimalarials-Malerone, developed by Glaxo-Wellcome, and drugs based on the ancient Chinese herbal remedy artemisinin -- are the only drugs that remain effective in areas most plagued by drug resistance, such as Thailand. Parasites resistant to these compounds have already emerged in the laboratory, and health agencies are closely monitoring their emergence in the field.

Given the speed with which parasites are becoming resistant and the length of time required to develop new drugs (even accelerated development takes 5 to 10 years from discovery to clinic), we face a looming crisis: multidrug-resistant malaria with no safe, effective alternatives for treatment. This problem exists today in Southeast Asia and will occur in most other malaria-endemic areas within the next decade.

Despite the obvious urgency of the situation, pharmaceutical companies are not developing new drugs. Over the past decade, the few major pharmaceutical companies that had antimalarial drug discovery and development programs have discontinued or downsized these programs, which were both costly and unprofitable. Today, only a few academic centers and government agencies are working on the discovery of antimalarial drugs: only a few new drugs in the late stages of clinical development remain in the pipeline. (Malerone still awaits final approval in some countries and new formulations of artemisinin are still being tested.)

There is an urgent need to develop novel compounds or compounds that focus on novel pathways -- processes essential to the growth and development of the parasite -- that are not the target of current antimalarial drugs. Moreover, researchers must address the problem of drug resistance from the earliest stages of drug development. One strategy to prevent resistant organisms from emerging is to use multiple drugs targeted at different pathways, or at different steps in a single pathway. Another is to identify ways to interfere with the mechanisms that spur mutation or regulate gene expression. A third important target is a protein in the membrane of the parasite that allows the organism to recognize and pump out drugs. Once the protein is expressed, the parasite can resist multiple, unrelated drugs, even those to which it had not previously been exposed. Preventing the expression of this protein or blocking its pumping action is another way to prevent or even reverse resistance.

While previous efforts to develop new drugs and vaccines have been based on empirical observations, new drug development techniques are likely to provide the basis for the next leaps in our knowledge. Techniques such as combinatorial chemistry (creating new compounds by systematically combining sets of chemical groups) and computer-aided drug design (using x-ray crystallography and computer modeling to analyze protein-drug interactions) have accelerated the process of finding new drugs and vaccines for other diseases. We need to apply these tools to malaria before we face the widespread threat of untreatable disease. Since expertise in drug development is concentrated in the private sector, the participation of the pharmaceutical industry -- perhaps supported by government funding -- is essential to the success of this effort.

Back to Basics

Unfortunately, knowledge of the fundamental biology of the malaria parasite has lagged behind that of many other organisms, largely because of a lack of funding for basic research in this area. Computer-aided drug design or combinatorial chemistry cannot be applied in a vacuum: researchers need to identify the biological processes or specific enzymes that can serve as targets for new drugs or vaccines. To take advantage of these techniques, we need to learn more about the genetic makeup of the organism, its growth and development, and its relationships with the mosquitoes that carry it, the human host, and the environment. For example, we now know that the malaria parasite digests hemoglobin as its source of amino acids. Studying ways to prevent the digestion of hemoglobin could lead to new drugs.

Genetics research promises new insight into mechanisms by which the malaria parasite operates and might be defeated. For instance, techniques for producing parasites that contain a specific modification in a single gene will allow scientists to determine whether specific genes are associated with virulence, drug resistance, or enhanced transmission. This promises to usher in a period of rapid growth in our knowledge of the fundamental processes in the parasite.

A powerful new tool is the Malaria Genome Sequencing Project, a cooperative effort to sequence the genome of *P. falciparum*, sponsored by the Wellcome Trust, the Burroughs Wellcome Fund, the National Institutes for Health, and the U.S. Department of Defense. The goal of this project is to define every gene in the organism by 2000 and, armed with this information, to identify new targets for drug and vaccine development. By comparing gene sequences in the parasite with those of other microorganisms, for instance, we can determine whether enzymes that are used as drug targets in other microorganisms are present in the malaria parasite; if so, they could serve as targets for new antimalarial drugs. Genome scanning techniques, in which scientists study the impact of

specific stimuli on the whole array of genes simultaneously, will help scientists discover how different genes interact as the organism responds to new vectors, drugs, or the host's immune system. The ability to dissect these kinds of complex responses is likely to bring a whole new dimension to our understanding of the parasite.

Information from the genome project may also help scientists develop new DNA-based vaccines. The principle is similar to the approach used in gene therapy: researchers inject into human tissue genes that code for one or more of the parasite's surface proteins. Following the genes' instructions, the human cells manufacture the protein, using the same machinery they use to make human proteins. The immune system recognizes the vaccine-induced protein as foreign and develops protective antibodies. Since DNA-based vaccines can incorporate several genes, they could stimulate the production of antibodies to several antigens at once, thereby strengthening the immune system's defenses as the parasite switches from one antigen to another. However, this alone will not solve the problem of immune evasion: there are simply more variant antigens than a single vaccine can deliver.

Because they are inexpensive and require no refrigeration (a major consideration in the rural areas where malaria is prevalent), DNA-based vaccines provide a promising alternative to traditional vaccines. Using the same surface proteins as those targeted by existing malaria vaccines, scientists are now testing DNA-based vaccines on animals. These trials show promise, but the real test will come in people. The FDA should speed its preliminary approval of DNA-based malaria vaccines so that they can be tested for safety and efficacy in humans.

Today, we have the tools we need to achieve dramatic improvements in prevention, early diagnosis and treatment and, in the long run, to develop new drugs and effective vaccines. But applying them will require a dramatic increase in financial and political support. In endemic countries, governments from the national to the community level must guarantee sustained and stable support for malaria control. At the same time, they will have to exert political pressure on international agencies and the private sector to commit funding and expertise to this disease over the long run. The participation of the private sector is essential and will have to be achieved through some combination of moral pressure and financial incentives. More than money, what it will take to defeat malaria is the political and moral determination to save the lives of millions of children.

Sidebar:

The War at Home

One of the few victories in the war against malaria occurred in the United States under the direction of the Tennessee Valley Authority (TVA), the regional development agency created in 1933. At that time, malaria was endemic in the southeastern United States, sapping the health and productivity of the region's residents. To protect its workers as well as ensure the success of its economic development projects, the TVA stepped in to tackle the problem.

The agency's first step was to reduce the population of parasite-carrying mosquitoes in endemic areas. After conducting intensive research on the environmental conditions that foster breeding, the TVA initiated a comprehensive environmental management program. Because mosquitoes lay eggs in or near water -- the eggs cannot survive dry -- the agency built and maintained an extensive network of drainage ditches to keep water levels in reservoirs low, thereby reducing the area in which mosquitoes could breed. The agency also cleared vegetation from reservoir and river shorelines every summer. (Vegetation contributes to the survival of mosquito larvae by keeping them from being swept away by wind or water currents.)

To limit transmission of the disease, the agency installed window screens in houses and encouraged cattle grazing near reservoirs in order to divert mosquitoes from biting humans. In addition, the TVA initiated an active surveillance program to track and treat suspected cases of malaria, an effort that ultimately led to the establishment of the Centers for Disease Control. The cost of the campaign thus went far beyond the initial high capital investment in preparing the reservoirs. Expenditures on malaria control remained high even as the rate of infection went down. Between 1942 and 1950 the United States spent more than \$50 million (about \$317 million in 1995 dollars) to control malaria in the South.

What lessons can the TVA campaign provide for malaria control in developing countries? Although malaria eradication is possible under certain circumstances, the approach that worked so well in the American South is not readily transferable to malaria-endemic areas today. In the Tennessee Valley, less than a third of the population was at risk of contracting malaria -- and then only during the summer months. Yet enormous financial, human, technical, and infrastructural resources were needed to eliminate malaria in this region. In most of Africa, by contrast, the entire population suffers from malaria, and year-round transmission occurs in many areas. The mosquito species in Africa are the most efficient vectors of all the malaria-carrying mosquitoes, and ecological conditions allow them to thrive. The goal of eradicating malaria through a sustained, comprehensive environmental management and disease surveillance program in these countries is far beyond their financial and institutional reach.

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P.O. Box 19312
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President William Jefferson Clinton
The White House
1600 Pennsylvania Avenue NW
Washington, DC 20500

February 3, 1998

Dear President Clinton:

During your recent State of the Union address, you called for a substantial increase in Federal spending for basic biomedical research in the forthcoming budget. As you are aware, enhancing biomedical research funding and the budget of the National Institutes of Health has bipartisan support in Congress.

While the United States prepares to invest more heavily in research and technologies for public health, I am writing to ask that the needs of the world's poor, who suffer greatly from infectious diseases, be given special attention in the funding process. As Vice-President Gore, speaking before the National Council for International Health in 1996, recognized, emerging infectious diseases are among "the most significant health and security challenges facing the global community". Yet, despite the importance of this challenge to America, our commitment, both before and after Mr. Gore's onetime priority call, to researching the vicious, re-emergent scourges of the developing world remains embarrassingly low.

In this letter, I focus on the example of malaria: a disease which is an everyday fact of life in the developing world, but for which there is very little research funding. Although last year was the centenary of the discovery of the cause of malaria (it is caused by a parasite transmitted by the bite of an infected mosquito), the disease remains an epidemic of undiminished force at the end of the millennium. In the words of the World Health Organization:

Malaria is endemic in 91 countries, with about 40% of the world's population at risk. Each year there are 300-500 million clinical cases of malaria, 90% of them in Africa, and between 1.5 million and 2.7 million deaths. Among all infectious diseases, malaria continues to be one of the biggest contributors to disease burdens in terms of deaths and suffering. By undermining the health and capacity to work of hundreds of millions of people, it is closely linked to poverty and contributes significantly to stunting social and economic development...[And] in many parts of the world, malaria is becoming an even greater problem than before.¹

Numbers like these are so alien to American experience that they are hard to comprehend. To envision the number of children killed by malaria annually,

imagine seven jumbo jets, full of children, crashing *every day*. To get a sense of malaria's ubiquity in the tropical world, consider that if Americans, rather than Africans, were malaria's victims, every American would be hospitalized on average once a year. Many would be hospitalized twice.

As if this were not enough, malaria kills the weak and rends the fabric of families. Children under five years old are much more likely to die of malaria than adults: about a million African children are killed by the disease each year² -- or one child in twenty³. Women, too, are especially vulnerable. By the simple act of pregnancy, a woman increases her risk of serious or lethal malaria by four-fold⁴. If she is lucky enough to survive, malaria will frequently cause reduced birthweight in her infant. The parasite can even infect her fetus, condemning her newborn to begin life with malaria⁵.

Yet no matter how compelling these humanitarian arguments may be, scientists have been given little opportunity to bring malaria under control. There is as yet no proven vaccine against malaria; and only a handful of drugs, most of which have been overused and are now ineffective. In Southeast Asia, scientists have even discovered strains of "multidrug-resistant malaria with no safe, effective alternative for treatment" -- *i.e.* malaria virtually without a cure -- which they expect will spread to other continents within a decade⁶. Such developments should worry us, because our global pharmacopeia is already sparse, and existing drugs are losing efficacy by the day. As scientists bemoaned in the *Journal of the American Medical Association* last year, "few new drugs will be available in the future because of reduced funding for antimalarial drug research and development."⁷

Indeed, malaria scientists are correct to complain about a scarcity of research funding. In FY1993, the world spent about \$84 million on malaria research⁸. The Federal Government contributed about half that amount, or \$42 million. By contrast, the Government presently spends about \$2.3 billion on cancer research, and \$1.5 billion on HIV/AIDS research. To put it another way, in an era when the United States spent as much as \$36,000 on research for each fatal case of AIDS within its borders, it spent only about \$21 on research for each fatal case of malaria abroad⁹.

The AIDS problem deserves the funding it receives, but it must not be forgotten that malaria is no less of a scourge, and as the overall federal biomedical research budget grows, malaria surely deserves better than neglect. Indeed, malaria kills almost as many people, per annum, as have died of AIDS in the last 15 years¹⁰.

Malaria's neglect has roots in the policies of past Administrations, and has continued into your own term of office. For example, in 1994 USAID's malaria vaccine development program was cut by more than half¹¹. It is because of brutal cuts such as this that one science reporter today calls America's malaria effort "a pittance"¹².

What is to be done? Government must take the lead. The pharmaceutical industry is economically unwilling or unable to recoup an investment in malaria research, for the simple reason that the prospective market for antimalaria products is not sufficiently affluent¹³. The Institute of Medicine of the National Academy of Sciences notes that "not a single major Western pharmaceutical company is now developing new drugs for malaria"¹⁴, and the number of companies working on malaria vaccine technologies can be counted on a single hand. But as with other areas of technology where Federal funding led the way, to the benefit of America as a whole, malaria research too promotes our national self interest. There are at least four reasons for this.

First, although malaria is no longer endemic to the United States (it was very common in the early part of this century), the disease still afflicts Americans. *Every* business traveler, soldier or vacationer returning home from a malarious area is at risk of the disease, no matter how brief their sojourn abroad. About 1500 American travellers each year are hospitalized in the US with this sort of "imported" malaria¹⁵. And as international travel grows, especially business travel to newly-industrializing countries, some of which harbour multidrug-resistance, the incidence of malaria among Americans is certain to rise.

These dangers are illustrated by the experience of American troops abroad. In Vietnam, malaria was the most frequent cause of hospitalization after combat wounds, affecting nearly 10% of soldiers at a given time¹⁶. Troops deployed to Somalia for Operation Restore Hope were no more fortunate. Despite military training and discipline in the use of antimalarial drugs, soldiers got 48 cases of malaria while in Somalia¹⁷. On returning home, the soldiers got another 112 "imported" cases, all requiring hospital treatment¹⁸. Many of the soldiers' cases were drug-resistant, and up to 43% of soldiers who were treated suffered one or several relapses later¹⁹. In all, malaria was the number one cause of hospitalization for troops who saw service in Somalia²⁰.

The lesson for civilian travelers could not be clearer: traveling in a malarious area, no matter how prudent one may be, is dangerous. No antimalarial drug is perfect; no exposure is without risk; and no person is immune. Suffice it to say that scientists have even recorded cases of malaria among travelers who were simply on board an aircraft that made a brief refuelling stop in West Africa²¹.

Second, the global burden of malaria has serious economic implications for developing countries, and by extension, implications for American foreign policy. Malaria is a perennial plague, and works like a "disease tax" in Africa: limiting inward capital investment, squelching development, damping trade in goods and services, and generally depressing the standard of living.

Third, research in malaria has the potential to enhance American activity in core, commercially valuable technologies. As I mentioned, nobody has succeeded in vaccinating humans effectively against malaria, or for that matter, any other parasitic disease. But it is precisely because malaria vaccine development is so technically challenging that the knowledge gleaned in research is so valuable. As the Institute of Medicine of the National Academy of Sciences observed:

The inherent complexity of the malaria parasite and the resulting immune response make it a natural target for cutting-edge fundamental and applied research. As a result, malaria vaccine research has historically been a leader in the development of new technologies with broad applicability to human health. For example, the world's first recombinant vaccine produced in bacteria and the first synthetic peptide vaccine to be tested in humans were malaria vaccines. The most complex vaccine yet devised...is a malaria vaccine now undergoing testing in humans...In addition, some of the most advanced adjuvant work has been driven by malaria vaccine research, and these agents are likely to be important components of vaccines against HIV/AIDS, herpes, cancer, and other diseases.²²

Just as public support for space science in the 1960s, or particle physics today, are seen as valuable to the cultivation of American scientific advances, malaria vaccine research presents an unequalled opportunity to give rise to technologies that would help us combat other diseases endemic to America. These could be parasitic diseases, such as cryptosporidiosis, which caused 400,000 illnesses in Milwaukee in 1994²³; or they could be terrible scourges such as AIDS. Needless to say, the commercial significance of these technologies for American industry is certain to be enduring.

Lastly, malaria research can help promote America's stature in the developing world, which is wise foreign policy, while at the same time promoting Americans' traditional values of helping the weakest help themselves. Last year, at the instigation of Dr. Harold Varmus, Director of the National Institutes of Health, the malaria research community met in Dakar to create the Multilateral Initiative on Malaria (MIM). The objective of the MIM is to create networks of American, European and African laboratories to work in collaboration on malaria research²⁴. For a modest investment in the MIM, the United States can build scientific capacity in Africa, promote contacts between American researchers and their European colleagues, and work toward conquering a devastating disease -- all of which makes for excellent scientific diplomacy.

I cannot stress enough, Mr. President, that biomedical research on malaria is not about traditional, third-world aid: it is about basic science, done largely in American laboratories, that has the potential to help the least fortunate countries of the world throw off the yoke of disease that stifles their life expectancy and material progress. There is no "cycle of dependency" in funding malaria research. There is only Americans' goodwill to stop the pointless death of children; to support the health of women; and to foster economic security for all people of the globe.

Malaria deserves serious attention from your Administration. I would recommend that the White House become involved by convening the best experts the field has to offer, to design and steer a renewed American research effort, backed by a funding commitment equal to the scientific challenge. An early, initiatory gathering of these knowledgeable persons with you at the White House would demonstrate the priority given this scourge by your Presidency.

Sincerely,

A handwritten signature in black ink, appearing to read "Ralph Nader". The signature is fluid and cursive, with the first name "Ralph" being more prominent than the last name "Nader".

Ralph Nader

¹ World Health Organisation, The World Health Report 1996 (WHO, Geneva, 1996), p. 47 [hereinafter *World Health Report*].

² For percentage, see World Bank, World Development Report 1993: Investing in Health (Oxford University Press, Oxford, 1993), at 208-9 [hereinafter *World Development Report*].

³ J. Anderson *et al*, Malaria Research: An Audit of International Activity (The Wellcome Trust, London, 1996), at 12 [hereinafter *Wellcome Malaria Report*].

⁴ N. Diagne *et al*, (1997) "Incidence of clinical malaria in pregnant women exposed to intense perennial transmission", *Transactions of the Royal Society of Tropical Medicine and Hygiene* 91(2):166-70.

⁵ P. Fischer (1997) "Congenital malaria: an African survey", *Clinical Pediatrics* 36(7):411-13; H. Silver, "Malarial infection during pregnancy", *Infect Dis Clin North Am* 11(1):99-107.

⁶ D. Wirth and J. Cattani (1997) "Winning the war against malaria", *MIT Technology Review*, August/September 1997.

⁷ H. Lobel and P. Kozarsky (1997) "Update on prevention of malaria for travelers", *Journal of the American Medical Association* 278(21):1767-1771.

⁸ The numbers are even less (about \$67 million) if one excludes non-State funded research, e.g. foundation grants and other charitable funding. See M. MacLean *et al*. (1997) "Making malaria research bite", *Nature Medicine* 3(1):14; and Wellcome Malaria Report, *supra*, at 17.

⁹ AIDS figure from Rep. Robert Livingston, Chairman, House Appropriations Committee, cited in M. Pines, "Can AIDS be Tamed?", in A Report from the Howard Hughes Medical Institute: The Race Against Lethal Microbes (Howard Hughes Medical Institute, Chevy Chase, Maryland, 1996), p. 49-50; Malaria figure calculated by taking US funding contribution (\$42 m) from Wellcome Malaria Report, *supra*, and dividing by WHO's estimate of about 2 million malaria deaths annually, from World Health Report, *supra*.

¹⁰ The Malaria Foundation Factpack (October 1997), <http://www.malaria.org/factpack.htm>.

¹¹ Wellcome Malaria Report, *supra*, at 16-7.

¹² Daniel S. Greenberg, "A Pittance to Fight Malaria", *Washington Post*, January 4, 1998.

¹³ Institute of Medicine, National Academy of Sciences, America's Vital Interest in Global Health (National Academy Press, Washington, 1997), p. 36-7.

¹⁴ *Ibid*.

¹⁵ Centers for Disease Control, *MMWR* (Jun 13, 1997) 46(23):536-539.

¹⁶ S. Neel (1973) "Vietnam Studies: Medical Support, 1965-1970" Washington, D.C.: US Department of the Army.

¹⁷ Wallace MR *et al*. (1996) "Malaria among United States troops in Somalia", *Am J Med* 100(1):49-55.

¹⁸ Newton, *supra*.

¹⁹ Smoak BL *et al*. (1997) "*Plasmodium vivax* infections in U.S. Army troops: failure of primaquine to prevent relapse in studies from Somalia", *American Journal of Tropical Medicine and Hygiene* 56(2): 231-234.

²⁰ Dr. R. De Fraites, Preventative Medicine Staff Officer, Office of the Army Surgeon General, January 1998 (personal communication to Dr. A. Attaran of my office).

²¹ M. Isaacson (1989) "Airport malaria: a review", *Bulletin of the World Health Organization* 87:737-43; H. Lobel *et al* "Long-term malaria prophylaxis with weekly mefloquine", *Lancet* 341:848-51. Both cited in Institute of Medicine, National Academy of Sciences, Vaccines Against Malaria: Hope in a Gathering Storm. (National Academy Press, Washington, 1996), p. 7.

²² Institute of Medicine, National Academy of Sciences, Vaccines Against Malaria: Hope in a Gathering Storm. (National Academy Press, Washington, 1996), p. 13-4.

²³ M. Kramer *et al* (1996) "Surveillance for waterborne disease outbreaks - United States 1993-1994" *MMWR CDC Surveillance Summary* 45(1):1-33.

²⁴ B. Mons *et al* "Partnership between South and North crystallizes around malaria", *Science* 279:498-99.

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19 February 1998

Tom Friedman
Room 213, Old Exec. Office Bldg.
Washington, DC 20502

Dear Tom,

Further to our phone call today, I am writing to give you an overview of what contacts Ralph and I have had in the last several weeks on the malaria issue. We have met with nothing but enthusiasm, and agreement that current levels of malaria research funding must be seriously augmented to become commensurate with the scope of the problem.

As you read this, please keep in mind the caveat that we have concentrated our lobbying efforts on increasing funding for malaria within the HHS agencies (NIH and CDC). Limited resources led us to choose this focus. Yet, there are also malaria research programs at USAID and DoD, both of which are also underfunded. They ought not to be overlooked in the development of a larger malaria strategy.

What follows is a précis of the meetings we have had to date. I also commend to you, for a sense of the malaria problem and the dearth of research funding, to read the short documents entitled "Malaria Facts" and "Malaria Quotes", as well as Ralph's letter on malaria to the President, which are found in the enclosed packet.

• **Health and Human Services**

We met with Secretary Shalala on February 3, to discuss both the malaria lobbying project and the Princeton tuberculosis project. Present at the meeting were both representatives of NIH and CDC.

The Secretary unhesitatingly agrees that malaria research must be enhanced -- indeed, she preempted our presentation on the need for research and jumped right to the question of how best to involve HHS in foreign research projects. The Secretary is correct that malaria research, by its nature, must be done largely overseas, in endemic areas; however, she is concerned that if HHS agencies extend their reach overseas, they tempt a turf war with USAID, which also has malaria projects abroad. This she sees this as powerfully counterproductive: she adamantly believes there should be a single, central authority to oversee and coordinate all the government's malaria research (a belief we concur in). Therefore, to avoid jurisdictional conflict with USAID, she's planning new legislation to expand the mandate of HHS agencies to operate overseas.

The Secretary's concerns over turf conflicts are well founded, but in our view there is no jurisdictional constraint posed by the present legislation, a view concurred in by general counsel for the CDC. Existing law provides that, "The Secretary may conduct biomedical research, directly or through grants or contracts, for the identification control, treatment and prevention of diseases (including tropical diseases) which do not occur to a significant extent in the United

States.¹" She may also, "make grants or loans of equipment and materials, for use by public or nonprofit institutions or agencies, or by individuals, in participating foreign countries"². Indeed, these powers have proven sufficient to support the existence of NIH and CDC labs abroad, as well as NIH's underwriting of overseas labs owned and operated by foreign governments.

• NIH and the National Institute of Allergy & Infectious Disease

Ralph and I met with Dr. Harold Varmus (head NIH) and Dr. Tony Fauci (head NIAID) on February 6 to discuss both the malaria and TB projects. Both believe that government must take the lead in malaria research, because of a market failure in which pharmaceutical companies have abandoned their vaccine and antimalarial drug research programs. What is more, both are convinced that if government shirks this role, the catastrophe of global, multi-drug resistant malaria is on the horizon. To put it shortly, both want to be doing very much more malaria research than is presently the case. They are opposed to earmarking funds at the appropriations process; but they are very glad for language from Congress encouraging them to proceed with certain projects, so long as the language is not just exhortatory but is backed by additional money to carry out those projects.

At present, NIAID (where all of NIH's malaria research is done) is spending about \$25 m per year on malaria research, divided about 80% to 20% among extramural and intramural research, respectively. While this amount has increased modestly (having doubled in the last ten years), it remains far from sufficient to intensively undertake what NIAID believes are two leading priorities: the development of new drugs and vaccines, respectively. Thus, NIH contemplates two new major research programs, each of which deserves a decade of support in the first instance, to design, produce and field-test candidate drugs and vaccines. The cost of such programs is notoriously hard to estimate, but NIAID suggests that vaccine development would cost about \$350 m over 10 years; and it is my guess that a similar amount again would be required for drug development. NIAID could estimate the actual cost, and the lead time necessary to ease into these major programs, more precisely.

Dr. Varmus is also keen to involve NIH more deeply in international malaria research. To this end, he has been the prime mover behind what is called the Multilateral Initiative on Malaria (MIM). On Dr. Varmus' own motion, a conference of American, European and African scientists was held in January 1997 at Dakar, Senegal, to forge a consensus on goals for malaria research, and the means to attain these goals. This group has convened three times subsequently in Europe to refine the *raison d'être* of the MIM itself: to build multinational scientific "networks", in which American, European and African researchers work in collaboration with one another; to exploit synergies in the combination of Western nations' technical facilities, with African nations' ability to facilitate clinical investigations and field studies; to furnish basic scientific infrastructure, such as Internet connectivity, to African laboratories; and to promote human capacity for science in Africa, through the training of researchers and African leadership in research networks.

The selling point of the MIM is that it is a vehicle both for attaining necessary research objectives, and for promoting a benevolent foreign policy based on scientific diplomacy. Present NIAID expenditure consistent with the MIM is very little: about \$1 m / year to the Tropical Disease Research program of the World Health Organization for scientific education and capacity building in Africa; and about \$ 2.5 m / year for Internet connectivity at the NIH field research stations in Mali, and annual scientific meetings in Africa. Once the first MIM research networks get underway (research proposals are presently being fielded), then naturally additional resources for MIM will be required.

¹ 42 USC §241

² 42 USC §242[1]

- **CDC**

We met with Dr. Helene Gayle, Dr. Trent Ruebush and Bill Gimson of the CDC February 18. Again, the sentiment was that the CDC malaria research effort, which is presently about \$7.3 m / year, is well short of what the agency should be doing.

Considering the pittance that CDC receives for malaria, the diversity and importance of the research they perform is astonishing: new drug testing; stretching the useful life of existing drugs; mosquito control; and malaria prevention by bednets are all in the research portfolio. Future activities will likely include vaccine development and statistical epidemiology of the disease.

CDC is very clear that no more projects can be taken on without augmenting funding. As with NIH, the agency does not want an earmark, but will be glad for language from Congress directing them to proceed with certain projects. CDC has a list of several new projects that are waiting in the wings and ready to implement at once, and for which the collective cost is about \$10 m / year. These include projects to reduce the incidence of malaria among American travelers, immunology studies for vaccine development, and contributions toward capacity building in Africa and the MIM.

- **House Health Appropriations Subcommittee**

The minority side of the health appropriations subcommittee appears to be strong. Discussions with aides for Representatives Obey, Pelosi and Stokes have gone well. All are waiting for us to draft and submit language on malaria funding, which they will consider for inclusion in the subcommittee's report. We are presently consulting widely in the malaria research community, in preparation for drafting this language.

The offices of Reps. Pelosi and Stokes are also considering organizing a malaria "brownbagger". Our aim for this would be to cultivate the interest of members on the health appropriations subcommittee, the Black Caucus (relevant, since malaria is such a scourge of Africa), and the proponents of the Africa Trade Act (wherein US-Africa cooperation on health is explicitly mentioned).

Aides for Rep. Porter (Chairman) are interested in the issue, but are concerned that because NIH and CDC did not explicitly request for funding for malaria in their budgets, it will be difficult to augment the FY99 budget unless representatives of NIH and CDC speak to the need for enhanced funding in testimony before the subcommittee. Aides from the offices of Reps. Pelosi and Stokes have agreed to accept questions from us, and to ask them in testimony, that we may work around this problem.

- **Senate Health Appropriations Subcommittee**

On the minority side, the office of Senator Harkin (Ranking Member) has instructed the subcommittee staff to receive from us draft language for the subcommittee's report. As mentioned above, we are now in consultations aimed at preparing this language. Also, aides in Senator Bumpers' office have been enthusiastic, notably because Mrs. Bumpers, who is interested in childhood diseases, shall visit a children's hospital in Africa next month. We expect to brief her for that trip.

On the majority side, the office of Senator Specter (Chairman) has similarly instructed the subcommittee staff to receive report language from us.

• **DESIRED ACTION FROM THE WHITE HOUSE:**

There are several ways that the White House could work to move this issue forward. These range from promoting the issue publicly, to taking administrative steps.

To begin with, a Presidential speech on malaria research would charge the issue before the appropriations subcommittees. The topic is timely in light of the President's upcoming trip to Africa, where malaria has taken its place on the political radar screen. Last year, the heads of state of the OAU nations issued the *Harare Declaration on Malaria Prevention and Control*-- the first time ever that African leaders or the OAU expressed a collective will on a disease. Considering the intractability of Africa's political problems, a foreign policy based increasingly on health and capacity building (as with the MIM) is both uncontroversial and popular on the continent. A speech now would help set the foundation for NIH and CDC to make substantially larger requests for malaria research in FY2000, enough so that the major projects such as vaccine and drug development could get underway.

Second, an Administration-wide strategy for malaria research and control is long overdue. On the face of it, dividing malaria research among four agencies (NIH, CDC, USAID, DoD) without central coordination is both inefficient and invites turf battles. For example, all four agencies are, or soon will be, involved in malaria vaccine development, but no vaccine "master plan" or authority for the rational division of research effort exists -- an omission that the Institute of Medicine decried in its 1996 report, *Vaccines Against Malaria: Hope in a Gathering Storm*. Secretary Shalala, as mentioned above, is of the view that the malaria research effort needs centralization. Proposals for centralization are beyond the compass of this briefing, but the question should be taken up along with funding increases.

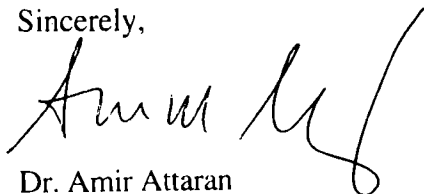
Third, to the extent that the Administration is seeking a supplemental appropriations bill for FY99, extra money for malaria research could be included, notwithstanding that special funding for malaria was not requested by NIH and CDC in the FY99 budget. This option permits a speedy legislative response to be taken to any initiative that is mooted in connection with the President's Africa trip.

Fourth, if there is an flexibility left in the President African itinerary, a visit to NIH or CDC research facilities in Africa could be arranged. The flagship NIH facility is in Mali, and that of the CDC in Kenya. The CDC Kenya lab is especially photogenic, and was a filming site for the popular TBS documentary on infectious diseases entitled "The Coming Plague".

I think that gives you a fair idea of where we have progressed in the last several weeks. Do not hesitate to call if I can be of help in answering your questions. I will be on the West Coast by the time you read this: (604) 222-1256. I'll be returning to Washington later in March (387-8030), or sooner if required, and can meet with you then if you wish.

Thanks, above all, for your interest in this.

Sincerely,



Dr. Amir Attaran

a brief index of malaria facts

[extent of the disease]

Number of countries where malaria is endemic:
90

Percentage of world population at risk of malaria:
40%

Number of cases of malaria per annum, globally:
500,000,000

Percentage of global population who get sick with malaria, per annum:
10%

Number of fatal cases of malaria, per annum:
2,700,000

Most common age at death:
4 years

Percentage of African children killed by malaria:
5%

Number of African children who die of malaria, per day:
2800

[impact on women and infants]

Multiple by which pregnancy increases mothers' risk of malaria:
4.2

Percentage of African infants who are born with malaria parasite:
up to 23%

Frequency that malaria is responsible for low birthweight in African babies:
40%

[scarcity of research funding]

American funding for biomedical research on malaria (FY1993):
\$42 million

American funding for biomedical research on cancer (FY1993):
\$2.3 billion

Ratio of cancer research funding to malaria research funding:
54 to 1

Federal subsidy to McDonald's to promote marketing of Chicken McNuggets in third world:
\$2 million

[military]

Percentage of American soldiers deployed in Vietnam War who got malaria (1965):
about 10%

Rank of malaria among causes of hospital admissions of troops who served in Vietnam:
2

Percentage of American soldiers deployed in Jilib, Somalia who got malaria (1993):
about 29%

Rank of malaria among causes of hospital admissions of troops who served in Somalia:
1

[civilian]

Number of American travelers hospitalized in USA for malaria contracted abroad (1995):
1419

Minimum number of days one must spend in a malarious area to risk infection:
under 1

Date the WHO announced the malaria problem had been "licked":
May 1975

Date the WHO's Deputy General was hospitalized for suspected malaria:
May 1975

[drug resistance]

Number of drugs commercially available for the treatment of malaria:
8

Number of drugs that scientists know are resisted by some strains of malaria:
8

Number of drugs which are consistently effective against the malaria parasite:
0

Number of major Western pharmaceutical companies now researching new malaria drugs:
0

Number of countries reporting malaria resistant to all known drugs:
1

Estimated number of years before multidrug-resistant malaria reaches other endemic areas:
about 10

[economic impacts]

Estimated direct and indirect cost of malaria in Sub-Saharan Africa (1995):
\$1.8 billion

Percentage of GDP, Sub-Saharan Africa:
0.6%

Cost to very low income African family for malaria treatment, per annum:
\$19

Total household revenue of very low income African family, per annum:
\$68

Percentage of household revenue spent to treat malaria alone:
28%

[sources]

<i>American Journal of Tropical Medicine & Hygiene</i>	18, 25, 28
<i>Annals of Human Biology</i>	11
Boston Globe	15
<i>Clinical Pediatrics</i>	10
G. Garden, <i>The Best Medicine</i> (St Martin's Press, 1984)	22, 23
Institute of Medicine, NAS (America's Vital Interest in Global Health)	27
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International Development Research Centre, Canada	8
Malaria Foundation	13
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National Institute for Allergy and Infectious Disease (1996 Profile)	20
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Personal Communication, Dr. R. De Fraites, Walter Reed Army Institute	19
<i>Transactions of the Royal Society of Tropical Medicine & Hygiene</i>	9
<i>Tropical Medicine and Parasitology</i>	32, 33, 34
US Department of the Army	16, 17
Wellcome Trust	7, 12
World Bank	31
World Health Organization	1, 2, 3, 4, 5, 21, 30, 31

FOR FURTHER INFORMATION please call:

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MALARIA RESEARCH

AN AUDIT OF INTERNATIONAL ACTIVITY

Key points from an audit of international research activity in malaria, including a survey identifying practical applications of research findings and future research opportunities.

A SUMMARY OF PRISM REPORT NO. 7



PRISM

THE UNIT FOR POLICY RESEARCH IN SCIENCE AND MEDICINE

Supporting evidence-based decision-making

MAIN FINDINGS

Malaria research is under-funded relative to the global incidence of the disease – approximately US\$42 is invested in research per fatal case – and to research investment in other disease areas.

The UK and especially the Wellcome Trust is increasing its support for malaria research, whereas the reverse is true in the USA.

Many countries are involved in malaria research, particularly in more applied research subfields such as epidemiology or intervention trials and health services research.

International publication activity over the last decade, which is low relative to other biomedical fields, was evenly distributed across most categories of malaria research.

The funding agencies that contribute most to malaria research are most frequently cited.

Respondents to an international survey identified *Plasmodium* genetics and *Plasmodium* biology as the subfields in which advances in knowledge are most likely over the next five years, while the subfield intervention trials and health services research was considered most likely to benefit from additional resources.

Many respondents in the international survey had personal experience of the practical application of research results, but also identified a number of key obstacles to the uptake of those results.

INTRODUCTION

Malaria is a major and increasing threat to global health. Recent estimates from the World Health Organization put the annual number of clinical cases at 300–500 million, and deaths at 1.5 – 2.7 million¹. The disease threatens 2400 million people – 40 per cent of the world's population – in more than 90 countries. Most cases occur in sub-Saharan Africa, but Asia and Central and South America are also badly affected.

The incidence of malaria is on the increase. There is a growing resistance of the malaria parasite to antimalarial drugs, including multidrug resistance in several countries. Control has become more difficult due to insecticide resistance of the anopheline vectors and to activities such as mining, changing agricultural practices, or armed conflict and refugee movements.

New and improved approaches to disease prevention, treatment and control are required and

present an urgent challenge to the underpinning sciences. There is a pressing need for research in the field of malaria, and for the effective translation of research results into practical application.

This short version of the full report summarizes a comprehensive study of international research activity on malaria. The key findings will help inform individuals or organizations who fund, manage or conduct malaria research.

PRISM'S APPROACH

The study examined the funding inputs to malaria research internationally, as well as the published outputs and broader outcomes, such as improvements in clinical treatment and development of new therapeutic products. In addition, the study examined research opportunities and also research areas requiring an input of resources. Opinion was sought on barriers perceived to be limiting the translation of research results into practice, and on measures to tackle these obstacles.

METHODOLOGY

The study comprised five analytical stages.

Stage 1: A survey of international funding for malaria research over the past decade.

Stage 2: An analysis of malaria-related publications and citations over the same time period, to compare the outputs and scientific impact of different countries and funding bodies.

Stage 3: An assessment of publishing activity in the subfields of malaria research, to compare research activity in different subfields.

Stage 4: A qualitative assessment of the portfolio of publications arising from research supported by the Wellcome Trust, to identify achievements and areas of strength.

Stage 5: An opinion survey of the malaria community – involving researchers as well as funders and users of research – on the main issues of research, future opportunities and the translation of research results into practice.

RESULTS AND DISCUSSION

Funding

The total identifiable global expenditure on malaria research in 1993 was approximately US\$84 million (1992 base year). Over half the total came from the USA (especially the US Agency for International Development, USAID, and the National Institute of Allergy and Infectious Diseases, NIAID). Much of the remainder came from Europe (notably the Wellcome Trust and the Medical Research Council, MRC, in the UK) and from the Programme in Research and Training in Tropical Diseases (TDR) which is co-sponsored by the United Nations Development Programme, the World Bank and the World Health Organization (WHO), as well as several governments, especially in Scandinavia. Funding has declined in some organizations over the last decade, most notably in USAID. However, there have been increases elsewhere, especially at the Wellcome Trust, NIAID and the US Department of Defense.

Global investment in malaria research over the past ten years has been very low compared with other disease areas, and appears to be declining.

FIGURE 1: FUNDING FOR MALARIA RESEARCH FROM THE MAJOR CONTRIBUTORS IN THE USA AND THE UK, AND FROM THE WHO PROGRAMME IN RESEARCH AND TRAINING IN TROPICAL DISEASES (TDR)

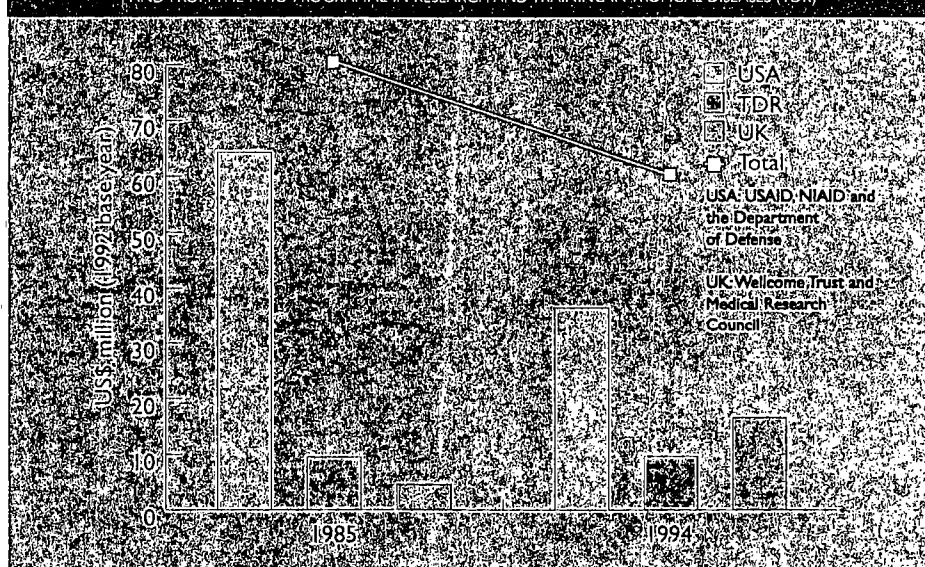
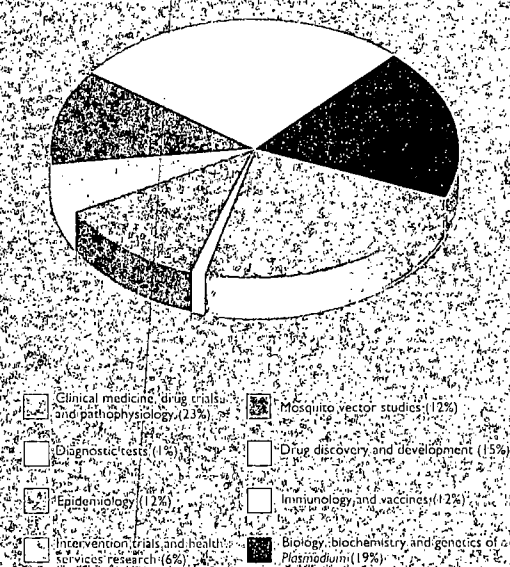


FIGURE 2. INTERNATIONAL MALARIA RESEARCH PUBLICATIONS



further (see figure 1). Expressed as investment in research per death, malaria research – at approximately US\$42 per fatal case – receives less funding by one or two orders of magnitude, than other diseases such as cancer, HIV/AIDS or asthma.

Research outputs

International publishing activity was lower than in other biomedical fields reflecting the relatively low funding input. The USA is currently the largest single contributor to the malaria research literature (34 per cent of the global total in 1994), but its world share of publications has declined over the past ten years (from 42 per cent in 1984). Meanwhile, the UK share increased, from 14 per cent of the world total in 1984 to 18 per cent in 1994. The world share of malaria publications also increased for France, Australia and Thailand. International co-authorship was fostered by collaborative research centres located in malaria-endemic countries: 38 per cent of UK output was internationally co-authored, largely reflecting work at the overseas units of the Wellcome Trust in Thailand, Kenya and Vietnam, as well as the MRC unit in The Gambia. Co-authorship was also high between UK researchers and scientists in Malawi and Papua New Guinea.

Citations largely reflected funding – the six largest contributors to malaria research had more citations to papers than other organizations. The proportion of USAID papers having a high impact decreased between 1984 and 1989. Papers acknowledging the NIAID and the MRC appeared to have the greatest citation impact.

Activity in different subfields

Malaria research was subdivided into 14 subfields. 'Clinical' research papers – describing studies of malaria in humans, ranging from descriptions of clinical management and pathophysiology to human immune responses and genetic susceptibility – accounted for 42 per cent of the world total. The remainder were 'non-clinical' papers – studies of malaria in animal models or *in vitro* and basic studies on mosquito vectors.

International publication activity over the last decade was evenly distributed across most categories (see figure 2). Publications were most numerous in two major research categories: (1) clinical treatment and pathophysiology and (2) basic science studies of the parasite. Research into antimalarial drugs, immunology, epidemiology and mosquito vectors were also well represented by publications. There were fewer publications concerning intervention trials and health services research in malaria-endemic countries.

On the basis of the address of the first author only, the USA dominated all subfields except those relating to clinical medicine and pathophysiology. UK authors published most frequently in pathophysiology and disease symptoms, while Thailand was the world leader in clinical management of malaria and drug trials. High co-authorship between researchers in the UK and Thailand suggests that the UK also had an important role in this area.

The Wellcome Trust portfolio

Papers acknowledging the Wellcome Trust and published in 1984, 1989 and 1994 were reviewed by 13 subfield experts. Reviewers felt that the Wellcome Trust's research outputs made a contribution both to advancing basic knowledge, and to improving malaria treatment and control. Realization of practical benefits from Trust-funded research was expected largely within five years of publication.

Publication output in different subfields generally reflected funding inputs but publications were low relative to expenditure in three subfields: (1) immunology and vaccine development, (2) epidemiology, and (3) intervention trials and health services research. Conversely, outputs were high relative to inputs for studies on both the biology and the biochemistry of the parasite.

Current practice and future directions of malaria research

A total of 115 individuals – including researchers, clinicians, health services managers and

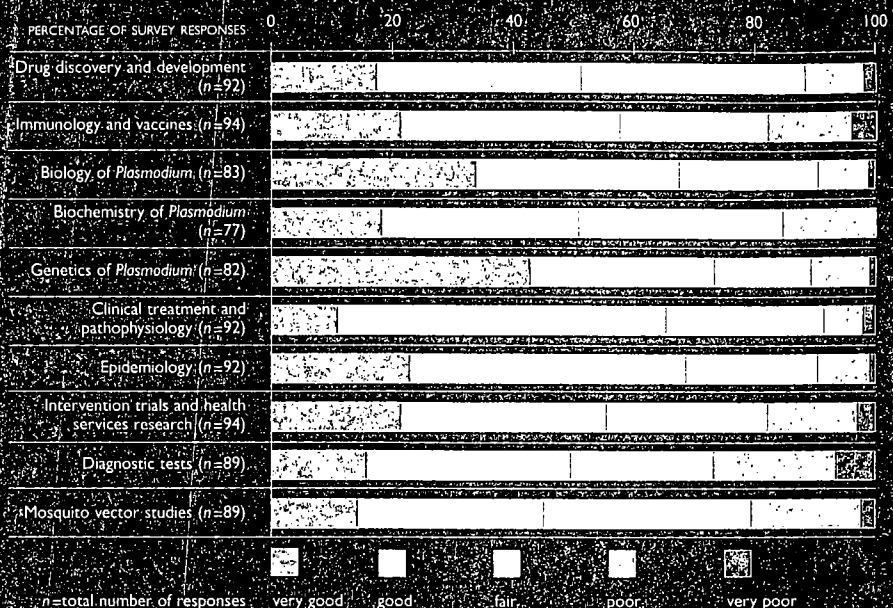
practitioners, industrialists and administrators in both malaria-endemic and non-endemic countries – responded to an international survey on current practice and future directions in malaria research.

Parasite genetics and biology were identified most frequently as having very good prospects for making substantial advances in knowledge over the next five years (see figure 3). Intervention trials and health services research were considered to be very under-resourced. Investment was also encouraged in a number of other areas: (1) basic studies of the parasite, (2) epidemiology, (3) immunology and vaccine development, and (4) antimalarial drug development.

A large number of respondents had personal experience of the practical application of research results. However, respondents also identified a number of key obstacles to the uptake of research results, including: (1) insufficient orientation of research programmes to public needs in malaria-endemic countries, (2) inadequate standardization of field techniques, (3) inadequate assessment of research results and development of applications, and (4) resource limitations in malaria-endemic countries.

A number of measures for tackling the perceived barriers were identified: (1) renew efforts to promote active communication across professional and national boundaries, (2) standardize methods in field trials, (3) increase investment in operational research, (4) widen dissemination of research results, (5) establish a centre or centres to prepare, maintain and disseminate systematic reviews of the results of malaria research, and to develop new products from the results of research that would contribute to the treatment and control of malaria, and (6) create more training opportunities for researchers based in malaria-endemic countries. Some respondents suggested an increased role for the World Health Organization in a number of these areas.

FIGURE 3. PROSPECTS IN EACH SUBFIELD FOR SUBSTANTIAL ADVANCES IN UNDERSTANDING OVER THE NEXT FIVE YEARS





PRISM (the Unit for Policy Research in Science and Medicine) was established by the Wellcome Trust in 1990 as a centre for independent analysis and advice on science policy. Its mission is to help inform decisions on the most effective means of supporting scientific research. PRISM supports evidence-based policy making particularly by:

- evaluating research outcomes
- auditing scientific activity in different research fields and countries
- applying novel approaches to strategic planning and priority setting

As well as carrying out independent policy research, PRISM offers two unique services to funding organizations, policy makers, government departments, universities and industrialists:

- SPIN (Science Policy Information News) – a weekly round up of news in biomedical science policy
- ROD (Research Outputs Database) – developed by PRISM to track research outputs in biomedical sciences. For the first time research funding agencies are able to identify and acquire details of research papers attributable to them.



Further details
For a copy of the full report
Malaria Research
P.R.I.S.M. Report No. 7
(ISBN 1 869835 68 0),
or for more details about P.R.I.S.M.
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- REPORT No.2 1994 (ISBN 1 869835 40 9) J Anderson, J Rogers & M O'Driscoll
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- REPORT No.3 1995 (ISBN 1 869835 45 X) J Anderson & N Williams
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Funding of population-related aid and research: UK and international perspectives
- REPORT No.6 1995 (ISBN 1 869835 61 1) M O'Driscoll & J Yates
Equipping UK universities
- REPORT No.7 1996 (ISBN 1 869835 68 9) J Anderson, M MacLean & C Davies
Malaria research: an audit of international activity
- REPORT No.8 (in preparation)
An audit of developmental biology research



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4 May 1998

FAX (6 pages) to Tom Friedman: (202) 456-7431
From Amir Attaran, Malaria Project Director, CSRL: (202) 387-8030

URGENT: Malaria and the upcoming G-8 leaders summit

Dear Tom -

Since being in touch shortly before the President's trip to Africa in March, there have been a few striking, multilateral developments on the campaign against malaria, all of which invite a response from the White House. I bring two of these to your attention briefly here, and direct you to the attached letter from Ralph Nader to the President for further details.

First, I have just learned that the Japanese and British governments intend to make sizable program announcements (\$100 million, in the latter case) for malaria control and research at or around the time of upcoming G-8 leaders summit. Malaria will appear on the G-8 agenda under the rubric of "global economic issues". It is of paramount importance that the U.S. act together with its partners, in order that the G-8 meeting result in a strong, multilateral approach on malaria.

Second, I understand that on the day following Dr. Gro Harlem Brundtland's election to the leadership of the WHO (*i.e.* May 12th), Dr. Brundtland will give an address on the subject of WHO's new "Roll Back Malaria" plan. My sources in WHO say that malaria will become a centerpiece of her leadership. The Roll Back Malaria announcement comes only a few days before the G-8 summit, and I believe that the final text of the summit will make direct reference to the WHO plan.

The launching, in the span of a week, of the G-8 and WHO initiatives on malaria is an unprecedented confluence of events that points the way for America to act in tandem with its international partners to vanquish the second worst infectious cause of death in the world. Multilateral, diplomatic action is among the measures contemplated by the President's June 1996 Decision Directive on Infectious Diseases. The coming weeks will present an opportunity to give effect to that Directive.

In preparation for these events, I recommend the White House begin immediate consultation with NIH, CDC, USAID, DoD, and Surgeon General Satcher. The objective must be to forge an American position that includes vocal support for multilateral action against malaria, and significantly enhanced funding for disease research and control. I am at your disposal to assist in developing that position, and I am amenable to assisting in press outreach as well.

Please read the following letter from Ralph Nader to President Clinton, dated today, and do not hesitate to call me at (202) 387-8030 if I may answer your questions or otherwise be of help.

Sincerely,



Dr. Amir Attaran
Malaria Project Director

P.O. Box 19312
Washington, DC 20036
Tel. (202) 387-8030

May 4, 1998

President William Jefferson Clinton
The White House
1600 Pennsylvania Avenue NW
Washington, DC 20500

Dear President Clinton:

Thank you for your letter of March 22 on infectious diseases, which arrived only a couple of days after your address of March 24 in Mukono, Uganda, in which you spoke of the tragic malaria problem in Africa and announced a further \$1 million for the West African Malaria Center in Mali.

While this is a welcome, first step toward a reinvigorated American malaria effort, I must concur with your sentiment that "this should be only the beginning of our efforts to attack this problem" of infectious diseases of the developing world.

I am encouraged by your statement in Uganda that, as a nation, "we want to do more." The timing of this is fortuitous: America's global partners also want to do more at the moment. I am, accordingly, writing on this occasion to suggest how your Administration may, through unilateral and multilateral action, renew America's commitment to controlling the scourge of malaria.

1. "A disaster of immense proportions"

The malaria epidemic is worse than ever, particularly in Sub-Saharan Africa. Since the failure of malaria eradication efforts in the 1960s, the disease has regained the upper hand. Sri Lanka, which had only eighteen malaria cases in 1963, today has over *one million annually*.¹ In Senegal, the final stop of your African tour, French scientists reported a *seven-fold increase in malaria deaths over the last five years*.² Every year, almost *half a billion* people are diagnosed with malaria and 2.7 million human beings lose their lives to the disease³. As you noted in Uganda, malaria takes a far greater toll of African lives than does AIDS. About as many Africans will die of malaria in 1998 alone, as have died of AIDS in the last fifteen years⁴.

In Uganda, you were correct to warn that Americans cannot ignore the malaria problem – that "with increasing globalization we are all at risk." Every year, about 1500 Americans returning home from foreign travels are hospitalized with malaria, after spending as little as one day abroad⁵. For those who reside overseas, such as American military forces or Peace Corps workers, the risks are even more severe. Malaria was the leading cause of hospitalization among troops who served in Somalia⁶, and caused over 1600 cases of serious illness among Peace Corps workers in West Africa in the late 1980s alone⁷. Even persons who do not travel may contract malaria from contaminated blood transfusions: two Americans died last year in just this way⁸.

What is worse, resistance to anti-malarial drugs, and the absence of an effective malaria vaccine, are threatening to make the disease incurable for the first time since the 17th century. Researchers in South East Asia recently discovered strains of malaria that cannot be treated by *any* drug now on the market⁹. The introduction of these strains to Africa within a decade, where 90% of malaria

cases occur, would be "a disaster of immense proportions," in the words of researchers at Harvard University and the WHO published recently in the *Journal of the American Medical Association*¹⁰. Yet despite this looming crisis, the National Academy of Sciences reported in 1996 that "not a single major Western pharmaceutical company is now developing new drugs for the disease."¹¹

Although the United States contributes half of the world's malaria research budget, the overall numbers are far too low. A research audit by the Wellcome Trust in 1996 found the malaria research budgets of *all* nations, charities, drug companies, and the WHO total *under \$90 million annually* – about as much as the budget of a single, modestly-sized hospital in the United States.

To redress the neglect of malaria, your Administration needs a two-track approach. As a matter of domestic policy, America must fortify its research commitment through inter-agency cooperation and a real increase in appropriations. As a matter of foreign policy, America must put malaria research and control squarely onto the diplomatic agenda, where it already has the support of our international partners. The following are my specific recommendations.

1. Inter-Agency Coordination is Essential to Efforts on Malaria & Infectious Disease Generally

At present, America's malaria effort is divided, not always rationally, between four agencies: the Centers for Disease Control, Department of Defense, National Institutes of Health, and the US Agency for International Development. This division has been criticized before. Two separate National Academy of Sciences, Institute of Medicine panels (in 1991 and 1996) called the division of effort "disarticulated", and warned that, "there is inadequate joint planning and coordination among U.S.-based agencies that support malaria research and control activities"¹².

Your Administration should take two steps to bring the malaria agenda under one strategic umbrella. First, the recommendation of the NAS-IOM panels, for "the establishment of a national advisory body on malaria", should be acted on at once. Such a body would coordinate, monitor and report on the progress of malaria research and control¹³. In these ways, it would emulate other inter-agency bodies that were pivotal in fighting diseases: the Polio Vaccine Committee and the National Task Force on AIDS Drug Development are two examples¹⁴. Seven years after the first NAS-IOM recommendation, it is high time the American government formally coordinate its malaria research and control effort.

Second, you should convene the heads of several Executive Branch agencies to develop an Administration-wide agenda for infectious diseases generally. In my discussions with members of your Administration, all have agreed there should be an assembly of this type, namely: Secretary Donna Shalala; Surgeon General David Satcher; Ambassador J. Brian Atwood, USAID Administrator; Dr. Harold Varmus, NIH Director; Mark Gearan, Peace Corps Director; Dr. Helene Gayle, Director of CDC's Center for HIV, STD, and TB Prevention; Ambassador Richard Morningstar, State Department Coordinator of Assistance to the Newly Independent States; and Josh Gotbaum, Executive Assistant Director of OMB. This meeting could reaffirm your June 1996 Presidential Decision Directive on infectious diseases, and set the stage for a major Presidential address on the challenges of infectious diseases – from malaria to AIDS to TB – at a later date.

2. America Must Support Multilateral Activities Against Malaria

Since 1997, the global community has become much more aware of malaria, and a number of multilateral and diplomatic initiatives have been or will soon be taken against the disease. Diplomatic action and multilateralism are part of your June 1996 Presidential Decision Directive,

which called for a the U.S. to collaborate with other nations and international bodies on emerging infectious diseases. In that spirit, your Administration should pay especially close attention to the following three developments.

2(i). The Multilateral Initiative on Malaria

Your Administration must work aggressively to build the Multilateral Initiative on Malaria (MIM) – a scientific and diplomatic collaboration between the U.S., eleven European countries, twenty-one African countries, four Asian countries, the Burroughs Wellcome Fund, the Malaria Foundation, the Organization of African Unity, the Wellcome Trust, the World Bank, and the World Health Organization – to coordinate new research essential to controlling the rising global incidence of the disease. The leadership of NIH Director Dr. Harold Varmus was instrumental in convening the first MIM conference in Dakar, Senegal in January 1997. The MIM continues to merit American support now that it has become a pre-eminent international research collaboration – one that involves, for the first time, African scientists on an equal footing with American scientists.

At Dakar, the MIM partners identified areas in which they agree that research is acutely needed. The CDC, DoD, NIH and USAID all have research plans aimed at these areas, but most are inactive for want of funding. For example, the DoD is sitting on about fifteen drug and vaccine candidates suitable for testing, and NIH has a vaccine plan that would test another thirty vaccine candidates within a decade¹⁵. *The limitations are not technical, so much as financial.* Your Administration ought to seek special appropriations, in this Congress, so that these and other research plans may proceed. Also, OMB must be instructed to consult with the above agencies, to ensure that their malaria research plans are accommodated in the forthcoming budget.

In deciding to make available more funding for malaria research, history lends a helpful perspective. The last time the United States seriously grappled with malaria was in the years from 1958-63. Back then, Congress gave its bipartisan support to a global malaria eradication program which cost the equivalent of *billions* of today's dollars¹⁶. President Eisenhower called for the "unconditional surrender" of the disease; and Senator John F. Kennedy predicted that children would be born into a world naive of this scourge. Unfortunately, in the end malaria eradication failed, but this is hardly surprising: the eradication plan was proposed just one year after scientists deciphered the structure of a mysterious thing called "DNA". Four decades later, our expertise in vaccinology, pharmacology and genetics is beyond the imaginations of the architects of that program, and the technical barriers are no longer so daunting. There is no doubt that today we can, for a fraction of the cost of that program, develop effective drugs or vaccines¹⁷.

2(ii). WHO's Roll Back Malaria Plan

You will have heard the news that Dr. Gro Harlem Brundtland will be confirmed later this month as director of the World Health Organization. Under her leadership, the WHO is imminently to launch the "Roll Back Malaria" campaign, which is aimed at halving the number of malaria deaths by the year 2010, and halving them again by 2015. This will require a large-scale, sustained malaria control program, primarily in Africa. It will also require more research, much of it under the auspices of the WHO's Tropical Disease Research (TDR) program.

United States scientific and aid agencies both contribute to and receive funds from TDR. In recent years, U.S. projects have in fact received more money from TDR than they have contributed¹⁸. Your Administration ought to watch Dr. Brundtland's Roll Back Malaria plan with the greatest of interest, and strengthen the involvement of American scientists and development specialists in TDR research as a means of supporting this very noble plan.

2(iii). Malaria and the Agenda of the Group of Eight (G-8) Summit

In preparation for the upcoming G-8 summit of leaders this month, Japan and Britain are calling for concerted action on malaria research and control, and this will be raised in the G-8 session and discussions on "global economic issues". The rationale for treating malaria under this rubric is inescapable: as the G-8 economies grow increasingly connected to developing country markets, the *health* of people in those countries becomes a matter of global economic and political security. You alluded to this linkage when, in Uganda, you commented that, "By weakening as well as killing people, malaria contributes to poverty and undermines economic growth."

Your Administration should ensure the U.S. goes into the G-8 summit with a position on malaria no weaker than that of our partners. At last year's G-8 summit, Prime Minister Hashimoto urged more international cooperation on parasitic diseases: the Japanese are returning this year with a firmer proposal¹⁹. Similarly, the Blair government shall also announce a large disbursement – on the order of £60 million (\$100 million) – for malaria control and research around the dates of the summit, and this will be very heavily promoted to the press. If the U.S. is to not lose its position as the world's preeminent supporter of malaria research – a fact you cited with pride in Africa – it too must be prepared to grant an increase to American funding. That increase should not be an exercise in tokenism, but a major augmentation consonant with the devastating, global proportions of malaria. With the summit less than two weeks away, your Administration must make a decision on doing this shortly.

* * *

Your growing recognition of the global malaria crisis is a first step toward committing the seriously increased budgetary resources that are needed to banish this scourge. I look forward to being of assistance as your Administration turns to further action on this problem.

Sincerely,



Ralph Nader

For additional information, please call:

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- ¹³ NAS-IOM Malaria Report #1, *supra*, p. 12.
- ¹⁴ NAS-IOM Malaria Report #2, *supra*, p. 21.
- ¹⁵ NIAID Research Plan for Malaria Vaccine Development (1997), NIAID, NIH. Also Military Infectious Diseases Research Program, Department of Defense (as at April 1998)
- ¹⁶ *The Coming Plague*, *supra*, p. 49.
- ¹⁷ For instance, NIAID suggests that vaccine development would cost about \$350 m, spread over 10 years.
- ¹⁸ Personal Communication, Nelle Temple-Brown, WHO External Relations Officer, Washington (Jan. 13, 1998).
- ¹⁹ Summary of "A Report on Global Parasite Control", Draft of 9 March, 1998; Government of Japan.



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FAX TRANSMITTAL

FAX: 202-395-6974
DATE: ~~3/3~~ 3/17
TO: Tom Freedman
FROM: Wendy Taylor

*Just found out this
didn't go through last
week. Sorry. Still working
on getting malaria info.*

Total number of pages (Including Transmittal Sheet):

18

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Comments:

Shelley's speech at Atlanta conference and Stetler's
testimony on Global Health. Both have good general info.
on infectious diseases + the need for action.

**FOR RELEASE UPON DELIVERY
MONDAY, MARCH 9, 1998**

***REMARKS BY
DONNA E. SHALALA
U.S. SECRETARY OF HEALTH AND HUMAN SERVICES**

AT

**CDC INTERNATIONAL CONFERENCE
ON EMERGING INFECTIOUS DISEASE**

ATLANTA, GEORGIA

***THIS TEXT IS THE BASIS OF SECRETARY SHALALA'S ORAL REMARKS.
IT SHOULD BE USED WITH THE UNDERSTANDING THAT SOME
MATERIAL MAY BE ADDED OR OMITTED DURING PRESENTATION.**

I could not begin today without recalling an important anniversary in the history of fighting infectious disease. Two hundred years ago, the U.S. Public Health Service, of which CDC is an essential part, began as a humble maritime hospital in New York City. Its mission was simple—to stop infectious disease from coming in on ships and spreading across our country. And for two centuries, under outstanding leaders like David Satcher and Bill Foege, the CDC has continued to fulfill the mission of preventing the spread of infectious disease.

Today, as we celebrate the anniversary of the Public Health Service, and one of its leading lights becomes our Surgeon General, another historic event has also re-emerged. As most of us are probably aware, last month, one of the great detective hunts of the 20th century finally came to an end. Scientists at the U.S. Defense Department confirmed that tissue from a woman's body buried near the Bering Strait contains genetic material from the 1918 Spanish flu virus—the virus which caused the worst pandemic the world has ever known. And this latest discovery will help us map the genetic structure of the microbe that sent a wave of death crashing around the globe 80 years ago.

It's hard to believe today that a simple flu could be so nearly apocalyptic. In just eleven months, at least 24 million people were killed, while the majority of humanity was infected. And the infected often never knew what hit them. In the morning you would feel fine, by night you could be dead—drowned as your lungs filled with fluid. There was no explanation, no protection, no cure. The pandemic produced scenes from a Gothic horror novel—but it was all too real. In Philadelphia alone, 11,000 died from the flu in a single month. The dead were left in gutters—and death carts roamed the city in a surreal scene from Medieval times. And as the deaths mounted all over the world, orderly life began to break down. Schools and churches closed; farms and factories shut down; homeless children wandered the streets, their parents vanished. The acting U.S. Army Surgeon General, Victor Vaughn, calculated that if the pandemic continued its mathematical rate of acceleration—it soon could spell the end of humankind.

But then, as silently, as mysteriously, as quickly as it came—the terror began to fade away. People stopped dying. The victims were buried. Life returned to normal. The great flu was soon pushed off the front pages...and out of the public imagination. But we all wondered if perhaps another pandemic had begun when the avian flu first appeared last year. It was an influenza subtype that had never before produced illnesses or deaths in humans—and now it did. And while it appears that the spread of the avian flu has halted, without the appearance of human-to-human transmission, we know that the danger is far from over. Because the critical period may be just beginning—since we're now at the start of the traditional flu season in Hong Kong.

But the emergence of avian flu points up a broader concern. We must guard against complacency over infectious disease. It's easy to assume that modern medicine has defeated this enemy once and for all. Our comfort is a natural byproduct of our progress and success—the remarkable breakthroughs in antibiotics and vaccines, thanks to the work of scientists and researchers at CDC, NIH and worldwide. Most recently, we finally eradicated smallpox from every nation on earth—consigning one of history's deadliest killers from the medical books to the history books. But, in reality, infectious disease remains the leading cause of death, worldwide, and the 3rd leading cause in the United States. While we may be winning some old battles, we're struggling with some new adversaries -- the emerging infectious diseases such as Ebola ... Hantavirus ... new strains of tuberculosis ... HIV and AIDS ... and Lassa Fever, to name a few. In fact, the World Health Organization has labeled the growing threat of infectious disease a global crisis.

Undeniably, the time has come to replace complacency with a new sense of urgency -- to launch a renewed, unified, global effort to fight infectious disease. This conference is a great start. Nature may have the power to create a pandemic—but together we have the power to prevent it; to stop it; to overcome it; to cure it. And there is no time like the millennium. For today, history and human progress have created an “ironic contradiction” in the fight against infectious disease. That some of the same forces that invite pandemics can also be harnessed to fight pandemics. With the globalization of travel and trade, of immigration, communication and industrialization, we have a smaller world with porous borders. Nations are more interconnected ... people are more interdependent ... and humanity is less divided by what the Indian poet Tagore called our “narrow domestic walls.” So the bad news is, we have fewer barriers against the spread of infectious disease. Yet the good news is, those fewer barriers mean new avenues to progress and the potential for sharing information and efforts to stop infectious disease.

We now have the power to push infectious diseases off the world stage—but only if governments, world health organizations, the private sector, scientists and researchers work together to hasten their exit with a global strategy. So I'm glad we're here today. But how do we successfully wage this global battle against infectious disease? I believe the answer lies in what we can learn from the 1918 pandemic. It provides three important lessons—lessons that are also challenges for all of us.

The first lesson is that we must assume it could happen again. We know that influenza pandemics have regularly swept the world every 10 to 40 years. And it has now been 30 years since the last influenza pandemic, the Hong Kong flu, killed 700,000. We also know that nature is creative, and the flu has great potential for mutating. If a strain changes dramatically, then we could suddenly have a virus for which we may have no immunity—no vaccine, and no cure. But, of course, the threat's not just the flu -- the spectrum of new infectious diseases is constantly expanding. While old infectious diseases, such as tuberculosis, have evolved into entirely new killers—because they developed antibiotic resistance.

The advent of the antibiotics in the 1940's was one of the chief reasons we began to defeat infectious disease. However, we know that almost as soon as antibiotics were available—the microbes mutated and developed resistance. In the 1950's to 1970's, we produced so many new antibiotics that there was always an alternative medication. But today, the flood of new antibiotics has diminished to a trickle—while the microbes have continued to grow resistant. Antibiotic-resistant bacteria are becoming more common in hospitals and among patients with depressed immune systems. In Japan in 1996, and in the U.S. last year, we started to see a strain of staph infection, the most common hospital acquired infection, which could sometimes withstand vancomycin—our most potent treatment. But almost simultaneously, the first antibiotic to fight a new generation of "super bugs," Synercid won limited approval from an FDA advisory panel. If it wins full approval, it will be the first drug in a new arsenal of weapons. This is certainly good news. And the FDA continues to work with drug manufacturers to bring new antibiotics to market as safely and rapidly as possible.

But antibiotic resistance isn't just a medical problem—it's also a behavioral problem. Right now, patients too often demand antibiotics for every illness—even for viral infections like the flu that don't respond. And they often don't finish the course of medication, allowing the remaining bacteria to develop resistance. What's more, many doctors over-prescribe. And the pharmaceutical industry has limited its antibiotic development due to cost. The widespread use of antibiotics in farm animals may also be helping the spread of drug-resistant germs. Given the consequences, we must act now to combat the diminishing effectiveness of antibiotics. That's why the CDC is strengthening surveillance and implementing education campaigns about the problem; why NIH is studying resistance; and why the FDA is promoting judicious antibiotic use. But this isn't a job for government agencies alone. Each and every one of us who understand the risks needs to spread the message that antibiotics are being misused, abused and overused.

Of course, the next pandemic could also result not from a mutating bug or ineffective antibiotics—but from an act of bio-terrorism. And whether bio-terrorism is state sponsored, or undertaken by a lone terrorist, it's not just a problem for the military or law enforcement—it's also a challenge for the entire public health community. If a specific threat is issued—perhaps someone claims to have released a toxic agent in a public place—then it's trained public health officials who must first verify that an incident has actually occurred. And they may need to decontaminate the area; identify exposed populations; and deliver preventive measures and treatments. But, too often, a threat isn't issued—no warning is given. In such a situation, public health officials must first quickly determine the deadly agent, the route of exposure and the likely source.

My department is coordinating with our partners in other agencies and the military to ensure the proper training of state and local health officials; the availability of vaccines and drugs; and the enhancement of our surveillance capacity and expertise. There's also an administration-wide effort to train emergency response teams and health care providers in 120 cities. It's critical that we enhance our ability, now, to address the growing threat of potential bio-terrorism.

Which brings me to my second lesson. If a pandemic could happen again, then we must do everything we can to be prepared. We cannot wait until the next deadly microbe appears on the world stage. That's why my Department has been leading a federal, state and local effort to develop a "pandemic influenza plan" since 1993. As a result of the avian flu episode, we've sped up the process to complete the plan, and to pursue its full implementation. Meanwhile, the CDC is studying the impact of anti-viral medications and alternative ways to produce vaccines. The NIH is working in partnership with the pharmaceutical industry to develop and test innovative vaccines—including a nasal spray that delivers an inoculation dose of the virus. And the FDA is issuing new drug permits for experimental influenza vaccines. I know you'll be hearing a lot more about all of this work during the course of the conference. With new viruses knocking at the door, we can't afford to be caught unprepared. Because it's only in the movies—like the film "Outbreak"—where we can save the world from a deadly disease in just 24 hours.

Of course, we need this same kind of commitment in responding to all emerging infectious disease. What we need, and what the CDC has championed, is the creation of a world-wide "surveillance and response network" that can quickly identify and stop an outbreak. We've already laid the groundwork for such a system with bilateral and multilateral talks on disease monitoring with our partners in Europe, Japan, Asia and Africa. For example, at the Denver Summit in 1997, the group of eight industrialized nations, including the United States, pledged to help develop a global disease surveillance network and coordinate an international response to infectious disease. And working through the Trans-Atlantic Agenda with the European Union, the United States and EU countries have begun to share surveillance data on Salmonella infections. Additionally, through the US-South Africa Bilateral Commission our two countries are working to train health personnel in South Africa in surveillance and applied epidemiology. And I look forward to working closely with the newly nominated Director-General of the World Health Organization, Dr. Gro Bruntland, on her commitment to further globalize our approach to surveillance and response.

U.S. agencies such as the CDC are already supporting the efforts of the World Health Organization to improve communications networks, and to build regional centers for monitoring disease. Currently, the CDC and WHO jointly run 12 world monitoring stations for the flu alone. Perhaps the best example of the kind of monitoring and surveillance system we need to have, worldwide, is the excellent system that stopped the avian flu outbreak in Hong Kong. On a routine basis, officials collect throat swabs from people with flu-like symptoms. The samples are analyzed; and if something looks suspicious, it's immediately sent to the CDC—which functions as one of the WHO International Reference Labs for East Asia. So when the very first known case of the avian flu was diagnosed in a 3 year old boy, the warning bells went off immediately. When a second case appeared in November, health officials around the world went on alert—and a team from the CDC left for Hong Kong.

Over the next two months, the CDC worked to define the extent of the outbreak: including who was becoming ill; why they were becoming ill; and whether the virus could spread from person to person—and so cause a pandemic. Fortunately, the slaughter of over one million chickens seems to have halted the virus—at least for now.

Hong Kong's surveillance system proved that early detection of infectious disease can prevent their spread. David Heymann of WHO once asked a provocative question: What would have happened if we had had an excellent surveillance system in place in Africa when the AIDS outbreak first occurred? Perhaps we could also have halted that virus in its tracks. And perhaps we would have spared ourselves the second great pandemic of the 20th century. AIDS taught us that, regardless of a person's sexual orientation...or color...or wealth...or home, if we hesitate in our fight against infectious diseases, if we fail to detect and track them early, they will eventually affect us all.

But we cannot simply deal with each potential pandemic as it arises. In this age of wonder and change, we must also look over the horizon and seize new possibilities to head off infectious diseases before they can occur. We need to fully harness this golden age of global telecommunications, from satellites to the internet, to create a truly global surveillance and monitoring network. And we need to fully harness this golden age of scientific discovery, to find new ways to prevent, stop, overcome and cure infectious disease. That's one of the reasons that President Clinton proposed the 21st Century Research Fund. It's a historic national effort to spur the best minds of this generation to unlock scientific discoveries, to unravel scientific mysteries, and to uncover scientific advances. Today, the pace of medical discovery today isn't limited by science, or imagination, or intellect—but all too often by resources. So the research fund will provide a 1.1 billion dollar budget increase for the NIH next year. It's the first down payment on an unprecedented 50 percent expansion of NIH over the next five years. And it will enable NIH to do more to develop new ways to diagnose, treat and prevent disease. We're also seeking a boost in CDC funding to step up our ability to identify and investigate infectious disease outbreaks, including food born outbreaks. And the CDC will play a key role in a new initiative by the U.S. Agency for International Development to develop programs in targeted countries to fight the growing threats of bacterial resistance, tuberculosis and malaria. This new American investment in fighting infectious disease will not only pay off in America. Because in this world without borders, a discovery by any one nation will benefit us all—and brings us a little closer to preventing the next pandemic.

Which brings me to the third lesson of the great pandemic of 1918. We have the power to prevent the next pandemic, and defeat emerging infectious diseases—but only if our nations step up the fight together. Because diseases recognize no borders, in our fight against them, neither can we. Or as Dr. Bruntland has stated, when it comes to public health, "solutions, like the problems, have to be global in scope."

That's why, U.S. and Japanese scientists have held three international conferences together on infectious diseases and research. It's why some members of the Asian-Pacific Economic Cooperation Area, including Thailand, Indonesia and the Philippines, have developed a communications network to track cases of multi-drug resistant tuberculosis. And it's why the CDC, the FDA and other U.S. agencies are providing assistance to the Russian Federation and the Newly Independent States, which have faced a significant increase in infectious disease in the post-Soviet era.

But if we truly want to end the threat of infectious disease, then we must do even more together. And so, I want to offer the following challenges:

We must inject into global gatherings—no matter where they are, no matter what the subject—the urgency of working together to defeat infectious disease. We must never let research into infectious disease become a forgotten step-child of medical research. We must all continue to invest in vaccine research and development, and ensure that preventive vaccines are available, affordable and effective everywhere. We must work with all of our partners in the private sector to ensure that drugs, vaccines and tests are available during an infectious disease emergency. We must try to ensure that all urban populations have access to essential facilities—especially clean water, because vaccines and medicines can do little if water is unclean. We must work together to deal with conditions such as urban overcrowding, poverty and poor sanitation which are spreading infectious disease in many parts of the world. Finally, we must do what we are doing at this conference: We must pool our greatest resources—our restless imagination and intellect—to fight this collective fight. For as Joshua Lederberg once noted, "Pitted against microbial genes, we have mainly our wits."

Let us pit our wits—and our will—to this battle, together, to heed the lessons of the great pandemic, and so ensure that it does not happen again; that we are prepared; and that we always work together. And if we do, then our children—the children of the millennium—will remember the 21st century as a time of health and hope...a time of promise and possibility...a time of medical miracles and scientific marvels. And I've absolutely no doubt that we can do it...that we must do it...that we will do it.

DRAFT
February 26, 1998
Noon

STATEMENT OF

DAVID SATCHER, M.D., Ph.D.

ASSISTANT SECRETARY FOR HEALTH

U. S. SURGEON GENERAL

U.S. PUBLIC HEALTH SERVICE

DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

COMMITTEE ON LABOR AND HUMAN RESOURCES

SUBCOMMITTEE ON PUBLIC HEALTH AND SAFETY

U.S. SENATE

MARCH 3, 1998

Good morning. I am Dr. David Satcher, Assistant Secretary for Health and U.S. Surgeon General at the Department of Health and Human Services. I am pleased to be here this morning to discuss an important issue -- "Global Health: U.S. Response to Infectious Diseases." I want to thank you, Mr. Chairman, for calling this hearing today.

Emerging infectious diseases are a continuing threat to the health of U.S. citizens and of people around the world. They cause suffering and death, and impose an enormous financial burden on society. The recent outbreak of a new and virulent strain of influenza in Hong Kong raised the specter of a pandemic and illustrated the potential danger posed by these diseases to all countries. This incident also illustrated, yet again, the need for the United States to work closely with other countries and the World Health Organization to assure that there is adequate global capacity to detect and address such outbreaks.

Background

Over the past century, tremendous strides have been made in medicine and science to combat infectious diseases. The development and widespread use of antibiotics and vaccines, coupled with earlier improvements in urban sanitation and water quality, have dramatically lowered death and disability from infectious diseases and have led to a near doubling of life expectancy in this country. Progress had been so great that three decades ago some experts predicted we would soon see the end of infectious diseases.

However, our optimism, though understandable, was premature. Today, we see a global resurgence of infectious diseases, including the identification of new infectious agents, the reemergence of old infectious agents, such as tuberculosis (TB) and the rapid spread of antimicrobial resistance. Between 1980 and 1992, the death rate in the United States from infectious diseases, excluding HIV/AIDS, rose by 22 percent. Worldwide, infectious and parasitic diseases remain the leading cause of death. These deaths disproportionately affect the developing countries of the world, with the most vulnerable segment of the population being children under the age of five years. Moreover, the factors that contribute to the resurgence of these diseases -- including increasing global travel, the globalization of the food supply, population growth and urbanization, ecological and climatic changes, and the evolution of drug-resistant microbes -- show no sign of abatement.

The CISET report

In 1995, I had the honor of chairing a workgroup on emerging diseases for a committee of the National Science and Technology Council (NSTC), which was charged with conducting a government-wide review of our ability to protect our citizens from emerging infectious diseases. The NSTC Committee -- the Committee

on International Science, Engineering and Technology (CISSET) -- was staffed by the Department of State. The issue of emerging infectious diseases was regarded as urgent by many U.S. agencies, 17 of which sent representatives to the first CISSET meeting, with 23 agencies ultimately participating.

Within a short time, the Committee issued a report that concluded existing mechanisms for surveillance, response to, and prevention of outbreaks of new and reemerging infectious diseases were inadequate, both at home and abroad. The report made specific recommendations that became the basis of a 1996 Presidential Decision Directive (PDD) that established a new national policy. The Directive called for a coordinated U.S. government response to address the growing health and national security threats posed by infectious diseases. The new policy acknowledged that domestic and international health are intimately linked, that microbes do not respect borders, and that the United States cannot protect the health of its citizens without playing a leadership role in international health. Copies of the CISSET report have been provided to the Subcommittee.

The Task Force

Immediately after the CISSET report was issued, the NSTC transformed the CISSET policy group into an Implementation Task Force, which I co-chair with Dr. Kerri-Ann Jones, Associate Director for National Security and International Affairs of the White House Office of Science and Technology Policy. The lead agencies on the Task Force include three agencies from the Department of Health and Human Services: the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA) and the National Institutes of Health (NIH); as well as the U.S. Agency for International Development (USAID) and the Department of Defense (DOD). The U.S. Department of Agriculture (USDA) has played an increasingly important role. The National Oceanic and Atmospheric Administration (NOAA) of the Department of Commerce, the National Aeronautics and Space Administration (NASA), and the Department of Veterans Affairs are also active participants. The Department of State and the Office of Science and Technology Policy have provided guidance on international policy and have supported us in our efforts to strengthen relationships with other countries, including India, Japan, Mexico, Pakistan, South Africa, Vietnam, and the countries of the European Union, to name just a few.

From the beginning, the basic principles of the Task Force and the working group on emerging diseases have been collaboration and coordination. We know that the challenge ahead outstrips the means available to any one agency, organization, or country. However, if we pool our talents and resources, a great deal may be accomplished. This is well illustrated by the great success of smallpox eradication and the ongoing polio and guinea worm eradication programs. Globally, polio cases have decreased by more than 90% since 1988; and, \$230 million will be saved by

the United States annually, when the goal of polio eradication is achieved. An estimated \$1.5 billion will be saved globally.

These principles of collaboration and coordination are being applied both at home -- where U.S. agencies have coordinated the effort to address emerging infectious diseases among themselves as well as at the state and local level -- and overseas, where U.S. agencies are working with the World Health Organization (WHO) and other international partners to improve global health communications, set standards for global surveillance of antimicrobial resistance, and share experience and training on disease prevention and control on a regional basis.

Progress/Implementation

I am pleased to say that much progress has been made. A detailed account of what has been achieved through the Ciset process can be found in the first annual Emerging Diseases Progress Report, copies of which have been provided to the Subcommittee. I will mention a few highlights in four key areas featured in the Ciset report and emphasized in the PDD to give you a sense of what has been accomplished. They are:

- Strengthening the global surveillance and response system to keep local outbreaks from growing into pandemics
- Supporting research and training to detect, treat, prevent, and control disease outbreaks.
- Working with the private sector to ensure that drugs, vaccines, and diagnostic tests are available during infectious disease emergencies.
- Making the issue of emerging infectious diseases a priority with our international partners.

Surveillance and Response

In the area of disease surveillance and response, the Ciset report recommended action both at the domestic and international levels. CDC has led the effort to revitalize the component of the U.S. public health infrastructure that protects the public from infectious disease, working closely with state and local health departments, community-based organizations, universities, professional organizations, and other U.S. agencies. CDC will discuss its ongoing efforts to improve the detection and containment of emerging diseases entering the United States. As evidenced by several recent multi-state outbreaks of diseases transmitted through contaminated food (including strawberries, raspberries, lettuce, apple juice, alfalfa sprouts, and ground beef), food-borne diseases are a special domestic concern. Three agencies -- CDC, FDA, and USDA-- established the Active

Foodborne Disease Surveillance Network (FoodNet) through CDC's Emerging Infections Program sites in 1996.

The goals of FoodNet are to:

- Describe the epidemiology of new and emerging bacterial, parasitic, and viral food-borne pathogens.
- Estimate the frequency and severity of food-borne diseases that occur in the United States each year.
- Determine how much food-borne illness results from eating specific foods, such as meat, poultry, and eggs.

The public health challenges of food-borne diseases are changing rapidly. Changes in food production have led to new safety concerns. Many foods, previously thought to be safe, such as eggs and fruit juice, have both transmitted *Salmonella* in recent outbreaks. Other food-borne diseases included infections caused by *Shigella*, *Campylobacter*, *Escherichia coli* O157, *Listeria*, *Yersinia*, and *Vibrio* bacteria.

Internationally, U.S. government agencies have intensified their efforts to respond to outbreaks of highly contagious, highly lethal, or drug-resistant diseases, especially when they occur in countries that lack the resources and infrastructure to contain them. USAID, CDC, and other agencies are also supporting the efforts of the WHO to improve communications networks and build regional centers for surveillance of and response to infectious diseases. The WHO is sponsoring the development of sub-regional teams, or "hubs," for disease surveillance and outbreak control -- an idea that is in full accord with the goals of the Ciset working group.

The DOD has contributed to the international surveillance and response effort by expanding the mandate of its overseas laboratories to include epidemiological training and laboratory capacity related to diagnosis of infectious disease outbreaks. These DOD facilities work closely with experts in the countries where they are located, thereby helping to build local capacity.

Research and Training

A major Ciset goal is to promote research on tropical diseases by combining the scientific and clinical experience of doctors and scientists in less-developed countries with the scientific resources of industrialized countries. The NIH is the lead agency in this area.

Over the past year, the National Institute of Allergy and Infectious Diseases (NIAID) at NIH has substantially expanded its research efforts on emerging diseases and the

Fogarty International Center (FIC) at NIH, in close cooperation with NIAID, has launched a \$1.9 million program to provide infectious disease training for scientists in developing countries. NIH has also launched a Multilateral Initiative on Malaria that includes participation by other agencies of HHS, French and English research institutes (the Pasteur; INSERM, France's counterpart to NIH; ORSTOM, part of France's overseas development effort; and the British Medical Research Council), the Wellcome Trust, and the European Commission. As part of this initiative, the NIH has committed more than \$1 million for a WHO program to strengthen malaria research in Africa.

On Sunday, March 8, the American Society for Microbiology (ASM), CDC, and NIH are convening a workshop, "Training in Emerging and Re-Emerging Infectious Diseases." This and other workshops related to emerging infectious diseases globally will be convened prior to and after the *International Conference on Emerging Infectious Diseases* to be held March 8-11, 1998, in Atlanta. This international conference is being organized by CDC, the Council of State and Territorial Epidemiologists, ASM, and the CDC Foundation, and has more than sixty cosponsors. There will be participation by many of our partner countries as well as WHO, PAHO, the World Bank, and USAID.

I would like to mention two other relatively new areas of infectious disease research that may be of interest to this Committee. One is the use of remote sensing technologies and global positioning systems to examine links between weather changes (such as those due to El Nino) and the incidence of infectious diseases carried by insects and animals. The hope is that this avenue of research will lead to the development of methods for predicting outbreaks of such diseases as malaria and dengue fever. CDC, NIH, NOAA, and NASA are collaborators in these efforts. The other area is research on infectious agents that may cause or exacerbate chronic conditions like ulcers, heart disease, or some types of cancer.

Engaging the Private Sector

FDA has taken the lead in creating partnerships with the private sector. In collaboration with WHO and private sector partners, the Ciset agencies are preparing an international procedures manual for obtaining medical products during emergencies. FDA and its partners are also consulting with representatives of the U.S. pharmaceutical industry on how to promote the development of new drugs, vaccines, and diagnostic tests. In addition, FDA has engaged the regulatory bodies and pharmaceutical industries of Japan and the European Union (EU) in an effort to promote international harmonization of standards for medical products.

Private sector partnerships have been crucial in responding to particular outbreaks and emergencies over the past year. For example, CDC and FDA collaborated with drug manufacturers to address the shortage of vaccines for use in controlling a

meningitis outbreak in Sub-Saharan Africa during the 1996-97 winter season. During the avian flu crisis in Hong Kong last fall, CDC, FDA, and NIH worked with the pharmaceutical industry to begin the development of novel vaccines that could be used to prevent disease due to this strain.

In addition, Rotary International is a private sector partnership that has been instrumental in achieving the outstanding progress in the global polio eradication effort. By the year 2005, Rotary International will have contributed more than \$400 million to polio eradication. But Rotary International does more than just contribute money. In December 1996, I personally witnessed in India how active the Rotary can be in obtaining legislative support and mobilizing participation of over 150,000 Rotarians. Over 120 million children in India were immunized during their national 1996 polio immunization day.

Making Emerging Infections a Priority with Other Nations

Addressing the threat of emerging infectious diseases depends on international cooperation. Our confidence that nations can come together to improve global health has been reinforced by the success of smallpox eradication program as well as current efforts to eradicate polio and guinea worm. These were and are truly global efforts. The U.S. agencies are working with partners on every continent to develop a shared sense of responsibility and mutual confidence in the global effort to combat infectious diseases.

Some of these efforts are conducted through our development assistance program. Over the past year, USAID has continued its effort to strengthen basic public health infrastructures in developing countries and to develop in-country capacity to combat infectious diseases. For Fiscal Year 1998, Congress has allocated an additional 50 million dollars in developmental assistance to further this aim. USAID plans to focus on four new areas, which will be integrated into its on-going health programs. They are: antimicrobial resistance, tuberculosis, malaria, and the improvement of global disease surveillance and response.

U.S. agencies are also engaging other nations in the effort to combat infectious diseases. Many governments view emerging infections as an economic issue as well as a public health issue, because healthy people are more productive and more able to contribute to their country's economy. Moreover, outbreaks can impede economic development by interfering with tourism and trade. Since 1995, emerging infectious diseases has become an agenda item at several bilateral and multilateral meetings.

For example, in 1997, at the Denver Summit, the Group of Eight industrialized nations, including the United States, pledged to help develop a global disease surveillance network, coordinate international response to outbreaks of infectious

disease, and help build capacity to prevent, detect, and control emerging infectious diseases. In addition, some members of the Asian-Pacific Economic Cooperation (including Thailand, Indonesia, Philippines) have developed an emerging infectious disease communications network that tracks cases of multi-drug resistant tuberculosis. Bilateral talks that cover emerging infectious diseases have also been held with India, Japan, South Africa, the Russian Confederation, and the European Union.

Working through the Trans-Atlantic Agenda with the European Union, U.S. agencies and EU member countries have begun to share surveillance data on *Salmonella* infections, a major cause of food poisoning. This is an especially important project, in view of the globalization of the food supply, the increasing recognition of multinational disease outbreaks, and the disturbing occurrence of *Salmonella* infections that are resistant to many drugs. The long-term aim of the US-EU project is to expand the *Salmonella* network to cover other food-borne diseases and include other developed countries, outside Europe and North America.

Under the US-South Africa Binational Commission, U.S. agencies are working with the South African Department of Health to train personnel in surveillance and applied epidemiology. The Mandela government is committed to extending the South African public health infrastructure to include the entire country.

Through the US-Japan Common Agenda and the U.S.-Japan Cooperative Medical Science Program, United States and Japanese scientists have held three international conferences on infectious disease research and science policy. As the first follow-up action to the July 1996 meeting in Tokyo of the Common Agenda ERIDS Working Group, a team from CDC and FDA was invited to Tokyo to participate in an investigation of outbreak of *E. coli* O157:H7. Japan has sent one of its scientists to CDC for long-term training in epidemiologic investigations. The level of engagement between the U.S. and Japan on infectious diseases and related issues is substantial and growing. In addition, under the auspices of the U.S.-Japan Common Agenda ERIDS Working Group, NIAID is working with Japan to develop an action plan to address the public health problem posed by *E. coli* O157:H7. A meeting of NIH, CDC and Japanese scientists was held in Baltimore in 1997 to discuss research advances and opportunities to learn more about this shiga-like toxin that causes the lethal hemolytic-uremic syndrome seen in outbreaks of food-borne diseases.

USAID, CDC, and FDA are also providing assistance to the Russian Federation and the Newly Independent States. In some of these States, there has been a significant breakdown in public health services since the fall of the Soviet Union. Resurgences of vaccine-preventable diseases (such as diphtheria, polio, and whooping cough) have been reported. For example, while I was visiting with the Russian Minister of Health in 1995, he received a report of 33 new cases of polio in

Chechnya, during the height of the political instability. The CIsET agencies are working under the umbrella of the Gore-Chernomyrdin Commission to strengthen epidemiological capacity in Russia, improve vaccine quality control and to help prevent the further spread of tuberculosis, STDs, and HIV/AIDS, which are now at epidemic levels. The Gore-Chernomyrdin Commission have its next meeting in Washington, D.C. next week--March 10 and 11. At that time, we expect to agree on next steps on a number of fronts.

A Demonstration Project

I'd like to leave you with a special illustration that demonstrates what can be accomplished when international partners pool their resources and expertise.

In the Sub-Saharan countries of Burkina Faso, Cameroon, Chad, Mali, Niger, and Nigeria, seasonal outbreaks of meningitis occur every 2 to 4 years, causing high morbidity and mortality in older children and young adults. In 1996, there were about 154,000 cases of meningitis and 20,000 deaths in the largest meningitis epidemic yet recorded. To prevent a predicted recurrence in 1997, several CIsET agencies encouraged WHO and other partners to help prepare local public health workers for the next meningitis season. The CDC-based WHO Collaborating Center for Control of Epidemic Meningitis provided the technical lead.

The project involved five U.S. government agencies (CDC, FDA, NIH, USAID, DOD); several non-governmental organizations (Medecins Sans Frontieres, CARE, Epicentre, and the Fondation Merleux); three WHO offices; and three vaccine manufacturers. In addition, two other WHO Collaborating Laboratories -- in Oslo and Marseilles -- supplied diagnostic reagents and provided training in laboratory diagnostics in the affected countries. Major funds were provided to WHO by the British Overseas Development Agency and the Government of Japan.

The meningitis project was initiated in summer 1996. The number of cases in the "meningitis belt" countries was reduced from approximately 154,000 since the winter of 1995-96 to 60,000 in the winter of 1996-97. We must interpret this result with some caution, as some of the dramatic decline may be attributable to natural variation in disease patterns, as well as to improved detection and control. Nevertheless, the project strengthened human and technical resources in the affected countries, and forged on-going links among many international partners.

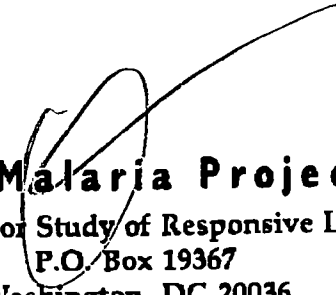
Conclusions

I am proud of the interagency work that has moved this policy and accomplished so much in such a short time. I believe that the U.S. position of leadership should be fostered, for the sake of our people and for the sake of the global community.

Promoting the international effort to combat emerging diseases is a natural role for the United States, and one that benefits people everywhere. The Ciset process has proved to be an excellent vehicle for getting this effort underway.

We must not stop now. The challenges ahead demand our continued attention. Our goal is to ensure that we are able to protect ourselves and the global community from emerging pathogens, whenever and wherever they may arise.

Thank you for the opportunity to testify before the Subcommittee. I will be happy to answer any questions you may have.



The Malaria Project

Center for Study of Responsive Law

P.O. Box 19367

Washington, DC 20036

29 September, 1998

By fax: Tom Friedman, (202) 456-7431, 2 pages total

Dear Tom -

I am writing to forward you a letter from the American Society of Tropical Medicine and Hygiene, inviting the President to address the annual meeting of the Society in Puerto Rico on October 19, 1998. Ralph Nader (in whose office I work) will be addressing the Society, as will be Dr. Anthony Fauci, the Director of the National Institute of Allergy and Infectious Disease. For both those speakers, the primary focus will be malaria.

The Society's meeting is an *unparalleled* opportunity for the President to throw his weight behind American efforts to promote global health, and to take a diplomatic initiative that can leave a profound, salutary mark on foreign relations with the third world. By announcing new funding for tropical disease research, the President will hold out a gesture of goodwill that is sure to be warmly greeted in most countries of the world, and he will reinforce the efforts of his allies such as Prime Minister Blair, who announced a further £60 m toward malaria research this year.

The timing is ideal. In this year the G-8 leaders called for action against malaria; Dr. Gro Harlem Brundtland made her plan to "Roll Back Malaria" the number one priority of the WHO; the First Lady warned about malaria in her address to the World Health Assembly; and the President mentioned malaria in an address in Uganda. It is now time to honor the scientists and doctors who work on the disease, and give them adequate resources to translate this rhetoric into reality.

There is no political downside. There is only the opportunity to be credited with a gesture of unequalled magnanimity, for the 500 million people who will be sickened by malaria this year.

Goodness knows that Ralph Nader would be delighted to congratulate the President on a decision to significantly increase funding for malaria research and control; and the Malaria Project, which is well connected with scientists and the international press, would help publicize the same.

Please give the Society's proposal serious consideration, and do not hesitate to call me in Washington (202/387-8030) or in Vancouver (604/258-7333) if I may be of help.

Sincerely,



Dr. Amir Attaran
Malaria Project Director



AMERICAN SOCIETY OF TROPICAL MEDICINE AND HYGIENE

ASTMH Headquarters • 60 Revere Drive • Suite 500 • Northbrook, IL 60062 • 847/480-9592 • FAX 847/480-9282

September 28, 1998

The Honorable William J. Clinton
President
The White House
Washington, DC 20500

Dear President Clinton:

On behalf of the American Society of Tropical Medicine and Hygiene (ASTMH), I am writing to extend an invitation to you to speak at our upcoming 47th Annual Meeting in San Juan, Puerto Rico October 18th through 22nd. We would be pleased to have you address the meeting during the opening session on October 19th.

Approximately 1,500 ASTMH members are expected to attend the meeting which will feature presentations by Ralph Nader on "Health as a Human Right", and Dr. Anthony Fauci of the National Institute of Allergy and Infectious Diseases (NIAID) on "Global Health, the NIAID, and the 21st Century." Other topics which will be addressed during the meeting include the control of malaria, a major cause of death in Africa; the emergence of tropical infectious diseases as health problems in the United States; bioterrorism threats and possible responses; and new approaches to controlling food- and waterborne infectious diseases.

ASTMH, founded in 1903, is a professional society of researchers and practitioners who are dedicated to addressing the growing global threat of tropical infectious diseases through research and education. ASTMH members work closely with colleagues in Latin America, Africa and Asia in partnership to improve the scientific and public health infrastructure in these regions. It is likely that many scientists from these areas will also be in attendance at the meeting.

Your participation in this meeting would be of interest given the recent discussion on malaria at the G8 summit and the launch of the World Health Organization's "Roll Back Malaria" plan. The United States has been a leading partner in the international collaborative research project, the Multilateral Initiative on Malaria. A strong commitment by the U.S. to aggressively continue research efforts on tropical infectious diseases, such as malaria, is essential to our national security. As you well understand, the increased mobility of our society puts us all at risk from these deadly diseases.

We hope that you will be able to join us in Puerto Rico. Please do not hesitate to have your staff contact me at (617) 432-1563 or dfwirth@hsph.harvard.edu if you have questions or need more information. I appreciate your consideration of this request.

Sincerely,

Dylan Wirth
Dylan Wirth, Ph.D.
President-elect

Total Pages: 16

LRM ID: REJ600

EXECUTIVE OFFICE OF THE PRESIDENT
OFFICE OF MANAGEMENT AND BUDGET
Washington, D.C. 20503-0001

Wednesday, September 23, 1998

LEGISLATIVE REFERRAL MEMORANDUM

TO: Legislative Liaison Officer - See Distribution below

FROM: Jeffrey A. Weinberg (for) Assistant Director for Legislative Reference

OMB CONTACT: Ronald E. Jones *RJ*

PHONE: (202)395-3386 FAX: (202)395-3109

SUBJECT: JUSTICE Views on S2110 Violence Against Women Act II

DEADLINE: Noon Friday, September 25, 1998

In accordance with OMB Circular A-19, OMB requests the views of your agency on the above subject before advising on its relationship to the program of the President. Please advise us if this item will affect direct spending or receipts for purposes of the "Pay-As-You-Go" provisions of Title XIII of the Omnibus Budget Reconciliation Act of 1990.

COMMENTS: Sen. Biden's staff has asked for Justice's views. The department plans an informal transmittal of these views early next week.

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FAX RETURN of **pages, attached to this response sheet**

FAX RETURN of 10 **pages, attached to this response sheet**

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MEMORANDUM

This memorandum provides the preliminary views of the Department of Justice on S. 2110, the Violence Against Women Act II. The Department may provide additional views on sections not addressed by this memorandum at a later date.

Section 2: Definitions

The Department strongly recommends that the definition of domestic violence in section 2003 of VAWA be amended to include dating relationships and encourages the use of language such as "social relationship of a romantic or intimate nature". This language has been proposed in the House VAWA II bill, and is consistent with the proposed technical amendments that the Department has submitted to the Senate that would expand the definition of "spouse or intimate partner" in 18 U.S.C. §2266 in order to cover dating relationships under the federal criminal offenses created by VAWA. The need for including dating relationships in the definition of domestic violence is amply supported by Bureau of Justice Statistics (BJS) data that indicate that domestic violence is a significant issue among young persons aged 16-19 and among non-married partners in general. See "Violence by Intimates," Bureau of Justice Statistics, March, 1998.

Further, this change would be consistent with and ensure the effectiveness of other provisions of S. 2110. Section 106 authorizes grants to reduce violent crimes against women on campus, including domestic violence, but does not provide a separate definition of domestic violence. The current definition in section 2003 of VAWA does not specifically include the kind of intimate, romantic relationships that predominate on campus. By covering only current or former spouses, or those who cohabitate as spouses or have children in common, the statute excludes the vast majority of domestic violence crimes against women on campus. The proposed change is therefore needed if the grants authorized under this section are to be effective in combating violence against women on campus. Similarly, section 401 of S. 2110, which supports education and training of health professionals, defines domestic violence to include "woman battering" and "partner abuse". Programs established under section 401 thus would cover a broader range of domestic violence than would programs established under the original VAWA, an inconsistency that should be resolved in favor of the more inclusive approach to protection and assistance to victims of violence.

Finally, the term "sexual assault" as used throughout the legislation is defined either underinclusively or not at all. When defined, it refers solely to offenses under chapter 109A. However, trafficking of women and minors for prostitution (see chapter 117) are sex crimes as well. These crimes should be included in the definition of sexual assault. This definition should be made clear in Section 201, which provides for legal assistance to victims of sexual assault. Sections 401 and 402 also do not define sexual assault.

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Title I Strengthening Law Enforcement to Reduce Violence Against Women

Section 101. Improve Full Faith and Credit Enforcement of Protection Orders

Section 101 would amend Part U of Title I of the Omnibus Crime Control and Safe Streets Act of 1968, 42 U.S.C. § 3796hh et. seq. to enable states to improve widespread enforcement, including interstate enforcement, of protection orders by directing technical assistance and funding to police departments, prosecutors, and courts, including funding for computerized communications systems. This section would amend and rename the Grants to Encourage Arrest Policies program to make interjurisdictional enforcement of protection orders a funding priority, authorize funding for technical assistance, computer and other equipment; instruct the Department to develop and disseminate practices; and identify protection order data base development as a funding priority. The section would require the Attorney General to disseminate information about successful data collection and communications systems.

The Department supports the goals of this section, but would like it to be redrafted specifically to include Indian tribal jurisdictions so as to be consistent with the full faith and credit provision of VAWA. Our specific concerns are as follows:

Section 101(a)(2) does not address the issues of cross-jurisdictional enforcement between tribal jurisdictions and between tribal and state jurisdictions.

Section 101(a)(3)(A)(ii) should be amended to include tribes. Section 101(a)(3)(A)(iii) should be amended to include tribes after the reference to "other States".

The Department opposes the proposal in subsection (A)(iii) to add paragraph (4) to the priority areas of the Grants to Encourage Arrest Policies Program. Exclusive priority should not be given to technology grants. While technology is an important component of jurisdictions' ability to accord full faith and credit to protection orders, other components are of equal importance, such as extensive training of law enforcement, judges, other criminal justice personnel, and domestic violence victim advocacy organizations.

The Department strongly supports the purposes of section 101(b)(1), and recommends the following modifications to ensure that the goals of this provision are realized. The proposed subsection (d) would make clear that a state must enforce a foreign protection order whether or not the order has been registered or filed in the enforcing state. Some jurisdictions require the registration of foreign orders as a precondition to their enforcement. The proposed language attempts to clarify that the full faith and credit provision of VAWA, 18 U.S.C. §2265, cannot be construed to require registration. However, since the statute does not refer to registration, the issue is not one of construction but rather one of imposing additional requirements that the statute facially does not require. Therefore, we recommend the following language in order to

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avoid any ambiguity:

It is not a condition for according full faith and credit to and enforcing a protection order under this section that the order be registered or filed in the enforcing State or Indian tribe.

Similarly, this section attempts to preclude states and tribes from notifying a batterer that a foreign protection order has been registered or filed in their jurisdiction. The goal is an important one. Victims of domestic violence who flee across state or tribal lines to escape abuse should not be required to disclose their whereabouts to their abusers. Technical requirements in some jurisdictions presently force victims to choose between protection from the criminal justice system and maintaining the confidentiality of their location.

The language of the proposed section, however, does not clearly prohibit states from adopting such notification requirements. By stating that "nothing in this section can be construed to permit" notification, the language allows states to require notification based on any authority other than VAWA. If this section intends to prohibit mandatory notification of abusers, as we believe it should, then we propose the following alternative language:

A State or Indian tribe shall not notify the party against whom the order has been made that a protection order has been registered or filed in that State, unless requested by the party protected under the order.

Allowing victims to elect to send official notification of registration to the abuser enables those victims whose location is known to the abuser, such as those working in a neighboring state or moving to live with a relative known to the abuser, to convey to the abuser that the order will be enforced in the other jurisdiction.

We support the proposed section (e), but also urge a stronger formulation for similar reasons. We would eliminate the reference to the statute's construction and state clearly as follows:

Any protection order that is otherwise consistent with this section shall be accorded full faith and credit and enforced, notwithstanding the failure to provide notice to the party against whom the order is made of its registration or filing in the enforcing State or Indian tribe.

Section 102. Enhance the Role of Courts in Combating Violence Against Women

The Department supports the inclusion of the court systems in the STOP grants allocations in section 102(a)(1) and an independent allocation for courts and increased allocation

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for victim services under section 102(a)(2). We support section 102(d) and the amendment of this program specifically to include courts, and support a five percent minimum tribal set-aside with a reallocation provision. We are concerned, however, that a deadline of nine months does not allow sufficient time for the application process and a minimum period of 12 months would be more appropriate.

Section 103. Reauthorizes STOP Grants through 2002

Section 103 would amend section 1001(a)(18) of Title I of the Omnibus Crime Control and Safe Streets Act of 1968, 42 U.S.C. § 3793(a)(18), to reauthorize the STOP Grant Program at \$185 million per year through 2002.

The Department strongly supports reauthorization of the STOP Grants program, but opposes the flat funding levels of this provision because they do not allow for continued growth and expansion of the STOP program. The language authorizing amounts for 2002 should be revised to provide for an annual increase to allow states, local governments, and Indian tribal governments to build on projects funded in prior years.

The Department supports section 103(c), which provides that 2% of the STOP funds are to be set aside for State Coalitions. The State Coalitions play a valuable role in accomplishing the goals of VAWA and are also an important resource for the Department.

The Department strongly supports the reallocation provisions; however, a deadline of 12 months into the fiscal year is unreasonable, given the processes that states have in place to award subgrants. The structure of the VAWA encourages the states to engage in a strategic planning process with victim advocates, which realistically requires some time. Many states use a competitive process to select recipients of subgrants, which they cannot initiate until they receive their annual STOP award. In the best-case scenario, if Congress appropriates funds in October and the Violence Against Women Grants Office (VAWGO) awards the STOP grants in November, the states will begin their planning process in December (which is likely to extend through January, given the holidays), issue a subgrant solicitation in February or March, allow 45-60 days for local jurisdictions to respond, set a deadline for submission of applications in May or June (the ninth month of the fiscal year). The time frame proposed in section 103(d) does not give states enough time to evaluate the quality of the applications received and make funding decisions.

The Department supports section 103(e)'s clarification of the kinds of assistance that can be funded through the STOP program and supports the restriction in this section that excludes services for batterers from the definition of "victim services".

Section 105. Reauthorization of Grants to Encourage Arrest Policies

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Section 105 would amend section 1001(a)(19) of Title I of the Omnibus Crime Control and Safe Streets Act of 1968, 42 U.S.C. § 3793(a)(19) to extend the expired DOJ direct grant program through 2002 with a flat annual authorization. As with the STOP Grants program, the Department is concerned about the flat level of funding. Such funding does not allow for continued growth and expansion of the program. The authorized amounts for years 2001 and 2002 should provide for annual increases to enable additional states, local governments, and Indian tribal governments to initiate projects and previous or current grant recipients to enhance projects funded in prior years.

Section 106. Grants to Reduce Violent Crimes Against Women on Campus

The Department supports the goals of this provision, but recognizes it would require additional overhead for administration. We also reiterate our concerns, set forth under Section II, above, regarding the need to expand the definition of "domestic violence" to cover dating relationships if the campus grants program is to be effective in addressing domestic violence against women on campus.

Within the text of the new section 2601 that is proposed to be added to the Omnibus Crime and Safe Streets Act of 1968, the language of the proposed section 2601(b) allows grants to be used for data collection, but the wording "data collection, and other equipment" leads to unnecessary ambiguity as to what is intended. The language should be modified to make clear that data collection activities may be funded.

The Department strongly opposes the deadline of 60 days from application receipt to award. Discretionary grants administered by VAWGO are generally peer reviewed by a panel of outside experts, which adds quality control, objectivity, and time to the award process. As a result, a period of at least 120 days is required.

The Department supports the proposed section 2603 (a), with one modification. The Attorney General has the authority to direct, not simply *request*, as stated in this section, the Department of Justice and its components to provide the types of assistance to campuses detailed in this provision. The provision should be modified to clarify this point.

The Department strongly opposes any requirement that the Attorney General issue regulations or guidelines as directed in proposed section 2603(b). Regulations or guidelines are not necessary, because sufficient guidance can be provided in the application materials. The publication of regulations significantly slows down the grant award process. If, however, this requirement is retained, the issue of what is meant by "geographic size" in the context of campus grants should be clarified. If this language is intended to ensure funding for rural or small town universities, which may be much larger than urban colleges, then it should so state, and it should

DRAFT - FOR DISCUSSION PURPOSES ONLY

make clear that the size of the campus is irrelevant. If the language is intended to ensure that a range of kinds of schools are funded, then it should state clearly the criteria to be used.

Section 108. Hate Crimes Prevention

Section 108 would amend provisions of the federal hate crimes law 18 U.S.C. § 245 to permit federal prosecution for crimes based on gender, sexual orientation, and disability. The section would require the United States Sentencing Commission to study the issue of adult recruitment of juveniles to commit hate crimes and to amend sentencing guidelines to provide sentencing enhancements for such adults. This section would provide for grants by the Office of Juvenile Justice and Delinquency Prevention to combat hate crimes committed by juveniles and for funds for additional personnel to respond to such crimes.

The Department strongly supports this provision.

Section 109. Reauthorization of Rural Domestic Violence and Child Abuse Enforcement Grants

The Department fully supports continued reauthorization of this grant program, but notes that the funding level of \$35 million through 2002 is set too low. The proposal in this section does not allow for continued growth and expansion of the program. The authorized amounts for years 1999 through 2002 should provide for annual increases to enable additional jurisdictions and Indian tribal governments to initiate projects, and previous or current grant recipients to enhance the projects funded in prior years.

The Department supports the five percent set-aside for tribes with a clause allowing funds to revert to the general applicant pool if there are an insufficient number of qualifying and viable applications from Indian tribes. Currently, between six and seven percent of all program funds in VAWA discretionary grant programs, including the Rural Program, are awarded to tribes. The nine-month deadline for reallocation is too short for reasons stated above.

Finally, the Department strongly encourages inclusion of a new definition of "rural," as we have previously proposed. Some states, including Kentucky and West Virginia, are not categorized as rural states because, although they have large rural populations, they also have large population centers that disqualify them under the current definition. To address this problem, the Department recommends that the Rural Program be amended to strike the current definition of rural state (based on 42 U.S.C. 3796bb(B)), and insert a new definition that comports more closely with current demographics.

Section 111. Amendments to Domestic Violence and Stalker Offenses

DRAFT - FOR DISCUSSION PURPOSES ONLY

The Department strongly supports the proposed amendments to the criminal provisions of VAWA. We note with concern, however, that our proposed amendment to the definition of "spouse or intimate partner" in 18 U.S.C. 2266 has not been included. The Department has recommended amending this provision in order to remedy its exclusion of certain types of intimate relationships where domestic violence crimes frequently occur. Our proposed amendments focus on including "substantial dating relationships" in order to prosecute violent intimate partners who are presently beyond the reach of the statute because they are not married, do not cohabit, and do not have children in common.

In addition, we urge the inclusion of several amendments to 18 U.S.C. §§2261A, 2262, 2265 and 2266 to assure that the statutory provisions are clear as to their application in the context of Indian lands and effectively achieve the goal of addressing violence against women in Indian country.

We propose amending 18 U.S.C. 2261A by striking "A" on line 11 through "country" on line 13, and inserting the following, "Whoever travels across a State line, enters or leaves Indian country, or within the special maritime and territorial jurisdiction of the United States". Some questions have arisen as to whether this section applies to Indian country. Adding this phrase clarifies the applicability of this statute to travel within Indian country.

While tribal courts lack criminal adjudicatory jurisdiction over non-Indians, United States v. Oliphant, 435 U.S. 191 (1979), they do have civil jurisdiction over non-Indians living on tribal lands and over the activities of non-Indians entering into consensual relations with tribal members within Indian reservations. This jurisdiction includes the issuance of civil protection orders in the interests of the health and welfare of the tribe. In addition, these orders should be entitled to full faith and credit. We propose amending 18 U.S.C. 2265 by adding the following new subsection:

(d) For purposes of this section, tribal courts shall be deemed to have jurisdiction over persons and activities occurring on lands within the tribal government's territory.

We also recommend an amendment to the definition of "spouse or intimate partner" contained in 18 U.S.C. 2266, by inserting "or Indian tribe" after "laws of the State." Indian tribes, as a function of their inherent sovereignty and powers of self-government, enact laws against regarding domestic relations and family violence. See 25 U.S.C. 1901(5) (congressional finding that the state "judicial bodies ***have often failed to recognize the essential tribal relations of Indian people and the cultural and social standards prevailing in Indian communities and families.") This proposed amendment clarifies that the laws of an Indian tribe may be relevant in determining who is recognized as a spouse or intimate partner for the purposes of VAWA.

DRAFT - FOR DISCUSSION PURPOSES ONLY

Finally, we propose an amendment to 18 U.S.C. 2266 to address the situation when an individual travels from one reservation to another adjacent reservation and otherwise violates the criminal provisions of VAWA. There are areas of Indian country, where crimes may occur while crossing from one tribe's jurisdiction into another, without technically leaving Indian country. We would recommend 18 U.S.C. 2266 be amended by adding at the end the following:

"Enters or leaves Indian country" includes leaving the jurisdiction of one tribal government and entering the jurisdiction of another tribal government.

Title II Strengthening Services to Victims of Violence

Section 201. Legal Assistance and Attorney Volunteers

Section 201 would help victims of domestic violence gain access to appropriate legal assistance by expanding the pool of trained and available attorneys and lay advocacy services, particularly pro bono legal services. This section would authorize an existing grant program for direct legal assistance to domestic violence victims. The proposed authorized annual appropriation is \$20 million through 2002.

The Department strongly supports the grant program created by section 201(a). However, we strongly oppose section 201(b), which would require the Attorney General to "establish, operate and maintain" a centralized, national network of attorneys to help victims of domestic violence. This section, although reflecting a worthy goal, is quite problematic.

The bill would authorize the Attorney General to spend up to \$5 million of the \$20 million authorized under Section 201 to set up and run a nationwide network of attorneys to provide legal assistance to domestic violence victims by "facilitating" designation, appointment, or assignment of qualified providers; identifying, recruiting, and training qualified pro bono and low cost providers; and coordinating with existing legal networks and domestic violence assistance programs.

There is little question that a significant need exists for legal assistance to domestic violence victims. Help is needed, and is not widely available, in obtaining protection orders, and in a range of other areas of law (e.g., housing, divorce, custody, employment) for problems stemming from domestic violence. The grant program will clearly help increase the availability of civil legal assistance. The question is whether the need for additional legal resources is best addressed through a centralized, nationwide network of providers, and whether the Department of Justice is the most appropriate institution to manage such a network. We believe it is not. A centralized national system of lawyers is not optimal, and the Department of Justice is, in any event, not an appropriate entity to establish and operate such a system.

DRAFT - FOR DISCUSSION PURPOSES ONLY

This provision would require that the Department of Justice establish a national network of lawyers and legal assistance. Legal services, however, particularly for individual clients, are almost always provided at a local level. Lawyers are licensed at the state level, and generally tend to practice in limited geographic areas. Applicable law and procedures derive from state or local, not national, rules. The need for -- and availability of -- lawyers is a function of local conditions. These circumstances are not compatible with the concept of a national network of providers. Finding an attorney (paid or pro bono) for an individual case involving an individual victim in a small town in a rural area, for example, is not something that can be organized or operated effectively from Washington.¹ This is particularly likely to be true in cases involving domestic violence, where the need for legal help is often urgent.

Not only is it difficult to determine local availability from Washington, it also is very difficult to monitor qualifications of individuals. It is troublesome enough for those in the local community to determine whether a particular practitioner is qualified; it is virtually impossible for a centralized, national network to do so.²

Similarly, supervision of pro bono attorneys, which is critical to the delivery of quality legal services, is not contemplated by the legislation nor provided in the limited funding set aside for this program. Supervision, to be effective, would have to occur at the local level, by qualified, trained, experienced attorneys able to commit a substantial amount of time to the task."

Even if a centralized, national network of providers were considered to be an effective mechanism for ensuring adequate legal assistance to domestic violence victims, the Department of Justice would not be the appropriate entity to establish, operate, or maintain it. The federal government should not be placed in a position of appearing to put its imprimatur on individual attorneys. Giving a federal agency the responsibility for maintaining a network of attorneys and for facilitating designation, appointment or assignment of qualified lawyers could possibly subject it to liability for poor service. It could also be subject to liability for failure to place someone on any lists that it kept.

Furthermore, the Department of Justice, as the primary litigator for the United States and its agencies, should not be put in a position to make judgments about the quality of specific

Even the Legal Services Corporation administers an extremely decentralized program. It primarily provides funds for local organizations to use on locally-set priorities.

Attempts have been made, by the American Bar Association and others, to develop national networks of pro bono lawyers to handle certain types of cases. To our knowledge, no independent evaluation has been made of the effectiveness of such programs, nor of their effectiveness of handling the kinds of cases for which domestic violence victims will need representation.

DRAFT – FOR DISCUSSION PURPOSES ONLY

attorneys. There is a potential for conflicts of interest, real or perceived.

In our view, it would be much more effective to provide grants to local (or state-wide) entities to provide civil legal services, rather than requiring the Attorney General to develop and operate a national network with a portion of the money authorized under Section 201. The subsection (a) grant program serves largely the same goals as subsection (b): to increase the available legal services available to domestic violence victims. That grant program should be used to provide funds to programs, such as legal services programs, pro bono programs,³ law schools and others, that can help increase the amount of legal assistance at a local or state level.

There may be pieces of the program proposed in subsection (b) to which the Department could usefully contribute, if these pieces were retained as part of a revised section. For example, in addition to funding the expansion of available civil legal assistance through the subsection (a) grant program, the Department could provide (directly or through grants) technical assistance and training to ensure that lawyers who are providing civil legal assistance for domestic violence victims across the country have the proper background. The Department could also recognize accomplishments as per subsection (b)(2)(C).

It is important to recognize that a network of attorneys to help provide civil legal services for domestic violence victims already exists to a considerable degree through the Legal Services Corporation and its grantees. Adequate funding of those programs, which employ attorneys experienced in many of the areas in which domestic violence victims need legal assistance (e.g., housing, employment, family law), and encouragement of collaboration between these attorneys and their local domestic violence victims' advocacy organizations, would be among the most effective ways to meet those needs.

Section 204. National Domestic Violence Hotline

Section 204 would amend section 316(f)(1) of the Family Violence Protection and Services Act, 42 U.S.C. § 10416(f)(1), to increase and extend authorization to meet the growing demands on the National Domestic Violence Hotline established by VAWA to 2002. The Department supports this provision.

Section 205. Federal Victims' Counselors

Although pro bono assistance should be a part of the mix of available services, there is some feeling that it cannot realistically be relied upon to meet a substantial part of the need in this area. Domestic violence cases often need to be handled on an emergency or expedited basis, are expensive, and are emotionally complicated. These factors may make it particularly difficult to find effective and timely pro bono assistance.

DRAFT - FOR DISCUSSION PURPOSES ONLY

Section 205 would amend section 40114 of the Violent Crime Control and Law Enforcement Act of 1994 (P.L. 103-322; 108 Stat. 1910) to reauthorize the expired VAWA program for appointing Victim/Witness Counselors for the prosecution of sex crimes and domestic violence crimes. The proposed authorized annual appropriation is \$1 million through 2002. The Department strongly supports this provision.

Section 208. Battered Immigrant Women

The Department supports the provisions of subsection (d)(1) and (d)(2) that would both insulate petitioners from loss of status by their citizen or resident spouse or parent and allow petitioners to benefit from any positive reclassification of status. We would prefer, however, that the reclassification of a petitioners status not be automatic. The onus should be on the petitioner to inform INS of any changes in the status of her citizen or resident spouse or parent. We note that the definition of "immediate relative" found at INA section 201(b)(2)(A) should be amended to conform with subsection (d)(1).

The Department supports Section 208(c), which would allow recipients of Legal Services Corporation (LSC) funding to use non-LSC funding to provide legal assistance to alien victims of domestic abuse.

We support the intent of subsection (o)(1), clause II, but note that it should conform to the definition of "child" found in the INA. In addition, this provision should require a nexus between the crime, plea or conviction and the abuse, and either an indication on the record of the abuse or evidence that a protection order was issued between the parties. Also, this section should state that the child or children to be included in the suspension/cancellation application must be physically present in the United States at the time of application.

The Department opposes subsection (e)(3) in its current form. It applies to all aliens seeking admission, not just battered alien self-petitioners. This provision should be restricted to persons with approved self-petitions. In addition, like subsection (e)(1), this provision should require a nexus between either the crime, plea or conviction and the abuse, and either an indication on the record of the abuse or evidence that a protection order was issued between the parties.

We support crafting subsection (f)(1) more narrowly to preserve INS's ability to challenge marriages in which both parties are willing accomplices in bigamous marriages, while affording relief to battered "spouses" who unknowingly find themselves in illegal marriages. The references to "intent" and "intended" should be deleted and replaced with "bigamous" in order to avoid any confusion as to whether "intended" refers to fiancées.

The Department strongly opposes the filing of self-petitions with embassies or consulates

DRAFT - FOR DISCUSSION PURPOSES ONLY

overseas. Petitions should be filed via mail with the Vermont Service Center. Adjudication of these petitions has been centralized in the Vermont Service Center for very specific reasons. We have been successful in implementing and monitoring this program because it is based in one location. Adjudicators have received domestic violence training and technical assistance regarding the self-petitioning process. Self-petitions from spouses on overseas military bases therefore should be filed with the Vermont Service Center, in conformity with current self-petitioning procedures.

The provisions of subsection (f)(2) through (f)(8) also should make clear that the battered spouse or child must have resided abroad at the assigned foreign duty station (on or off the base) with the abusive spouse or parent, who is serving in the military on active military duty. This clarification would ensure that the military provisions conform with the regular self-petitioning provisions, which require the self-petitioner and the abuser to have resided together in the United States.

The Department strongly supports amending INA section 245(a) and (c) to enable battered immigrants with approved VAWA self-petitions to remain in the United States while awaiting residency status. The Department supports the provisions of the Senate VAWA II bill that would accomplish that goal, with one small caveat. Since INA section 245(i) continues to apply to petitions approved before January 14, the provision should cover aliens whose petitions are approved on or after January 14, 1998, rather than those approved before, on, or after that date.

We support the provisions that would exempt battered aliens applying for suspension of deportation or cancellation of removal from the 4,000 annual cap.

Although we support the intent of section 208(g)(1) and (2), the Department must oppose this section, which provides for the use of STOP funds to train INS officials and immigration judges. The STOP program was designed for State and local programs only. The Department would welcome the opportunity to work with the Committee to identify other funds that could be used for this purpose.

We suggest amending subsection (j) to clarify that INS is required to collect data only on those suspension/cancellation applicants who are seeking relief under the VAWA-related provisions. We would also suggest that this section specify which District offices are to be sampled.

Section 301. Safe Havens for Children.

The Department Supports the creation of a grant program to enable States and Indian tribal governments to help nonprofits to set up supervised visitation centers. The Department,

DRAFT - FOR DISCUSSION PURPOSES ONLY

however, opposes the requirement in section 301(c)(2) that the Attorney General issue regulations for the Safe Havens grant program. We do not believe regulations will be necessary, as sufficient guidance can be provided in application materials. The publication of regulations significantly slows down the grant award process. In addition, this section refers only to States and does not mention Indian tribes, though tribes are identified as eligible grantees. This should be clarified.

In addition, the Department opposes section 301(d). As drafted, this section will impose on grantees an elaborate and expensive data collection burden that could not be readily met, and which would drain resources from the services intended to be funded. The Department proposes instead that provision be made for evaluation of the quality and impact of services, and that authorized funds be augmented to support such an evaluation.

Finally, the Department supports section 301(e)(3), which sets aside 5 percent of funds for Indian tribal governments, so long as it continues to be accompanied by a reallocation provision. We oppose, however, the 9 month deadline for use of these funds contained in this section. We recommend a 12 month deadline, at minimum.

Section 303. Reauthorization of Runaway and Homeless Youth Grants.

Some victims of crime involve runaway and street youth, some of whom are recruited by pimps for prostitution. Therefore, we support the inclusion of programs providing education, prevention, and rehabilitation of youth prostitutes under this section of the legislation.

Section 409. Research to Combat Violence Against Women

The Department is concerned that the proposed section 40294(a)(1) designates the Secretary of Health and Human Services as the grantmaking authority and limits the Attorney General to a consultative role. They should be given joint authority, as is done in proposed section 40294(b)(1), in order to further the work of both entities in this area. There is no apparent reason for conferring joint authority in subsection (b)(1) but not in subsection (a)(1).

Subsection (d) of this section directs the Secretary of Health and Human Services, "in conjunction with the Attorney General," to make grants for research on pregnancy and sexual assault. It is unclear whether this language confers joint authority or whether it confers primary authority on the Secretary of HHS. If joint authority is intended, then the language should be amended to use the more common formulation, "the Secretary of Health and Human Services and the Attorney General", as in proposed section 40294(b)(1).

We suggest amending subsection (e)(1) by adding at the end, "or any other appropriate component of the Department of Justice."

DRAFT - FOR DISCUSSION PURPOSES ONLY

In addition, this title does not recognize the National Institute of Justice supported violence against women research agenda mandated by Congress in VAWA . This program is being carried out in collaboration with the Centers for Disease Control (CDC).

The Department strongly encourages the continuation of this innovative, multidisciplinary program that effectively responds to the Congressionally mandated agenda. Therefore, we recommend the inclusion of an acknowledgment of the current NIJ multi-year research program and related HHS research, and the inclusion of a permanent authorization for the continuation of this research program. Specifically, we recommend the inclusion in S.2110, of the planned \$5.2 million authorization for FY 1999 (from VAWGO STOP funds) and a \$6.2 million authorization for FY 2000, 2001 and 2002 as planned for the NIJ Violence Against Women Research Agenda. Near equivalent funding was sought by CDC for this joint program.

If the above is not pursued, we recommend the inclusion of language in this section that would state that nothing in this section shall be taken to cause the elimination of existing multi-year projects and programs on violence against women research.

The Department also recommends that the Sentencing Commission Study authorized in this section be done with the involvement of NIJ and the Bureau of Justice Statistics, given their understanding of offender and sentencing data.

Finally, we would suggest including all direct contact sex crimes under chapters 109A, 110, and 117 in the research on violence against women. Some consideration also might be given to the variances in the state determination of age of consent.

We look forward to working with the Committee as it considers these and other issues raised by S. 2110.