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Infectious Diseases

PRESENTED BY AMERICA'S PHARMACEUTICAL COMPANIES

Pharmaceutical Companies Are Developing 136 Medicines, Vaccines to Treat Infectious Diseases

A new PhRMA survey has identified 136 new medicines in development to treat or prevent infectious diseases, humankind's oldest and most persistent enemy.

The Black Death. Diphtheria. Bubonic plague. Childbed fever. Malaria. Polio. Measles. Tuberculosis. Smallpox.

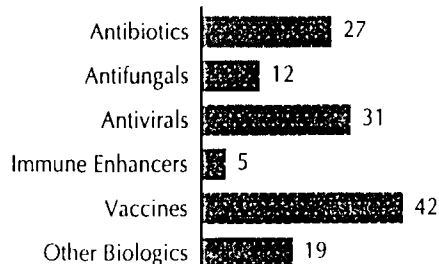
For millions of years, infectious diseases such as these ravaged the earth, killing and crippling children and adults, baffling scientists and eluding cures. Beginning with the first successful vaccination—against smallpox in 1796—humankind began to fight back against the microbes, or disease-causing germs. By the 1940s, pharmaceutical companies succeeded in mass-producing penicillin, saving the lives of thousands of soldiers who would otherwise have died from wounds suffered on the battlefields of World War II and ushering in "the age of antibiotics." Vaccines, antibiotics and other medicines began to banish the dread diseases of the past to history books. Pneumonia, tuberculosis, syphilis, diphtheria, whooping cough, and measles—leading disease killers of the 1920s—were either under control or virtually eradicated. These innovations meant that infected limbs didn't have to be amputated, that a ruptured appendix didn't mean death, that the iron lungs confining polio victims were relegated to medical museums.

In the late 1960s, U.S. Surgeon General William Stewart said we could "close the book" on infectious diseases—a prediction that turned out to be merely wishful thinking. In fact, current Surgeon General David Satcher recently told Congress that deaths from infectious diseases rose 22 percent between 1980 and 1992—not counting AIDS deaths. Dr. Satcher described "a global resurgence of infectious diseases"—from emerging infections such as avian flu virus and from the re-emergence of diseases that have become resistant to available antibiotics.

The medicines and vaccines now in development by 78 pharmaceutical and biotechnology companies provide new weapons against both new and ancient infectious diseases. Among these medicines, now either in human clinical trials or awaiting approval by the Food and Drug Administration, are:

- the first in a new class of antibiotics which, in clinical trials, proved effective against severe infections that were resistant to existing antibiotics;
- the first vaccine for prevention of cervical cancer and genital warts caused by human papillomavirus;
- the first oral treatment of hepatitis B, which affects more than 100,000 Americans per year and is a major cause of liver cancer;
- a flu vaccine administered via a nasal spray;
- a two-week—as opposed to six-month—drug treatment for tuberculosis, which could improve compliance with the treatment regimen and save some of the 3 million lives lost worldwide to this disease;

MEDICINES IN DEVELOPMENT FOR INFECTIOUS DISEASES



- a vaccine to prevent ear infections, which afflict 85 percent of all children before the age of three and cost more than \$3 billion a year to treat;
- a new drug for severe pediatric meningococemia, a deadly disease that occurs when the meningitis bacteria enters the bloodstream;
- a new "edible vaccine" for traveler's diarrhea using raw potato. Edible vaccines enter the body through the stomach—where mucosal tissues, which make up 75 percent of the body's immune system, are found.

The medicines include 27 antibiotics to fight such bacterial infections as "staph" in low birthweight infants, periodontal disease, bronchitis, pneumonia, urinary tract infections, diabetic foot ulcers, ear infections, tuberculosis, meningitis and others; 12 antifungals to treat diseases such as candidiasis and cryptococcosis, opportunistic infections that attack the weakened immune system of AIDS patients; 31 antivirals to treat such virus-borne diseases as hepatitis, genital herpes, and influenza; 5 immune enhancers to bolster the body's resistance to such diseases as hepatitis and herpes; and 42 vaccines to prevent such infections as avian flu virus, Epstein-Barr virus (which causes infectious mononucleosis), Lyme disease and respiratory syncytial virus (RSV), which kills more than 4,500 children under five in the U.S. annually.

All together, infectious diseases claim more than 100,000 American lives each year and cost more than \$30 billion in direct treatment expenses alone. The 136 medicines and vaccines currently being developed by America's pharmaceutical companies provide our best hope of reducing that toll.

Sincerely,

Alan F. Holmer
President
PhRMA

New Medicines in Development For Infectious Diseases

ANTIBIOTICS

Product Name	Company	Indication	Development Status
Altastaph hyperimmune globulin	NABI Rockville, MD	prevention of <i>Staphylococcus aureus</i> infections in low birth weight infants	Phase I/II
Atridox™ 8.5% doxycycline in a biodegradable liquid polymer drug delivery system	Atrix Laboratories Fort Collins, CO Block Drug Jersey City, NJ	chronic adult periodontal disease	application submitted
BAY 12-8039	Bayer Corporation, Pharmaceutical Division West Haven, CT	respiratory tract infections	Phase I/II/III
cefditoren	Tap Holdings Deerfield, IL	adult acute exacerbation of chronic bronchitis adult community-acquired pneumonia adult acute maxillary sinusitis adult and pediatric streptococcal pharyngitis adult uncomplicated skin and skin structure infections pediatric otitis media	Phase III
clinafloxacin (CI-960)	Warner-Lambert Morris Plains, NJ	nosocomial pneumonia sepsis in neutropenia endocarditis intra-abdominal infections complicated skin and skin structure infections resistant pneumococcal infections	Phase III
daptomycin	Cubist Pharmaceuticals Cambridge, MA	bacteremia in endocarditis complicated skin and soft tissue infections	Phase II completed
DepoAmikacin™ amikacin	DepoTech San Diego, CA	bacterial infections	Phase I
GAR-936 glycylcycline	Wyeth-Ayerst Laboratories Philadelphia, PA	infection caused by antibiotic-resistant bacteria	Phase I
HMR 3647 ketolide	Hoechst Marion Roussel Bridgewater, NJ	first-line therapy for respiratory tract infections in children and adults	Phase III
Levaquin™ levofloxacin	R.W. Johnson Pharmaceutical Research Institute Raritan, NJ	acute exacerbation of chronic bronchitis uncomplicated urinary tract infections	application submitted
		community-acquired pneumonia (new pathogens) complicated skin and skin structure infections febrile neutropenia nosocomial pneumonia	Phase III
linezolid (oxazolidinone antibiotic)	Pharmacia & Upjohn Bridgewater, NJ	gram-positive infections (skin and soft tissue, pneumonia)	Phase III

ANTIBIOTICS

Product Name	Company	Indication	Development Status
LY33328 diphosphate (semisynthetic glycopeptide)	Eli Lilly <i>Indianapolis, IN</i>	gram-positive bacteria infections vancomycin- and teicoplanin-resistant enterococci methicillin-resistant <i>Staphylococcus aureus</i> methicillin-resistant coagulase-negative staphylococci penicillin-resistant <i>Streptococcus pneumoniae</i>	Phase II
Maxaquin™ lomefloxacin HCl	Unimed Pharmaceuticals <i>Buffalo Grove, IL</i>	chronic bacterial prostatitis	Phase III
MiKasome amikacin liposome injections	NexStar Pharmaceuticals <i>Boulder, CO</i>	nosocomial (hospital-acquired) pneumonia stable pseudomonas-colonized cystic fibrosis complicated urinary tract infections	Phase II
MK826	Merck <i>Whitehouse Station, NJ</i>	bacterial infections including urinary tract, lower respiratory tract and abdomen	Phase II
Neuprex™ rBPI-21 (recombinant bactericidal/permeability increasing protein)	XOMA <i>Berkeley, CA</i>	complications due to severe traumatic blood loss meningococemia	Phase III
		adjuvant in severe intra-abdominal infections complications following partial hepatectomy	Phase II
		adjuvant in lung infections in cystic fibrosis patients	Phase I
nitazoxanide	Unimed Pharmaceuticals <i>Buffalo Grove, IL</i>	cryptosporidiosis	Phase III
pexiganan acetate	Magainin Pharmaceuticals <i>Plymouth Meeting, PA</i>	infection in diabetic foot ulcers	application submitted
Primisol® trimethoprim hydrochloride oral solution	Ascent Pediatrics <i>Wilmington, MA</i>	acute otitis media (ages 6 months to adult)	application submitted
rifalazil (PA 1648)	PathoGenesis <i>Seattle, WA</i>	tuberculosis	Phase II
SB 265805	SmithKline Beecham <i>Philadelphia, PA</i>	broad-spectrum antibiotic	Phase II
Synercid® streptogramin (injectable)	Rhone-Poulenc Rorer <i>Collegeville, PA</i>	hospital treatment of severe infections such as vancomycin-resistant enterococci, multi-resistant pneumococci and skin infections	application submitted
Tequin™ gatifloxacin	Bristol-Myers Squibb <i>Princeton, NJ</i>	bronchitis gonorrhea pneumonia sinusitis uncomplicated skin and soft tissue infections complicated and uncomplicated urinary tract infections	Phase III

ANTIBIOTICS

Product Name	Company	Indication	Development Status
Tobi™ tobramycin solution for inhalation	PathoGenesis Seattle, WA	tuberculosis	Phase II
Trovan® trovafloxacin	Pfizer New York, NY	pediatric meningitis	Phase III
Ziracin (IV)	Schering-Plough Madison, NJ	resistant gram-positive bacterial infections	Phase III
Zithromax® azithromycin	Pfizer New York, NY	lower respiratory tract infections atypical pneumonia	application submitted
		cryptosporidiosis toxoplasmosis	Phase III

ANTIFUNGALS

Product Name	Company	Indication	Development Status
AmBisome® liposomal amphotericin B for injection	Fujisawa Healthcare Deerfield, IL NeXstar Pharmaceuticals Boulder, CO	cryptococcosis histoplasmosis	Phase III
BMS 207147	Bristol-Myers Squibb Princeton, NJ	aspergillosis mucosal candidiasis endemic mycosis onychomycosis	Phase I
Lamisil terbinafine	Novartis Pharmaceuticals East Hanover, NJ	subcutaneous and systemic fungal infections	Phase III
LY303366 echinocandin B	Eli Lilly Indianapolis, IN	aspergillosis <i>Candida</i> (albicans and non-albicans) pneumocystis	Phase II
Mentax™ butenafine HCl	Penederm Foster City, CA	onychomycosis	Phase III
MK991	Merck Whitehouse Station, NJ	aspergillosis <i>Candida</i> (including azole-resistant) other fungal infections	Phase III
NYOTRAN™ liposomal nystatin	Aronex Pharmaceuticals The Woodlands, TX	cryptococcal meningitis	Phase II/III
		candidemia	Phase II completed
		aspergillosis	Phase II
Oramed™ glyminox 0.5% oral rinse	Biosyn Philadelphia, PA	oral candidiasis	Phase I/II
Sporanox® Capsules itraconazole	Janssen Pharmaceutica Titusville, NJ	dermatomycoses	application submitted

ANTIFUNGALS

Product Name	Company	Indication	Development Status
Sporanox® I.V. itraconazole	Janssen Pharmaceutica <i>Titusville, NJ</i>	aspergillosis blastomycosis candidemia histoplasmosis empiric therapy of febrile neutropenic patients	application submitted
triazole (oral)	Schering-Plough <i>Madison, NJ</i>	opportunistic fungal infections	Phase II
voriconazole	Pfizer <i>New York, NY</i>	serious fungal infections	Phase III

ANTIVIRALS

Product Name	Company	Indication	Development Status
ABT-606	Abbott Laboratories <i>Abbott Park, IL</i>	herpes zoster	Phase II
AccuSite™ fluorouracil/ epinephrine injectable gel	Matrix Pharmaceutical <i>Fremont, CA</i>	genital warts	application submitted
adefovir dipivoxil	Gilead Sciences <i>Foster City, CA</i>	hepatitis B	Phase III
Alferon N Gel® interferon alfa-n3 (human leukocyte derived)	Interferon Sciences <i>New Brunswick, NJ</i>	human papillomavirus infections	Phase II
Alferon N Injection® interferon alfa-n3 (human leukocyte derived)	Interferon Sciences <i>New Brunswick, NJ</i>	chronic hepatitis C infections	Phase III
		hepatitis C and HIV co-infection	Phase II
Ampligen	HemispherRx Biopharma <i>New York, NY</i>	chronic fatigue immune dysfunction syndrome	Phase III
BMS 200475	Bristol-Myers Squibb <i>Princeton, NJ</i>	hepatitis B	Phase II
Epivir®-HBV™ lamivudine	BioChem Pharma <i>Laval, Quebec</i> Glaxo Wellcome <i>Rsch. Triangle Park, NC</i>	chronic hepatitis B	application submitted
Famvir® famciclovir	SmithKline Beecham <i>Philadelphia, PA</i>	suppression of genital herpes hepatitis B	Phase III
FTC	Triangle Pharmaceuticals <i>Durham, NC</i>	hepatitis B	Phase I
GR121167 (neuraminidase inhibitor)	Glaxo Wellcome <i>Rsch. Triangle Park, NC</i>	influenza	Phase III

ANTIVIRALS

Product Name	Company	Indication	Development Status
GV118819 (oral trinem)	Glaxo Wellcome <i>Rsch. Triangle Park, NC</i>	community-acquired bacterial infections	Phase II
HNK20	OraVax <i>Cambridge, MA</i>	respiratory syncytial virus (RSV)	Phase III
Intron A® interferon alfa-2b (recombinant)	Enzon <i>Piscataway, NJ</i>	hepatitis C (PEG-Intron A®)	Phase III
	Schering-Plough <i>Madison, NJ</i>	hepatitis C (PEG-Intron A®/ Rebetrol™ combination)	Phase I
Lidakol® n-docosanol	LIDAK Pharmaceuticals <i>San Diego, CA</i>	herpes labialis	application submitted
lobucavir	Bristol-Myers Squibb <i>Princeton, NJ</i>	hepatitis B herpes simplex (recurrent and suppressive) herpes zoster	Phase III
		cytomegalovirus (CMV) prevention in HIV and transplantation	Phase II
Malarone	Glaxo Wellcome <i>Rsch. Triangle Park, NC</i>	malaria treatment and prophylaxis	Phase III
Maxamine histamine dihydrochloride	Maxim Pharmaceuticals <i>San Diego, CA</i>	hepatitis C	Phase I/II
MEDI-493	MedImmune <i>Gaithersburg, MD</i>	treatment of RSV disease in adult bone marrow transplant patients	Phase II
Mepron atovaquone	Glaxo Wellcome <i>Rsch. Triangle Park, NC</i>	<i>Pneumocystis carinii</i> pneumonia (PCP) prophylaxis	Phase III
neviraminidase inhibitor (GS4104/ RO64-0796)	Gilead Sciences <i>Foster City, CA</i> Hoffmann-La Roche <i>Nutley, NJ</i>	treatment and prevention of influenza type A and B	Phase III
Ostavir™ human anti-hepatitis B antibody (OST-577)	Protein Design Labs <i>Mountain View, CA</i>	chronic hepatitis B treatment	Phase II
PEN203	Pentose Pharmaceuticals <i>Cambridge, MA</i>	human papillomavirus infections	Phase I/II
penciclovir (IV and topical)	SmithKline Beecham <i>Philadelphia, PA</i>	herpes infections	application submitted
pleconaril (SR 63843)	Sanofi Pharmaceuticals <i>New York, NY</i> ViroPharma <i>Exton, PA</i>	viral meningitis viral respiratory infection	Phase III
Rebetron™ (Intron® A and Rebetrol™ combination therapy)	Schering-Plough <i>Madison, NJ</i>	hepatitis C (naive patients-not previously treated with interferon)	application submitted

ANTIVIRALS

Product Name	Company	Indication	Development Status
valganciclovir	Hoffmann-La Roche <i>Nutley, NJ</i>	treatment and prevention of CMV retinitis	Phase II/III
Valtrex® valacyclovir	Glaxo Wellcome <i>Rsch. Triangle Park, NC</i>	CMV suppression/prevention	Phase III
Veldona® interferon-alpha lozenges	Amarillo Biosciences <i>Amarillo, TX</i>	treatment of human papillomavirus-induced oral warts related to HIV infection	Phase I/II
Vitravene™ fomivirsen	Isis Pharmaceuticals <i>San Diego, CA</i>	CMV retinitis in AIDS patients	application submitted
Wellferon alpha interferon	Glaxo Wellcome <i>Rsch. Triangle Park, NC</i>	hepatitis C	Phase III

IMMUNE ENHANCERS

Product Name	Company	Indication	Development Status
Betafectin PGG-glucan	Alpha-Beta Technology <i>Worcester, MA</i>	prevention of post-operative infection in patients undergoing upper gastrointestinal surgery and who are at high risk of post-operative infection	Phase III
Leukine® sargramostim	Immunex <i>Seattle, WA</i>	prevention of opportunistic infections	Phase III
R848	3M Pharmaceuticals <i>St. Paul, MN</i>	herpes	Phase II
recombinant human interleukin-12 (rhIL-12)	Genetics Institute <i>Cambridge, MA</i> Wyeth-Ayerst Laboratories <i>Philadelphia, PA</i>	hepatitis C	Phase I/II
Zadaxin® thymalfasin alpha 1 with interferon	SciClone Pharmaceuticals <i>San Mateo, CA</i>	hepatitis C	Phase III

VACCINES

Product Name	Company	Indication	Development Status
ActHIB® <i>Haemophilus B</i> conjugate vaccine with tetanus toxoid conjugate reconstituted with Tripedia® diphtheria and tetanus toxoids and acellular pertussis vaccine, adsorbed	Pasteur Merieux Connaught <i>Swiftwater, PA</i>	primary series of immunization against diphtheria, tetanus, <i>Haemophilus</i> <i>influenzae B</i> and pertussis in infants 2, 4 and 6 months of age	application submitted

VACCINES

Product Name	Company	Indication	Development Status
adjuvanted influenzae vaccine (FLU+MF59)	Chiron Vaccines Emeryville, CA	influenza	Phase III
<i>C. difficile</i> toxoid vaccine	OraVax Cambridge, MA	<i>Clostridium difficile</i> infections	Phase I
<i>Campylobacter</i> vaccine	Antex Biologics Gaithersburg, MD	diarrhea gastroenteritis	Phase II
cytomegalovirus vaccine	Chiron Vaccines Emeryville, CA	CMV	Phase II
diphtheria, tetanus, pertussis, hepatitis B, Hib combination vaccine	SmithKline Beecham Philadelphia, PA	pediatric use	Phase III
diphtheria, tetanus, pertussis, polio, Hib, hepatitis B combination vaccine	Pasteur Merieux Connaught Swiftwater, PA	pediatric use	Phase III
Epstein-Barr virus vaccine	Aviron Mountain View, CA SmithKline Beecham Philadelphia, PA	prevention of Epstein-Barr virus infection (cause of infectious mononucleosis)	Phase I
EPV-ETEC vaccine (raw potato edible vaccine)	Axis Genetics Cambridge, England Boyce Thompson Institute for Plant Research Ithaca, NY	traveler's diarrhea	Phase I
FluMist™ live, attenuated intranasal influenza vaccine	Aviron Mountain View, CA	influenza prevention	application submitted
<i>Haemophilus influenzae</i> nontypeable vaccine	Antex Biologics Gaithersburg, MD Pasteur Merieux Connaught Swiftwater, PA	otitis media	Phase I
<i>Haemophilus influenzae</i> vaccine	Chiron Vaccines Emeryville, CA	<i>Haemophilus influenzae</i>	Phase II
<i>Helicobacter pylori</i> vaccine	Antex Biologics Gaithersburg, MD	<i>H. pylori</i> infections peptic ulcers	Phase I
hepatitis A/B combination vaccine	SmithKline Beecham Philadelphia, PA	hepatitis A and B	Phase III
hepatitis B DNA vaccine	Glaxo Wellcome Rsch. Triangle Park, NC Powderject Vaccines Madison, WI	hepatitis B prevention	Phase I
herpes simplex vaccine	Wyeth-Ayerst Laboratories Philadelphia, PA	herpes simplex	Phase I/II
herpes vaccine	SmithKline Beecham Philadelphia, PA	herpes	Phase III

VACCINES

Product Name	Company	Indication	Development Status
HPV (human papillomavirus) vaccine	Merck <i>Whitehouse Station, NJ</i>	cervical cancer genital warts	Phase I
HPV vaccine	MedImmune <i>Gaithersburg, MD</i> SmithKline Beecham <i>Philadelphia, PA</i>	human papillomavirus	Phase I
HSV vaccine (DISE technology)	Cantab <i>Cambridge, England</i> Glaxo Wellcome <i>Rsch. Triangle Park, NC</i>	treatment of recurrent herpes simplex	Phase I
ImuLyme™ Lyme disease vaccine	Pasteur Merieux Connaught <i>Swiftwater, PA</i>	Lyme disease	application submitted
intranasal parainfluenza type 3 vaccine	Aviron <i>Mountain View, CA</i>	prevention of parainfluenza type 3 infection	Phase II
LYMERix™ Lyme disease vaccine	SmithKline Beecham <i>Philadelphia, PA</i>	Lyme disease	application submitted
MEDI-491	MedImmune <i>Gaithersburg, MD</i>	B19 parvovirus-induced miscarriages and transient aplastic viruses	Phase I
meningitis conjugate vaccine	Pasteur Merieux Connaught <i>Swiftwater, PA</i>	pediatric use	Phase II/III
meningococcal conjugate vaccine	Wyeth-Ayerst Laboratories <i>Philadelphia, PA</i>	meningococcal systemic type C disease	Phase III
meningococcus C vaccine	Chiron Vaccines <i>Emeryville, CA</i>	meningococcus C infections	Phase III
pandemic flu vaccine	Protein Sciences <i>Meriden, CT</i>	prevention for people who are at risk of exposure to the avian flu virus	Phase I
pneumococcal conjugate vaccine	Wyeth-Ayerst Laboratories <i>Philadelphia, PA</i>	pneumococcal systemic diseases (otitis media, pneumonia, meningitis)	Phase III
pneumococcal conjugate vaccine	Pasteur Merieux Connaught <i>Swiftwater, PA</i>	pediatric use for protection against bacteremia, meningitis, otitis, pneumonia	Phase II
pneumococcal conjugate vaccine (pediatric)	Merck <i>Whitehouse Station, NJ</i>	bloodstream infections meningitis middle ear infections pneumonia	Phase II
PSC™ rHA influenza virus vaccine, purified hemagglutinin, trivalent, type A and B	Protein Sciences <i>Meriden, CT</i>	influenza	Phase I/II

VACCINES

Product Name	Company	Indication	Development Status
Quilimmune-PT TM pneumococcal polysaccharide vaccine	Aquila Biopharmaceuticals Worcester, MA	pneumococcal infections	Phase II
rotavirus vaccine	SmithKline Beecham Philadelphia, PA Virus Research Institute Cambridge, MA	pediatric rotavirus infection	Phase II
RSV subunit vaccine	Wyeth-Ayerst Laboratories Philadelphia, PA	respiratory syncytial virus (RSV)-mediated lower respiratory disease for at-risk children and the elderly	Phase II
RSV vaccine	Wyeth-Ayerst Laboratories Philadelphia, PA	RSV	Phase I/II
RSV vaccine	Pasteur Merieux Connaught Swiftwater, PA	RSV	Phase I
rUrease vaccine	OraVax Cambridge, MA	<i>Helicobacter pylori</i> infections	Phase II
STAPHVAX TM bivalent staphylococcal glycoconjugate vaccine	NABI Rockville, MD	<i>Staphylococcus aureus</i> infection stimulation of <i>S. aureus</i> immune globulin in plasma donors	Phase III
TA-GW vaccine	Cantab Cambridge, England SmithKline Beecham Philadelphia, PA	genital warts	Phase II
TETRACEL TM diphtheria/tetanus/acellular pertussis/ <i>H. influenzae</i> b vaccine	Wyeth-Ayerst Laboratories Philadelphia, PA	diphtheria, tetanus, pertussis and <i>Haemophilus influenzae</i> B diseases (acellular pertussis component)	Phase III
varicella vaccine	SmithKline Beecham Philadelphia, PA	chickenpox	Phase III

OTHER BIOLOGICS

Product Name	Company	Indication	Development Status
ABT-773	Abbott Laboratories Abbott Park, IL	anti-infective	Phase I
CytoGam® cytomegalovirus immune globulin intravenous (human)	MedImmune Gaithersburg, MD	prevention of CMV disease in all solid organ transplant patients	application submitted

OTHER BIOLOGICS

Product Name	Company	Indication	Development Status
CytoTab™ affinity-purified anti-TNF alpha, ovine FAb (polyclonal antibody)	Therapeutic Antibodies <i>Nashville, TN</i>	cerebral malaria	Phase II
DiffGAM™ hyperimmune globulin (bovine milk), oral (enteric coated)	ImmuCell <i>Portland, ME</i>	treatment and prevention of diarrhea and colitis caused by <i>Clostridium difficile</i>	Phase II
E5531	Eisai <i>Teaneck, NJ</i>	sepsis	Phase II
H-BIG® IV hepatitis B immune globulin- intravenous	NABI <i>Rockville, MD</i>	prevention of liver transplant reinfection by hepatitis B	Phase II/III
H-CIG™ hepatitis C immune globulin	NABI <i>Rockville, MD</i>	prevention of hepatitis C infection in liver transplant patients	Phase I
LeukoScan® sulesomab	Immunomedics <i>Morris Plains, NJ</i>	appendicitis osteomyelitis in patients with diabetic foot ulcers osteomyelitis (long-bone)	application submitted
Lexirin LXR-015-1	LXR Biotechnology <i>Richmond, CA</i>	AIDS-associated severe diarrhea	Phase I
LY355636 CDAD antitoxin (oral)	Eli Lilly <i>Indianapolis, IN</i>	<i>Clostridium difficile</i> -associated disease	Phase I
MPL® immunomodulator (25+ antigens for adult and pediatric applications)	Ribi ImmunoChem <i>Hamilton, MT</i>	infectious diseases	in clinical trials
NE-0080	Neose <i>Horsham, PA</i>	<i>Helicobacter pylori</i> infections in patients with gastritis gastric ulcers	Phase II
Provir™	Shaman Pharmaceuticals <i>S. San Francisco, CA</i>	diarrhea in AIDS patients	Phase III
		traveler's diarrhea	Phase II
Pyloricide™	REFAC Biochemics <i>New York, NY</i>	eradication of <i>H. pylori</i> bacterium (non-antibiotic)	Phase I
saccharomyces boulardii	Biocodex <i>Seattle, WA</i>	adjunct treatment with standard therapy for recurrent <i>Clostridium difficile</i> infection	Phase III

OTHER BIOLOGICS

Product Name	Company	Indication	Development Status
Savvy™ glyminox 1.2% vaginal gel (microbicide)	Biosyn <i>Philadelphia, PA</i>	topical contraceptive to prevent transmission of sexually transmitted diseases	Phase I/II
SYNSORB-Pk®	SYNSORB Biotech <i>Calgary, Alberta</i>	reduce progression to hemolytic-uremic syndrome (HUS) in children (under age 15) who have tested positive for toxigenic <i>E. coli</i> infections	Phase III
Tenovil interleukin-10	Schering-Plough <i>Madison, NJ</i>	hepatitis C	Phase I
TravelGAM™ anti-enterotoxigenic <i>E. coli</i> bovine milk immune globulin (oral)	ImmuCell <i>Portland, ME</i>	prevention of traveler's diarrhea caused by enterotoxigenic <i>E. coli</i>	Phase II

The content of this survey has been obtained through government and industry sources based on the latest information. **Survey current as of August 31, 1998.** The information may not be comprehensive. For more specific information about a particular product, contact the individual company directly. The entire series of "New Medicines in Development" is available on PhRMA's web site.

PhRMA Internet address: <http://www.phrma.org>

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GLOSSARY

application submitted—Application for marketing has been submitted to the Food and Drug Administration (FDA).

aspergillosis—Infection caused by *Aspergillus fumigatus*, a fungus found in old buildings or decaying plant matter.

blastomycosis—A rare, non-contagious infection caused by breathing in a unique fungus found in wood and soil. The infection originates in the respiratory tract and usually disseminates to the lungs, skin and bone.

candidiasis—A fungal infection, caused by *Candida albicans*, usually of the moist cutaneous areas of the body.

Clostridium difficile—A bacterium that produces an irritating toxin that causes a form of colitis characterized by profuse, watery diarrhea with cramps and low-grade fever.

community-acquired infections—Communicable diseases spread among the general population, as opposed to those acquired in a hospital or long-term care facility.

cryptosporidiosis—An infection caused by the parasite *Cryptosporidium* and characterized by a chronic, profuse, watery diarrhea, accompanied by fever, marked weight loss and enlarged lymph nodes.

cytomegalovirus (CMV)—An opportunistic infection that afflicts people whose immune systems are weak, such as AIDS patients, and can be fatal.

enterococcus—A *Streptococcus* bacterium normally present in the human intestine. It can cause infections during or after surgery.

Escherichia coli (E. coli)—A common bacteria that is a cause of traveler's diarrhea. Certain strains of *E. coli* infect the large intestine and produce serious complications.

febrile—Feverish or related to fever.

gastroenteritis—An inflammation of the stomach and intestines usually caused by bacteria, viruses, and other organisms that may contaminate food or water.

genital warts—Soft warts that grow in and around the entrance of the vagina and the anus and on the penis. They are transmitted by sexual contact and are caused by a human papillomavirus.

gram-negative/gram-positive bacteria—Gram's stain is a method of staining bacteria in order to identify them. Gram-negative bacteria stain pink; gram-positive stain violet.

Haemophilus influenzae—A type of bacteria found in the respiratory tract that causes acute respiratory infections and meningitis in children but rarely in adults.

hepatitis—Inflammation of the liver with accompanying liver cell damage or death, caused most often by viral infection, e.g., hepatitis A, B and C.

herpes zoster/simplex—**Herpes simplex virus I** causes cold sores or fever blisters on the mouth or around the eyes and can be transmitted to the genital area.

Herpes simplex II causes painful sores of the anus or genitals. **Herpes varicella-zoster virus**, also called shingles, consists of very painful blisters on the skin and follows nerve pathways. It may appear in adulthood as a result of having had chickenpox as a child.

Helicobacter pylori—A bacterium that can cause peptic ulcers and other stomach ailments.

human papillomavirus (HPV)—Viral agent of warts, believed to be contagious and mostly harmless, affecting only the skin's topmost layer.

Lyme disease—Caused by the bacterium *Borrelia burgdorferi* and transmitted by the bite of a tick that usually lives on deer but can infest dogs. The disease is characterized by a mild skin rash, flu-like symptoms and joint inflammation.

malaria—A serious parasitic disease, spread by the bite of the *Anopheles* mosquito. Malaria is characterized by severe fever and chills and complications affecting the kidneys, liver, brain and blood.

meningitis—An inflammation of the membranes that cover the brain and spinal cord caused by viral, bacterial and fungal infections. Viral meningitis is usually mild and more common than the bacterial type. All meningitis may be life-threatening.

neutropenia—An abnormally low number of neutrophils (a type of white blood cell) in the circulating blood, leaving a patient vulnerable to bacterial and fungal infections.

nosocomial—Hospital-acquired infection.

onychomycosis—Disease, deformity or wasting of the nails caused by fungal infection.

osteomyelitis—Infection of the bone and bone marrow, usually caused by bacteria.

otitis media—Inflammation of the middle ear, often caused by a pneumococcal infection.

parvovirus—A family of viruses that can infect humans and cause erythema infectiosum (a contagious disease of children, marked by a rose-colored, coarse rash) and also can cause an aplastic crisis in hemolytic anemia.

pelvic inflammatory disease (PID)—Severe or recurrent infection of the internal female reproductive organs.

Phase I—Safety testing and pharmacological profiling in humans.

Phase II—Effectiveness testing and identification of side effects in humans.

Phase III—Extensive clinical trials in humans to verify effectiveness and monitor adverse reactions.

pneumococci—Strains of streptococcal bacteria that cause acute pneumonia, some middle ear infections and meningitis. These bacteria can also infect surgical wounds.

Pneumocystis carinii pneumonia (PCP)—A type of lung infection found rarely in the general population but frequently present in AIDS patients and others who are immunocompromised.

prophylaxis—Treatment intended to preserve health and prevent the spread of disease.

respiratory syncytial virus (RSV)—One of the most important causes of lower respiratory tract disease in children. In severe cases, cyanosis (bluish discoloration of skin and mucous membranes due to deficient oxygenation of the blood) can result.

rotavirus—A group of viruses that are wheel-like in appearance and are a major source of infant diarrhea throughout the world.

sepsis—The presence of bacteria and/or their toxins in the blood or tissues.

Staphylococcus aureus—A common bacterium that is a frequent cause of hospital infections, including pneumonia, surgical wounds and systemic blood infections.

systemic—Affecting the whole body.

toxoplasmosis—Infection with the protozoan *Toxoplasma gondii*, which frequently causes inflammation of the brain, heart, lungs, adrenal glands, pancreas and testis.

tuberculosis—An infectious disease caused by the organism *Mycobacterium tuberculosis*. It most frequently infects the lungs; however, other organs also may be infected.

SELECTED FACTS ABOUT INFECTIOUS DISEASES

Overview

- **Infectious diseases** cost the United States more than \$30 billion each year in direct costs alone.¹
 - Each year up to 60,000 adults, many age 65 or older, die of **preventable infectious diseases**, such as influenza, pneumococcal infection and hepatitis B. Pneumonia and influenza together are the sixth leading cause of death in the United States.²
 - At least 100 times as many adults as children die each year in the United States from **vaccine-preventable diseases**.³
 - Up to half of Americans over 50 years of age are inadequately immunized against **tetanus** and **diphtheria**.³
 - **Hospital-acquired infections** affect about 2 million Americans annually, and nearly 90,000 of them will die.²
 - **Sexually transmitted diseases (STDs)** are among the most common infectious diseases in the United States today. More than 20 STDs have been identified, including AIDS, genital herpes, genital warts, human papillomaviruses and gonorrhea. STDs affect more than 13 million men and women in this country each year. Nearly two-thirds of all STDs occur in people younger than 25 years of age.⁴
-

Bacterial Infections

- The incidence of vancomycin-resistant **enterococci** increased from 0.3 percent in 1989 to 7.9 percent in 1993. Enterococci are the second most common cause of hospital-acquired urinary tract infections and the third most common cause of skin, soft tissue and bloodstream infections.⁵
 - **Lyme disease** is a rapidly emerging infectious disease and the most common disease spread by ticks in the United States. More than 16,000 cases were reported by 45 states in 1996.⁶
 - **Peptic ulcer disease** affects approximately 25 million Americans and has a \$6 billion impact on the nation's health care costs. Most ulcers are caused by an infection with the bacterium *Helicobacter pylori*, which can be cured in about two weeks with antibiotics. *H. pylori* causes more than 90 percent of duodenal ulcers and more than 80 percent of gastric ulcers.⁷
 - **Pneumococcal pneumonia** is the most common type of pneumonia, accounting for up to one-third of all types of pneumonia that lead to hospitalization. The pneumococcal vaccine can prevent up to 60 percent of serious pneumococcal infections, but it will not protect from other types of pneumonia.²
 - **Group B streptococcus**, the most common cause of blood infections and meningitis in newborns and a frequent cause of newborn pneumonia, causes disease in about 18,000 people in the United States each year, 8,000 of whom are newborns. The number of adult infections nearly doubled during the 1980s and continues to increase.⁶
 - **Tuberculosis (TB)** has re-emerged as a serious public health problem in this country, with a total of 25,287 active TB cases reported in 1993, an increase of 14 percent since 1985. An estimated 15 million people in the United States have latent TB infections that may develop into active TB at some time in their lives.⁴
-

Viral Infections

- **Chickenpox** is so contagious in its early stages that an exposed person who has not had it has a 70–80 percent chance of getting the disease. Almost everyone gets chickenpox by adulthood. In the United States, it affects about 4 million people annually, mostly children. Each year, 4,000 to 9,000 people are hospitalized with chickenpox, and up to 100 die. Although U.S. adults make up fewer than 5 percent of cases, they account for half of the deaths from the disease.⁶
 - Up to 1 out of 10 Americans has **genital human papillomavirus** infections. Between 500,000 and 1 million new cases of **genital warts** occur every year.⁸
 - **Hepatitis A**, the seventh most commonly reported infectious disease in the United States, infects about 180,000 people yearly. It ranks sixth among the top 10 causes of foodborne disease.⁶
 - **Hepatitis B** virus infects 100,000–140,000 Americans annually. It is 100 times more infectious than the virus that causes AIDS.³
 - **Hepatitis C** virus (HCV) causes approximately 150,000 cases of acute viral hepatitis each year in the United States. Recovery from infection is rare, and between 70–90 percent of infected persons become chronic carriers of the virus.⁹
 - In an average year, **influenza** is associated with about 20,000 deaths nationwide and many more hospitalizations. More than 90 percent of influenza-related deaths occur in people age 65 and older. Influenza vaccine can prevent up to 70 percent of hospitalizations and 85 percent of deaths from influenza-related pneumonia.²
 - By age three, more than 80 percent of children have had at least one episode of **otitis media (ear infection)** and nearly half have had three or more episodes. In the United States, the annual cost of treating ear infections is between \$3–\$4 billion.⁹
 - **Respiratory syncytial virus (RSV)** infects approximately 50 percent of infants and young children in the United States each winter season. It causes about 90,000 hospitalizations and 4,500 deaths annually in children under the age of five.⁶
-

Sources:

1. U.S. Department of Health and Human Services Fact Sheet, "HHS Initiatives to Combat Emerging Infectious Diseases"
2. Centers for Disease Control and Prevention
3. National Coalition for Adult Immunization
4. Jefferson Health System, 1997
5. The American Society of Consultant Pharmacists, Clinical Consult: Supplement 10.
6. Association of State and Territorial Directors of Health Promotion and Public Health Education
7. National Center for Infectious Diseases
8. Planned Parenthood Federation of America, Inc.
9. National Institute for Allergy and Infectious Diseases

THE DRUG DEVELOPMENT AND APPROVAL PROCESS IN THE '90S

It takes 15 years on average for an experimental drug to travel from the lab to U.S. patients. Only five in 5,000 compounds that enter preclinical testing make it to human testing. One of these five tested in people is approved.

Early Research/ Preclinical Testing		Clinical Trials			FDA		Phase IV
		Phase I	Phase II	Phase III	1.5	15 Total	
Years	6.5	1.5	2	3.5			
Test Population	Laboratory and animal studies	20 to 80 healthy volunteers	100 to 300 patient volunteers	1,000 to 3,000 patient volunteers	Review process/ approval		Additional post- marketing testing required by FDA
Purpose	Assess safety and biological activity	Determine safety and dosage	Evaluate effectiveness, look for side effects	Confirm effectiveness, monitor adverse reactions from long-term use			
Success Rate	5,000 compounds evaluated	5 enter trials			1 approved		

THE DRUG DEVELOPMENT AND APPROVAL PROCESS

BY BERTRAM A. SPILKER, M.D., PH.D.,

SENIOR VICE PRESIDENT FOR SCIENTIFIC AND REGULATORY AFFAIRS, PHRMA

The U.S. system of new drug approvals is perhaps the most rigorous in the world. On average, it costs a company \$500 million to get one new medicine from the laboratory to U.S. patients, according to a January 1996 report by the Boston Consulting Group.

It takes 15 years on average for an experimental drug to travel from lab to U.S. patients, according to the Tufts Center for the Study of Drug Development, Tufts University, based on drugs approved from 1993 through 1995. Only five in 5,000 compounds that enter preclinical testing make it to human testing. And only one of those five is approved for sale.

Once a new compound has been identified in the laboratory, medicines are developed as follows:

Preclinical testing. A pharmaceutical company conducts laboratory and animal studies to show biological activity of the compound against the targeted disease, and the compound is evaluated for safety.

Investigational New Drug Application (IND). After completing preclinical testing, a company files an IND with the U.S. Food and Drug Administration (FDA) to begin to test the drug in people. The IND becomes effective if FDA does not disapprove it within 30 days. The IND shows results of previous experiments; how, where and by whom the new studies will be conducted; the chemical structure of the compound; how it is thought to work in the body; any toxic effects found in the animal studies; and how the compound is manufactured. All clinical trials must be reviewed and approved by the Institutional Review Board (IRB) where the trials will be conducted. Progress reports on clinical trials must be submitted at least annually to FDA and the IRB.

Clinical Trials, Phase I. These tests involve about 20 to 80 normal, healthy volunteers. The tests study a drug's safety profile, including the safe dosage range. The studies also determine how a drug is absorbed, distributed, metabolized, and excreted as well as the duration of its action.

Clinical Trials, Phase II. In this phase, controlled trials of approximately 100 to 300 volunteer patients (people with the disease) assess a drug's effectiveness.

Clinical Trials, Phase III. This phase usually involves 1,000 to 3,000 patients in clinics and hospitals. Physicians monitor patients closely to confirm efficacy and identify adverse events.

New Drug Application (NDA). Following the completion of all three phases of clinical trials, a company analyzes all of the data and files an NDA with FDA if the data successfully demonstrate both safety and effectiveness. The NDA contains all of the scientific information that the company has gathered. NDAs typically run 100,000 pages or more. By law, FDA is allowed six months to review an NDA. The average NDA review time for new molecular entities approved in 1997 was 16.2 months.

Approval. Once FDA approves an NDA, the new medicine becomes available for physicians to prescribe. A company must continue to submit periodic reports to FDA, including any cases of adverse reactions and appropriate quality-control records. For some medicines, FDA requires additional trials (Phase IV) to evaluate long-term effects.

Discovering and developing safe and effective new medicines is a long, difficult, and expensive process. The research-based pharmaceutical industry will invest \$21.1 billion in research and development this year.

New Medicines in Development for Infectious Diseases is presented by PhRMA in cooperation with the following organizations:

AIDS Action
AIDS Project Los Angeles
Allergy and Asthma Network • Mothers of Asthmatics
American Academy of Allergy, Asthma & Immunology
American Academy of Physician Assistants
American Association of Immunologists
American Foundation for AIDS Research (AmFAR)
American Nurses Association
American Social Health Association
American Society for Microbiology
Association of Nurses in AIDS Care
Association of Women's Health, Obstetric and Neonatal Nurses
Asthma and Allergy Foundation of America
CAVDA—Citizens Alliance for VD Awareness
Child Health Foundation
Childrens' AIDS Fund
Foundation for Advances in Medicine and Science
Gay & Lesbian Medical Association
Haitian Centers Council / Haitian Coalition on AIDS
Health Education Resource Organization (HERO)
Immune Deficiency Foundation
Infectious Diseases Society of America
Interamerican College of Physicians & Surgeons
International Association of Physicians in AIDS Care
National Association of People with AIDS
National Coalition of Hispanic Health and Human Services Organizations (COSSMHO)
National Council for International Health
National Foundation for Infectious Diseases
National Institute of Allergy and Infectious Diseases
National Institute of Child Health and Human Development
National Medical Association
National Native American AIDS Prevention Center
Project Inform

Being listed in this report in no way implies that the above-mentioned organizations endorse or recommend the use of any of the products in development contained in this publication. For further information, patients should consult their physicians or health care providers.



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CRS Report for Congress

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The Federal Role in Technology Development

Wendy H. Schacht
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Science, Technology, and Medicine Division

Summary

The federal government has traditionally played a role in fostering technological progress. This has involved both direct federal research and development (R&D) funding and indirect measures that create incentives for increased private sector investments in innovation. However, this mix of initiatives was challenged in the 104th Congress and again in the 105th Congress. While support has been made available for all on-going efforts, some programs have been funded at reduced levels. As the Congress continues to debate the budget, the government's approach to technological advance is again being explored.

Technology Development: The Federal Role¹

The federal government funds research and development (R&D) to meet the mission requirements of the departments and agencies (e.g., defense, public health, environmental quality). It also finances work in areas where there is an identified need for research, primarily basic research, not being performed in the private sector. Federal support reflects a consensus that while basic research is the foundation for many innovations, the rate of return to society as a whole generated by investments in such work is significantly larger than the benefits that can be captured by the performing institution. This often leads to underinvestment in research by the business community.

Over the last 15 or more years, congressional initiatives have expanded the government's role to include the promotion of technological innovation to meet other national needs, particularly the economic growth that flows from the commercialization and use of new products and production processes. Technological advance can drive the economy because it contributes to the creation of new goods and services, new industries, new jobs, and new capital. It can expand the range of services offered and extend the

¹For a detailed discussion: Congressional Research Service, *Industrial Competitiveness and Technological Advancement: Debate Over Government Policy*, by Wendy H. Schacht, CRS Issue Brief 91132



geographic distribution of those services. The application of technology also can contribute to the resolution of those national problems that are amenable to technological solutions. Experts widely believe that technological progress is responsible for up to one-half the growth of the U.S. economy, and is one principal driving force in long-term economic expansion and increases in the nation's standard of living.

Dual Approaches

The Congress has often been the source of federal inducements to technological progress. The legislative approach which evolved generally reflects the basic tenet that while commercialization of technology is the responsibility of the private sector, there are benefits which may be derived from additional mechanisms to stimulate industrial innovation. As a result of bipartisan efforts, various laws have removed barriers to technology development in the business community and provided incentives for increased private sector R&D. Many involve cooperative relationships among government, industry, and academia.

The laws affecting the R&D environment have included both direct and indirect measures to facilitate technological innovation. In general, direct measures are those that concern budget outlays and the provision of services by government agencies. Indirect measures include financial incentives and legal changes (e.g., liability or regulatory reform; new antitrust arrangements). Supporters of indirect approaches argue the market is superior to government in deciding which technologies are worthy of investment. Mechanisms that enhance the market's opportunities and abilities to make such choices are preferred. It is assumed that reliance on the discretion of federal agencies to assist one technology in preference over another will inevitably be subjected to political pressures from entrenched interests. Proponents of direct government assistance maintain, conversely, that indirect methods can be wasteful and ineffective, and may compromise other goals of public policy in the hope of stimulating innovative performance. Advocates of federal spending argue it is important to put the country's scarce resources to work on those technologies which have the greatest promise as determined by industry and supported by the community's willingness to match government funding.

In the past, while Republicans tended to prefer reliance on free market investment, competition, and indirect federal support, participants in the debates generally did not make definite (or exclusionary) choices between the two approaches, nor consistently favor one over the other. For example, some proponents of a stronger direct role for the government in innovation are also supporters of enhanced tax preferences for R&D spending, an indirect mechanism. Opponents of direct federal support for specific projects (e.g., SEMATECH, flat panel displays) nevertheless may back similar activities focused on more general areas such as manufacturing or information technology. However, many of these activities were called into question during the 104th Congress as reflected in the House Republican Contract with America, associated budget proposals, and various authorization and appropriations legislation.

While most of the programs survived termination challenges, such efforts implied a significant change from the past. Under President Bush, government's stated role was "... to support the development of generic or enabling technologies at the pre-competitive stage of R&D" and included direct federal cost-shared funding for several industrial programs. Increased private sector investment was encouraged as was public-private

collaboration through the National Technology Initiative. Also proposed were reductions in the capital gains tax rate, making permanent the research and experimentation tax credit, increasing international intellectual property protection, limiting product liability, and eliminating unwarranted regulation.

The Clinton Administration expanded upon this approach in the context of a national strategy for commercial technological advancement as part of a defined national economic policy. There have been efforts to increase direct federal funding for "industry led" technology programs (with matching private sector commitments); to augment cooperation among all levels of government, industry, and academia; to move from defense R&D toward civilian R&D support; and to shift emphasis from basic research to include development of commercial products and processes. The Administration's strategy for civilian technology investment is based upon support of both direct and indirect federal assistance

Current Initiatives

An overview of the current mix of indirect and direct measures designed to facilitate technological advancement is offered below.

Indirect Measures. Among the most visible indirect mechanisms was the **Research and Experimentation Tax Credit** originally mandated by the 1981 Economic Recovery Tax Act (P.L. 97-34). Extended several times, but permitted to expire June 30, 1998, the law allowed a 20% credit for increases in a firm's qualified research costs above the average expenditures for the previous 3 tax years. Qualified costs included in-house expenditures such as wages for researchers, materials, and payments for use of equipment; 65% of corporate grants towards basic research at universities and other relevant institutions; and 65% of payments for contract research. The credit was applicable to 75% of a company's tax liability. Small, start-up firms also were eligible. Several bills have been introduced to reinstate the research and experimentation credit.

Investments in research and development are often costly, long term, and risky. To encourage increased private sector R&D activity, various legislative initiatives have been enacted to facilitate joint ventures among government, business, and academia. It is argued that collaborative R&D reduces risks and costs, and permits work to be performed that crosses traditional boundaries of expertise and experience. This is the intent of the **National Cooperative Research Act** (P.L. 98-462) which clarifies the antitrust laws as they relate to joint research and eliminates treble damage awards for those ventures found in violation if prior disclosure to the government has been made. These changes came in response to industry's reluctance to enter into cooperative efforts because of the threat of antitrust prosecution. Over 700 joint research ventures have filed with the Department of Justice since passage of this legislation.

The success of this law in stimulating collaborative work precipitated the enactment of the **National Cooperative Production Amendments Act of 1993** (P.L. 103-42). The legislation extends the provisions of the National Cooperative Research Act to joint manufacturing ventures with certain reservations concerning location and ownership of the participating enterprises.

Another indirect approach to augment commercialization involves the transfer of technology from federal laboratories and contractors to the industrial community mandated by the **Stevenson-Wydler Technology Innovation Act** (P.L. 96-480), as amended.² This law created institutional mechanisms by which federal agencies and their laboratories can move technology to the private sector as well as integrate industrial expertise into the federal R&D enterprise. Additional incentives are contained in the **Federal Technology Transfer Act** (P.L. 99-502) and the **Defense Authorization Act of 1990** (P.L. 101-189) which allow government laboratories to enter into cooperative R&D agreements (CRADAs) with universities and industry. In pursuing joint efforts, the laboratory may accept funds, personnel, services, and property from the collaborating party and may provide personnel, services, and property (but **not** funds) to the other organization. The work performed must be consistent with the laboratory's mission. Preference for cooperative ventures is given to small businesses, companies which will manufacture in the United States, or foreign firms from countries that permit American companies to enter into similar arrangements. To date, over 5,000 CRADAs have been signed (including NASA Space Act Agreements).

P.L. 96-517, **Amendments to the Patent and Trademark Act** (commonly referred to as the "**Bayh-Dole Act**"), utilizes the ownership of inventions arising out of government-sponsored R&D to encourage development of new technologies. The law provides for title to inventions made with federal R&D funding to be vested in the contractor if it is a small business, university, or not-for-profit institution. Patent ownership is seen as a way to promote the additional private sector investment necessary for commercialization. Certain rights are reserved for the government.

Direct Measures. Government programs which directly fund technology development experienced the most scrutiny in the 104th Congress and again have been explored in the current Congress. While many of these activities require cost sharing of at least 50% with non-federal partners and usually are responsive to industry-led priorities, there are indications that some Members view them as inappropriate federal government involvement in market choices.

The **Advanced Technology Program** (ATP), provides seed funding, matched by private-sector investment to companies or consortia of universities, businesses, and government laboratories for development of generic technologies that have broad application across industries.³ Managed by the National Institute of Standards and Technology (NIST), a laboratory of the Department of Commerce, this program was established by the Omnibus Trade and Competitiveness Act of 1988 (P.L. 100-418). Awards, based on technical and business merit, are made for work which is high-risk and past the basic research stage but not yet ready for commercialization. Initial funding for ATP in FY1991 was \$36 million, \$48 million in FY1992, \$67.9 million in FY1993, and \$199.5 million in FY1994. In FY1995, appropriations expanded significantly to \$341 million (after rescissions). However, in FY1996 the figure decreased to \$221 million with a small increase to \$225 million in FY1997, later reduced to \$218 million after rescissions.

²For further detail see: Congressional Research Service, *Technology Transfer: Use of Federally Funded Research and Development*, by Wendy H. Schacht, CRS Issue Brief 85031.

³For more information see: Congressional Research Service, *The Advanced Technology Program*, by Wendy H. Schacht, CRS Report 95-36.

FY1998 appropriations for ATP totaled \$192.5 million. For FY1999, the House appropriations legislation provides \$180.2 million; the Senate version offers \$192.5 million. These figures are significantly less than the Administration's request of \$259.9 million.

Also created by the 1988 Trade Act was a program of regional manufacturing technology transfer centers, now known as the **Manufacturing Extension Partnership (MEP)**.⁴ Knowledge and technologies developed under the auspices of the National Institute of Standards and Technology are used to assist small and medium sized companies. To date all states have manufacturing technology centers or smaller outreach centers. Funding was \$11.9 million in FY1991, \$15.1 million in FY1992, and \$16.9 million in FY1993. FY1994 appropriations totaled \$30.3 million for the expanded MEP which combined the Centers Program, the Manufacturing Outreach effort, and the State Extension Program. Funding for FY1995 was \$84 million (post rescission) and included a new program, LINKS, to tie together federal, state, and local agencies, the private sector, and the manufacturing outreach institutions through communications and computer data systems. While the FY1996 appropriation declined to \$80 million, support for FY1997 increased to \$99.9 million. In FY1998, appropriations funding again increased to \$113.5 million. The House and Senate appropriations bills for FY1999 would both support MEP at \$106.8 million, the same as the Administration's request.

The **Small Business Innovation Research Program**, created by P.L. 97-219, as amended, is an activity to assist small, high technology companies perform research, development, and commercialization in areas of interest to the government.⁵ Each federal agency with an R&D budget over \$100 million is required to set aside a percentage of that funding (2.5% in 1997 until sunset in 2000) for grants to small firms. Financing is, in part, dependent on companies obtaining private sector support for the commercialization of the resulting products or processes. A pilot program also was created to encourage small firms to work with universities or federal laboratories to facilitate the commercialization of research performed in these institutions. This activity is funded by a 0.15% (phased in) set-aside. Originally expected to sunset in FY1996, the program has been extended through FY2001.

Issues For Consideration: A New Approach?

In the past, government support for technology development has been reflected in the balance between legislatively mandated incentives for private sector investment and direct government financing of R&D. The activities of the 104th Congress displayed a preference for the first approach. The first session of the 105th Congress further explored technology policy within the context of budget decisions. On-going programs were funded, however, some support at reduced levels. What happens next might be dependent on how the debate is framed. Will federal funding of specific technology ventures continue to be seen by the majority as "picking winners and losers" or will spending for efforts such as ATP be seen as fostering productive collaboration among firms? Is the government making

⁴See: Congressional Research Service, *The Manufacturing Extension Partnership*, by Wendy H. Schacht, CRS Report 97-104.

⁵Additional detail in: Congressional Research Service, *The Small Business Innovation Research Program*, by Wendy H. Schacht, CRS Report 96-402.

decisions which should best be left to the marketplace or is there an overriding national need for federal investment in these industry-led programs?

There appears to be agreement with the basic premise that the government does have a role in fostering technological advancement in the private sector; the debate is over how this is best achieved within existing and future budget constraints. In place of direct federal appropriations, some have suggested the creation of tax incentives which, proponents argue, would provide the capital resources necessary for industry to invest in additional R&D. Thus, efforts such as a permanent and expanded research and experimentation tax credit are considered a viable substitute for government cost-shared programs. Changes in the capital gains tax to encourage long term investments, particularly in high technology companies, also have been proposed to increase the amount of funding available for industrial use.

Regulatory reform may be used to facilitate technology development by diminishing the costs associated with bringing a new product or process to the marketplace. Disincentives to new technology development embodied in the threat of large punitive damage awards might be addressed by liability reform. In addition, other ideas might be considered to encourage collaborative work among industry, university, and government. These include changes to the antitrust laws pertaining to cooperative development and/or commercialization activities, increasing state government participation in relevant federal decisionmaking, and strengthening intellectual property protection.

Research and development funding constitutes the largest single portion of total federal discretionary spending and is therefore subject to cuts as legislators move toward a balanced budget. As a result, it is unrealistic to expect significant increases in government funding for such work. Thus, priorities concerning the allocation of financing may need to be established. Simultaneously, it might be helpful to create new methods to encourage increased activities by other parties in the innovation process, particularly if the goal is to continue the technological advancement which has been so instrumental to this nation's economic growth and high living standard.



Memorandum

October 6, 1999

TO : Honorable Nancy Pelosi
Attention: Chris Collins

FROM : Gary Guenther
Analyst in Business Taxation and Finance
Government and Finance

SUBJECT : Effectiveness of the Proposed Tax Credits for Vaccine Research in H.R. 1274

Responding to your request, this memorandum assesses the likely effectiveness of the proposed tax credits for vaccine research in H.R. 1274. Effectiveness in this case signifies the likely rise in domestic investment in vaccine research and development (R&D) in response to the tax credits. This method of assessing the proposed credits' effectiveness boils down to comparing the additional vaccine R&D induced by one dollar of tax credit claimed, which is a way of analyzing the benefit-cost ratio for the credit. The proposed credits also raise the issue of whether such a subsidy can be justified on economic grounds. This issue is discussed briefly in the final section.

Two noteworthy conclusions emerge from the analysis presented here. One is that the proposed tax credits can be expected to spur increased investment in vaccine R&D by the private sector, by both increasing expected after-tax returns on this investment and improving the access of small startup firms to equity capital for investment in vaccine R&D. The second conclusion relates to the economic rationale for the proposed tax credits: they are justified on economic grounds to the extent that they attempt to correct failures in the market for vaccines that result in economically inefficient levels of domestic investment in vaccine R&D.

If you have any questions about this analysis, please call me at 7-7742.

The Economics of Vaccine Innovation

Vaccines are among the most cost-effective weapons in the arsenal of modern medicine against the spread of contagious diseases, lethal and non-lethal. By strengthening an individual's immune system to resist a wide range of infectious diseases, they offer a relatively inexpensive means of lowering a society's overall cost of medical care. While historically vaccines have been used to prevent a variety of diseases, intensive efforts are being made to develop vaccines that can treat certain diseases -- mainly cancer and AIDS -- after an individual contracts them.

On the whole, the development of new vaccines is a long, costly, and risky process. It typically takes 10 years and requires outlays of \$100 million to bring a new vaccine from the research laboratory to the medical marketplace.¹ In addition, firms seeking to develop new vaccines face a considerable risk of failure. A 1989 study estimated that only 3 out of 10 vaccines that enter clinical trials end up being approved for general use.² For the most part, vaccine development passes through the same stages as the development of new therapeutic drugs: a period of basic research or discovery, followed by the filing of an investigational new drug application with the U.S. Food and Drug Administration (FDA), followed by three stages of clinical trials. Vaccine development, however, departs from the path of new drug development during the third phase of clinical trials, when a firm developing a new vaccine must file both a product license application and an establishment license application with the FDA; firms developing new therapeutic drugs only are required to file a new drug application at this stage. Once the FDA is satisfied that the vaccine is safe and effective and that the plant where it is produced meets the FDA's stringent standards for purity, cleanliness, and quality control, the vaccine can be marketed in the United States. This means that the FDA requires vaccine firms to construct and start up manufacturing facilities for new products several years before they can gain marketing approval -- and thus begin to earn a return on the funds invested in their development.

The economics of vaccine innovation has important implications for the structure of the vaccine industry. High fixed costs for research, production setup, and obtaining and maintaining FDA marketing approval result in marginal vaccine production costs that are significantly below average vaccine production costs. Such a cost structure is not conducive to the existence of multiple sellers of the same vaccines. As a seller's output expands, its average costs decline; and as those costs fall, its ability to underprice its competitors and still cover its costs grows.³ The degree of competition in the world vaccine industry seems to confirm this crucial point. Vaccine production in the United States and the rest of the world has been highly concentrated: in 1994, four firms (Institut Merieux, Merck, SmithKline Beecham, and American Cyanamid) accounted for between 65% and 80% of world sales of vaccines; and in 1993, the same four firms produced nearly all the pediatric vaccines purchased in the United States.⁴

In the United States, the federal government finances the lion's share of basic research in vaccines, where the emphasis is on understanding the fundamental mechanisms of infectious disease and the immune system. Once a vaccine research project advances to the level of applied research and development, where the emphasis is on producing and testing specific products with commercial potential, the private sector takes the lead in financing.

¹ Sing, Merrile and Mary Kaye Willian. "Supplying Vaccines." *Supplying Vaccine: An Economic Analysis of Critical Issues*. Pauly, Mark, et.al., editors. Washington, D.C., IOS Press, 1996. P. 61.

² Grabowski, Henry G. and John M. Vernon. *The Search For New Vaccines*. Washington, D.C., American Enterprise Institute Press, 1997. P. 20.

³ Pauly, Mark V. and Bridget E. Cleff. "The Economics of Vaccine Policy: A Summary of the Issues." *Supplying Vaccines*. P. 7.

⁴ Sisk, Jane E. "The Relationship between Scientific Advances and the Research, Development, and Production of Vaccines in the United States." *Supply Vaccines*. p. 181; and FIND/SVP. *The World Market for Vaccines*. New York, October 1995. P. 169.

collaboration through the National Technology Initiative. Also proposed were reductions in the capital gains tax rate, making permanent the research and experimentation tax credit, increasing international intellectual property protection, limiting product liability, and eliminating unwarranted regulation.

The Clinton Administration expanded upon this approach in the context of a national strategy for commercial technological advancement as part of a defined national economic policy. There have been efforts to increase direct federal funding for "industry led" technology programs (with matching private sector commitments); to augment cooperation among all levels of government, industry, and academia; to move from defense R&D toward civilian R&D support; and to shift emphasis from basic research to include development of commercial products and processes. The Administration's strategy for civilian technology investment is based upon support of both direct and indirect federal assistance.

Current Initiatives

An overview of the current mix of indirect and direct measures designed to facilitate technological advancement is offered below.

Indirect Measures. Among the most visible indirect mechanisms was the **Research and Experimentation Tax Credit** originally mandated by the 1981 Economic Recovery Tax Act (P.L. 97-34). Extended several times, but permitted to expire June 30, 1998, the law allowed a 20% credit for increases in a firm's qualified research costs above the average expenditures for the previous 3 tax years. Qualified costs included in-house expenditures such as wages for researchers, materials, and payments for use of equipment; 65% of corporate grants towards basic research at universities and other relevant institutions; and 65% of payments for contract research. The credit was applicable to 75% of a company's tax liability. Small, start-up firms also were eligible. Several bills have been introduced to reinstate the research and experimentation credit.

Investments in research and development are often costly, long term, and risky. To encourage increased private sector R&D activity, various legislative initiatives have been enacted to facilitate joint ventures among government, business, and academia. It is argued that collaborative R&D reduces risks and costs, and permits work to be performed that crosses traditional boundaries of expertise and experience. This is the intent of the **National Cooperative Research Act** (P.L. 98-462) which clarifies the antitrust laws as they relate to joint research and eliminates treble damage awards for those ventures found in violation if prior disclosure to the government has been made. These changes came in response to industry's reluctance to enter into cooperative efforts because of the threat of antitrust prosecution. Over 700 joint research ventures have filed with the Department of Justice since passage of this legislation.

The success of this law in stimulating collaborative work precipitated the enactment of the **National Cooperative Production Amendments Act of 1993** (P.L. 103-42). The legislation extends the provisions of the National Cooperative Research Act to joint manufacturing ventures with certain reservations concerning location and ownership of the participating enterprises.

Another indirect approach to augment commercialization involves the transfer of technology from federal laboratories and contractors to the industrial community mandated by the **Stevenson-Wydler Technology Innovation Act** (P.L. 96-480), as amended.² This law created institutional mechanisms by which federal agencies and their laboratories can move technology to the private sector as well as integrate industrial expertise into the federal R&D enterprise. Additional incentives are contained in the **Federal Technology Transfer Act** (P.L. 99-502) and the **Defense Authorization Act of 1990** (P.L. 101-189) which allow government laboratories to enter into cooperative R&D agreements (CRADAs) with universities and industry. In pursuing joint efforts, the laboratory may accept funds, personnel, services, and property from the collaborating party and may provide personnel, services, and property (but **not** funds) to the other organization. The work performed must be consistent with the laboratory's mission. Preference for cooperative ventures is given to small businesses, companies which will manufacture in the United States, or foreign firms from countries that permit American companies to enter into similar arrangements. To date, over 5,000 CRADAs have been signed (including NASA Space Act Agreements).

P.L. 96-517, **Amendments to the Patent and Trademark Act** (commonly referred to as the "**Bayh-Dole Act**"), utilizes the ownership of inventions arising out of government-sponsored R&D to encourage development of new technologies. The law provides for title to inventions made with federal R&D funding to be vested in the contractor if it is a small business, university, or not-for-profit institution. Patent ownership is seen as a way to promote the additional private sector investment necessary for commercialization. Certain rights are reserved for the government.

Direct Measures. Government programs which directly fund technology development experienced the most scrutiny in the 104th Congress and again have been explored in the current Congress. While many of these activities require cost sharing of at least 50% with non-federal partners and usually are responsive to industry-led priorities, there are indications that some Members view them as inappropriate federal government involvement in market choices.

The **Advanced Technology Program** (ATP), provides seed funding, matched by private-sector investment to companies or consortia of universities, businesses, and government laboratories for development of generic technologies that have broad application across industries.³ Managed by the National Institute of Standards and Technology (NIST), a laboratory of the Department of Commerce, this program was established by the Omnibus Trade and Competitiveness Act of 1988 (P.L. 100-418). Awards, based on technical and business merit, are made for work which is high-risk and past the basic research stage but not yet ready for commercialization. Initial funding for ATP in FY1991 was \$36 million, \$48 million in FY1992, \$67.9 million in FY1993, and \$199.5 million in FY1994. In FY1995, appropriations expanded significantly to \$341 million (after rescissions). However, in FY1996 the figure decreased to \$221 million with a small increase to \$225 million in FY1997, later reduced to \$218 million after rescissions.

²For further detail see: Congressional Research Service, *Technology Transfer: Use of Federally Funded Research and Development*, by Wendy H. Schacht, CRS Issue Brief 85031.

³For more information see: Congressional Research Service, *The Advanced Technology Program*, by Wendy H. Schacht, CRS Report 95-36

FY1998 appropriations for ATP totaled \$192.5 million. For FY1999, the House appropriations legislation provides \$180.2 million; the Senate version offers \$192.5 million. These figures are significantly less than the Administration's request of \$259.9 million.

Also created by the 1988 Trade Act was a program of regional manufacturing technology transfer centers, now known as the **Manufacturing Extension Partnership (MEP)**.⁴ Knowledge and technologies developed under the auspices of the National Institute of Standards and Technology are used to assist small and medium sized companies. To date all states have manufacturing technology centers or smaller outreach centers. Funding was \$11.9 million in FY1991, \$15.1 million in FY1992, and \$16.9 million in FY1993. FY1994 appropriations totaled \$30.3 million for the expanded MEP which combined the Centers Program, the Manufacturing Outreach effort, and the State Extension Program. Funding for FY1995 was \$84 million (post rescission) and included a new program, LINKS, to tie together federal, state, and local agencies, the private sector, and the manufacturing outreach institutions through communications and computer data systems. While the FY1996 appropriation declined to \$80 million, support for FY1997 increased to \$99.9 million. In FY1998, appropriations funding again increased to \$113.5 million. The House and Senate appropriations bills for FY1999 would both support MEP at \$106.8 million, the same as the Administration's request.

The **Small Business Innovation Research Program**, created by P.L. 97-219, as amended, is an activity to assist small, high technology companies perform research, development, and commercialization in areas of interest to the government.⁵ Each federal agency with an R&D budget over \$100 million is required to set aside a percentage of that funding (2.5% in 1997 until sunset in 2000) for grants to small firms. Financing is, in part, dependent on companies obtaining private sector support for the commercialization of the resulting products or processes. A pilot program also was created to encourage small firms to work with universities or federal laboratories to facilitate the commercialization of research performed in these institutions. This activity is funded by a 0.15% (phased in) set-aside. Originally expected to sunset in FY1996, the program has been extended through FY2001.

Issues For Consideration: A New Approach?

In the past, government support for technology development has been reflected in the balance between legislatively mandated incentives for private sector investment and direct government financing of R&D. The activities of the 104th Congress displayed a preference for the first approach. The first session of the 105th Congress further explored technology policy within the context of budget decisions. On-going programs were funded, however, some support at reduced levels. What happens next might be dependent on how the debate is framed. Will federal funding of specific technology ventures continue to be seen by the majority as "picking winners and losers" or will spending for efforts such as ATP be seen as fostering productive collaboration among firms? Is the government making

⁴See: Congressional Research Service, *The Manufacturing Extension Partnership*, by Wendy H. Schacht, CRS Report 97-104.

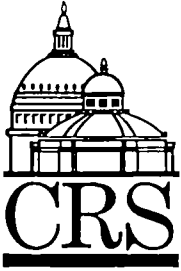
⁵Additional detail in: Congressional Research Service, *The Small Business Innovation Research Program*, by Wendy H. Schacht, CRS Report 96-402.

decisions which should best be left to the marketplace or is there an overriding national need for federal investment in these industry-led programs?

There appears to be agreement with the basic premise that the government does have a role in fostering technological advancement in the private sector; the debate is over how this is best achieved within existing and future budget constraints. In place of direct federal appropriations, some have suggested the creation of tax incentives which, proponents argue, would provide the capital resources necessary for industry to invest in additional R&D. Thus, efforts such as a permanent and expanded research and experimentation tax credit are considered a viable substitute for government cost-shared programs. Changes in the capital gains tax to encourage long term investments, particularly in high technology companies, also have been proposed to increase the amount of funding available for industrial use.

Regulatory reform may be used to facilitate technology development by diminishing the costs associated with bringing a new product or process to the marketplace. Disincentives to new technology development embodied in the threat of large punitive damage awards might be addressed by liability reform. In addition, other ideas might be considered to encourage collaborative work among industry, university, and government. These include changes to the antitrust laws pertaining to cooperative development and/or commercialization activities, increasing state government participation in relevant federal decisionmaking, and strengthening intellectual property protection.

Research and development funding constitutes the largest single portion of total federal discretionary spending and is therefore subject to cuts as legislators move toward a balanced budget. As a result, it is unrealistic to expect significant increases in government funding for such work. Thus, priorities concerning the allocation of financing may need to be established. Simultaneously, it might be helpful to create new methods to encourage increased activities by other parties in the innovation process, particularly if the goal is to continue the technological advancement which has been so instrumental to this nation's economic growth and high living standard.



Memorandum

October 6, 1999

TO : Honorable Nancy Pelosi
Attention: Chris Collins

FROM : Gary Guenther
Analyst in Business Taxation and Finance
Government and Finance

SUBJECT : Effectiveness of the Proposed Tax Credits for Vaccine Research in H.R. 1274

Responding to your request, this memorandum assesses the likely effectiveness of the proposed tax credits for vaccine research in H.R. 1274. Effectiveness in this case signifies the likely rise in domestic investment in vaccine research and development (R&D) in response to the tax credits. This method of assessing the proposed credits' effectiveness boils down to comparing the additional vaccine R&D induced by one dollar of tax credit claimed, which is a way of analyzing the benefit-cost ratio for the credit. The proposed credits also raise the issue of whether such a subsidy can be justified on economic grounds. This issue is discussed briefly in the final section.

Two noteworthy conclusions emerge from the analysis presented here. One is that the proposed tax credits can be expected to spur increased investment in vaccine R&D by the private sector, by both increasing expected after-tax returns on this investment and improving the access of small startup firms to equity capital for investment in vaccine R&D. The second conclusion relates to the economic rationale for the proposed tax credits: they are justified on economic grounds to the extent that they attempt to correct failures in the market for vaccines that result in economically inefficient levels of domestic investment in vaccine R&D.

If you have any questions about this analysis, please call me at 7-7742.

The Economics of Vaccine Innovation

Vaccines are among the most cost-effective weapons in the arsenal of modern medicine against the spread of contagious diseases, lethal and non-lethal. By strengthening an individual's immune system to resist a wide range of infectious diseases, they offer a relatively inexpensive means of lowering a society's overall cost of medical care. While historically vaccines have been used to prevent a variety of diseases, intensive efforts are being made to develop vaccines that can treat certain diseases -- mainly cancer and AIDS -- after an individual contracts them.

On the whole, the development of new vaccines is a long, costly, and risky process. It typically takes 10 years and requires outlays of \$100 million to bring a new vaccine from the research laboratory to the medical marketplace.¹ In addition, firms seeking to develop new vaccines face a considerable risk of failure. A 1989 study estimated that only 3 out of 10 vaccines that enter clinical trials end up being approved for general use.² For the most part, vaccine development passes through the same stages as the development of new therapeutic drugs: a period of basic research or discovery, followed by the filing of an investigational new drug application with the U.S. Food and Drug Administration (FDA), followed by three stages of clinical trials. Vaccine development, however, departs from the path of new drug development during the third phase of clinical trials, when a firm developing a new vaccine must file both a product license application and an establishment license application with the FDA; firms developing new therapeutic drugs only are required to file a new drug application at this stage. Once the FDA is satisfied that the vaccine is safe and effective and that the plant where it is produced meets the FDA's stringent standards for purity, cleanliness, and quality control, the vaccine can be marketed in the United States. This means that the FDA requires vaccine firms to construct and start up manufacturing facilities for new products several years before they can gain marketing approval -- and thus begin to earn a return on the funds invested in their development.

The economics of vaccine innovation has important implications for the structure of the vaccine industry. High fixed costs for research, production setup, and obtaining and maintaining FDA marketing approval result in marginal vaccine production costs that are significantly below average vaccine production costs. Such a cost structure is not conducive to the existence of multiple sellers of the same vaccines. As a seller's output expands, its average costs decline; and as those costs fall, its ability to underprice its competitors and still cover its costs grows.³ The degree of competition in the world vaccine industry seems to confirm this crucial point. Vaccine production in the United States and the rest of the world has been highly concentrated: in 1994, four firms (Institut Merieux, Merck, SmithKline Beecham, and American Cyanamid) accounted for between 65% and 80% of world sales of vaccines; and in 1993, the same four firms produced nearly all the pediatric vaccines purchased in the United States.⁴

In the United States, the federal government finances the lion's share of basic research in vaccines, where the emphasis is on understanding the fundamental mechanisms of infectious disease and the immune system. Once a vaccine research project advances to the level of applied research and development, where the emphasis is on producing and testing specific products with commercial potential, the private sector takes the lead in financing.

¹ Sing, Merrile and Mary Kaye Willian. "Supplying Vaccines." *Supplying Vaccine: An Economic Analysis of Critical Issues*. Pauly, Mark, et.al., editors. Washington, D.C., IOS Press, 1996. P. 61.

² Grabowski, Henry G. and John M. Vernon. *The Search For New Vaccines*. Washington, D.C., American Enterprise Institute Press, 1997. P. 20.

³ Pauly, Mark V. and Bridget E. Cleff. "The Economics of Vaccine Policy: A Summary of the Issues." *Supplying Vaccines*. P. 7.

⁴ Sisk, Jane E. "The Relationship between Scientific Advances and the Research, Development, and Production of Vaccines in the United States." *Supply Vaccines*. p. 181; and FIND/SVP. *The World Market for Vaccines*. New York, October 1995. P. 169.

Near the end of the development cycle for vaccines, the federal government becomes more involved again by helping fund clinical trials to test the safety and efficacy of new vaccines.⁵ According to one estimate, the federal government provided \$500 million (or 36%) of the \$1.4 billion spent on U.S. vaccine R&D in 1995, and the private sector contributed the remaining \$900 million (or 64%), with the lion's share coming from four large, established sellers of vaccines: Merck, the Wyeth-Lederle division of American Home Products, SmithKline Beecham, and the Pasteur Merieux Connaught division of Rhone Poulenc.⁶

In the past decade, the private sector has shown a vibrant interest in vaccine innovation, and investment in vaccine R&D has risen accordingly. While a number of factors have come together to spur this interest, a key driving force has been the revolutionary advances in the understanding of the molecular basis of the immune system and disease engineered by biotechnology. Recombinant technology is now being used to improve existing vaccines and to produce new ones, to design more efficient combinations of existing vaccines, and to find better ways of delivery than a shot in the arm. Moreover, most vaccine industry executives are convinced that the new vaccines developed through the application of recombinant technology will gain patent protection, unlike traditional vaccines which are derived from naturally occurring organisms and thus not eligible for patent protection. Patented vaccines tend to command much higher prices in private markets than those lacking patent protection. By one account, as of May 1998, at least 50 biotechnology firms had joined the large, established producers of vaccines in the search for new vaccines, and about 75 new vaccines were in various stages of development worldwide.⁷ The economies of scale in vaccine production, however, make it unlikely that many of small startup firms now engaged in vaccine R&D will grow into large, independent producers. Although public data on vaccine R&D are sparse and not systematically collected, figures on pharmaceutical R&D reported by the Pharmaceutical Research and Manufacturers of America (PhRMA) appear to underscore the renewed interest in vaccine R&D in the pharmaceutical industry. In its latest profile of the U.S. pharmaceutical industry, PhRMA reports that domestic R&D investment in biologicals, a product class that is dominated by vaccines, rose from \$274 million (or 4.7% of domestic pharmaceutical R&D) in 1989 to \$716.8 million (or 5.3% of domestic pharmaceutical R&D) in 1996.

Intended Purpose of H.R. 1274, the Lifesaving Vaccine Technology Act of 1999

The central aim of H.R. 1274 is to boost U.S. investment in the development of vaccines for diseases that kill large numbers of people each year, especially in developing countries. Its chief policy instrument for achieving this objective is a tax credit equal to 30% of qualified vaccine research expenses in a tax year. Under the bill, qualified vaccine research expenses are defined as a firm's in-house and contract research expenses related to the discovery and development of vaccines for malaria, tuberculosis, HIV, or any infectious disease that kills over one million persons annually, as determined by the World Health Organization. The definition of qualified research expenses under H.R. 1274 is identical to

⁵ Sisk, Jane E. *Supplying Vaccines*. P. 177.

⁶ Marcuse, Edgar K., et. al. "United States Vaccine Research: A Delicate Fabric of public and Private Collaboration." *Pediatrics*, December 1997. P. 1017.

⁷ Vaccines: Big Shots. *Economist*, May 9, 1998. P. 63.

the definition of research expenses that qualify for the research and experimentation (R&E) tax credit, with one significant exception: the proposed vaccine research tax credit would apply to 75% of qualified contract research expenses, whereas the R&E tax credit applies to only 65% of such expenses -- except in the case of contract research performed by certain research consortia, where 75% of the expenses qualify for the credit. Like the R&E tax credit, public or private grants for vaccine research are ineligible for the credit. In addition, any research expenses claimed for the vaccine research credit cannot also be claimed for the R&E tax credit, although qualified vaccine research expenses could be used to calculate the base amount for the R&E credit; and with the exception of expenses for human clinical testing conducted abroad, no credit is available for foreign vaccine research. H.R. 1274 also specifies that the proposed vaccine research credit would become part of the general business credit and thus subject to its limitations; any portion of the vaccine research credit that cannot be used in the tax year in which it is earned could be carried forward to a succeeding tax year, but the unused portion could not be carried back beyond the year in which the credit was enacted. Finally, like the R&E credit, qualified research expenses that are deducted under section 174 of the Internal Revenue Code (IRC) must be reduced by the amount of any vaccine research credit claimed. This requirement has important implications for the marginal effective rate of the credit, because whatever vaccine research credit is claimed in effect is taxed at a firm's marginal corporate income tax rate.

H.R. 1274 would also create a less direct tax subsidy for vaccine R&D. This subsidy is targeted at investors and is intended to make it easier for small firms involved in vaccine R&D to raise money in equity markets. Specifically, the bill would grant individuals or firms that purchase the "qualified research stock" of small firms undertaking or funding qualified vaccine research a tax credit equal to 20% of the amount they pay for the stock, provided two conditions are met. First, the firm whose stock is bought must use the proceeds within 18 months of the date of purchase to pay for research that qualifies for the vaccine research credit. Second, the firm must waive its right to claim a tax credit for the vaccine research funded by the stock purchases. Under H.R. 1274, qualified research stock is defined as any stock issued by a firm that is subject to the corporate income tax and has gross assets of \$50 million or less; the stock must be issued after the date the bill is enacted and acquired "at its original issue in exchange for money or other property (not including stock)."

Likely Impact of H.R. 1274 on U.S. Vaccine R&D

How are the proposed tax subsidies in H.R. 1274 likely to affect vaccine R&D? The answer hinges largely on the effect of the subsidies on two key determinants of business R&D investments: the expected after-tax rate of return on such investments and the availability and cost of capital to finance the investments.

For firms seeking to develop new or improved vaccines, the decision to invest in R&D is no different in principle from a decision to invest in any other capital asset, such as a new production facility. The key considerations are the expected after-tax returns on the proposed R&D projects, the cost of capital or funds for the projects, and the availability of funds to finance the projects. Small startup firms are more likely than large, well-established firms to have trouble funding R&D projects out of retained earnings or raising funds in debt or equity markets to finance these projects. In theory, a vaccine firm will invest in R&D projects up to the point where the expected after-tax rate of return on a possible project matches the firm's cost of capital. Projects with the largest gap between expected after-tax rates of returns and the cost of capital are likely to receive the highest priority.

H.R. 1274 can be expected to increase the level of domestic vaccine R&D by both increasing the expected after-tax rates of return on possible research projects and improving the access of smaller, newer vaccine firms to equity markets. The proposed flat 30-percent tax credit on qualified vaccine research would be one of the factors shaping the expected after-tax returns on vaccine R&D investments. Other important factors are the eventual size of the market for the vaccine, the predictability of prices and usage rates for the vaccine, expected production costs, exposure to liability suits for side effects of the vaccine, patent protection, the ease of entry into the market for the vaccine, and the cost of capital.⁸ The proposed credit would increase expected after-tax rates of return. Under current tax law, firms performing vaccine R&D can claim the 20% R&E tax credit for qualified research. But because of the rules governing the use of the credit, the marginal effective rate of the credit is 6.5% or 13% on each additional dollar spent on vaccine research by firms in the 35-percent corporate tax bracket. If H.R. 1274 were enacted, the same firms could claim a tax credit for qualified research with a marginal effective rate of 19.5%; the rate would not be 30% because of the requirement that any credit claimed must be added to a firm's taxable income. All other things being equal, as a firm's marginal effective rate for the vaccine research credit goes up, the after-tax rate of return to this research rises.

In addition, vaccine firms that are constrained by a lack of funds in pursuing research opportunities could be expected to invest more in vaccine R&D if H.R. 1274 were enacted. Investors would be eligible for a flat 20% tax credit on purchases of common stock issued by small vaccine firms, provided the firms invest the proceeds from the stock purchases in qualified research within 18 months of the purchase. As a result, investors would face lower marginal tax rates on the returns to these investments than on the returns to alternative investments. This difference could lead them to invest more in small vaccine firms than they otherwise would, augmenting their available funds for R&D. Innovation is the main route of entry into the vaccine business for small firms.

How much is vaccine R&D spending likely to increase in response to the proposed credit? This is difficult to analyze in the absence of reliable estimates of the responsiveness of vaccine R&D to changes in its after-tax price. The proposed credit lowers the after-tax price of qualified R&D, and in theory vaccine firms can be expected to perform more R&D as a result. A variety of studies have estimated that in the 1980s the "tax price elasticity of total (U.S.) R&D spending" was unity or even higher, meaning that U.S. firms responded to a 1% decline in the after-tax price of R&D by increasing their R&D spending by 1% in that decade.⁹ Assuming vaccine firms exhibit the same tax price elasticity today, a research tax credit with a marginal effective rate of 19.5% could lead to a rise of as much as 19.5% in domestic vaccine R&D spending. However, this estimate cannot be regarded as reliable and could be greatly exaggerated, because it is unlikely that the sensitivity of R&D investment to changes in its after-tax price remains constant over time and is the same for all kinds of R&D projects, and because vaccine firms would be likely to differ in their ability to use the credit in any given year.

⁸ Sisk, Jane E. *Supplying Vaccines*. P. 175.

⁹ Hall, Bronwyn H. and John van Reenen. *How Effective Are Fiscal Incentives for R&D: A Review of the Evidence*. Working Paper 7098. Cambridge, MA, National Bureau of Economic Research, April 1999. P. 21.

Furthermore, there is some reason to believe that the proposed vaccine research tax credit would eventually be as cost-effective as direct spending by the federal government on vaccine R&D. A number of studies have concluded that the existing R&E tax credit yields roughly a dollar-for-dollar increase in reported R&D at the margin, but that in the early years of the credit firms were not as responsive as they were adjusting to the credit's availability.¹⁰ In other words, these studies suggest that government spending programs and the R&E tax credit are equally effective in increasing the amount of qualified research performed in the United States.

Economic Justification for a Tax Credit for Vaccine Research

Under conventional economic theory, the use of a subsidy such as a research tax credit is justified if it's ultimate aim is to correct some sort of market failure. In the case of R&D, the R&E tax credit is one way to offset the tendency of firms to underinvest in R&D because of the gap between the social and private returns to research. Economists argue that in the absence of government support for R&D, firms are likely to invest too little in R&D because they cannot appropriate all the returns to those investments. So the R&E tax credit, by lowering the after-tax cost of qualified research, is intended to spur firms to invest more in R&D than they otherwise would. Ideally, the added R&D stimulated by the credit is enough to raise domestic R&D spending to the level commensurate with the social returns to R&D. The market failure that the R&E tax credit is attempting to remedy is underinvestment in R&D arising from the inability of firms performing R&D to capture all the profits generated by the investment.

These considerations raise the issue of whether the proposed tax credit for vaccine research in H. R. 1274 is justified on economic grounds. Is there a failure in the market for vaccines that would warrant the adoption of such a subsidy? As was suggested earlier, there are external economic benefits from controlling the spread of infectious diseases. The cost to society of preventing an outbreak of an infectious disease tends to be much lower than the cost of treating the outbreak that might occur in the absence of immunization. This raises the possibility that private firms invest less in vaccine R&D than its potential social benefits warrant. Partly in an effort to correct for such a market failure, the federal government supports vaccine R&D through its funding of basic research in vaccines and clinical trials for new vaccines. Its research support is also intended to direct vaccine investment to address current and future public health needs. In addition, it offers two tax subsidies for R&D, namely: the R&E tax credit and the expensing of R&D costs under IRC section 174. Although these subsidies are not targeted at vaccine research but are available to all firms that perform qualified research, they benefit vaccine firms by increasing their potential after-tax rate of returns on R&D investments. The proposed vaccine research tax credit would supplant the R&E tax credit for vaccine firms, but its treatment of qualified research would be more favorable, increasing the expected profitability of vaccine R&D investment relative to other kinds of R&D investment.

Thus, an important policy issue for Congress is whether the current level of domestic vaccine R&D investment is socially desirable or efficient. And if not, would the proposed tax credit in H.R. 1274 be more efficient than added federal funding of vaccine R&D or some other policy measure (such as government grants to international agencies that

¹⁰ Hall, Bronwyn H. *How Effective Are Fiscal Incentives for R&D?* P. 21.

purchase and distribute needed vaccines in poor countries) in raising total investment to such a level. From the perspective of economic efficiency, the R&D projects that should be promoted are those with the largest gaps between the social and private rates of return. Yet vaccine firms are likely to use any research tax credits to fund first those projects with the highest expected private rates of return. At the same time, there is no certainty that the federal government could do a better job of targeting those vaccine R&D projects with the largest spillover effects. If it is determined that domestic vaccine R&D is less than socially optimal, perhaps a combination of a targeted tax credit like the one proposed in H.R. 1274 and increased government support for basic and applied vaccine research would be more attractive than relying solely on one instrument or the other.

Another policy issue for Congress raised by the proposed tax credits in H.R. 1274 relates to the external benefits of mass immunizations. The economic benefits to a society from vaccinations far outweigh the benefits to individual consumers, who in deciding whether or not to purchase vaccines for themselves or their children tend to consider only the costs and benefits to themselves and not the potential benefits to others in the community. Even if the market for vaccines were perfectly competitive, it is unlikely that immunization levels would be socially optimal.¹¹ Thus government intervention in the development and distribution of vaccines is certainly justified on economic grounds. The proposed tax credits would spur the development of new vaccines, but they would not lessen any of the barriers to the achievement of universal immunization with available vaccines. Low immunization rates are due to a variety of factors, including out-of-pocket costs, parental attitudes and knowledge, access to health clinics or doctors' offices, the perceived efficacy of vaccines, and the perceived risk of contracting diseases for which vaccines exist.¹² Clearly, other policy initiatives would be needed to address these factors.

¹¹ Holtmann, Alphonse G. "The Economics of U.S. Immunization Policy." *Supplying Vaccine*. P. 155.

¹² Pauly, Mark V. and Bridget E. Cleff. "The Economics of Vaccine Policy." *Supplying Vaccine*. P. 12-16.



National Institute of Allergy and Infectious Diseases • National Institutes of Health

Evolution of Vaccine Development

English physician Edward Jenner's observation that milkmaids stricken with a disease called cowpox were rarely victims of smallpox prompted him to devise the first vaccine 200 years ago. One of the world's great medical successes, a modern-day version of this vaccine led to the total eradication of smallpox by 1980. Since Jenner's time, advances in the science of virology, bacteriology, and immunology have led to an enhanced understanding of how the human body defends itself against invading microorganisms. The development of vaccines against more than 20 infectious diseases has revolutionized our approach to public health. Since 1980, at least 15 new or improved vaccines have become available. Today, tremendous advances in molecular biology enable scientists to devise new approaches to developing vaccines against diseases that continue to plague the world's population.

Scientists in the laboratories of the National Institute of Allergy and Infectious Diseases (NIAID) and NIAID-supported investigators at research institutions around the country are pursuing novel approaches to the development of new and improved vaccines. The Institute has fostered the development of vaccines against such diseases as influenza, pneumococcal pneumonia, pertussis, rubella, rabies, bacterial meningitis, hepatitis B, and adenovirus-associated respiratory disease. NIAID also supports innovative scientists who are using vaccine technology to combat autoimmune disorders and allergies.

Vaccines are made in a variety of ways, depending in part on the nature of the organism and the disease it causes. Animal viruses, weakened microbes, killed microbes, and toxins are the most common components of the vaccines that have been in use throughout much of the 20th century.

Animal Viruses

Unknown to Jenner, his vaccine worked because the cowpox virus he used, which does not cause severe disease in healthy humans, shares some proteins with its more virulent cousin, the variola virus that causes smallpox. These proteins, called antigens, stimulate the body's complex immune response, including the production of memory cells. The next time that an individual encounters that same antigen, the immune system is primed to destroy it quickly, before it can cause disease.

Jenner's approach to vaccines is still being used today. NIAID

investigators are using viruses that cause diseases in animals to make vaccines designed to offer protection against rotaviruses, the leading cause of infant diarrhea worldwide, and against parainfluenza viruses, which cause severe respiratory tract infections in children.

Weakened Microbes

In the late 19th century, the French microbiologist Louis Pasteur used another approach to create a vaccine against human rabies. The vaccine he developed, using weakened live rabies virus, was later refined, but his idea has been used to create many highly effective vaccines. Microbes weakened by growing them for many cycles in animals or in tissue cultures in the laboratory can be used to infect individuals without causing serious symptoms of the disease. Scientists have also created vaccines from naturally weakened strains of microbes that have been isolated from humans.

The oral polio vaccine is made from live, weakened virus as are vaccines for mumps, measles, and rubella. In addition, NIAID-supported researchers are using weakened viruses to create vaccines designed to protect against diseases caused by rotaviruses, respiratory syncytial virus, parainfluenza and influenza viruses.

Killed Microbes

A number of other vaccines have been developed from whole organisms that have been killed. Safe and relatively easy to produce, these inactivated vaccines do not cause infection in people who receive them, but they are able to stimulate the immune system. However, the immunity produced may be less complete and shorter lasting than that produced by a live vaccine or by natural infection. Such vaccines in use today include those against polio, whooping cough, and influenza.

Toxins

Some bacteria cause disease by producing toxins that invade the bloodstream. Around the turn of the century, the identification of the tetanus and diphtheria toxins led to another type of vaccine that stimulates the production of antibodies against these toxins. The diphtheria and tetanus vaccines are made from inactivated toxins and have been used successfully to prevent these diseases since the early 1900s. Improved vaccines against whooping cough (caused by the pertussis bacterium) that are made up of inactivated pertussis toxin and other toxic bacterial products of the pertussis organism have recently been demonstrated to be both safe and effective in preventing whooping cough in babies and young children.

Subunit Vaccines

Recent research has focused on developing vaccines that use only part of the infectious agent. Such subunit vaccines, which are now

available for meningitis, pneumonia, typhoid, and hepatitis B, produce the desired immunity without stirring up separate and potentially harmful immune reactions to the many antigens carried, for instance, on a single bacterium. Other subunit vaccines under development include those for respiratory syncytial virus and parainfluenza virus infections.

Conjugate Vaccines

Bacterial diseases such as pneumonia and meningitis cause considerable illness, disability, and death among babies and children in the United States. Some of the bacteria that cause these diseases have an outer coat that cannot be recognized by the immature immune systems of young infants, and therefore vaccines made from these bacteria are not effective in babies. In addition, these vaccines are of limited benefit to the elderly who have a diminished immune response.

NIAID-supported researchers and scientists at the National Institute of Child Health and Human Development devised a way to produce vaccines that link together proteins or toxins from a second organism to the outer coat of the bacteria. This enables a baby's immune system to respond to the combined vaccine and produce antibodies, immune system proteins that bind to the bacteria and prevent disease. The first of this new breed of conjugate vaccines was licensed in December 1986 to protect against *Haemophilus influenzae* type b (Hib), the major cause of bacterial meningitis in babies and young children. In 1990, two conjugate vaccines were licensed to protect against Hib in babies as young as 2 months. The widespread use of these vaccines has virtually eliminated Hib meningitis in the United States.

Vaccines Through Biotechnology

Through genetic engineering, scientists can isolate specific genes and insert them into the DNA of certain microbes or mammalian cells grown in the laboratory, which become living factories, mass producing the desired antigen. Then, using another product of biotechnology, a monoclonal antibody that recognizes the antigen, researchers can separate the antigen from all the other material produced by the microbe or cell. This technique has been used to produce safe vaccines that stimulate the human immune system against such organisms as the hepatitis B virus.

In another approach, scientists have inserted genes for desired antigens into the DNA of related but harmless viruses such as the vaccinia virus, a relative of the cowpox virus that was used in modern smallpox vaccines. When the re-engineered vaccinia virus is inoculated, it stimulates an immune reaction to both the vaccinia and the products of its passenger genes. These have included, in animal experiments, genes from the viruses that cause hepatitis B, influenza, rabies, and AIDS. Scientists similarly are using bacteria such as salmonella as vaccine vectors to carry portions of microbes.

Instead of adding a gene, some scientists have snipped a key gene

out of an infectious organism. Thus crippled, the microbe can produce immunity but not disease. This technique has been tried with the cholera bacterium and with herpes simplex virus.

DNA vaccines employ a new approach in which genes from disease-causing microbes are isolated and injected directly into a person. Some of these genes enter host cells, which then synthesize the proteins encoded by the injected genes. The foreign proteins elicit an immune response that may protect against subsequent infection by the microbe. A DNA vaccine against AIDS is now being tested in people.

A totally different approach to vaccine development lies in chemical synthesis. Once scientists have isolated the gene that encodes an antigen, they are able to determine the precise sequence of amino acids that make up the antigen. They then pinpoint small key areas on the large protein molecule, and assemble it chemical by chemical. Wholly synthetic vaccines are being explored for malaria and diarrheal diseases prevalent in developing countries.

Vaccines remain among the most powerful tools we have for disease prevention. Advances in biotechnology have ushered in a new era in vaccine development. NIAID has maintained a leadership role in the basic research and development of new and improved vaccines and will continue to nourish this exciting renaissance in vaccine development.

NIAID, a component of the National Institutes of Health, supports research on AIDS, tuberculosis and other infectious diseases as well as allergies and immunology.

Prepared by:
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Vaccines in Clinical Trials

The National Institute of Allergy and Infectious Diseases (NIAID) has supported and conducted clinical trials of vaccines for many years. Today's enhanced understanding of the immune system as well as extraordinary advances in molecular biology have fostered the accelerated development of many new and improved experimental vaccines. Designed to protect against a wide range of diseases from the flu to AIDS, these new vaccines are now being evaluated in clinical trials. Several of these vaccine trials are described below.

Genital Herpes Vaccine

Genital herpes causes both physical and psychological discomfort, and many infected people experience painful recurrences of genital blisters throughout their lives. Even when symptoms are not apparent, the herpes simplex virus, which causes genital herpes, can be transmitted to sexual partners. In addition, each year about 1,500 babies contract neonatal herpes infection from their infected mothers during labor or delivery, and about half of these infected babies die or suffer serious neurologic damage.

NIAID researchers and scientists supported by NIAID recently completed preliminary testing of the first genetically engineered vaccine for genital herpes in a small number of infected and uninfected adults. The vaccine proved to be safe and prompted an immune response that matched what occurs during a natural genital herpes infection. In volunteers who have genital herpes, the vaccine reduced the number of herpes outbreaks compared to those given a placebo. An expanded trial in infected volunteers is continuing to further determine the vaccine's safety, its ability to stimulate the immune system, and its effectiveness in preventing recurrences of herpes lesions. The vaccine also is being tested in uninfected people to evaluate its ability to prevent infection with the virus that causes genital herpes.

Vaccines for Respiratory Tract Infections

Pneumococcal pneumonia is a life-threatening respiratory tract infection caused by the bacterium *Streptococcus pneumoniae*. The current vaccine, available since 1983, does not protect children younger than 2 years and has been shown to be not highly effective in some elderly populations. NIAID-supported researchers and others have developed conjugate pneumococcal vaccines that link the outer coat of the pneumococcal bacterium with proteins. These conjugate vaccines are more effective than existing pneumococcal

vaccines in stimulating the immune system in babies and older people. The new vaccines contain up to 11 of the most common *S. pneumoniae* strains that cause bloodstream infections, meningitis, and middle ear infections. NIAID is supporting clinical trials in high-risk populations such as the elderly and infants.

Influenza is a respiratory disease that can be particularly serious in older people and very young children. Influenza viruses are notorious for their ability to change the proteins on their outer surfaces, causing new outbreaks and periodic epidemics throughout the world. Although influenza vaccines have been available for many years, they provide short-lived protection and must be produced each year to protect against the particular strains of influenza prevalent during a given year.

NIAID scientists have developed a vaccine using live, weakened virus. This vaccine may be more effective because the virus is adapted to growing at colder temperatures, which means that it can infect the cooler upper respiratory tract, stimulating immunity, but not cause disease in the warmer lungs. NIAID conducted a 5-year trial, among thousands of volunteers, that showed this vaccine to be as effective as the currently available inactivated vaccine. Further studies are under way in NIAID's Vaccine Treatment and Evaluation Units to examine the vaccine's safety and ability to stimulate an immune response in children when delivered as a nasal spray. NIAID continues to work with researchers and pharmaceutical companies to evaluate alternative vaccine delivery approaches.

Cholera Vaccine

Cholera is both a common and extremely deadly disease in many parts of the world. During 1991, it spread to South America, affecting more than a million people in the first epidemic there since the turn of the century. By causing unremitting diarrhea, which results in dehydration, the toxin produced by cholera bacteria can kill a person in less than 24 hours. Although antibiotics and oral rehydration therapy can effectively treat persons with cholera, the disease still kills many of those who do not have quick access to medical care. This was most recently demonstrated among the refugees in Rwanda, when cholera swept through refugee camps.

NIAID-supported investigators have developed an experimental oral cholera vaccine using live cholera bacteria in which the toxin genes have been modified. This vaccine was well-tolerated, stimulated the immune system, and protected volunteers who received just a single dose. It has been tested, with technical assistance from NIAID, in adults and young children in the U.S., Chile, Indonesia and Peru and was shown to be safe and able to stimulate an immune response. A large trial involving more than 60,000 people is now under way in Indonesia to determine if the vaccine is effective in preventing cholera. This vaccine has been licensed in several European countries, and U.S. licensure will be sought by the manufacturer in the near future. Other experimental vaccines directed against a new strain of the cholera bacterium also have been developed with NIAID research support and are being evaluated in clinical trials in U.S. volunteers.

AIDS Vaccines

In 1987, NIAID began the first clinical trial of an experimental vaccine against HIV, the virus that causes AIDS. Since the first trial, about three dozen preventive HIV vaccine trials have been initiated worldwide. As of January 1996, nearly 1,800 men and women had participated in HIV vaccine trials conducted at six NIAID-supported AIDS Vaccine Evaluation Units. To date, all the vaccine candidates tested have been well tolerated, generally producing only mild side effects typical of most vaccines.

The challenges in HIV vaccine development are enormous. Researchers do not know what constitutes immune protection against HIV or whether a natural protective state can exist. Unlike other vaccines, an HIV vaccine may need to stimulate both cellular and mucosal immunity. Moreover, HIV continually evolves as a result of genetic mutation and recombination, so that a successful vaccine must generate immune responses that protect noninfected people from all the different HIV subtypes to which they may be exposed; Although the challenges are daunting, scientists remain optimistic that safe and effective HIV vaccines can be developed.

Impact of New Vaccines

As new vaccines emerge from the laboratory into clinical testing and finally into general use, many commonplace diseases will become as rare as polio and diphtheria are today in the United States. This has been demonstrated recently by the virtual elimination in just a few years of childhood meningitis caused by *Hemophilus influenzae* type b, which is now prevented by effective conjugate vaccines. A recently licensed vaccine to prevent hepatitis A, developed by NIAID scientists, is likely to have a major impact on the incidence of this disease in the future. By continuing to refine the technology used to create vaccines, new ones are likely to be developed that will be more available and more easily administered to people in other parts of the world as well.

NIAID, a component of the National Institutes of Health, supports research on AIDS, tuberculosis and other infectious diseases as well as allergies and immunology.

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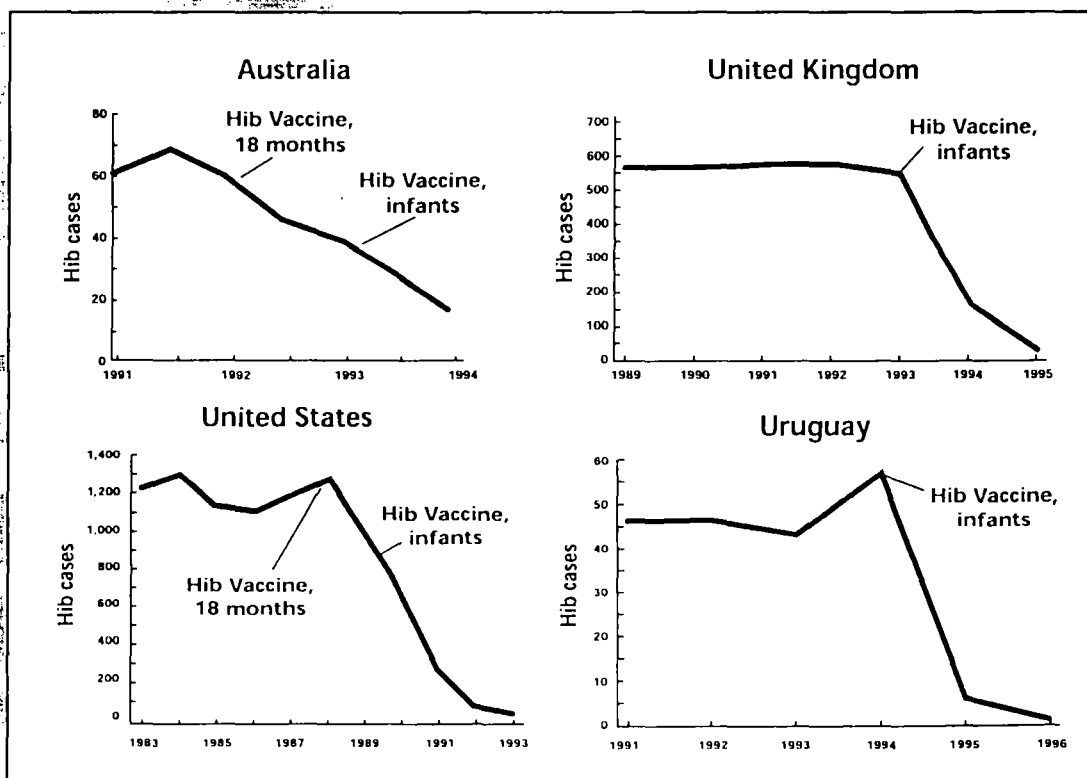
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The Jordan Report

Accelerated
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Kuwana K, Ichida T, Kamimura T, Ohkoshi S, Ogata N, Harada T, Endoh K, Asakura H. Risk factors and the effect of interferon therapy in the development of hepatocellular carcinoma: A multivariate analysis in 343 patients. *J Gastroenterol Hepatol* 1997; 12(2):149-155.

Lemon SM, Thomas DL. Vaccines to prevent viral hepatitis. *N Engl J Med* 1997; 336(3):196-204.

Linnen J, Wages J Jr, Zhang-Keck ZY, Fry KE, Krawczynski KZ, Alter H, Koonin E, Gallagher M, Alter M, Hadziyannis S, Karayiannis P, Fung K, Nakatsuji Y, Shih JW, Young L, Piatak M Jr, Hoover C, Fernandez J, Chen S, Zou JC, Morris T, Hyams KC, Ismay S, Lifson JD, Kim JP, et al. Molecular cloning and disease association of hepatitis G virus: A transfusion-transmissible agent. *Science* 1996; 271(5248):505-508.

Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. *Lancet* 1997; 349(9055):825-832.

Simons JN, Leary TP, Dawson GJ, Pilot-Matias TJ, Muerhoff AS, Schlauder GG, Desai SM, Mushahwar IK. Isolation of novel virus-like sequences associated with human hepatitis. *Nature Med* 1995; 1(6):564-569.

Terrault NA, Wright TL. Hepatitis C virus in the setting of transplantation. *Semin Liver Dis* 1995; 15(1):92-100.

Tsarev SA, Tsareva TS, Emerson SU, Govindarajan S, Shapiro M, Gerin JL, Purcell RH. Successful passive and active immunization of cynomolgus monkeys against hepatitis E. *Proc Natl Acad Sci USA* 1994; 91(21):10198-10202.

Yanagi M, Purcell RH, Emerson SU, Bukh J. Transcripts from a single full-length cDNA clone of hepatitis C virus are infectious when directly transfected into the liver of a chimpanzee. *Proc Natl Acad Sci USA* 1997; 94(16):8738-8743.

Zuckerman A. Alphabet of hepatitis viruses. *Lancet* 347:558-559.

Human Immunodeficiency Virus (HIV) Disease

Overview

As acquired immunodeficiency syndrome (AIDS) continues to take its toll globally, the development of a safe and effective vaccine against HIV is critical to worldwide efforts to control the epidemic. Although educational and counseling efforts have had some success, it has become evident that prevention activities alone are not sufficient to contain the spread of disease.

Thousands of people continue to be infected with HIV every day: an estimated 3.1 million new HIV infections occurred worldwide in 1996, roughly 8,500 per day. Approximately half of the new infections were in women. New cases of HIV are also disproportionately affecting young people: the majority of new cases worldwide are in individuals under 25 years of age. In the United States, an estimated 40,000 individuals are newly infected with HIV each year.

Given the need for a safe and effective HIV vaccine, President Clinton recently challenged scientists to develop a vaccine by the year 2007. Key to responding to that challenge will be the AIDS Vaccine Research Committee and the AIDS Vaccine Research

Center, established by the National Institutes of Health (NIH). The AIDS Vaccine Research Committee, chaired by Dr. David Baltimore, will be critical in helping to stimulate HIV vaccine research and will assist the NIH in developing a comprehensive research program aimed at expediting the discovery and development of a safe and effective AIDS vaccine. By bringing together intramural scientists from across the NIH, the AIDS Vaccine Research Center will stimulate multidisciplinary research from basic and clinical immunology and virology through to vaccine design and production. The Center will complement the comprehensive extramural research activities of the Division of AIDS, National Institute of Allergy and Infectious Diseases (NIAID). [Clinical trials of HIV vaccines, many of which are conducted by the NIAID-supported AIDS Vaccine Evaluation Group (AVEG), are described in detail in Appendix C.]

NIAID also recently unveiled a new grant program called the Innovation Grant Program for Approaches in HIV Vaccine Research, which is designed to speed the pace of AIDS vaccine discovery and development. It will do so by supporting research projects that may involve a high degree of innovation and risk, that show clear promise in improving vaccine design or evaluation, and that bring new investigators into the field of HIV vaccine research.

In addition to the efforts of the NIH are those of other Federal agencies, including the Centers for Disease Control and Prevention, the Department of Defense, the Food and Drug Administration, pharmaceutical companies, and nongovernment agencies. Augmenting all these research activities are the HIV vaccine research activities sponsored by other countries.

There are sound scientific and strategic reasons that support these extensive efforts in HIV vaccine discovery and development.

- Immunization is a well-established method of preventing viral infections.
- Passive transfer of anti-HIV or anti-SIV (simian immunodeficiency virus) antibodies to chimpanzees or monkeys has prevented infection under certain conditions.
- Some vaccines for HIV and related retroviruses have protected against challenge in certain animal models.
- To date, several HIV vaccine candidates in early human trials have been safe and immunogenic.
- Biostatistical modeling suggests that even a partially effective preventive intervention may have a powerful effect on the epidemic.

In addition, as a result of recent scientific advances, many of the obstacles to vaccine development appear to be much less formidable than had been previously thought. For example, it has long been feared that the variation of HIV within populations and individuals would enable HIV to evade specific cytotoxic T lymphocyte (CTL) and antibody responses that may be crucial for protection against HIV/AIDS. Recent studies of HIV receptors have revealed a spectrum of coreceptors, including CCR5 and CXCR4, used by HIV that may eventually form a basis for devising vaccines that can induce broadly neutralizing antibodies. A few monoclonal antibodies and some sera from infected individuals react against a variety of primary isolates of HIV. In addition, new methods for measuring CTLs have shown that CTLs from people infected with one subtype of HIV can recognize target cells representing subtypes from other geographic regions. In addition, mea-

sured against a panel of isolates from around the world, CTLs from vaccinated individuals can often recognize several genetic variants of HIV. This suggests that if CTLs (or other T cell antiviral activities) are critical to controlling or eradicating HIV infection, one vaccine may be able to immunize diverse populations against many different strains of HIV. These new findings suggest that the remarkable genetic diversity of HIV is not an insurmountable obstacle to developing a broadly reactive preventive vaccine.

In the past, there has also been concern that it would be more difficult to prevent HIV infection from sexual transmission as compared to HIV acquired through parenteral transmission (Sabin). Increasing evidence from animal models suggests that there is a short period during which the establishment of chronic infection may be prevented if infection occurs through vaginal, rectal, or oral exposure. Clinical and laboratory methodology for identifying binding antibodies and for cloning CTL from mucosal fluids or cellular specimens may help elucidate the local immune response during mucosal infection. Additionally, genetically altered toxins and physical carriers are also being developed to enhance mucosal presentation, and they may be effective in inducing mucosal immunity in humans. Thus, it may be more feasible than previously thought to prevent sexual or mucosally based transmission through either parenteral or mucosal immunization.

As researchers struggle to overcome these and other scientific challenges, individuals in the communities from which study volunteers will be recruited are working to overcome fears and preconceived notions about vaccine trials. (Volunteers will include both men and women at high risk of HIV infection because of their sexual behavior or drug use.) In addition to potential biologic risks of any new vaccine, there are concerns about the social impact of receiving a candidate HIV vaccine. Because vaccination can induce antibodies against components of HIV, some volunteers may test positive for HIV on standard HIV diagnostic tests. Although the vaccines being tested cannot result in HIV infection, volunteers may fear the social consequences and discrimination of falsely testing positive. NIAID continues to work proactively to minimize the potential for discrimination against study volunteers and over the past several years has developed strong linkages with various communities to address many of their questions and concerns about HIV vaccines. Public health and diagnostic laboratories, insurance companies, and manufacturers of diagnostic kits are helping to address volunteers' concerns.

Investigators continue to design and test novel ways to present HIV proteins to the immune system and evaluate new antigen/adjuvant and various vaccine formulations. Traditional approaches to immunization (live-attenuated, whole-inactivated) are technically complex and raise substantial safety concerns. Clinical trials involving candidates for prophylactic vaccines enroll volunteers who are not infected with HIV. Such trials have been conducted to test vaccines made through chemical synthesis or biotechnology: subunit vaccines including envelope proteins or small particles as well as recombinant poxviruses bearing genes encoding one or more viral proteins and DNA vaccines. To date, the AVEG, which supports the intensive study of novel HIV vaccine candidates in human trials, has enrolled more than 2,300 uninfected volunteers, in 47 studies involving 22 vaccine candidates. Of these, three vaccines have proceeded to phase II trials: two different recombinant gp120 envelope proteins and one recombinant

canarypox-HIV vaccine, which incorporates genetic material from the HIV envelope, gag and protease genes.

A brief description of the various types of HIV vaccines being tested and the status of research in each of these areas follows.

Protein and Peptide Subunit Vaccines

Subunit vaccines consist of small protein or peptide portions of pathogenic virus. They can be made by genetically engineering bacteria, yeast, insect, or mammalian cell cultures to produce protein subunit antigens. Envelope subunit and peptide approaches were among the earliest attempts to make an HIV vaccine, based on the premise that the envelope protein would be the most important target since it binds to cells and allows viral entry.

Phase I trials have been conducted with the full-length *env* gene product (gp160) or the envelope protein gp120 produced in insect cells, yeast, or mammalian cells. The highest titer and most broadly reactive neutralizing antibodies were induced by the mammalian gp120 vaccines. However, the first vaccines were based on laboratory-adapted strains of HIV that used the CXCR4 receptor to enter T cells; the antibodies induced by these vaccines do not neutralize primary HIV isolates grown in phytohemagglutinin (PHA)-stimulated peripheral blood mononuclear cells, which rely largely on CCR5 for entry into monocytic cells. Two gp120 vaccines produced in mammalian cells have been evaluated in phase II trials. These vaccines are now being modified to include additional components derived from Thai or U.S. isolates; these vaccines will be evaluated to determine whether they induce antibodies that block infection via CCR5.

Preclinical research is attempting to increase the quality and breadth of neutralizing antibodies by selecting Env proteins from primary isolates of HIV as the vaccine antigen and by creating forms that may better reflect the native structure of the Env protein in infectious HIV.

In addition to subunit proteins, peptide vaccine approaches are also under investigation. Peptides can be produced by chemical synthesis. Branched-chain peptides, peptides that include both T cell and B cell epitopes, and peptides conjugated to lipids to stimulate cytotoxic lymphocytes are in evaluation. The goal of these approaches is to increase immunogenicity.

Live-Attenuated Vaccines

Historically, live-attenuated vaccines have been among the most efficacious viral vaccines. These vaccines use live virus that has been modified (attenuated) to make the virus less virulent. They induce both humoral and cell-mediated immunity and generally require only one or two immunizations, since the immune responses induced by live-attenuated vaccines are very durable.

Because of safety considerations, live-attenuated HIV vaccines have not been tested in humans. Safety issues include the possibility that such a vaccine could cause AIDS, at least in some individuals; that attenuated virus in the vaccine could revert to the wild-type, disease-causing virus; or that long-term infection could cause autoimmune or malignant disease. This concern is underscored by observations that small deletions in HIV accessory genes, those used to attenuate the virus, can be "repaired" after *in vivo* infection.

Live-attenuated AIDS vaccine studies have, however, been conducted using SIV in macaques. These SIV studies have shown that both a naturally occurring attenuated virus with multiple mutations and one created by deletion of one or more genes can serve as vaccines. Protective efficacy appears to vary inversely with the level of attenuation, increases over time after vaccination, and is strongest when the challenge virus is closely related to the vaccine. (Challenge virus is used in animal studies after vaccination to determine whether protection occurred.) One of these vaccines, in high dose, has caused death in neonatal macaques, and some individual juvenile or adult macaques may be susceptible to disease from these vaccines.

Research is ongoing to determine the mechanisms responsible for protection with live-attenuated HIV vaccines and to find safer ways to mimic the immune responses.

Particle or Whole-Inactivated Vaccines

Whole-inactivated viral vaccines are prepared by rendering the pathogenic virus unable to replicate, usually by a chemical treatment. These "killed vaccines" are potentially safer than live-attenuated vaccines; however, whole-killed vaccines often lose the potent, long-lasting immunogenicity of the live virus because the treatment used to inactivate the virus often destroys or alters important protective antigens. Incomplete inactivation could result in infection of vaccinated individuals by residual pathogenic virus.

To overcome some of these obstacles, researchers have produced virus-like particle (VLP) or "pseudovirion" experimental AIDS vaccines by recombinant technology. They express all or a portion of one or more structural genes of HIV or SIV and mimic the native expression of the particular viral protein(s). However, the pseudovirions do not contain the HIV genome, so they cannot produce progeny virus. The manufacture of these VLPs is complex, and given the genetic variability of HIV, these vaccines may need to include gene products from multiple strains of HIV.

To date, whole-killed HIV vaccines have not protected immunized chimpanzees against infection with the virus. Although macaques were protected against SIV challenge when immunized with inactivated SIV, the protection was due to antibodies to human cell line xenoantigens present in the vaccine preparations and challenge stocks. Macaques that were immunized and challenged with SIV grown in monkey cells were not protected from infection.

To date, only one VLP experimental AIDS vaccine (p17/p24:TY) has been tested in prophylactic phase I trials. This particle contains only a portion of core, without envelope, so it is more like a subunit than a complete HIV particle. Low levels of HIV-specific binding antibodies and T cell memory responses were generated in most of the volunteers after three or four immunizations. However, little HIV gag-specific CTL activity has been observed to date. In an ongoing study, volunteers receive intramuscular immunizations followed by boosts of the VLP orally or rectally to determine whether HIV-specific mucosal antibody responses are induced. Other recombinant particle vaccine candidates are in development or in the planning stages.

Recombinant Live-Vector Vaccines

Recombinant live-vector vaccines represent a novel vaccine strategy currently under development for HIV. These vaccines are produced by engineering viral or bacterial genomes to express the desired HIV antigen(s). Viral vectors can be constructed to contain one or more viral genes that cause infected cells to make the coded protein in native form. Recombinant viral vectors enter cells and allow the HIV or SIV proteins to be generated inside the cells; these proteins are then presented to the immune system in the same way that proteins from a virus-infected cell would be. As a result, vector-based vaccines induce both humoral and cellular immune responses. Importantly, immune responses can be generated to the vector as well as to the incorporated antigens. The immune responses to the vector could limit the effectiveness of subsequent immunizations using the same vector. When given in combination with recombinant subunit products, live-vector experimental vaccines have been shown to prime the recipient for augmented immune responses.

Live, infectious viral or bacterial vectors, genetically engineered to express genes of HIV or SIV, are being evaluated in animal models for their potential to prevent infection by HIV, SIV, or SHIV. (SHIV is a genetically engineered hybrid that has an HIV envelope and an SIV core.) Poxvirus recombinants were the first to be evaluated in nonhuman primates. Vaccines based on vaccinia virus, modified vaccinia ankara, or NYVAC (two attenuated vaccinia strains) have protected nonhuman primates from SIV, HIV-2, or HIV-1 infection when they were given alone or followed by immunization with purified envelope protein to boost the antibody response (prime-boost protocol). The data are varied, however; some animals have been protected against infection, some only against disease, and some have not been protected at all.

The AVEG has conducted phase I clinical trials to evaluate recombinant vaccinia-HIV gp160 with and without boosting with one of six different candidate recombinant gp120 or rgp160 vaccines. By itself, the vaccinia-gp160 induced little antibody; however, one or two doses of it primed for both gp160-specific CTLs and anti-HIV neutralizing antibodies. The priming effect was strongest in those volunteers who had never been vaccinated against smallpox. A phase I trial of a recombinant vaccinia-HIV vaccine, incorporating Env, Gag, and Pol antigens and boosted by rgp120 candidate vaccine, is under way in the AVEG.

Vaccines based on the canarypox virus have also protected nonhuman primates from SIV, HIV-2, or HIV-1 infection when given alone or followed by a boost. These vaccines are considered safer than vaccinia vaccines since canarypox fails to replicate in mammalian cells. Recombinant canarypox-HIV vaccines have also been shown to induce both anti-HIV neutralizing antibodies and CTLs in humans, regardless of prior vaccination with vaccinia. Boosting or concomitant administration of rgp120 or rgp160 increases the production of HIV neutralizing antibodies and may induce HIV-specific antibodies. Three different types of canarypox-HIV gp160 and canarypox-HIV gp120 experimental vaccines are undergoing testing in phase I trials in France and in the United States. In addition, a phase II trial of recombinant canarypox-HIV gp120, alone or in combination with rgp120, is being jointly conducted by the AVEG and the HIVNET (HIV Vaccine Prevention Trials Network) in 420 uninfected (seronegative) volunteers, many recruited from populations at high risk of HIV infection.

Another live recombinant vector experimental vaccine that has shown protection in nonhuman primates is an adenovirus-HIV envelope vaccine. It generated neutralizing antibodies and anti-HIV CTLs when administered in a prime-boost regimen with HIV envelope protein. The prime-boost regimen protected all chimpanzees from HIV infection when they were challenged shortly after the last immunization. These chimpanzees were protected 1 year later even though they did not receive a boost and were challenged with a higher dose of the same challenge virus.

A variety of other vector-based approaches are also being developed for HIV vaccines, including recombinant poliovirus, mengovirus, Venezuelan equine encephalitis virus, herpes virus, Semliki Forest virus, influenza virus, salmonella, Bacille Calmette-Guérin (BCG), Shigella, and lactococcus. Poliovirus-SIV, BCG-SIV recombinants, and Semliki Forest virus-SIV recombinants have been tested in nonhuman primates. Although initial studies have not shown protection against infection in small numbers of monkeys, further studies are under way. Much of this work is being performed through grants awarded in NIAID's Innovation Grant Program, and testing of a recombinant salmonella-HIV gp120 candidate vaccine in a phase I trial is planned by the AVEG.

Additional research is needed in several areas regarding live recombinant vector AIDS vaccines. Increasing the level of expression of HIV proteins in the recombinant vector may improve immune responses; vectors containing genes from primary isolates and nonclade B isolates should be evaluated; the optimum route, dose, and schedule of administration need to be determined; and the best way(s) to combine recombinant vector vaccines with subunit, DNA, or other vector experimental vaccines to maximize or optimize the immune response need to be determined.

DNA Vaccines

In DNA immunization, the host is immunized by direct administration of viral genes; the genes are composed of DNA that encodes for the antigen that would normally be produced by the cell infected with the virus. Several experimental DNA vaccines for HIV/AIDS have been produced and tested in small animals and nonhuman primates. In general, the results of these studies

have been promising. DNA vaccines delivered intramuscularly or by gene gun have been shown to induce both neutralizing antibodies and CTL responses against HIV and SIV antigens. In one study, DNA immunization induced neutralizing antibodies and a vigorous CTL response; however, this immunization did not protect rhesus macaques from infection or disease on subsequent challenge with a pathogenic SIV after peak CTL and neutralizing antibody titers had waned. DNA immunization was, however, successful in protecting chimpanzees against a nonpathogenic HIV infection and in protecting rhesus macaques against a nonpathogenic chimeric virus (SHIV). In the latter study, the animals were first immunized with a DNA vaccine expressing HIV-1 IIIB Env and later received a booster immunization with a subunit protein vaccine composed of HIV-1 envelope protein prior to challenge.

Key issues for DNA vaccine development include optimizing antigen expression by DNA vaccine plasmids and optimizing immune responses to DNA vaccines in nonhuman primates and in human subjects. The development of new expression systems with more potent promoters, immunomodulatory cytokine genes, or costimulatory molecules, as well as formulation of DNA vaccines with adjuvants, cytokines, or novel delivery systems, is also being evaluated as ways to enhance the immunogenicity of DNA vaccines. Research is also needed to determine the most effective routes of administration and the kinetics of immunization and to evaluate the utility of sequential immunization (prime-boost) strategies using DNA as the primary immunogen followed by secondary immunization with subunit protein or vector-based vaccines.

A phase I clinical trial of two DNA candidate vaccines, one containing an HIV-1 Env and rev and the other a Gag-Pol construct, is under way through NIAID's intramural program and the AVEG. Additional trials are being planned.

NIAID remains committed to the discovery and development of a safe and effective vaccine for the prevention of HIV infection or disease. Toward that end, NIAID will continue to pursue a comprehensive range of basic, preclinical, and clinical research and will continue to evaluate these and other vaccine strategies and products as they become available.

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PROMOTING AN AIDS VACCINE FOR DEVELOPING COUNTRIES

PRETORIA, July 29, 1999 — Senior policymakers from South Africa and the region, researchers and private sector representatives met on Tuesday to discuss ways that international agencies could help speed up the development of an AIDS vaccine that will be effective and affordable in developing countries.

The meeting was one of a series of consultations around the world, involving UNAIDS and AIDS Vaccine Task teams in the World Bank and the European Union (see box). South Africa's views were sought because of its commitment to developing an AIDS vaccine, and advanced scientific and medical research capability.

Dr Malegapuru William Makgoba, President of South Africa's Medical Research Council (MRC), says that the scientific community of South Africa is fully committed to the fight against AIDS. Just as the Black Death or the Great Plague was a challenge to the European Renaissance in the 14th Century, the AIDS epidemic poses a similar challenge to Africa's Renaissance in the 21st Century. By creating the South African AIDS Vaccine Initiative (SAAVI) under the auspices of the MRC, South African scientists have organized themselves to play an important, and in many ways a unique, role in developing and implementing effective, affordable, and universal preventive vaccination. He stresses that this can only be achieved by full cooperation and involvement of the public and private sectors, especially regarding policy decisions and funding. Dr. Makgoba is appealing to all South African institutions to join in this noble and brave initiative.

There are still formidable scientific, political, and financial hurdles to overcome, and it is by no means certain that a suitable and effective vaccine will be developed. The hope of a vaccine should not undermine a determined, strong, and unrelenting fight to prevent the spread of HIV through existing preventive measures. At best, a vaccine may be a valuable future addition to the set of interventions. But every day, 16,000 more people are infected worldwide, 1,600 of whom are South Africans. Only strong preventive measures now will change this.

The AIDS epidemic is having a profound effect on economic and social development in many countries. Nearly 34 million men, women, and children worldwide are infected with HIV or suffering from AIDS. Nine out of every ten infections are in developing countries. Life span in the hardest hit countries has declined by 10-20 years, wiping out decades of hard-won gains in health improvement. The vast majority of those infected are adults in their prime earning years. It is estimated that 3.6 million South Africans are living with HIV or AIDS, and the explosive spread of the epidemic in South Africa shows no sign of slowing.

"Since there is neither a cure for AIDS, nor a preventive vaccine, the best hope of bringing HIV under control for the present is by changing the behaviors that facilitate its spread. South Africa still faces a formidable challenge in

World Bank and EU AIDS Vaccine Task Teams

The European Union and World Bank have

*reducing HIV transmission through behavior change, although there are some promising interventions. But developing countries urgently need an AIDS vaccine to add to their prevention efforts," says **Geoff Lamb, World Bank Director and member of the AIDS Vaccine Task Force.***

Global spending on research and development (R&D) for an AIDS vaccine is minimal—only about \$300-\$600 million per year—and virtually all is being spent on vaccines more suitable for the HIV strains, health delivery systems, and economic conditions of industrialized countries.

While the basic science for a vaccine already benefits from large public subsidies, the testing and development of vaccine products is generally done by the private sector. However, the private sector may not have sufficient incentives to develop an AIDS vaccine that is effective and affordable in poor countries.

*"The knowledge and technology for an AIDS vaccine that can be effective in developing countries is an international public good. International collective action is vital to speed up development of an AIDS vaccine that will meet the needs of countries in greatest need," said **Jose Esparza, Leader of the UNAIDS Vaccine Team.***

The discussion at Tuesday's meeting, chaired by the Medical Research Council, will help guide the actions of the World Bank and EU in working with their partners to accelerate development of an HIV/AIDS vaccine for developing countries.

both launched institution-wide HIV/AIDS Vaccine Task teams to consider how each agency could help accelerate development and availability of an AIDS vaccine for developing countries. In addition to supporting high-level dialogue with policymakers and industry on the issue, the World Bank Task Force is considering two major sets of actions. One aims to "push" private R&D by subsidizing vaccine trials or reducing the risks involved in vaccine development in the short run. The World Bank has been a major contributor to the International AIDS Vaccine Initiative (IAVI), which directly subsidizes R&D for AIDS vaccine for developing countries, including funding for SAAVI, South Africa's own vaccine research initiative.

The second aim is to demonstrate or assure a future market for an AIDS vaccine in developing countries. The Task Force is considering expanded lending for existing and new vaccines, like hepatitis B, to demonstrate to industry a viable vaccine market in developing countries. Other possibilities include an AIDS vaccine purchase fund for the poorest countries and "contingent" loans to purchase AIDS vaccines to be activated when a suitable vaccine is available.

The European Union is currently supporting HIV-related vaccine research; reviewing regulatory frameworks for pharmaceuticals; and is planning to collaborate with the World Bank on a series of studies to assess potential demand for a vaccine in selected countries and the potential impact and cost-effectiveness of a vaccine.

For more information about the Medical Research Council of South Africa, please visit: <http://www.mrc.za.com>

For more information about UNAIDS, please visit: <http://www.unaids.org>

For more information about the World Bank Group, please visit: <http://www.worldbank.org/>

For more information about World Bank work on the economics of HIV/AIDS and links to the International AIDS Economic Network (IAEN), please visit: <http://www.worldbank.org/aids-econ/>

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Accelerating an AIDS vaccine for developing countries: Issues and options for the World Bank*

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Accelerating an AIDS vaccine for developing countries: Issues and options for the World Bank

I. Introduction

The worldwide AIDS epidemic is a human tragedy that is reversing the gains in life expectancy of the last 30 years and exacerbating poverty in developing countries (see Box 1). Worldwide, 33.4 million people are infected with HIV and 13.9 million have already died of AIDS. More than nine out of every ten HIV infections are in developing countries, and two-thirds are in Sub-Saharan Africa. Every day, 16,000 people become infected. AIDS is a fatal infectious disease for which there is no cure and no vaccine. Antiretroviral therapies that have extended the lives of patients in industrialized countries are out of reach in the poorest developing countries because they are too expensive and difficult to administer effectively in these settings. Since 1986, the World Bank has lent \$989 million for HIV/AIDS prevention and care in 81 projects in 51 countries, primarily for information campaigns, behavioral change (like raising condom use), and treatment of sexually transmitted diseases.¹

At present, the best hope for reducing the spread of HIV and its human and economic impacts is through behavioral change—reducing the number of sexual partners among people with many, raising condom use, and enabling safer injecting behavior. Governments like those in Australia and Thailand have shown that these measures *can* have an impact in reducing the spread of HIV on a national scale. Too few countries have shown the level of political commitment necessary for an effective response. The World Bank and its development partners, including the Joint United Nations Program on HIV/AIDS (UNAIDS), are continuing their efforts to raise the level of policy dialogue on AIDS as a development issue, to obtain greater political commitment and more effective programs.

Substantial benefits could be gained in terms of slowing the epidemic through concerted public action on prevention, and this strategy must be vigorously pursued. In addition, countries where HIV is already widespread in the general population urgently need an HIV vaccine to add to their arsenal in the struggle to control the epidemic. A vaccine that is effective and affordable in developing countries would greatly improve the prospects for dramatically reducing the scope of the epidemic, not just in developing countries but the world over. HIV does not respect geographic boundaries and spares no racial, ethnic, or religious group. No country or population is exempt.

¹ In addition, the World Bank has contributed \$18 million over the past 13 years to the Global Programme on AIDS and its successor, the Joint United Nations Programme on HIV/AIDS (UNAIDS).

BOX 1: The impact of AIDS on development

The AIDS epidemic has managed to wipe out nearly all of the progress of the last three decades in raising life expectancy in Sub-Saharan Africa. In the hardest-hit countries the lifetime risk of dying of AIDS is 40-50% and life expectancy is 10-20 years less than it would have been in the absence of AIDS.

The demand for AIDS-related health care is overwhelming fragile health systems. AIDS is exacerbating poverty in the poorest countries. In hospitals in major African cities, half or more of hospital beds are occupied by AIDS patients, displacing patients with conditions that might be cured. Access to the most basic palliative care and treatment of opportunistic infections is severely limited. It is killing prime-age adults—the breadwinners of households who leave behind young orphaned children in the care of relatives or the state. In Northwestern Tanzania, families are coping with the economic impact of AIDS deaths by consuming less, selling assets, drawing on contributions from the extended family, and removing older children from school to work in the home. In coping with this short term shock, the poorest families are sacrificing investments in human capital that are important to the welfare of the next generation.

Source: World Bank (1997), Stover and Way (1998).

Scientists now believe that an effective preventive HIV vaccine is feasible (see Box 2), but this does not make its development a foregone conclusion. Although the public sector often has financed or subsidized basic research for vaccines, it has limited expertise in transforming these discoveries into marketable products. The development of vaccine products and the technology for their manufacture is usually undertaken by the private sector, which can do this more efficiently. In the case of an HIV/AIDS vaccine, both public and private investment is currently small and oriented toward the needs of the richest countries. There are at least two reasons why private investment in an HIV vaccine is likely to be less than the socially optimum amount:

- The technology for an HIV vaccine is an *international public good*. Regardless of which firm or country develops it, the benefits of an HIV vaccine technology will be global. Even those who do not invest in the research and development (R&D) will benefit. Those who invest in the technology will not be able to recoup revenue from many who will benefit.
- The private sector is unlikely to invest adequately in products tailored to the needs of developing countries or populations with low ability to pay.

At the current pace it is likely to be several decades before an effective vaccine becomes available in OECD countries, let alone in developing countries. An HIV/AIDS vaccine that is effective and affordable in developing countries is even less likely to become a reality if the private sector is left to respond to existing incentives.

In April 1998, the World Bank set up an institution-wide Task Force to examine ways in which it could help accelerate the development of an AIDS vaccine for developing countries, as one element of its broader program to combat AIDS. The AIDS Vaccine Task Force has consulted with numerous experts and sponsored studies both the pharmaceutical industry and of the potential demand for an AIDS vaccine. It has also examined and discussed a range of possible Bank responses, including financial instruments that could be used to assure future markets for an HIV vaccine in developing countries. This work is ongoing, and country-specific case studies will shortly be launched.

BOX 2: The scientific challenges of an HIV/AIDS vaccine

The development of a safe and effective AIDS vaccine poses several scientific challenges. A successful vaccine must elicit immune responses capable of blocking infection by sexual, intravenous, and mother-to-child transmission. It must be capable of stimulating immune responses like antibodies, which may be effective at neutralizing free virus particles, as well as cellular immune responses, which destroy incoming virus-infected cells. In addition, the tremendous geographic diversity of the subtypes of HIV worldwide suggests that mixtures or "cocktails" of vaccines may be required for universal protective immunity. Finally, there is a lack of understanding of which anti-HIV immune responses are required for generating protective immunity against HIV and therefore which components of HIV are necessary for an effective AIDS vaccine.

Despite these challenges, there is now broad agreement within the scientific community that an effective AIDS vaccine is possible. First of all, a small but growing number of people who have been repeatedly exposed to HIV have remained uninfected and have elicited anti-HIV immune responses that could explain their resistance to infection. Second, there are now several candidate vaccines that have protected monkeys from infection and/or disease caused by the simian immunodeficiency virus (SIV), which is very similar to HIV. Third, some candidate vaccines already in clinical trials have induced strong anti-HIV immune responses in human volunteers. Finally, vaccines have successfully been developed against several other viruses—measles, mumps, rubella, polio, hepatitis B, and rotavirus, for example—with much less knowledge of their fundamental biology and pathogenesis than HIV.

This paper reviews what the AIDS Vaccine Task Force has learned to date about the nature of the problem of under-investment in an HIV/AIDS vaccine for developing countries, and summarizes some of the approaches under consideration. Its objective is to launch a discussion within the World Bank, and – critically – with its bilateral, multilateral, and developing country partners, on the best course of action for the institution, given its mandate, its comparative advantages in relation to the other agencies involved in the international effort, and the likely effectiveness of alternative measures for accelerating the development of an HIV/AIDS vaccine for developing countries.

II. Worldwide investment in an HIV/AIDS vaccine

Total global research and development (R&D) for preventive HIV vaccines in both the public and private sectors in 1998 was on the order of only US\$300 million.² Most of this is public expenditure and is focused on basic research, as opposed to applied research and vaccine

² Provisional estimate by International AIDS Vaccine Initiative (IAVI). This number is being updated. The United States National Institutes of Health allocated \$200 million for HIV/AIDS vaccine research in fiscal year 1999.

development. Privately funded R&D on HIV vaccines was probably less than \$50 million per year and fewer than 200 scientists in the private sector worldwide are dedicated to AIDS vaccine-related work, some of it subsidized by the public sector (Batson and Whitehead 1999). Progress has been slow. While more than 25 candidate vaccines have been developed and tested for safety and immune response in small groups of volunteers, only one firm has embarked on Phase III clinical trials of an HIV vaccine—the stage at which a vaccine is tested for efficacy in a large human population.³

There are 10 or more subtypes of HIV in the world. Research to date has focused on a vaccine for HIV subtype (or clade) B, which is the predominant strain in North America, Europe, Australia, and Japan. However, the predominant subtypes in Subsaharan Africa and Asia—where the epidemic has hit hardest—are subtypes A, C, D, and E. There is no guarantee that a vaccine based on subtype B will be effective against these other subtypes. Further, cellular immunity—which is thought to be important for protection against HIV—is influenced by the genetic makeup of the individual. Even if a vaccine is not specific to a subtype of the virus, the effectiveness could vary across populations. An HIV/AIDS vaccine for use in developing countries should also be inexpensive and easily administered (preferably oral). Other important characteristics include: a minimum number of doses, preferably one; long-term immunity; heat tolerance; and long shelf life. The vaccine should be as efficacious as possible.⁴ In addition, since it would be costly to test every potential recipient for HIV before being vaccinated, the preventive vaccine should not be harmful to people who are already infected.

According to the International AIDS Vaccine Initiative (IAVI), only about \$5 million per year is being spent on AIDS vaccines that are specifically designed for use in developing countries. One efficacy trial for a clade B/E vaccine is underway in Thailand; the only other ongoing efficacy trial is in the United States.⁵ In its 1998 “Scientific Blueprint”, IAVI laid out a research plan that was most likely to result in an AIDS vaccine for world use by 2007. The estimated cost of the plan was \$350-\$500 million over this period (IAVI 1998).

³ Many of these candidates, while safe, have a low probability of being effective because of poor immunogenicity. Nevertheless, it is difficult to know whether laboratory assays will predict the effectiveness in human beings. There are at least a half dozen of these that warrant additional clinical study and efficacy trials (Peggy Johnston, IAVI, personal communication).

⁴ Vaccine efficacy is defined as one minus the ratio of the incidence of infection in vaccinated and unvaccinated groups of people. However, efficacy as measured in vaccine trials is not the only factor affecting the impact of a vaccine on community levels of infection (McLean and Blower 1995). The duration of immunity, the level of infectiousness and incubation period of HIV among vaccinees are also key variables. “...in areas of moderate to high transmission, low-efficacy vaccines administered at high coverage levels could act to significantly reduce the endemic prevalence of HIV-1” (Anderson and Garnett 1996). Haber, Watelet and Halloran (1995), point out that a vaccine that is not efficacious at an individual level but that reduces the infectiousness of HIV (the probability of transmission) among those vaccinated could have an important effect in reducing infection in the population. Anderson, Swinton, and Garnett (1995) find even that a low-efficacy vaccine that protects for only a few years “...can save many lives if significant coverage is maintained over many years.”

⁵ VaxGen is supporting a trial of a bivalent B/E gp120 envelope vaccine in Thailand and is also conducting a US trial of a clade B vaccine.

In contrast to the limited funds spent on AIDS vaccine development, an estimated \$2 billion annually is being spent worldwide on research for AIDS treatment, much of it in the private sector.⁶ There is far more certainty for the private sector about the profitability of this research. There are more than 33 million people infected worldwide, almost all of them adults who would be willing to pay some amount for treatment when they fall ill. Three million of those infected live in industrialized countries where purchasing power is high. Hogg and others (1998) estimate that \$2.9-\$3.3 billion was spent on antiretroviral drugs for AIDS patients in North America and Europe in 1997.⁷ Middle-income countries are also becoming important purchasers of these expensive drugs, which must be taken continuously for the rest of the patient's life at a cost of \$7,000-\$12,000/year. In 1998, Brazil spent \$303 million on antiretroviral drugs for treating AIDS patients, and in 1999 it is projected to spend \$544 million.⁸

III. The potential market for an AIDS vaccine in developing countries

There are 2.5 billion adults of reproductive age in developing countries who are not infected with HIV, including 260 million in the hardest-hit region, Sub-Saharan Africa. This is the number of people who might benefit today from an AIDS vaccine. However, this is not the same as the "demand" for the vaccine, which is the number of doses that would be purchased by government and private individuals at different prices. The demand for an AIDS vaccine in developing countries will depend, among other things, on:

- the characteristics of the vaccine, in terms of its efficacy for relevant strains of the virus, its safety, the number of doses to infer immunity, and its ease of administration in the conditions in developing countries;
- the price of the vaccine;
- levels of income in developing countries and the willingness of international donors to purchase the vaccine for the poorest countries or the poorest people;
- the perceived vulnerability of different populations to becoming infected, their potential for spreading the virus, and their political clout;⁹ and
- the costs and capacity of the public and private sectors to administer the vaccine.

⁶ The US National Institutes of Health budgeted \$482 million for research on therapeutics and \$526 million for research on etiology and pathogenesis of HIV/AIDS in FY 1999, out of a total AIDS research budget of \$1.73 billion. These preliminary estimates are under revision.

⁷ Based on data from British Columbia, Hogg and others (1998) assumed that a quarter of all HIV-positive persons are using antiretroviral therapy at any point in time; they used the average 12-month drug costs in British Columbia as the average annual expenditure per patient treated in North America and Western Europe.

⁸ Pedro Checquer, Brazil AIDS Control Program (personal communication, 7/99)

⁹ The political climate is a key factor affecting demand. Political pressure could force the hand of government—even if the vaccine is very expensive—to guarantee access to an HIV vaccine to everyone. For example, some Latin American governments must provide expensive triple-drug antiretroviral therapy to all AIDS patients who ask for it, irrespective of the cost. On the other hand, if the vaccine is perceived to be less than 100% safe, people who are at relatively low risk of contracting HIV may refuse to be vaccinated, lowering demand. These reactions are difficult to anticipate.

The relation between the price of an HIV vaccine and the number of doses purchased is not known. Childhood vaccines are provided at very low prices to the public sector in developing countries and free to the population. The price of all four basic childhood vaccines¹⁰ combined is less than US\$1 per child. Nevertheless, even at these low prices, coverage is far from universal—about 70-80 percent of children under one year of age. The initial price of an HIV/AIDS vaccine is likely to be much higher, measured in dollars or tens of dollars, not cents. Delivery costs—estimated at about \$14 per child in the poorest developing countries for the childhood vaccines¹¹—could also be higher for HIV, since delivery systems for immunization of other groups in the population, like young adults, may have to be set up. Thus, only a share of all who could benefit from an HIV vaccine will ever be vaccinated.

Global spending on childhood vaccines is estimated at \$4 billion annually, of which spending in low- and middle-income countries accounts for about \$200 million, most of it financed by the public sector. But this may not be a good guide to potential spending for an HIV/AIDS vaccine. First, the current market for childhood vaccines in developing countries represents a “maintenance” phase, as older children were immunized in previous years. When an HIV/AIDS vaccine becomes available, there will be initial large “catch up” demand, since none of the population will have been previously immunized. Second, AIDS is almost always fatal and it primarily affects prime-age adults. While most childhood vaccines are purchased by or for government programs, adults (even poor adults) may be more willing to pay for an HIV vaccine than for childhood immunizations. No study has attempted to measure the public or private demand response to hypothetical HIV vaccines of different prices or characteristics in a developing country setting.

Historically, vaccines become available and affordable for developing countries after the market in OECD countries has matured. Only after substantial saturation of the OECD market do competition and over-capacity generate the willingness among firms to sell their product at marginal prices that are affordable in developing countries. For example, the hepatitis B vaccine appeared in 1982 but did not effectively become available in developing countries for 10-15 years, when its price had dropped from \$150 to about \$2-4 for the 3-dose vaccine series. Thus, even when a new product becomes available in OECD countries, it often takes many years for the product to become available and affordable in developing countries.

IV. Why isn't industry investing?

A study commissioned by the World Bank AIDS Vaccine Task Force of industry's perspective on HIV/AIDS vaccine R&D concluded that companies do not believe there will be a realistic commercial return on the required investment for an HIV vaccine in developing countries (see Box 3). There are two important contributing factors.

¹⁰ BCG, oral polio vaccine (OPV, 4 doses), diphtheria-pertussis-tetanus (DPT, 3 doses), and measles.

¹¹ UNICEF/WHO (1996).

BOX 3: Industry's perspective on HIV vaccines

The World Bank and the International AIDS Vaccine Initiative (IAVI) recently commissioned a study of the factors affecting private sector research and development of an AIDS vaccine. The study team interviewed 15 companies and seven international experts on AIDS vaccine development. Of the firms interviewed, two were large firms involved in AIDS therapy, six were large vaccine manufacturers, and seven were smaller biotechnology firms that specialize in early stage research. Biotechnology firms eventually sell their technological discoveries to larger pharmaceutical companies that have the infrastructure, resources, and technical know-how to conduct clinical trials and large-scale production. Only one of the interviewed firms was involved in Phase III efficacy trials for an HIV vaccine, four were involved in Phase I and II early clinical trials, and seven were in pre-clinical stages of an AIDS vaccine. Two firms were very large and not involved in HIV vaccine work, and a third had discontinued work on an HIV vaccine. In each firm, senior managers and/or CEOs were interviewed.

The study recommended that the World Bank pursue activities to guarantee a profitable developing country market for an AIDS vaccine, which could be influential to private R&D in the long run. The World Bank should also consider making short-run investments that will speed the access of developing countries to an AIDS vaccine when it becomes available. Enhanced lending for existing vaccines in developing countries and investments in infrastructure necessary to implement them quickly will help to demonstrate that viable LDC markets exist. The study also recommended that the World Bank consider activities in the short term that will accelerate the pace and relevance of HIV vaccine clinical trials in developing countries.

Source: Batson and Whitehead (1999, forthcoming).

The potential market is perceived to be small

Private investment in research on an HIV/AIDS vaccine is based mainly on firms' assessment of the potential market in high-income, OECD countries. There are two points of view. Some firms believe that there will be substantial demand for a safe and efficacious HIV vaccine of the order of magnitude of that for the hepatitis B vaccine. Other firms believe that because HIV is spreading slowly in the developed world and therapies have been successful in extending the life of patients, the OECD market will be small at the outset and slow to develop. Firms that believe there is a potential OECD market are investing in HIV vaccine R&D.

With only one exception, the Task Force's study of industry found that the potential market for an AIDS vaccine in developing countries was not cited as a factor in R&D investment decisions, nor is it a factor in decisions on investing in most products. The more involved a firm already was in developing country markets, the lower was its estimate of the potential sales of an HIV/AIDS vaccine in those markets. Even firms that anticipated some developing country demand expected that their R&D costs will be recouped in the OECD market. Acceptance of market segmentation for the purpose of pricing—price “tiering”, enabling firms to maintain high prices in OECD markets while charging marginal costs in developing countries—will be critical if firms are to introduce an HIV vaccine in developing country markets for a price that these

countries could reasonably afford. Based on their experience to date, the firms cited lower-than-expected uptake of new vaccines developed since the 1970s, like hepatitis B, yellow fever, and Hib¹², as evidence that work on future “high-priority” vaccines may not necessarily be rewarded by adequate sales.

The late-stage development costs of an HIV vaccine are high and the probability of success uncertain

There are many steps in bringing new vaccines to the market, which under normal circumstances can take a decade or more (see Box 4). The normally very long time horizon for developing a commercial product—from 10 to 30 years—means that the commercial benefits of developing an AIDS vaccine are far in the future and thus highly discounted in making investment decisions. In the case of an HIV/AIDS vaccine, there has been no good animal model and the correlates of immune protection remain unknown. As a result, the science has been challenging and the level of industrial investment low. More than a decade after the effort to develop an HIV vaccine was launched, there is only limited clinical testing underway and no scientific consensus on the best approach. Safety issues have prevented the testing of live attenuated or whole killed vaccine candidates in humans. While there are a few novel approaches in the early phase of testing, only one recombinant vaccine candidate globally has entered an efficacy trial.

A large-scale trial is needed to show the efficacy of any given vaccine candidate, but because of the huge expense of such trials (\$10-30 million) industry is unwilling to pay for them unless there is a high degree of certainty that the vaccine will be efficacious. The main approaches for an HIV/AIDS vaccine at present have few or no current vaccine analogues, which means there is still a large degree of uncertainty about their efficacy in a large trial, even after safety and immunogenicity are demonstrated. HIV vaccine efficacy trials in industrialized countries are particularly expensive because the incidence of HIV is low and the sample size would have to be very large. Trials in developing countries with higher HIV incidence could be smaller, but there are hidden costs such as political barriers and inadequate infrastructure. Since levels of protection against different strains of HIV cannot be assumed, it is highly likely that vaccines based on different strains will have to be tested in areas where those strains are prevalent. The additional costs of expanding the trial of a single vaccine candidate beyond one OECD country to include a vaccine for multiple strains of HIV in additional sites has been estimated at \$100 million. Further, efficacy trials usually involve some limited investment in manufacturing process and plant, investment that is lost if an efficacy trial does not result in a commercial product.

¹² Haemophilus influenzae type B.

BOX 4: Vaccine clinical trials

Once a vaccine has been shown effective in animal models, it must be tested in people. These studies, called clinical trials, determine the safety, immunogenicity, and efficacy of candidate vaccines. They provide the data necessary for regulatory agencies to decide whether or not a product should be licensed for use in their market. Before a vaccine will be recommended globally, efficacy studies are also required in different epidemiological sites (Asia, Africa, Europe, North America, Latin America). Often, governments will also require efficacy studies be repeated in their own country before agreeing to license a product. There are three types of human clinical trials that must be conducted without exception before a vaccine will be considered for licensure.

Phase I: Safety Phase I trials determine the safety and preliminary dosing studies of a vaccine candidate in a small sample of 10-30 people. They are generally conducted in healthy adults at low risk of HIV infection, take six months to one year, and cost about \$1-3 million.

Phase II: Immunogenicity. Phase II trials measure the safety and immune response in a larger sample of several hundred volunteers. They measure whether the vaccine candidate is stimulating the immune function or some other marker that may be indicative of protection. These studies are usually conducted in persons at high risk of HIV infection, typically take 6-24 months, and cost roughly \$2-4 million.

Phase III: Efficacy. In the third and final phase before licensure, the efficacy of the vaccine candidate in protecting against disease is tested in a large population (5,000 to over 50,000 people). Efficacy is measured as the difference between rate of disease in people who receive the vaccine and in others who receive a placebo. The lower is the incidence of the disease in the population or the smaller is the anticipated impact of the candidate vaccine, the larger must be the sample of people who participate to demonstrate an effect. These studies take 2-4 years and can cost \$10-30 million, depending on the size of the study.

A high level of efficacy does not guarantee an equivalent level of effectiveness when a vaccine is offered in the field. Efficacy trials typically select healthy volunteers and administer the vaccine or placebo under very carefully controlled conditions. Neither of these are assured in field conditions in developing countries. In a number of instances, so-called "Phase IV" "effectiveness" trials have been conducted to demonstrate the true costs and effectiveness of vaccines in typical field conditions.

V. What can the World Bank do?

The mission of the World Bank is to alleviate poverty and to promote economic growth. It pursues these objectives through three traditional channels—lending to developing country governments, engaging in policy dialogue, and conducting economic research.¹³ In the case of an HIV vaccine, the World Bank objective is not only to ensure that a vaccine is developed, but also to guarantee the broad and early access of developing countries to a vaccine adapted to their needs. The World Bank does not lend money to the private sector of any country. However, the International Finance Corporation (IFC)—the World Bank group's investment bank for developing countries—can lend directly for private sector projects in developing countries. International Development Association (IDA) credits are available to the poorest countries on

¹³ In fiscal year 1999, total World Bank commitments to developing countries amounted to \$22.2 billion in IBRD lending and \$7.0 billion in IDA credits. Since 1970, total World Bank lending for health, nutrition, and population (HNP) amounted to \$15.8 billion. Over the years 1995-98, average annual lending for HNP was \$1.6 billion.

highly concessionary terms. With the exception of a small amount of money provided through the Development Grant Facility (about \$130 million per year), the World Bank does not make grants to developing countries or institutions.

Given its institutional mandate, what can the World Bank do to accelerate the development and availability of an HIV vaccine for developing countries? There is a range of possibilities that warrant consideration. First and foremost, the Bank can engage governments in policy dialogue, pointing out the economic impact of AIDS, the government responsibility for prevention, the issues surrounding development of an HIV/AIDS vaccine in developing countries, and actions that will promote the process. Such a dialogue will condition the effectiveness of any other instruments or mechanisms that the Bank might propose to accelerate an AIDS vaccine, and can also help to broaden and reinforce the commitment within governments and thereby buttress the work of agencies with a more specialized health focus. Beyond this, the Bank can seek to influence the private R&D investment for an AIDS vaccine through existing and future financial mechanisms or instruments. There are two strategies for this: “push” activities that directly contribute to increasing R&D for an AIDS vaccine in the short run, and “pull” activities that provide incentives for private R&D by raising the expectation of a future return on these investments. An example of “pull” activities are different types of “assurances” on the size and profitability of a future market for vaccines in developing countries should a safe, effective, and low-cost vaccine be developed. A successful strategy is likely to incorporate intense policy dialogue accompanied by both “push” and “pull” interventions.¹⁴

Policy dialogue

The World Bank can play a crucial role in accelerating global HIV/AIDS vaccine development by elevating the seriousness of the AIDS epidemic in the dialogue with developing country policymakers, raising the level of political commitment to support HIV/AIDS vaccine research and development, and helping to forge partnerships between developing countries, industry, and international donors. The Bank’s credibility and access to treasury and finance officials, as well as development/health leaders, puts it in a strong position to engage all actors in the policy dialogue, and reinforce the efforts of specialized agencies.

To raise the support for AIDS vaccine development, policymakers must first be convinced that AIDS is a serious development issue that will set back investments in all sectors of the economy if not addressed as early as possible with effective prevention efforts.¹⁵ Since there is no HIV/AIDS vaccine and no cure for AIDS, the highest priority must be to prevent HIV in the most cost-effective manner, using existing proven interventions to change behavior. Policymakers also need to understand that an

¹⁴ For a more detailed discussion of the specific “push” and “pull” instruments and issues of implementation, see the Background paper by Rosenhouse (1999).

¹⁵ The Bank is in fact already engaged in this dialogue through current lending operations and analytic contributions, such as *Confronting AIDS* (World Bank 1997). These efforts could be reinforced.

AIDS vaccine will be a useful, even critical, prevention tool, but its availability at an affordable price and in a form that can be effective in developing countries cannot be assumed. Without the proactive involvement of developing countries themselves, it could easily be 20-30 years before an affordable vaccine becomes available for their needs. Partnerships between governments, industry, and civil society can pave the way for ensuring broad access to an effective and affordable vaccine by fostering political support and greater research and development for AIDS vaccines in developing countries with appropriate and transparent locally-determined safeguards. Vaccine development is a protracted process in which multiple candidates will have to undergo multiple efficacy trials in populations where the vaccine will be applied. While there are always risks involved in such endeavors, the developing countries bear very high risks of inaction.

“Push” interventions

Both basic research and clinical testing are essential in developing a new vaccine. In the case of HIV/AIDS, the basic research strategy is well funded by national research institutions in industrialized countries. Clinical testing and development of a marketable vaccine product has always involved the private sector. “Push” interventions lower the costs and risks of private R&D for an HIV/AIDS vaccine, either through direct subsidies or by lowering transactions costs.

1. Direct support for vaccine research

The most direct way of accelerating R&D for an HIV/AIDS vaccine in developing countries is to directly subsidize the relevant scientific research. However, as previously noted, the World Bank has very limited ability to confer grants and the grants that are awarded are small. Further, the World Bank does not have the capacity to evaluate the merits of alternative scientific approaches for developing an AIDS vaccine.

Nevertheless, the World Bank has supported HIV vaccine research indirectly through participation in the International AIDS Vaccine Initiative (IAVI), an international non-profit, non-governmental organization set up by the Rockefeller Foundation in 1996. IAVI’s mission is to ensure the development of safe, effective, accessible preventive HIV vaccines for use throughout the world. Its objective is to stimulate investment and demand for HIV vaccines that will benefit the whole world, including developing countries. IAVI works with both the public and private sectors, pursuing this objective through advocacy, targeted support to R&D for novel vaccine approaches, and measures that reduce obstacles to private investment. Last year, it launched two vaccine development partnerships in sub-Saharan Africa. The World Bank contribution to IAVI has grown from \$200,000 in 1997 to roughly \$1 million annually in 1998 and 1999,¹⁶ and it is represented on IAVI’s Board of Directors. Given the limited availability of grants from the World Bank (about \$20 million in grants is available annually for the health sector), it is unlikely that its own financial contribution could be increased

¹⁶ 1998: \$1 million (\$400,000 from the Global Forum for Health; \$600,000 from the DGF); 1999: \$940,000 from the DGF; 2000: \$700,000 from the DGF.

substantially under the existing structure.¹⁷ Irrespective of whether additional grant funds could be found, the World Bank could play a role in leveraging contributions to IAVI from international organizations and bilateral donors to accelerate the vaccine product development and testing effort.

2. Reducing the costs or risks of vaccine clinical trials in developing countries

This strategy will accelerate the development of vaccines for developing countries, ensure that whatever product is developed will address the infrastructure and delivery constraints, and encourage investments by industry and donors in the infrastructure that would make immunization possible. Investments and improved collaboration will enhance the capacity of developing country researchers to engage in this type of research and the prospects for eventual local production of vaccines or important components of them.

This would be a new activity for the World Bank, but there are several ways that it might participate using its traditional instruments. This might include: elevating HIV/AIDS vaccines in the policy dialogue with developing country governments and smoothing the way for collaboration with industry for conducting clinical trials (discussed above); lending to developing countries for infrastructure and capacity building that are necessary to conduct vaccine trials; and lending for the finance of vaccine trials themselves in countries where partnerships have been established.¹⁸ In this activity, the Bank would presumably focus on elements that add to what is already being done through its financial contributions to IAVI.

“Pull” interventions

Pull interventions create incentives for increasing private R&D for an HIV vaccine for developing countries by demonstrating or guaranteeing a substantial market in developing countries or other form of financial return on investment.

1. Expanded lending for existing vaccines

¹⁷ Larger contributions could be sought from the Bank’s net income (after any necessary increases in reserves). However, this would require the approval of the entire membership of the World Bank, which would have to weigh the use of net income for funding HIV vaccines against other alternative uses—notably additional resources for IDA, which serves the poorest countries, or the Highly Indebted Poor Countries Initiative (HIPC). Furthermore, as net income is expected to experience a downturn in the next few years, the share for reserves is likely to increase.

¹⁸ One interesting possibility would be a “learning and innovation loan”, or LIL for roughly \$5 million that could be used to strengthen the capacity of drug and vaccine regulatory authorities and to finance a share of the expenses of an AIDS vaccine clinical trial. This “buy in” from a developing country into an AIDS vaccine trial could be used to leverage better terms from its pharmaceutical partner on quick and low-cost access to the eventual vaccine and/or advance agreement on sharing of intellectual property rights. The LIL would strengthen local capacity, reduce the gap in time between discovery and access to a vaccine, and reduce the short term costs to companies of conducting these trials.

Long-term promises to guarantee a market for an HIV vaccine would have greater credibility to industry if the international community found a way to stimulate the market in developing countries for priority vaccines that already exist. World Bank lending for vaccines and immunization programs historically has been relatively small—less than \$20 million annually. Until recently, funding by UNICEF and bilateral donors was deemed adequate to finance vaccine purchase and delivery needs of developing countries. However, with the introduction of new vaccines that are more expensive (>\$1/dose), this will no longer be the case.

The World Bank's institutional commitment to finance existing vaccines and immunization programs is already on the rise. In March 1998, World Bank President James Wolfensohn met with heads of public agencies and the vaccine industry at a meeting on "Vaccine Development and Delivery: Leadership for the 21st Century". The World Bank has launched an immunization demonstration project to explore how loans in 6-8 countries could increase the support for immunization and new vaccines. WHO, UNICEF, and the U.S. Centers for Disease Control and Prevention (CDC) will provide technical expertise on setting the priorities for immunization, structuring the loan component, and monitoring results. Building on the demonstration projects, the World Bank will identify a number of countries each year to target for heightened immunization support. It has committed to work more closely with industry and with other immunization partners such as WHO and UNICEF. The World Bank will also explore ways to increase vaccine financing through new financial instruments.

2. Providing better information on developing country markets

Private firms' decisions to invest in R&D for an HIV vaccine, as with other products, are highly dependent on their perception of some future lucrative market for sale of that product. The study of industry revealed that the investment decisions to date have been based almost exclusively on the potential market in OECD countries. Potential markets in developing countries have not entered their calculations. The level of private demand for the purchase of an HIV vaccine is unknown, and public sector purchase of other "new" priority vaccines in developing countries has been limited. Better information on the characteristics of vaccines that are likely to be demanded in developing countries and on the responsiveness of both public and private purchasers of an HIV/AIDS vaccine may alert firms to an important market segment they might otherwise ignore.

A desk study commissioned by the AIDS Vaccine Task Force reviewed the available information on the potential global demand for an HIV/AIDS vaccine estimated the public sector demand for AIDS vaccines under two different sets of decision rules (Bishai and others 1999). However, the validity of these decision rules is not known and to date there has been no basic research on the public or private willingness to pay for hypothetical HIV vaccines with different characteristics and prices. The process of collecting this information would have the added benefit of raising awareness among developing country policymakers about the current state of vaccine research, the characteristics and price of an HIV vaccine, and issues related to improving the access to a vaccine once it is available. Commissioning this work is within the mandate of the World Bank's AIDS Vaccine Task Force, and with sufficient resources could be included in its work program. Related to this, the World Bank could work with the UNAIDS secretariat and representatives from industry and developing countries to

develop a set of priorities and guidelines concerning the optimal characteristics of an HIV vaccine for use in developing countries. Meeting such criteria could be the “trigger” point for market guarantee mechanisms, below.

3. Market assurances¹⁹

Increased knowledge of the potential developing country market for an appropriate HIV/AIDS vaccine alone is unlikely to be sufficient to change firms’ R&D behavior because: (a) the potential commercially viable market may be small; and (b) there is still great uncertainty as to whether the potential market will materialize, given all of the political and economic shocks that can occur (or even development of a cure for AIDS) in the intervening time before an HIV vaccine is introduced. Uncertainty about the future market for an HIV vaccine in developing countries can be substantially reduced through agreements that “guarantee” purchase of a certain number of doses of an appropriate HIV/AIDS vaccine at an agreed-upon price at some future date, if such a vaccine is developed.

There appears to be no precedent for this type of activity in the international community—creating or assuring a future market so that the private sector will develop a technology. The World Bank has some experience with financial guarantees in its operations, but on a shorter time frame than would be necessary for development of an HIV/AIDS vaccine (Rosenhouse 1999). New financial instruments could be developed to meet the need for longer-term market assurances, taking into account different contingencies. Such instruments could be important new mechanisms for generating private investment in other high-priority public goods. In the course of deliberations, the World Bank AIDS Vaccine Task Force identified three main types of market guarantee activity that might be pursued.

(a) Vaccine purchase fund. A fund could be established for the purchase of HIV vaccines for the poorest countries or to provide matching funds provided developing countries themselves. The fund would be capitalized by contributions primarily from industrialized countries, although middle-income countries would also be invited to contribute. The trust fund could be financed now, allowing the fund to accrue interest, or financed in the future through government pledges or promissory notes. The trust fund monies would become available only if and when a vaccine was developed that meets very specific criteria, in terms of its price, effectiveness, and applicability for developing countries. This fund could be managed by the World Bank through an independent facility, according to agreed-upon access rules and a “trigger” mechanism or “contingency clause” that defines when the criteria for a vaccine have been met.

The World Bank has ample experience in setting up and administering trust funds created for specific purposes. The Global Environmental Facility (GEF) and the Heavily Indebted Poor Countries Initiative (HIPC) are two examples. It is also quite experienced in dealing with donor pledges, as they constitute the bulk of IDA’s resources. However, the trust funds administered by the World Bank

¹⁹ For a detailed description of existing types of World Bank guarantees, contingent-type loans, and options for market assurances, see Rosenhouse (1999).

generally disburse soon after they are replenished, and the government promissory notes that finance IDA are valid over a 3-year time frame. An HIV/AIDS vaccine for developing countries could take 10-15 years to develop. The main issue to be addressed is whether donors would be willing to commit funds with a 10-15 year lead time, and whether industry believes that these promises will materialize.

(b) Contingent loans and credits. The World Bank could issue IBRD loans²⁰ and/or IDA credits to developing countries to finance the strengthening the borrower's vaccine delivery capacity and the purchase of HIV/AIDS vaccines when a suitable vaccine is developed. The loans or credits would be agreed to in the present; part or all of the disbursements would be contingent on the development of a viable vaccine—that is, one that meets the same criteria as might be established for the trust fund, discussed above.

The World Bank has some experience in contingent lending. It has made loans to back up government facilities that provide guarantees against commercial and political risk to the private sector. These loans only disburse if claims are made.²¹ Contingent loans have also been used to reduce the impact of liquidity shocks on the borrower's banking system in the event of severe capital flight. However, the period over which risk is covered in both cases has never exceeded five years. Given the unknown demand for funds for alternative uses in the distant future by both the World Bank and client countries, the main issues for contingent loans for an HIV/AIDS vaccine are, first, whether the IBRD and IDA would be willing to commit resources with such a long time horizon, and second, whether developing countries would be willing to borrow on a contingent basis so far out into the future.²² A related issue is whether such "promises to borrow" are viewed as credible promises by firms responsible for investing in R&D for an HIV/AIDS vaccine.

(c) High-profile international public signing of intent. Public visibility can be a powerful incentive for public action and strengthen the commitment of the international community to eventually purchase an HIV/AIDS vaccine for developing countries. The World Bank would coordinate public pledges to purchase an HIV/AIDS vaccine by donors and client countries, in international forums with wide press coverage and attendance of heads of state or other high officials. This would give greater prominence to the problem of generating adequate R&D on technology that is an international public

²⁰ International Bank for Reconstruction and Development, the arm of the World Bank that lends primarily to middle-income developing countries at market rates.

²¹ The World Bank has made these types of loans when conditions do not permit the involvement of the Multilateral Investment Guarantee Agency (MIGA), which cannot cover short-term non-equity transactions, or IFC, which cannot lend to governments.

²² While there are disincentives for both borrowers and the Bank, under the existing framework, to commit to future lending, the Bank has recently developed a new lending instrument—the Adaptable Program Loan—that is designed to fund a program of activities to achieve an agreed upon development objective over a long-term horizon. The project is designed as a sequence of loans for phased support of the program, with agreed objectives, triggers, and indicators of outcomes/impacts for each phase of the program. For additional discussion on how the APL might be adapted to the issue of AIDS vaccines, see Rosenhouse (1999).

good, in general, and specifically for an AIDS vaccine. It would give greater visibility to governments who commit themselves by providing resources now or in the future.

VI. Issues

As an international institution committed to economic growth and poverty alleviation, the World Bank has a vital interest in the development of a preventive HIV/AIDS vaccine that will stop the spread of a virus that is already having such a huge impact on the poorest countries. Scientists believe that an AIDS vaccine is possible. This note has provided an analysis of the problem of underinvestment in R&D for an HIV/AIDS vaccine, a discussion of the main reasons from the perspective of firms, and a summary of the main mechanisms by which the World Bank might accelerate the development and availability of an AIDS vaccine for developing countries.

The AIDS Vaccine Task Force must now develop proposals to World Bank management and the Board of Directors for the most effective way forward to accelerate an AIDS vaccine for developing countries as part of the Bank's broad strategy to combat AIDS. Such proposals might draw on existing World Bank instruments or propose the development of new ones; it will certainly incorporate a combination of policy dialogue and both "push" and "pull" activities. However, the success of the strategy and any new instruments will depend centrally on the extent to which they are seen as relevant and practical by the World Bank's members, by task managers within the institution, and by industry. New financial instruments can be effective only if there is some demand for them by developing country borrowers and by those who might contribute.

At this stage, therefore, the AIDS Vaccine Task Force is requesting feedback from the development community through a number of international consultations on the following issues:

- 1) What are the views of industrialized countries, developing countries, and international institutions on the feasibility, desirability, and potential support for different World Bank options such as those set out in this paper?
- 2) Are there other ideas or activities that would accelerate development of an HIV vaccine for developing countries in which the World Bank could play a particularly useful role?
- 3) Are there complementarities between these options and current or planned activities on vaccines by bilateral, multilateral, and developing country partners – and can these be developed and exploited?

Sources

Anderson, R.M., and G. P. Garnett (1996). "Low-efficacy HIV vaccines: Potential for community-
Lancet 348: 1010-1013.

Anderson, R.M., J. Swinton, and G.P. Garnett (1995). "Potential impact of low efficacy HIV-1 vaccines in populations with high rates of infection". *Proceedings of the Royal Society London* 261: 147-151.

Batson, Amie, and Piers Whitehead (forthcoming). "HIV/AIDS vaccines: What motivates private investment in R&D?" Background paper for the AIDS Vaccine Task Force. World Bank, Washington, D.C., and Mercer Management. Draft.

Bishai, David, Maria Lin, and C.W.B. Kiyonga (1999). "The global demand for an AIDS vaccine". Background paper for the AIDS Vaccine Task Force. Department of Economics, Johns Hopkins University, Baltimore, MD, USA. January 1999 Draft.

Clemens, John, Ruth Brenner, Malla Rao, Nebiat Tafari, and Charles Lowe (1996). "Evaluating new vaccines for developing countries: Efficacy or effectiveness?" *JAMA* 275(5): 390-397.

Haber, Michael, Luc Watelet, and M. Elizabeth Halloran (1995). "On individual and population effectiveness of vaccination". *International Journal of Epidemiology* 24(6): 1249-1260.

Hogg, Robert S., Amy E. Weber, Kevin J.P. Craib, Aslam H. Anis, Michael V. O'Shaughnessy, Martin T. Schechter, and Julio S.G. Montaner. (1998) "One world, one hope: The cost of providing antiretroviral therapy to all nations." *AIDS* 12(16): 2203-2209.

International AIDS Vaccine Initiative (1998). *Scientific blueprint for AIDS vaccine development*. June.

McLean, Angela R. and Sally M. Blower (1995). "Modelling HIV vaccination". *Trends in Microbiology* 3(12): 458-462.

National Institutes of Health, Office of AIDS Research (1998). "Information on the NIH AIDS Research Program." March 10, 1998.

Rosenhouse, Sandra (1999). "Potential mechanisms for the World Bank to accelerate the development of and HIV/AIDS vaccine for developing countries". Background paper for the AIDS Vaccine Task Force. World Bank, Washington, D.C.

Russell, Philip K. (1997). "Economic obstacles to the optimal utilization of an AIDS vaccine". *Journal of the International Association of Physicians in AIDS Care*, September 1997:31-33.

Stover, John and Peter Way (1998). "Projecting the impact of AIDS on mortality". *AIDS* 12 (supplement 1): S29-S39.

UNICEF/WHO (1996). *State of the World's Vaccines and Immunizations*

World Bank (1997). *Confronting AIDS: Public Priorities in a Global Epidemic*. Washington, D.C.: Oxford University Press for the World Bank.

**MAKING AN AIDS VACCINE AVAILABLE
IN THE DEVELOPING WORLD:
ECONOMIC AND FINANCING ISSUES**

REPORT OF A CONSULTATION

THE COMMISSION OF THE EUROPEAN COMMUNITY,
DIRECTORATE GENERAL FOR DEVELOPMENT
VIII/A/2: SOCIAL, HUMAN, CULTURAL
DEVELOPMENT; GENDER UNIT

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MAKING AN AIDS VACCINE AVAILABLE IN DEVELOPING COUNTRIES: REPORT OF
AN EU CONSULTATION. APRIL 1999

Donors are in a unique position to mobilise international support for the creation and dissemination of knowledge and technology that is transferable across countries... knowledge and technology should be regarded as public goods. The EU believes that a global effort to make an AIDS vaccine accessible and available quickly to all who need it is required – the need for public sector involvement is likely to be temporary but critical. The prospect of a successful preventive AIDS vaccine is now a real one. An AIDS vaccine will be an international public health good of inestimable value to the people of the world --- wherever they live. Although there are many obstacles to be overcome, some of which will demand solutions that have never before been tried, the EU is convinced that a concentrated effort will succeed in developing and making available a vaccine for developing countries.

MAKING AN AIDS VACCINE AVAILABLE IN DEVELOPING COUNTRIES: REPORT OF
AN EU CONSULTATION. APRIL 1999

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1. EXECUTIVE SUMMARY

- 1.1 Despite the remaining challenges, researchers now believe that an AIDS vaccine is scientifically or technologically feasible. The development and distribution of a safe, effective and inexpensive vaccine to prevent HIV infection would greatly improve the prospects of controlling the global HIV/AIDS epidemic.
- 1.2 However, scientific research has so far failed to provide a safe and effective vaccine. Investment in vaccine research and development has not targeted the needs of the poorest countries. In the 10-15 year timeframe usually required to develop and make vaccines affordable to all, more than 150 million people may be infected with HIV, most of them in the developing world.
- 1.3 Resources spent on vaccine development are minimal compared with those spent on therapeutics research or other preventive interventions. The present vaccine development process is clearly inadequate, few candidate vaccines are at an advanced stage of development and little research and development is focusing on vaccines against those HIV clades that are prevalent in the developing world. Action is needed now to accelerate research and development and to ensure that a future vaccine is accessible to people in developing countries as soon as possible.
- 1.4 International agencies involved in health and development, such as the European Community, have a clear responsibility to support the development and provision of international public goods like AIDS vaccines, particularly where there is under-investment by the private sector.
- 1.5 In this context, the Commission of the European Community organised a technical consultation in Brussels on March 18-19 1999 to explore the economic and financial aspects of developing and making available an AIDS vaccine suitable for developing countries.

- 1.6 The meeting brought together specialists in public health, economics and legal issues, policy makers, representatives from developing countries, industry and donor agencies. Participants considered market, financing and legal barriers to vaccine development and accessibility, strategies to address these barriers, and possible areas for future action by the European Union, in collaboration with its international, regional and developing country partners.
- 1.7 Barriers to private sector investment identified by participants included scientific uncertainty, industry's perceptions about developing country markets, intellectual property, the opportunity costs and the potential high risk and lack of incentives associated with vaccine research and development, lack of commitment to vaccines by venture capital, in addition to concerns about safety and legal liability.
- 1.8 These constraints reflect, to a large extent, inadequacies in existing systems and knowledge. Participants agreed that, while industry participation is essential in the development and production of a preventive AIDS vaccine, it is unrealistic to expect the private sector alone to develop an AIDS vaccine that is appropriate for developing countries. Strategies are required to overcome obstacles to commercial investment and to develop innovative financial and regulatory mechanisms. Critical areas to be addressed include focusing research and development on relevant HIV clades, heightening political commitment, improving market understanding, identifying the requirements for effective vaccine supply and delivery, and barriers posed by existing legal and regulatory systems. In all of these areas the public sector can play an important role.
- 1.9 Participants identified a range of possible interventions. These include:
 - The development of fast track mechanisms for vaccine research, development and commercialisation
 - Establishing a better inventory of research and development efforts
 - More effective analysis of developing country markets
 - The development of minimum criteria and standards, for example related to acceptable levels of vaccine efficacy
 - Identifying risk sharing mechanisms, incentives and imaginative partnerships to encourage private sector investment and competition and address commercial disincentives

- Utilising intellectual property as an incentive to progress
 - Measures to reduce the risk of legal liability
- 1.10 The meeting concluded that using public finance at leverage and regulatory and patent mechanisms to guarantee markets may facilitate commercial investment.
- 1.11 AIDS vaccines are not unique. There have been major uncertainties in the development of other vaccines, but these have been overcome. The special nature of the HIV/AIDS epidemic means that the process must be accelerated to avoid delays between product development and availability and widespread use.
- 1.12 Therefore, concomitant, rather than sequential, efforts are required in science, research and development, in creating a supportive policy environment, and in identifying financial instruments for large scale supply and distribution. A first important step in the process is to develop a comprehensive overview of existing activities and players, in order to identify the comparative advantage of different partners and the potential for complementarity.
- 1.13 Using its comparative advantage, and the range of services and mechanisms at its disposal, the European Union could potentially take action in a number of key areas. These include:
- Supporting public health and economic research to respond to gaps in existing knowledge
 - Initiating policy dialogue with international, European and developing country partners to promote the AIDS vaccine agenda and support vaccine preparedness measures
 - Identifying, with its partners, options for effective public-private partnerships
 - Exploring the potential to amend the European regulatory process and to use European financial instruments, such as the European Investment Bank, to reduce the risk and increase the incentive for commercial investment in AIDS vaccine development
 - Encouraging collaborative Europe-wide initiatives involving research bodies and industry
 - Establishing a European-wide AIDS Vaccine Task Force

2. BACKGROUND

2.1 THE NEED FOR AN AIDS VACCINE

- 2.1.1 In the developing world the spread of HIV/AIDS shows no sign of slowing down. More than 90% of the 6 million new HIV infections each year occur in Africa, Asia, Latin America and the Caribbean. HIV/AIDS has already caused the deaths of 15 million people, mostly in the developing world, and projections suggest that, 20 years from now, over 150 million people worldwide will be infected with HIV.
- 2.1.2 Unless the spread of HIV/AIDS is reduced, the achievement of other development goals will be seriously affected. The HIV/AIDS epidemic is dramatically reducing life expectancy and reversing the health gains of recent decades in countries most affected. AIDS is also causing reductions in productivity and family income, driving families and communities into poverty.
- 2.1.3 While acknowledging the importance of continuing to support prevention, donor agencies and governments recognise that current efforts are failing to stop the spread of HIV quickly enough. HIV/AIDS is also still incurable and, although combinations of antiretroviral drugs and protease inhibitors can substantially improve the length and quality of life of people with HIV, the high cost of these treatments means that they are not an affordable option in most developing countries.
- 2.1.4 Given the limited success of preventive efforts and the high cost of anti-HIV treatments, there is growing interest in the potential role of preventive AIDS vaccines.
- 2.1.5 The urgent need for an AIDS vaccine for developing countries was reinforced by the Minister of Health for Swaziland, Dr Dlamini, at the start of the meeting. The Minister pointed out that the first hurdle to overcome is the development of a suitable candidate vaccine focusing on clades that are prevalent in developing countries. She noted that, while most developing countries lack the financial and technical resources to support vaccine research, they can and should be active participants in the research and development process.

- 2.1.6 The second hurdle, once a suitable vaccine is developed, will be making such a vaccine available in developing countries. Dr Dlamini emphasised that, in countries with HIV infection rates of 30%, there is a potential market for AIDS vaccines, and that governments will have a responsibility to ensure that people have access to a vaccine. Action is needed now to sensitise developing country governments and to ensure that they play a proactive role, working in partnership with international agencies, donors and the pharmaceutical industry.

2.2 RECENT DEVELOPMENTS IN AIDS VACCINES

- 2.2.1 Some 25-candidate vaccines have been developed in the laboratory and the development of an effective preventive vaccine looks promising, for a number of reasons:

- Adults infected with a form of the virus, which has been attenuated, appear to stay relatively healthy for a considerable time.
- Animal trials have shown that a range of candidate vaccines can produce a strong immunogenetic reaction.
- Transmission of HIV through sexual intercourse is relatively inefficient.
- Even a vaccine that succeeded in limiting viral load could have public health benefits.
- It is now clear that humans can regulate HIV replication, and some people who have been regularly and frequently exposed to HIV have not developed any symptoms of AIDS – so called “long term non-

- 2.2.2 Recently there have been significant steps forward, including:

- The European Community is supporting vaccine research under its new 1998-2002 framework programme, and is likely to increase expenditure on AIDS vaccine activity through its science and research directorate.
- The EU HIV/AIDS programme in developing countries, together with its many partners, is investigating financing and economic aspects of vaccine development and availability, and organising several forums to prepare a large-scale response.

- The International AIDS Vaccine Initiative (IAVI) has announced two new HIV vaccine development projects with funding of over US\$9 million, based on partnerships between institutions in industrialised countries and in Kenya and South Africa.
- The World Bank has a special task force, which is examining possible financial mechanisms to promote HIV vaccine development.
- A Phase III trial of one candidate vaccine is scheduled to take place in Thailand, Uganda has been preparing for a vaccine trial for some time, and vaccine trials are being considered by the governments of Brazil, Cuba and China.
- The National Institutes of Health in the United States has increased its budget allocation to HIV vaccine research and development in 1999.
- The Government of India has expressed interest in developing an indigenous AIDS vaccine.
- The UK Department for International Development is funding vaccine development through IAVI, and the French government is providing substantial funding for vaccine research through Pasteur Mérieux Connaught.

2.3 CHALLENGES IN AIDS VACCINE RESEARCH AND ACCESSIBILITY

- 2.3.1 Despite these positive developments, participants noted that investment in AIDS vaccine development needs to be increased. While it is estimated that US\$20 billion is spent every year on the prevention and treatment of AIDS and HIV-related illness and US\$2 billion on AIDS treatment research, only US\$300 million is spent on AIDS vaccine research, and most of this is on basic research, using public rather than private funds. Only US\$50 million a year is spent on applied vaccine development and, of this, only US\$10 million is spent on AIDS vaccines that could be appropriate for the developing world.

- 2.3.2 The concentration of investment in basic research has produced an abundance of good ideas for a vaccine, but the funds required to translate these ideas into clinical trials in humans, where real progress in solving the problems of vaccine development can be made, have not been made available. As a result, only three candidate vaccines have advanced into Phase II clinical testing. There is currently only one Phase III vaccine trial underway, the clade B gp120 candidate in the United States. No vaccine has yet been tested for efficacy against the most common strains of HIV in developing countries.
- 2.3.3 Although the science of AIDS vaccine development is complex because of, for example, the genetic variability of the virus, non-scientific challenges are likely to prove the greatest barriers to developing and producing a vaccine that is accessible to the developing world. Commercial investment has been limited by financial, market and legal barriers and by competing demands for available resources for research and development of other types of vaccines.
- 2.3.4 To date, most investment in AIDS vaccine research has been supported by the public sector in OECD countries and has focused primarily on HIV strains predominant in these countries. Individual governments may be reluctant to invest in vaccine research because others outside the country will potentially derive benefit from successful research and development efforts, the 'free rider' problem.
- 2.3.5 Donor agencies and governments have traditionally supported public goods (products or ideas that the private sector is unwilling to invest in), such as immunisation programmes, and many developing countries continue to rely on donor support for childhood vaccines, condoms and other public goods. There is also considerable support for other prevention strategies. However, despite the fact that the development of a suitable vaccine for preventing HIV in developing countries would constitute an important international public good, most development agencies have so far invested little or nothing in AIDS vaccine research.

- 2.3.6 The current situation raises questions about whether vaccine development should be backed by substantial public funding, given the reluctance of the market to invest in an AIDS vaccine, how much potential founders would be willing to contribute to funds established to develop or purchase vaccines, when available, and how public funding could facilitate commercial investment in appropriate research and development.

3. BARRIERS AND OPPORTUNITIES

Recent scientific advances have increased the feasibility of the commercial sector developing a preventive AIDS vaccine. And the development of pricing mechanisms in order to increase access to HIV therapeutics in developing countries illustrates the potential for convergence of private and public sector interests, which could be applied to AIDS vaccine access. However, despite the opportunities presented by these factors, investment in vaccine development by the commercial sector is constrained by issues related to: political sensitivity and visibility; the costs of development; safety and liability; intellectual property; sources of funding; demand; and efficacy.

The meeting was asked to focus its discussion on three broad areas that constitute obstacles to vaccine development and accessibility - market failure; gaps in existing knowledge about markets; and legal and regulatory barriers - and also heard the private sector perspective on which of these barriers are most critical.

3.1 UNDER-INVESTMENT BY THE PRIVATE SECTOR

- 3.1.1 Under-investment in AIDS vaccine research and development by the private sector is related to market failure, the perception that the ability to pay for a vaccine is limited in developing countries, high risk, uncertainty about the outcome of vaccine trials, and the cost of trials, particularly phase III trials.

- 3.1.2 World Bank research suggests that industry considers markets for a preventive vaccine to be either too small (in industrialised countries) or uncertain (due to the widely held perception that the ability of consumers in the developing world to pay for a vaccine is poor). Tiered pricing, one approach suggested to address the problem of developing countries' inability to pay for vaccines, has its problems but meeting participants noted, that tiered pricing is already accepted for other vaccines and for antiretroviral treatment.
- 3.1.3 Vaccine development is a long-term and expensive effort, potentially costing up to US\$ 250 million to develop a new product, US\$ 150 million to establish production facilities and US\$ 25 million to conduct a single efficacy trial. The number of companies with the potential and resources to develop an AIDS vaccine is limited and the industry is contracting. Vaccine development is also a high-risk venture, particularly in the early stages. Only one in five vaccines that leave the pre-clinical stage end up on the market and the probability of success is, therefore, low. It was pointed out that other vaccines have been developed without perfect scientific knowledge, and that outstanding research questions need not be a barrier to investment in development of an AIDS vaccine.
- 3.1.4 The most critical constraint to industry investment is the risk associated with the early stages of research and development, in view of uncertainty about the longer term ability to sell a product and the opportunity cost this represents for the pharmaceutical companies. In addition, different companies may be replicating research on different clades and strategies could be considered to reduce duplication and, hence, costs. Unanswered questions about the level of investment required to develop factory capacity and to enable health system infrastructure to deliver a vaccine are also barriers to commercial investment.
- 3.1.5 However, the potential profitability of an AIDS preventive vaccine, even at low volumes and low prices, was noted, based on a range of industry projections and assumptions.

- 3.1.6 It is clear that, under existing conditions, the private sector will not develop or provide an AIDS vaccine suitable for developing countries in the short term. Given the problem of private sector under-investment, participants concluded that international interventions are required to provide incentives, or to reduce the risk, for industry, particularly small biotech firms, to invest in early stage research and development. Participants also concluded that using public finance to support the later stages of product development or to guarantee markets, would be less appropriate, since experience with other vaccines indicates that if a candidate vaccine were developed this would be taken forward by industry without public subsidy, and potential markets do exist.

3.2 INADEQUATE INFORMATION ABOUT DEVELOPING COUNTRY MARKETS

- 3.2.1 Reluctance to invest is also related to limited knowledge of developing country markets and to experience with the market for other products in developing countries.
- 3.2.2 Commercial perceptions of ability to pay for vaccines in developing countries are largely based on information about ability to pay in industrialised countries, and research and development decisions are based on potential OECD markets. Participants noted the dearth of information about developing country markets.
- 3.2.3 The perception that the market for an AIDS vaccine in developing countries will be small is based on the experience of markets for existing vaccines and slow uptake of new vaccines. Currently only \$200 million of the \$4 billion global market for childhood vaccines is represented by developing countries. However, this may not be a good guide to potential spending on an AIDS vaccine, since the current market for childhood vaccines represents a 'maintenance' phase. If an AIDS vaccine becomes available there will be a large initial 'catch-up' demand, since none of the population will have previously been immunised. This suggests that a large market exists.

- 3.2.4 There is a growing gap between north and south in terms of access to new vaccines, with the poorest countries least likely to have access to HIB, hepatitis B, pneumococcal and rotavirus vaccines, even when these countries have effective delivery systems and have achieved relatively high coverage of other vaccines. Poorer countries are not introducing newly available vaccines, due in part to limited resources and in part to the expectation – of governments, donors and the public - that vaccines will be provided free or at low cost.
- 3.2.5 Investigation of the potential market for an AIDS vaccine in developing countries needs to consider both public sector and private demand, and the size of any future vaccine market will depend on a range of factors:
- Characteristics of the vaccine itself (for example, level of efficacy, duration, safety, side effects, number of doses required, and ease of administration)
 - Price
 - Ability and willingness to pay (for example, of individuals, households, governments and donors)
 - Cost of delivery and capacity of health services to deliver vaccines
 - Population at risk, likely public health impact and cost-effectiveness of a vaccine
 - Policy decisions (for example, about who receives the vaccine)
 - Political considerations (for example, the influence of activist groups)
- 3.2.6 Current knowledge related to all these factors is limited and the meeting agreed that research studies to provide a clearer picture of the potential market for AIDS vaccines in developing countries should be given high priority.
- 3.2.7 An important information gap, from the perspective of the commercial sector, is defining acceptable levels of efficacy until such time as a single dose, cheap, highly efficacious product is developed. An AIDS vaccine, like any other product, will require ongoing development and refinement and, in the meantime, industry needs better information about likely demand and willingness to pay for vaccines with different levels of efficacy and at different stages of development.

3.3 INTELLECTUAL PROPERTY

- 3.3.1 Intellectual property, which relates to patents, copyright, know-how, trade secrets and biological materials, presents both barriers and opportunities for vaccine development and distribution for developing countries.
- 3.3.2 Vaccine research and development involves many steps. The recombinant hepatitis vaccine, for example, requires fourteen different patents to produce. Patents, which are country specific, are the right to exclude others from using, making or selling an invention, usually a product. Patents can act as barrier if the patent owner prevents manufacture, use or sale, or demands royalties, thereby increasing costs, or the patented invention is part of the development, manufacture or composition of the final product. The proliferation of patents in the vaccine development chain - for genes, proteins, factors, adjuvants and carriers – increases the time and costs involved and acts as a disincentive to commercial investors.
- 3.3.3 Patents also depend on consistency of enforcement by legal systems. Fear of infringement is a major commercial concern, particularly since intellectual property laws vary between countries and in many developing countries they are virtually unenforceable. Fear of irreversible leakage of know-how, trade secrets, copyright and biological materials is also a barrier, preventing the transfer of most advanced processes from developed to developing countries.
- 3.3.4 Intellectual property can, however, also enhance opportunities for vaccine development. Intellectual property is the major currency for the transfer of innovative products from the developer – often a small biotech company – to the final manufacturer and marketer – usually a large pharmaceutical company. It therefore represents a useful “transaction definer” for the transfer of technology, processes and products from industrialised countries to the developing world, given suitable legal protections.
- 3.3.5 In the USA, and increasingly in Europe, patents are used by universities to induce industrial investment in early-stage technology. Universities grant and give exclusive licence to companies willing to risk investment in unproven advancements in order to develop a product for the market. In the USA, 10-20% of these licenses are to new ventures, and this approach is encouraging earlier investment by industry and venture capital in university discoveries and more rapid development of innovative products.

The IAVI AlphaVax collaboration (see box) is an example of how careful planning can harness intellectual property to enhance opportunity.

THE IAVI ALPHAVAX COLLABORATION AGREEMENT

Under this agreement, the development of a vaccine against HIV based on AlphaVax's "Replicon" Venezuelan Equine Encephalitis vector is exclusively licensed from the University of North Carolina, with venture capital provided by IAVI. The AlphaVax product will be based on clade C strains from South Africa. Intellectual property rights have been agreed as follows:

- AlphaVax will own patents developed under IAVI funding
- If AlphaVax cannot meet the lowest cost for manufacture, IAVI is granted the license to all necessary intellectual property rights, including AlphaVax's background rights
- AlphaVax pays IAVI low royalty on programme patents used for products sold to industrialised countries; no royalties will be paid on public sector sales in developing countries

AlphaVax benefits from substantial funding, increased credibility, access to third party advisers and materials, access to clinical trial sites and partners, political access, reduced technical risk, and freedom to publish findings. If successful, the collaboration will enable IAVI to achieve its objectives of early stage research and development of an HIV vaccine focused on developing country clades, dissemination of new findings, product manufacture and distribution at accessible costs, and freedom of action to use the results if AlphaVax chooses not to follow through.

4. CURRENT ACTIVITIES AND POTENTIAL PARTNERSHIPS

- 4.1 Discussion of the current activities of the World Bank, UNAIDS, European Union and UK Department for International Development, and the recently launched South African AIDS Vaccine Initiative, provided an indication of the potential roles that could be played by international, regional and national partners in supporting vaccine development and access. In addition, it prompted meeting participants to agree that there is a need to identify a wider range of potential partners and to develop a better overview of the different activities of different players, to ensure that all partners contribute to an overall global effort according to their comparative advantage.
- 4.2 This view was reinforced by the UK Department for International Development (DFID), whose primary concern is to ensure a co-ordinated effort and synergy between donors, and to utilise public sector financing to achieve the most effective outcome. Vaccine support is a relatively new area for DFID, despite its long-term and increasing commitment to HIV/AIDS. The Department is currently supporting the activities of IAVI and the MRC, and could play a role in promoting vaccine development and access through its international, European, Commonwealth and developing country partnerships, through providing technical support for developing country partners, and through future vaccine subsidies.
- 4.3 The World Bank pursues its objectives through lending to developing country governments, policy dialogue and economic research. An AIDS Vaccine Task Force has been established to examine how the Bank can accelerate vaccine development and access through existing instruments and to identify what new mechanisms might need to be established.
- 4.4 The World Bank Task Force is concentrating on four areas of activity: analysing why industry investment in developing country vaccine research and development is low; learning more about potential public and private demand; defining what instruments might be most effective; and consulting with a range of partners to determine the most appropriate role for the Bank.

- 4.5 With regard to the latter, options currently being investigated include: 'pull' initiatives, such as expanding lending, providing better information on developing country markets, providing market guarantees through contingent lending or establishing a vaccine purchase fund, and extending patents; and 'push' initiatives, such as providing direct support for vaccine research and development to developing countries or organisations like IAVI, and identifying mechanisms to reduce the risks and costs of vaccine clinical trials and to provide protection against legal liability for the commercial sector. The Bank is also exploring, through policy dialogue with developing country governments, sustainable financing mechanisms for vaccines that are already provided through immunisation programmes.
- 4.6 The European Union has the potential to support vaccine development and access through its different services. The priorities of the European Union HIV/AIDS programme of the development directorate, DGVIII, include policy dialogue, collaborative policy research, developing innovative strategies, and identifying instruments for investing in international public goods, such as an AIDS vaccine and microbicides.
- 4.7 The science and research directorate, DGXII, is supporting research relevant to AIDS vaccine development within its framework programme for the period 1998-2002. This includes research on reagents and on systematic standardised evaluation of candidate antigens in primates, and exploring new work on clade C research in collaboration with institutions in China. A call for proposals has been issued for research to address key actions, one of which relates to control of infectious diseases, including HIV/AIDS. The aim is to develop clusters of projects addressing issues that are common to vaccine development for HIV, malaria, hepatitis and TBC, such as adjuvants, new animal testing models, clinical trial networks, and scaling up the technology for vaccine production. This cluster approach also aims to foster collaboration, inter-disciplinary work, and information sharing between research networks and industry. Experience with using public funds to support development of a malaria vaccine by an industry consortium has shown that it is possible to establish a mechanism to co-ordinate European-wide vaccine development activity. One option under consideration is a European HIV/AIDS Vaccine Initiative, along similar lines to the malaria vaccine initiative.

- 4.8 DGIII is currently taking forward a proposal for European regulation of orphan drugs that meet specific epidemiological, economic and health criteria. The proposal introduces a number of incentives, including 10 year market exclusivity, a fast track mechanism in the regulatory process, assistance with protocols, access to centralised procedures leading to marketing authorisation in the Community, and fee waivers, as well as establishing a new committee within the European Agency for the Evaluation of Medicinal Products (EMA). The regulation makes provision for products to prevent or treat life-threatening or seriously debilitating communicable diseases to be designated as orphan medicinal products, where it can be shown that, without incentives, the marketing of such products would not generate sufficient return to justify the necessary investment. This could clearly apply to AIDS vaccines, and participants noted that it is most likely that SMEs and start-up companies, the type of firms that conduct early research and development, would take advantage of such legislation.
- 4.9 Although participants agreed that establishing local vaccine production capacity and ensuring quality control has proved to be problematic in some settings, the South African AIDS Vaccine Initiative (SAVI) is an example of the proactive developing country role in finding solutions envisaged by Dr Dlamini. The Initiative was established in response to the extent of the AIDS problem in South Africa and recognition that current approaches to AIDS vaccine research are unlikely to address the needs of developing countries. The objective is to develop and make available an effective, accessible and affordable 'public-sector owned' vaccine that is suitable for South Africa and surrounding countries. SAVI is funded by the public and private sectors and donor agencies, and involves collaboration between government, industry, research bodies and non-government partners in South Africa, and IAVI and AlphaVax.
- 4.10 The meeting concluded that any global effort to develop and make available AIDS vaccines for developing countries must involve the widest range of partners, including international, multilateral and bilateral agencies, developing country governments, research organisations and co-ordinating bodies, charities and foundations, non-government organisations and the AIDS community, the private sector, churches and the media.

- 4.11 Participants discussed various possible approaches to global co-ordination. There was limited support for the establishment of a new global co-ordinating structure and no consensus about whether one organisation should take a leadership role within existing structures. However, the meeting agreed on a number of key principles: the need for greater information sharing, for an ongoing dialogue between different stakeholders and for greater involvement of developing countries and industry in this dialogue.
- 4.12 Opportunities presented by upcoming meetings – including the World Bank meeting on AIDS vaccines in April, the SADC Ministers meeting in April, the global vaccine co-ordination initiative meetings and launch in June and September, and follow-up meetings to ICPD – should be used to further dialogue and to explore mechanisms for ensuring ongoing information exchange, so that agencies deploy their resources in the knowledge of others' plans and activities.

5. FUTURE NEEDS AND PRIORITIES FOR ACTION

There was a consensus that it is critical for scientific, economic and political initiatives to be taken forward in parallel and for these initiatives to intersect. Action to obtain political support and establish effective financing structures must start now, rather than waiting for a product to become available.

Meeting participants identified a range of potential actions worthy of further consideration and issues where more information is required, in the following key areas:

- Research and development to identify a candidate vaccine for trial in Africa
- Public health and economic research
- Vaccine preparedness
- Manufacturing capacity
- Strengthening distribution capacity and infrastructure
- Creating a supportive political environment and political will at the highest levels
- Addressing barriers represented by intellectual property and regulations

5.1 VACCINE RESEARCH AND DEVELOPMENT

Action is required to:

- Increase resource allocation to develop and conduct trials of vaccines suitable for developing countries, including assessing the potential to use existing mechanisms, such as tendering by international agencies, to leverage vaccine research and development.
- Conduct systematic analysis of current research and development activity and to identify mechanisms to reduce replication and duplication.
- Provide clearer information about commercial risk and opportunity costs associated with initial research and development.
- Increase dialogue with industry and venture capital to explore the role of the public sector in leveraging capital support for early high risk research and development and identify incentives needed to encourage the involvement of smaller companies.
- Define options for risk sharing and incentives.
- Establish minimum acceptable standards and criteria for vaccine characteristics, to enable industry to set targets.
- Learn lessons from the experience of trials of other interventions, such as for the prevention of mother to child transmission, in order to design vaccine trials that will yield relevant information.

5.2 PUBLIC HEALTH AND ECONOMIC RESEARCH

Action is required to:

- Analyse potential public and private demand for AIDS vaccines in developing countries and the determinants of demand in these sectors. Such studies need to provide better information about ability and willingness to pay by individuals, households, governments and donor agencies in a range of developing country settings, and determine how potential demand may be affected by vaccine efficacy, side effects, safety, duration of protection and the number of doses required.
- Define appropriate price and pricing structures, including the role of tiered pricing.
- Assess the potential public health impact and cost-effectiveness of an AIDS vaccine with different levels of efficacy in different populations at different stages of the epidemic, both in comparison and combination with other preventive interventions at a population level.

5.3 VACCINE PREPAREDNESS, MANUFACTURING CAPACITY AND INFRASTRUCTURE

Action is required to:

- Develop partnerships so that human trials can be conducted in developing countries.
- Conduct studies to identify priority countries and populations.
- Provide better information about manufacturing capacity requirements and associated costs.
- Analyse the likely infrastructure requirements for AIDS vaccine delivery in developing countries, existing health service capacity and the cost of effective delivery systems and strengthening health service infrastructure.

5.4 POLICY ISSUES

Action is required to:

- Initiate policy dialogue to place AIDS vaccines higher on the agenda of donor agencies, governments and industry.
- Advocate for the role of vaccines and the potential cost-effectiveness of an AIDS vaccine in stopping the spread of HIV/AIDS.
- Initiate policy dialogue with developing country government ministries of finance and health to explore options for future financing.
- Conduct studies to provide better information about the negative impact of HIV/AIDS on the economies of developing countries.

5.5 INTELLECTUAL PROPERTY

Action is required to:

- Conduct systematic analysis of existing patents related to steps in development of an AIDS vaccine, and of the cost of utilising these patents.
- Address uncertainties related to old intellectual property rights.
- Explore the potential for replicating the IAVI-AlphaVax collaborative model.

6. RESULTS

THE NEED FOR AN AIDS VACCINE.

HIV/AIDS continues to spread throughout the developing world, threatening progress to date and the future achievement of development goals, reducing life expectancy and increasing poverty. More than 90% of infections occur in Africa, Asia, Latin America and the Caribbean. HIV/AIDS has already infected 40 million people, mostly in the developing world, and it is projected that a further increase will be exponential.

Medicines for the treatment of HIV/AIDS are not affordable to the majority of people in developing countries, nor do they provide a cure. A suitable AIDS vaccine could play an important role in preventing infection of millions of people in developing countries. Recent progress in vaccine developments give hope, but time is of the essence and ensuring a suitable vaccine is developed and distributed widely to people in developing countries as soon as it is available, will require urgent and increased international actions.

ADDING TO EXISTING EU ACTIONS IN HIV/AIDS PREVENTION.

The Communication from the Commission to Council and the European Parliament "For Increased Solidarity to Confront AIDS in developing countries" proposes action to support the development and availability of an AIDS vaccine suitable for use in developing countries. The communication (Doc com (98) 407 final) mandates the European Commission to explore new mechanisms as part of an integrated initiative.

This new action will complement existing EU HIV/AIDS co-operation with developing countries. The EU is successfully supporting cost-effective and targeted preventative interventions and strengthening primary health care in developing countries. The success of countries like Senegal and Uganda -which have managed to stem the spread of the disease- illustrate the importance of dialogue and partnership with developing countries in identifying effective policies aimed at HIV/AIDS prevention.

THE EUROPEAN COMMISSION INITIATES "AN INTERNATIONAL CONSULTATION OF EXPERTS".

Building on the experiences with its international and developing country partners in prevention efforts to date, the European Commission organised a 2-day international consultation to explore the financial and economic aspects of making an AIDS vaccine available in the developing world. Apart from representatives from the Commissions' various services a Member States representative, the meeting included representatives from the World Bank, UNAIDS, the International AIDS Vaccine Initiative, the South African AIDS Vaccine Initiative, the Pharmaceutical Industry, an Intellectual Property Regulatory Organisation and the Minister for Health of Swaziland.

The meeting resulted in a valuable and wide-ranging exchange of information on a rapidly evolving situation. Five years ago the possibility of a preventive AIDS vaccine was not on the political or research agenda: now it is a real possibility. To ensure that this possibility translates in to prevention of millions of new infections in developing countries will require an international strategy with simultaneous and parallel actions in different fields.

Actions to promote further scientific research -where recently considerable progress was made in vaccine development- are already underway with substantial European Union backing under the 5th programme. Simultaneously, urgent action is needed to overcome the barriers to vaccine development and availability for developing countries which are related to commercial, legal, economic and financial constraints. Finding a solution to overcome these barriers is important in order to attract more investment from the private sector in vaccine development and at the same time ensure access to a vaccine for the poorest as soon as it is available. Pharmaceutical Industry investment is presently limited due to concerns about risk/safety of new vaccines trials, the lack of developing country markets and the inability of governments and households in the developing world to pay for them. In addition, current knowledge about issues such as willingness to pay by households, government and donors is limited.

THE NEED FOR PUBLIC AND PRIVATE PARTNERSHIP.

The 'consultation of experts' focussed on the fact that an innovative approach to public-private partnership would be required to overcome these barriers. A number of parallel actions need to be planned and pursued at the same time. It was agreed that these include, amongst others, support to:

- bio-technological research and trials, to ensure vaccines suitable for use in developing countries
- political advocacy to engage public support and the development of related policies and
- priorities
- innovative approaches in intellectual property questions as well as patent and liability issues
- the development of manufacturing and distribution capacities.
- economic research to establish whether new financial instruments need to be designed to entice commercial investment in AIDS vaccine development.

Recommendations at the meeting focussed on how to move these parallel yet interdependent paths forward simultaneously through innovative joint public and private sector actions. One specific example, was the proposal to provide international public funds as 'venture capital' to small bio-technological companies. The meeting also identified a number of priority areas for research where it was felt that there was still a lack of knowledge (for example on private and public willingness to pay for a vaccine).

Timely action was emphasised by all and it was stressed that further research should not delay the implementation of those actions which can be taken immediately. This should include action to stimulate the formation of partnerships with industry, other public and private agencies, and, crucially –with developing country partners. This acknowledges that developing countries include potential producers, as well as potential purchasers of a preventive vaccine. It was agreed that the EC experts consultation should signal the start of a process of on-going dialogue, consultation and information exchange between the various stakeholders.

IMMEDIATE EU ACTION AND A COMMISSION INTER-SERVICE 'AIDS VACCINE TASK TEAM

The potential for the European Union and its Member States to make a significant contribution to the effort to make a preventive AIDS vaccine available to people in developing countries is considerable. The EC already has a long standing involvement in HIV/AIDS prevention and a reputation for initiating valid approaches (such as integration of HIV/AIDS and STD strategies) and innovative policy research (such as research on market demand for microbicides and research on the viability of condom manufacture in developing countries).

At the 'international consultation of experts' it was felt that the European Commission's comparative advantage lies in its: strong policy dialogue with developing countries as well as its mandate for policy co-ordination with EU Member States, including on HIV/AIDS; its ability to act as a legal policy formulating body (for example in intellectual property); the variety of instruments at its disposal both within the EU and in Developing Country; its strong track record of support to the private sector both inside the EU and in developing countries; its extensive experience -including on HIV/AIDS- on policy formulation and co-operation with international agencies;

Four distinct levels for EC/EU action were identified as related to an Aids vaccine:

- 1) Existing instruments can be used to initiate immediate action – For example, a call for proposals to respond to some important economic and financing research gaps has been made, using the AIDS Budget Line.
- 2) Close co-operation between the different services involved needs to be strengthened on this specific subject, with a view to developing new approaches and implementing a coherent EU strategy in support of an AIDS vaccine for developing countries. The formation of an inter-service 'AIDS Vaccine Task Team' was put forward as a valid mechanism.
- 3) Making a preventive AIDS vaccine accessible to all within an acceptable time will require an accelerated effort by a number of agencies. It is important that the EC enables co-ordination of own additional efforts- based on its comparative advantage- with those of other international agencies.
- 4) The consultative process as initiated by the European Commission will need to be taken further, in particular with regard to discussions at the level of EU Members States experts, but also in the framework of envisaged World bank consultations, and deliberations at the level of the G8 meeting in Cologne in 1999.

Annex 2 AGENDA

THURSDAY 18th MARCH

9.30 a.m. Welcome (*Philippe Darmuzey, Head DGVIII/A2, Directorate General VIII – Development*)

9.45 a.m. Introduction to the meeting and the EU's interest in AIDS vaccines (*Lieve Fransen*)

The need for an AIDS vaccine

10.00 a.m. Minister of Health Dlamini, Swaziland

Barriers to making an AIDS vaccine available (*Chair: William Makgoba*)

10.15 a.m. Market barriers (Market failure, willingness and ability pay issues) (*Martha Ainsworth*)

10.30 a.m. Knowledge barriers (Gaps in current knowledge about markets) (*Martha Ainsworth*)

10.45 a.m. Legal barriers (Intellectual property law and practice and manufacturing patents) (*Lita Nelsen*)

11.00 a.m. Commercial barriers (The industry perspective) (*Peter Young*)

11.15 a.m. Coffee

11.45 a.m. Questions and discussion (*Chair: William Makgoba*)

1.00 p.m. Lunch

The response: current activities and future needs (*Chair: Cliff Lenton*)

2.15 p.m. The developing country perspective (*William Makgoba*)

2.30 p.m. The UNAIDS perspective (*Anita Alban*)

2.45 p.m. The industry perspective (*Peter Young*)

3.15 p.m. A bilateral perspective (*John Gordon*)

3.30 p.m. Coffee

4.00 p.m. Research and mechanisms required to make an AIDS vaccine available in the developing world (*Martha Ainsworth*)

4.30 p.m. Questions and discussion (*Chair: Cliff Lenton*)

MAKING AN AIDS VACCINE AVAILABLE IN DEVELOPING COUNTRIES: REPORT OF
AN EU CONSULTATION. APRIL 1999

5.00 p.m. Close

FRIDAY 19th MARCH

9.00 Am. Summary of discussion and key issues from day one (*Cliff Lenton*)

9.30 Am. Overview of current EU activities and potential areas of activity in making an AIDS vaccine available (*Michel Pletschette and Lieve Fransen*)

Discussion of future EU policy, research and partnership priorities related to economic and financing aspects of making an AIDS vaccine available in developing countries

9.45 Am. Priorities for research in economic and financing aspects of AIDS vaccines (*Chair: Amie Batson*)

11.15 Am. Coffee

11.30 a.m. Policy priorities (*Chair: Inge van den Bussche*)

1.00 p.m. Lunch

2.00 p.m. International, bilateral, member state and developing country partnership priorities (*Chair: Chip Lindner*)

3.30 p.m. Coffee

4.00 p.m. Conclusions and the way forward (*Philip Lowe, Director-General, Development; Lieve Fransen*)

4.30 p.m. Close

Annex 1 LIST OF PARTICIPANTS

Online Version of

8 Years and Counting...

What Will Speed Development of an AIDS Vaccine?



Table of Contents

AIDS Vaccine Advocacy Coalition

May 1999

THE WHITE HOUSE

WASHINGTON

March 1, 2000

VACCINE INITIATIVE EVENT

DATE: March 2, 2000

LOCATION: Cabinet Room

TIME: 11:30 a.m. - 12:30 p.m.

FROM: SAMUEL BERGER
GENE SPERLING Rob Wescott For
NEAL LANE Laura Efros For
MARY BETH CAHILL MBC

I. PURPOSE

To meet with senior White House and Cabinet officials, heads of United Nations Organizations, foundations, the World Bank, vaccine and biotech experts, and the CEOs of the world's major vaccine producers. This is an opportunity to:

- Demonstrate your continued leadership in the fight against diseases disproportionately affecting the developing world;
 - Highlight your new \$1.5 billion-plus initiative to accelerate vaccine development for diseases such as AIDS, TB, and malaria;
 - Achieve a united front with the private sector in supporting the Administration proposals;
 - Gain commitments from the private sector to match Administration efforts on vaccine development.
- We expect each CEO to 1) express support for your vaccine initiative, 2) suggest to us that more public/private research partnerships and guaranteed markets for products would help provide incentives for investing in development of new vaccines for malaria, TB, and AIDS. 3) We expect a series of commitments for investment in vaccines and vaccine development.

II. BACKGROUND

In your speech to the U.N. General Assembly last September, you called for a White House meeting to find ways to accelerate the development and delivery of vaccines for malaria, TB, and AIDS - vaccines for which there is huge need, but little market incentive for industry to develop. In your State of the Union address, you rolled out a significant multi-part proposal to address this need:

- \$50 million to the Global Alliance for Vaccines and Immunization to purchase existing high-tech vaccines for developing countries;
- Sharp increases in NIH vaccine research;
- A \$1.0 billion tax credit for sales of vaccines for malaria, TB, and AIDS when they are developed;
- Call to the World Bank to dedicate an additional \$400-900 million in concessionary loans for health;
- Call to the G-8 and other countries to join us in meeting the challenge.

III. PARTICIPANTS

See Tab B for list of participants.

IV. PRESS PLAN

Pool spray at end of meeting.

V. SEQUENCE

The meeting will start at 11:30, chaired by Gene Sperling.

Gene will open the meeting and summarize the problem. Secretary Shalala and Secretary Summers will outline the key elements of your initiative. The Minister of Health from Uganda will set the stage from the developing country point of view.

You will join in progress.

Attachments

- Points to be Made
- List of Participants
- Closing Remarks
- Seating Chart

POINTS TO BE MADE UPON JOINING THE VACCINE MEETING

- Thank everyone for coming. Acknowledge Dr. Kiyonga [Kee-yongga] (Minister of Health from Uganda); Larry Summers and Donna Shalala, John Podesta, Sandy Berger, David Satcher, Brady Anderson, Jim Wolfensohn, Dr. Gro Brundtland (DG, WHO and former PM of Norway); Carol Bellamy (UNICEF) and the CEOs of the pharmaceutical companies John Stafford (American Home Products); Raymond Gilmartin (Merck); Jean-Pierre Garnier (SmithKline Beecham); Richard Markam (Aventis Pasteur).

[Ask Gene Sperling to outline previous discussions.]

- Each year in the developing world, we lose millions of lives and billions of dollars to killer diseases like AIDS, malaria, and TB. Last year in Africa, AIDS alone killed ten times more people than all wars did.
 - We know the extent of the problem and we're here to focus on solutions. Ultimately the solution must include the development of safe, effective vaccines.
 - We've developed vaccines for polio, measles, mumps, rubella, and more than a dozen other diseases. We have the technology to do the same for today's killers.
 - I've proposed a significant package of proposals. At G-8 Summit in Okinawa, I will urge our partners to follow suit.
- I thank you for doing your part.

• Potential Discussion Items for Select Attendees by Category

Multilateral Organizations

- Ask Jim Wolfensohn (President, World Bank) to comment on how multilateral development banks are contributing to increasing access to vaccines and health care.

PRIVATE SECTOR (2-3 Minutes of Comments)

Pharmaceutical Companies

- Ask **John Stafford** (CEO of American Home Products) to comment on industry's interests, problems, solutions for development of new vaccines.
- Solicit comments from: **Raymond Gilmartin** (CEO, Merck); **Jean Pierre Garnier** (President, SmithKline Beecham); **Richard Markum** (CEO Aventis-Pasteur).

Biotech Companies

- Ask **Sean Lance** (Chiron) to briefly summarize how incentives for the smaller biotech companies differ from those of the larger companies.
- **Dr. Don Francis** (VaxGen): I understand you are moving along in testing of an AIDS vaccine. What would have made the development process easier?
- **Dr. Seth Berkley** (International Aids Vaccine Initiative): your organization is funding some significant AIDS vaccine trials as well. How close are we to results?

Foundations

- Solicit comments on approach to vaccine delivery and development from: **Bill Gates, Sr.** (Gates Foundation) (Gates Foundation just gave \$750 million over five years for vaccines.); **Tim Wirth** (UN Foundation); **Gordon Conway** (Rockefeller Foundation).
- Excellent discussion. We could go on all afternoon. I am gratified and heartened -- we all have so much yet to do. so many lives can be saved by working together.

In moving forward, I have asked Secretary Shalala to convene a meeting of experts from the pharmaceutical industry, biotech, government, and academic sectors to seek ways to hasten R&D for vaccine development. Secretary Summers, continue your work with industry to craft incentives to empower the vaccine development process.

Closing Remarks (Pool Spray)

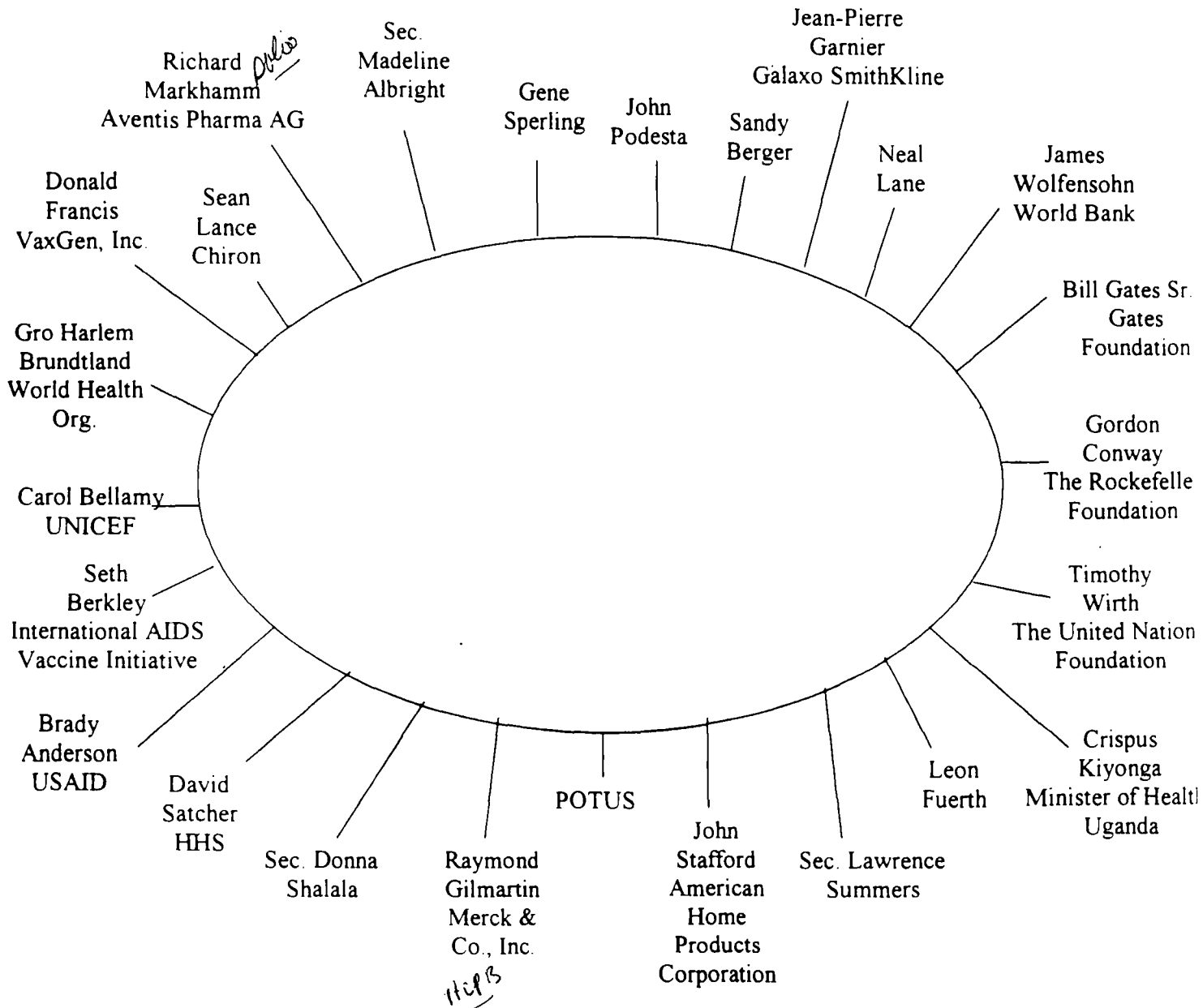
Points for Pool Spray Following Vaccine Meeting

- Meeting to join forces in the fight against diseases that kill people and progress in world's poorest countries. Urgent global challenge: AIDS took 10 times as many lives in Africa last year as war did. Malaria and TB still leave millions of children around the world without parents, millions of parents without children.
- Ultimate solution must include development of effective vaccines. That's how we got rid of smallpox, come close to eliminating polio. So today, we're beginning a partnership to eradicate the leading infectious killers of our time. We're speeding delivery of vaccines, and getting to the heart of this problem: the lack of incentive for private industry to invest in new vaccines potential customers can't afford.
- I've put comprehensive package on the table. \$1 billion tax credit to speed invention of vaccines. \$50 million contribution to a global fund to purchase vaccines. Big increase in research by NIH. Called on World Bank to dedicate more lending to improve health.
- Private sector is responding, and I want to recognize commitments companies are making.

- Merck is committing to develop an AIDS vaccine not just for strains of the virus that affect wealthy nations, but for strains that ravage poorest countries in the world. And it's donating 1 million doses of Hepatitis B vaccine to those who need it most.
- American Home Products will donate 10 million doses of a vaccine to prevent deadly strains of pneumonia and meningitis in children.
- SmithKline Beecham will expand its malaria vaccine program and begin new vaccine trials in Africa. And it will donate drugs worth \$1 billion to eliminate elephantiasis, a crippling tropical disease.
- Aventis Pasteur will donate 50 million doses of polio vaccine to 5 war torn African nations.
- Good beginning. It will save lives, and show we're serious. But more to do. Must build on bipartisan support in the Congress to enact tax credit and funding increase. And I will go to G-8 in Okinawa this summer to urge partners to take similar steps.

Call Stephanie -

**Presidential Meeting on Vaccines
March 2, 2000
Cabinet Room
11:30 a.m.**



List of Participants

Administration

The President

Secretary Lawrence Summers

Secretary Donna Shalala

John Podesta

Samuel Berger

Neal Lane

Gene Sperling

Leon Fuerth

Melanne Verveer

Sandra Thurman

David Beier

Mara Rudman

Chris Jennings

David Satcher, Surgeon General

Brady Anderson, Administrator, USAID

Major-General John Parker, Commander, Army Medical Research
Command

Ambassador George Moose, U.S. Ambassador to the UN, Geneva

Sheryl Sandberg, Chief of Staff, Department of the Treasury

Anthony Fauci, Director, National Institute for Allergy and
Infectious Diseases, NIH

Gary Nabel, Director, AIDS Vaccine Research Center, NIH

Outside Participants

Crispus Kiyonga, Minister of Health, Uganda

James Wolfensohn, President, World Bank

Gro Harlem Brundtland, Director-General, World Health
Organization

Carol Bellamy, Executive Director, UNICEF

Richard Markham, President and CEO, Aventis Pasteur

Jean-Pierre Garnier, President Designate, SmithKline Beecham

John Stafford, President and CEO, American Home Products

Raymond Gilmartin, President and CEO, Merck

Donald Francis, President, VaxGen

Sean Lance, Chairman and CEO, Chiron

Bill Gates, Sr., Bill and Melinda Gates Foundation

Gordon Conway, President, Rockefeller Foundation

Timothy Wirth, President, United Nations Foundation

Jeffrey Sachs, Professor, Harvard University

Seth Berkley, President, International AIDS Vaccine Initiative

Nils Daulaire, President and CEO, Global Health Council

Herbert Brown, Past President and Chairman-elect, Rotary
International

DEPARTMENT OF THE TREASURY
WASHINGTON, D.C.
December 17, 1999

SECRETARY OF THE TREASURY

MEMORANDUM FOR THE PRESIDENT

FROM: Lawrence Summers 
SUBJECT: Encouraging the Development of Vaccines

This memo responds to your request for more information about the vaccine proposal noted in our weekly report. This proposal is being considered by an interagency group including OSTP, OMB, NSC, NEC, USAID, ONAP, HHS and Treasury and is still in the development stage.

This proposal responds to your commitment to the United Nations that the United States make a concerted effort to improve the development and delivery of vaccines to developing countries. The proposal also supports our overall strategy for global development, which gives a central role to "global public goods" – like health or the environment – in which positive actions taken in one country benefit other countries as well. In an interconnected world, health crises in other countries are a threat to us all, as we have seen with HIV/AIDS, the resurfacing of tuberculosis, and the outbreak earlier this year of West Nile-like encephalitis in New York.

The core problem is that the market does not provide incentives for pharmaceutical companies to develop vaccines for diseases that disproportionately affect developing nations. The pharmaceutical companies have an understandable concern that because these nations are poor, the companies will be forced to sell products at a price that does not provide a positive return on their R&D investment.

Infectious diseases pose a mounting social and economic burden on developing countries, causing almost half of all deaths worldwide of people under age 45. Vaccination is one of the most cost-effective ways to improve the wellbeing and productivity of the poorest countries – and the developed nations have the scientific and technological capacity to make new vaccines possible. Recent work on the human genome will open vast possibilities.

Proposal

The interagency group is considering a proposal that addresses these concerns in three ways.

1. A new financial commitment to purchase and deliver existing vaccines in poor countries.
 - Contribute \$50 million to the existing purchase fund of the Global Alliance for Vaccines and Immunizations (or GAVI, a collaborative effort of UNICEF, the World Health Organization, and others). Several days after the State of the Union address, GAVI will officially announce a contribution of \$750 million by the Bill

and Melinda Gates foundation. By contributing, the United States could help catalyze the maximum amount of public and private funds. (Note: No Cabinet Secretary has proposed this item in their budget or as part of their settlement.)

2. Steps to accelerate the invention and production of new vaccines.
 - Increase funding for basic research on diseases that affect developing nations, particularly on malaria and TB, at the National Institutes of Health.
 - Call for the creation of a Millennium Trust Fund, which would combine public and private resources to ensure that vaccines for AIDS, malaria, TB, and other killers will be purchased when they become available.
 - Propose a tax credit for sales of new vaccines, though this raises a variety of concerns.
3. Increase the investments that poor countries make in their own health, which are as central to economic progress as investments in education and physical infrastructure.
 - Call on the World Bank and other multilateral development banks to earmark an additional 5 to 10 percent of their lending to poor to expand immunization, to prevent and treat common diseases, and to build competent and corruption-free delivery systems for other basic health services. This action would build on the new focus on basic health services that we have supported as part of the Highly Indebted Poor Countries (HIPC) debt initiative.

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