



International Federation of Pharmaceutical Manufacturers & Associations
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Pharmaceutical and Vaccine Research and Development for the World Medical Needs

The WHO Intergovernmental Working Group on Public Health, Innovation and Intellectual Property Rights (IGWG), was created by the World Health Assembly in 2006 in response to concerns raised by several WHO Member States about the need for new and improved medicines to treat diseases which particularly affect developing countries.

The mandate given to the IGWG in WHA 59.24 is the following:

(1) to establish...an intergovernmental working group ... to draw up a global strategy [that] would aim, inter alia, at securing an enhanced and sustainable basis for needs-driven, essential health research and development relevant to diseases that disproportionately affect developing countries, proposing clear objectives and priorities for research and development, and estimating funding needs in this area;

This mandate covers a number of issues, including what is meant by “needs-driven, essential health research and development relevant to diseases that disproportionately affect developing countries”. If this phrase implies that the current, market-based R&D model for pharmaceuticals and vaccines is ignoring health needs, especially those that disproportionately affect developing countries, then such an implication is factually incorrect, however, as evidence in this document shows.

This paper reports on industry’s work underway in a number of categories of medicines’ research and development, ranging from those for diseases primarily affecting developing countries, medicines for children, medicines for cancer, and for various infectious diseases. An Appendix is included to describe existing industry research centers dedicated to R&D for tropical diseases. This research includes medicines in clinical and pre-clinical development for TB, malaria, African trypanosomiasis, Leishmaniasis, Dengue and Onchocerciasis.

With regard to global health needs, the international R&D-based pharmaceutical industry has been successful in developing products to address the major global causes of mortality and morbidity, including, for example, cardiovascular medicines in 8 different classes, the most effective cancer drugs in 8 classes, new antibiotics for respiratory infections, 21 HIV/AIDS drugs in 4 different classes, and new drugs in 4 different classes to treat depression.

The information in this document is publicly available and reflects actual surveys of company projects¹. It should be noted, however, that the figures presented here are most probably an underestimation of ongoing research, given that they cover only trials conducted in the United States and, furthermore, only include products in clinical trials in human subjects (i.e., pre phase I trials are not included.) Additional and updated information can also be accessed via the IFPMA Clinical Trials Portal².

¹ See http://www.phrma.org/read_surveys/ ; for diseases primarily affecting developing countries, and industry research centers see <http://www.ifpma.org/pdf/IFPMA%20Building%20Healthier%20ENG%202007.pdf>

² Available at <http://www.ifpma.org>



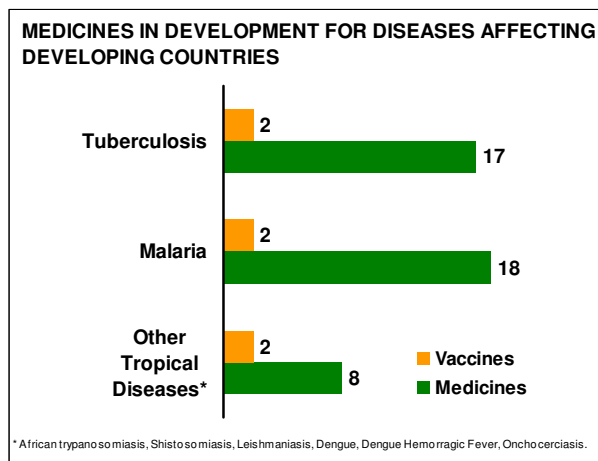
Guide to Pharmaceutical R&D, per Disease

	Page
Medicines in Development for Diseases Primarily Affecting Developing Countries.....	3
Medicines in Development for HIV/AIDS	6
Medicines in Development for Children	7
Medicines in Development for Women	7
Medicines in Development for Infectious Diseases	8
Medicines in Development for Cancer	9
Biotechnology Medicines in Development	10
Medicines in Development for Rare Diseases	10
Medicines in Development for Heart Disease and Stroke	11
Medicines in Development for Neurological Disorders	12
Medicines in Development for Mental Illnesses	13
Medicines in Development for the Elderly	14
Appendix:	
R&D Pharmaceutical Industry Facilities Dedicated to Research into Diseases of the Developing World	15



Medicines in Development for Diseases Primarily Affecting Developing Countries³

Pharmaceutical company projects to research new medicines and vaccines for the diseases primarily affecting developing countries include: 17 medicine projects and 2 vaccine projects for Tuberculosis; 18 medicine projects and 2 vaccine projects for Malaria; and, 8 medicine projects plus 2 vaccine projects for Other Tropical Diseases. These diseases have been prioritized by the WHO / UNICEF / UNDP / World Bank Special program for Research & Training in Tropical Diseases (TDR)⁴.



Roughly half of these R&D programs are being undertaken by companies on their own, the remainder by industry within public-private partnerships⁵.

Tuberculosis

Disease impact: Estimated 2 million deaths per year, 90% in developing countries. Some 2 billion infected.

Available therapies: WHO recommends Directly Observed Treatment, Short-Course to ensure patients adhere to long treatment with anti-TB cocktail (options include Isoniazid, Rifampicin, Pyrazinamide, Streptomycin and Ethambutol), but this places a heavy burden on health care resources. Length of treatment encourages non-adherence which facilitates development of resistance and now multi-drug resistance, which is increasingly difficult to treat. TB is linked to HIV/AIDS, so compatibility of therapies is an issue.

TDR R&D priority: 2 (development and testing of new disease control tools and strategies)

Industry R&D:

AstraZeneca	company	DNA synthesis inhibitors	Lead ident.	M
AstraZeneca	company	Methyl Erythritol Pathway inhibitors	Lead ident.	M
AstraZeneca	company	Screening & Target Identification	Lead optimiz.	M
Bayer HealthCare	TB A	Moxifloxacin	Phase II	-
Lupin	TDR	Gatifloxacin	Phase III	M
GlaxoSmithKline	TB A	Bacterial Topoisomerase (BTI)	Lead optimiz.	M
GlaxoSmithKline	TB A	Pleuromutilins	Lead optimiz.	M
GlaxoSmithKline	TB A	InhA Inhibitors	Lead identif.	M

³ Sources: company responses to IFPMA survey queries and open source information.

⁴ TDR priority diseases are: African trypanosomiasis, Dengue & Leishmaniasis (Priority 1), Malaria, Schistosomiasis & Tuberculosis (Priority 2), Chagas Disease, Leprosy, Lymphatic Filariasis & Onchocerciasis (Priority 3). Safe, effective medicines for Leprosy, Lymphatic Filariasis & Onchocerciasis are made available through company donation programs.

⁵ Aeras Global TB Vaccine Foundation (Aer), Drugs for Neglected Diseases initiative (DNDi), Medicines for Malaria Venture (MMV), Malaria Vaccine Initiative (MVI), Pediatric Dengue Vaccine Initiative (PDVI), TB Alliance: Global Alliance for TB Drug Development (TB A), US Walter Reed Army Institute of Research (W Reed) and WHO / UNICEF / UNDP / World Bank Special Program for Research & Training in Tropical Diseases (TDR). US National Institute of Allergy and Infectious Diseases (NIAID) is also active in neglected disease research. "M" denotes projects recorded in The New Landscape of Neglected Disease Drug Development, by Dr. Mary Moran, the Pharmaceutical R&D Policy Project, published in 2005 by the London School of Economics and Political Science and the Wellcome Trust.



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GlaxoSmithKline	TB A	Antimicrobial Screening Program	Discovery	M
Johnson & Johnson	company	TMC207 Diarylquinolines (DARQ)	Phase I	-
Novartis	TB A	Nitroimidazole PA-824	Phase I	-
Novartis	TB A	PA 824 backup compounds	lead optimiz.	M
Novartis	company	PDF inhibitors	Phase I	M
Otsuka	company	Nitroimidazole OPC-67683	Phase II	-
Otsuka	company	Nitroimidazole backup compound	Preclinical	-
Pfizer	company	U 100480	Preclinical	M
sanofi-aventis	company	Improving existing treatments	Preclinical	-
Crucell	Aer	Aeras-402 vaccine	Phase I	-
GlaxoSmithKline	Aer	Vaccine (Mtb72F/AS02A)	Phase I	-

TB A is talking to AstraZeneca about a screening program and to Otsuka. Lupin (an IFPMA member via OPPI, India) licensed Gatifloxacin from Kyorin Pharmaceutical (an IFPMA member via JPMA, Japan). Biotech companies like Sequella also working on TB therapies.

Malaria

Disease impact: Estimated 1 million deaths per year, 90% in sub-Saharan Africa, mostly children under five years. Annually, 300-500 million people contract malaria.

Available therapies: WHO recommends combinations to slow continually evolving treatment resistance: Artemether-lumefantrine or Artesunate + Amodiaquine / Mefloquine / Sulfadoxine-pyrimethamine. GlaxoSmithKline, Novartis and sanofi-aventis run access programs with various partners, including WHO.

TDR R&D priority: 2 (development and testing of new disease control tools and strategies)

Industry R&D:

Bristol-Myers Squibb	MMV	Protein franesyltransferase inhibitors	Discovery	-
GlaxoSmithKline	MMV	Chloroproguanil-Dapsone-Artesunate	Registration	M
GlaxoSmithKline	W Reed	Tafenoquine / Etaquine	Phase III	-
GlaxoSmithKline	MMV	n-tert butyl Isoquine GSK369796	Preclinical	M
GlaxoSmithKline	MMV	4(1H) pyridones back-ups	Preclinical	M
GlaxoSmithKline	MMV	Falcipains (Cysteine Protease)	Lead optimiz.	M
GlaxoSmithKline	MMV	Fatty Acid Biosynthesis (FabI)	Lead optimiz.	M
GlaxoSmithKline	company	Antimicrobial Screening program	Discovery	-
Novartis	MMV	Pediatric Coartem	Registration	M
Pfizer	company	Azithromycin & Chloroquine	Phase III	M
Ranbaxy	MMV	Synthetic Peroxide (OS277)	Phase I	M
sanofi-aventis	DNDi	Artesunate-Amodiaquine FDC	Registration	M
sanofi-aventis	company	Thiazolium	Lead optimiz.	M
sanofi-aventis	company	Choline uptake inhibitors	Lead optimiz.	M
sanofi-aventis	company	Ferroquine (SSR 97193)	Phase I	M
sanofi-aventis	company	Trioxaquine	Lead optimiz.	M
sanofi-aventis	company	Intrarectal Quinine	Phase III	M
Sigma-Tau (et al)	MMV	Artekin (DHA Piperazine)	Registration	M
Crucell	NIAID	AdVac vaccine	Phase I	-
GlaxoSmithKline	MVI	Vaccine (RTS,S/AS02A)	Phase III	-

Two GlaxoSmithKline-MMV projects listed by Moran, Peptide deformylase inhibitor and 4(1H)-pyridone derivative (GW844520) have been stopped, as has the Bayer HealthCare-MMV Artemifone project. Roche has handed OS277 to Ranbaxy (IFPMA member via OPPI, India).



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MMV is negotiating new partnership projects with Novartis and GlaxoSmithKline has further early stage projects, beyond those listed above.

African trypanosomiasis (Sleeping Sickness)

Disease impact: Estimated 250-300,000 deaths per year. 300-500,000 currently infected.

Available therapies: All intravenous. Suramin (1920, serious adverse effects), Melarsoprol (1932, used for late-stage disease, adverse effects), Pentamidine (1941, ineffective against late-stage disease, resistance), Eflornithine (1991, effective for late-stage disease, less adverse effects than melarsoprol).

TDR R&D priority: 1 (acquisition of new knowledge, design of new disease control tools and systems)

Industry R&D:

Bayer HealthCare, sanofi-aventis	TDR, DNDi	Oral Nifurtimox & Eflornithine	Phase III	M
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Shistosomiasis

Disease impact: Estimated 150,000 deaths per year. Some 200 million infected, 85% in sub-Saharan Africa.

Available therapies: Praziquantel allows safe & effective treatment. Cheap, but so far only used on a large scale in China.

TDR R&D priority: 2 (development and testing of new disease control tools and strategies)

Industry R&D:

Pfizer	TDR	oxomiquine + praziquantel	early	-
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Leishmaniasis (Kala Azar)

Disease impact: Estimated 80,000 deaths per year, but totals will surge in epidemics, as in Sudan in the early 1990s. Approximately 12 million infected, with 1.5-2 million new cases per year.

Available therapies: pentavalent antimony (intravenous, adverse effects, effectiveness questioned), AmBisome® (highly effective, but expensive ≥USD1,500 / person, only registered in India, manufacturer Astellas talking to DNDi about trials elsewhere with view to obtaining wider registration).

TDR R&D priority: 1 (acquisition of new knowledge, design of new disease control tools and systems)

Industry R&D:

Zentaris	TDR	Miltefosin	Phase IV	-
GlaxoSmithKline	<i>company</i>	Sitamaquine (WR6026)	Phase IIb	M

Dengue / Dengue Hemorrhagic Fever

Disease impact: Estimated 24,000 deaths per year (probably an underestimate; deaths could be as much as 1% of all infections). 50-100 million infections per year, of which 250-500,000 are the potentially fatal hemorrhagic form.

Available therapies: None

TDR R&D priority: 1 (acquisition of new knowledge, design of new disease control tools and systems)



Industry R&D:

Novartis	company	NS3 helcase	Discovery	M
Novartis	company	NS3 polymerase	Discovery	M
Novartis	company	NS3 protease	Discovery	M
GlaxoSmithKline	PDVI	Vaccine	Phase II	-
sanofi-aventis	PDVI	Vaccine	Phase II	-

Onchocerciasis (River Blindness)

Disease impact: Negligible directly attributable mortality, but extensive long-term morbidity. 16-18 million infected, 99% of whom in sub-Saharan Africa.

Available therapies: Ivermectin allows safe & effective treatment. Merck & Co. runs an access program.

TDR R&D priority: 3 (improvement and wider dissemination of existing tools and strategies, risk avoidance)

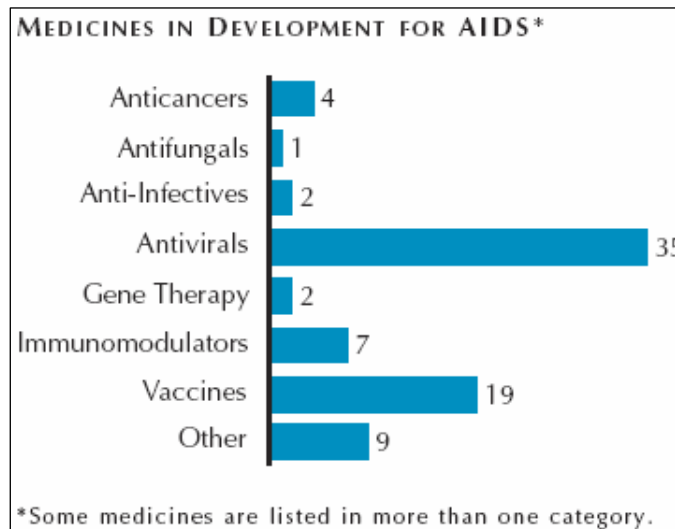
Industry R&D:

Wyeth	TDR	Moxidectin	Phase II	M
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Medicines in Development for HIV/AIDS (2006)

HIV/AIDS is one of the world's most devastating diseases. According to the Joint United Nations Programme on HIV/AIDS, over the last quarter century, nearly 65 million people were infected with HIV, and an estimated 25 million have died of AIDS-related illnesses.

Today it is estimated that close to 40 million people worldwide live with HIV—yet the vast majority are unaware of their status. Of these, about 2.3 million were children, most of them living in sub-Saharan Africa.



While treatment access has dramatically expanded—from 240 000 people in 2001, 1.3 million people in low- and middle-income countries received antiretroviral therapy in 2005-, a dramatic breakthrough is still needed to prevent the further increase of new infections by 2010.

Pharmaceutical researchers are testing 77 medicines for HIV/AIDS and related conditions and intensifying their work toward the development of vaccines. The medicines now in the pipeline will add to the 88 already approved since the AIDS virus was first identified more than 20 years ago. Vaccine research is crucial to the fight against AIDS. Currently, 19 vaccines are in development. In addition to these, 35 antivirals, two anti-infectives, four cancer treatments, seven



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immunomodulators, one antifungal, two gene therapies, and nine other medicines are now in human clinical trials or before the U.S. Food and Drug Administration awaiting approval.

Examples of innovative AIDS medicines and vaccines in the pipeline include:

- A medicine, the first in a new class of drugs known as integrase inhibitors, has been shown to decrease viral load in patients with significant HIV drug resistance.
- A medicine in development binds itself to a receptor protein found on the surface of human cells and blocks the HIV virus from entering the cell.
- A vaccine that combines DNA snippets from the AIDS virus with a protein that boosts immune response. The vaccine may prevent infection, limit the damage the virus causes, or both.
- An antisense gene therapy that uses two novel technologies to boost immune responsiveness against HIV. One involves the insertion of a new type of genetic material into blood cells to inhibit the growth of the virus. The second involves inserting new genes into target cells and integrating the gene into the chromosome of the cell. The cells containing the new genes are then transferred to the patient.

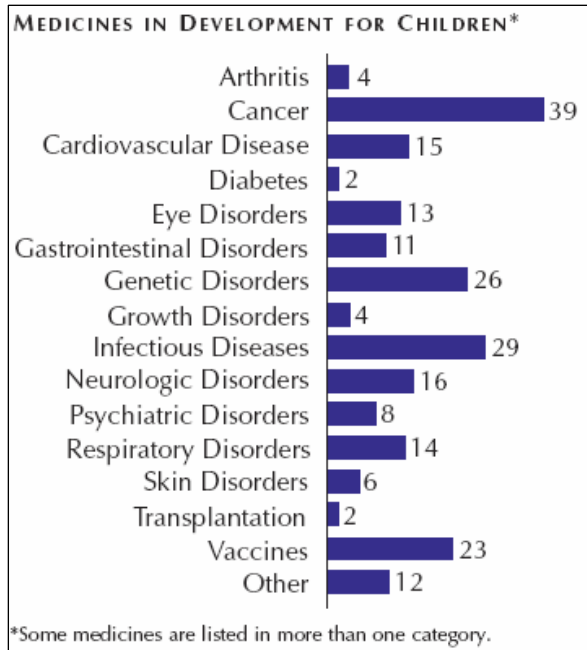


Medicines in Development for Children (2007)

Pharmaceutical researchers are testing 219 medicines to meet the special health needs of children. These medicines offer hope that the significant improvements achieved in children's health over the past few decades will continue and even accelerate. Vaccines and antibiotics alone have prevented many children deaths. According to a New England Journal of Medicine report, pneumonia deaths among children dropped 97 per cent between 1939 and 1996.

Companies are working to continue this progress and to meet new challenges to children's health. The medicines in the pipeline include:

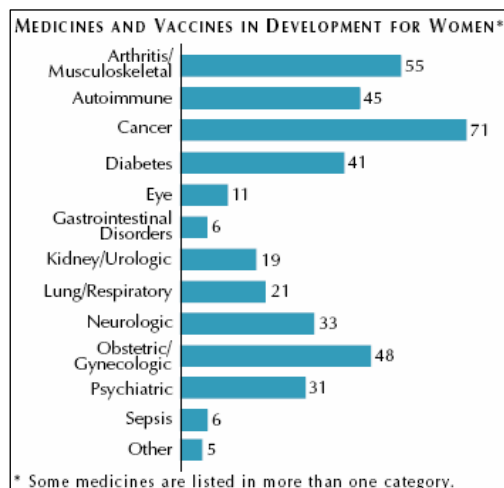
- 39 for cancer, including medicines for leukaemia, solid tumors, brain tumors, and lymphomas -- the WHO estimates that each year more than 160,000 cases of childhood cancer are diagnosed and at least 90,000 children die; about 80% of children with cancer live in developing countries -.
- 29 for such infectious diseases as HIV infection, ear infections, pneumonia, and hepatitis.
- 26 for genetic disorders, including medicines for cystic fibrosis.
- 16 for neurological disorders, including medicines for epilepsy.
- 15 for cardiovascular disease, including hypertension, high cholesterol, and congenital heart disease.
- 14 for respiratory disorders, including medicines for asthma, the leading serious chronic disease among children.



In addition to creating medicines specifically to meet the needs of children, pharmaceutical companies are testing many existing medicines to determine safe and effective dosage levels for children. According to the Tufts Centre for the Study of Drug Development, more than 120 medicines today contain new safety, efficacy, dosing, and risk information for children and teenagers in its labelling. New medicines, and new knowledge about paediatric use of existing medicines, will mean that children will recover from illnesses more quickly and that more children will enjoy childhood and grow into healthy adults.

Medicines and Vaccines in Development for Women (2004)

Pharmaceutical researchers are developing 371 medicines for diseases that disproportionately affect women. Potential new medicines in the pipeline for women include: 71 for cancer -- including 41 for breast cancer, the most common type of cancer affecting women worldwide, 34 for ovarian cancer, and 10 for





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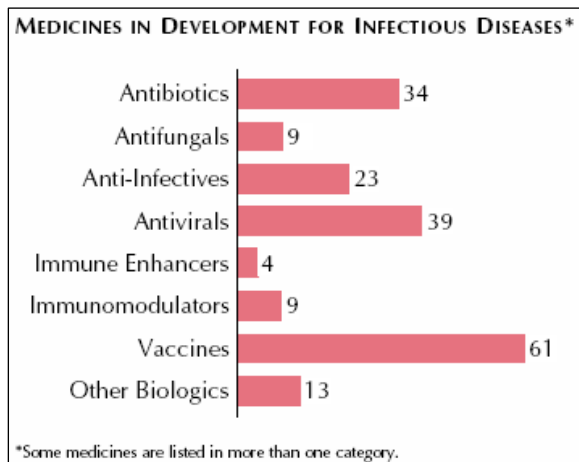
cervical cancer -, and 48 for obstetric/gynaecologic conditions.

Among the potential new Medicines in development for women are: a medicine for multiple sclerosis -- the first in a new class of drugs— that is a humanized monoclonal antibody designed to prevent the adhesion of immune cells to blood vessel walls and the migration of inflammatory cells from blood vessels into tissues; a medicine for rheumatoid arthritis that uses a “trap” technology to stop the growth of the disease; a new medicine for metastatic breast cancer designed to bind to and inhibit vascular endothelial growth factor (VEGF), a protein that plays a critical role in the formation of new blood vessels that feed the tumor.

Medicines in Development for Infectious Diseases (2004)

Pharmaceutical scientists are developing 185 medicines to combat humankind's oldest and most tenacious enemy -- infectious diseases.

Infectious diseases have killed and crippled throughout history. Vaccines and, later, antibiotics held many of these diseases at bay, but they still pose a very serious threat. Several infectious pathogens have become resistant to current treatments, and diseases once considered conquered, such as tuberculosis, have re-emerged.



Among the new medicines now being tested are 34 antibiotics, including the first in a new class; 39 antivirals for treating such viruses as hepatitis, herpes and influenza; and 61 vaccines to prevent diseases from staph infections to pneumococcal infections in the elderly. These are in addition to medicines in development for HIV/AIDS (see page 6).

Some examples of the potential medicines for fighting infectious diseases include:

- A medicine for hepatitis B that specifically targets the virus and suppresses its replication.
- A medicine for the treatment of hepatitis C that is part of a new class of drugs to regulate innate immunity. It is believed the new medicine interacts with a specific receptor that is present on certain immune system cells. The WHO estimates that about 180 million people, some 3% of the world's population, are infected with hepatitis C virus.
- An immune-regulating hormone may make inroads against malaria—a parasitic, mosquito-borne disease. Rather than targeting the malaria pathogen directly, the medicine works by correcting the dysfunction of the patient's immune system to enable it to fight the disease.
- A first in class medicine that kills bacteria by clogging the machinery they use to make proteins. This new way of attacking bacteria has been effective against several drug-resistant strains that cause pneumonia and bronchitis.
- A medicine that blocks the growth of fungal cells increased the survival rate of patients in clinical trials with severe fungal infections.



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- As antibiotics have become less effective against *Staphylococcus aureus* - or staph - a potential vaccine in development would prevent patients from ever being infected in the first place.

Researchers also are focusing their efforts on new treatments for anthrax, fungal infections, herpes, hepatitis, influenza, malaria, meningitis, pneumonia, respiratory infections, rotavirus, sepsis, smallpox, tuberculosis, urinary tract infections, and many other infectious diseases.



Medicines in Development for Cancer (2006)

According to the WHO, each year 7 million people die from cancer (7.6 million in 2005 alone) and 11 million new cases are diagnosed worldwide. Cancer deaths in the world are projected to continue rising, with an estimated 9 million cases in 2015 and 11.4 million in 2030.

Cancer deaths worldwide account for more than those from HIV/AIDS, malaria and tuberculosis combined: 12.5% of all deaths each year.

In developing countries, 80% to 90% of cancer patients already suffer from advanced and incurable cancers at the time of diagnosis. In addition, more than 70% of all cancer deaths occur in low and middle income countries.

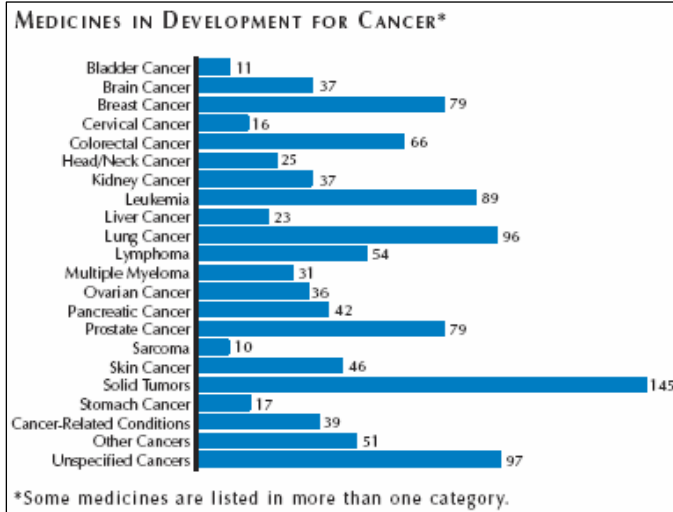
Pharmaceutical researchers are now working on 646 medicines for cancer. Many are high-tech weapons to fight the disease, while some involve innovative research on using existing medicines in new ways.

The medicines in development include 96 for lung cancer (first cause of cancer deaths among men); 79 for breast cancer (first cause of cancer deaths among women); 66 for colorectal cancer; and 79 for prostate cancer. Additional medicines target brain cancer, kidney cancer, ovarian cancer, pancreatic cancer, skin cancer, and others. In addition, companies are working on medicines to improve the quality of life for cancer patients. Cutting-edge new cancer treatments have been made available to patients, for example:

- A breakthrough medicine to treat metastatic colorectal cancer is the first treatment approved to prevent the formation of new blood vessels that provide tumors with oxygen and nutrients—a process known as angiogenesis.
- A medicine for the treatment of non-small-cell lung cancer inhibits the formation and growth of tumor cells.

Many of the medicines in the pipeline also use new approaches to fight cancer. They include:

- A medicine that inhibits production of a protein that may interfere with the effectiveness of chemotherapy.
- A drug that delivers a synthetic version of a substance derived from scorpions directly to brain tumor cells.
- A medicine designed to induce a powerful immune response to melanoma.





Biotechnology Medicines in Development (2006)

Millions of people have already benefited from medicines and vaccines developed through biotechnology. Today, there are 418 biotechnology medicines in development for more than 100 diseases.

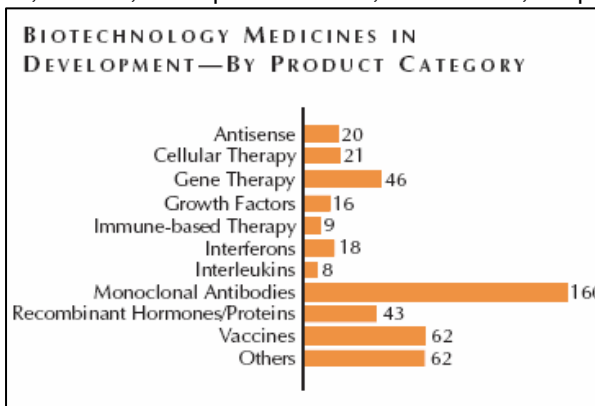
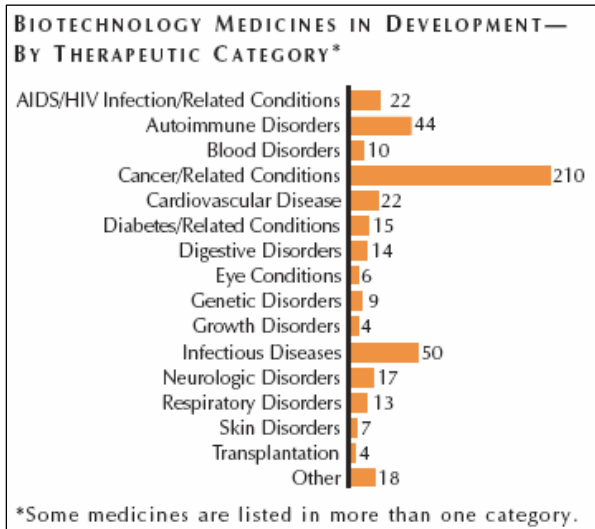
These include 210 medicines for cancer, 50 for infectious diseases, 44 for autoimmune diseases, and 22 for AIDS/HIV and related conditions.

These potential medicines, all of which are either in human clinical trials or under review by the Food and Drug Administration, will add to the list of 125 biotechnology medicines already approved and available to patients for treatment or prevention of heart attacks, stroke, multiple sclerosis, leukaemia, hepatitis, rheumatoid arthritis, breast cancer, diabetes, congestive heart failure, lymphoma, kidney cancer, cystic fibrosis, and other diseases.

The biotechnology medicines now in development are based on existing technologies already in use (protein drugs, monoclonal antibodies, interferons, antisense drugs, etc.), as well as on breakthrough innovations.

For example, a medicine in the pipeline for rheumatoid arthritis is a recombinant protein that may help treat autoimmune disorders. Monoclonal antibody medicines in the pipeline target asthma, Crohn's disease, rheumatoid arthritis, lupus, and various types of cancer.

Therapeutic vaccines, designed to jump-start the immune system to fight disease, are in development for HIV/AIDS and several types of cancer. Medicines based on antisense technology are potential treatments for several types of cancer, Crohn's disease and heart disease. Gene therapies, which augment normal gene functions or replace or inactivate disease-causing genes, are being tested for several cancers and heart disease.





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Medicines in Development for Rare Diseases (2007)

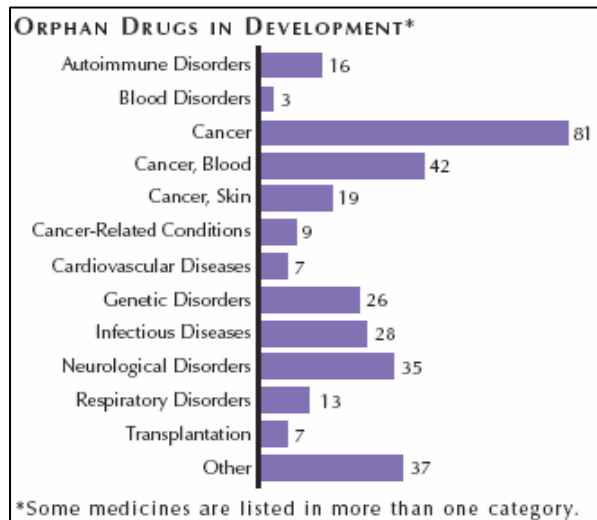
For millions of patients diagnosed with a rare disease treatment options can be limited. But over the last few years, great progress has been made with the approval of several new medicines for rare diseases such as Pompe disease, myelodysplastic syndromes, enzyme deficiencies, and rare cancers.

Pharmaceutical companies have 303 medicines currently in human clinical trials or awaiting approval by the U.S. Food and Drug Administration for many rare diseases. This compares to 133 medicines in development in 1989 and 189 in 1992.

Since 1995, more than 160 medicines were approved to treat rare diseases, compared to 108 in the decade before and fewer than 10 in the 1970s. Advances in science, such as a better understanding of molecular and genetic causes of disease, have given researchers new tools to explore rare diseases, which are often more complex than more common diseases.

In addition, some countries -- as the United States, the European Union, Japan and Singapore-, have introduced Orphan Drug legislation providing tax reliefs and other benefits to companies that develop a drug for a rare disease.

In the United States for example, this legislation is credited with the explosion in drug approvals for rare diseases after 1983. Under the US Orphan Drug Act, 1,679 medicines have been designated orphan drugs (not all are approved) as of January 10, 2007.



A major area of research in rare diseases is cancer. Rare cancers, such as solid tumors of the liver and thyroid, cancer of the blood, and melanoma account for more than one-third of all rare disease research, with 139 medicines in development. Other important areas of research include: neurologic disorders, such as multiple sclerosis and muscular dystrophy, with 35 medicines in development; infectious diseases, such as anthrax and West Nile virus, with 28 medicines in development; and genetic disorders, such as cystic fibrosis, with 26 medicines in development.

Other examples of medicines in development for rare diseases include:

- A monoclonal antibody for chronic sarcoidosis, an immune system disorder.
- A medicine for Lennox-Gastaut syndrome, a severe form of epilepsy.
- A gene therapy for cystic fibrosis.
- A medicine for epidermolysis bullosa, a group of inherited disorders where skin blisters develop in response to minor trauma.
- A medicine for Friedreich's ataxia, a genetic disorder.

Thanks to the growing understanding of the genome and powerful scientific research tools, experts predict the number of orphan drugs will rise in the coming years as more new medicines are developed that target specific genetic disorders.



Medicines in Development for Heart Disease and Stroke (2007)

Rates from heart disease and stroke are falling. This reduction in death rates is “one of the great triumphs of medicine in the past 50 years,” according to cardiologist Dr. Eugene Braunwald of Harvard Medical School. Also, a recent study published in the Journal of the American Medical Association found that death rates of and rates of heart failure in hospitalized heart attack patients were cut nearly in half since 1996, probably due to better treatments like new cholesterol-lowering drugs and blood thinners, and angioplasty.

In fact, much of the progress is due to the development of effective medicines to control both blood pressure and cholesterol.

In addition, treatment of heart attacks has vastly improved. Twenty-five years ago, the treatment for heart attacks was simply bed rest. Today, doctors have medicines that can stop a heart attack in mid-stream as well as other high-tech treatments.

But, experts warn, the war against heart disease and stroke is not yet won. Million of people have one or more types of cardiovascular disease, and many people who survive heart attacks develop congestive heart failure: according to the WHO every year an estimated 17 million people die of cardiovascular diseases, particularly heart attacks and strokes, most of them in the developing world (it is expected that 82% of the future increase in coronary heart disease mortality will occur in developing countries).

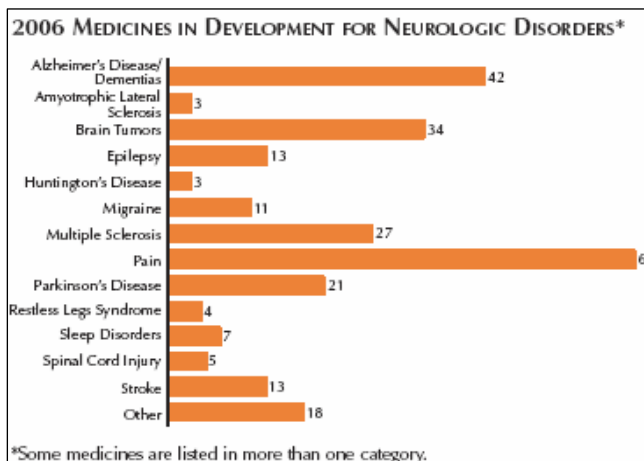
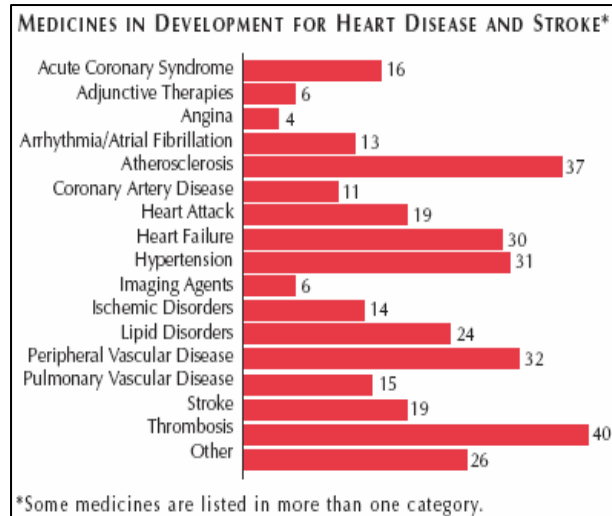
Pharmaceutical companies are working on 277 medicines for hearth disease and stroke. The medicines in development include 30 for heart failure, 31 for high blood pressure, 19 for heart attacks, and 19 for stroke. Many of the potential medicines use cutting-edge technologies and new scientific approaches. For example:

- Human stem cells that may restore cardiac function by forming new heart muscle.
- A new anticoagulant that regulates clot formation to prevent stroke in atrial fibrillation.
- A vaccine that may be able to promote “good” cholesterol by preventing the transfer of “good” cholesterol to “bad” cholesterol.

Medicines in Development for Neurological Disorders (2006)

WHO estimates that 50 million people have epilepsy; 62 million are affected by cerebrovascular disease; 326 million people suffer from migraine; and, 24 million are affected by Alzheimer disease and other dementias globally.

In addition, most people with dementia live in developing





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countries: 60% in 2001 rising to an estimated 71% by 2040; and, the WHO also forecasts numbers in developed countries will increase by 100% between 2001 and 2040, but by more than 300% in China, India and neighbouring countries in South-East Asia and the Western Pacific⁶.

Research-based pharmaceutical and biotechnology companies are developing 241 new medicines to treat debilitating neurological disorders such as Alzheimer's, epilepsy, multiple sclerosis, Parkinson's, and stroke.

The medicines in development include:

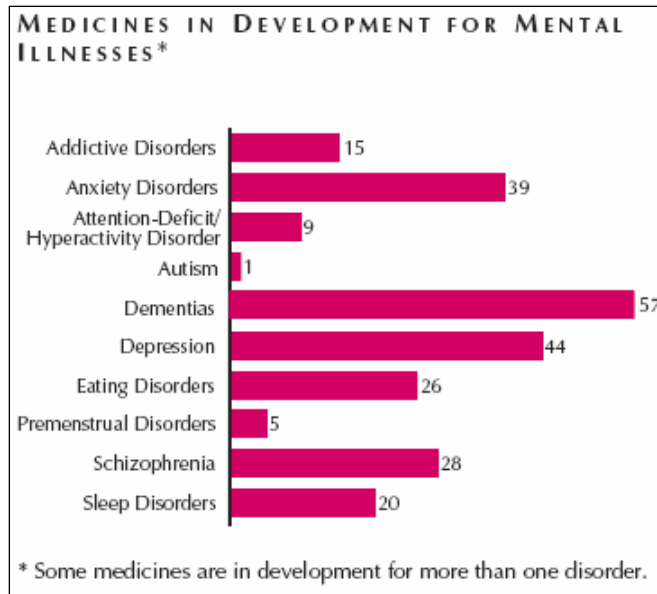
- 62 medicines for pain,
- 34 medicines for brain tumors,
- 42 medicines for Alzheimer's disease,
- 21 medicines for Parkinson's disease,
- 13 medicines for stroke,
- 11 medicines for migraine,
- 27 medicines for multiple sclerosis,
- 13 medicines for epilepsy.

Other medicines in development target brain injuries, Huntington's disease, spinal cord injury, myasthenia gravis, juvenile cerebral palsy, and restless legs syndrome. Promising new medicines in development include: a medicine that uses normal human cells to enhance brain levels of dopamine, the neurotransmitter deficient in Parkinson's patients; a medicine for glioblastoma (brain cancer) that singles out and latches onto the receptors on the surface of the malignant cells — but not the healthy cells— and destroys them; and, a medicine for Alzheimer's that both inhibits plaque formation and blocks the degradation of the neurotransmitter acetylcholine.

Medicines in Development for Mental Illnesses (2006)

Pharmaceutical research companies are currently developing 197 medicines for patients suffering from some form of mental illness - from Alzheimer's disease to depression, to schizophrenia, to dependence on alcohol or drugs.

Medicines for treating depression are helping thousands of people suffering from this disease to live productive lives. Breakthrough schizophrenia medicines enable most patients to be treated in the community, and medicines for Alzheimer's disease are helping elderly people maintain their independence longer outside of nursing homes.



Despite the progress, mental illnesses continue to exact a heavy human and economic toll. According to the World Health Organization, some 450 million people worldwide suffer from a

⁶ See: WHO, "Neurological Disorders: Public Health Challenges". Geneva, 2006.



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mental health disorder. Mental illness, including suicide, accounts for more than 15 percent of the burden of disease in established market economies, which is more than the disease burden caused by all cancers.

New medicines today in the research and development pipeline include: 44 for depression, which affects nearly 154 million people globally; 15 for addictive disorders, including dependence on alcohol, tobacco or illicit drugs; 39 medicines for anxiety disorders; 57 for dementias, including Alzheimer's disease; and 28 for schizophrenia, which affects 25 million people around the world. Other potential medicines target attention deficit/hyperactivity disorder, autism, eating disorders, premenstrual disorders and sleep disorders. Examples of some medicines now being tested to treat mental illnesses include:

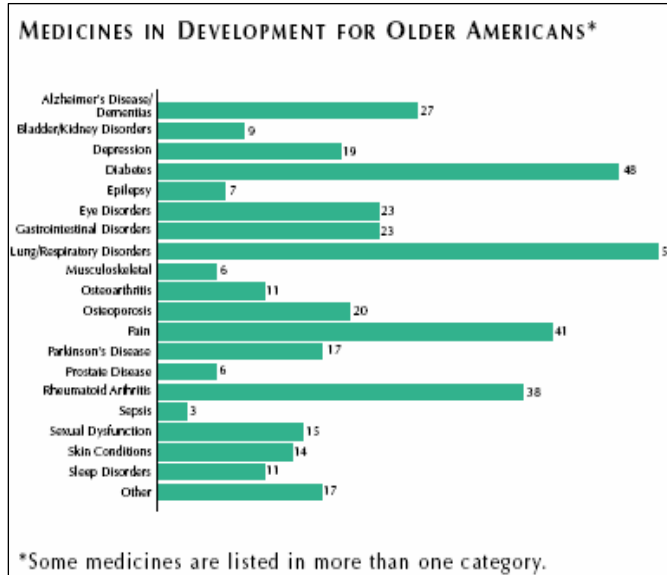
- A medicine that modulates the transmission of gammaamino butyric acid (GABA). By normalizing the action of GABA in the brain, the medicine may reduce the abnormal neuronal activity associated with anxiety and panic attacks.
- A medicine that treats both the positive symptoms (distortion or excess of normal function) and negative symptoms (reduction or loss of normal function) associated with schizophrenia.
- A therapeutic vaccine designed to fight cocaine addiction by inducing antibodies (immune system proteins) that block the uptake of cocaine into the brain.



Medicines in Development for the Elderly (2005)

The WHO estimates that from 2000 until 2050, the world's population aged 60 and over will more than triple from 600 million to 2 billion. Most of this increase will occur in developing countries - where the number of older people will rise from 400 million in 2000 to 1.7 billion by 2050.

As life expectancy continues to expand, older people face new and growing challenges to their health, productivity and independence —from geriatric conditions to complications from diseases like cancer, cardiovascular disease and diabetes.



The pharmaceutical industry has more than 900 medicines in development for diseases of aging, including 146 for heart disease and stroke, 399 for cancer, and 373 for such debilitating diseases as Alzheimer's, diabetes, and osteoporosis.

Specific medicines in development include:

- 27 for Alzheimer's disease
- 9 for depression
- 48 for diabetes
- 20 for osteoporosis
- 17 for Parkinson's disease

Other medicines target bladder and kidney diseases, eye disorders, gastrointestinal disorders, osteoarthritis, pain, prostate disease, respiratory and lung disorders, rheumatoid arthritis, skin conditions and other conditions of aging.

Many of the medicines in development use cutting edge knowledge and technology to attack diseases in different ways. These include a potential medicine that blocks the new blood vessel growth that causes one form of macular degeneration, and a medicine for Alzheimer's that both inhibits plaque formation and blocks the degradation of the neurotransmitter acetylcholine.



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Appendix

R&D Pharmaceutical Industry Facilities Dedicated to Research into Diseases of the Developing World

AstraZeneca Bangalore Research Institute

The AstraZeneca Bangalore Research Institute in India, opened in June 2003, is dedicated to finding a new therapy for tuberculosis (TB) that will act in drug-resistant disease and reduce the complexity and/or the duration of treatment. AstraZeneca made a \$20 million initial investment in buildings and state-of-the-art equipment, and spends at least \$5 million a year supporting the research program. More than 80 scientists now work at the facility, in collaboration with AstraZeneca's infection research center in Boston, USA and with external academic leaders.

The research team at Bangalore has focused its efforts on four specific goals:

- 1) Shortening the duration of therapy to improve patient compliance;
- 2) Eradicating disease, even latent disease, to reduce the chances of relapse;
- 3) Developing new agents that will act on drug-resistant strains; and
- 4) Developing agents that are compatible with HIV therapies.

AstraZeneca is also part of a new, European Union Framework Program VI collaboration (NM4TB - New Medicines for Tuberculosis). Consisting of around fifteen groups of Europe's most prominent scientists and researchers in the field, this consortium seeks to combine academic and pharmaceutical skills to further the discovery of new therapies for TB.

Lilly Not-For-Profit Partnership for TB Early Phase Drug Discovery

Eli Lilly announced on 13 June 2007 a public-private partnership to conduct early-phase discovery research of new medicines urgently needed to treat tuberculosis (TB), including emerging resistant strains. The partnership will be a not-for-profit, drug-research organization based in Seattle, employing some 25 full-time researchers, who will screen well-characterized chemical libraries and improve access to medicinal chemistry, both important missing elements in current TB research. The partnership will seek grants and contracts for additional funding, and aims to be self-sustaining.

Lilly is committing \$15 million to the partnership over the next five years and will provide laboratory space and screening and testing systems. Lilly will also open its library of more than 500,000 compounds for screening as possible TB treatments. A high-level Lilly Chemistry Advisory Committee will provide expertise to the research staff.

Partner organizations include The National Institute of Allergy and Infectious Diseases (NIAID), the National Institutes of Health (NIH) Foundation, Afya World Medicines, the Infectious Disease Research Institute, Jubilant Biosys, Merck and Co., the Seattle Biomedical Research Institute, and the University of Washington's Department of Global Health. The TB Alliance will participate in the governing committees of the partnership, to ensure coordination with TB research elsewhere.

Novartis Institute for Tropical Diseases, Singapore



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The Novartis Institute for Tropical Diseases (NITD) is a public-private partnership between Novartis and the Singapore Economic Development Board, and is dedicated to discovering novel therapies and preventive treatments for major tropical diseases, which the Novartis Group intends to make available at no profit to poor patients in endemic developing countries. NITD activities range from target discovery, screen development and compound optimization, to preparation for clinical testing. The institute employs 100 scientists and focuses on dengue fever, tuberculosis and malaria, with a view to having new therapies ready by 2012.

The NITD works with leading scientific and clinical researchers, the World Health Organization, health ministries, the Stop TB Partnership, the Drugs for Neglected Disease Initiative, the Global Alliance for TB Drug Development, *Médecins Sans Frontières*, the Grand Challenges for Global Health Foundation of the National Institute of Health, and the Pediatric Dengue Vaccines Initiative.

Tuberculosis: The NITD is using modern research tools including high-throughput screening and crystallography/NMR studies to design, synthesize and optimize small molecule compounds as potential treatments for multi-drug-resistant TB. The NITD, Imperial College and other collaborators have a grant from the Grand Challenges for Global Health Initiative, funded by the Bill and Melinda Gates Foundation and Wellcome Trust, to discover new targets for latent and persistent TB infection. The NITD has teamed up with the Hasanuddin University and the Eijkman Institute in Indonesia to conduct clinical research into dengue fever, tuberculosis and malaria.

Malaria: The NITD has a grant from Medicines for Malaria Venture, the Singapore Economic Development Board and the Wellcome Trust to discover next-generation of malaria medicines. The partnership is focusing on development of a one-dose cure for *P. falciparum* and a curative modality for *P. vivax*. The NITD will manage the program and conduct research jointly with the Genomics Institute of the Novartis Research Foundation, the Swiss Tropical Institute and the Biomedical Primate Research Center.

Dengue: The Singapore Dengue Consortium was founded in 2003 by the NITD, the Environmental Health Institute, Genome Institute of Singapore, SingHealth Group, National Healthcare Group and Temasek Life Science Laboratory, to research dengue fever for which there is currently no cure or vaccine. The project aims to characterize viral- and host-specific factors responsible for the onset of the disease and to develop small molecule interfering compounds. The project is annotating clinical data and patient histories to improve surveillance and understanding of different serotypes' genetic variations, and is correlating viral genetic markers with the disease's clinical severity.

GSK's Diseases of the Developing World Drug Discovery Centre, Tres Cantos

The Diseases of the Developing World (DDW) R & D Initiative at GlaxoSmithKline (GSK) was formed in 2002 for the discovery and development of new drugs for neglected diseases. The DDW Drug Discovery Centre is based at Tres Cantos, near Madrid, Spain. Its 105 scientists are dedicated exclusively to the discovery of new medicines for diseases of the developing world with a special focus on malaria and TB. They cover the entire drug discovery process from development target identification, through to preclinical candidate selection. GLP pre-clinical development is carried out along with that of other anti-infectives at R&D sites in Pennsylvania and North Carolina, while DDW clinical development has a dedicated group in Brentford, UK. DDW projects are prioritized for their social and public health benefits rather than their commercial returns and medicines discovered by DDW partnerships will be made available in endemic areas on a not-for-profit basis.



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Tuberculosis: The TB Alliance supports 25 full-time scientists at Tres Cantos, while GSK contributes a matching number of staff and remaining overhead costs; the partnership is for an indefinite period. The TB research work covers two novel classes of antibiotics, pleuromutilins and gyrase inhibitors, an InhA target-based project, plus the screening of GSK's antimicrobial libraries for anti-TB activity – some three thousand compounds to date. Goals are to shorten treatment duration, increase cure rates, reduce side effects, limit resistance and find a regimen compatible with HIV/AIDS therapy.

Malaria: A research mini-portfolio was signed by GSK and the Medicines for Malaria Venture (MMV) in June 2003. This agreement currently includes three discovery programs and is for an indefinite period, allowing flexibility and a long-term strategic view. To date, two candidates have been selected for development as a result of this mini-portfolio collaboration. This PPP also comprises two further development projects. The MMV is subsidizing 30 scientists at the Tres Cantos facility and also provides input from its Expert Scientific Advisory Committee.