Progress in Research: AIDS Vaccine Development




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Country and Regional Programmes

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12th Meeting of the "HIV/AIDS Think Tank Brussels"

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IAVI: research partnerships to fill the gap between and combine resources of the public and private sector

Mission:
To ensure the development of safe, effective, accessible, preventive HIV vaccines for use throughout the world

Political will & finance → **R&D** → **Clinical trials** → **Production** → **Health & other systems** → **Access & uptake**

- **Integrated model of R&D (lab bench to the G8)**
- **Policy and advocacy for the global effort**
- **Sustained commitment to developing countries**
- **5 regional offices, active in 24 countries**
- **Supported by 10 governments (of which 8 European), the EU, foundations, private sector and generous individuals**

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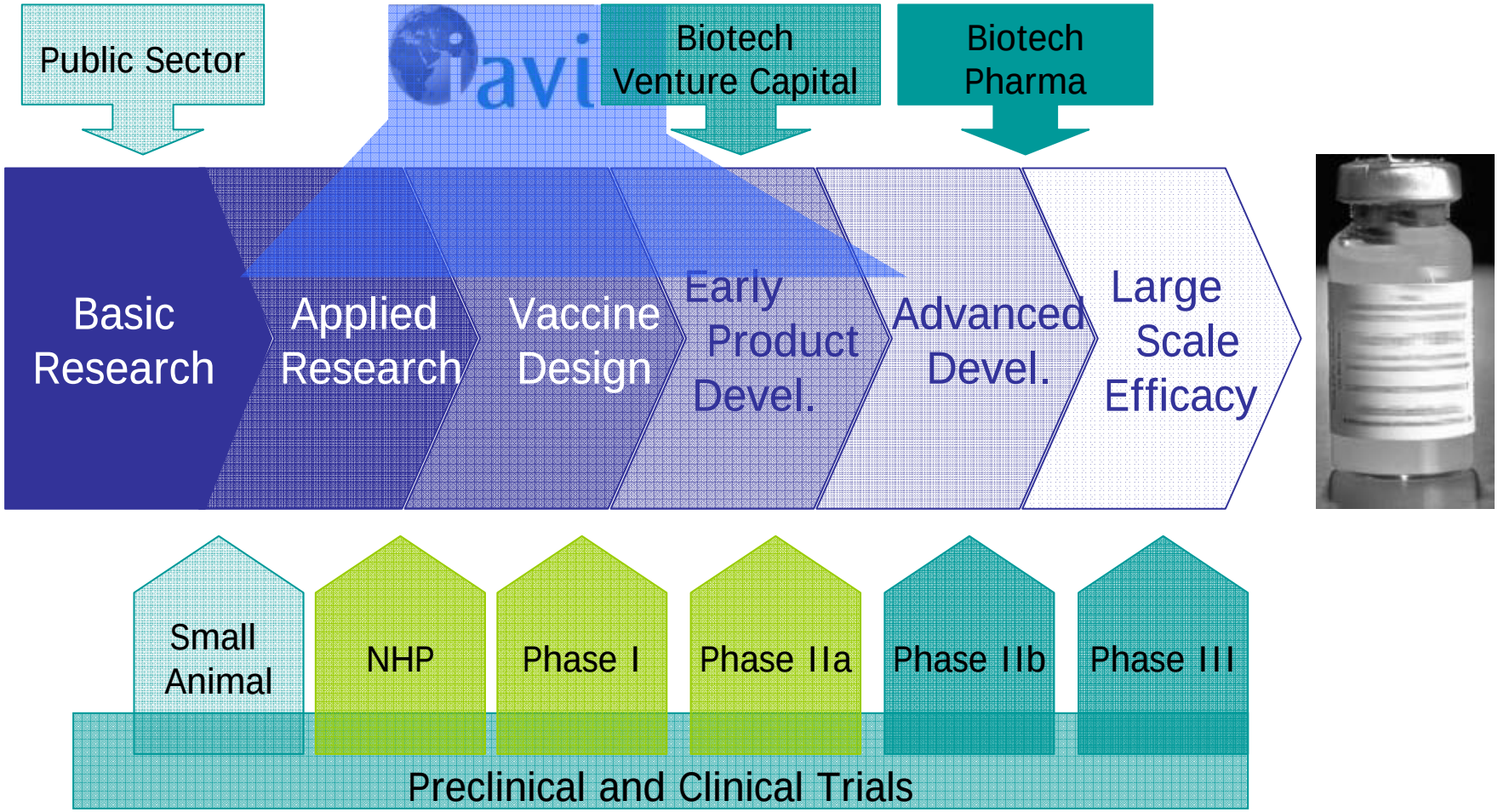
IAVI's role in the pipeline



IAVI'S R&D Program – Quick Facts

Largest global organization solely focused on AIDS vaccine; second largest R&D program

- 40+ R&D partnerships
- 6 vaccine candidates into humans, pipeline
- Trials in 11 countries

Integrated model of R&D

- Emphasis on applied research and product development – targeting gaps and promoting rational vaccine design
- Industrial project management
- Policy & advocacy linked (lab bench to the G8)

IAVI's Innovation Mechanisms

Scientific Consortia directed at major scientific challenges

- Neutralizing antibodies
- Live-attenuated/correlates of protection
- Rational vector design: high-risk, replicating, novel

Vaccine Development Laboratory

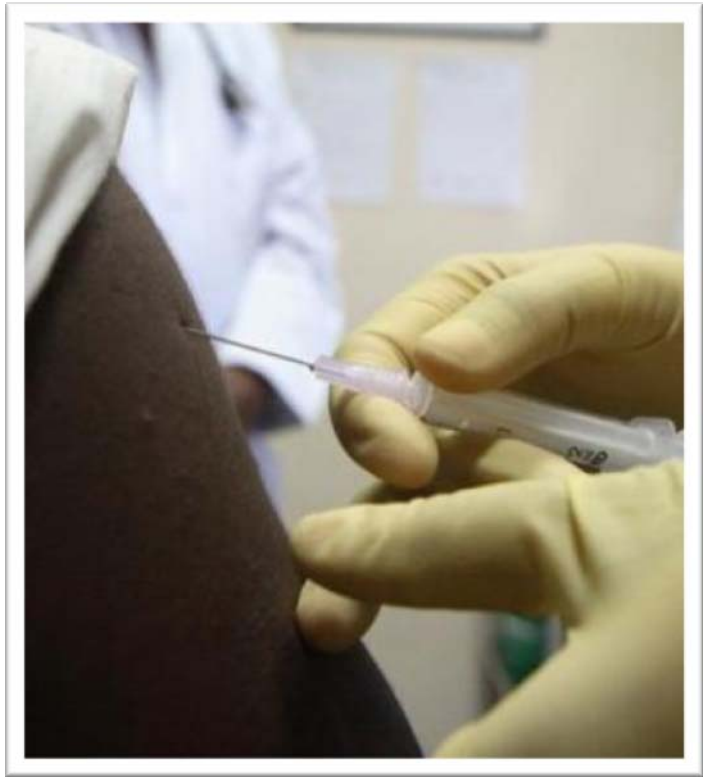
- Industrial style lab working on high risk approaches industry will not move

Innovation Fund

- Provide seed capital funding to advance early stage, potentially breakthrough technology
- Cross fertilization of innovative approaches from wide range of disciplines
- Reach beyond mainstream HIV research

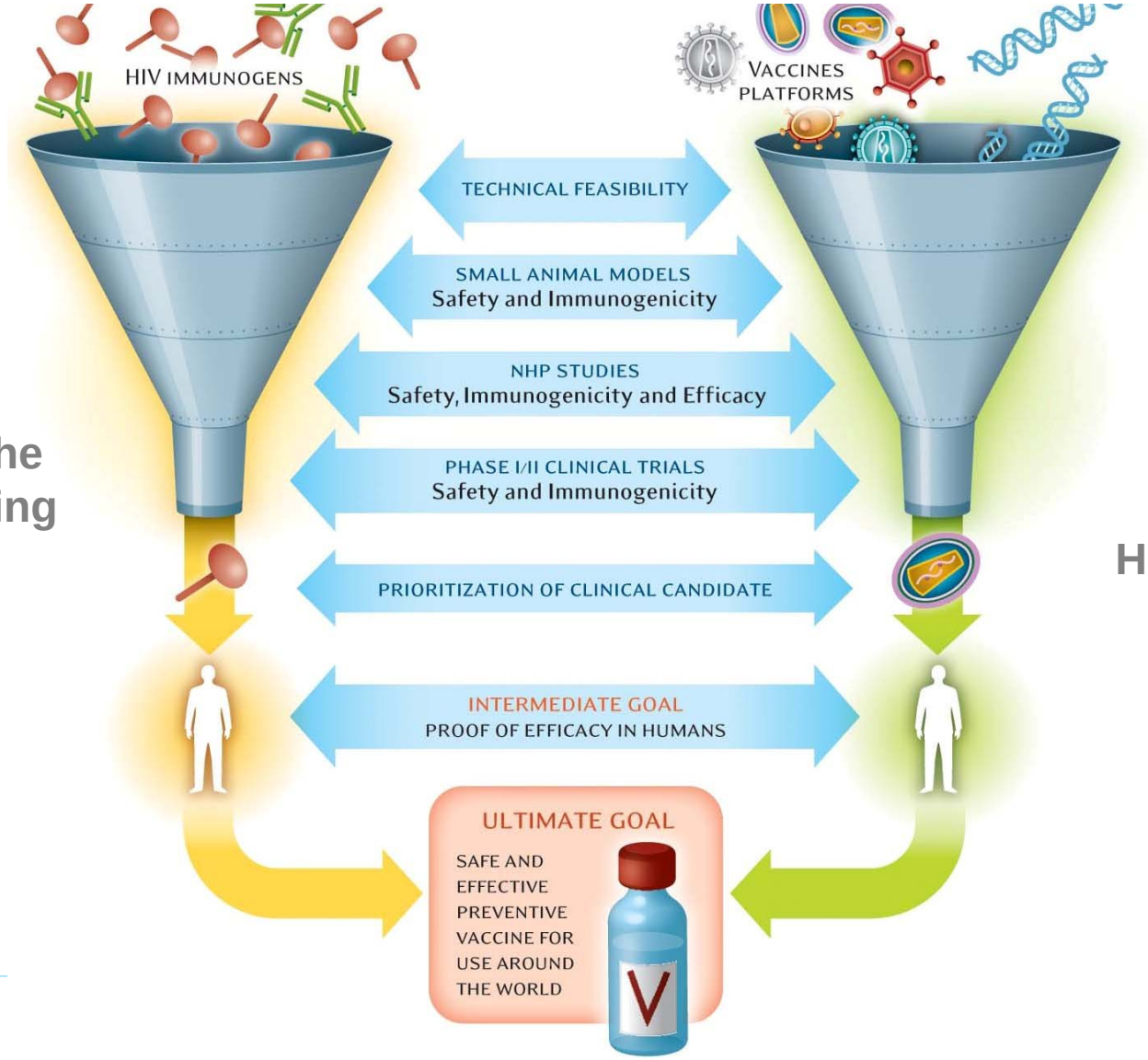
Next Steps in AIDS Vaccine Development

- Demonstration of protection in humans by an AIDS vaccine
- Design, develop and advance to efficacy trials a vaccine candidate that:
  - Elicits broadly neutralizing antibodies against HIV;
  - Controls HIV infection ; live-attenuated SIV protects against pathogenic SIV challenge
    - Products that trigger mucosal immunity
    - Replicating viral vectors capable of persistent and long-term protection
- Clinical Research Program in the developing world available to:
  - Inform vaccine design
  - Assess novel candidates for safety/immunogenicity (Phase I/II)
  - Preliminary assessment of most promising candidates for efficacy (Screening Test of Concept Trials)



Roadmap for Developing an AIDS Vaccine

Solving the Neutralizing Antibody Problem



Solving the Problem of How to Control HIV Infection

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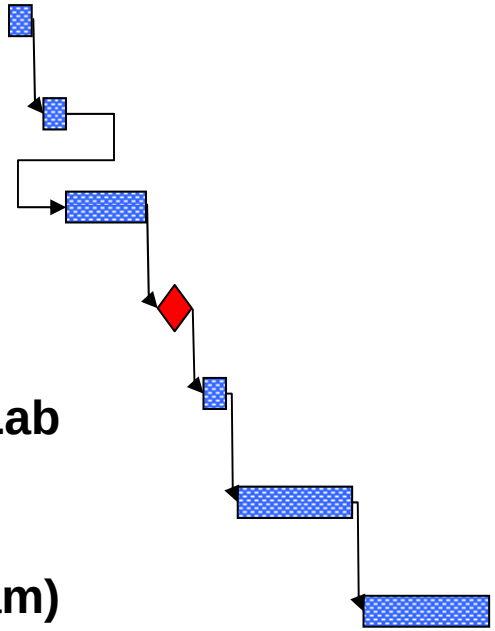
Protocol G Update: March 2009

The Search for Broadly Neutralizing MAbs from HIV+ Subjects



	March
Serum Collected	>2,000
Shipped and Stored (Core Lab)	>1,800
Neutralization Assay (Monogram)	>1,800
Donor of interest identified	>200
PBMC's collected/shipped to Core Lab	>150
Monoclonal Ab Identified	>80
Neutralization Assay MAb (Monogram)	20
Monoclonal Ab Characterized	(2)*

NAC Investigators

* NOTE: Approximately 20 "elite neutralizers" have been identified, and majority of such samples still need to be screened for bnMAbs

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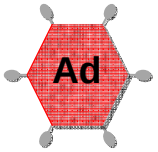
Live HIV Vaccine Vector Development Field

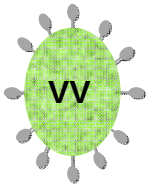
External Vector Development

Measles virus
GSK / Crucell

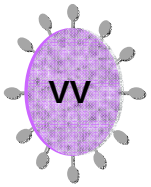
Attenuated VSV
Wyeth / Profectus



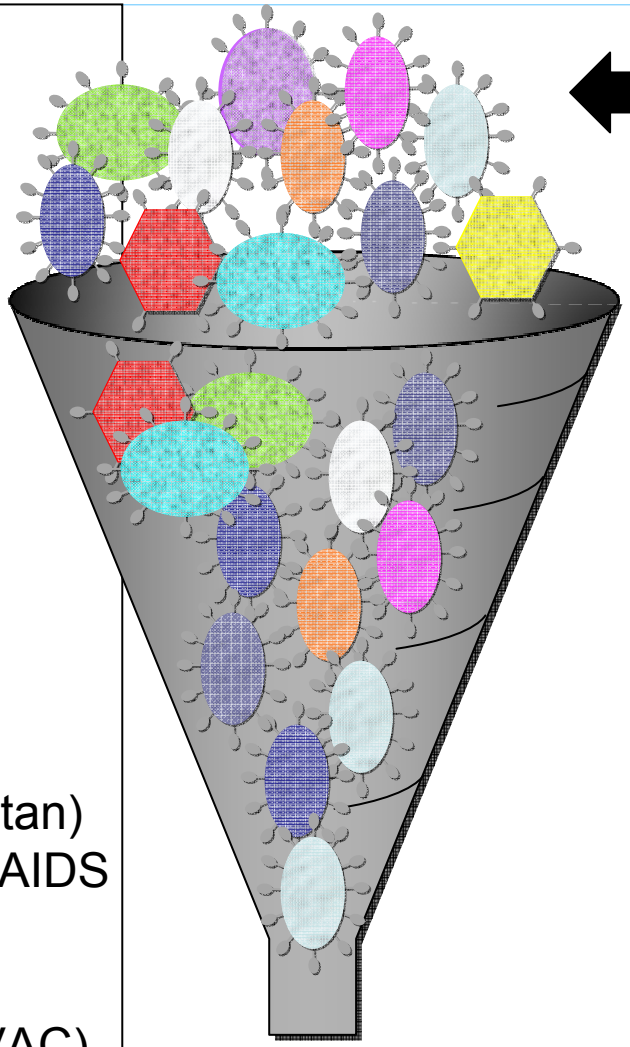
Adenovirus 5 / 7
NCI



Vaccinia virus (Tiantan)
National Center for AIDS
Beijing



Vaccinia virus (NYVAC)
EuroVac



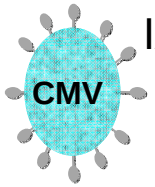
IAVI VEC Programs

IAVI / Gates
Vector Design
Program

IAVI
Lab

Nibert

Johnston



IAVI / Academic
Partner
(Picker)

IAVI / Biotech
Partner
(DNAVEC)

IAVI / Biotech
Exploratory
(Biovex)

Advances Towards Improving Immunogens to Control HIV Infection

- Prototype persistently replicating Cytomegalovirus (CMV) Vector (L. Picker, IAVI Vectors Consortium) provides partial control of SIV infection in non-human primate studies;
  - SAC endorses IAVI recommendation to advance CMV to clinical development.
  - CMV: High risk, high return
- Design Lab achieves 1st key step in the development of next generation replicating vectors: Rescue of the vector
  - Mucosal delivered Canine Distemper Virus (CDV) vector
  - Chimeric Vesicular Stomatitis vector (VSV)

IAVI's AIDS Vaccine Discovery and Development Network

AIDS VACCINE CONSORTIUM

NEUTRALIZING ANTIBODY CONSORTIUM (NAC)

Indian Institute of Science	Bangalore, India
International Center for Genetic Engineering & Biotech	New Delhi, India
Karolinska Institute	Stockholm, Sweden
Institute for Research in Biomedicine	Bellinzona, Switzerland
Academia Sinica	Taipei, Taiwan
Mahidol University-Henry Jackson Foundation	Bangkok, Thailand
St. Stephen's AIDS Trust	London, UK
University of Oxford	Oxford , UK
Vaccine Research Center, NIAID	Bethesda, MD, USA
Dana-Farber Cancer Institute	Boston, MA, USA
Harvard Medical School	Cambridge, MA, USA
The Scripps Research Institute	La Jolla, CA, USA
University of Wisconsin-Madison	Madison, WI, USA
International AIDS Vaccine Initiative	New York City, NY, USA
Children's Hospital of Philadelphia	Philadelphia, PA, USA
University of Pennsylvania	Philadelphia, PA, USA
University of Washington	Seattle, WA, USA

VECTORS CONSORTIUM (VEC)

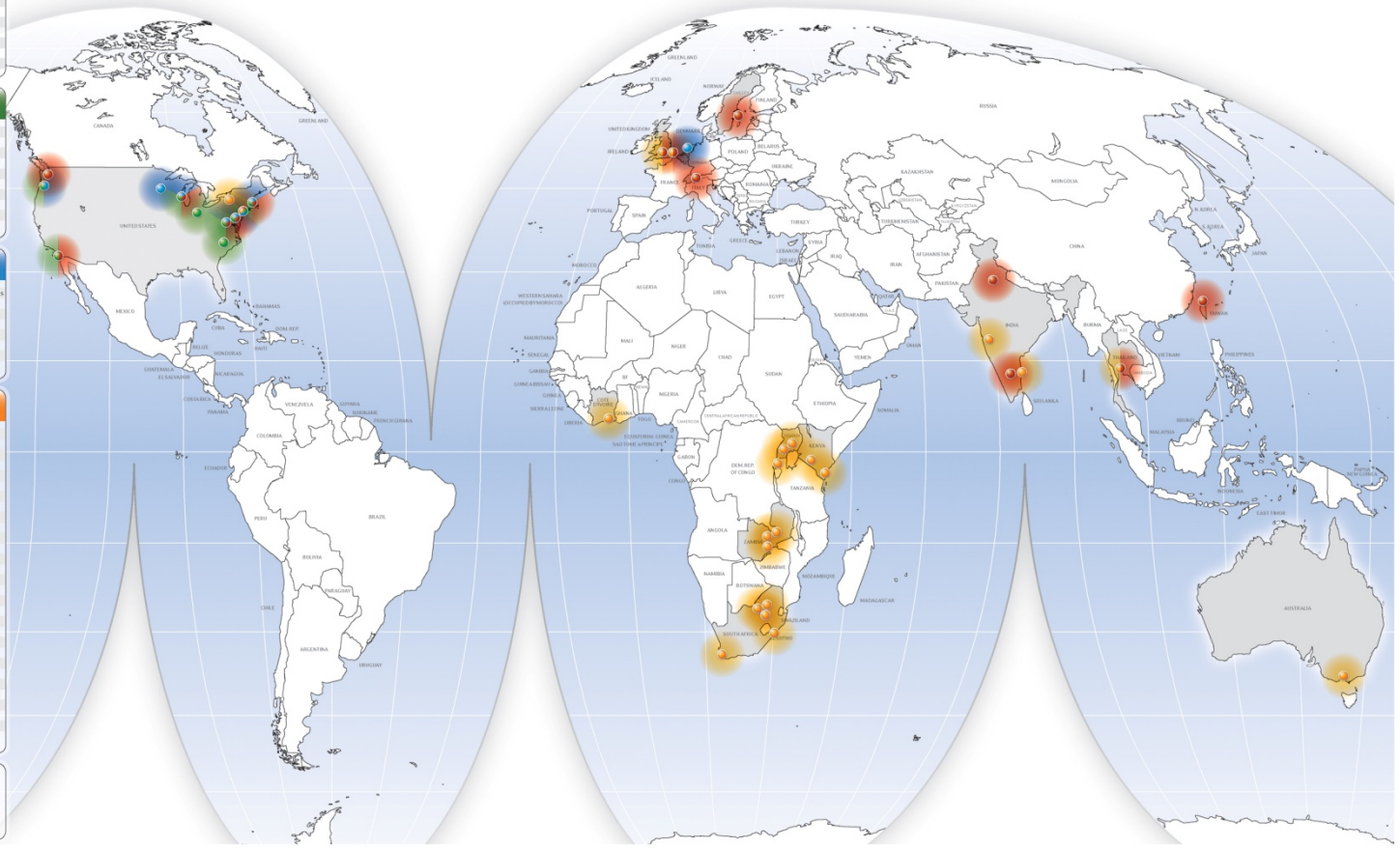
National Cancer Institute	Bethesda, MD, USA
Harvard Medical School	Cambridge, MA, USA
New England Primate Research Center	Cambridge, MA, USA
Global Vaccine Inc.	Chapel Hill, NC, USA
Cincinnati Children's Hospital Medical Center	Cincinnati, OH, USA
The Scripps Research Institute	La Jolla, CA, USA
University of Wisconsin-Madison	Madison, WI, USA
International AIDS Vaccine Initiative	New York City, NY, USA
Children's Hospital of Philadelphia	Philadelphia, PA, USA
Oregon Health & Science University	Portland, OR, USA

CONTROL OF HIV/LIVE ATTENUATED CONSORTIUM (LAC)

University of Amsterdam	Amsterdam, The Netherlands
National Cancer Institute	Bethesda, MD, USA
Harvard Medical School	Cambridge, MA, USA
University of Wisconsin-Madison	Madison, WI, USA
University of Minnesota	Minneapolis, MN, USA
International AIDS Vaccine Initiative	New York City, NY, USA
Children's Hospital of Philadelphia	Philadelphia, PA, USA
Oregon Health & Science University	Portland, OR, USA

CLINICAL RESEARCH AND TRIAL CENTERS (CRTC)

National Serology Reference Laboratory	Melbourne, Australia
CeDReS/PACCI	Abidjan, Cote d'Ivoire
YRG CARE	Chennai, India
Tuberculosis Research Centre	Chennai, India
National AIDS Research Institute	Pune, India
Kenya AIDS Vaccine Initiative	Kangemi, Kenya
Centre for Geographic Medicine Coast - MRC	Kilifi, Kenya
Kenya AIDS Vaccine Initiative-University of Nairobi	Nairobi, Kenya
Emory University, Projet San Francisco-Kigali	Kigali, Rwanda
Desmond Tutu HIV Foundation, Masiphumelele Clinic	Cape Town, South Africa
Desmund Tutu HIV Foundation, Nyanga, Ulundu Health Center	Cape Town, South Africa
Medical University of Southern Africa	Gauteng, South Africa
Contract Laboratory Services	Johannesburg, South Africa
Perinatal Health Research Unit	Johannesburg, South Africa
Aurum Institute for Health Research	Rustenburg, South Africa
Armed Forces Research Institute of Medical Sciences	Bangkok, Thailand
Vaccine Trial Center, Mahidol University	Bangkok, Thailand
MRC Uganda: Entebbe	Entebbe, Uganda
Uganda Virus Research Institute - IAVI	Entebbe, Uganda
MRC Uganda: Masaka	Masaka, Uganda
Human Immunology Laboratory	London, UK
St. Stephen's AIDS Trust	London, UK
University of Oxford	Oxford, UK
Aaron Diamond AIDS Research Center	New York City, NY, USA
International AIDS Vaccine Initiative	New York City, NY, USA
SUNY Downstate Medical Center	New York City, NY, USA
University of Rochester	Rochester, NY, USA
Emory University, Zambia-Emory HIV Research Project	Kitwe, Zambia
Emory University, Zambia-Emory HIV Research Project	Lusaka, Zambia
Emory University, Zambia-Emory HIV Research Project	Ndola, Zambia



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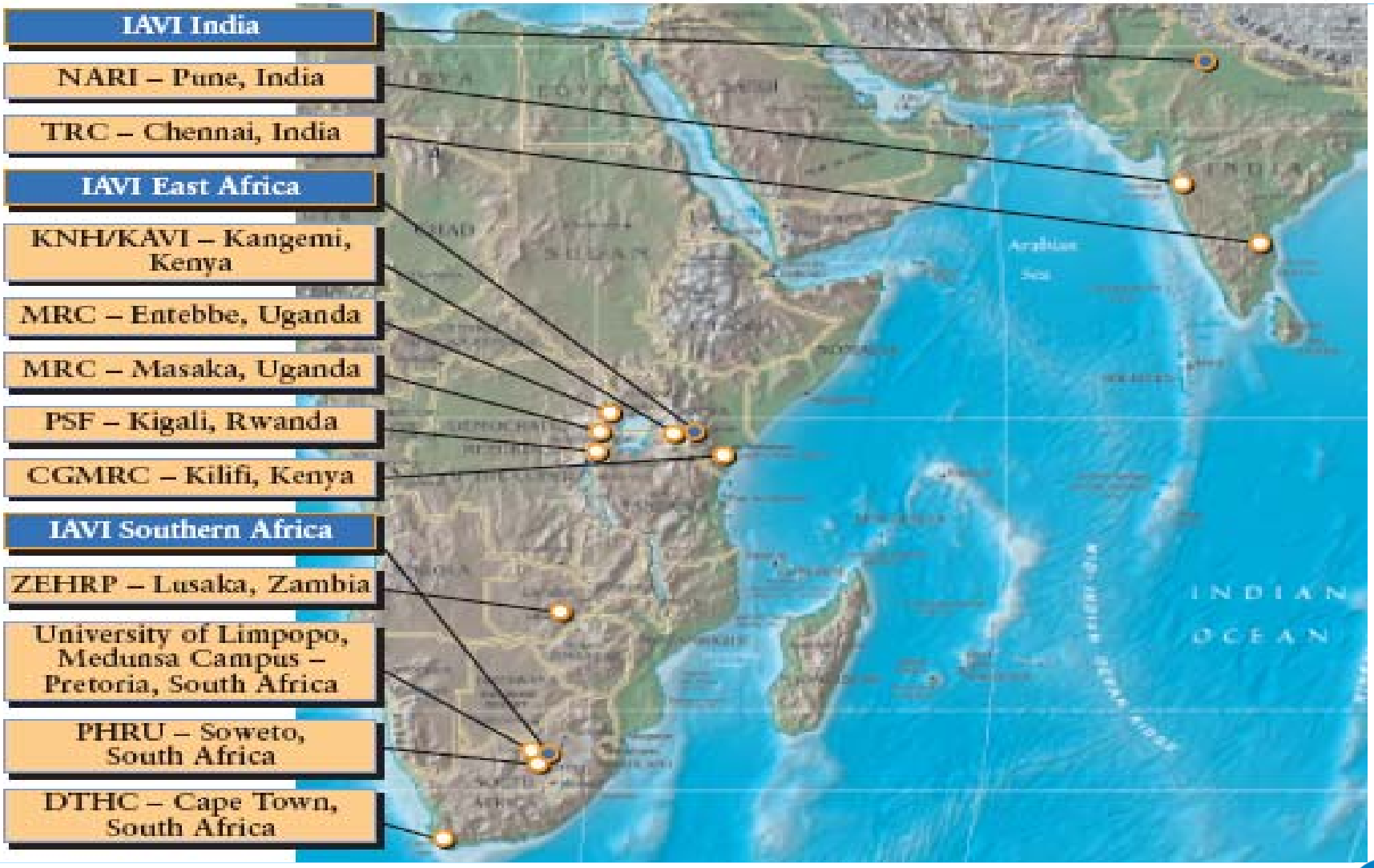
IAVI Clinical Trials Network



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Clinical research in Africa

Phase I/II vaccine trials

- Generally low risk populations
- 6 phase I/II trials conducted at 7 centres to date
- Approximately 400 volunteers enrolled so far

Epidemiology studies

- Preparatory research for STOC trials.
- Study HIV prevalence, incidence, retention.
- Research natural history of disease, early infection, neutralizing antibodies, immunology of exposed individuals.
- 5 ongoing studies at 9 centres involving around 3000 volunteers
- 100.000 people received VCT

Social Science

- MSM, Fisher folks

Budget

- African clinical research centres - $US 13M (2008)
- 430 FTE staff funded

IAVI is grateful to its partners in Europe

Industry

- Algonomics, Belgium
- Berna, Switserland
- Bioption, Sweden
- Crucell, The Netherlands
- Cobra, UK
- Cytos, Switserland
- FIT Biotech, Finland
- GSK Biologicals, Belgium
- IDT, Germany
- Intercel, Austria
- Lipoxen, UK
- Statens Serum Institute, Denmark
- Symphogen, Denmark
- Transgene, France

AIDS organizations

- AIDES, France
- AIDS Fondet, Denmark
- Aids Fonds, The Netherlands
- Deutsche AIDS-Stiftung, Germany
- DSW, Germany
- GAT, Portugal
- Global SIDA, Spain
- gTt, Spain
- Finnish AIDS Council, Finland
- HivNorge, Norway
- National AIDS Trust, UK
- Noah's Ark, Sweden
- SENSOA, Belgium

Academia

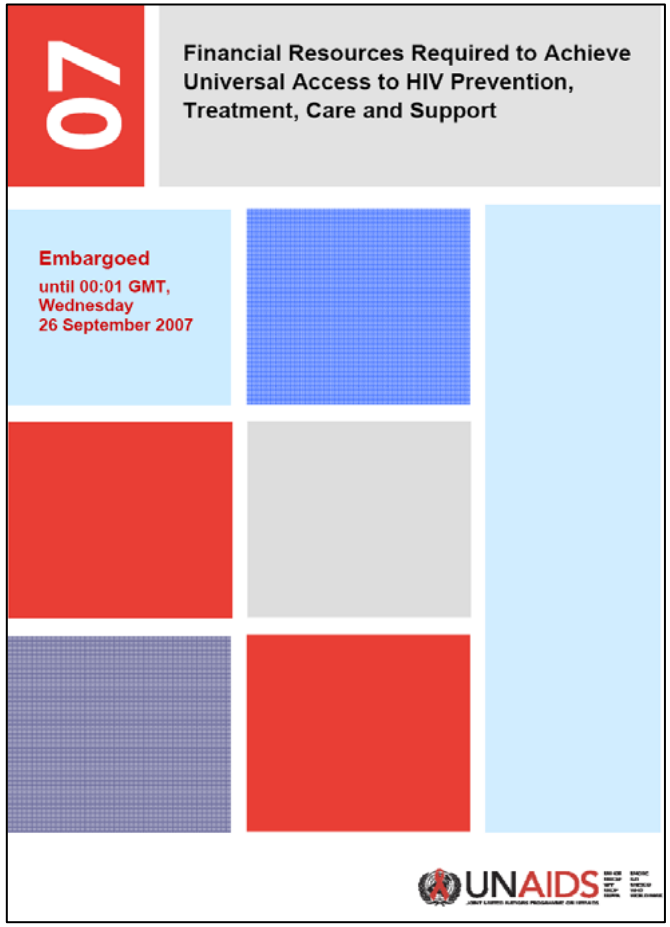
- Centre d'Immunologie de Marseille-Luminy, France
- Imperial College, London, UK
- Institute for Research in Biomedicine, Switserland
- Karolinska Institute, Sweden
- Medical Research Council, Oxford, UK
- Pierre et Marie Curie, France
- St. Georges University of London, UK
- St. Stephen's AIDS Trust, UK
- University of Amsterdam, The Netherlands
- University of Oxford, London, UK

Europe's commitment to the development of an AIDS vaccine

The Dublin Declaration on Partnership to Fight HIV/AIDS. Signed in 2004 by 53 countries of the WHO European Region.

- Action 19 - *Increase commitment to research and development for new technologies that better meet the prevention needs of people living with or most vulnerable to HIV transmission including increasing public sector investment in vaccines and microbicides to prevent HIV infection."*

The Price of Universal Access



July 2005 Gleneagles Summit of G8 countries:

"…to develop and implement a package for HIV prevention, treatment and care, with the aim of moving as close as possible to universal access to treatment for all those who need it by 2010"

Universal access will cost $54 billion / year by 2015

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Vaccines are part of a sustainable, comprehensive response to HIV and AIDS

Well-known statistics

- Worldwide 33 million people are infected with HIV; over 7,000 new infections daily
- For every 2 people receiving treatment, another 5 people become infected with HIV

A comprehensive response

Deliver for today – better use of tools

- Prevent further spread of the virus
- Treat those already infected
- Mitigate social impacts

Develop better tools for the future

- Invest in innovation for new technologies (drugs, diagnostics, microbicides, vaccines)

Development of an AIDS vaccine is critical for the affordability and sustainability of our commitments to universal access

Source: UNAIDS 2006

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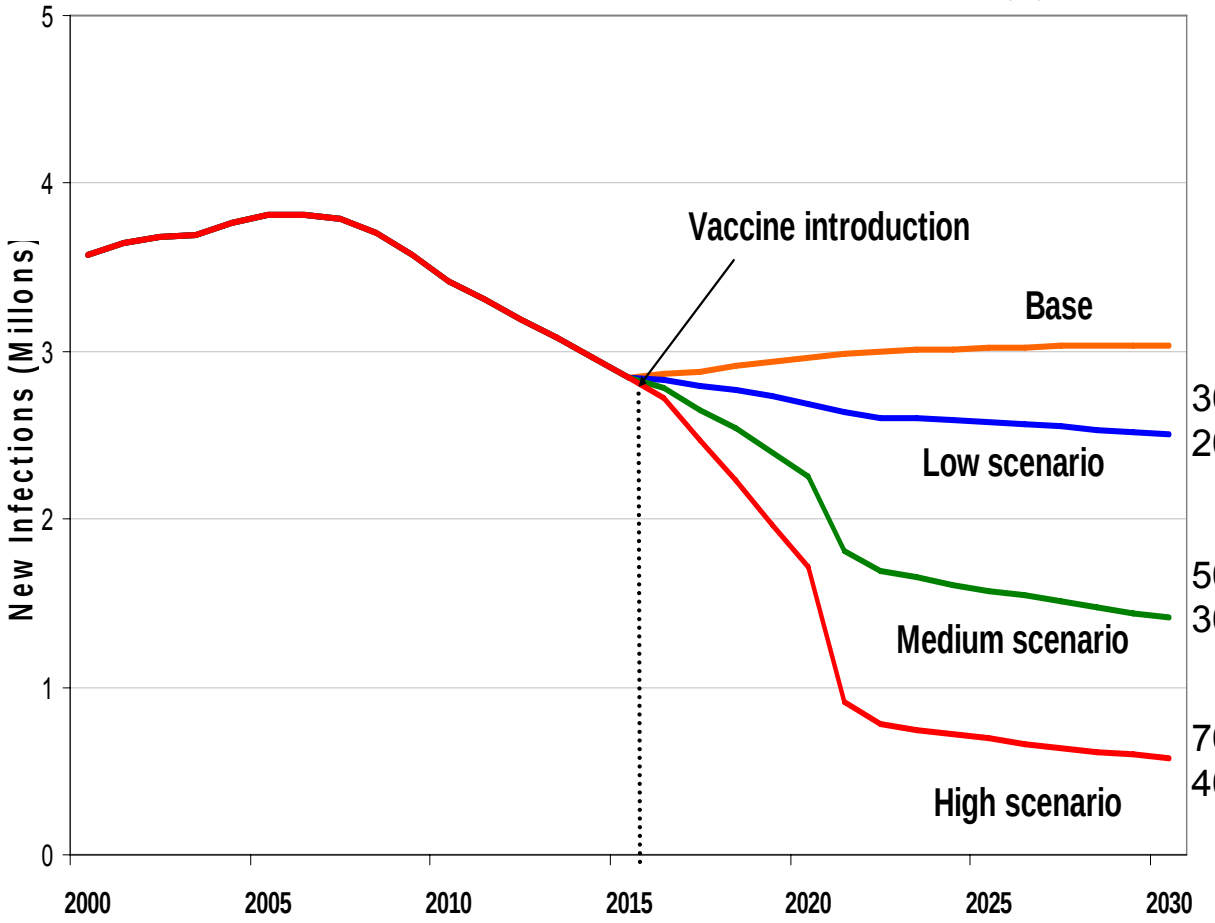
Ultimately,
a vaccine offers the best hope of ending AIDS

New adult HIV infections in low- and middle-income countries by year and vaccine scenario



Total new infections averted by an AIDS vaccine between 2015-2030

30% efficacy, 20% coverage → 5.5 million

50% efficacy, 30% coverage → 17 million

70% efficacy, 40% coverage → 28 million

Source: IAVI (2006) The impact of an AIDS vaccine in developing countries: a new model and preliminary results.

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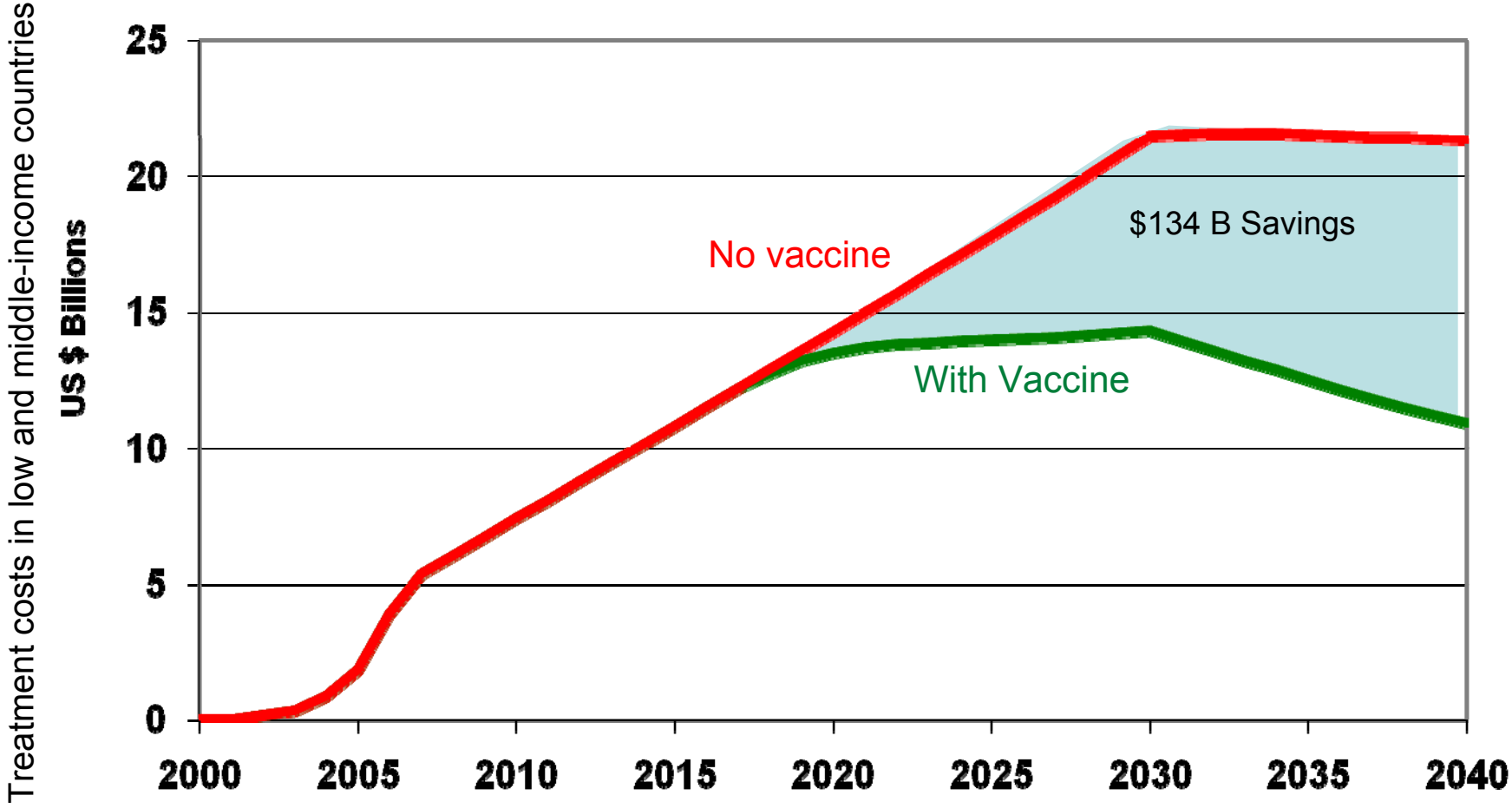
An AIDS vaccine could save $$ billions in treatment costs for LMICs

[Assumes 50% efficacy and 40% adult coverage]



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Developing a AIDS vaccine is complicated

Scientific

Issue

- HIV integrates; short window
- HIV hyper-variability; clades
- Immune correlates of protection are still unknown
- HIV suppresses and kills cells of the immune system
- Relevant animal models are lacking
- Clinical trials are long and costly

What it means

- We are tackling an aggressive and fast moving target
- We have to test in people
- Success will take time

Policy & Political Will

- Long term effort requires long term, high level global commitment - leading to action
- Market incentives for industry activity lacking
- Ethical, regulatory, IP issues
- Health systems challenges

- We need sustained political support
- We need to build private sector engagement
- We need to optimize the environment for safe, ethical trials

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State of The Global AIDS vaccine R&D Effort

Advances	**Limitations**
More candidates in the pipeline…	…yet only two fully tested for efficacy, all candidates focused on one hypothesis = cellular immunity
More countries and scientists are involved…	…but response is still insufficient in some countries and from industry
Developing countries are becoming more active partners…	…yet we need to invest in their capacity to stay the course over the long run
Science knowledge is growing…	…but scientific challenges remain a major impediment to progress

We must persevere - vaccines are powerful tools, but can take decades to develop

Infectious agent (disease)	Agent linked to disease	Vaccine licensed in U.S.	Years elapsed
Pertussis (whooping cough)	1906	1948	42
Polio	1908	1955	47
Measles	1953	1963	10
Hepatitis B	1965	1981	16
Haemophilus influenza	1889	1981	92
Typhoid	1884	1989	105
Varicella zoster (chicken pox)	1953	1995	42
Rotavirus (diarrheal disease)	1973	2006	33
Human papilloma virus (cervical cancer)	Early ’80s-mid ‘90s	2006	12-25
Malaria	1893	-	112+
Human immunodeficiency virus –HIV (AIDS)	1983	-	24+

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Progress in the field is providing important clues for the design of an AIDS vaccine

- There are individuals who have been repeatedly exposed to HIV, but have not become infected.
- There are individuals who have been infected for 25 years or more and have shown no ill effects.
- In non-human primates, it is possible to provide protection against infection with SIV, a simian cousin of HIV, with a live-attenuated vaccine. By studying how this model works, the AIDS vaccine field can gain clues about how to make a safe vaccine for humans.
- A handful of antibodies against HIV have been isolated from infected individuals over the years, and these provide vital clues towards designing vaccines that induce similar antibodies.

AIDS Vaccine R&D 2008 – 2009 highlights from the field

Clinical research

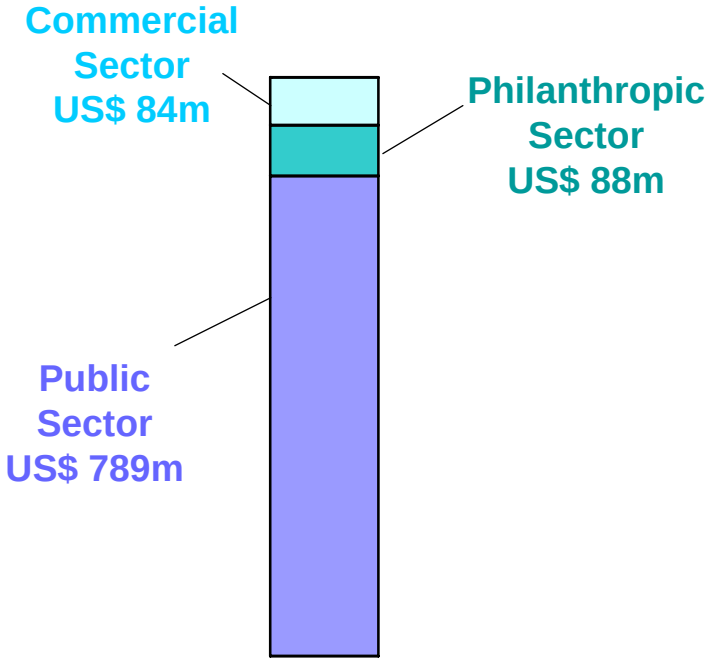
- The Search for Why Merck Adeno-HIV Vaccine Failed?
  - Lack of circumcision and concurrent HSV-2 infection> Ad5 pre-existing immunity re: acquisition risk
- Phase III trial results
  - Canarypox + gp120: Data expected in 3Q09 from the Thai trial

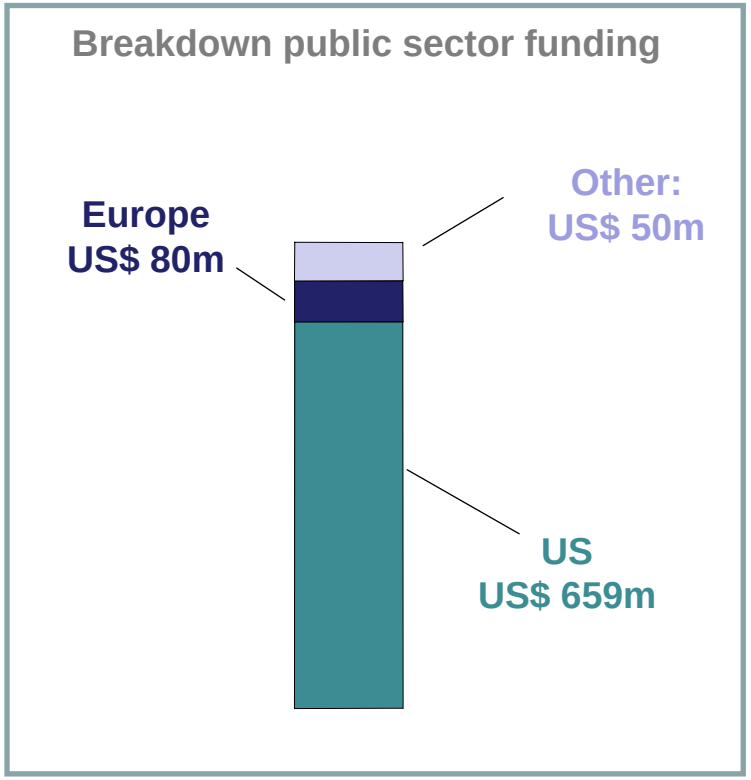
New and Promising preclinical Data

- Vaccine Approaches to Control HIV Infection
  - Several types of SIV analog vaccines now pass the bar of virus load reduction by at least 100-fold
  - Less Antibody May Be Required to Prevent HIV Infection

Investments in AIDS vaccine R&D globally

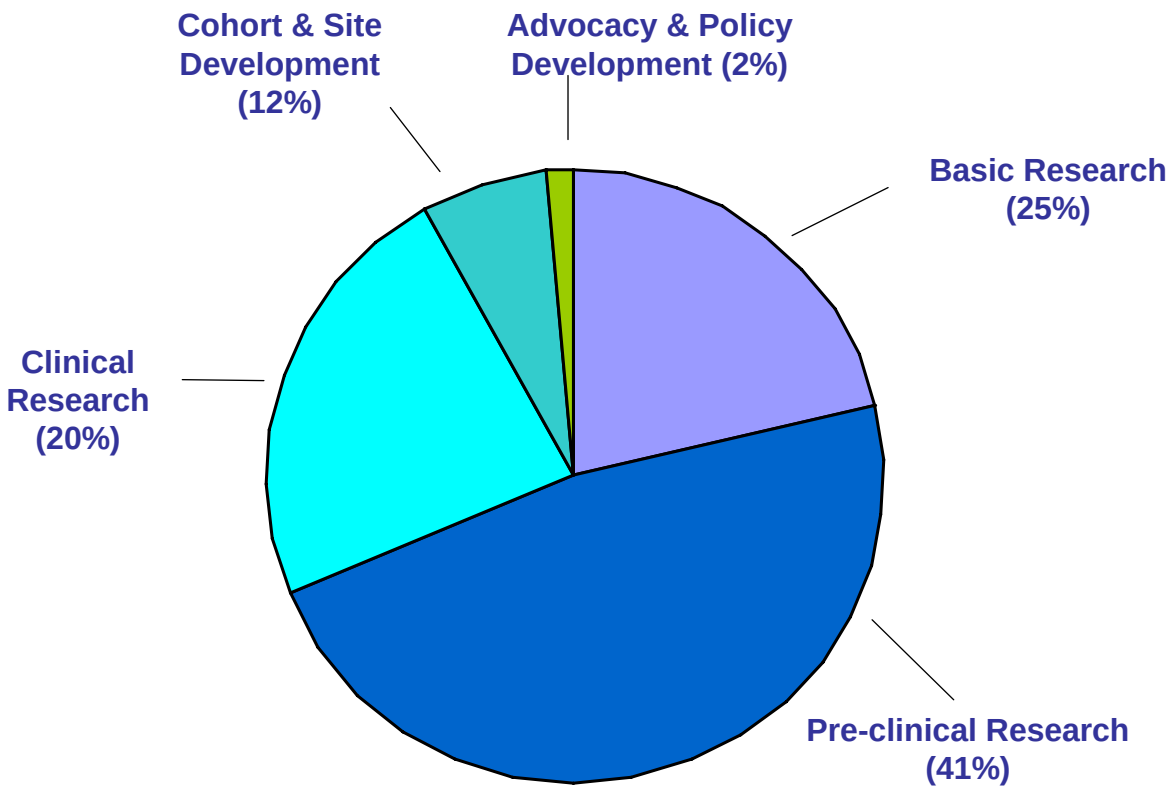
Total 2007 Investment = US$961 mn





Source: HIV Vaccines and Microbicides Resource Tracking Working Group (2008). "Sustaining the HIV Prevention Research Agenda: Funding for Research and Development of HIV Vaccines, Microbicides, and Other New Prevention Options (2000 to 2007)".

Global R&D Funding Allocation by Category in 2007



Source: HIV Vaccines and Microbicides Resource Tracking Working Group (2008). “Sustaining the HIV Prevention Research Agenda: Funding for Research and Development of HIV Vaccines, Microbicides, and Other New Prevention Options (2000 to 2007)”.

Barriers in Europe for driving research and development for global health

- Focus on organizing rather than driving R&D
  - Preference for large consortia focussed on coordination of research, rather than smaller consortia focussed on accelerating R&D and developing products
- Disconnect between European and International research
  - Aspiration to initiate European networks, but often no plan on how to link and syncrhonize this with international research efforts
- Structural and financial barriers to R&D innovation
  - High pressure on universities to generate IP revenues → less incentives for exploring high risk applications for health
  - Same is true in biotech sector: maximize revenues for survival avoids exploring novel applications, certainly not in the area of poverty-related and neglected diseases
  - Gap between academia and biotech prevent that scientific ideas are translated efficiently into new technologies and products

EU urged to fund research on 'terrible triangle' of disease

The European Commission is failing to pay its "fair share" in funding research into the main poverty-related killers HIV/AIDS, malaria and tuberculosis, according to health NGOs.

EurActiv 14 Nov 2008

(MSF and Oxfam speaking during a conference on poverty-related diseases on 13 November 2008 in Brussels)

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The way forward

- **Action the commitment in the Dublin Declaration: support and stimulate AIDS vaccine R&D globally and in Europe**
- **Strengthening dedicated R&D infrastructure for - AIDS vaccine - translational research in Europe** – public institutions that excel in infectious disease research should receive more funding to create a critical mass of resources.
- **Public funding for biotechs** – more public funding to promote later stage research could help alleviate Europe's translational gap
- **Promote and support the funding of international product development public private partnerships (PDPs)**: encouraging collaborative translational research partnerships to create a critical mass of expertise and skills.
- **Develop innovative finance mechanisms to promote research for global health needs**

Research and global health during the financial crisis

Financial crisis expected to slow R&D investment "The current global credit crunch could dent investment in biotech research and seriously delay the discovery of new medicines." *Professor David Wield , UK Economic and Social Research Council*

"Sustained investment in innovation can help to relaunch the overall economy, because major societal challenges will remain long after the resolution of the financial crisis." *EU Science and Research Commissioner Janez Potočnik.*

EurActiv 28 October 2008

The vital role of research for health at a time of financial crisis "My plea is that, as we argue the case for protecting and promoting health in this period of financial crisis and as we look for innovative ways of financing this, that we explicitly include research for health as an essential component of that agenda, in order to ensure that we keep the reduction of health inequities at the centre of attention." *Stephen Matlin, Executive Director, Global Forum for Health Research*

www.globalhealthforum.org 22 Jan 2009

President Obama is making the biggest bet on science and technology in history. A $120 billion stimulus package – NIH receives 29.5 billion

New Scientist March 7 2009

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IAVI Gratefully Acknowledges the support of its Donors

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Basque Autonomous Government
Becton, Dickinson and Company (BD)
Bill & Melinda Gates Foundation
Bristol-Myers Squibb (BMS)
Broadway Cares/Equity Fights AIDS
Canadian International Development Agency
Continental Airlines
European Union
Foundation for the National Institutes of Health
Google Inc.
The Haas Trusts
Henry Schein, Inc.
Irish Aid
James B. Pendleton Charitable Trust
The John D. Evans Foundation
Kathy Bole & Paul Klingenstein
Merck & Co., Inc.
Ministry of Foreign Affairs and Cooperation, Spain
Ministry of Foreign Affairs of Denmark
Ministry of Foreign Affairs of The Netherlands
Ministry of Foreign Affairs of Sweden
The New York Community Trust
Norwegian Royal Ministry of Foreign Affairs
Pfizer Inc
The Rockefeller Foundation
Swedish International Development Cooperation Agency
U.K. Department for International Development
Until There's a Cure Foundation
The U.S. President's Emergency Plan for AIDS Relief through the U.S. Agency for International Development
The William and Flora Hewlett Foundation
The World Bank through its Development Grant Facility

And many other generous individuals from around the world.

*As of 04/08