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RD models: lessons from vaccine history

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R&D Models: Lessons from Vaccine History

IAVI Public Policy Department

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<i>IAVI's mission is to ensure the development of safe, effective, accessible, preventive HIV vaccines for use throughout the world.</i>
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R&D Models: Lessons from Vaccine History

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IAVI's Policy Research Working Paper series disseminates important new research findings in order to promote the exchange of information and ideas that facilitate the effective development and global distribution of vaccines to prevent HIV infection.

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Acronyms and Abbreviations

AFEB	Armed Forces Epidemiology Board
AIDS	Acquired immunodeficiency syndrome
CAVD	Collaboration for AIDS Vaccine Discovery
CDC	Centers for Disease Control and Prevention (U.S.)
CHAVI	Center for HIV/AIDS Vaccine Immunology
EDCTP	European and Developing Countries Clinical Trials Partnership
FDA	Food and Drug Administration (U.S.)
DTaP	Diphtheria, tetanus, and acellular pertussis vaccine
EU	European Union
GMP	Good manufacturing practice
GSK	GlaxoSmithKline
HBV	Hepatitis B virus
Hib	Haemophilus influenzae type b
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
HVTN	HIV Vaccine Trials Network
IAVI	International AIDS Vaccine Initiative
IP	Intellectual property
NAC	Neutralizing Antibody Consortium
NCI	National Cancer Institute (U.S.)
NFIP	National Foundation for Infantile Paralysis (U.S.)
NIAID	National Institute of Allergy and Infectious Diseases (U.S.)
NIH	National Institutes of Health (U.S.)
NSF	National Science Foundation
OspA	Outer surface protein A
PDP	Product development public-private partnership
R&D	Research and development
SKB	SmithKlineBeecham
STOC	Screening test of concept
TRIPS	Trade-related Aspects of Intellectual Property Rights agreement
VLP	Virus-like particle
VRC	Vaccine Research Center, U.S. National Institutes of Health
WRAIR	Walter Reed Army Institute of Research

Executive Summary

A preventive HIV vaccine offers the best hope for ending the AIDS pandemic. Scientific evidence suggests that an HIV vaccine is possible, and funding for HIV vaccine research and development (R&D) has increased substantially in recent years. The speed of progress toward an HIV vaccine will depend on the management of the effort as well as on its scale, however, and organizational issues have been the subject of vigorous debate. With this paper, we seek to shed light on these debates by examining the history of vaccine development, as well as some examples of large R&D initiatives in other areas. We focus on two issues: the roles of the public and private sectors, and the merits and risks of strong central direction of R&D. We also consider the scientific, regulatory, and institutional changes that complicate extrapolation from past experience to the case of HIV vaccines. Our analysis draws on extensive interviews with experts in the field as well as a literature review.

Historical models of vaccine development

It is often asserted that the private sector possesses unique capacities in vaccine R&D and that greater involvement of industry, especially the large pharmaceutical companies, is essential to developing an HIV vaccine. To evaluate this claim, we analyze the institutional settings in which innovative vaccines have been successfully developed. In particular, we identify the organizations primarily responsible for each stage (vaccine design, development and clinical trials, manufacturing and licensing) of the development of vaccines licensed since 1945. By classifying these organizations by sector (public, private nonprofit, or private for profit), we define four basic “models” of vaccine development.

- *Predominantly private sector development.* This model is exemplified by the hepatitis B (HBV) vaccine, licensed by Merck in 1981. Although earlier work done in academic labs suggested a strategy, the vaccine was designed, tested, and manufactured by Merck.
- *Public (or nonprofit) sector vaccine design, with handover to the private sector for trials and manufacturing.* The human papillomavirus (HPV) vaccine is an example of this common pattern. Several university labs independently developed the “virus-like particles” on which the vaccine is based and then licensed their ideas to the private sector. Merck, whose vaccine was licensed in 2006, and GlaxoSmithKline (GSK), whose vaccine should reach the market in 2007, conducted process development, clinical trials, and manufacturing.
- *Predominantly public-sector development.* The influenza vaccine, developed in the 1940s, typifies this model. The U.S. Army designed the vaccine and carried out clinical trials, although vaccine manufacture was contracted to industry.
- *Coordination by a nonprofit entity.* The Salk polio vaccine is so far the only example of this organizational pattern. The vaccine was designed in a university lab and manufactured by industry, but under the close supervision of the National Foundation for Infantile Paralysis (NFIP), which also oversaw clinical trials. This model may become more important because investments in product development public-private partnerships (PDPs) have grown dramatically over the past decade.

Our historical review demonstrates that universities, public agencies, and private firms have divided the tasks of vaccine R&D in a number of ways. Basic research has in most cases

been conducted at universities or research institutes, often supported by public funding. At the other end of the pipeline, almost all the vaccines that we consider were initially manufactured by industry, although the public sector produces many generic vaccines outside the U.S. Thus vaccine development has generally involved a handover from the public (or academic) sector to industry; the various models differ primarily in when the handover occurs.

When the entire period since 1945 is considered, no particular model dominates: six vaccines were designed and tested by private industry, 16 were designed in the academic/public sector and handed to the private sector for clinical trials, and nine were taken to the production stage in the public sector. Moreover, no particular model (or sector) is more strongly associated than any other with innovation or with development of more “difficult” vaccines. In recent years, however, a standard model of vaccine development has dominated, in which promising candidates are developed by university labs and biotech firms and then licensed to big pharma for clinical trials, licensing, and manufacture. Of the 20 vaccines on our list that were licensed since 1980, 18 were carried through trials at least partially by industry. The skills and experience required to develop large-scale manufacturing processes, as well as to carry out licensing trials, currently reside almost exclusively at a handful of large firms.

Recent history suggests that the research and innovation necessary for an HIV vaccine are likely to come from university labs and biotech firms rather than from big pharma. Moreover, although the involvement of industry in trials—especially trials to support licensure—is highly desirable, growing experience in HIV vaccine trials should allow the public sector to test promising candidates if necessary. The expertise of the established vaccine firms will be crucial to manufacturing and licensing a vaccine, however. We argue that it makes sense to continue to strengthen the capacity of the public and nonprofit sectors to design and test HIV vaccines while preparing to engage the private sector on mutually attractive terms once proof of concept has been established.

The organization of R&D efforts: lessons from beyond vaccines

Some have argued that competitive pressures, misaligned incentives, and lack of communication in the HIV vaccine field have resulted in duplication of effort in some areas and insufficient attention to others. We ask whether the HIV vaccine field should seek to mimic—to the extent possible in a very different institutional context—the highly centralized organization that characterized major national R&D initiatives in the past, such as the Manhattan Project. We call this approach to organizing R&D “mission mode” and define it by four characteristics: strong commitment backed by sufficient resources, a clear and politically compelling goal, centralized leadership with control over resources, and tight focus on a restricted set of tasks. We emphasize the third and fourth features, which distinguish mission mode from alternative ways of organizing large R&D initiatives. We briefly describe two examples of past mission mode efforts and then consider the implications of these experiences for the HIV vaccine field.

The Manhattan Project. The Manhattan Project refers to the American effort to develop the first nuclear weapons during World War II. Although the theoretical basis for an atomic weapon had already been established when the project began, the necessary fissionable material had never been produced on a large scale, and many daunting technological problems remained to be solved. A central laboratory for all of the project’s theoretical and

experimental work was established at Los Alamos, NM, and participating scientists were required to focus exclusively on directly relevant lines of research. At the same time, the project's leadership assumed tight control over efforts to produce fissionable material, choosing among competing approaches and moving rapidly to full-scale production.

The Manhattan Project developed the bombs that exploded over Hiroshima and Nagasaki less than three years after the project was launched. Strong central control (and pervasive secrecy) undoubtedly contributed to this outcome by allowing decisions to be made rapidly, by focusing effort on the chosen approaches, and by coordinating the many necessary tasks.

The War on Cancer. In January 1971, President Nixon called for an appropriation of US\$100 million to launch the War on Cancer, saying “the time has come in America when the same kind of concentrated effort that split the atom and took man to the moon should be turned toward conquering this dread disease.” A national panel recommended strong central direction by the National Cancer Institute (NCI), a systematic plan of attack focusing largely on applied research, and a large increase in resources. This broad conception of the National Cancer Program quickly faded, however, and progress toward the program's goals was disappointing: more than US\$23 billion had been appropriated by 1993, yet age-adjusted mortality rates from cancer were higher than they had been in 1970. Although the causes of failure are disputed, the sheer complexity of the cancer problem and lack of knowledge about which areas would reward more research are seen as the major reasons that the ambitious goals of the 1971 act were not met.

Although it is impossible to draw definitive conclusions about mission mode from two examples, these cases suggest that the success of this organizational form may depend on the nature of the R&D challenge. We argue that mission mode is appropriate only when the way forward is relatively clear and when the necessary development work is intrinsically large in scale. In contrast, when the best path to success is not clear, centralized decision-making can suppress innovation and the development of new strategies. There is therefore a trade-off between the efficiency of mission mode and the greater innovative potential of a more dispersed, less structured organization of R&D.

In retrospect, the Manhattan Project appears to meet the two criteria for mission mode, while the War on Cancer does not. Not enough was known about cancer in the early 1970s to justify a focus on one or a few approaches. Moreover, most cancer research is relatively small in scale and can be done in many places at once.

We argue that the path to an HIV vaccine is not sufficiently clear to justify primary reliance on a highly centralized approach, especially in the early stages of R&D, and that there is a real risk of narrowing the field's focus too far. Nonetheless, new, larger-scale approaches that focus on key outstanding challenges and incorporate features of mission mode can be important components of a diverse global effort, as long as sufficient resources remain available for exploring currently unpopular avenues of research. True mission mode as epitomized by the Manhattan Project does not seem appropriate for these stages, although voluntary measures to enhance cooperation, including many of those advocated by the Global HIV Vaccine Enterprise, could enhance cooperation and R&D efficiency while still preserving independent initiative.

Vaccine efficacy trials, in contrast, are by their nature large, highly structured undertakings involving thousands of subjects and costing tens of millions of dollars. Moreover, trial capacity is clearly limited and will remain so even with substantial efforts to support new sites in the developing world. This is a compelling argument for adopting a more systematic and coordinated approach to choosing which trials to conduct. Innovative trial designs permitting rapid screening of candidates could constitute an important element of a new approach and could contribute as well to easing the demands on trial capacity. In addition, greater coordination of large-scale efficacy trials themselves could allow for better comparison of candidates and a more efficient path to an effective first-generation product.

I. Introduction

Twenty-five years after the first cases of AIDS were documented, the global HIV pandemic has become one of the greatest public health crises facing the world. Nearly 40 million people were living with HIV at the end of 2005, and more than 4 million new infections occur each year, 95% of them in developing countries (UNAIDS 2006).

Despite significant progress over the past decade in expanding prevention and treatment programs, the number of new infections continues to climb each year. The AIDS crisis requires a comprehensive and integrated response, balancing the expansion of current programs with the development of better tools for the future. Unless the rate of new infections is lowered through better prevention, the escalating costs of the pandemic will undermine commitments to universal access for treatment and potentially to other expenditures for global health and development.

Funding for HIV vaccine research and development (R&D) has increased substantially in recent years. But progress toward an HIV vaccine depends on more than the volume of resources and the scale of scientific work: the organization and management of this effort matters too. A better understanding of which kinds of organizations are best suited for which roles in vaccine development, of the most productive balance of collaboration and competition at different stages of the process, and of whether and how mechanisms for coordinating the overall effort could accelerate the search for a vaccine and improve the chances of success. These issues have been discussed since the earliest days of HIV vaccine research but have taken on a greater urgency with the growing institutional complexity of the field.

This paper seeks to contribute to ongoing discussions about the priorities, organization, and management of the HIV vaccine field by examining the history of vaccine development and, to a lesser extent, large R&D initiatives outside the vaccine field.

1.1 Status of the HIV vaccine quest

Evidence suggests that an HIV vaccine is possible: cellular immune responses typically suppress the virus for up to a decade, and both live-attenuated vaccines and broadly neutralizing antibodies have been shown to protect monkeys. More than 30 HIV vaccine candidates are undergoing clinical trials now, including two being assessed in large-scale efficacy trials. Yet researchers working on HIV vaccines face a number of critical challenges, including the hypervariability of the virus and the difficulty of eliciting neutralizing antibodies against it. HIV, a retrovirus, hides within cells, meaning that the window of opportunity for a vaccine to cut off infection could be as short as seven to ten days. HIV also attacks and kills a critical class of immune cells that could otherwise help control infection.

Standard vaccine strategies attempt to mimic natural infection, but broadly neutralizing antibodies are not generated in response to HIV infection. No correlates of immunity have been identified, and no ideal animal model exists for HIV infection. Candidates can thus only be adequately evaluated in human clinical trials, which are expensive and logistically difficult. Partially as a result of these challenges, there are major gaps in the current HIV

vaccine pipeline. For instance, virtually no candidates elicit broadly neutralizing antibodies or mucosal immune responses in humans. For more information on the special challenges to creating an HIV vaccine, see Box 1 on page 8.

1.2 Players in HIV vaccine R&D

Funding for HIV vaccine R&D has increased steadily over the years, reaching US\$759 million per year in 2005. More than three-quarters of this total comes from the U.S. government, while the private sector accounts for about 10% (HIV Vaccines and Microbicides Resource Tracking Working Group 2006). Recent major new commitments included US\$287 million over five years from the Bill & Melinda Gates Foundation to establish 11 vaccine discovery consortia and up to US\$300 million over five years from the U.S. National Institute of Allergy and Infectious Diseases (NIAID) to establish the Center for HIV/AIDS Vaccine Immunology (CHAVI) (Global HIV Vaccine Enterprise 2005).

The U.S. National Institutes of Health (NIH), the largest single funder of HIV vaccine R&D, supports basic and applied research as well as clinical trials. Basic research is largely funded through investigator-initiated R01 grants, while much vaccine design work sponsored by the NIH is done through collaborative agreements and contracts. Important work is also done in-house by the NIAID's Dale and Betty Bumpers Vaccine Research Center (VRC).

Other public sector funders include the European Union (EU), which provides grants to various groups in Europe and has also established the European and Developing Countries Clinical Trials Partnership (EDCTP) to support trial site capacity building. Many other individual countries support HIV vaccine research in academic and government laboratories.

Four large pharmaceutical companies (GlaxoSmithKline or GSK, Merck, sanofi-aventis, and Wyeth) are involved in HIV vaccine R&D, although this work is often funded by the public sector or by nonprofit organizations. A number of small biotech companies, most in the U.S. or Europe, have developed or are developing vaccine platforms or candidates, some of which have moved into clinical trials.

The International AIDS Vaccine Initiative (IAVI), a product development public-private partnership (PDP), receives funding from governments and other sources to accelerate the search for an HIV vaccine. IAVI directs and finances a portfolio of research projects and clinical trials in partnership with both private sector firms and academic labs. At the same time, it works to build worldwide political and financial support for the HIV vaccine field as a whole.

The Global HIV Vaccine Enterprise, first proposed in 2003 and endorsed by the Group of Eight major industrialized nations (G8) in 2004, is made up of a wide variety of partners from the public, private, academic, and nonprofit sectors and is aimed at mobilizing resources for the HIV vaccine field, increasing coordination among researchers, and addressing the key problems identified in its 2005 Scientific Strategic Plan. The Enterprise does not conduct or fund research but is rather intended as a forum for partners to decide on the best ways to move forward, including targeting resources to priorities in the scientific strategic plan (Coordinating Committee of the Global HIV/AIDS Vaccine Enterprise 2005).

1.3 Major themes

Despite substantial increases in funding and the creation of innovative partnerships and organizations devoted to HIV vaccines, many players involved in HIV vaccine R&D, including IAVI itself, have argued that the field suffers from duplication of effort, misplaced priorities, and insufficient focus on applied research and rapid testing of promising candidates (Coordinating Committee of the Global HIV/AIDS Vaccine Enterprise 2005; IAVI 2006). Some believe that these deficiencies could be remedied by greater coordination of R&D efforts. Another common contention is that only industry, especially the big pharmaceutical companies, has the discipline and experience that later stages of vaccine development require and so must be persuaded to become more involved. Others have argued that until it is clear which approach will lead to success, a loosely organized effort that fosters independent thinking and healthy competition is most likely to generate the necessary innovation. They note that academic labs and small biotech companies are probably best equipped to pursue this kind of exploratory work.

This paper is an attempt to explore these questions. It will focus primarily on two related but distinct issues: the roles of the public and private sectors in vaccine development, and the advantages and disadvantages of a centrally directed, narrowly focused approach to large R&D challenges, which we will call “mission mode.” In addressing the first issue, we develop a simple taxonomy of successful vaccine development efforts based on the sector that carried out critical stages of the process. In discussing mission mode, we try to examine the conditions under which such an approach to organizing R&D accelerates progress. In both cases, we explore the implications of our findings for the HIV vaccine field.

We note here that IAVI has often distinguished between “industrial” and “academic” models of R&D said to typify, respectively, product development in large pharmaceutical firms and publicly funded research in university labs.¹ Although there is considerable overlap between the issues underlying this distinction and those addressed here, this paper does not attempt to better define the “industrial model” by analyzing how firms manage R&D internally, nor does it assume that applying such a model to the HIV vaccine field as a whole would be appropriate or possible. We discuss some aspects of the industrial versus academic distinction in Section III on mission mode.

This paper rests on the premise that vaccine history can help guide the development of HIV vaccines. We recognize, however, that both the science and the business of vaccines have changed in fundamental ways since most of the vaccines now in wide use were developed. We discuss some of these changes when we analyze the implications of historical precedents for vaccine R&D today. Moreover, the scientific obstacles to an HIV vaccine are different from those faced by earlier vaccine developers, and in some ways more daunting. Although our focus is not on the science of HIV vaccines, we raise some of these differences when they are relevant to the organization of research and development.

¹ The terms “industrial” and “academic” have been used rather loosely to describe a variety of R&D types. This terminology tends to blur important distinctions between R&D stages and between decision-making within and among organizations.

Box 1. Is HIV different?

It is sometimes argued that the challenges to developing an HIV vaccine are so different, in nature and magnitude, that little can be learned from the development of other vaccines. There is no doubt that the challenges are substantial. For example, nearly all current vaccines protect against pathogens that cause acute infections and can be cleared by the immune system. But no one has been known to recover from HIV and acquire immunity to subsequent infection, so researchers cannot base a vaccine on natural immune responses. Nor can they use simple live-attenuated or killed whole virus vaccines, which have been successful in the past even in the absence of information on immune responses, because they are considered too risky for HIV.

In addition, infectious agents for which vaccines have been developed tend to be relatively stable over time, so the immune response generated by a vaccine can protect against the real pathogen later. But HIV exists in many strains and is capable of extremely rapid and varied mutation. There is no guarantee that a vaccine could protect against all strains circulating in a given population, or that the virus would not soon escape from a vaccine in widespread use.

Assessing vaccine candidates is unusually difficult for HIV vaccines. There is no convenient animal model for HIV, so candidates can only be fully assessed in human clinical trials. In addition, researchers have not yet identified “correlates of protection,” simple measures of effective immune response that would greatly simplify the testing of candidates.

Although these obstacles are serious, most have been overcome in the past. For example, many vaccines were developed before immune correlates of protection could be analyzed; no animal model existed for (among others) rotavirus, measles, or mumps. The cancer-causing strains of human papillomavirus establish persistent infections that are not typically cleared by the immune system. And influenza rapidly mutates from year to year, necessitating new versions of the vaccine. Safe, effective vaccines for all these diseases are available today.

Moreover, the unusual difficulty of the HIV vaccine challenge does not mean that previous ways of organizing the search are not appropriate, only that more resources may be required or that the probability of success is lower. The unique features of HIV mean that some previous scientific approaches may not be useful, but nothing suggests that the challenge is so qualitatively different that the experience of past vaccine efforts cannot present useful lessons for how the HIV vaccine effort should be organized.

1.4 Methods and organization

The analysis and conclusions presented in this paper are built on two sources of data: interviews and a literature review.

We conducted structured interviews with experts in vaccine research, development, and manufacturing, as well as with leaders in HIV science and advocacy. The goal of the interviews was to identify factors that had contributed to the successful development of vaccines in the past and to consider how those factors might apply to the HIV vaccine field today (see Annexes II and III). These discussions informed all aspects of our analysis; some comments from the interviews are presented in boxes throughout the paper.

Models of vaccine R&D were defined through a literature review; the development of vaccines licensed since 1945 was analyzed in detail, with a particular emphasis on the institutional setting in which critical stages of development occurred. A small number of vaccines chosen as exemplars of particular R&D models were explored in more detail. These results are presented and analyzed in Section II, which focuses on the roles of the public and private sectors in vaccine development. Section III addresses the arguments for and against greater focus and centralized control (mission mode) in large R&D initiatives. In both sections we explore the implications of our conclusions for the HIV vaccine field.

II. Historical models of vaccine development

2.1 Vaccine basics

Vaccine history and major types of vaccines

The first vaccine was discovered in 1796, when Edward Jenner noticed that exposure to a smallpox-like pathogen offered protection against smallpox itself. After smallpox, no other vaccines were developed for nearly a century.

Elucidation of germ theory and the development of bacterial culture techniques in the 1880s and 1890s resulted in the development of a wave of new vaccines. Louis Pasteur theorized that exposing bacterial pathogens to environmental insults could weaken or "attenuate" them, leading to the first attenuated vaccine against anthrax (though it was not intended for humans). Aside from the bacille Calmette-Guérin (BCG) vaccine against tuberculosis, however, very few attenuated bacterial vaccines were successful, though the attenuation strategy was used for the first viral vaccine against rabies in 1885 (Baker and Katz 2004). Bacterial culture proved more useful for the development of killed bacterial vaccines, including vaccines against typhoid fever, cholera, plague, and pertussis (whooping cough). Few of these vaccines were effective, however, and only a few are still in use today.

Recognition of the extracellular toxins released by diphtheria-causing bacteria, which could then be inactivated, resulted in the licensure and widespread use of diphtheria and tetanus toxoids, both of which are still in use (Baker and Katz 2004). The discovery of viral propagation in embryonated chicken eggs in 1931 led to vaccines against yellow fever and influenza.

In 1949, a team at the Children's Hospital of Boston discovered viral propagation in cell culture, a critical new avenue for developing antiviral vaccines that won a Nobel Prize for the researchers and led directly to Jonas Salk's development of a killed polio vaccine. Cell culture proved to be an excellent means of attenuating viruses as well as propagating them, and attenuated virus vaccines were rapidly (and relatively easily) developed against polio, measles, mumps, and rubella.

Following these successes, a relatively quiet period of new vaccine development occurred through the 1970s. Exceptions were pneumococcal and meningococcal vaccines directed against polysaccharide components of the bacterial capsules, based on a technique that had been developed in the 1940s. In 1981, a hepatitis B (HBV) vaccine based on an antigen derived from the blood plasma of HBV carriers appeared on the market; this unusual strategy has yet to be repeated for any other vaccine.

In the 1980s and 1990s, the advent of molecular biology led to the development of a new generation of vaccines. A protein-conjugated capsular polysaccharide vaccine against *Haemophilus influenzae* type b (Hib) was licensed in 1987, and this technique has since been used to create improved meningococcal and pneumococcal vaccines as well.

Genetic engineering techniques resulted in two recombinant subunit vaccines—against HBV and Lyme disease—although the Lyme vaccine has since been taken off the market. The new vaccine against human papillomavirus (HPV) uses a recombinant platform to generate a

“virus-like particle” (VLP) that elicits strong immunity. A recombinant influenza vaccine, which does not rely on virus propagation in eggs, is expected in 2007 or 2008. Finally, recombinant vector vaccines have shown theoretical promise, though none has yet been licensed (Hilleman 2002).

Table 1. First examples of different types of vaccines, by year

Method of making vaccine	First example	Year available
Related animal virus	Smallpox	1798
Chemical attenuation	Rabies	1885
Inactivated whole bacteria	Typhoid	1896
Toxoid	Diphtheria	1923
Attenuation by passage in chick embryos	Yellow fever	1932
Inactivated whole virus	Influenza	1945
Attenuation by cell culture passage	Polio (oral trivalent)	1963
Capsular polysaccharide	Meningococcal	1974
Viral subunit	Hepatitis B (plasma-derived)	1981
Attenuation by deletion mutation	Ty21a oral typhoid	1981
Expressed recombinant viral subunit	Hepatitis B (recombinant)	1986
Protein-conjugated capsular polysaccharide	Hib conjugate	1988
Purified bacterial protein	Acellular pertussis	1991
Expressed recombinant bacterial protein	Lyme disease	1998
Virus-like particle	HPV	2006

Sources: Hilleman 2000; Plotkin 2005.

Stages of vaccine R&D

Although vaccine development does not always follow a conventional progression, this paper identifies four standard stages of R&D (National Vaccine Advisory Committee 1999).

- *Basic research* includes the identification of the disease-causing organism and its propagation in the laboratory, studies of disease pathology and natural immune response, and epidemiological surveillance.
- *Applied research and vaccine design* include the identification of a strategy to elicit immunity and development of vaccine candidates, as well as preclinical evaluation of safety and immunogenicity (typically in animal tests).
- *Vaccine development and clinical trials* include determination of a manufacturing process, preparation of pilot vaccine lots, and clinical evaluation in small- and large-scale human trials.
- *Manufacturing and licensure* include manufacturing the vaccine for commercial use and licensure by national regulatory agencies.

2.2 Overview of taxonomy

To better understand the institutional settings in which successful vaccines have been developed, we created a simple taxonomy of licensed vaccines based on the roles that universities, public agencies, and private industry played in their development. We compiled a list of innovative vaccines since 1945 and gathered information on their development and

licensure.² In particular, we identified the organizations primarily responsible for each stage of each vaccine’s development (vaccine design, clinical trials, manufacturing, and licensing) and classified these R&D actors by sector (public, private nonprofit, or private for profit) (see Annex 1). University labs were included with public sector agencies, in part because they are often funded from public sources, although this simplification is reexamined in the discussion below. Basic research was not included in this analysis, since it nearly always occurs in academic and government settings.

Using this approach, we identified four basic “models” of vaccine development and classified the vaccines accordingly.³ The number of innovative vaccines licensed since 1945 in each category is shown in parentheses.

1. Predominantly private sector development (6)
2. Public-sector vaccine design, with handover to the private sector for trials and manufacturing (16)
3. Predominantly public-sector development (9)
4. Coordination by a nonprofit entity (1)

This classification has several limitations. First, it covers only vaccines that were eventually licensed, leaving out the presumably large number of vaccine projects that failed at some stage. Though including these projects might have allowed us to compare the success rates of the different R&D models, the very limited data on failed vaccines would not allow this type of analysis. Second, the time required for each phase of development was not considered (except anecdotally in the case studies) because of the lack of comprehensive data and the difficulty of comparing across vaccines. Third, assigning primary responsibility for each stage of development inevitably involved some subjective choices, since vaccine R&D has often involved quite complex collaboration among multiple organizations.

The classification focuses on the site of vaccine development and on the division of labor between the public and private sectors. It thus omits many other potentially important aspects of development, including sources of funding, the nature of cooperation between sectors, and the oversight or integration of the development process as a whole. Perhaps most importantly, our taxonomy does not address the organization of the R&D effort within the institutions that carried out each stage of development. These details are difficult to obtain in most cases, but they are more fully explored in the case studies that follow.

² The term “innovative vaccines” includes first vaccines for diseases with no previous vaccine available at the time of licensure, plus second-generation vaccines using a distinct strategy for vaccine design. For instance, both pneumococcal polysaccharide and pneumococcal conjugate vaccines are included. Vaccines before 1945 were excluded because data on early examples are very limited and because the very different regulatory and commercial settings in which these early vaccines were developed mean that they may not necessarily provide useful analogues to the present.

³ In some cases where a stage occurred in more than one sector, the vaccines were classified in terms of the lead participant for that stage—typically the one that was overseeing the effort (and often the funder).

2.3 Models and case studies

Predominantly private sector development: Hepatitis B

Merck's Heptavax-B vaccine against the hepatitis B virus (HBV), licensed in 1981, was largely developed in-house at Merck under the direction of Maurice Hilleman, head of the company's virus and cell biology research. The disease's serious public health impact and rising incidence made it a commercially attractive target for a preventive vaccine (Galambos and Sewell 1995).

In 1965, academic researcher Baruch S. Blumberg identified a surface antigen of HBV that appeared in the blood of all human carriers; the discovery led to the development of a relatively simple blood test for the disease. In addition, Blumberg observed the development of antibodies to this antigen (Hilleman 1999). New York University physician Saul Krugman, who had been studying hepatitis in human subjects throughout the 1960s with Army sponsorship, had injected subjects with a solution of boiled HBV carrier blood and found that the mixture could stimulate specific antibodies to HBV. He challenged these subjects with the virus and found that they were protected.

The Merck team embarked on HBV vaccine research in 1968. HBV could not be grown in cell culture, so the researchers had to depart from the strategy they had previously used to develop vaccines for polio, measles, mumps, and rubella. The work of Blumberg and Krugman convinced Hilleman that the surface antigen HBsAg could be the basis for an effective vaccine and that carrier plasma contained enough antigen to make a vaccine (Galambos and Sewell 1995). Thus the Merck laboratory set about developing a process to purify and inactivate the antigen from plasma (Hilleman 1999). Previous work at NIAID provided critical information on centrifugation procedures; NIAID researchers also conducted some initial primate studies, results of which were shared with Merck researchers at a number of open scientific meetings. Following these and promising studies in chimpanzees, the first human trials were carried out on a group of senior-level Merck employees (on the rationale that they would have the lowest chance of natural exposure) in 1975 (Hilleman 2000; National Vaccine Advisory Committee 1999).

As the research team worked out a dosing regimen, plans were laid for a more extensive clinical trial at the New York Blood Center. This two-year Merck-funded trial, which started in 1978, showed virtually perfect protection against HBV. A study organized by the NIAID (with help from the hepatitis unit of the Centers for Disease Control and Prevention [CDC]) gave a similar result, and the vaccine was licensed in November 1981 (Galambos and Sewell 1995).

Following licensure, Hilleman's team continued to refine the manufacturing process. From start to finish, the vaccine took 65 weeks to manufacture and required large amounts of HBV carrier blood. By mid-1982, Merck had tripled antigen recovery and managed to supply enough vaccine for all recommended high-risk groups in the U.S. (Galambos and Sewell 1995).

Still, at more than US\$100 total for the three doses, Heptavax-B was unusually costly, and it was unlikely that there would be enough carrier plasma available to accomplish the more

ambitious public health goal of vaccinating the entire U.S. population. In addition, the emergent AIDS pandemic cast doubt on the safety of all plasma-derived products. In response to these issues, Merck ramped up its work on using recombinant DNA techniques to express the HBsAg antigen. In this case, rather than developing the vaccine in-house, Merck collaborated with the universities of California and Washington, using recombinant technology from the small European company BioGen to develop an adequate expression platform. The vaccine resulting from this partnership, Recombivax-HB, was licensed in 1986 and was the world's first vaccine based on recombinant technology.

Although the foundation for the hepatitis vaccine was laid by academic research, and NIAID played a role in clinical testing and made contributions to vaccine design, Merck was primarily responsible for practical development of the candidate, clinical trials, manufacturing, and licensure. This vaccine thus serves as an example of vaccine development in the private sector.

Handover to the private sector for trials and manufacturing (1): Lyme disease

The first vaccine against Lyme disease was created largely in an academic setting and then licensed to the private sector, which organized and supported the later stages of development.

Scientists at Yale University discovered the tick-borne bacteria that cause Lyme disease in 1975, and the university continued to conduct substantial research into the condition over the next decades. In 1985, NIAID initiated a large extramural grant program focused on Lyme disease (NIAID 2002), which resulted in several important discoveries, including studies in hamsters indicating that ready-made antibodies could confer immunity passively (Johnson et al. 1986). Two American companies had developed inactivated whole-cell vaccines for use in dogs in the late 1980s, indicating the possibility of a human vaccine (Thanassi and Schoen 2000).

The Yale team decided to focus on identifying recombinant proteins for use in a vaccine. The researchers cultured the bacteria and identified a key protein, Outer Surface Protein A (OspA), that was virtually identical in every strain of Lyme bacteria. After developing a mouse model for the disease, the team reported that mice could be protected by immunization with recombinant OspA expressed in *E. coli*.

The success of the mouse model convinced the pharmaceutical company SmithKline Beecham (SKB) to license the vaccine candidate from Yale. They recognized a market based on the considerable public concern over Lyme disease and the well-documented increase in its incidence and geographic reach over the 1980s and early 1990s (Thanassi and Schoen 2000). The company organized and sponsored a large Phase III trial in collaboration with the Yale research team. The SKB trial involved 31 trial sites around the New York metropolitan area and nearly 11,000 participants. The results showed the vaccine to be 78% effective against Lyme disease and 100% effective against asymptomatic infection after three doses. The United States Food and Drug Administration (FDA) licensed SKB's LYMERix in December 1998. It was the first vaccine against Lyme disease and the first to use recombinant technology to express bacterial proteins that then generated immunity.

SKB (later GlaxoSmithKline, or GSK) marketed LYMERix to high-risk groups over the next several years, but the vaccine did not sell as well as had been expected. Widely publicized safety concerns linking the vaccine to joint pain and other autoimmune side effects almost certainly contributed to these disappointing sales, although no connection between the vaccine and these adverse effects was ever definitively established. In February 2002, GSK pulled LYMERix from the market, citing inadequate sales (NIAID 2002).

It is worth noting that Pasteur Mérieux Connaught also developed a Lyme disease vaccine based on recombinant OspA. Although this candidate performed well in Phase III trials, it was never licensed, probably because the market was not seen as sufficiently attractive. Since the Pasteur vaccine was apparently developed entirely in-house, this example illustrates the potential shortcomings of basing the taxonomy only on licensed vaccines.

Handover to the private sector for trials and manufacturing (2): HPV

As with the Lyme disease vaccine, much of the design work that led to HPV vaccines occurred in academic settings. Given the large investments needed to bring a candidate through to production and the high risk of the project, university groups actively sought industry's involvement in the late design and clinical stages. Merck's vaccine, Gardasil, was approved in June 2006, making it the first to market. Its development was paralleled by that of GSK's Cervarix vaccine, which is expected to receive licensure in 2007.

The prospects for an HPV vaccine were unclear at the outset. Virtually all previous vaccines had been directed at systemic disease, in which the pathogen passes through the bloodstream where it is particularly vulnerable to antibody responses, whereas HPV causes a local infection of the cervix. In addition, the familiar strategies of using attenuated or killed virus were not feasible for HPV because of concern about oncogenes carried by the cancer-causing strains. A subunit vaccine seemed to be the only possibility, and no subunit vaccine had ever been tested against local infection (Lowy and Schiller 2006).

As a result, early progress toward a vaccine resulted from fortuitous discoveries at academic laboratories that had not initially set out to design a vaccine. Researchers at the National Cancer Institute (NCI), the University of Rochester, Georgetown University, and the University of Queensland in Australia independently found that recombinantly expressed copies of L1, one of the proteins that make up HPV's viral capsid, would automatically assemble into a particle that mimicked the structure of the full virus. Researchers then realized that these VLPs could potentially elicit protective antibodies to the virus (Inglis et al. 2006).

The timing of the discovery and design of VLPs among these institutions is unclear, and a lengthy and complex patent dispute was not resolved until more than a decade after the original applications. Although the Queensland group reported VLPs first, the Georgetown group was eventually awarded the dominant patent for demonstrating that self-assembled L1 was recognized by a specific class of neutralizing antibodies (C. McNeil 2006). While patent rights were still in dispute, the U.S. Patent Office allowed Merck, GSK, and MedImmune (the companies that ultimately took on HPV vaccine projects using VLP technology) uninterrupted access to the relevant inventions so that their research could move forward. Eventually the companies signed royalty agreements with all four institutions (Inglis et al. 2006; D.G. McNeil 2006).

In Australia, the biotech company CSL, Ltd., licensed the VLP technology from the University of Queensland and sponsored their work for several years, with ambitions to develop a marketable vaccine. They eventually licensed their technology to Merck based on the perceived need for very large resource inputs. MedImmune, on the other hand, took on the initial stages of preparing for clinical trials itself, partnering with GSK after early-stage trials (Inglis et al. 2006). With no animal model for HPV, both companies sought to initiate human trials as quickly as possible.

Although the university groups had developed the key concepts that led to the HPV vaccine, some aspects of vaccine design, notably the expression system, the adjuvant, and the vaccination strategy, became the responsibility of the companies (Lowy and Schiller 2006). Substantial effort was thus required to develop reliable, consistent production processes before initiating trials. Both Merck and GSK eventually conducted Phase IIb “test-of-principle” trials of their candidates, with HPV infection as an endpoint, before moving on to Phase III trials in more than 60,000 participants worldwide, which examined the vaccines’ efficacy in preventing cervical dysplasia. Both vaccines were shown to be highly efficacious at preventing the strains of HPV to which they are targeted, and the total value of the HPV vaccine market has been estimated at US\$4 to 7 billion per year by 2010 (GSK 2005).

Predominantly public sector development: Influenza

The first whole killed virus vaccine, against influenza, was developed almost entirely within the public sector by the U.S. Army during World War II. The influenza virus had been isolated at the National Institute for Medical Research in London. In the early 1940s, an academic researcher in Australia developed a method for growing the influenza virus in embryonated chicken eggs, putting vaccine development and production within reach.

The U.S. military had a strong interest in developing a vaccine against influenza after the massive loss of American soldiers to the disease in the 1918-19 pandemic; some estimate that up to 80% of U.S. World War I casualties were caused by influenza (Department of Defense 1998). In 1941, the Surgeon General’s Office set up the Board for Investigation and Control of Influenza and other Epidemic Diseases in the U.S. Army in 1941, which later became the Armed Forces Epidemiology Board (AFEB). This Board set up a Commission on Influenza to contract civilian scientists to work on influenza.

The Commission’s director, Thomas Francis, led a laboratory at the University of Michigan working to design a vaccine candidate using this cultured virus, which they grew in eggs and then inactivated with a formaldehyde solution. Meanwhile, the Commission set up contracts with several academic bodies for work to improve virus yields, titration accuracy, and purification procedures (Hoyt 2006; NIAID 2002).

Once the vaccine had been refined by Francis’s team, the Commission issued contracts to a number of American pharmaceutical companies to produce sample lots; Francis then tested the lots for purity and consistency in his laboratory and provided feedback and advice (Hoyt 2006). Meanwhile, the Surgeon General’s Office authorized a large-scale trial of the vaccine within training units of the Army, and the AFEB immunized 12,500 Army troops with Francis’s vaccine in October and November 1943. Testing in troops considerably

simplified the clinical trial process, because troops acted as a stable population with high compliance, and uniform observation and follow-up were relatively straightforward and simple for the researchers (Hoyt 2006).

The trial indicated that the vaccine was 70 to 90% effective in preventing influenza type A, and licenses were very rapidly granted to the companies with which Francis had been collaborating for manufacturing. These companies were able to expand to civilian markets by early 1946 (NIAID 2002).

The military continued to serve an important role in improving influenza vaccines after the vaccines showed disappointingly little effect during the flu season of 1947. Researchers at the Walter Reed Army Institute of Research (WRAIR) confirmed that circulating influenza viruses change over time, and they developed tests to quantify differences among viruses from different years. This led directly to the development of reliable procedures for producing effective killed-virus immunizations against influenza year by year (Hilleman 1999).

Although the U.S. Army funded and directed all stages of the effort to develop an influenza vaccine, it carried out only the clinical trials. Applied research and vaccine design were contracted to academic labs, while vaccine production was first contracted and then licensed to private firms.

Coordination by a nonprofit entity: Polio

The first polio vaccine provides an example of vaccine development coordinated by a nonprofit actor, the National Foundation for Infantile Paralysis (NFIP, also known as the March of Dimes). To date it is the only licensed vaccine developed under this model, although the influenza case also featured a dominant entity that coordinated work carried out by others.

In the 1930s, as the number of poliomyelitis cases steadily rose in the U.S., little was known about the virus that caused the disease, and it could not be grown in the laboratory. Working with virus extracted from infected monkeys, researchers tested crude attenuated vaccines on 10,000 children, resulting in six deaths and widespread negative publicity (Baker 2000).

The NFIP, a private charity started by President Franklin Delano Roosevelt in 1938, was a key agitator for polio vaccine development throughout the late 1930s and 1940s. Its funds supported a wide variety of polio-related research (Baker and Katz 2004). In the late 1940s, the Foundation decided to move away from funding open-ended research and to focus on work that would lead directly to a vaccine (Cohen 2001). This move was prompted by a critical 1949 breakthrough, when a team led by John Enders at the Children's Hospital of Boston propagated the virus in non-nervous tissue, giving researchers a straightforward means of culturing the virus for use in vaccine development (Baker 2000; Blume 2005).

Jonas Salk, a researcher who had worked at Thomas Francis's laboratory developing the killed influenza vaccine, established a laboratory at the University of Pittsburgh in 1947 to work on identifying different types of poliovirus under an NFIP grant (Pearce 2004). Having identified three types by the end of 1948, Salk set out to develop a killed virus

vaccine. His team developed a procedure for growing the virus in monkey renal cell cultures and inactivating it with formaldehyde, and successful results from animal studies encouraged them to go forward into human tests.

The first human trials of Salk's vaccine, aimed at assessing antibody responses, were conducted at the D.T. Watson Home for Crippled Children on children who had previously suffered from polio. The study was kept secret, with the exception of Salk's laboratory staff, key D.T. Watson staff, and a few senior individuals at NFIP, which provided funding. The next test was conducted on institutionalized children at the Polk State School who had no history of polio; it would likely have been highly controversial had it been publicized (Baker and Katz 2004; Cohen 2001). These trials indicated that the vaccine could be effective, and Salk and NFIP officials set out to initiate a very large field trial as quickly as possible. Despite considerable criticism from senior virologists (including Enders and Alfred Sabin), Salk and NFIP director Basil O'Connor were so convinced that the vaccine would succeed that they at first refused to allow for placebo controls in the field trial (Baker 2000). After vocal concerns from several state officials who were wary of the trial's NFIP sponsorship, O'Connor appointed Thomas Francis to conduct an independent evaluation of the trial's design (Baker 2000; IAVI 2006).

The trial was initiated in 1954 in 1.8 million children at 211 test sites across the country, using a combination of placebo controls and "observed controls" (Meldrum 1998). O'Connor contacted six companies early in the trial to begin to produce the vaccine so that warehoused stock would be available for launching an immunization campaign as soon as the trial results were in (Baker 2000). At a highly anticipated press conference in April 1955, Francis announced that the trial had shown the vaccine to be over 90% effective against virus types 2 and 3 and 60 to 70% effective against type 1 (Blume 2005). Within hours, the Secretary of the Department of Health, Education, and Welfare had licensed six companies to produce the vaccine (Baker 2000). Salk himself famously refused to patent or profit from his vaccine (Pearce 2004; Robbins 2003).

2.4 Discussion

This historical review reveals considerable diversity in the organization of vaccine R&D since 1945. When the entire period is considered, no particular model dominates (see Table 2). Among the vaccines that we considered, six were developed primarily by private industry (model 1), while nine were taken to at least the production stage by universities or the public sector (model 3). In a further 16 cases, the candidate vaccines were developed in academic or public labs and then handed to the private sector for large-scale trials and manufacture (model 2). (We did not identify examples in which a candidate was transferred from the private to the public or nonprofit sector.⁴ Moreover, no model (or sector) is more strongly associated with innovation, since the eight vaccines that were the first examples of a new type are also well distributed across the three models (see Table 2).⁵

⁴ Several drugs have followed this path recently, as PDPs or other nonprofit entities resume development of promising candidates abandoned by the private sector.

⁵ In extracting lessons for HIV vaccines, one would perhaps prefer to focus on the "hardest" vaccines, those whose development required overcoming the greatest scientific or technological hurdles. But there is no straightforward way to objectively rank difficulty.

Our fourth model—direction by a nonprofit entity—applies only to the Salk polio vaccine. But this case highlights an important nuance in analyzing the organization of R&D: the distinction between carrying out the work and managing the process. Although the NFIP did not develop candidates or conduct trials itself, it managed the entire process of vaccine development, overseeing university and private sector partners. Similarly, the U.S. Army directed the development of the influenza vaccine, although many steps in the process were contracted to academic labs or pharmaceutical firms. This model is likely to become more common as firms specialize in particular stages of the product cycle and as PDPs and other integrating agents become more important. Thus overall management, including decisions on research priorities and choices among candidates, could be considered a separate task or role in vaccine development, distinct from the conventionally defined stages of the process. This role is central to the issues discussed in the next chapter.

Table 2. List of vaccines, by model

Note: Bold entries are first examples of different types (see Table 1, page 12)

Model	Vaccines
1. Predominantly private sector development	Cholera, inactivated (1952) Mumps, live (1967) Hepatitis B, plasma-derived (1981) Hepatitis B, recombinant (1986) Typhoid Vi polysaccharide (1992) Pneumo conjugate, 7-valent (2000)
2. Public-sector vaccine design, with handover to the private sector for trials and manufacturing	Measles, live (1963) Rubella (1967) Pneumo polysaccharide (1977) Typhoid, live oral (1981) Hib polysaccharide (1985) Hib conjugate (1988) DTaP (1991) Hepatitis A (1991) Cholera, live oral (1994) Varicella (1995) Lyme disease (1998) Rotavirus (1998) Influenza, live attenuated intranasal (2003) HPV (2006) Rotavirus, live oral pentavalent (2006) Zoster (2006)
3. Predominantly public-sector development	Influenza (1945) Polio, oral trivalent (1963) Mumps, inactivated (1948) Adenovirus (1957) Anthrax (1970) Meningococcal polysaccharide (1974-5) Adenovirus, live oral (1980) Meningococcal (types B and C) (1989) Japanese encephalitis B, killed (1992)
4. Coordination by a nonprofit entity	Inactivated polio (1955)

A simple enumeration of vaccines produced by various institutional models sheds little light on the relative *efficiency* of vaccine development in these settings. As discussed earlier, it would be useful to compare the success rates of the different models, that is, the fraction of adequately funded initiatives that led to a useful vaccine or the fraction of promising leads that were taken all the way to a licensed product. But success rates of this kind would be extremely difficult to define or measure, because there is much less information on failed vaccine development projects than successful ones and because it would be hard to define an “adequately funded initiative” or a “promising lead.” Moreover, it would be risky to draw conclusions from a direct comparison of success rates for the different models, since the models adopted for particular challenges are almost certainly influenced by the nature of the challenge; that is, industry may shy away from “harder” vaccines, leaving the public sector with a lower rate of success. Thus we cannot say whether a particular R&D model has in the past been more or less likely to produce a vaccine. Similarly, we have not compared the speed or cost of vaccine R&D in the various models (and thus in the public or private sector), although in theory this might be possible, at least for the later phases of vaccine development.⁶

The lack of information on paths not taken or candidates abandoned before licensure also makes it difficult to analyze the relative performance of different types of organizations in managing the overall process of vaccine development. It has been asserted that portfolio management is a particular strength of big pharma, attributable to long experience and the discipline of the market.⁷ While these arguments are plausible, they also suggest that public or nonprofit institutions could strengthen these capacities by hiring managers with private sector experience and by creating internal incentives that mimic those that prevail within successful firms.

“[Nonprofits are] unable to stop a project – in industry you have to be able to make these decisions. This is the disciplining power of money, which a lot of other incentives don’t have.”

Looking at our data by development stage, we find that basic research has in most cases been conducted at universities or research institutes, often with public funding. Industry does conduct basic research and could presumably do more. But basic research is generally considered a public good—with benefits far greater than can be captured by the researcher—and the role of governments in supporting it is broadly accepted.

“The government functions less efficiently than corporations at achieving scale-up and commercialization. I think only the private sector knows how to deal with regulatory agencies, take a product to market, and do manufacturing and distribution.”

“Many skills are exclusively ‘owned’ by industry.”

⁶ In particular, it might be possible to compare the average time it has taken industry and the public/nonprofit sector to move a vaccine candidate through clinical trials. Such a comparison would only be possible for the relatively small number of vaccines developed after the current system of trial regulation was well established, and would be subject to some of the same objections as is the much more difficult analysis of “success rates.”

⁷ We note that the perhaps the most criticized decision in the history of HIV vaccines, to undertake Phase III trials of VaxGen’s gp120 protein subunit candidate, was made in the private sector, although not by an established vaccine firm.

At the other end of the pipeline, almost all the vaccines that we list were at least initially manufactured by industry. The public sector is certainly capable of producing vaccines: several European countries made vaccines until relatively recently, and the states of Massachusetts and Michigan once had production facilities. The Soviet bloc, of course, made its own vaccines in the public sector, and a number of countries in the developing world, including China, Cuba, and Brazil, do so today, accounting for a large proportion of vaccines used globally. But in the U.S., and increasingly in Europe, vaccine production has been largely ceded to the private pharmaceutical industry (Blume 2005). Since vaccine development has typically begun with research in the public sector and ended with manufacture by industry, the three common models that we have defined are distinguished by the sectors responsible for vaccine design, development, and large-scale clinical trials.

Changes in the vaccine industry in recent decades

So far we have considered vaccine history since 1945 as a whole. As our review showed, a number of institutional models of vaccine development flourished in this period, and both the public and private sectors repeatedly demonstrated the capacity to develop vaccine candidates and to bring them through clinical trials. Dividing the record into earlier and later periods, however, reveals that patterns of vaccine R&D have become less diverse in recent decades. In particular, large-scale clinical trials have become the nearly exclusive province of industry. Of the 20 vaccines on our list that were licensed since 1980, 18 were carried through trials at least partially by industry. The only exception was the meningococcus B and C vaccine, developed by a public-sector institution in Cuba, and the Japanese encephalitis B vaccine developed in Japan on the basis of work done earlier by the U.S. Army. Applied research and candidate development continue to take place primarily but not exclusively in the public sector, with academia in particular making substantially more contributions than during the period before 1980; we see no obvious change in industry's contribution to these stages.

The withdrawal of the public sector from later stages of vaccine development is explained in part by the diminishing role of the U.S. military (represented by WRAIR), although a similar trend can be seen outside the U.S. as well. Many factors probably contributed to this shift, including competition with the private sector for funding and researchers and (in the U.S.) with the NIH, and perhaps also a political climate unfavorable to public-sector approaches to social problems. But it seems likely that the dramatic decline in the burden of infectious disease in the developed world (at least until the advent of AIDS) played an important role by reducing public pressure for new vaccines.⁸

“The Army used to play an extremely important role and attracted high-quality people. But its potential has been taken away by a loss of funding, and competition with the NIH has created redundancies and basically demoralized the Army researchers.”

By shifting public attention from the benefits of vaccines to their risks, declining fear of infectious disease has probably contributed to another important trend in the vaccine industry: higher development costs associated with more stringent regulatory oversight. We

⁸ Wyeth-Lederle's withdrawal of its rotavirus vaccine RotaShield soon after it was licensed in 1999, after it was associated with a small number of cases of intussusception in infants, is a particularly dramatic example of this trend.

note in particular the introduction of rules of good manufacturing practice (GMP) in 1980, which have raised the cost of a manufacturing plant for vaccines to as high as US\$200 million (Douglas 2003). Moreover, candidate vaccines now tested in humans must often be produced in the same way and to the same standard as marketed products (Baylor and Midthun 2003). Standards for licensure have arguably become more stringent as well; it is likely that some vaccines licensed in the past would not now be approved. Meanwhile, ethical standards for trials have also been refined and more consistently implemented in recent decades. These changes, put in place to protect trial participants and patients, increase the cost and complexity of R&D and mean that companies face huge financial setbacks if products fail. This risk, in turn, means that in general products must promise very high revenues and high probabilities of success for firms to find them worth developing. Moreover, it has become difficult for all but the largest, most experienced firms to manage the cost, risk, and regulatory complexity of vaccine development.

“Once you could initiate clinical research with materials that weren’t perfectly pristine ... but now, clinical trials for safety have become so vast that most candidates cannot even get to this stage.”

“Now there are huge costs just to get to Phase I. Companies won’t take anything into trials until a GMP process is already done.”

“Maybe a lower-efficacy vaccine would be useful, but you can’t give the FDA 30 or 40%. Advanced countries are very stuffy and risk-averse.”

Regulatory and scientific risk, along with concerns about litigation—despite a no-fault award system for vaccines in the U.S.—have made vaccines less attractive to industry.⁹ Slow demand is also a factor: vaccines make up less than 2% of the global pharmaceutical market and, at least until recently, sales were growing by just 1% per year (Center for Global Development Advance Market Commitment Working Group 2005; IOM 2004).¹⁰ Most of the burden of infectious disease—including diseases for which no vaccine yet exists—is now borne by developing countries with little ability to pay for even life-saving new products, particularly because new, more complicated vaccines come at a high price. As a result, in the previous three decades the number of firms supplying vaccines to the U.S. market has dropped from more than 30 to five, with a similar decline occurring in Europe (Rappuoli et al. 2002). Although some of this trend reflects a broader consolidation in big pharma, there is little doubt that the industry as a whole has shifted investment away from vaccines. There is reason to hope, however, that vaccines are becoming attractive again to industry: boosted by expected blockbuster sales of new vaccines like HPV, the market is projected to grow at double-digit rates in coming years (Sheridan 2005).

An important consequence of these underlying trends has been to leave the skills and experience necessary for several essential steps in vaccine R&D—notably development of manufacturing processes and conduct of trials capable of supporting licensure—almost exclusively in the hands of a small number of large firms. As a result, most vaccines have followed a similar path from basic science to market in recent years. Promising approaches or vaccine candidates developed in universities or public labs have been passed on to a small set of big firms, which then carry them through large-scale clinical trials, manufacturing, and licensure.

⁹ One study found the market entrance probability of a vaccine candidate at the preclinical stage to be just over half that for all pharmaceutical products (Struck 1996).

¹⁰ This excludes sales related to the global polio eradication campaign.

Box 2. The changing role of intellectual property

The increasing cost and complexity of pharmaceutical R&D in the past few decades has been accompanied by a trend toward more comprehensive intellectual property (IP) protection. Patents have increasingly been granted to technologies and platforms as well as to commercially marketed products. This trend, along with a 1984 U.S. law allowing universities to patent discoveries arising from publicly funded research, has led universities to focus more on building patent portfolios and encouraged individual researchers to create spin-off biotech companies (Mahoney et al. 2003).

Some critics are skeptical that the ability to patent early-stage research advances is useful, arguing that it causes publicly supported institutions to focus too much on potential profit and neglect areas with less obvious payoff. Meanwhile, some researchers have suggested that the IP landscape is so complex, with webs of IP protection extending over virtually all technologies and platforms involved in all R&D stages, that innovation may be stifled. The HPV vaccine example, however, suggests that complex and contentious IP situations can be managed to allow product development to move forward.

The creation of the World Trade Organization, and in particular the Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement, has led to greater enforcement of IP provisions for pharmaceuticals worldwide. Although these changes will probably have their most immediate impact on generic production of existing drugs and vaccines, they can be expected to affect pharmaceutical R&D as well. While the increased protection could discourage research, greater certainty of patent protection might make vaccines for developing-country markets more attractive.

There has also been concern that the increased strength of global IP protection could block access in poor countries to new vaccines once they are developed (Commission on Intellectual Property Rights, Innovation and Public Health 2006). Although this is a very real concern, IP arrangements that ensure access for the developing world have been developed since the mid-1990s. IAVI's licensing agreements with private sector partners, which protect companies' IP rights in the developed world but require affordable access for poor countries, are just one example.

This simple picture of early-stage development in the public sector followed by later stages in big pharma is complicated somewhat by the public sector's renewed capacity for carrying out large trials, at least in the case of HIV vaccines (see next section), and by the growing role of biotech. The public sector is preparing to carry out large efficacy trials of HIV vaccines, although it has not yet demonstrated that it can conduct licensure trials in today's demanding regulatory context. Moreover, while biotechnology companies, often working in close collaboration with academic labs, now do much of the early-stage research that lies behind products marketed by large pharmaceutical companies, relatively few—only about 40 of the thousands of companies worldwide—work on vaccines (Sheridan 2005). Several recently licensed vaccines passed through a smaller firm before being picked up by an experienced vaccine manufacturer, and it is commonly supposed that big pharma will rely increasingly on the biotech industry for candidate vaccines. But overall, the contribution of biotech to the vaccines on our list is small. So far, it appears that fundamental innovation continues to take place primarily at universities (although the intimate relationship between university labs and biotech companies blurs the boundaries between the private and public sectors), and the primary contribution of biotech is likely to be to applied research and candidate design.

**Box 3. Product development public-private partnerships (PDPs):
a growing role in vaccine R&D**

In the past ten years, a notable share of public and philanthropic support for R&D on neglected global diseases has gone to PDPs. These institutions unite public-sector commitment to public goods with private sector expertise and methods to promote R&D through systematic candidate portfolios. PDPs also advocate for new funding and commitment to R&D for diseases in the developing world.

PDPs can serve as a major stimulus to R&D throughout the process, combining low capital costs and a commitment to global public goods with an industry-like R&D model, including strong incentive to bring products all the way through to market. These efforts are already showing tangible results: by 2005, one analysis found that more than 60 projects for new therapeutic drugs for neglected diseases were under way, with over two-thirds undertaken by PDPs in partnership with the private sector. This is in stark contrast to the period before the advent of PDPs: between 1975 and 1997, just 13 new drugs were developed specifically for neglected diseases (Moran et al. 2005).

In addition, by pioneering new ways of working and raising the profile of diseases of the developing world, the PDPs are helping to drive change in both the public and private sectors. Governments are contributing more funds for R&D for neglected diseases, and industry is also becoming more active. Over the past five years, four of the 12 largest multinational pharmaceutical companies have established infectious disease divisions.

IAVI, launched in 1996, has been at the forefront of the PDP movement and is the only PDP dedicated to finding an HIV vaccine. In its first ten years, IAVI has developed six new vaccine products, established major new clinical trial capacity in Africa and Asia, and mobilized nearly half a billion dollars in new funding. Through this work, IAVI has served as a model for numerous other PDPs leading efforts in other fields to find solutions to the world's most pressing health challenges.

This overview of public and private sector contributions obscures a striking feature of the history of vaccine development, especially during the middle decades of the last century: the dominant roles of WRAIR and Merck. For several decades these very different institutions remained centers of excellence in vaccine development and between them accounted for a large share of new vaccines. Although its goals were not completely aligned with those of general public health, the Army's focus on rapid product development, as well as its access to large pools of potential trial subjects, helped WRAIR become an important center of vaccine development and clinical testing. Of the 14 vaccines in which the public sector had a role in conducting trials, eight involved the Army. For its part, Merck contributed to 10 of the 20 vaccines in which the private sector had a role in the applied research/candidate design phase. The cases of Merck and the Army illustrate the importance of specific organizations, and perhaps special leadership, in creating the conditions for sustained productivity.

"The Army played a very important role, with its history and infrastructure for development and long experience with clinical trials."

"Vaccine design has almost never [been done by] corporations, except for Hilleman and Merck."

Since the unusual qualities of the Army and Merck cannot be attributed to all pharmaceutical firms or to all public sector research institutions, there are clearly risks in generalizing about the roles of the public and private sectors from 20th-century vaccine history.¹¹ Important insights could be gained by focusing on the qualities that successful organizations share regardless of the sector to which they belong, although this is outside the scope of this paper. For example, the Army apparently shared with successful firms a disciplined focus on an ultimate product, while the Merck Corporation nurtured innovation by giving Maurice Hilleman's laboratory unusual autonomy and the latitude to conduct early-stage research (Hilleman 1999).

In summary, our historical review demonstrates that vaccines have been developed in a variety of institutional settings. In recent years, however, the withdrawal of the public sector from the later stages of vaccine development, coupled with the increasing concentration of certain critical capacities in a handful of large firms, have established the notion of a "standard" model of vaccine development in which promising candidates are developed by university labs and biotech firms (often working together and often with public funding) and then licensed to big pharma for clinical trials, licensing, and manufacture. This model has worked well in the past and makes good use of the relative strengths of the various classes of organizations as they stand today. The public (or private nonprofit) sector could rebuild the capacity to carry promising vaccine candidates through later stages of development in cases where industry is unable or unwilling to do so, but increased regulatory complexity makes these steps more challenging than in the past.

Implications for HIV vaccine development

Our review shows that the most common path of vaccine development begins with research and candidate design in university or public sector labs and finishes with industry taking vaccines to market. This historical pattern suggests that an HIV vaccine will eventually be produced by or with the active involvement of the private sector. The large pharmaceutical companies now clearly have the greatest expertise in process development, clinical trials, large-scale manufacturing, and licensure, and it makes sense to take reasonable steps to make HIV vaccines as attractive to industry as possible and to prepare for a smooth and rapid hand-over. But the historical record also shows that other R&D models have also worked well, and recent developments have altered the landscape in important ways.

"Vaccine development has to be small scale and scattered widely, because you never know where the right idea is going to come from."

"You have to be willing to indulge creative ideas ... NIH should support goal-driven kinds a bit less and encourage a more NSF-style¹² research, with open-ended funding."

¹¹ The great diversity of organizations within each "sector" is particularly apparent on the public side, which includes universities (many of them, of course, not public but private nonprofit), federal and state funding agencies like NIH, and public research institutions in the U.S. and elsewhere, including the WRAIR. Although it might be useful to further disaggregate these very different entities, doing so would require disentangling the links among them and distinguishing roles in funding, supervision, and overall priority-setting, and therefore is not addressed within the scope of this paper.

¹² National Science Foundation

For early stages of development, the universities remain the primary site of innovation, and maintaining a climate that supports new ideas will be essential to overcoming the basic scientific challenges to an HIV vaccine (see Section III). The public sector's ability to contribute to the next steps in HIV vaccine development, applied research, and candidate design has been strengthened by the establishment of the NIH's VRC. In the private sector, the biotechnology industry is likely to become more important for these stages, and it is critical to involve it further in HIV vaccine research.

In contrast, the role of big pharma in candidate development is likely to shrink further (although Merck's active program constitutes an important counter-example). This distinction is important, because the measures required to encourage the involvement of the two classes of firms may be quite different. While changing the calculations of the largest pharmaceutical firms might require altering the market prospects for a vaccine, biotech firms can be engaged through various kinds of grants and contracts, and perhaps by other innovative non-market incentives. The highest priority for early stages of HIV vaccine development should be continued vigorous funding of university research, along with finding new ways to further engage the biotech industry. Although greater involvement of big pharma in early stages of HIV vaccine development is surely desirable, it is not essential.

In contrast to earlier stages of R&D, large clinical trials of recently licensed vaccines have been conducted almost exclusively by big pharma. But the private sector generally assumes this burden only when candidates show sufficient promise of reaching market. It is far from clear that current HIV vaccine candidates meet this standard, yet there are compelling reasons to conduct at least some large trials, in part because some vital information can be obtained only in this way. While the big firms can probably conduct trials more efficiently, the public sector has successfully shepherded vaccines through trials in the past and can do so again if necessary. Moreover, industry has less experience with large trials in developing countries, and in the specific case of HIV vaccines, the HIV Vaccine Trials Network (HVTN) and IAVI, together with partners in developing countries, have given the public sector substantial new trial capacity.¹³ This capacity should be strengthened further. For HIV vaccines, it may not be necessary for the public sector to conduct actual licensing trials, since a promising vaccine would likely be picked up by industry before then (see below). But building the capacity to carry a vaccine all the way to licensure would be a useful insurance policy and might facilitate the development of other vitally needed vaccines (for example, for TB or malaria) that may never be commercially viable.

"Pharma is just not really designed for early-stage research and early trials – they'll do it if they see a very high-revenue product at the end, but not for smaller projects."

There is little recent precedent for the manufacture of new vaccines by the public sector, and every effort should be made to engage industry in this stage of development when the time comes. This will probably not be difficult for a vaccine that does well in trials, however, since the potential market for an HIV vaccine is quite large, especially if it can be sold in wealthy countries. Industry's involvement is currently limited primarily by scientific uncertainty; if this were overcome, and substantial costs had already been borne by the public sector, an HIV vaccine would become quite attractive. Additional incentives may be

¹³ It is important to note that a significant portion of the public sector's vaccine trial capacity is now focused on HIV vaccines.

necessary to persuade firms to adapt and test a vaccine for the developing world. Moreover, if no partner is willing to take a vaccine forward on a purely commercial basis, it should be possible for a public or nonprofit entity developing a vaccine to contract out manufacture, possibly to a firm in the developing world. Thus the comparative advantage that industry now clearly enjoys in vaccine production should not be an obstacle to development of an HIV vaccine even if few firms show interest in early stages.

In summary then, while it makes sense to explore ways to bring the private sector's expertise and experience to HIV vaccine development wherever possible, the importance of the various segments of the industry differs considerably at different stages of vaccine development. The involvement of the big pharmaceutical companies will be most important at later stages, after a candidate vaccine has demonstrated promise in human trials. University labs remain the most likely sites of innovation, while the biotechnology industry may have much to contribute to applied research and candidate design. The public sector has carried out many large trials in the past and should continue to rebuild this capacity. It is worth remembering that many important vaccines were developed primarily in the public sector, even though they were intended for populations in wealthy countries. Since HIV vaccines—and vaccines for such diseases as malaria and tuberculosis, which are even less attractive to the private sector—are most needed in the developing world, it is vital to preserve and strengthen the public (or nonprofit) sector's capacity to develop and test vaccine candidates.

III. The organization of R&D efforts: Lessons from beyond vaccines

3.1 Defining the issues

In the last chapter we focused on where vaccine development takes place, that is, on the roles that the public, private, and nonprofit sectors have historically played in the various stages of vaccine R&D. In this chapter we turn to how R&D is organized, especially when many organizations are involved. How are decisions made and enforced in the face of scientific or technological uncertainty? How can cooperation and collaboration be fostered without stifling creativity and healthy competition? In order to shed light on these issues, we will look beyond vaccines to large-scale R&D initiatives in other areas.

Although vaccine development has almost always involved a degree of collaboration among organizations, in most cases the number of players has been relatively small, and one entity has generally had clear responsibility for each phase of development. In contrast, the effort to develop an HIV vaccine now involves a staggering number of organizations, including public and private sector funders, universities, non-governmental organizations (NGOs), large and small commercial firms, PDPs like IAVI, and consortia and coordinating bodies of various kinds. This institutional complexity reflects the scale and scientific difficulty of the effort, its global nature, the growing role of private foundations (especially the Gates Foundation), the appearance of PDPs, and changes in the pharmaceutical industry, particularly the development of the biotechnology sector. In part the apparent simplicity of past vaccine development efforts is an illusion: by focusing on the organizations that contributed to the development of the vaccines that were ultimately licensed and used, we ignore those that worked on other candidates or approaches. In the case of HIV vaccines, of course, it is not yet possible to say which approach will succeed, and thus which organizations will play a role in developing a successful candidate. Nonetheless, it seems clear that the HIV vaccine field is more complex than any previous vaccine effort.

The variety and number of entities working on HIV vaccines has led some to call for greater coordination and more centralized decision-making (Coordinating Committee of the Global HIV/AIDS Vaccine Enterprise 2005; IAVI 2006). These

commentators argue that competitive pressures, misaligned incentives, and lack of communication have resulted in duplication of effort and waste of critical resources, particularly scarce trial capacity; lack of collaboration and barriers to comparison of research and trial results; and insufficient attention to areas of work crucial for the field but unlikely to yield immediate rewards to individual researchers or organizations. Moreover, they argue that research efforts are insufficiently focused on tasks essential to vaccine development, in large part because the academic system and traditional research funding mechanisms reward open-ended exploration rather than the disciplined pursuit of useful results.

“At the development stages you need discipline or you’ll never develop anything. You need a hands-on management approach, because otherwise different groups will take shortcuts that will cause problems and delays down the line.”

“In science, there’s competition, lack of openness, and secrecy in publishing. People publish data at conferences and then leave it at that—they don’t care about following through on results.”

“Almost all the promising work I see at my own research center just comes to a halt, because there is not enough energy or capacity in the system to drive it through.”

The apparently unfocused nature of the search for an HIV vaccine—and the disappointing results so far—are sometimes contrasted with the focus and discipline, and the spectacular success, of major national commitments in the past, particularly the Manhattan Project, which developed the atom bomb during World War II, and the space program that put astronauts on the moon in 1969. In both cases, unambiguous national commitment to clearly defined goals, backed by enormous resources, led to success in a remarkably short time despite daunting technological obstacles. It is easy to understand why these inspiring examples are so often invoked by those frustrated by slow progress toward socially desirable goals, from developing renewable energy sources to ending poverty.

In this chapter, we explore whether these initiatives offer useful lessons for the HIV vaccine quest. More specifically, we will ask whether the HIV vaccine field should seek to mimic—to the extent possible in a very different institutional context—the highly centralized organization that characterized both the Manhattan Project and the space program, which we call “mission mode.”

There is no single, widely used definition of mission-mode R&D, though it is generally used to describe focused, publicly funded R&D efforts to achieve a well-defined goal (Nichols 1971). We define mission mode by four characteristics:

- 1) *Strong commitment and leadership, backed by sufficient resources:* In the cases we consider, the commitment was made by the U.S. government, which then provided the resources, but it is possible to imagine a private commitment on a similar scale. “Sufficient resources” is of course difficult to define, but the funds made available to the Manhattan Project and the space program were enormous, almost unlimited in practical terms.
- 2) *A clear and politically compelling goal.*
- 3) *Centralized leadership with control over resources:* For an initiative to qualify as a “mission,” the controlling body, whatever its nature, must have the authority to decide on approaches, allocate tasks, impose discipline and collaboration, and enforce adherence to an overall plan.
- 4) *Tight focus on the ultimate goal and the tasks necessary to achieve it:* In practice this has generally meant an emphasis on applied research and engineering rather than more basic research.

We restrict our discussion to initiatives that had to overcome substantial scientific or technological challenges. Ambitious projects that rely primarily on well-established knowledge and technology could meet the four criteria, and might share important characteristics with R&D missions. But the central importance of innovation to the initiatives we consider (and to the search for an HIV vaccine) is an essential consideration in weighing the merits of mission mode.

The first two characteristics are necessary but not sufficient for mission mode as we define it. Moreover, understanding why some social goals inspire greater political commitment and receive more resources than others is beyond the scope of this paper, which concerns the organization rather than the scale of the R&D effort. The goal of developing a safe and effective HIV vaccine seems clear (and important) enough to satisfy the second criterion. For

this reason we focus on the third and fourth features of mission mode, which distinguish it from other ways of organizing a large-scale R&D initiative.

Both the Manhattan Project and the moon effort appear to meet the four criteria for missions. The public sector's Human Genome Project also qualifies, although the presence of the competing private sector initiative adds some complexity. President Carter's initiative to develop alternatives to imported oil might also be eligible, although it could be argued that the objectives were too diffuse and that political commitment was not sustained. We will argue here that the so-called "War on Cancer" of the 1970s and 80s qualifies in important respects, at least in its initial stages, and thus can serve as a useful example of a mission that failed to achieve its original aims, although we recognize that this characterization can be contested.

What is the alternative to mission mode? We will contrast this highly centralized way of organizing a major R&D challenge to an approach characterized by dispersed decision-making, competition as well as collaboration, the absence of a rigidly defined and enforced division of responsibilities, and the pursuit of a more diffuse set of intermediate objectives. Probably few would dispute that the current search for an HIV vaccine, as well as the war on cancer as it is fought today, fits this description. Moreover, one might make the case that most of the technological successes of recent years, including the invention of the personal computer and the explosive growth of the internet, were characterized by highly dispersed decision-making and competition, although these advances were not responses to clearly defined national objectives.

This contrast between mission mode and a looser approach involves some of the same issues that are implicit in discussions of the "industrial" and "academic" models of R&D. The industrial model, like mission mode, is said to feature centralized decision-making, clear division of responsibility, and narrow focus. Academic research, in contrast, is thought to be driven by the relatively uncoordinated pursuit of a broader set of objectives by individual researchers, under the loose guidance of the NIH or other funding agencies. For our purposes, however, this description muddies the waters in three ways.

First, it confuses the way R&D efforts are managed within and across organizations. The managerial challenges and options facing the NIH, or the HIV vaccine field as a whole, are clearly very different from those facing Merck, or for that matter the Army. Second, it explicitly assigns one model to the private sector and the other to the public or academic sector, though the organization of R&D by WRAIR (or at Los Alamos during the war) surely resembles the "industrial model" in important respects. Even some large academic labs are highly organized along the lines of an "industrial model." Conversely, the pursuit of new technology by industries as a whole, composed of numerous competing firms, is highly decentralized and uncoordinated. Finally, the industrial/academic distinction contrasts modes of organization that are typically used at different stages of the R&D process and thus are not directly comparable. In fact, as illustrated by the case studies presented in the previous section, the development of many vaccines involves a transition from one R&D "model" to the other. Thus, while the idea of an industrial model may yield valuable insights into the

"Investigator-driven versus large-scale—I think this is an artificial duality of model. The HPV vaccine was developed by investigator-driven work and then commercialized by Merck and GSK. It didn't take a PDP to develop an HPV vaccine."

characteristics that help individual organizations succeed at certain R&D stages, it is not very useful for analyzing the organization of the HIV vaccine field as a whole.

With these definitions and general considerations in mind, we turn to brief descriptions of two examples of mission-mode R&D, the Manhattan Project and the War on Cancer. In the final part of this chapter, we will ask what lessons can be learned from these experiences for the organization of the quest for an HIV vaccine. Would the HIV vaccine field benefit, now or at a later stage, from the more centralized decision-making and tighter focus that define mission mode? If at some point a move toward mission mode would be likely to accelerate progress, how will we know when that moment has arrived?

3.2 Examples of centralized R&D initiatives

The Manhattan Project

The Manhattan Project refers to the effort from 1942 and 1946 to develop the first nuclear weapons, directed by the U.S. Army Corps of Engineers. The main theoretical basis for an atomic weapon had already been established when the Manhattan Project began, and four independent research groups were already investigating methods of uranium enrichment.

When Army engineer Leslie P. Groves took command of the military effort in mid-1942, he determined that decisions on bomb production had to be made by the end of the year, meaning that the four groups were under considerable pressure to prove their method the best before then. On November 12, 1942, the Military Policy Committee decided to shut down one of the four projects; the Committee called for projects on two other methods to proceed directly to full scale without a pilot plant stage and for work to continue on plutonium production (Gosling 1999).

On December 28, President Roosevelt initiated the official Manhattan Project by authorizing US\$500 million for plant construction. The intense secrecy with which the project proceeded helped Groves and other project leaders retain tight central control and facilitated rapid decision-making (Gosling 1999). That these decisions were made on the basis of very little data and without a pilot plant stage indicates Groves's emphasis on moving technology to production as fast as possible, even at the expense of traditional evaluation steps. This resulted in some serious unforeseen problems with the uranium plants but was considered essential for ensuring that sufficient uranium would be available in time to influence the course of the war.

In spring 1943, a centralized laboratory for all of the project's theoretical and experimental work opened at Los Alamos, NM, under the direction of J. Robert Oppenheimer, and a wide range of academic physicists and engineers were very rapidly recruited to work at the site. Groves insisted that scientists working on the project focus all their effort on making the weapon and drop lines of research not directly relevant to this end. Four divisions were established, under Oppenheimer's central operational control: theoretical physics, experimental physics, chemistry and metallurgy, and ordnance. The theoretical physics division worked to determine key properties of uranium and plutonium to ensure that the weapon would work correctly.

In July 1944, faced with problems at the uranium plants, Groves and Oppenheimer orchestrated a major reorganization of the Los Alamos laboratory, freezing further work on the uranium bomb and focusing virtually all the scientists' effort on developing a plutonium implosion bomb, the engineering of which was much more difficult. As a result, the uranium bomb was never tested before its use at Hiroshima. The implosion method had proven successful by the summer of 1945 (at the Trinity test) and was used in the attack on Nagasaki.

The Manhattan Project well illustrates the four characteristics of mission mode and can be considered the canonical example of this form of R&D organization. Two features of the project may lessen its value somewhat as a model for other R&D initiatives. First, the extreme urgency of the effort, imposed by the less desirable alternative of invading the Japanese mainland and the fear of a competing German nuclear project, distorted decision-making in ways that in other circumstances might even have reduced the chances of success. Second, the significant resources available to the project allowed it to pursue several very expensive alternative development paths simultaneously, thus mitigating the tradeoffs that a disciplined, centralized approach typically entails (if you don't have to choose, there's no gain from being able to make tough choices).

The War on Cancer

In 1970, health activist Mary Lasker, whose medical lobby conceived of the War on Cancer, arranged for a Senate resolution creating the National Panel of Consultants on the Conquest of Cancer. On the assumption that new techniques in cell biology and recent advances in treatment had opened up new avenues for improving care, the panel laid out a comprehensive vision of a publicly funded cancer response. Their plan contained three major components: administration with strong authority, a national plan for a systematic attack, and a large increase in resources. They focused largely on applied R&D over basic research and recommended centralized planning and program direction by the National Cancer Institute (NCI). In fact, the original draft of the Panel's report made explicit comparisons between their proposed program and NASA (though this language was eventually modified); NASA had many characteristics they wished to see in a cancer program, including independence and direct reporting to the President, clearly defined goals, a massive budget, and a systematic R&D approach (McGeary 2003).

There was considerable political momentum behind this idea. In his January 1971 State of the Union address, President Nixon called for an appropriation of US\$100 million to launch the War on Cancer, saying "the time has come in America when the same kind of concentrated effort that split the atom and took man to the moon should be turned toward conquering this dread disease" (NCI 2006).

The National Cancer Act was signed into law in December 1971. This law gave the director of the NCI much broader responsibilities and made the position a presidential appointment, with planning authority over all cancer-related activities within the NIH and many other government and NGOs. The Act also gave the NCI some authority over surveillance and clinical care as well as cancer research, incorporating into the NCI the responsibility to rapidly apply existing knowledge to patient care (United States P.L. 92-218, 1971).

The law resulted in an immediate and rapid increase in funding for cancer: NCI's budget rose from US\$233 million in 1971 to \$492 million in 1973 and reached nearly \$900 million in 1978. The program itself was initiated in a 1973 strategic plan, with the explicit goal of "reduc[ing] the incidence, morbidity, and mortality of cancer in humans" (Rettig 1977).

This broad conception of the National Cancer Program as organizer of a coordinated national approach quickly faded, however. NCI research expanded greatly in the first few years as funding increased, but the reach of the NCI director beyond his own institute did not long survive the original legislation, in part because of the demands of running the greatly expanded NCI itself. Some interagency committees were set up, but they hardly constituted a comprehensive mechanism for coordination and planning. Meanwhile, the strategic plan was barely used at all for actual day-to-day management (McGeary 2003; Rettig 1977).

Many of the more innovative substantive aspects of the National Cancer Program failed to grow at all, arguably because lack of basic knowledge left the program with little useful information on care, diagnosis, or treatment to disseminate to clinicians and stymied further progress. For instance, at the outset of the War on Cancer the fundamental biochemistry of cancer cells and the spread of tumors was largely unknown and the mechanisms of chemotherapy drugs remained unclear (President's Cancer Panel 1999). Little distinction was made between the majority of cancers and those about which enough was known to benefit from a planned program (such as Hodgkin's disease). The project was often criticized on these grounds, as well as for the perception that it was somehow betraying the NIH mission, which was seen as protecting basic research from being bound to specific goals.

In 1993, the House appropriations subcommittee noted that since 1971 more than US\$23 billion had been appropriated for cancer activities at NCI (McGeary 2003). Yet age-adjusted mortality due to cancer in 1994 was 6.0% higher than in 1970, reflecting the same steady increase that had been seen since the 1950s. Important declines in some cancers were attributed to reduced cigarette smoking and improved screening procedures, but new therapies were seen as having very little effect (Bailar and Gornik 1997). In general, the sheer complexity of the cancer problem and lack of knowledge about which areas would reward more research are seen as the major roadblocks to achieving the ambitious goals of the 1971 act.

3.3 Discussion

It is of course impossible to draw definitive conclusions about mission mode from the success or failure of two or even a small number of examples, given the myriad ways that each differs from the others and the inescapable historical contingencies. Moreover, missions can fail because the problem they set out to solve is insoluble, because they are poorly implemented or insufficiently funded, or because mission mode is not the appropriate approach to the problem in the first place. Our focus is on the third reason for failure, and in this section we will propose two criteria for deciding whether mission mode is appropriate for a particular R&D challenge, using the two case studies to illustrate our arguments. We then ask whether the search for HIV vaccines meets our proposed criteria.

We begin by asking why the War on Cancer failed. Two very different types of explanation have been given. According to some, it failed because it was never really implemented as a mission, despite the ritual invocation of the moon landing and the Manhattan Project by its backers. To start, its goals were too many and too diffuse. Not only did the initiative take on prevention as well as treatment, it also aimed to improve the use of existing tools at the same time as it sought new ones. This all-encompassing vision is clearly very different from the tightly defined goals of the successful missions and surely made it far more difficult to break the problem into pieces and assign responsibilities. Perhaps if the initiative had restricted itself to the search for a cure, it could have more closely resembled its models. Second, the War on Cancer was mostly fought in many small, independent labs rather than in a few large facilities, by academic researchers motivated by curiosity and publication, making centralized control much harder. And the NCI's ability to provide the strong central control required by mission mode was apparently compromised by excessive bureaucratic responsibilities and unclear or inadequate authority. Finally—and ironically (see below) — some have argued that it focused too much on basic rather than applied research, thereby violating the fourth criterion for mission mode.

An alternative explanation is that the War on Cancer failed because it tried to apply mission mode to a problem for which it was not suited. According to this line of argument, not enough was known about cancer at the time to define a clear way forward and thus to reap the benefits of a highly structured, disciplined approach. Unlike the challenge of building the bomb in 1940s or of putting a man on the moon, the problem of curing cancer could not be broken into a small number of essentially engineering challenges. This conclusion would imply that the research funded by the War on Cancer was actually too applied and that more basic research was needed to guide the choice of approaches and to suggest new, previously unsuspected approaches.¹⁴

Both explanations for the failure of the War on Cancer surely have elements of truth, but if it is true that the problem itself was not appropriate for mission mode, the effort would probably have failed even if it had been better implemented. The contrast between the state of knowledge at the time the War on Cancer was launched and the far better defined challenges facing the Manhattan Project prompts us to propose a general principle: mission mode is appropriate only when the path to success is relatively clear. There need not be consensus on a single approach; the Manhattan Project pursued several approaches to uranium enrichment simultaneously. But the set of viable approaches needs to be small and well defined.

Focus, discipline, and coordination are surely desirable things. What then is the danger of going to mission mode too soon? In essence, the dilemma is that concentrating on one or a small number of approaches inevitably means abandoning others, including new ones that might have arisen from exploratory work (which a more narrow focus might curtail). This is particularly true when research is still at an early, more basic stage. The kinds of exploration that will yield the most useful new insights cannot be predicted and often

¹⁴ There is of course no guarantee that this alternative would have succeeded either. We now, finally, understand a great deal about the biological processes that go awry in cancer, but it's still not clear how to translate this knowledge into treatments. Also, the basic research that gave us this understanding might not have been possible in the 1970s, when the techniques of modern molecular genetics were not yet in hand.

appear highly serendipitous in retrospect. Thus the chance of a breakthrough may be greatest when researchers are allowed to pursue many different paths, most of which will lead nowhere. (In fact, our current understanding of cancer processes comes in large part from basic research on yeast, fruit flies, and viruses.) Moreover, an open, unstructured environment is most conducive to new ideas and to avoiding groupthink. For these reasons, a highly decentralized system relying to a substantial degree on individual curiosity, for all its apparent inefficiency, is probably the best way to pursue new understanding and fundamental innovation.

This kind of argument is familiar not only from the world of academic research, but from the theory of capitalism. Market competition is thought to be more likely than central planning to produce desirable outcomes, including innovation, in part because no planner can have enough information or sufficiently reliable judgment to outperform the combined efforts of many independent decision-makers. The analogy is imprecise, of course, and only an analogy; our argument here is about the advantages of dispersed decision-making, not about the relative strengths of the public and private sectors.

We argue, therefore, that there is an unavoidable trade-off between the efficiency of mission mode and the greater innovative potential of a more dispersed, less structured organization of R&D, and that the choice between the two modes should depend in part on whether enough is known about the problem and its possible solutions that the way forward is clear. To put it differently, what matters is whether rapid progress in following up on existing ideas is more important than generating new ideas.

It's worth clarifying that what matters in deciding whether a particular challenge is appropriate for mission mode is not whether there's confidence that success is possible (although this may be necessary for obtaining funding and sustaining political commitment) but whether the way forward is sufficiently clear. For example, the U.S. launched the Manhattan Project with no certainty of success. The choice of a highly centralized structure for the initiative was nonetheless justified because the necessary tasks and plausible approaches could be clearly defined.

Our second criterion concerns the intrinsic scale of the activities necessary to reach the goal. Most of the critical tasks faced by the Manhattan Project were irreducibly large in scale, requiring enormous facilities. Similarly, the moon mission involved designing, building, and testing huge rockets. This kind of work must be done

"The organizational structure that will work for HIV vaccines is not predictable. Ideas 'out of left field' are going to be the most useful."

"Most breakthroughs in immunology have come from different groups coming together and feeling some mobility between disciplines."

by large, highly structured teams. Moreover, at most a few different approaches can be pursued at once. In contrast, much of cancer research is relatively small in scale, involving bench research, experiments on small animals, or relatively small clinical trials. This kind of work can be done in many places at once, and many approaches can be pursued at the same time. Thus if the necessary activities are intrinsically large in scale, one is obliged to adopt mission mode, whether or not the nature of the problem calls for it in other respects. Dispersed small-scale activities don't require highly structured management, and indeed probably make it difficult, as the War on Cancer demonstrated.

We argue, then, that the appropriateness of mission mode depends on two considerations: the nature of the remaining challenges (is the path forward clear?) and the nature of the necessary work (does it require large-scale facilities or processes?).

Implications for HIV vaccine development

With these general considerations in mind, we now ask whether greater centralization and focus of R&D—mission mode—would likely speed progress toward an HIV vaccine.

The first of our proposed criteria for adopting mission mode is clarity of the way forward. In our judgment, there is at present no consensus on this point for HIV vaccines. On one hand, there is broad agreement that refinement and testing of DNA and viral vector T-cell vaccines, of the kinds now in clinical trials, should continue. At the same time, there are strong arguments for renewed efforts to find a way to stimulate robust antibody responses and improved cellular immune responses to control infection. One promising approach involves systematic identification and characterization of naturally occurring broadly neutralizing antibodies, coupled to high-throughput screening for immunogens that can elicit them, with continued screening in parallel for immunogens to elicit cellular immune responses. Several new initiatives will focus on this kind of work, including the Collaboration for AIDS Vaccine Discovery (CAVD), CHAVI, and IAVI's Neutralizing Antibody Consortium (NAC) (see the Introduction for descriptions of these initiatives). IAVI is also considering a large-scale research effort, the AIDS Vaccine R&D Institute, to pursue these more systematic, larger-scale approaches.

These initiatives are important and promising, but success is far from certain. We believe that substantial resources must remain available for exploring other avenues, including ones that cannot yet be precisely defined, and that there is a real risk of narrowing the field's focus too much. Support for "industrial" screening efforts, consortia, and other large-scale initiatives should be balanced by support for small-scale, diverse research in other areas. In the face of uncertainty, pursuing many approaches at once may be the best policy over the long run.

Box 4. New technologies in vaccine R&D

The past few decades have seen a revolution in techniques for studying and manipulating cellular and biochemical processes, beginning with the elucidation of the structure of DNA and continuing with the development of recombinant DNA techniques and genome sequencing. These new techniques have created opportunities for entirely new vaccine designs. For instance, recombinant technology allows viral or bacterial proteins to be produced in vitro and has led to vaccines and vaccine candidates based on viral vectors, virus-like particles, and plasmid DNA. Moreover, new techniques have greatly increased our understanding of the immune system.

The power of these new techniques has also encouraged a shift in the basic strategy of drug and vaccine development, as the idea of rational design of interventions based on molecular knowledge of diseases and disease organisms has become more and more compelling. Although this approach has succeeded spectacularly in some areas, including the design of HIV drugs, some have argued that it has distorted the effort to find a vaccine, leading researchers to disdain traditional empirical approaches in favor of untested strategies (Cohen 2001).

In thinking about the right balance between efficiency and innovation, it is useful to distinguish between true mission mode—which implies a central authority with the power to impose a choice of research priorities—and essentially voluntary measures that enhance cooperation without posing a significant risk to independent initiative. Most of the measures advocated by the Global HIV Vaccine Enterprise, such as shared reagents, standards, and data analysis to ensure comparability, would fall in the latter class, as would measures to remove unnecessary obstacles to collaboration. These measures would undoubtedly be very useful for ensuring efficient comparisons of different approaches.

In contrast, creating a single body that had the authority to decide which vaccine candidates would be allowed to progress to the next stage of clinical trials or that could reallocate resources toward a limited number of applied or basic research priorities would be a step toward full mission mode. Although the integration of laboratories and the creation of teams focused on specific goals could make vital contributions, they should be seen as components of a diverse global effort.

Are the activities required to develop an HIV vaccine sufficiently large scale to satisfy the second criterion for mission mode? The answer depends on the stage of development. Basic research, candidate development, and early-stage clinical trials are not in general “big science,” although some proposed approaches to high-throughput immunogen screening require larger investments and greater centralization than traditional bench science. In contrast, traditional vaccine efficacy trials are by their nature large, highly structured undertakings involving thousands of subjects and costing tens of millions of dollars. Trial capacity is clearly limited and will remain so even with substantial efforts to support new sites in the developing world. The emergence of new prevention technologies, continuing controversies over trial ethics, and declining HIV incidence in many regions are likely to make trials even larger and reduce the number of viable sites further.

“In clinical trials, we need to ‘fail’ to see what does not work. There needs to be more coordination between the EU, NIH, and IAVI, each of which is separately building capacity in clinical trials overseas, for example. In any case this is a practical issue, since none of these alone is enough to show the results unambiguously. Trials need to be standardized, and we need comparative trials.”

Late-stage HIV vaccine trials thus do appear to meet the scale criterion for mission mode, and there is a compelling argument for adopting a more systematic mechanism for choosing which trials to conduct. The argument for more rational selection of candidates for large trials is reinforced by the fact that failed trials may erode public support. For this reason, trial capacity can be thought of as a commons shared by the HIV vaccine community, requiring joint management and regulation.

The need for centralized allocation of scarce trial capacity might be partially alleviated by the use of small screening test of concept (STOC) trials to provide fast, efficient interim assessments of candidate vaccines. These trials would measure whether candidates reduced viral load in participants who become infected, but would not attempt to determine if they prevented infection. Moreover, since these trials would not be intended to support licensure, they could aim for a less statistically robust result and could be much smaller and simpler than Phase III trials. In principle, several candidates could be pushed through STOC trials relatively quickly and their results compared. This approach could both ease pressure on

trial capacity and provide an agreed basis for deciding which candidates should move forward to larger trials.

At the same time, some measure of central control may still be required to ensure that sponsors are willing to subject their candidates to this type of head-to-head comparison. In addition, whatever the mechanism by which candidates enter Phase III, high-level coordination for efficacy trials is likely desirable. By standardizing protocols and outcome measures, greater coordination of trials would allow candidates to be compared more directly. Similarly, process development and manufacturing, which are closely linked to efficacy trials by regulatory considerations, are relatively large-scale activities.

We conclude, then, that the HIV vaccine field should adopt some of the features of mission mode in later stages of development, in particular by imposing

“You can’t get creativity from massive organizations. But you need a massive approach for some issues. So for AIDS, you need both.”

greater control over clinical trials. In contrast, this kind of organization is probably not appropriate for earlier stages of HIV vaccine R&D, though some relatively large-scale initiatives could be included in a diverse mix of approaches. Although progress toward certain intermediate objectives could be accelerated by more structure and central authority, the way forward is not clear enough to risk discouraging innovation and the pursuit of other, currently less popular approaches. Some more modest steps to ease collaboration, however, could speed progress with little risk to innovation.

IV. Conclusions

Progress toward an HIV vaccine will depend not only on resources and science, but on the organization and management of the R&D effort. Our review of the history of vaccine development and of large centrally managed initiatives like the Manhattan Project supports several conclusions.

- Some vaccines were developed primarily in the private sector and some in the public sector, and in other cases the public sector handed over primary responsibility to industry at an intermediate stage of development. Although over the entire period since 1945 no particular model has predominated, a standard model of vaccine development has emerged over the last few decades, in which promising candidates are developed by university labs and biotech firms and then licensed to large pharmaceutical companies for clinical trials, licensing, and manufacture. A few large firms now possess a near monopoly on the skills required for licensing trials and manufacturing process development. These steps in vaccine development have been made much more challenging by more stringent safety regulation.
- Although research and innovation occur primarily in universities, the biotechnology industry is increasingly involved in translating breakthroughs into candidate products. Engaging this segment of industry, which might respond to incentives that would be less attractive to big firms, should be a high priority, along with continued support for university research. Although industry has the most recent experience in large-scale vaccine testing, the public and nonprofit sectors retain (or have regained) the capacity to manage trials, especially in developing countries and especially for HIV vaccines. This capacity should be strengthened, as it may be needed for other vaccines as well. The final stages of HIV vaccine development (process development, manufacturing, and licensing) are best carried out by industry. It should not be difficult to interest firms in a candidate that has proven itself in trials, but if necessary the private sector could be engaged on a contractual basis.
- The Manhattan Project and the moon landing demonstrated the power of centralized management (mission mode), while the War on Cancer suggested that this model may not be appropriate for all R&D challenges. The efficiency of mission mode in accomplishing well-defined tasks must be balanced against the risk of suppressing innovation. The appropriateness of mission mode depends on the clarity of the way forward and on the intrinsic scale of the required activities.
- The case for mission mode in early HIV vaccine R&D is equivocal; the necessary activities are often rather small in scale and the way forward is much debated. There is a risk that too much centralization could encourage groupthink and stymie creativity. On the other hand, some of the most promising approaches to the field's critical challenges involve larger-scale techniques and greater coordination among laboratories. Thus, it makes sense to include some promising larger-scale initiatives—and aspects of mission mode—within a diverse portfolio of approaches. For later stages of HIV vaccine development, the case for greater coordination is strong, because advanced efficacy trials are unavoidably large undertakings, capacity is limited, and decisions made by one developer affect others.

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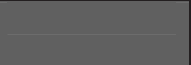
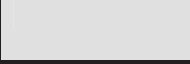
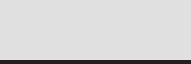
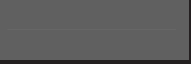






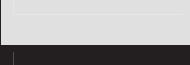
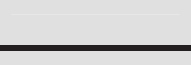
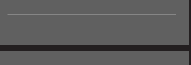


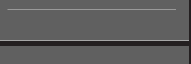






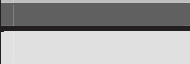

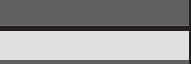



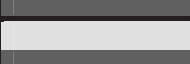
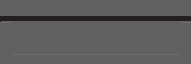
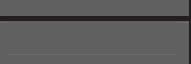
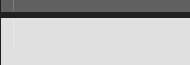
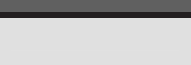


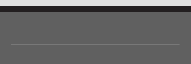





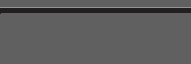
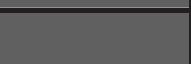

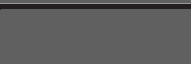
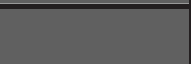



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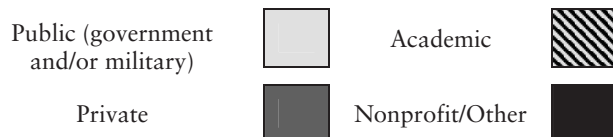
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Appendix I: Stages of R&D for innovative vaccines since 1945, by sector

Sector				
Public (government and/or military)		Academic		
Private		Nonprofit/Other		
Type of vaccine	Applied research and vaccine design	Development and trials	Manufacturing and licensure	Licensure date
Influenza				1945
Mumps, inactivated				1951
Cholera, inactivated				1952
Polio, inactivated				1955
Adenovirus				1957
Polio, oral trivalent				1963
Measles, live				1963
Mumps, live				1967
Rubella				1969
Anthrax				1970
Meningococcal A and C, polysaccharide				1975
Pneumococcal polysaccharide				1977
Adenovirus, live oral type 4 and 7				1980
Hepatitis B, plasma-derived				1981
Typhoid, live oral Ty21a				1989
Hib polysaccharide				1985
Hepatitis B, recombinant				1986



Type of vaccine	Applied research and vaccine design	Development and trials	Manufacturing and licensure	Licensure date
Hib conjugate	Public (government and/or military)	Private	Private	1988
Meningococcal B and C	Public (government and/or military)	Public (government and/or military)	Public (government and/or military)	1989
DTaP	Public (government and/or military)	Public (government and/or military)	Private	1991
Hepatitis A	Public (government and/or military)	Public (government and/or military)	Private	1991
Japanese Encephalitis B, killed	Public (government and/or military)	Public (government and/or military)	Public (government and/or military)	1992
Typhoid Vi polysaccharide, inactivated	Private	Private	Private	1992
Cholera, live oral	Academic	Private	Private	1994
Varicella, live	Academic	Private	Private	1995
Lyme disease	Academic	Private	Private	1998
Rotavirus	Public (government and/or military)	Private	Private	1998
Pneumo conjugate, 7-valent	Private	Private	Private	2000
Influenza, live attenuated intranasal	Public (government and/or military)	Public (government and/or military)	Private	2003
HPV	Academic	Private	Private	2006
Rotavirus, live oral pentavalent	Academic	Private	Private	2006
Zoster	Academic	Private	Private	2006

Source: Blume 2005; Galambos and Sewell 1995; Hilleman 1998, 1999, 2000; Hoyt 2006; Immunization Action Coalition 2003, 2006; Mitchell et al. 1993; National Immunization Program 2006; National Vaccine Advisory Committee 1999; NIAID 2002; Pérez et al. 1999; Plotkin 2005; Rader 2006

Appendix II: List of Interviewees

Name	Title/Affiliation	Location
Jorge Beloqui	Director Grupo de Incentivo à Vida	Brazil
Ben Cheng	Project Manager, Forum for Collaborative HIV Research Center for Health Services Policy and Research, George Washington Univ.	United States
Jon Cohen	Science writer <i>Science</i> magazine	United States
Michel de Wilde	Executive Vice President, Research and Development Aventis Pasteur	United States
Emilio Emini	Executive Vice President, Vaccine Research and Development Wyeth	United States
Jose Esparza	Senior Advisor, HIV Vaccines Bill & Melinda Gates Foundation	United States
Ian Frazer	University of Queensland Centre for Immunology and Cancer Research at the Princess Alexandra Hospital	Australia
Jaap Goudsmit	Chief Scientific Officer Crucell NV	Netherlands
Michel Greco	Former President, COO, and Deputy CEO Aventis Pasteur	France
Ian Gust	Professorial Fellow Department of Microbiology & Immunology, University of Melbourne	Australia
Carole Heilman	Director Division of Microbiology & Infectious Diseases, NIAID	United States
Peggy Johnston	Director, Vaccine and Prevention Research Program (VPRP) Division of AIDS, NIAID	United States
Pontiano Kaleebu	Principal Investigator Uganda Virus Research Institute	Uganda
Donald Light	Professor of Comparative Health Care University of Medicine and Dentistry of New Jersey	United States
Neal Nathanson	Associate Dean for Global Health Programs University of Pennsylvania School of Medicine	United States
Stanley Plotkin	Medical and Scientific Advisor Aventis Pasteur	France
Sai Prasad	Head of Business Development Bharat Biotech International	India
Rino Rappuoli	Global Head, Vaccines Research Novartis	Italy
Douglas Richman	Director, Center for AIDS Research VA Medical Center, San Diego	United States
Philip K. Russell	Professor Emeritus Johns Hopkins School of Public Health	United States
Pradeep Seth	President Seth Research Foundation	India
Jerald Sadoff	President and CEO Aeras Global TB Vaccine Foundation	United States
Edmund Tramont	Director Division of AIDS, NIAID	United States
Stephen Udem	Senior Vice President of Vaccine Development and Chief Scientific Officer International AIDS Vaccine Initiative	United States
Bruce Walker	Director Partners AIDS Research Center, Massachusetts General Hospital	United States
Mitchell Warren	Executive Director AIDS Vaccine Advocacy Coalition	United States

Appendix III: Interview guide and questionnaire

Goals of the interview

As you know from prior communication, I am performing a study for the International AIDS Vaccine Initiative (IAVI). The work will describe organizational and institutional features in vaccine research over time and will draw some inferences about how vaccine R&D efforts for cases such as HIV/AIDS can be improved and sped up. Today's interview is only one among many data sources that will be used for the study.

This interview has two aims: to explore the *organization* of research and development efforts for vaccines, including various actors and capabilities, and to understand the changing *institutional* arrangements for vaccine R&D over time broadly understood to include financing, social support, regulatory and other “rules”, “norms” or “practice” that affect what actors are involved, and speed with which a goal is reached that most in the research community agree is desirable (such as an HIV vaccine).

Anonymity

I intend to publish results without any attribution, meaning that any statements you make will not be publicly linked with identifying characteristics. Specific data will be published only if the reader would be unable to make a definitive link to a person or organization, and published comments will be reported anonymously, e.g., “a senior manager indicated that...”. You should be reassured that even in the collection and analysis of data, the project ensures full confidentiality for your views so that you feel comfortable to fully share them during the interview.

Answering the questions

I will pose 4 open-ended but structured questions, common to all the interviewees. Under each question are several related sub-questions, and I am likely to also ask a few additional short questions that will be more specific to your expertise and professional history. The interview should take approximately 45 minutes to an hour.

Please answer the associated questions as best you can, based on your own experiences and understanding of the institutional and organizational changes in R&D that they represent. For each answer, please be as specific as possible, with examples, dates, typologies, and identification of organizations and institutional settings in which the vaccine research or development occurred.

If you do not know the answer to any question, please indicate this. In addition, please note that you are under *no obligation* to answer any of these questions if you do not desire to. Please explain why you do not wish to answer a question if you are willing to share the reason.

The questions

Introduction: Please briefly describe how you came to be involved with vaccine R&D, and/or what brought you to the AIDS field.

1. *Science: Uniqueness and commonalities of HIV:*

- (a) What vaccines can provide useful or instructive comparisons to HIV vaccines? For example, can hepatitis C vaccine goals be contrasted for scientific, organizational or institutional insights? What about earlier vaccines?

2. *Links between science and organization (Form and function):*

- (a) *Advantages of certain forms and functions:* Is there a *defining difference* in the way vaccine research or development is conducted in different organizational forms? What exactly is different between vaccine *research* conducted in a university setting, an army-led/national research lab, or in the private for-profit sector? What about vaccine *development*?
- (b) *Two particular organizational forms:* What are the primary benefits and drawbacks to (i) large-scale, coordinated vaccine efforts and to (ii) investigator-driven, individual research programs?
- (c) *Unique functions for certain forms?* Which elements of the scientific work specifically related to HIV vaccines *cannot* be done in the public research domain? Which *cannot* be done in the private company domain? Why?

3. *Institutional history:*

- (a) *Different institutional models:* Assuming for the moment that one can make the distinction, are the ties between “R” and “D” and “manufacture” differently coordinated in Europe than in the U.S.? What, if anything, can European vaccine scientists accomplish that cannot be done here? Why? What can they *not* do that U.S. vaccine scientists can? Why? What about organization and institutional models of vaccine R&D in Japan and other parts of Asia? What makes the U.S. vaccine R&D “style,” however you want to define it, different: funding, regulation, NIH history and practice, capabilities of private for-profit companies, other?
- (b) *Other organizations, Not-for-profits, the Army, etc.:* Some not-for-profits, such as the Institute for One World Health, have restructured some aspects of R&D. Others, such as the army, have historically performed activities of both academia and the private, for-profit sector. What is the role for such organizations, distinct from universities and private companies, in vaccine R&D? Has this changed over time? How?
- (c) *The role of IP:* Do changes in intellectual property rules affect the speed of HIV vaccine R&D? If yes, how exactly?

4. *Coordinated efforts in R&D:*

- (a) *“Mission-mode” R&D:* What are the primary benefits/drawbacks of R&D efforts that combine aspects of both large-scale, coordinated vaccine efforts and investigator-driven, individual research programs? How do these change based on different alignments within these “mission-mode” programs (e.g., Manhattan Project, Human Genome Project, Moon Mission etc.)?
- (b) *Avoiding duplication, enhancing integration?* The Dale and Betty Bumpers Vaccine Research Center at the NIH is another model of pursuing HIV research,

as are IAVI and various other initiatives worldwide. Why not one “Mission-mode” approach to HIV vaccines—what would it take for all these different initiatives to be integrated? How (if at all) does the international nature of HIV/AIDS affect the ways in which national resources are allocated, given that prior “mission-mode” efforts have been primarily at a national level?

- (c) *Attracting the “best and brightest”?* Do the “best and brightest” come to vaccine R&D? What prevents having them all in one place working on various approaches to HIV vaccine R&D? Can their professional paths be differently structured to speed a vaccine?
- (d) *Present moment in national histories:* Are there specific opportunities now for “mission-mode” work that might allow this integration? How is this different from previous periods of U.S. or other history? What needs to be done, and by whom, for this to occur?

Completion and additional points

I have completed my prepared questions. Are there any other thoughts you wish to share on pertinent issues I may not have raised here? Do you have suggestions of other people/organizations that could provide further insights? (Suggestions could include those outside the HIV or vaccine R&D fields, if you think they have some experience or perspective that may assist me in this study.)

Follow-up

If we could not finish in the allotted time, or if you wish to comment further for any reason, could you please let me know by indicating if you are available for a follow-up interview by telephone?

Thank you very much for your assistance. IAVI will be in touch with you with the completed report of the study.

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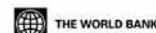
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