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The International Aids Vaccine Initiative (IAVI) in a Changing Landscape of Vaccine Development: A Public Private Partnership as Knowledge Broker and Integrator

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THE INTERNATIONAL AIDS VACCINE INITIATIVE (IAVI) IN A CHANGING LANDSCAPE OF VACCINE DEVELOPMENT: A PUBLIC PRIVATE PARTNERSHIP AS KNOWLEDGE BROKER AND INTEGRATOR.

In recent years advances in biotechnology and the growing toll imposed on poor countries by epidemic diseases have brought the development of safe and affordable vaccines to the heart of the debate on development. Almost exclusively economic policies are put forward to address the crisis focusing on market failures in the production of vaccines for neglected diseases. This paper argues that development policies aimed at fostering vaccine innovation should also consider the institutional and organizational uncertainties entailed in enabling research into, and production and delivery of, vaccines for diseases affecting primarily poor countries. This paper looks at one product development public private partnership, the International Aids Vaccine Initiative (IAVI). IAVI is attempting to increase vaccine production for neglected diseases by acting both as a broker and integrator of knowledge. Based on our understanding of IAVI and our assumption that IAVI might be representative of other product development PPPs, we suggest there is a tension between an emphasis on private pharmaceutical sector efficiency and sustainable development activities that requires understanding and managing if PPPs are to successfully vaccine reach their goals[1].

1. Introduction

Interactions between the scientific and technological knowledge required for vaccine development are complex and far from linear. Even today the mechanisms through which successful vaccines operate are not fully understood (D'Adesky, 2004, Cohen, 2001) and there is often a large element of trial and error involved in product development. The non-linear relationships between science and technology in vaccine development imply that it cannot be assumed that advances in vaccines will automatically or only derive from advances in scientific understanding. Furthermore, the development of a successful vaccine, i.e. of a vaccine that prevents the disease and that is successfully delivered to those who need it, requires not only the management of the complex

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relationships between science and technology, but also their integration with production, 'market creation'[2] and distribution activities.

Historically, large pharmaceutical companies have played a central role in integrating the various bodies of knowledge (scientific, technical, regulatory and market) needed to produce successful new vaccines. However, over the last thirty years the institutional landscape in which vaccine innovation takes place has undergone significant changes. The pharmaceutical industry has undergone major shifts in both its underlying knowledge bases and in its organization as a consequence of the emergence of biotechnologies (Henderson, Orsenigo and Pisano 1999). Universities and other public sector institutions have been under increasing pressure to demonstrate their productivity, in terms of both publications and patenting. Finally, a wide range of 'hybrid' organizations such as Public Private Partnerships (PPPs)[3] have been emerging and gaining importance in vaccine research, products and delivery (Moran, 2005; Widdus and White, 2005). Within the broad category of PPPs are a set of product development PPPs whose aim is to develop new medicines and vaccines for neglected diseases. These changes are widely perceived to have important, even if as yet not fully understood, consequences as they impact on the division of labour among the different actors and institutions involved in vaccine development, and the attendant knowledge flows, and on the ability of the system to produce and distribute effective and affordable vaccines.

PPPs represent new institutional actors in the system. Their contribution has been primarily seen as bringing 'private sector efficiency' and focus to a world so far dominated by cumbersome public sector institutions. There is evidence that they can offer new possibilities for the efficient production of vaccines with and for developing countries (Kettler and Towse, 2002; Moran, 2005; Morel et al, 2005; Widdus and White, 2003; Widdus and White, 2005). Recent research, however, has shown that some of these new actors have also drastically redesigned the activities involved in vaccine development, reinterpreting traditional 'grant making' roles and incorporating new roles usually associated with development agencies, such as advocacy and access (Chataway and Smith 2006; Chataway and Smith 2005). There are now key questions to be asked about the organisational and institutional direction in which PPPs are evolving. Based on our IAVI case study

[2] The health sector of course is dominated by market and non-market based institutions based on public and national and international system priorities. Vaccine production has always been strongly dependent on non-market distribution mechanisms,

[3] The broad range of PPPs include the GAVI alliance, the Global Fund to fight AIDS, Tuberculosis and Malaria. Examples of product development PPPs include: the Institute for One World Health; the Global Alliance for TB Drug Development; the Pediatric Dengue Vaccine Initiative (PDVI); the Malaria Vaccine Initiative (MVI); the Microbicides Development Programme (MDP); Medicines for Malaria (MMV).

we argue that an important distinction can be made between 'integrating' and 'brokering' activities related to the issue of the extent to which PPPs act like private sector companies. Integrating activities emerge from a perceived need to order and drive R&D activities, rather than simply collating information and sharing data between scientists, companies and research laboratories. Brokering involves activities essentially concerned with spreading information, generating new links between organisations and creating the basis for new operations. These activities include much of the advocacy work that PPPs undertake. Using the International Aids Vaccine Initiative (IAVI) as a case study this paper focuses on that distinction between integrating and brokering activities and the challenges posed by trying to follow the institutional logic of both sets of activities.

This paper is divided into four sections. First we look at the way the problem of neglected diseases has been framed in policy debates and the implications for the way constraints and solutions are identified. We suggest that increased focus on organisational and institutional issues is required. The second section introduces IAVI and describes broadly the way in which IAVI operates, relevant to its knowledge brokerage and integrator roles, in developing a preventative AIDS vaccine. The third section draws out some of the broader issues associated with the broker and integrator distinction drawing on the literature from innovation studies. The concluding section suggests that the phenomenon of IAVI and other non-commercial drug developers for a global market may necessitate a change in policy prescriptions and identifies areas for future research.

2. Addressing the problem of neglected diseases.

Neglected diseases are high on the development policy agenda. Related policy analysis usually focuses on the economic forces at play in the pharmaceutical industry and on specific health technologies such as vaccine development. However we suggest that focusing on the organisational and institutional issues involved in innovating would also provide a means for understanding the complex environment within which technological solutions for neglected diseases are discovered and disseminated.

2.1 Neglected disease policy

In the past few years the issue of neglected diseases has begun to receive attention and resources. The problem is hard to exaggerate. Diseases such as AIDS, tuberculosis and malaria, whilst considered treatable in rich country contexts, kill millions every year in poorer countries. One of the central causes is attributable to what has come to be known as the "10/90 gap". In 1990, the Commission for Health Research for Development estimated that 90% of all medical research is targeted at problems affecting only 10% of the world's population. The Global Forum

for Health Research does not see any recent dramatic reversal of this trend (www.globalforumhealth.org). This lack of attention to the health of the world's majority inflicts a terrible burden on sub-Saharan Africa in particular.

In 2005 an estimated 3.2 million people in sub-Saharan Africa (SSA) became newly infected. 2.4 million adults and children died of AIDS related illnesses. SSA has just over 10% of the world's population but is home to more than 60% of people living with HIV (www.UNAIDS.org). In the case of malaria at least 300 million acute cases of malaria occur worldwide each year resulting in more than one million deaths. 80% of these are in SSA (www.globalhealthreporting.org). Approximately 2 million people die each year from TB, the majority of which are in South East Asia, the Western Pacific and Africa (www.globalhealthreporting.org). The devastating impact of AIDS, malaria and TB are increasingly recognized. However, there are other diseases that are truly neglected. The WHO list of neglected diseases includes amongst others the following, all of which have very significant impact on populations in developing countries: Human African Trypanosomiasis (African sleeping sickness); Chagas disease; Dengue and; Leishmaniasis.

Discussion about how to improve the present system is typically framed in terms of health and economic policy, with the two sides often not easily communicating with each other. In the world of vaccinology (and perhaps in that of public health) the problem is expressed in terms of the speed with which new vaccines become available. In economic terms, the problem is framed in terms of market failures in the allocation of resources to goods whose social return exceeds the private return. Thus, the "standard" way of approaching the problem of vaccine innovation is cast in terms of efficient allocation of resources to vaccine research, where vaccines are usually treated as a public good (Archibuigi and Biazzari, 2005; Kremer and Glennerster, 2004). In particular, of course under the current regime many vaccines that are socially worthwhile do not receive the attention they warrant from private, for-profit firms.

Proposals for reform of the current system have largely been coached in the economic policy line of argument. Consistently with this frame of analysis, proposals for reform include either /or:

- more government funding of vaccine development, and greater involvement of public sector research organizations in the development work;
- the introduction of adequate incentive schemes to mobilise private research and to reduce the costs associated to monopoly power (e.g. advanced purchase agreements and prizes to innovators).

Thus, the central question becomes how to fund research, either through public support or the introduction of appropriate incentives to private investment. One of the mechanisms put forward to incentivise investment in vaccine development is through PPPs. In current efforts to develop a

HIV/AIDS vaccine for poorer countries a wide range of 'hybrid' organizations often involving partnerships between public and private sectors organizations have been emerging and gaining importance. These changes in the institutional landscape are widely perceived to have important, even if as yet not fully understood, consequences. However, relatively little attention has been paid to (a) how these changes impact on the division of labour among the different actors and institutions involved in vaccine development, and the attendant knowledge flows, and (b) how the changing patterns of division of labour influence the ability of the system of delivering effective and affordable vaccines.

While it is assumed that the probability of discovering a new vaccine is simply a function of the amount of resources invested in research, this assumption is not bourne out by analysis coming from those involved in innovation studies[4]. This analysis suggest that the rate and the patterns of innovation are significantly influenced by the evolution over time of the specific nature of the research space and of the research process. In some cases, innovation is hard or even impossible simply because the state of current understanding and knowledge is insufficient, irrespective of the amount of resources invested. The relationship between science, technology and innovation is often highly complex and intricate, being characterised by feedbacks and lags, and changing over time. While much innovation in modern time has been 'pushed' by scientific advances in understanding, often at times technology and solutions precede and pave the way to scientific understanding (Vincenti, 1991). This has been the case for vaccines (Cohen, 2001). The early discoveries in vaccinology (e.g. Jenner's discovery that vaccination with cowpox could protect against smallpox) were wholly empirical in nature and were not based on any understanding of why the vaccines actually worked. Later, Pasteur's microbial theory of diseases allowed researchers to focus their efforts towards the identification and isolation of the microbes associated with particular diseases. However, understanding of how and why vaccines worked emerged only much later and very gradually. The relatively recent development of immunology has been crucial here though, even today, understanding of the exact working even of long-established vaccines (such as the pertussis vaccines) is far from complete (Blume 2005).

Historians and sociologists of science have shown how scientific understanding, in the form of theories, is linked in complex and non trivial ways to experimentation and to a complex and changing division of work within scientific communities (Latour 1987; Galison 1997). Packages formed by relatively high-level theories and highly structured laboratory procedures tend to diffuse very rapidly among scientists, as they can be 'localised' to provide effective answers to the specific concerns, and publication needs, of individual research groups (Fujimura 1992). From the point of

[4] There is a very large literature that highlights the importance of institutional and organisational factors insuccessful innovation. Two early classic works in the area are by G. Dosi et al, 1988 and R. Nelson, 1993.

view of innovation studies, this means that innovation tends to proceed around relatively tightly focused trajectories, which are largely defined by the ways in which problems and their possible solutions are conceptualized by researchers.

While this undoubtedly has the effect of concentrating researchers' efforts on the avenues that seem at any one time more likely to produce (publishable) results, it also entails the risk of 'looking for the key under the street lamp' (Cohen, 2001). The problem can be further compounded by the increasing specialisation of research, and by phenomena of 'capture' of problems within specific scientific communities, so that broadly alternative explanations are not considered (Kono 1975; Shigematsu, Yanagawa, Yamamoto et al. 1975; Blume 2005). Overall, these studies suggest that they may be the equivalent of significant 'market failures' in the social technology and institutional infrastructure through which the scientific knowledge basis advances. These 'failures' are likely to exert an increasing impact on the development of vaccines, as the advent of rational drug discovery and biotechnology have tended to make drug (and vaccine) design increasingly dependent on a sophisticated scientific understanding of the biochemistry of infection and immune response (Henderson, Orsenigo and Pisano 1999)

This paper complements the focus on funding issues and on 'market' or 'public sector' failures that characterises the current analyses by taking the point of view of innovation studies and systems of innovation, i.e. by focusing on the dynamic interactions between the evolution of scientific and technical bodies of knowledge and the changing organizational and institutional structure in which vaccine innovation takes place. It also highlights the tension between integrating activities associated with focusing R&D and innovation efforts and the broader development agendas that PPPs aiming to produce vaccines for poorer countries need to pursue. The paper considers this through an analysis of the International AIDS Vaccine Initiative, IAVI, a PPP which provides an interesting example of the importance of institutional and organisational arrangements to complement the economic arguments, for the success of vaccine development.

These are critical issues because the landscape in which vaccine development takes place has changed significantly over the last thirty years. From being largely carried out in the public sector, vaccine development has now become an activity predominantly carried out in the private sector (Milstien and Candries 2000). At the same time, both the private and the public sector organizations involved in vaccine development have undergone substantial changes. The pharmaceutical industry has undergone major shifts in both its underlying knowledge bases and in its organization as a consequence of the emergence of biotechnologies (Henderson, Orsenigo and Pisano 1999). Universities and other public sector institutions have been under increasing pressure to demonstrate their productivity, in terms of both publications and patenting. The question

remains whether the new constellation involved in the production of vaccines[5] will prove any more successful over the medium and longer term that previous institutional infrastructures.

3. The International AIDS Vaccine Initiative (IAVI)

Set up in 1996, IAVI is a form of PPP that focuses both on creating a preventative vaccine for R&D but also on stimulating demand and appropriate institutional infrastructure for distributing a vaccine should one become a reality (Chataway and Smith, 2006). In some respects IAVI can be viewed as combining the roles a private pharmaceutical company with the objectives of a development agency. This hybridity sees IAVI operate as an integrator and broker of knowledge in developing a preventative AIDS vaccine.

3.1 IAVI's operations

IAVI seeks to further HIV vaccine research through the funding of clinical trials, and to ensure that any vaccine that displays sufficient efficacy will be cheap and readily available to the regions of the world where it is needed most, sub-Saharan Africa and Asia. Although IAVI is high profile as a product based PPP and sizable in financial terms[i], it is dwarfed by funders of HIV/AIDS research work such as the US National Institutes of Health (NIH) that devotes over US$ 2 billion annually to research connected to HIV/AIDS[6].

In 1996, IAVI sprang out of a particular political and economic moment in the business of research, development and innovation, and out of a particular scientific and technical moment in research, development and innovation (Chataway and Smith, 2006). It is an initiative originally fostered by a traditional actor in the field of developing country health initiatives, the Rockefeller Foundation, but one of the first that broke the mould of large consortia-based initiatives entrenched in UN politics and bureaucracy. Much of the early funding came from the Bill and Melinda Gates Foundation however in 2003 the Gates Foundation finally became a minority rather majority donor. Donors include a wide range of multilateral and bilateral donors including DfID, USAID, SIDA and the World Bank. The Gates millions were clearly very important to IAVI and have played a key role in early support to other health partnerships (The Lancet, 2005).

IAVI is currently operational in 23 countries, and has a network of scientific partners researching on various types or 'clades' of HI virus and developing vaccine concepts and candidates. IAVI

[5] This set of questions and the analysis in this paper may well apply to other non-vaccine based initiatives for neglected diseases, although because of the nature of science and R&D processes the issues for other areas of medicine may differ.

[6] There are many organisations involved in trying to prevent and treat HIV in developing countries including large international bodies and partnerships like UNAIDS and the International HIV/AIDS Alliance.

focuses on the broader innovation system and is also involved in analysis of distribution and delivery systems for preventive AIDS vaccines in several countries. This is explicit in IAVI's recognition of four areas of vaccine development and delivery that need to be addressed: the mobilization of support through advocacy and education, acceleration of scientific progress, encouraging industrial participation in AIDS vaccine development, and assuring global access.

3.2 IAVI as a hybrid

IAVI is novel in a number of respects, working in quite diverse ways in different countries and contexts, managing a complex range of partnerships, and remaining tightly focused on its goal of furthering efforts to produce a vaccine. Key to its operations and objectives is its funding of potential vaccine candidates which will address the strains of HIV/AIDS in developing countries. In this aspect of its activities it acts as a sort of venture capitalist, investing in promising candidates which, although technologically exciting, would not be taken further by the private sector alone. IAVI – similar to a traditional pharmaceutical company – maintains a portfolio approach to vaccine development, choosing to spread its investment rather than put all its eggs in one basket. It traditionally has funded projects at the development stage rather than more upstream research, differentiating itself from a research council which funds a wide variety of projects at earlier stages. It does not usually fund infrastructure and a large number of other costs associated with development.

IAVI was originated with the idea to address a perceived dangerous disconnection between basic research, and actual vaccine development for poorer countries and their populations. Indeed, the issue of vaccine innovation had been largely framed in terms of basic research activities. Issues of development of manufacturable vaccines (in particular the development of the production process), scaling up and distribution, although increasingly important in the agenda of health authorities, have not so far been considered in the debate of vaccine innovation beyond the observation that growing regulatory demands on quality and documentation of manufacturing and delivery processes is increasing the costs of vaccine development. IAVI addresses these issues in policy and advocacy work because its mission is both to play a role in the development of a vaccine and also to ensure delivery of that vaccine to those in poor countries suffering from HIV/AIDS. Of course unlike a large pharma company, IAVI does not have direct involvement and experience of distribution and delivery of final products[7].

[7] Distribution and delivery of drugs including vaccines poses an enormous challenge in the context of fragmented and dysfunctional health services that exist in many developing countries. The gap that exists between innovation and industrial policy and social development policy is another constriant to gettig products to those who need them (Hanlon et al, 2006)

Advocacy and preparing communities for vaccine field trials and identifying potential manufacturers are therefore other core IAVI activities. In developing countries advocacy works at a number of levels, at the level of the foundation, state or funding body to access resources, with the Indian and African governments, between appropriate NGOs, and with affected communities in India and Africa. In India, as noted, advocacy work with government bodies has been central to IAVI efforts so far, a recognition of some of the difficulties of dealing with both a hierarchical and pervasive bureaucracy, and a country with negative experiences of vaccine trials in the past.[ii] Advocacy has also become an important tool in generating HIV/AIDS awareness, and thus capacity for interventions, in a country where the impacts of HIV/AIDS are not as obvious as in Africa.

Advocacy and policy work also takes place at the international level, guided by high level international advisory boards. IAVI engages broadly in awareness raising and policy debates at a global level and is currently active in discussions about potential financing initiatives for vaccine related R&D.

IAVI has gone through different stages in terms of its own evolution. Initially, thinking seemed to be led from IAVI's New York office but establishing credibility as a genuine partner is key to IAVI as a substantial amount of its funding comes from development agencies. It takes capacity building seriously and will take a secondary position in shaping operations.

IAVI's approach to advocacy, education and policy can be seen as a meeting point between professional public relations and communications work and development advocacy work. However, IAVI is a broader operation and has presented itself as a 'virtual pharmaceutical company' looking to bring 'private sector efficiency' through contracting out stages in the vaccine development process. To some extent this characterisation as a virtual company rings true[8], in other respects, of course, its broader focus on advocacy, policy work and capacity building mean that operates more like a development agency.

4. Locating IAVI in the institutional landscape

IAVI is challenged with the need to manage two very different roles. It is called upon both to demonstrate 'broker' credentials by keeping on board a wide range of diverse stakeholders and being responsive and a 'good citizen' in the world of development. It is also by necessity of

[8] We noted earlier that whilst IAVI is committed to thinking through distribution and delivery of any preventative vaccine emerging for R&D it does not have this experience.

needing to be a good innovator pulled in the direction of integrating activities. This section discusses this tension further.

4.1 Partnerships and knowledge flow

A body of research has shown that networked innovative activities are often centred round a hub organisation (Chandler, 2005). In the pharmaceutical industry, the hub organization has typically been large pharmaceutical firm. Whilst IAVI does not have the means to direct operations in the full Chandlerian sense of a hub organisation, it does seem to be taking an increasingly leading role in driving research activities. IAVI has put a special effort in bringing together research institutions in both developed and developing countries, pharmaceutical companies (again in both developed and developing countries), government agencies, and other actors forming broad-based coalitions for the development of AIDS vaccines. These activities go much further than those traditionally carried out by grant-making institutions. It is however unclear exactly what role IAVI plays in these innovation networks, and in particular whether it acts as broker, exploiting its network position to gain knowledge and highlighting the opportunities this creates to otherwise disconnected partners (Hargadon and Sutton, 1997), or as knowledge integrator that integrates in-house knowledge deriving from different domains coordinate and partially shapes the innovative activities of the partners (Pavitt, 2000; Brusoni, Prencipe and Pavitt 2001).

Brokering can be seen as the activity of alerting 'distant' actors of the existence of common interest and complementary capabilities. Brokering may entail the transfer of information across actors, having retrieved it and changed it as required – thus using old knowledge for new purposes. On the contrary, knowledge integration entails placing the contribution of others in a wide 'interpretive' framework, which enables the evaluation of the function and value of the contribution of each. Knowledge integrators are the holders of systemic knowledge, and usually play an important role in setting the trajectories of knowledge development of other agents in the system.

These roles have different implications in terms of the competencies that PPPs maintain in house. In particular, we can make the hypothesis that a brokering role can be carried out by a relatively 'light' organization, employing a few key employees with a wide range of experience and scientific or technical credibility – the traditional profile of brokers and gate keepers. On the contrary, a knowledge integrator may need to maintain in-house a wide spectrum of competencies and some core operations that enable it to coordinate and direct the work of other partners (Brusoni, Prencipe and Pavitt 2001).

4.2 IAVI as knowledge broker or integrator?

IAVI's knowledge brokerage role is evidenced in much of its advocacy activities at national and international level. IAVI in this context is not the main central player in a network but one node in a wider network made up of local communities, government agencies, non-governmental agencies, industry etc. IAVI uses its place within this wider network to use and diffuse knowledge in a way that will progress HIV vaccine development on the ground and internationally. For example, IAVI's head office in New York produces what are known as the 'core materials'. This is a large information pack that provides information on HIV, on current research strategies, the current status of vaccine trials and, what happens in vaccine trials. This information pack provides the backbone of most 'HIV vaccine literacy work' that occurs in developing countries where trials are taking place. While IAVI provides the information, it is up to the staff at the trial sites (in discussions with IAVI Regional Office staff) to work out how best to make use of it.

As pointed out earlier IAVI's wish to be recognized as a partner in developing countries rather than as an organisation intent on imposing likely to fail 'techno-fix' solutions, means that it must work closely with governments and NGOs in different contexts (Chataway and Smith, 2006). Similarly, at international level, IAVI has the expertise to retrieve information and knowledge regarding the various financial incentives to engage the private pharmaceutical industry and makes this available to those who will act upon such knowledge to develop incentive schemes.

However, as briefly discussed earlier, in line with predictions that might emerge from theoretical work on innovators, in its role as stimulator and actor in vaccines R&D, IAVI is beginning to behave more as an integrator. IAVI's Neutralising Antibody Consortium (NAC) is an example of an initiative which was initially based on brokering but which has gradually involved IAVI playing a more integrating role. In discussing this evolution from transition to integrating activities we draw largely on IAVI produced material and interviews. This material provides insight into how IAVI itself sees the transition[9].

In 2002, IAVI established the NAC to consolidate – broker – research around a radical new approach to vaccine development. The NAC brought together groups of scientists from diverse institutions looking for ways in which a HIV vaccine breakthrough could develop not - as per current research – via cell mediated responses but via the creation of neutralizing anti-bodies:

> "The IAVI-facilitated Neutralizing Antibody Consortium is a novel and visionary collaborative undertaking to obtain answers to key questions regarding the design of

[9] The amount of material pertaining to its own development and evolution that IAVI makes available on its website is unusual for either private sector companies or development agencies and testimony perhaps to an openness in the culture of the organisation.

> broadly neutralizing antibodies to confer immunity against HIV/AIDS – one of the central challenges facing the vaccine field (IAVI, 2004b 9-10)."

Initially, IAVI took old knowledge relating to previous studies on neutralising antibodies, transformed it and bought it back into the spotlight for others to use and take forward. This could be thought of largely as brokering activity. In initiating the NAC IAVI and the US NIH, a group of academic centres and a series of industrial contracts – linked by project management systems – saw themselves as beginning to address a major scientific challenge on a limited scale. In driving research in this way, IAVI began to play a more active and directive role.

> "Since its establishment in 2002, the Neutralizing Antibody Consortium has generated several discoveries […]. The key elements to the success of the consortium include clearly defined goals, […] an effective industrial –project management system based on clearly defined work plans and deliverables […] and creative intellectual property agreements to provide incentives for data sharing and cooperative research. (IAVI 2004c:16-17)".

NAC involved a shift upstream in research, not a role that IAVI had originally envisioned. In moving upstream IAVI began to move in the direction of integrator, moving research in particular directions. The NAC is an example of how IAVI has become increasingly interested in actively influencing the activities of partners and is promoting increasingly stronger contractual and organizational integration among actors involved in vaccine development. Alongside brokering activities, more integrating and interpretative activities became very evident as IAVI describes the creation of its own laboratory:

> "[In 2004] IAVI has taken a crucial step towards the successful completion of its primary mission by establishing its own Vaccine Research and Design Laboratory. This represents a major paradigm shift in which IAVI now will help drive the creation and development of the next generation HIV vaccine candidates, in addition to advancing promising vaccines developed by its collaborators..(IAVI 2004b: 16) The Lab will improve the genetic stability and level of expression of candidate vaccines; develop assays to evaluate candidates; provide laboratory backup to IAVI-funded vaccine feasibility studies; and initiate work on new candidate vaccines." (IAVI 2004b: ii)

This dual nature of activities is also evidenced in the AIDS vaccine consortium, a follow up initiative to the NAC. Here, IAVI is not directly controlling activities but is playing an 'industrial project manager' role.

> "Along this line, IAVI proposes to build on the success of its Neutralizing Antibody Consortium to create an unprecedented, largescale AIDS Vaccine Consortium. The proposed new consortium would

> undertake all activities required to solve key scientific challenges (such as neutralizing antibodies), then rapidly develop concepts into products for accelerated clinical testing. The consortium would also work to understand – then develop products that mimic – the unmatched level of protection provided by the live attenuated vaccine in animal models. IAVI would not undertake such an effort in-house but would create an industrial project management effort linking leading laboratories, companies and institutions around the world. Such an effort would rely on linking core centers, companies and institutions globally having a critical mass of senior scientists and multidisciplinary teams that devote a majority of their time toward solving these problems. Centralized resources would contribute to production of reagents and immunogens and support access to state-of- the-art biotechnology tools. The proposed global consortium would develop multi-year business plans, identify key milestones, facilitate the rapid translation of concepts into clinical candidates, and provide the basis for future access through innovative intellectual property arrangements. IAVI has made provisions to jump-start this work within its core budget. Given the bold and long-term nature of this initiative, IAVI will attempt to acquire resources outside of the normal resource mobilization plan and will only scale it up if it is successful in doing so." (IAVI 2004a: 9-10)

The NAC and the vaccine consortium that followed highlight IAVI's role in actively influencing the activities of partners. In consolidating its position, IAVI is also strengthening its in-house capabilities:

> "The original *idea* of IAVI as a public-private incubator of new vaccine candidates has been turned into a concrete reality. Having recruited the range of expertise required to create a fully integrated (but mostly virtual) vaccine company, IAVI now has the capacity to offer its partners expertise in clinical, regulatory, manufacturing, product management, process engineering, and other critical areas. In addition to placing five vaccine candidates in human trials, IAVI has established a state-of-the-art core immunology laboratory that not only services IAVI's own scientific work but is also serving as a resource for the entire field. (IAVI 2004a: 8)

For IAVI, NAC, the vaccine consortium and their laboratory involved addressing a critical gap in HIV vaccine development for poor countries. The gap is perceived as a deficit of effective mechanisms to harness the necessary global talent and infrastructure for an applied research problem solving agenda. Documents on the IAVI website indicate that the perceived solution to these challenges will require multidisciplinary involvement from various sectors of HIV research and vaccine design and creative mechanisms linking basic research scientists with vaccine designers, in fields as diverse as structural biology, robotic crystallization, glycobiology and large-scale non-human primate testing. In IAVI's perception this involvement of a wide range of multidisciplinary stakeholders and actors requires IAVI to take a more directive role in leading innovation activities.

This move from broker to integrator at an initiative level is recognized by IAVI staff as being a more profound organizational and institutional shift. The following quotes taken from the IAVI website give a flavour of this.

> "In 2005-2007, IAVI will continue its transition from a grant-making institution to one that drives, manages, is fully responsible for the projects it funds and the products it sponsors. This will necessitate establishment of sufficient laboratory and clinical trial infrastructure, staffing of projects with qualified personnel, execution of appropriate contractual relationships, and assessment and mitigation of potential risks." (IAVI 2004a:33)

> "IAVI's R&D staff, recruited in large part from industry, collaborates with an international network of partners, including biotechnology companies, academic and government research institutes, contract laboratories and manufacturers, and clinical trial sites. *The sum of IAVI's in-house and virtual capacity in R&D covers all of the major functions of a biopharmaceutical product developer*." (IAVI 2004b: 1)

The establishment of in-house laboratories, more cohesive and directive management systems can be thought of as being part of IAVI's integrated approach to developing a vaccine appropriate for its target 'client group'. Website documents about IAVI's move towards integrating activities are echoed by this quote from an interview with one of IAVI's medical directors:

> In the research arena, IAVI has always said it doesn't do basic research. I think we are getting a little more into a void. Traditionally we've said we only do product research. I think we are getting a little more into the applied research area, realising that there are some stumbling blocks to finding a vaccine which are probably not going to be overcome by the traditional patterns of fragmented, non-collaborative, medical research. There was a very good article [pubished] a month ago which said why are we losing the war on cancer. And it said it's because the basic answer is there are tens of thousands of little fragmented grants, or big fragmented grants out there to address specific scientific questions often in mouse models which actually have very little relationship to the reality of cancer as a disease, usually in elderly people, usually with multiple diseases. And that actually, if you had a more pragmatic approach, you might get less scientific satisfaction but you might have saved many more lives. I think our approach to vaccines is somewhat similar, it's to say it's not our job to answer basic science questions but if for example there's this central science conundrum we have that we know that in monkey models […] a live attenuated vaccine does induce neutralising antibodies. And we know that in some humans in natural conditions you get neutralising antibodies for HIV, so you can't consider a live attenuating vaccine in humans for obvious safety reasons but until we come up with an answer to this question of how do you induce neutralising antibodies in humans, how do you induce a live attenuated vaccine-like effect without using a live attenuated vaccine, we are never going to have a vaccine which prevents infection. That doesn't mean we have to stop work on the current generation, the current generation are looking at cell mediated immunity and that could well be enough to dramatically reduce the impact of the epidemic. But at the same time there has to be some consortium, some innovative collaborative way of looking at the big science questions and I think we increasingly feel there's a role for us in doing that.

The move towards integrator activity is indicative of IAVI's identity as a 'virtual pharmaceutical company'; based on analysis, expertise and experience built up over its years of operation, IAVI is integrating knowledge and technology in such a way as to make it accessible to its 'market'. The following quote from a paper written by IAVI staff explains this:

> "There are two serious barriers to timely and efficient manufacturing of HIV vaccines. One is that most HIV vaccine developers work in academic institutions or small companies that lack access to the funding, expertise and specialized facilities to develop processes to manufacture promising vaccine candidates and to produce small lots of vaccine for trials (referred to in this paper as the "product development" challenge). This failure to integrate clinical development with bioprocess development is causing delays and inefficiencies in the HIV vaccine R&D pipeline. If left unaddressed, these inefficiencies will lead to major bottlenecks in the coming years, as an increasing number of HIV vaccine candidates move forward for clinical testing.
>
> The second looming barrier, while still a few years away, is that investments in the manufacturing capacity needed to supply widespread vaccine use will be severely delayed due to high levels of scientific uncertainty connected with HIV vaccine development and financial risks associated with launching a new vaccine in developing countries. This challenge is compounded by the fact that most HIV vaccine developers have no experience with large-scale manufacturing and will require industry partners. (Walker, Rowley and Hecht 2005: v)"

IAVI has involved manufacturers in its partnerships and is considering setting up a collaborative process development facility (IAVI 2004a) to speed up the solution to scaling up and manufacturing process issues of new vaccine concepts.

The multiple roles and identities of knowledge broker and knowledge integrator present different implications for the way in which IAVI manages itself, for the ability of the broader systems and networks that IAVI is involved in to sustain vaccine innovation. Therefore they have very different outcomes in relation to the policy of supporting PPPs in order to address neglected diseases. IAVI sees itself and speaks of itself as a virtual pharmaceutical company and on the other hand it has a more diffuse set of activities and identities including grant provider. It is also involve in a wide set of activities that might normally be associated with a development agency.

IAVI seems to have a culture which encourages learning and reflection on its own evolving organisational culture and this has made it an ideal case study for beginning to look at how it tries to balance its brokering and integrating activities. The extent to which IAVI is representative of vaccine or other product development PPPs is not something we can answer on the basis of this limited investigation. However, it is easy to see how the different organisational 'logics' of

integrating and brokering activities might pose managerial challenges for other PPPs. The next section looks in more detail at the current challenges facing IAVI.

4.3 IAVI's management challenge

These multiple roles of knowledge broker and knowledge integrator played by IAVI provide a complicated backdrop on which its day to day activities are undertaken. As an IAVI Medical Director put it:

> "The fact that IAVI is working in different places means that it forces different partners to come together and since IAVI is working from a participatory approach to partnership those involved have to come together. A pharmaceutical company would normally employ investigators and just wants them to bring the results. This isn't IAVI. IAVI is involved at every step and because there is more than one partner it is a collaboration. For example, there are meetings of all the investigators to discuss how research activities are to be carried out (and video conferencing for those unable to make the meeting in person). Thus the planning process is very different from that within a pharmaceutical company. There's an interesting phenomena in bringing people together: people get to meet and discuss in a way that very different from that which occurs in a hierarchical, centrally controlled company.
> ... To do clinical trials is a young activity in Africa and so expertise has been developed but not reached the extent to which researchers on ground can enter into brokered relationships with people [as per NAC]…
> … IAVI is also working with groups who are not doing HIV research but need to be informed. Brokering relations with them because we need mobilisation of lots of groups to get support. IAVI is integrating communities so do some kind of brokering of groups of those not normally involved… "

IAVI is a hybrid organisation and is struggling to contend with its role as a 'virtual pharmaceutical company' bringing private sector efficiency to a public sector activity while also trying to act within the bounds of the modern international development agency arena. One expression of the tensions is in the different types of people that IAVI employs. These difficulties are highlighted in the quote before taken from an interview with an IAVI Director:

> "… for that group of people who come in from the private sector. It's not their business to go on developing capacity, it's their business to do specific activities and make an achievement. So our indicators are all focused on that objective. And at the other end of the extreme we have people coming from development agencies. Who have these [words] – one is 'sustainability', two is 'integration', three is 'capacity building', four is 'M&E and accountability' (they go together)….So these are the buzz words here for people who work like at WHO for example. So whatever we do, we tend to ask these questions: is this sustainable? And why don't we integrate with other people who are doing the same work, you know? And when we do monitoring and evaluation we want to be accountable not only to our own organisation but also accountable to the country itself to say you have

been here, we've been here and we've made these achievements for the people of this country. So these two poles, you know…

…speed is of the essence - we are here to find a vaccine, we are not a development agency to build capacity for its sake. So that's one side. On the other hand, when we are asked when do you think a vaccine will be available the answer is no less than 10 years and to me 10 years is really a long term stay. So, I can't see how we can't be around for 10 years still renting a building, you know. And those 10 years, we haven't even started counting the 10 years. We'll count from the day we get a truly efficacious vaccine that is now going into phase III so it's never too late but really we have at least another 10 years. And so these are the two sides and the arguments continue."

IAVI is in many respects moving towards being an integrator. Can it move in this direction and avoid getting 'locked in' to tightly defined scientific and technological trajectories? IAVI has defined its mission as a multi-faceted one and needs to maintain its broader range of stakeholders. Thus, it needs to be involved a range of partnership and network arrangements, and in some it will be continue to be appropriate for IAVI to take a following rather than leading role. Its funding base which largely depends on development donors and its credibility in the field of development depends on its ability to broker and partner effectively. IAVI, whilst moving in the direction of being a knowledge integrator, needs to maintain its profile also as a broad based knowledge broker.

5. Conclusion

As Moran and colleagues have argued there is good evidence that PPPs offer new hope for addressing the pressing issue of drug development for neglected diseases (Moran, 2005). There are, however, clearly many questions raised by the emergence of this powerful new institutional form. By focusing on one PPP we hope that we have shed light on some of the tensions and issues involved in trying to resolve and balance conflicting demands of a very complex organisation. Many questions remain unanswered as yet about IAVI's multiple roles and identities. In this concluding section we highlight three sets of issues and questions that emerge from our analysis.

There are good reasons why IAVI has moved in the direction of knowledge integrator activities. As was explained in secton 2 of the paper a strong integrator drives innovation in certain directions, stimulating R&D and feedback linkages throughout the innovation chain. However, in doing this, scientific and technological possibilities get narrowed. This is a key issue for IAVI and for those who fund it. One of the questions here is how IAVI combines the benefits of being a 'hub' around which vaccine development takes place, a strong leader bringing together experience and

knowledge across the innovation chain and its role as a stimulator of a broad range of possible new scientific and technological avenues[10]. How can this tension best be managed? Is IAVI now behaving too much like an integrating innovation virtual firm and is this compromising its role as 'grant giver' and stimulator of new R&D trajectories?

IAVI donors and stakeholders are not unaware of these issues. One possible resolution to trying to resolve the dilemma of 'lock in' to narrow technological and product development trajectories is the proposed Global HIV Vaccine Enterprise[11]. The Enterprise would act a mechanism for coordinating research on HIV vaccines and for making sure that new ideas, laying outside the established research domains were not ignored or bypassed. The proposal to establish the Enterprise has been controversial and whether or not the Enterprise can effectively fulfil the mission assigned to it remains to be seen.

For IAVI the issue of how to balance between efficient innovator and successful funder of research remains. Can IAVI adopt the characteristics of a successful 'integrating' virtual pharmaceutical company whilst also fulfilling its role as an efficient funder of new scientific possibilities, remaining open to a full range of scientific and technological opportunities?

Second, another set of issues arise in relation to the dual role IAVI plays with regard to innovation and development. IAVI attempts to solve a neglected disease problem but attempts to do so by working at an international and country level using a hybrid organisational mechanism. It seeks to solve an economic dilemma which results in neglected diseases by engaging a wide range government, donors and private pharmaceutical companies in the area of neglected diseases. While IAVI and other PPPs may be successful in boosting investment into products for neglected diseases, in their functioning they change and create new divisions of labour among the different actors and institutions involved in vaccine development through control of knowledge flows. As such, an important question yet to be answered is whether IAVI and possibly other PPPs who might behave like IAVI operate in a sustainable manner to the benefit of those involved? In particular, can IAVI give leadership in innovation whilst directly serving the need for active engagement of developing country and development stakeholders? IAVI to date seems to have a good record in this area (Chataway and Smith, 2006) but a move in the direction of more exclusive focus on science and R&D, rather than combining this with a explicit focus on involvement, access and advocacy, would almost certainly be detrimental in this respect.

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[10] In some respects IAVI can perhaps be seen as microcosm of a larger institutional dilemma within pharma R&D; as large firms lose their dominant position, and other actors become important in developing and delivering roles, how do those previously dominant firms balance their role as 'hubs' and knowledge integrators with the need to mazimize their ability to stimulate and access a range of science and technology.

[11] www.hivvaccineenterprise.org (last accessed 21st Oct 2006)

Third, as we have stressed throughout this paper the knowledge broker and knowledge integrator roles develop and negotiate with each other as a result of a constant tension between the 'private' and 'public' ethos within IAVI; as a result of the tension between scientific efficiency and development sustainability. This of course represents very significant management challenges for IAVI. Assuming that IAVI is at least somewhat representative of other product development PPPs, it also raises an important policy issue. It suggests that future policy on vaccine development for neglected diseases, if it is to continue to promote the use of PPPs, needs to move away from its starting position on economic efficiency and look more critically at the internal dynamics of how vaccine development takes place to ensure it occurs not only as efficiently as possible but also to the benefit of all those taking part. Policy thinking needs to go beyond discussions of market based incentives and needs to be based on a better understanding of how PPPs are trying to put together routes through the vaccine and other drug development and delivery map and how different institutions and organisations might best work together.

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[i] By 2004 IAVI had raised over $340 million.

[ii] Interviews with Indian IAVI staff, May 2004.