THE SEARCH FOR AN AIDS VACCINE: A REVIEW OF THE LITERATURE ON VACCINE DEVELOPMENT

EUGENIA CACCIATORI, REBECCA HANLIN, LAURA LASIO AND LUIGI ORSENIGO

INNOGEN WORKING PAPER NO. 102

APRIL 2012

The research has been carried out within the EU funded project NEST-2006-PATH-Cul, CID - Cultural and Innovation Dynamics - Explaining the uneven evolution of human knowledge, Contract n.: FP6 - 043345.

CONTENTS **Page**

1. Introduction 3
2. The Market Failure Argument 4
2.1 Market failures since Arrow 5
2.2 Market failure in the vaccine industry....8
2.3 Policy solutions....11
2.4 Summary 17
3. Beyond Market Failures: Scientific, Technical and Social Challenges of Developing an AIDS Vaccine....18
3.1 Scientific challenges....19
3.2 Not just science: Manufacturing and delivery issues....22
3.3 Not just science: Social challenges 22
4. The organizational challenges of developing an AIDS vaccine....29
4.1 Searching for an AIDS vaccine....30
4.2 Organization matters 32
5. Conclusions 33
References....34

1. Introduction

After a period of neglect, vaccines have in recent years become the object of the increasing attention of policy makers, academics and pharmaceutical firms. There are several reasons for this renewed interest. First, there seems to be a widespread recognition of the importance of vaccines in preventing the spread of infectious diseases and of the threats that infectious diseases both known and (as yet) unknown once more pose to the industrialized world. The cases of HIV/AIDS, SARS, but also the resurgence of diseases believed to have been eradicated (e.g. polio) have renewed attention given to vaccines by the general public as well as among social scientists and medical doctors. Current fears of bioterrorist attack have further added to these worries. Second, in the Developing World, preoccupations about the failure to find satisfactory remedies for "old" diseases like malaria which are increasingly becoming drug resistant have been compounded by the appearance of new tremendously dangerous infections – e.g. Ebola - and of course by the explosion of the HIV pandemics, especially in Africa but also in large emerging countries like China. Third, conversely, advances in scientific knowledge and understanding have raised expectations about the ability of research to deliver new vaccines. For example, the sequencing of the human genome and that of animals and other disease carriers (such as the mosquito) where heralded as creating opportunities for fast, modern solutions to a variety of prevailing diseases. Fourth, more generally, the debate about vaccines is at the same time one of the main causes of, and a chapter in, the broader discussion about the evolution of the health care systems, facing at the same time major scientific and technological revolutions, binding budget constraints for the public programs, increasing demand for healthcare by the people. Within this context, the pharmaceutical industry is undergoing profound transformations and it is currently facing difficult challenges.

The combination of all these factors has led to a deep feeling of dissatisfaction among the medical community, researchers and the general public. Either the discovery of new vaccines appears to lag behind expectations (especially where diseases affecting the Developing World are concerned) or, when a vaccine is discovered and access is restricted because of cost (as initially happened with the hepatitis B vaccine). The debate on the inadequacies of the system of vaccine development has been framed as an issue of limited involvement of the private sector due to market failures. However, recently increasing interest has been devoted to the scientific, social and organizational challenges that surround vaccine development. This paper provides a review of the current debate in these areas, focusing in particular on the search for a HIV vaccine. The case of the search for an HIV vaccine is particularly important for two reasons. The first is the huge impact of AIDS. Current estimates place the total number of people infected with HIV at about 40 million, with 4.3 million people newly infected and 3 million deaths in 2006 (UNAIDS/WHO 2006). Despite the fact that AIDS is a global epidemic, much of the burden of the disease is carried by poor countries, and in particular sub-Saharan Africa, where 2.1 million people died of AIDS in 2006. The second reason for the selection of the HIV vaccine is that it is in this field that some of the more imaginative efforts to redesign the system of vaccine development, understood as the whole process from discovery to delivery, are carried out.

This review is organized as follows. Section 2 reviews the market failure argument and the current policy recommendations, which are overwhelmingly based on it. Section 3 examines the scientific, technical and social challenges of developing a vaccine for

AIDS. Section 4 examines the organizational challenges of AIDS vaccine development, while the Conclusions summarize the main findings of the review.

2. The Market Failure Argument

Much of the debate around vaccines derives from the observation that, under the current regime, many vaccines that would be socially worthwhile do not receive the attention they warrant from private, for-profit firms. The case of AIDS is emblematic. The economic and social consequences of HIV/AIDS are dramatic, once again particularly for developing countries. For instance, it is estimated that South Africa's GDP will fall by 17% by 2010 as a result of AIDS (Archibugi and Bizzarri 2005). On the basis of these figures, there are estimates placing the social return of an AIDS vaccine at 10 to 20 times the investment return to private industry (Kremer, 2000). Global investment in an AIDS vaccine in 2002 was US$650 million, 1% of total health R&D spend (IAVI, 2004c). The private sector contributed just 15.3% (IAVI, 2004b).[1] The situation is similar for a range of so called 'neglected diseases', which include HIV/AIDS, tuberculosis and malaria, alongside lesser known (and much more neglected) diseases such as human African trypanosomiasis, Chagas disease and leishmaniasis. A survey found 20 top pharmaceutical companies spent only 1% of their R&D budget on neglected diseases (Trouiller et al., 2002).

The literature attributes this situation to the fact that vaccines are subject to market failures, in particular because (a) they are public goods global in scope (Kremer, 2000; Berkley, 2006; Archibugi and Bizzarri, 2004) and (b) because they provide positive externalities, since when the large majority of a population is vaccinated, the chances of a non-vaccinated individual of becoming infected are extremely low and, therefore, individuals have incentives not to run the risks associated with vaccination.

Taking as a starting point these considerations, this section reviews the literature about vaccine development, in an attempt to shed some light on the market failure issue. Specifically, we investigate the following questions:
Is there a market failure in vaccine development, as broadly argued by the literature?
If so, which are its sources?
The answer to these questions is of great importance, since the policy mechanisms to be put in place are different for different types of market failure.

The section is organised as follows. Section 2.1 reviews the economic literature about market failure, providing definitions and a brief description of the topic evolution from Arrow (1962) to the most recent contributions. Section 2.2 analyses the debate on market failures in relation to vaccines, in the light of the definitions provided by the mainstream economic literature examined in Section 2.1. Section 2.3 discusses the possible solutions to the market failure in the vaccine industry, by examining the pros and the cons of the typical mechanisms suggested in order to deal with them. Section 2.4 will draw the conclusions.

[1] In 2005, global investment rose to US$759 million, and the private sector share declined to about 10%, largely as a consequence of the completion of large VaxGen Phase III trials (IAVI, 2006)

2.1 Market failures since Arrow

2.1.1 Some definitions

One of the earliest definitions of market failures in the economic literature is provided by Bator (1958), as "the failure of a more or less idealized system of price-market institutions to sustain "desirable" activities, or to stop "undesirable" activities" (Bator, 1958, p. 351). However, the origin of the concept is much older. Medema (2007) argues that it dates back to the nineteenth century, deriving from an expansion of the theory of the failure of the system of natural liberty, which would fail since self-interested economic agents do not take into account the full social impact of their activities. Hence, the market fails whenever, left to itself, is not able to allocate resources efficiently, thus not reaching the condition of Pareto-efficiency. In this case, social welfare is not maximised and there is still room left for improvements, until the situation where it is impossible to make anyone better off without making someone else worse off is reached (Bator, 1958).

The concept of market failure is however linked primarily to the name of Kenneth Arrow, who was the first to analyse it thoroughly and provide fundamental insights into the topic. Building on Arrow's (1962) work, the literature identifies four main sources of market failure: the existence of public goods, externalities, the abuse of market power and incomplete or asymmetric information. First, the market fails if a public good is the object of negotiations. As argued by Samuelson (1957), a good can be said to belong to such a category when it shows two characteristics: it is non-rival and non-excludable. Non-rivalry refers to the fact that it simultaneously provides benefits to more than one individual: my own consumption does not prevent another person to consume it at the same time and does not reduce the quantity available. Non-excludability means that it is impossible to exclude consumers from consuming the good. Non-excludability causes a market failure as it makes setting a price for the good impossible, since, once provided, the good is available to all consumers no matter if they pay for it or not (Davis and Whinston, 1967).

Second, a market failure may occur in the presence of externalities, defined as an impact (positive or negative) on any party not involved in a given economic transaction, so that the participants in that transaction do not necessarily bear all of the costs or reap all of the benefits of the transaction itself. In the case of positive externalities (so called external economies), the actors benefiting from them increase their utility, while the agent providing them cannot demand a price; in the case of negative externalities (external diseconomies), the actors suffering from them lower their utility, since no fee is due as a compensation for the damage.

Third, the abuse of market power, which can occur whenever a single buyer or seller can exert significant influence over prices or output, is another cause of the inability of the market to reach Pareto-efficiency. "Self-policy competition" (Bator, 1958) requires many producers in the market and, when this does not occur and only few large firms operate, the welfare maximisation cannot be reached (so called "failure by structure").

Finally, a last cause of market failure is the presence of information asymmetries, when the economic agents involved in a transaction possess different information about the variables that influence their decisions. In extreme cases, incomplete information may take the forms of moral hazard or adverse selection.

In the presence of one or more of these four factors, thus, the market fails because it provides diminished or no incentives to private firms to engage in the production of the good. The consequence is therefore underinvestment by private actors in comparison to the socially optimal level. As argued by Arrow (1962), the problem lies in the excessive risk borne by the actor, who is then unwilling to invest unless at least part of this risk is shifted. Insurance may be a solution to this problem. However, it is only a partial solution since it covers only a small range of relevant events and tends to be limited due to imperfect information and the risk of moral hazard. The common solution suggested in the literature is therefore Government intervention. The government possesses a higher risk bearing ability and, through a number of direct and indirect mechanisms, it can compensate for the market's inefficiency and help it reaching the socially optimal outcome. In addition, the Government is the only institution capable of providing sanctions or attractions distinct from the good itself and hence of partially reducing the impossibility to set a price. Through public policy actions, the Government can apply coercive selective incentives, by imposing sanctions on those who do not contribute and at the same time diffuse benefits across many individuals (Champney, 1988), thanks to the provision of socially desirable goods and services. This result may be accomplished through taxes or subsidies or direct public investment in activities considered to be valuable for society as a whole. Specifically, Government intervention is common whenever the social benefit exceeds the private benefit and this would end up in a sub-optimal private investment. For example, market failure in public goods is often mentioned to justify the monopoly power of the governmental bodies providing indivisible public goods for their members, the citizens such as education or defence (Olson, 1965, as quoted by Champney, 1988).

2.1.2 Arrow and market failure in research

One of the most famous and most cited works about market failure is the argument of Arrow (1962) about the 'publicness' of information and research. The major problem in this case concerns some inherent characteristics of information: indivisibility, inappropriability and the uncertainty that is intrinsic to the information production process, research. All of these three elements make information a public good and cause a failure in the market for it. A famous paradox emerges in the demand for information: its value for the purchaser is not known until the information is acquired and this can occur without cost. Its transmission is in fact possible at zero cost and its appropriability is indeed difficult or even impossible. Such a peculiar good has a peculiar production process that is risky by its own nature, since the output cannot be predicted.

In this situation, the optimum would be to make information available free of charge, a solution that is especially useful whenever it is to be used as an input in the production of new information, that is basic research. However, this decision would obviously provide no incentives for private investment in research. Again, Government intervention is needed, since neither a monopolist nor perfectly competitive firms would reach the socially optimal level of investment and thus maximise social welfare.

2.1.3 Is public intervention adequate?

Nevertheless, the argument of Government intervention in the economy, aimed at correcting market imperfections, is not without numerous vocal critics, who have long argued that the Government is not the most suitable institution to solve market failure.

Back in the nineteenth century, as reported by Medema (2007), Sidgwick (1883) stated drawbacks and disadvantages of Government intervention, mainly related to the consequences of lobbying activities and corruption, excessive expenditure and supervisory matters. Arrow (1962) points out two problems arising from Government involvement, related to the difficulty in determining the exact amount of resources to be devoted to invention and in encouraging efficiency in their use. These obstacles are made even more serious in the case of research, due to its inherent uncertainty. He also reports Hitch's argument (1958) that governmental allocation are especially biased towards risky invention processes and excessive centralisation and proposes better forms of organisations, where the Government may play a less crucial role.

Some authors have asserted that under certain conditions (in primis the provision of some sort of ownership or property rights) public intervention is not necessary and even in the presence of public goods the market might maintain its allocative function (Davis and Whinston, 1967). More recently, Barrowclough (1999), in her work about broadcasting, reports how Government intervention in the funding or provision of public goods is inefficient, due to the so called Government failure, which is worse than the market failure it is supposed to remedy; conversely, the market has shown its capacity of providing goods with some degree of publicness. Government failure as a side-effect of market failure represents indeed a common issue in economic literature. As stated by Datta-Chaudhuri (1990), the debate involving interventionists and critics of any public involvement is inevitably inconclusive, with neither side succeeding in convincing the other and a search for the most suitable corrective measure continuing to be necessary. His most interesting conclusion is that the Government must play a major role in the economy, through the support to the right kind of market institutions.

2.1.4 Recent contributions to the field

Within economics, after the seminal work by Arrow (1962), very few contributions have provided theoretical or empirically grounded discussions of the topic. These contributions have typically concentrated on specific industries, in particular health care and car safety. The literature on market failures in health care stems from the famous article by Arrow (1963) about the welfare economics of medical care. Arrow pointed out the patients' uncertainty about the consequences of purchasing medical treatments, which makes it difficult for them to learn about the quality of the service even after having purchased it (difficult evaluation also ex post) and is much more severe in this market than in any other. Taking as a starting point Arrow's crucial arguments, Pauly (1986) and more recent papers (Glied, 2001; Haas-Wilson, 2001; Hall, 2001) have stressed the problems of moral hazard and adverse selection that affect health insurance, due to a basic problem of information asymmetry. This is made even more serious by the specific characteristics of health care demand (Hall, 2001). First, its abovementioned uncertainty, due to the unpredictability of whether and when illnesses and accidents will occur, and of the success of a cure. Secondly, there is the presence of altruistic externalities, especially in the case of immunisation against or treatment for infectious diseases. However, related to the former, Haas-Wilson (2001) posits that after Arrow's work (1963) many things have changed and today patients' ability to evaluate treatments has improved, as well as their understanding about where to obtain health care services, thanks to the growth of the information available, especially online.

The element of altruistic externalities is not a health care prerogative. An interesting case is presented by Arnould and Grabowski (1981), in their article about auto safety regulation and the role of safety devices in cars (seat belts and air cushions). They define the low utilisation of these devices as a market failure, since these systems have proved to be highly effective to reduce the negative consequences of car accidents. In this case, the causes of market failure are twofold. First, incomplete information, since consumers are not perfectly informed about the benefits of safety devices. Second, externalities, both negative and positive: the former depend on the costs imposed on society by the non usage of seat belts; the latter are related to the expected savings in medical costs from reduced auto injuries if seat belts are used. The solutions are found by the authors in some forms of Government intervention, of various types: advertising campaigns to increase information and moral suasion; mandatory seat belt laws, accompanied by a system of effective fines and penalties; a specific insurance system to increase the financial incentives for individuals to voluntarily use effective safety equipment.

Besides the few contributions reviewed above, an examination of recent publications on most important economics journal shows that the notion of market failures is frequently used but that research in this field has not produced significant theoretical or empirical advancements since Arrow's seminal works (1962; 1963).

2.2 Market failure in the vaccine industry

As mentioned above, many authors involved in the debate over the unsatisfactory rate at which vaccines become available have based their recommendations on the argument that vaccines are subject to market failures, and that therefore industry, and large pharmaceutical companies in particular, underinvest in them. Indeed, while private sector involvement in vaccine development has recently increased with developments in technology and new patentable vaccines (Batson, 1998), it continues to remain low. In discussing the merit of the market failure argument for vaccines, it is useful to distinguish between vaccines, and vaccine research.

With regard to vaccines, the sources and effects of market failure are discussed by England (2000), who argues that the lack of investment in HIV/AIDS vaccine development derives from high barriers to entry into the vaccine business due to positive externalities and high fixed costs of new technology R&D, together with strong information asymmetries. The externalities are related to the fact that the benefit of taking a vaccine provides a private benefit and a benefit to others in the form of herd immunity (Fox-Rushby et al, 2004). As a result, consumers may undervalue the need for vaccination, due to assumptions regarding the (low) probability of infection and disease prominence. Hence, according to the author, these elements ensure that a natural monopoly is created.

References to market failure are frequent also among the few economic contributions to the debate about vaccines. In the work by Kremer (2000), the imperfections in the market for vaccines are said to be the presence of altruistic externalities, the fact that the major beneficiaries of vaccines are children, who cannot currently afford the vaccine, and patients' bias towards treatment rather than prevention. The latter is a consequence of information asymmetries and illiteracy, but also of the difficulty to perceive the benefits of vaccines even ex post, if compared to those of treatments. As a consequence, there

currently is underinvestment in vaccine research, since the private sector anticipates a future underconsumption and lacks incentives to pursue socially valuable research opportunities. Kremer's proposed solution is that of large Government purchases, at a lower price per dose than under monopoly pricing to individuals: a centralised purchase would exploit economies of scale, so as to benefit both patients and private developers. Batson and Ainsworth (2001) name also the publicness of the technology for an AIDS vaccine and for AIDS prevention as one of the sources of the general underinvestment. More specifically, the HIV vaccine would be a global public good, since its benefits extend beyond national borders and people who are vaccinated reduce the probability of transmission to those who are not (positive externalities). According to them, this explains not only the low investments by private firms, which cannot reap many of the benefits of their investments, but also those by national governments, which have little incentive to invest in vaccines for strains of the virus and for people outside their borders.

The idea that there is a diffused sub-optimal investment by both private and public entities is also present in the work of Archibugi and Bizzarri (2004). The reason, according to the authors, lies in the fact that vaccines' major costs reside in the initial research, whereas duplication is less costly; in addition, their diffusion and administration poses a number of organisational problems. Hence, vaccines are global public goods and some solution has to be found, in order to ensure that socially optimal investment is pursued.

A careful analysis of the literature, however, shows that, especially for neglected diseases, the issue may be missing markets rather than market failures. That is, the issue may be that, since developing countries do not possess the resources to purchase vaccines, private firms do not see any profit opportunities in the research behind them and eventually do not invest. For instance, Kremer (2000) argues that the notion of missing market is another reason, besides market imperfections, for the lack of involvement in research on vaccines against neglected diseases. Similarly, Rosiello and Smith (2004) see the private sector's limited investment not as a result of market failure at all, but in terms of missing markets due to individual consumer's budgetary constraints. The question of whether we are dealing with market failures or missing markets is important, as the policy recipes differ in the two cases. In the case of missing markets, demand has to be created and this result would be enough to provide the necessary incentives for private firms to invest. In the case of market failures, the economic literature suggests that Government intervention is needed in relation to the production of the good, since even in the presence of demand, the private sector would not provide the good at a socially optimal level.

The argument is favour of missing market rather than market failure is supported by the fact that vaccines *per se*, do not qualify as public good. The two attributes of non-excludability and non-rivalry are not applicable to a vaccine: it is possible to exclude others from consuming the vaccine dose and a person's usage prevents another person from taking it at the same time. Vaccines suit rather better the definition of *merit goods* (Musgrave, 1959), i.e. goods that would be under-consumed (and under-produced) in the free market economy, due to externalities or myopic decisions (short-term oriented), while an individual or society should have it, on the basis of a norm other than consumer preferences. The fact that vaccines can be defined as merit rather than public goods does not affect the way they are to be supplied, being in both cases provided by the

Government, but does impact the principles behind their public provision. Merit goods supply on the part of the Government forces consumption decisions, interfering with consumer autonomy, in order to reach a consumption level that is socially desirable, but not necessarily in line with individual preferences Pessoa (2006). Therefore, merit goods should be provided by the Government because of their great importance for society as a whole and Government's responsibility towards citizens, that is for reasons that go beyond merely economic evaluations and involve broader societal values of equity, fairness and justice in the access (at least at a minimum and decent level) to goods and services having an inherent value in themselves, such as health (Orsenigo et al., 2006).

The situation is however different in relation to vaccine *research.* As argued by Kremer (2000), the distortions in the market for vaccine research are greater than those for vaccines themselves: the sources are those explained by Arrow (1962) in his well-known article about R&D publicness and reside in the imbalance between private and social returns, being the latter typically twice the former, as reported by Kremer (2000). In addition to the classic arguments in favour of the public funding of research activities, the literature argues that vaccine research display further characteristics that amplify the underinvestment consequence of the public good nature of research. First, as for drugs in general, patents do not offer perfect protection and it is often possible to design around them. This factor makes it difficult to appropriate the benefits of the research and, as a result, private developers lack incentives to invest in costly socially valuable research projects (Kremer, 2000). In the case of vaccines, moreover, there is a so-called time consistency problem, since vaccine research is very expensive, but the vaccine can be produced at low cost: once it is developed Governments may use their power to keep prices close to marginal cost, hence not covering the initial R&D investments already sustained by firms, thereby deterring industry from investing in such R&D in the first place (Kremer, 2000; Glennerster et al., 2006). In addition, vaccine research and development is a global public good and creates the potential for a free riding at the country level, since its benefits expand beyond national borders and each country may be tempted not to invest in it and wait for gaining benefits from foreign vaccine R&D investments. Obviously, this is exacerbated for the smallest and poorest countries (Berndt et al., forthcoming). Hence, the argument of publicness in the research on vaccines, coupled with the peculiarities described above, provides evidence of the existence of some forms of market failure and justifies, again, public intervention, as in Arrow (1962).

All in all, from the analysis of the literature, the vaccine industry shows some characteristics (some of which it shares with drug development in general) that imply a lack of incentives for private firms to invest in vaccine research. First of all, due to a problem of missing markets, the private sector does not expect profits to compensate the significant costs of research for diseases affecting primarily poor countries and thus does not invest in it. Despite a widespread agreement, the issue of publicness of the vaccine itself lacks traction and can be removed from the causes of market failure, with the only possible exception of the presence of externalities in vaccine consumption due to the fact that people underestimate the value of the vaccine and tend to under consume it (Kremer, 2000).

While the notion of market failure does not capture the problems related to vaccine production and consumption, it does capture some of the problems connected to vaccine research and development. Vaccine R&D does qualify, at least to a certain extent, as a

public good, following the typical reasoning of Arrow (1962). This result implies that, according to the literature, the Government should be definitely involved in the production and provision of vaccine research and development, although it is not clear which practical solution is most desirable. The next section will deal with this challenge, by trying to identify pros and cons of the solutions currently in place.

2.3 Policy solutions

As discussed above, in the presence of market failures, Government is the only actor able to reach the best possible outcome, since it does not operate under a perspective of profit maximisation Arrow (1962). The issue is to align private incentives to social incentives, so that private purposes correspond to public ones and social welfare is maximised. This can be done through subsidies (if externalities are positive) or through sanctions (if negative); in addition, the Government can decide to regulate the market and create standards, which the private sector has to comply with. Hence, in general, the solutions to market failure proposed in literature, no matter which source has caused it, can be classified into two broad categories: on the one hand, public provision, on the other hand incentive creation/alignment mechanisms.

In the first case the Government is in charge of producing and providing the public good to citizens, usually in exchange for some kind of taxation. In the second case, Government does not intervene directly, but through incentivising mechanisms, such as subsidies to the private sector aimed at encouraging the production and provision of the public good. In the case of research, its publicness is solved through the same typologies of policy instruments: either the Government invests and undertakes research activities, or it does provide subsidies of various kinds (for example, tax credits) to those private firms performing these activities on behalf of the public sector.

According to David (1993), in the case of market failure caused by the presence of a public good, three specific solutions can be put in place, namely the provision of subsidies, direct governmental production, or a regulated monopoly. If the public good in object is research, the three arrangements for the allocational problems in the production of knowledge become the so-called three P's, patronage, procurement, property, which reflect the characteristics of the three solutions named above. Patronage is the system of awarding publicly financed prizes, research grants and other subsidies to private individuals, in exchange for full public disclosure. Procurement refers to government's contracting for intellectual work, aimed at public purposes. Property relates to providing inventors with exclusive rights, the most important of them being patents, to use and commercially exploit their invention. David (1993) describes advantages and drawbacks of each of the three mechanisms. Prizes and research grants (patronage and procurement) are flawed in that public authorities are not able to set efficient terms for prizes in advance; in addition, the agreement that might be reached, which is of necessity imperfect, involves high transaction costs in the process of arriving to it. Conversely, patents do not show this disadvantage: it is for the market to determine the appropriate economic reward ex post. However, patents prevent knowledge to be used by others in the pursuing of successive inventions; with patronage and procurement the knowledge must be, instead, completely disclosed, so as to secure the prize. Another problem regarding prizes and patents is that these mechanisms imply a reward based on priority, giving rise to competitions with a "winner-takes-all" structure. This might create a situation with too many contestants in the race for priority, as well as inefficiencies in

resource allocation, with the so-called common pool problem causing a tendency towards an excessive investment of R&D funds and a risk of dissipating private rents just to obtain the prize before competitors. The race for priority may undermine the quality of the final outcome of the research process, since it will be the earliest proposal to win, but there is no certainty that this will also coincide with the best. What if another contestant discovers a better invention after a while? Social welfare would suffer from having assigned the grant/prize to the fastest but not best discovery.

The arrangements commonly suggested to address the market failure in the vaccine industry reflect the types discussed by David (1993). Policy recommendations try to contemporary address the problems of the public good nature of vaccine research, the externality issues in vaccine use, and the missing market problem affecting vaccines for neglected diseases. In so doing, they attempt to address the trade-off between the goal of creating incentives for R&D, for which high prices are necessary, and that of ensuring a wide access to drugs and vaccines once developed, which would require low prices: it is commonly agreed upon that well designed incentive mechanisms can pursue both goals effectively (Glennerster et al., 2006). In this respect, two main type of policy solutions can be identified, “push” versus “pull” mechanisms. The former are those addressing the supply side of the problem, while the latter aim to correct the imperfections on the demand side.

Batson and Ainsworth (2001) provide a useful description of the most used push and pull strategies in the vaccine industry. Among push devices, they name first strengthening capacity in developing countries through investment in building national infrastructures for applied vaccine development (especially for clinical trials). A second strategy is to finance efficacy trials in developing countries. Last but not least is the mechanism of financing manufacturing capacity. The purpose of the first two is to make developing countries better partners for vaccine development, reducing the costs of R&D and improving the scope for efficacy trials, and to allow them to participate in trials of candidate vaccines vetted by international scientific review, helping to accelerate the global development of a viable product. The third strategy is aimed at reducing reluctance to invest early in capacity that might be wasted if the vaccine efficacy trial failed. Push mechanisms, thus, work as subsidies to create and orientate supply side incentives towards the socially optimal goal of a vaccine development.

The pull strategies reported by the authors are more numerous. First, they name increasing uptake of existing vaccines, since the establishment of commercially appealing markets in developing countries works well in attracting investment for future product development. Second, they mention the use of differential (tiered) pricing for developing country markets: in this way, the private sector can recover its investments in R&D thanks to the high margin obtained in the markets of rich countries, while offering the vaccine at low prices in poor countries. Other solutions often applied have the purpose of guaranteeing a future market for a potential vaccine, for example financing mechanisms, such as contingent loans to developing countries for the purchase of vaccines, or trust funds mobilizing support from the global community to purchase vaccines for the poorest countries. Obviously, these financing will become available only if a product with certain predetermined criteria is eventually developed. The last arrangements to be included by Batson and Ainsworth (2001) among pull mechanisms are prizes and transferable patent extensions, thanks to which a firm could be given the right to extend the patent of another product in its portfolio, in exchange for the

production and provision of a newly developed vaccine to developing countries. Hence, in general, pull mechanisms try to create incentives for private firms to invest, based on the guarantee of future sales. In doing so, they work also as a solution to the other major problem in vaccine development, especially for neglected diseases, namely the fact that there is no certainty that if and whenever a vaccine is developed there will be a market for it.

These two broad sets of mechanisms show different characteristics, advantages and disadvantages that make each of them suitable for some situations, while they prove useless if not counterproductive in others. As a consequence, a strong debate has developed, with contributors varying from economists to health policy experts to vaccine researchers. A detailed discussion about the relative suitability of each mechanism is provided by Kremer (2000), who argues that the two groups of strategies are appropriate for different stages of the vaccine development process. According to him, push mechanisms provide stronger incentives during early stages, while pull mechanisms are more pertinent in later periods. One of the major advantages of pull strategies lies in the fact that researchers are forced to focus their efforts and to carefully select research projects among those with the best prospects for success as useable products, rather than pursuing secondary goals such as publishing journal articles (Kremer, 2000; Glennerster et al., 2006). In fact, unless and until a vaccine is developed, no prize is due by the Government. However, the author refers to a risk of adverse selection, since those firms expecting high future profits will be the least inclined to accept public involvement in order not to share them. Thus, pull mechanisms allow a strong focus towards the goal, by linking payment to results, and avoid push mechanisms' monitoring problems. A clear example of the incentives provided by pull strategies is represented by the tax credit linked to the sale of a vaccine, introduced by President Clinton's 2000 US budget. Pull mechanisms avoid another problem pertaining to push solutions, namely the fact that research funds are often allocated on the basis of political rather than scientific considerations, while pull mechanisms provide a payment wherever and by whoever a vaccine is developed. Push strategies, though, are beneficial in that they act as a stimulus to basic research and create spillovers for other researchers, which may be crucial for exploring alternative research paths initially not considered, but that might later prove worthy attention. In addition, push mechanisms and the centralisation they imply allow risk sharing and knowledge spreading and thus avoid effort duplication; furthermore, they do not require specifying the output ex ante, which is a precious benefit in the case of vaccines, where the difficulty of defining the outcome in advance is made even stronger due to their scientific complexity.

In the literature there is a general agreement upon the idea that, given their peculiarities, push and pull mechanisms should be combined so as to reach the best possible incentive scheme towards vaccine development. While push programs are said to be better suited for early stages of vaccine development process, pull strategies are conversely preferred in later periods (Kremer, 2000). Push programs are specifically appropriate to sustain basic research and clinical development, while pull programs are preferred during later, more applied stages of research, so as to encourage private firms to turn research into products (Glennerster et al., 2006). Notwithstanding these considerations, the debate on push versus pull strategies is still open. Advocates of the former name the benefits arising from not choosing a research path too early; defendants of the latter mention the advantage of not paying until a vaccine is developed. Among the authors in favour of push mechanisms are Archibugi and Bizzarri

(2004), who propose a global fund to which each country (both industrialised and developing) contributes according to the ability to pay principle or proportionally to its GDP. The fund should be in charge of international coordination through decentralisation of funding decisions, though keeping control of them; it will oversee a periodic evaluation of the results, performed by scientific peer review and from subjects that do not belong to the scientific community. They criticise pull mechanisms, since, according to them, they generate too much competition among groups and implicitly promote knowledge secrecy. Another push-oriented contribution (at least partially) is provided by Nathan (2007), who advocates the creation of open access drug companies, fee-for-service sites for which Governments would provide subsidies and funds, aimed at the collaboration among academics and industry professionals.

Pull mechanisms are by far those attracting the most attention in current periods and they have been gathering momentum. Among them, the most common form is represented by Advance Market Commitments (AMCs), through which the public actor commits to the purchase of the product when it is developed. An example of AMC, currently being piloted is that for a pneumococcal vaccine (see http://www.vaccineamc.org/ for more details).[2] According to Glennerster et al. (2006), AMCs hold great potential to reduce economic uncertainty for private firms and give investors a guarantee that returns can be expected if scientific challenges are overcome and a product is eventually developed. This pull mechanism is aimed at reducing significantly the risks that are unique to the markets for diseases concentrated in poor countries, specifically that, once R&D investments had been made, a company would face enormous pressure to sell the product at a very low price. Hence, advance purchase commitments create a demand-side incentive scheme, by ensuring private firms that there will be a market for the vaccine developed. In this way, they represent a solution more to the problem of missing markets.

Similarly, Kremer (2000) strongly advocates AMCs as the best solution to market failure. He compares them with other pull mechanisms, and argues that an AMC's advantages significantly outweigh their disadvantages and concludes that the best initiative to provide the adequate incentives to research on vaccines is represented by a legally binding commitment to buy the final product. For example, he criticises patent extension to another drug, since they prolong monopoly, thus placing the entire burden of financing vaccine development to patients in need of another drug, acting like a tax on that medicine; in addition, there is no reason to believe that the designated firms are necessarily those with the best opportunities for vaccine research. Concerning cash prizes, which are more similar to commitments, he states their preferability to patent extension, since they create a greater link between payment and vaccine quality, and they promote free competition in manufacturing newly invented goods; however, they are still less attractive than purchase commitments, since they are not finalised to a specific outcome. Finally, the author identifies the problems of research tournaments (those mechanisms in which a sponsor promises a reward to whoever has progressed the furthest in research by a certain date): the disadvantages of these lie in the fact that a payment must be made no matter what is developed, in the risk of collusion between participants, and in the potentially biased decision about which research field choose.

[2] Website last accessed on 17/01/08

AMCs are not without their critics. For example, Licht (2005) argues that, as currently proposed, AMCs would resemble a long term contract aimed at late stage and existing vaccines more than they would resemble markets, providing neither a stimulus to research on new vaccines, nor direct research support. In addition, they reward scientific secrecy rather than knowledge sharing. Overall, AMCs do not provide enough incentives to small firms, where most innovation is taking place, and for basic research, addressing more the late stages of vaccine R&D. As a consequence, they would be more suitable to diffuse existing vaccines, rather than incentivising private firms to pursue research on new vaccines.

Other contributors, who favour pull-oriented approaches, present alternatives to AMCs. For instance, Winters (2006) proposes the institution of a substantial prize fund as an explicit solution to the free riding problem, consequence of global publicness of research on vaccines. Countries would continuously contribute by predetermined GDP percentage point donations to the fund, which would be administered by a lean secretariat. The prize would be negotiable, but always proportionate to clinical evidence of the innovation's ability to improve disability-adjusted life years (DALYs). Similarly, Stiglitz (2007) suggests a medical prize fund that would reward those who discover cures and vaccines. By employing the same funds already devoted to drug R&D, Governments could finance a prize fund, which would award the biggest prizes for developers of treatments or preventions for costly diseases affecting a large number of people, especially in areas in which needs are well known, so that clear goals can be set in advance. A scientific panel would be in charge of establishing priorities, by assessing the number of people affected and the impact on mortality, morbidity, and productivity and, once the discovery is made, it would be licensed. Other authors recommend linking rewards to the actual ability of the newly developed product (drug or vaccine) to improve patients' health. For instance, Nathan (2007) advocates the creation of an additional patent track that directly aligns incentives with medical needs. This 'track 2', voluntary and additional to the traditional patent system, would reward patent owners who address the most serious and diffused diseases and address their products to the largest number possible of people.

The debate about push and pull mechanisms can be interpreted in the light of the debate on which of the three P's is to be preferred in the case of market failure in the vaccine industry (David, 1993). More specifically, pull mechanisms act like prizes and hence display the same advantages and disadvantages; similarly, push strategies are a sort of procurement, with the Government encouraging private firms to perform research on behalf of public sector through direct or indirect subsidies.

Concerning pull approaches and in particular, prizes, which are the most cutting-edge solutions in place, their major problem in the case of vaccines is that, in order to set a prize, the outcome of the research has to be identified ex-ante. This implies that there needs to be an actor able to define it in a detailed way and evaluate it when some outcome is provided. In the specific case of vaccines, this issue is particularly relevant, due to the scientific complexity involved in the process (see next section). In addition, even the definition of the prize is not straightforward at all, since it really depends on the organization type in charge of developing the vaccine (Public, private or hybrid institutions): different organizations pursue different objectives and, as a consequence, different incentive systems have to be put in place in order to stimulate the right degree of investment/effort (this problem is shared even by push mechanisms). Furthermore,

the consequences of the fact that another contestant came up with an improvement of the original idea after the prize has already been granted would be particularly severe in the case of vaccines, where public health is involved. In vaccine development, especially for very complex vaccines, such as the HIV/AIDS vaccine, a pull/prize mechanism's characteristic which is often considered as an advantage could bring additional problems, namely the fact that research projects must be selected early. In the case of vaccines, however, this task is made more difficult by their scientific difficulty and there is a risk that important research paths are initially left out, as they are not considered worthy any investment.

The drawbacks of pull/prize mechanisms, though, would be overcome through implementation of push/procurement solutions or patents and property rights. For example, the problem of ex-ante definition of a prize (which prize and its amount) would be solved, since under both mechanisms it would be the market that decides the reward ex-post. However, other problems would be involved: for patents the most important would be related to the presence of a monopoly over a merit good and the patent infringement for each subsequent invention. This might prove counterproductive in the process of successively improving the vaccine, with severe consequences on public health. In addition, patents are not the best arrangement to give the right incentives to private firms, due to the well-known imperfect protection they guarantee. This is especially true for vaccines addressed at developing countries, which are well known for not providing adequate protection for IPRs for pharmaceuticals (Kremer, 2000).

Among the two extreme positions of the advocates of push versus pull mechanisms is the intermediate alternative solution to market failure in the vaccine industry represented by Public-Private Partnerships (PPPs). These programs involve the public and the private sector, which join their efforts towards a common goal, in this case vaccine discovery and development. PPPs are often defined as a merger between push and pull strategies, showing characteristics common to both of them. However, they are sometimes considered more of a push solution, since the public actor usually provides research subsidies in the form of funding or activity collaboration with private professionals. A definition of PPPs is provided by Buse and Walt (2000a), as "*a collaborative relationship which transcends national boundaries and brings together at least three parties, among them a corporation (and/or industry association) and an intergovernmental organization, so as to achieve a shared health-creating goal on the basis of a mutually agreed division of labour*". The authors also present a PPP categorisation, according to their organisational form (elite committee model, NGO model, quasi public authority model), the activity undertaken (consultation, co-ordination, operational), or finally the function they perform (product-based partnership, product development partnership, systems/issues-based partnership). Within the latter classification, the most interesting PPPs for the vaccine industry are product development PPPs, since they are specifically targeted at correcting market failure (Buse and Walt, 2000b).

PPPs show several advantages related to the division of labour among parties, with each party performing the tasks for which it is more skilled, and to the incentive alignment they create, through risk sharing. In addition, as argued by Buse and Walt (2000a), they are useful to private firms for public relations, image enhancement and brand development. In addition, according to Widdus (2001), they are especially beneficial in a number of situations: first, where traditional ways of working

independently have a limited impact on a problem; second, whenever potential collaborators can agree upon specific goals; third, if the two sectors display relevant complementary expertise; fourth, when the long-term interests of each sector are fulfilled and there are, thus, benefits to all parties; and finally, where the contributions of expertise and resources are balanced among parties. However, in order to enhance their effectiveness, PPPs must reduce the costs and risks borne by private firms, so as to provide them additional incentives to engage in R&D for the low-margin products needed by the developing world (Wheeler and Berkley, 2001). Since companies are required to shift resources from profitable activities to neglected diseases, they must perceive additional benefits in doing so, such as gaining access to knowledge, technology, competitive advantage, or markets that they might not otherwise obtain. Specifically, the public sector must be convinced that its investment will effectively pursue public health interests and provide an adequate return.

Critiques to PPPs have been raised by a number of authors. Among them, Nathan (2007) argues that, despite their advantages, they are suitable only for a few diseases and that they should be substituted by open access drug companies, which can institutionalise and improve the best features of PPPs. In addition, according to Archibugi and Bizzarri (2004), a PPP's effectiveness is limited by public institutions' insufficient expertise in contract dealing, with the risk for the public actor of losing control and ownership over the common initiative. Similarly, Richter (2004) raises doubts that the actual goal pursued by PPPs is public interest (defined in terms of health for all): each party might have different goals and, as a result, the final outcome of PPPs might be vitiated by partners' conflicting interests. As an alternative to PPPs the author suggests replacing the PPP policy paradigm by a policy paradigm really centred on public interest.

Nevertheless, PPPs appear to be the policy solution to market failure in the vaccine industry with the most relative advantages over alternatives, since they combine elements of push and pull mechanisms: for example, in line with push mechanisms, PPPs try to overcome the problems related to non-disclosure and duplication of efforts, typical of prize-based systems; on the other hand, by combining public and private efforts and sharing risk, though leaving the control over the common initiative in the hands of the public sector, they attempt to avoid that public resources are not finalised towards public interest goals. Indeed, public-private partnerships were born to solve the problems of both mechanisms, which had proven to be inadequate in dealing with market failure in vaccine development.

2.4 Summary

The literature reviewed in this section shows that a market failure can be identified in vaccines only in relation to positive externalities in vaccine consumption due to herd immunity. Vaccines per se are not technically public goods because they are excludable. Many of the perceived problems related to vaccines are instead linked to (a) their nature of merit (rather than public) goods, and, therefore, to judgements of value and social equity that go beyond pure economic rationality; and (b) to missing markets. These distinctions are important because market failures pose the problem of who is going to supply the good, whereas missing markets pose a different problem, i.e. how to create markets by increasing poor countries' purchasing power

A different conclusion can be reached in relation to vaccine research, which can be considered to some extent a public good and therefore warrant government intervention, either in the form of direct provision, or in the form of various types of incentives to the private sector.

3. Beyond Market Failures: Scientific, Technical and Social Challenges of Developing an AIDS Vaccine

Both the 'push' and 'pull' policies reviewed in the previous section are based on the assumption that innovation is a function of the amount of resources invested. While the availability of resources certainly is an important part of the equation, the current state of *fundamental* technological and scientific knowledge bounds what can be achieved (Mowery & Rosenberg, 1979). Scientific advances and innovation tend to proceed along relatively rigid paradigms or trajectories. The sciences have distinctive ways of conceptualizing problems and specific methodological approaches that typically accompany them (Hacking, 1996). The combination of specific ways to conceptualize problems and of methods with which to address them defines which questions are worth answering and how to answer them, bounding the path of advance. This makes simply pouring more money into research ineffective when the problems that need answering are outside of the current trajectory. In order to address the issue of vaccine innovation, therefore, it is useful to look at the type and evolution of the scientific disciplines involved.

The diversity in ways to frame problems and in methodological apparatus; the cumulativeness of 'normal science' (Kuhn, 1962); and social separation through separate careers, journals and conferences confer to these individual scientific disciplines the nature of cultural systems (Knorr Cetina, 1999; Pickering, 1992).[3] Scientific disciplines as cultural systems evolve in interaction with each other – however, such interaction is often characterized by conflict deriving from the clash of their different ways to frame and solve problems (Fujimura & Chou, 1994; Galison, 1996). Furthermore, to the extent to which scientific disciplines are also professionalized occupations, their interaction is characterised by a struggle over jurisdiction on problems to be solved and over status in the wider society (c.f. Abbott, 1988). Indeed, historians and sociologists of science have shown how the evolution of scientific understanding is linked to a complex and changing division of work within scientific communities (Galison, 1997; Latour, 1987). Similar issues of cultural and professional conflict characterise technological innovation (Garud & Munir, 2006; von Meier, 1999).

The cultural nature of scientific and technological innovation has important implications. First, while major scientific breakthroughs make it possible to frame old problems in new perspectives and to identify new problems and new routes for their solution, their acceptance and diffusion is an often difficult process of cultural change, which is likely to involve an important degree of conflict between a variety of social groups. Second, there may be the equivalent of significant 'market failures' in the social technology through which the scientific knowledge basis advances. For instance, the struggle between scientific professions can cause phenomena of 'capture' of problems within specific

[3] Culture here is used in the sense of a "historically transmitted pattern of meaning embodied in symbols, a system of inherited conceptions expressed in symbolic form by means of which men communicate, perpetuate, and develop their knowledge about and attitudes towards life" Geertz, C. 1973. ***The interpretation of cultures***. New York: Basic Books..

scientific disciplines, so that alternative explanations that could be proposed by looking at problems through different disciplinary lenses tend to be ignored (e.g., the SMON epidemic in Japan in the 1960s (Kono, 1975).

Finally, despite the importance of scientific theories in affording new ways of framing and addressing technological problems, technological research remains highly empirical in nature and innovations in many fields have been achieved without any clear understanding of why they work (Vincenti, 1990). These innovations typically pave the way for further scientific advancement, as they open up new fields of enquiry for scientists – as it has been the case, for instance, for thermodynamics, which derived from the need to understand and improve early engines. The relationship between science, technology and innovation is therefore often highly complex and intricate, being characterised by feedbacks and lags, and changing over time. It is therefore not automatic that progresses in science will deliver advances in technologies, and what is more, the process through which this may happen is far from linear or straightforward.

The complex processes through which science and technology advance and interact bring to the fore an issue that is only marginally considered in the current 'market failure' policy debate, i.e. the impact of the organizational and institutional set up on the effectiveness of the search for vaccines. Relevant technological and scientific knowledge is distributed across a wide range of organizations, including universities, research institutions, pharmaceutical and biotechnology companies, and not for profit institutions. In recent years, the organizational arrangements of vaccine development have been characterized by significant turbulence, with new types actors – Public Private Partnerships in particular - entering the field, and others - such as NIH or 'big pharma' - redefining their roles and changing the way in which they carry out their tasks. This turbulence reflects the complexity and uncertainty that characterizes the search for vaccines, and the accompanying uncertainty over how to distribute activities to organizations or groups, monitor them, evaluate their results, and integrate such results with those of other organizations or groups. As institutional and organizational set ups are typically very slow to change and play a central role in the creation and maintenance of specific ways to deal with problems (e.g., Malerba 2004; Cacciatori & Jacobides, 2005) and in cultural development and maintenance (Douglas, 1987), the 'market failure' analysis needs to be complemented by an examination of the ways in which the current organizational and institutional arrangements facilitate or hinder the search for effective vaccines.

This section will review the literature in the AIDS vaccine field that provides preliminary evidence in support of the arguments presented above. The first three sections have the objective of showing the multiple dimensions and particular difficulty of the problem of developing an AIDS vaccine by examining its scientific (Section 3.1), technical (Section 3.2) and social (Section 3.3) challenges. Section 4 will then move on to the organizational challenges, reviewing the little existing literature on the subject.

3.1 Scientific challenges

Several contributions have highlighted the reasons why HIV is unique in presenting vaccine researchers with a particularly difficult problem (Berkley & Koff, 2007; Garber, Silvestri, & B, 2004; IAVI, 2006; Little & Surjadi, 2000; Nkolola & Essex, 2006; Tonks, 2007). The challenges can be summarized as follows:

3.1.1 HIV is hypervarible.

The speed at which HIV changes is perhaps one of the main obstacles to the development of an effective vaccine. HIV does not per se mutate more rapidly than other viruses. It does, however, reproduce at an astonishingly high rate, producing about 10 billion copies of itself per day. For this reason, circulating HIV is much more diverse than any other virus for which a vaccine exists, so much so that the genetic diversity of HIV in an individual six years after infection is comparable to the diversity of influenza viruses circulating each year and that super-infection with different clades in a single individual is possible (IAVI, 2006). The diversity of HIV poses the important questions of whether a single universal vaccine can be created. Furthermore, it poses the question of whether the several years that are currently needed to bring a candidate vaccine to clinical test do in fact seriously harm the ability to effectively test vaccines, since by the time a candidate vaccine undergoes clinical trial, the circulating HIV is already significantly different. An added complication is that it has so far been difficult to establish the impact that HIV hypervariability will have on the usefulness of a vaccine, as the classification system through which diversity is measured is genetic, rather than immunologic. It is therefore unclear how genetic diversity impacts on the immune response required to prevent infection. In monkeys, however, live attenuated vaccines only protect against the same type of virus used in the vaccination.

3.1.2 The correlates of protection against HIV are unknown.

The second important challenge that AIDS poses to researchers is the fact that the correlates of protection – i.e. which specific immune response correlates with protection from the infection - are unknown. This knowledge is important, as it serves two purposes, (1) it enables researchers to focus their efforts toward stimulating that specific immune response and (2) it facilitates understanding as to whether vaccination is effective during trials, because measuring the correlates of protection in a vaccinated person will enable researchers to conclude whether he or she is protected. Despite its importance, there are modern vaccines that have been developed without prior knowledge of the correlates of protection, in particular the pertussis and rotavirus vaccines (Little et al., 2000). Furthermore, the definite proof of the correlates of protection is often achieved only through "retrospective analysis of data from a clinical trial in which the vaccine conferred partial protection against a naturally acquired disease" (from the 1994 presentation to the NIAID HIV Vaccine Working Group of Mary Lou Clements', running the AIDS vaccine trials at John Hopkins University, quoted in Cohen, 2001, p.238). In the case of AIDS, the uncertainty over the correlates of protection is worsened by the fact that there is no recorded case of an individual becoming ill and then clearing the infection. Scientists therefore do not have an effective immune response that they can try to imitate. The only clues come from individuals that do not become infected despite multiple exposures, and from the so-called long-term non-progressors or elite controllers, who, despite testing positive to the HIV, do not develop AIDS. These individuals are however extremely rare and systematic studies are fraught with difficulties (Cohen, 2001b; IAVI, 2006).

3.1.3 HIV's ability to evade immune response.

HIV is a retrovirus whose surface (the 'envelope') is covered by glycoproteins. Two of these glycoproteins, gp120 and gp41, are responsible for the attachment of the virus to

the receptors of human CD4 cells, which are part of the human immune system, and which enable the virus to infect them. The surface proteins of HIV responsible for attachment to the human CD4 cells are covered with carbohydrates, with the 'binding sites' typically shielded from neutralizing antibodies. Furthermore, the virus presents the immune system with decoys, which further reduce the production of neutralizing antibodies. These challenges make developing vaccines based on neutralizing antibodies, which is the strategy on which most vaccines are based, particularly difficult. In addition to these, however, HIV poses a particularly thorny issue because it is a retrovirus, which incorporates itself into the genetic code of the host and establishes an infection that lasts for the life of the subject. HIV infected cells appear no different from non-infected cells for long periods, and therefore escape immune defence reaction establishing a persistent reservoir of the virus in the body. A vaccine has a very short window of opportunity to prevent infection, as after the first week the virus is integrated within the host genome. So far no vaccine has been developed against a human retrovirus, and only one exists for an animal retrovirus. Finally, HIV attacks and infects CD4, which are key cells in the setting up of the immune response to its infection.

3.1.4 Lack of an animal model.

HIV is specific to humans, and therefore there is not a perfect animal model on which to run tests. The two closest models are the chimpanzee and asian macaque. Chimpanzee can become infected with HIV, but they do not progress to develop AIDS. Asian macaques can become infected with a relative of HIV, the Simian Immunodeficiency Virus (SIV). Researches have encountered significant difficulties in using chimpanzees, because of their cost and ethical issues in using them in experiments. Most animal experiments have been carried out on macaques. However, SIV differs in many respects from HIV. In particular, the identification of immunogenic regions for monkeys does not directly translate into the immunogenic regions for humans, as the immune system of the two species differ. The extent to which the monkey model is predictive of protection in humans is therefore uncertain and debated. The early discussions about when to begin trials often revolved over whether animal testing was necessary or not. There is now a growing consensus that animal testing is required. Monkeys are however very expensive, so large scale comparative animal testing was for a long time not possible.

3.1.5 Multiple routes of infection

HIV can be transmitted sexually, intravenously and orally (through breast feeding). Animal studies suggest that the immune response most effective to prevent infection may differ with each route of infection, and a vaccine that works against one route of infection may not work for others.

In short, HIV hypervariability, its ability to evade immune response, and, the short window of opportunity for a vaccine induced immune response to prevent infection imply that HIV is a particularly difficult problem to solve. The lack of correlates of protection, the lack of a good animal model and the fact that the imperfect models available are expensive imply that there is no clear direction in which to search for a vaccine and that experimentation, a key element in the development of both knowledge and industrial innovation (Thomke, von Hippel, & Franke, 1998; Thomke, 1998), is highly constrained. Because of these reasons, scientists are divided on whether a vaccine is possible given the current state of scientific understanding (e.g., Steinbrook, 2007), and even the

proponents of an AIDS vaccine argue that its development will require long term commitment (IAVI, 2006), particularly so after the disappointing results of recent clinical trials (IAVI, 2007).

3.2 Not just science: Manufacturing and delivery issues

Perhaps, the most noteworthy feature of the major PPP operating in the AIDS vaccine field, IAVI, is that it was born with the idea to address a perceived dangerous disconnection between basic research and actual vaccine development. Because of the difficulties of the scientific problem that most vaccines pose, in the policy debate the issue of vaccine innovation has 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 (Milstien, 2000). However, a large body of research testifies to the need for integration across R&D and manufacturing in order to sustain effective innovation. Linking research to development and manufacturing appears to be a critical issue in the case of the AIDS vaccine as exemplified by this quote:

> "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. Together, these problems comprise what this paper refers to as the "large-scale manufacturing" challenge." (Walker, Rowely, & Hecht, 2005: v)

3.3 Not just science: Social challenges

A number of what could be termed 'social' challenges also affect AIDS vaccine development. These are often challenges faced by researchers developing other vaccines and drugs as well, particularly when clinical trials take place and markets are based in the developing world. We term these 'social' challenges as opposed to economic or political challenges because they relate to the attitudes, beliefs and values held by various stakeholders particularly those directly involved with, but who are more usually external to, the vaccine development process.

Clinical trials occur once a drug or vaccine has been developed and requires testing outside of a laboratory. As already stated human participant based clinical trials often

take place once testing using animal models has been completed. Clinical trials are deemed necessary because:

> "the only way to truly determine a vaccine's safety, effectiveness in stimulating an immune response and ability to prevent HIV infection or delay progression of HIV disease, is to test it in people." (http://aidsvaccineclearinghouse.org/trials.htm; last accessed on 07/01/08)

There are three main phases of clinical trials (Phases I, II and III) and a final post-marketing phase sometimes termed Phase IV trials. These trials can be outlined as follows:

Phase I	A small scale trial with 20-80 people to evaluate the vaccine's safety, identify safe dosage rates and any side effects.
Phase II	A larger scale trial with between 100-300 participants to further evaluate its safety and effectiveness in terms of the type and strength of immune response that it creates.
Phase III	An even larger trial with between 1,000 – 3,000 participants to further test its effectiveness but also its efficacy (whether it delays or prevents HIV infection or disease progression) comparing it to current alternative treatments or previous studies.
Phase IV	Post marketing studies that provide additional information of the vaccine's risks, benefits and use (no such studies have yet occurred for an HIV vaccine).

In January 2008 there were 39 clinical trials on-going throughout the world (http://www.iavireport.org/specials/OngoingTrialsofPreventiveHIVVaccines.pdf; accessed 07/01/08). Increasingly these trials are taking place in developing countries where there is a high degree of disease burden (UNAIDS, 2007). Linked to this, data from trials conducted in developed countries may not be applicable to populations in developing countries and therefore testing is required in these developing countries (Deen & Clemens, 2006).

Bringing clinical trials of HIV vaccines to developing countries in Africa and elsewhere in the developing world creates social challenges. In this section we will discuss what can be termed the 'constant gardener effect' relating to negative attitudes towards the pharmaceutical industry, changing attitudes to science by various publics and the practical issues with social implications associated with these for the conduct of clinical trials in developing countries, as well as, the difficulties associated with maintaining support for vaccine development over the long term. In particular, this section will highlight the implications for integration resulting from the need to conduct clinical trials in developing countries. This relates to the need to integrate different competencies between developed and developing countries, science and healthcare, science and communities, and, for profit and not-for-profit entities.

3.3.1 The 'constant gardener effect': attitudes towards the pharmaceutical industry

The John le Carre book (and subsequent film), *The Constant Gardener*, discusses the sometimes unconventional practice of drug companies in the developing world. The success of the book and film resulted in publicity for campaigns such as that by Médecins Sans Frontières (MSF) regarding access to medicines for the world's poor and who are critical of the role of the pharmaceutical industry or 'big pharma'. In this section we will outline the changing attitudes towards 'big pharma' and clinical trials. The impact

through media reports of research fraud and unethical conduct of clinical trials is also mentioned (but will be discussed in the next section in more depth). The political and economic roles played by the pharmaceutical industry has been critically discussed and evaluated within the health policy research and pharmaceutical economics/ innovation research communities and by medical anthropologists as well as by concerned scientists and medical practitioners. A number of these discussions will be reviewed below highlighting the different attitudes regarding the politics of drug companies and clinical trials, the business of pharmaceuticals and societal requirements.

Healthcare around the world has become increasingly 'commercialized' (Mackintosh & Koivusalo, 2005) with private sector actors and approaches being introduced. This includes the increasing role of multi-national companies (MNCs) shaping trade related to healthcare. Of particular reference to this study is the role of large multi-national pharmaceutical companies and their influence on the World Trade Organisation and the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) (Chaudhuri, 2005). Chaudhuri argues that MNCs have used their influence to reduce the ability of Indian drug companies to produce generic low-cost drugs with implications on accessibility of drugs in developing countries generally, not just in India. This is one issue that MSF, for example, campaigns on.

Similarly, it has been argued by Petryna and colleagues (2005; 2006) in discussing the rise of clinical trials in Eastern Europe, that the concerns for market dominance – and the profit margins that go with this – create a situation where "deliberations over the ethics of research in crisis-ridden areas are set against – even eclipsed by – the market ethics of industry scientists and regulators." (Petryna, 2005: 192). This, Petryna argues, is related to the issue she terms 'ethical variability' (Petryna, 2005) or lack there of, where ethically guidelines are developed taking local contexts as given making ethical standards more cost-effective to conduct human research. This has not only been the case for ethical guidelines but also more general pharmaceutical product registration requirements too. Industry organisations were key to the setting up of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) which has become an industry, even international, standard and which in some cases now has lower requirements than previous national level regulators had set up (Abraham, 2002).

The pharmaceutical industry's adoption of a 'profit-over-people' approach outlined above has reduced public trust in the industry (Epstein, 2007). Thus books, such as Sonia Shah's entitled *The Body Hunters: Testing New Drugs on the World's Poorest Patients* (2006), are overtly critical of the role of the pharmaceutical industry in clinical trial research in developing countries arguing that 'big pharma' 'cannot be trusted'. Ford (2003) in discussing the role of pharmaceutical companies talks about the dominance of markets and profits over health needs in drug development. At the level of non-governmental organisations the website of the fore-mentioned MSF talks about how pharmaceutical companies put market profits at the expense of human lives (MacDonald, 2001). It was the result of such fears by people from all over the world – not just practitioners or academics in the area – that led to the blocking of an attempt by MNCs to persuade the South African government not to give low-cost generic drugs to people with HIV/AIDS (Dukes, 2002).

However Dickson (2006) in reviewing Shah's book does acknowledge that vocal criticism of the pharmaceutical industry and the process of clinical trials has created a situation in which there has been a 'globalisation of bioethics' whereby it is no longer a matter of whether regulation should be considered but what type of regulation is needed. Despite this, with the increasingly visual reporting of irregularities, fraud and medical disasters in clinical trials there is a lack of trust by the public on 'being experimented on' and more generally regarding the 'politics of medicine' (Slight, 2004).

3.3.2 Changing attitudes to science

Building on the public understanding of science literature but also other literatures from sociology, science and technology studies and anthropology we will now discuss stakeholders changing attitudes towards science, in particular focusing on the changing attitudes towards risk (as evidenced above by ideas towards 'being experimented on') in relation to wellbeing and new medical products. The emphasis of this section will be on both attitudes towards the introduction of new vaccines as well as the underlying concerns around the science of the vaccine. The reason for this is that while many studies have focused on public attitudes towards vaccines there is a parallel scientific based discussion that at times mirrors many of the public debates about the benefits of certain types of vaccine. This creates a number of practical issues with social implications affecting clinical trial activities in developing countries.

Similar to a number of arguments made in the above section which relate to changing attitudes towards science (public and volunteer's perceptions of trust, risk etc.) are changes within the 'industry' of science regarding risk-benefit calculations to vaccine trials. For example, these may differ as a result of decisions made in developed countries for vaccines then when they are introduced in developing countries due to lack of strong national regulatory frameworks, product divergence due to different disease burden, vaccine efficacy or different population's health characteristics, and differing ethical concerns (Milstien, Cash, Wecker, & Wikler, 2005). The result is that:

> "Vaccines that cause serious, tangible net harm to appreciable numbers of healthy people are unlikely to succeed in the marketplace or in popular opinion. These complexities have contributed to an unfortunate and dangerous rigidity in international vaccine practices. The… discussion on rotavirus vaccine is a case in point. Whatever the proper threshold for vaccine risk, the key quantity in question is net predicted risk, which differs hugely in industrialized compared with many disease-endemic countries. Children in the disease-endemic countries have much more to fear from rotavirus than from the rotavirus vaccine." (Milstien et al., 2005: 723-724)

This same argument was made by Cohen in an article in Science in 2001 (Cohen, 2001a) when discussing the debate caused by the pulling off the market of a rotavirus vaccine in 1999 but he argued that for some people – not just pharmaceutical industry personnel – the issue was as much the result of potential negative press image as a cost-benefit equation per se.

Negative press images of vaccinations and clinical trials were introduced in the last section. The impact of public perceptions of risk and vaccines, particularly as a result of media reporting, has received attention in recent years. This may in part be due to the number of highly reported cases of problems with vaccinations and clinical trials in a way that previously were not so widely reported. For example, media reporting of

controversies around the Measles, Mumps and Rubella (MMR) vaccine in the UK but also in other European countries, such as Denmark, led to a reduction in MMR vaccinations, misleading the public about the fears of the vaccine – at the expense of its risk-benefit ratios (see for example Bedford and Elliman, 2000; Begg, Ramsay, et al., 1998; Dobson, 2003).[4]

Other studies have shown the role of the international media as a source of knowledge for activists regarding clinical trials of tenofivir (a pre-exposure propholaxis for HIV/AIDS) in Camaroon and Cambodia (Mills et al., 2005). While this study does not conclude that media reporting led to the closure of the trials they do, as the studies on MMR above, highlight the important role the media play in shaping opinion which the authors argue has the potential to derail future HIV/AIDS prevention studies. Similar problems were encountered by AIDS researchers in Kenya due to negative press reporting regarding intellectual property rights issues relating to the first HIV vaccine trial conducted in the country. An illustration of this reporting is provided by the cartoon in Figure 1. More recently, media reporting of both the 'elephant men' – as the UK volunteers of the clinical trial of TGN1412 (a potential anti-inflammatory drug) in 2006 became known in the media – and the falsified stem cell test results in South Korea also in 2006, may also have a future impact on public attitudes towards both science and clinical trials being examples of what can be termed 'provocative stories' (Gellin & Schaffner, 2001).

Figure 1 – Kenyan AIDS vaccine research cartoon
Published by Paul Kelemba, alias Madd, East African Standard, Nairobi (Geissler & Pool, 2006)

[4] Such reductions in vaccination numbers provides a lead in to wider debates about science communication as often vaccine controversies are framed in terms of "public (mis)understanding or lack of understanding of science, technology and its risks." (Fairhead and Leach, 2007). For more discussion on the interplay of publics and science/ technology see for example the work of Brian Wynne (e.g. Irwin and Wynne, 1996)

Scientific concerns regarding vaccines have not only been voiced and vocalised within the general public. Industry and its related spheres of actors (health policy practitioners, doctors etc.) have also voiced concern at times at the way science is portrayed but also about how science is conducted especially in relation to risk-benefit ratios. One such example is the scientific discussions that have occurred in the past with regards the use of live attenuated and other forms of vaccines. This is of particular relevance to the issue of HIV vaccines where a live attenuated vaccine has, in the past, been put forward as a potential avenue of scientific search (Cohen, 2001b). But, as highlighted above, this has also occurred recently with the introduction of rotavirus vaccine (a live attenuated based vaccine) for developing countries. One earlier example was discussions of how best to produce polio vaccines which mirrors, to some extent, the discussions more recently with regards to the way forward for HIV vaccines (Cohen, 2001b).

It is perhaps not surprising then that Fairhead and Leach (2007: 2) write, "Controversies over vaccines feed cornerstone debates of our time. For while vaccination is easily represented as a universal, neutral good, it is actually deeply bound up with politics: with struggles over status, authority and value, writ small and writ large…" In discussing the controversy over the decision by many northern Nigerian parents not to have their children vaccinated for polio in 2003 (due to fears of a 'genocidal plot against Islamic Africa'), they write:

> "Again debates and commentary expanded into far wider questions of governance. They invoked the relations between local and national government; trust in federal government and its global sponsors; the motivation of US foreign policy; scientific impartiality (Whose science? Whose vaccines?); the value of different health priorities, and, as Nigerian news spread across the airwaves and polio cases reappeared across the region, the role and responsibility of the media in a globalized world." (Fairhead et al., 2007: 2)

The practical difficulties experienced in developing countries (and where AIDS vaccine research increasingly takes place) such as that experienced in Nigeria for polio vaccination are being increasingly researched by anthropologists such as Fairhead and Leach. Accounts of the difficulties of ensuring enrolment, awareness, understanding and retainment of trial volunteers during the activities of vaccine development partnerships such as IAVI was highlighted by previous unpublished work conducted by some of the authors and other medical research centres based in developing countries (c.f. Molyneux, Peshu, & Marsh, 2005). We will now discuss further some of the influences of community beliefs and attitudes that impact practically on clinical trial activities. In particular, we will discuss volunteer enrolment and retention in clinical trials and ethical dilemmas around the trial sites relationship with mainstream healthcare provision.

Community attitudes towards clinical trials are visualised in the cartoon in Figure 1 and examples have been provided above of the potential and real impact these have on vaccine uptake and clinical trial enrolment (for example in the case of MMR vaccines in Europe and polio vaccines in Nigeria amongst others). Fairhead and Leach have studied public understanding of vaccine trials in The Gambia and provide evidence of similar situations were public perceptions have impacted on clinical trial activity. Together with Mary Small they outline (Fairhead, Leach, & Small, 2006) the various and often differing attitudes held by different stakeholders towards a childhood pneumococcal vaccine in The Gambia. They highlight how public health researchers and parents' perspectives differ with a emphasis by parents on "a perceived balance of benefit and danger – in the

extreme, of free medical treatment, versus one's child being drained of blood for sale in Europe." (Fairhead et al., 2006: 103) Often therefore discussions around ensuring vaccine trials are successful are couched in terms of trust, mis-trust and gaining trust (Molyneux et al., 2005).

These discussions in the health policy arena often take place in reference to 'bioethics debates' particularly related to issues of informed consent (the practice of an individual's agreement to an activity based on provision and understanding of all information relevant to assisting them to make their decision) and the related issue of healthcare provision during the clinical trial process. As Ferguson points out in a recent paper regarding the 2006 UK TGN1412 trial, questions of the degree to which complete understanding of the trial's activities were known together with issues of insurance (as an example of a provision made for volunteer's healthcare) were not necessarily well understood by volunteers and at times were eclipsed by other reasoning for their participation in the trials (such as monetary incentive) (Ferguson, 2008). Issues of the degree and quality to which healthcare provision is provided for clinical trial volunteers during vaccine trials has also been highlighted in studies as to the decisions informing volunteer enrolment (c.f. Fairhead et al., 2006; Molyneux et al., 2005) but also as a reason for 'big pharma's' decisions, motives and activities in (not) getting involved in the conduct of, and regulation of, clinical trials in developing countries (c.f. Abraham, 2002) which brings us back to the big pharma discussions outlined earlier.

3.3.3 Maintaining support

Even when volunteers enrol in clinical trials, there are other issues that hamper vaccine clinical trials related to attitudes linked to issues of capacity and (political) will. We will now briefly discuss the difficulties of maintaining support for AIDS vaccine development due to issues of regulatory capacity, government support and the uncertain timeline of vaccine development. We will provide an overview of how this effects funding issues at a global level but also has implications on volunteer numbers at clinical trial sites.

The uncertain timeline of HIV vaccine production due to vaccine production pipeline timings has funding implications. In a recent editorial of the New England Journal of Medicine, Richard Steinbrook, writes that scientific challenges are blocking the development of an effective HIV vaccine to the point were it may be impossible to sustain support for the research required to develop such a vaccine when there is a distinct possibility that such a vaccine will be impossible to develop (Steinbrook, 2007). McCluskey *et al* (2005) outlines the fact that this is because – as discussed in the scientific challenges section of this review – the HIV-1 virus is able to elude the human body's attempts to create natural immunity adapting and changing all the time making creating a vaccine difficult.

Lansang and Dennis (2004) discuss the importance of strong enabling environments whereby there is strong political will and vision to place an emphasis on health research such as clinical trial activities at the national level in developing countries. This is obviously required on top of international funding and commitment towards HIV vaccine development at an international or global level. The support required at a national level includes the need for promotion of research capabilities (strong public research organisations for example), training of scientists and job opportunities for newly qualified staff, finances and infrastructural and regulatory support (Kettler & Modi, 2001).

However, as some of the authors heard when interviewing health and technology related policy makers in Kenya, often the long time span before an HIV vaccine will become available makes it difficult to place an emphasis on vaccine prevention over treatment mechanisms in the light of current statistics on HIV/AIDS incidence and prevalence.

3.3.4 The implications of social challenges

This section has outlined the impact of differing attitudes by a range of actors towards the pharmaceutical sector, 'big pharma', clinical trials and vaccines as health products. Each of these difficult 'social' challenges present important implications for the organizational mechanisms and competencies required for successful vaccine development to take place. These will be discussed in more depth in the next section but in relation to social challenges, it is possible to summarize a number of different mechanisms that are mentioned earlier in this section. Negative attitudes by a variety of actors towards both 'big pharma' and clinical trials have resulted in changes in focus and competencies, not only for the pharmaceutical industry and clinical research organizations conducting clinical trials but also for activist and policy analysts in the area. The studies by Molyneux and colleagues are an example of the growing awareness and attention being given to these issues. All actors have to take on board a variety of 'new' issues from community 'sensitization'/ 'education'/ 'awareness raising'/ 'participation' to issues of intellectual property law. This requires new capabilities, skill and knowledge sets and new networks of actors working together to ensure vaccine development around clinical trials in particular can take place.

4. The organizational challenges of developing an AIDS vaccine

The technical difficulties of developing and manufacturing an AIDS vaccine, and the social difficulties involved in its development and in guaranteeing that it will be used once it becomes available require the bringing together of a wide range of diverse competencies ranging from the sub-disciplines of molecular biology to community management issues. These competencies are typically located in different organizations in the public, private for-profit, and private not-for-profit sector. How the task is divided among these organizations, the mode and extent through which they collaborate; and how the understanding and advances they produce are brought together are going to be critical for the success of the effort. The problem is made even more complicated by the fact that the mix of competencies necessary to pursue the search for a vaccine changes as understanding about HIV, vaccine technology, and social issues evolve. Therefore, the mode and extent through which the internal competencies of the organizations involved in the search and the ties among them are adjusted over time as understanding evolves are also critically important.

Although largely ignored in the policy debate, and almost absent in the academic literature, the issue of how the effort for the development of an AIDS vaccine should be organized has been rather lively debated among the scientists and the institutions involved, particularly in the US (Cohen, 2001b; Wilson, Post, & Srinivas, 2007). Building primarily on Cohen (2001b), this section provides a brief history of the early years of the search for an AIDS vaccine in the US. The focus on the US, although limiting, is due to the fact that the vast majority of research in this field has until recently been carried out there. This brief history will show the impact of the organizational and institutional set up of the AIDS vaccine field in the US on how the search has been carried out. Specifically,

it will bring to the fore how between the cultural and organizational set up of the field intertwined, influencing how the search has been conducted. A cultural approach to the study of the efforts to develop an AIDS vaccine reveals several different dimensions, in particular in relation to cultural diversity between developed and developing countries; between public and private sector; between for profit and not-for-profit organizations. In this brief overview, we highlight in particular the role of cultural heterogeneity between the scientific and occupational groups involved in addressing the scientific challenges involved in the development of an AIDS vaccine – as these played a particularly important role in the early phase of the search.

4.1 Searching for an AIDS vaccine

Soon after HIV was identified as the cause of AIDS in 1984, the search for a vaccine began. Two main sets of actors were involved. The first were a handful of small, start-up US biotechnology firms, some of whom had the backing of large pharmaceutical companies. The second were US academics who worked on the basis of funding provided by the National Institute of Health, in particular through its National Institute of Allergy and Infectious Diseases (NIAID). To these two groups can be added the scientists working in other public sector institutions, particularly the US Army which has an important track record in vaccine development. Large pharmaceutical companies stayed clear from direct involvement in the field. In Cohen's account, the main reasons for this was not so much the lack of a market, as for a time analysts produced market estimates of significant sizes (Cohen, 2001b, ch 6). Rather, it was some of the social challenges discussed above, and in particular the fear of legal actions and reputation problems. Overall, although much systematic data on R&D expenditure on HIV/AIDS vaccines is not available until the early 1990s, the investment in the search for an AIDS vaccine was very low, and lower than the investment in the development of drugs.[5]

The biotechnology firms and the academic community involved in the search were dominated by virologists and molecular biologists, many of whom did not have any vaccine experience. These researchers strongly favoured a 'rationalist' approach to the development of an AIDS vaccine, which aimed at using the tools of molecular biology to understand the precise mechanisms through which HIV infects the human body, and then to engineer a vaccine that would target those specific mechanisms. This translated into the search for a vaccine almost entirely concentrating on genetic engineered vaccines, and in particular on vaccines stimulating neutralizing antibodies, i.e. antibodies that would bind to gp160 or a part of it. Traditional vaccine strategies, such as live attenuated or killed vaccines, were not pursued, with the exception of one company.[6]

[5] Most research was US based, and within the US, NIH's NIAID had by far the largest budget. In 1987, NIAID's budget for AIDS was $261 million, of which 10% went to the search for a vaccine. As discussed here, industry was only very marginally involved, and remained so in the later years.

[6] Vaccines can be classified in various ways. The simplest classification groups them into three broad classes (Payette and Davis, 2001). Killed (or whole, inactivated) vaccines are obtained by killing, typically chemically or through other means, the pathogens. Live, attenuated vaccines are based on processes that weaken the pathogenic organisms to the point that they do no longer cause disease, but are still capable of inducing immunity. Sub-unit vaccines are vaccines based on parts of the pathogenic organisms, which are delivered into the body and are sufficient to induce immunity. There are several types of subunit vaccines, including naked DNA vaccines, and vector-based vaccines in which parts of the pathogenic organism DNA are inserted into a non-pathogenic organism, called vector, which delivers it to the body.

"Chiron is not interested in those approaches because Chiron is a biotech company … The attenuated or whole inactivated approaches held no interest for us. It's like asking a car maker to make an airplane because they both have wheels and go places." (P. Luciw, retrovirologist working at Chiron on AIDS vaccine, quoted in Cohen, 2001: 52)

As the quote above indicates, a rational approach to vaccine design was a significant departure from the traditional model of vaccine research. Since its inception with Jenner's smallpox vaccination in the late 1700s, vaccine development has been an essentially empirical enterprise. The discoveries of bacteria and viruses as causes of disease were important in providing researchers with broad targets. However, most vaccines were developed by killing or inactivating bacteria and viruses,[7] without a precise understanding of the immunological mechanisms through which they worked (Payette et al., 2001) i.e. using an empiricist approach. Despite the promises held by the molecular biology revolution, and the development of the hepatitis B vaccine through genetic engineering in the 1980s (a success to which Chiron contributed), even modern vaccines, such as the pertussis vaccine, have been developed through essentially empirical techniques. During a conference sponsored by the National Academy of Science in December 1986, Maurice Hilleman, a famed Merck scientist who had been involved in the development of several vaccines, remarked:

> "I think the big problem of trying to get up here and talk about how vaccines work is that we don't know a damn thing about how they work, and in the old days, you know, we used to try to solve problems without understanding them, and it was great. … This is the first time we ever had need to understand anything … I am sorry I couldn't talk about how vaccines work because I don't know" (quoted in Cohen, 2001:77)

Although virologists and molecular biologists have continued to dominate the field, early on they were joined by a small group of influential experienced vaccine makers and physicians, who had Jonas Salk among its most preeminent figures. Because of their occupation, this group was less interested in HIV and its mechanisms and more concerned with the personal and social consequences of HIV infection. This group begun advocating a more traditional empiricist approach, including the testing of scientifically inelegant but tried and tested methods - such a whole killed and live attenuated vaccines. The differences in approaches and methods between these two groups were significant, to the point that a well know epidemiologist remarked:

> "No one's ever accused Jonas Salk of being a scientist" (quoted in Cohen (2001: 63))

The debate between rationalists and empiricists, rooted in the scientific and professional cultures of the two groups, continued for several years, at times becoming very heated and personal (Cohen, 2001: 275-279). This debate was however also tightly linked to a growing debate on the organization of US scientific research, and the - until recently - unchallenged assumptions on which it was based. The US science system was based around the distinction between "pure" and "applied" research; around the idea that pure research tends to be driven out by the applied and should therefore receive public funding; and around the idea that scientists as a community should be left free to both choose what research to pursue and evaluate its results. The cornerstone of the system were the so called 'investigator-initiated grants', given by NIH on the basis of a peer review process. This system, which originated with the Vannevar Bush report "Science:

[7] Notable exceptions are the diphtheria and tetanus vaccines, which are based on toxoids.

The endless frontier" immediately after the Second World War, came out reinforced by the failure of the centralized research and development efforts of the so-called "War on Cancer" in the 1970s. The result was that the appropriateness of this model was for a long period unquestioned and unquestionable.

By the early 1990s, however, the lack of progress in the development of an AIDS vaccine was such that there was a growing dissatisfaction with current system. In particular, many thought that investigator initiated grants were unsuitable to tackle the search for a vaccine, and that a more coordinated and directed effort should be in place.

> "In the United States, investigator-initiated research is holy, you see … You can' say anything against it. But when you try and apply it, it is all these little pieces. It's all R and no D" (Maurice Hilleman, Merck, quoted in Cohen (1993)

The problem was often framed as a 'lack of leadership' on the part of NIH, who had the largest AIDS vaccine budget. The NIH spent the vast majority of its funds on relatively small investigator initiated grants, on the basis of a peer review process of the quality of the applications. This limited the funds that NIH could devote to non investigator initiated research and undermined the legitimacy of NIH deciding whether specific questions or issues, requiring significant funding, were critical and should be addressed. In the field, however, there was a growing unease with the fact that many activities which were useful were not pursued because they were unsuitable for investigator initiated grants. These included, among others, the development of assays, the development of monkey blood cell lines for growing SIV to test protection, and the development of reagents and similar; all of which are important for HIV/AIDS vaccine research. These activities are critical to enable comparison among different studies, but are considered dull and are difficult if not impossible to publish – so that few scientists would want to engage in them and, if they would, they would very likely be turned down during the peer review process. Other activities, which were critical to vaccine design, such as preclinical research on monkeys, were extremely costly. Large comparative monkey studies featuring an adequately sized control group were typically beyond the size of an investigator-initiated grant, so that there was perpetual uncertainty on the value of the results of the animal experiments that were carried out.

These perceived weaknesses of the US science system, together with the fact that after ten years of research there still was no vaccine candidate in clinical trials with many private companies having almost abandoned the field led to growing calls for a 'Manhattan project' for AIDS. By the mid-nineties things began to change. NIH reorganized its AIDS research program, the International AIDS Vaccine Initiative (IAVI) was founded and by the early 2000s the field had shifted to a much more empirical approach with several vaccines in clinical trial.

4.2 Organization matters

The brief summary of the early history of the search for an AIDS vaccine shows how the institutional set up of the US vaccine field had a strong influence on what questions were being asked and on how they were addressed. First, it shows that the combination of peer-review system and investigator initiated grant managed by a single organization, NIH, led to a prolonged dominance of the virologists' community and of their specific, rationalist, approach to the problem.

Secondly, from an organizational point of view, the early history of the search for an AIDS vaccine shows that the relatively rigid separation of labour between publicly-funded, academic, investigator-initiated basic research on the one hand and private applied research on the other led to a system that answered many scientific questions, but was unable to translate them into vaccine candidates. In turn, this resulted in a widespread perceived need for integration, which took the form of calls for a 'Manhattan Project' for AIDS within the public sector, and a growing policy debate over how to 'lure' large pharmaceutical companies into the field, generating the debate over market failures described in Section 2. While there is an increasing interest about what the history of vaccines can tell us about the role of public and private actors in the different phases of vaccine research (Galambos & Sewell, 1997; Wilson et al., 2007), available research has yet to uncover the implications of each model in terms of the competences of the different actors. Specifically, it is unclear whether (a) there were particular actors that were able to formally or informally provide integration to the field (b) what sort of activities they carried out in order to do so (c) what competencies they needed to carry them out and (d) to what specific characteristics of the scientific and technical problem and the institutional set up their competencies and actions are linked.

5. Conclusions

This review has examined the existing literature on vaccine development, in particular in relation to AIDS. In Section 2, we have examined the merit of the 'market failure' argument that currently dominates the policy debates. We have found that this argument is often misplaced from the point of view of economic analysis, and is employed as a rhetorical device to sustain the uneasiness of various constituencies with a the speed with which vaccines are developed and made available to those who need them. From the point of view of innovation studies, the market failure argument tends to draw attention to the amount of resources invested, downplaying the importance of the current state of fundamental scientific knowledge and of the processes through which science and technology advance and interact. In Section 3, we have thus examined the scientific, and technical challenges of developing an AIDS vaccine. Furthermore, the market failure argument tends to assume that, if a vaccine were available, those who would benefit from it would use it. Section 3 has therefore also examined the several social challenges that research encounters in developing a vaccine, particularly testing it, and that health officials encounter in administering vaccination programmes in both developed and developing countries. In Section 4 we have then examined the early history of the search for an AIDS vaccine in order to show that the way in which the problem of developing a vaccine has been framed was the result of cultural assumptions of individual scientific communities, related to their system of values and to methodological standards. This translated into a debate between 'rationalists' and 'empiricists', which was essentially a debate over what type and amount of knowledge was necessary in order begin developing an AIDS vaccine and to test it. As the virologist community was for a long time dominant in the field, its preference for a deep understanding of the mechanisms of infection on which to base the design of a vaccine held sway over the few vaccinologists and medical doctor who opted for a more empirical approach. Furthermore, the early history of the search of an AIDS vaccine show how these cultural processes were closely linked with the organizational and institutional set up of the US AIDS vaccine field. This set up led to a situation in which

there were growing request for more 'leadership' and integration in the field – in response to which the organizational set up of the field changed.

Overall, while the existing literature sheds significant light on many important issues in vaccine development, it leaves open equally important questions about the nature of the leadership and integration required, about the characteristics of the actors that should lead and integrate, and about the competencies they should have to do so.

References

Abbott, A. 1988. *The System of the Professions: An Essay on the Division of Expert Labour*. Chicago: University of Chicago Press.

Abraham, J. 2002. The pharmaceutical industry as a political player. *The Lancet*, 360: 1498-1502.

Archibugi, D. and Bizzarri, K. (2004), "Committing to Vaccine R&D: A Global Science Policy Priority" *Research Policy,* Vol. 33(10), PP 1657-1671

Arnould, R. J. and Grabowski, H. (1981), "Auto safety regulation: an analysis of market failure", *Bell Journal of Economics*, Spring81, Vol. 12 Issue 1, p27-48

Arrow, K. J. (1962). "Economic Welfare and the Allocation of Resources for Invention". In: *The Rate and Direction of Inventive Activity: Economic and Social Factors*. New York, National Bureau of Economic Research: 609-625.

Arrow, K. J. (1963), "Uncertainty and the welfare economics of medical care", *American Economic Review*, vol. 53, pp. 940-973

Barrowclough, D. (1999), "Lighthouses, television and the theory of public goods", in: *Economic Theory and applied analysis*, Barrowclough, Diana; Sardoni, Claudio; Kriesler, Peter. Keynes, Post-Keynesianism & Political Economy, 1999

Bator, F. M. (1958), "The anatomy of market failure", *Quarterly Journal of Economics*, Vol. 72, No. 3, (Aug., 1958), pp. 351-379

Batson, A and M. Ainsworth (2001) "Private investment in AIDS vaccine development" Bulletin of the World Health Organisation Vol. 79, PP721-727

Batson, A. (1998) "Win-win interactions between the public and private sectors" Nature Medicine Vol. 4(3), PP 487-491

Berkley, S. (2006) "Ending an Epidemic: The International AIDS Vaccine Initiative Pioneers a Public-Private Partnership" Innovations, Winter 2006, pp 52-66

Berkley, S. F., & Koff, W. C. 2007. Scientific and policy challenges to development of an AIDS vaccine. *Lancet*, 370(July 7): 94-101.

Berndt, E.; Glennerster, R.; Kremer, M.; Lee, J.; Levine, R.; Weizsäcker, G.; Williams, H., "Advance Market Commitments for Vaccines Against Neglected Diseases: Estimating Costs and Effectiveness" , forthcoming in *Health Economics*.

Buse, K. and Walt, G. (2000a), "Global public-private partnerships: part I - a new development in health?" *Bulletin of the World Health Organisation* Vol. 78(4), PP549-561

Buse, K. and Walt, G. (2000b), Global public-private partnerships: part II - What are the health issues for global governance? *Bulletin of the World Health Organisation*, Vol. 78:699-709

Cacciatori, E., & Jacobides, M. G. 2005. The dynamic limits of specialization: Vertical integration reconsidered. *Organization Studies*, 26(12): 1851-1883.

Champney, L. (1988), "Public goods and policy types", *Public Administration Review*, Nov/Dec88, Vol. 48 Issue 6, p988

Chaudhuri, S. 2005. Indian Pharmaceutical Companies and Accessibility of Drugs under TRIPS. In M. Mackintosh, & M. Koivusalo (Eds.), *Commercialization of healthcare*: 155-169. Basingstoke: Palgrave Macmillan.

Cohen, J. 1993. A "Manhattan Project" for AIDS? *Science*, 259: 1112-1114.

Cohen, J. 2001a. Rethinking a Vaccine's Risk. *Science*, 293: 1576-1577.

Cohen, J. 2001b. *Shots in the Dark - The Wayward Search for an AIDS Vaccine*. New York: W. W. Norton & Company.

Datta-Chaudhuri, M. (1990), "Market failure and government failure", *The Journal of Economic Perspectives*, Vol. 4, No. 3 (Summer, 1990), pp. 25-39

David, P. (1993). "Intellectual Property Institutions and the Panda's Thumb: Patents, Copyright, and Trade Secrets in Economic Theory and History". In *Global Dimensions of Intellectual Property Rights in Science and Technology*. National Research Council, National Academy Press: 19-42; 54-57)

Davis, O. A. and Whinston, A. B. (1967), "On the distinction between public and private goods", *The American Economic Review*, Vol. 57, No. 2, Papers and Proceedings of the Seventy-ninth Annual Meeting of the American Economic Association, (May, 1967), pp. 360-373

Deen, J. L., & Clemens, J. D. 2006. Issues in the design and implementation of vaccine trials in less developed countries. *Nature Drug Discovery*, 5(November): 932-940.

Dickson, D. 2006. Calling into question clinical trials in developing countries. *The Lancet*, 368: 1761-1762.

Douglas, M. 1987. *How Institutions Think*. London: Routledge & Kegan Paul.

Dukes, M. D. G. 2002. Accountability of the pharmaceutical industry. *The Lancet*, 360: 1682-1684.

England, S. (2000) “Pushing and Pulling HIV/AIDS Vaccines” paper presented at IAVI/IAEN Internet Forum on Economics of AIDS Vaccines, April-May 2000 www.iavi.org (accessed 07/08/05)

Epstein, M. 2007. Clinical trials in the developing world. *The Lancet*, 369: 1859.

Fairhead, J., & Leach, M. 2007. *Vaccine Anxieties: Global Science, Child Health and Society*: Earthscan.

Fairhead, J., Leach, M., & Small, M. 2006. Public engagement with science? Local understandings of a vaccine trial in The Gambia. *Journal of Biosocial Science*, 38: 103-116.

Ferguson, P. R. 2008. CLINICAL TRIALS AND HEALTHY VOLUNTEERS. *Med Law Rev*: fwm020.

Ford, N. 2003. Public health and company wealth. *British Medical Journal*, 326: 1296.

Fox-Rushby, J.M., Kaddar, M., Levine, R. and L. Brenzel (2004) “The economics of vaccination in low and middle income countries” Bulletin of the World Health Organisation Vol. 82(9) P 640

Fujimura, J. H., & Chou, D. Y. 1994. Dissent in science - Styles of scientific practice in the controversy over the cause of AIDS. *Social Science & Medicine*, 38(8): 1017-1036.

Galambos, L., & Sewell, J. E. 1997. *Networks of innovation - Vaccine development at Merck, Sharp&Dohme, and Mulford, 1895-1995*. Cambridge (MA): Cambridge University Press.

Galison, P. 1996. Computer simulations and the trading zone. In P. Galison, & D. J. Stump (Eds.), *The Disunity of Science*: 118-157. Stanford, California: Stanford University Press.

Galison, P. 1997. *Image & Logic - A Material Culture of Microphysics*. Chicago and London: University of Chicago Press.

Garber, D. A., Silvestri, G., & B, F. M. 2004. Prospects for an AIDS vaccine: Three big questions, no easy answers. *The Lancet Infectious Diseases*, 4(July): 397-413.

Garud, R., & Munir, K. 2006. Socio-technical dynamics underlying radical innovation: The case of Polaroid's SX-70 camera, *Academy of Management Meeting*. Cambridge: Judge Business School.

Geertz, C. 1973. *The interpretation of cultures*. New York: Basic Books.

Geissler, P. W., & Pool, R. 2006. Editorial: Popular concerns about medical research projects in sub-Saharan Africa – a critical voice in debates about medical research ethics. *Trop Med Int Health*, 11(7): 975–982.

Gellin, B. G., & Schaffner, W. 2001. The risk of vaccination - the importance of "negative" studies. *New England Journal of Medicine*, 344(5): 372-373.

Glennerster, R., Kremer, M., Williams, H. (2006), "Creating Markets for Vaccines," *Innovations*, 2006, 1(1): 67-79.

Glied, S. A. (2001), "Health Insurance and Market Failure since Arrow", *Journal of Health Politics, Policy and Law*, Vol. 26, No. 5, October 2001

Haas-Wilson, D. (2001), "Arrow and the information market failure in health care: the changing content and sources of health care information", *Journal of Health Politics, Policy and Law*, Vol. 26, No. 5, October 2001

Hacking, I. 1996. The disunities of sciences. In P. Galison, & D. J. Stump (Eds.), *The Disunity of Science*: 37-74. Stanford, California: Stanford University Press.

Hall, J. (2001), "Health, health care and social welfare", Policy Forum: The Economics of health and health policy, *The Australian Economic Review*, Vol. 34, No. 3, pp.320-331

Hitch, C. J. (1958), "The character of research and development in a competitive economy", *The RAND Corporation*, p. 1297, May 1958

Iansiti, M., & Clark, K. B. 1994. Integration and dynamic capability: evidence from product development in automobiles and mainframe computers. *Industrial and Corporate Change*, 3(3): 557-605.

IAVI, 2007, R&D Models: lessons from vaccine industry, IAVI Public Policy Department, Policy Research Working Paper 14, June 2007

IAVI. 2006. *AIDS Vaccine Blueprint 2006*. New York.

IAVI. 2007. IAVI responds to the announcement that Merck's AIDS vaccine candidate trial demonstrated a lack of efficacy. *IAVI Press Release* (21 September).

Irwin, A., & Wynne, B. 1996. *Misunderstanding science? The public reconstruction of science and technology*. Cambridge: Cambridge University Press.

Kettler, H. E., & Modi, R. 2001. Building local research and development capacity for the prevention and cure of neglected diseases: the case of India. *Bull World Health Organ*, 79(8): 742-747.

Knorr Cetina, K. D. 1999. *Epistemic cultures. How the sciences make knowledge*. Cambridge: Harvard University Press.

Kono, R. 1975. The SMON virus theory. *Lancet*, 2: 370-371.

Kremer, M. (2000) "Creating Markets for New Vaccines – Part 1: Rationale" Working Paper # w7716 Cambridge, Mass: NBER

Kuhn, T. 1962. *The structure of scientific revolutions*: University of Chigago Press.

Lansang, M., & Dennis, R. 2004. Building capacity in health research in the developing world. *Bull World Health Organ*, 82(10): 764-769.

Latour, B. 1987. *Science in Action: How to Follow Scientists and Engineers Through Society*. Milton Keynes: Open University Press.

Licht, D. W. (2005), "Making practical markets for vaccines", *PLoS Medicine*, Vol. 2, Issue 10, October 2005

Little, K., & Surjadi, M. 2000. A scientific overview of the developmen of AIDS vaccines. *Journal of the association of nurses in AIDS care*, 11(6): 19-28.

Maleraba, F. (2004), *Sectoral Systems of Innovation.* Canbridge: Cambridge University Press.

MacDonald, R. 2001. Website of the week: drug company ethics. *British Medical Journal*, 322: 58.

Mackintosh, M., & Koivusalo, M. (Eds.). 2005. *Commercialisation of healthcare: Global and local dynamics and policy responses*. Basingstoke: Palgrave.

McCluskey, M. M., Alexander, S. B., Larkin, B. D., Murguia, M., & Wakefield, S. 2005. An HIV Vaccine: As We Build It, Will They Come? *Health Aff*, 24(3): 643-651.

Medema, S. G. (2007), "The hesitant hand: Mill, Sidgwick and the evolution of the theory of market failure", *History of Political Economy*, 39:3

Mills, E., Rachlis, B., Wu, P., Wong, E., Wilson, K., & Singh, S. 2005. Media reporting of tenofovir trials in Cambodia and Cameroon. *BMC International Health and Human Rights*, 5(1): 6.

Milstien, J., & Candries, B. 2000. Economics of vaccine development and implementation: Changes over the past 20 years. Geneva, Switzerland: WHO.

Milstien, J., Cash, R. A., Wecker, J., & Wikler, D. 2005. Development Of Priority Vaccines For Disease-Endemic Countries: Risk And Benefit. *Health Aff (Millwood)*, 24(3): 718-728.

Molyneux, D., Peshu, N., & Marsh, K. 2005. Trust and informed consent: insights from community members on the Kenyan coast. *Soc Sci Med*, 61: 1463-1473.

Mowery, D. C., & Rosenberg, N. 1979. The influence of market demand upon innovation:A critical review of some recent empirical studies. *Research Policy*, 8(2): 102-150.

Musgrave, R. A. (1959), *The Theory of Public Finance*, *a Study in Political Economy,* Mcgraw-Hill, New York

Nathan, C. (2007), “Aligning pharmaceutical innovation with medical need”, *Nature Medicine*, Vol. 13, No. 3, March 2007

Nkolola, J. P., & Essex, M. 2006. Progress towards an HIV-1 subtype C vaccine. *Vaccine*, 24: 391-401.

Olson, M. (1965), *The logic of collective action*, Cambridge: Harvard University Press

Orsenigo, L., Dosi, G. and Mazzucato, M. (2006), “The dynamics of knowledge accumulation, regulation and appropriability in the pharma-biotech sector: policy issues”, in *Knowledge accumulation and Industry evolution – The case of Pharma-Biotech*, edited by: Mariana Mazzucato and Giovanni Dosi, Cambridge University Press, 2006

Pauly, M. V. (1986), “Taxation, Health Insurance, and Market Failure in the Medical Economy**”,** *Journal of Economic Literature*, Vol. 24, No. 2 (Jun., 1986), pp. 629-675

Payette, P. J., & Davis, H. L. 2001. History of vaccines and positioning of current trends. *Current Drug Targets - Infectious Disorders*, 1(3): 241-247.

Pessoa, A. (2006), "Public-Private Sector Partnerships in Developing Countries: Prospects and Drawbacks," *FEP Working Papers 228*, Universidade do Porto, Faculdade de Economia do Porto

Petryna, A. 2005. Ethical variability: Drug development and the globalization of clinical trials. *American Ethnologist*, 32: 183-197.

Petryna, A., Lakoff, A., & Kleinman, A. (Eds.). 2006. *Global Pharmaceuticals: Ethics, Markets, Practices*. Durham, NC: Duke University Press.

Pickering, A. 1992. *Science as practice and culture*. Chicago: University of Chicago Press.

Richter, J. (2004), “Public-private Partnerships for Health: A trend with no alternatives?”, *Development*, 2004, 47(2), (43–48)

Robson, A. (2007), “A public good is not just something which is good for the public” *Institute of Public Affairs Review*, Jul2007, Vol. 59 Issue 2, p39-40

Rosiello, A. and J. Smith (2004) “A Sociological Economy of HIV/AIDS Vaccines Partnerships in Africa and India” paper given at Economic Sociology conference 2004 www.soc.uoc.gr/social/anakoin/syn_econ-soc/papers/

Sidgwick, H. (1883), *The principles of political economy*, 3rd edition, London: MacMillan

Slight, P. 2004. Where are clinical trials going? society and clinical trials. *Journal of Internal Medicine*, 255: 151-156.

Steinbrook, R. 2007. One Step Forward, Two Steps Back -- Will There Ever Be an AIDS Vaccine? *N Engl J Med*, 357(26): 2653-2655.

Stiglitz, J. (2007), "Dying in the name of monopoly", *Business Day*, March, 15th 2007

Thomke, S. H. 1998. Managing experimentation in the design of new products. *Management Science*, 44(6): 743-762.

Thomke, S., von Hippel, E., & Franke, R. 1998. Modes of experimentation: an innovation process - and competitive - variable. *Research Policy*, 27(3): 315-332.

Tonks, A. 2007. The quest for the AIDS vaccine. *British Medical Journal*, 334(7608): 1346-1348.

Trouiller P., Olliaro P., Torreele E., Orbinksi J., Laing R., and N. Ford (2002) "Drug Development for neglected diseases: a deficient market and public-health policy failure" *Lancet* Vol. 359: PP 2188-94

UNAIDS. 2007. 2007 AIDS Epidemic Update. Geneva: UNAIDS.

Vincenti, W. G. 1990. *What Engineers Know and How They Know It - Analytical Studies from the Aeronautical Industry*. Baltimore and London: The Johns Hopkins University Press.

von Meier, A. 1999. Occupational cultures as a challenge to technological innovation. *IEEE Transactions on Engineering Management*, 46(1): 101-114.

Walker, S., Rowely, J., & Hecht, R. 2005. Speeding the manufacture of an HIV vaccine. New York: IAVI.

Wheeler, C. and Berkley, S. (2001), "Initial lessons from public–private partnerships in drug and vaccine development", *Bulletin of the World Health Organisation*, 2001, 79(8)

Widdus, R. (2001), "Public–private partnerships for health: their main targets, their diversity, and their future directions", *Bulletin of the World Health Organisation*, 2001, 79(8)

Wilson, P., Post, S., & Srinivas, S. 2007. R&D Models: Lessons from Vaccine Industry: IAVI Policy Research Working Paper #14.

Winters, D. J. (2006), "Expanding global research and development for neglected diseases", *Bulletin of the World Health Organisation*, May 2006, 84(5)

Ziemba, E. (2005), *Public-private partnerships for product development: financial, scientific and management issues as challenges for future success*, final report for CIPR (World Heath Organisation Commission on Intellectual Property Rights, Innovation and Public Health), March, 31st 2005