

Advanced Medical Science

Ensuring Worldwide Access to an HIV Vaccine in the Future



<http://www.iavi.org>

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List of abbreviations:

AAVP:	African AIDS Vaccine Programme
AIDS:	Acquired immunodeficiency syndrome
ARVs:	Antiretroviral medicines
AVAC:	The AIDS Vaccine Advocacy Coalition
CSW:	Commercial sex workers
EC:	The European Community
EPI:	Expanded Programme on Immunisation
FDA:	The US Food and Drug Administration
G-8:	The group of 8 major industrialised nations. These include France, the United States, Germany, Britain, the United Kingdom, Italy, Canada and Russia.
GAVI:	The Global Alliance for Vaccine and Immunisations
GSK:	GlaxoSmithKline
HIV:	Human immunodeficiency virus
IAVI:	The International AIDS Vaccine Initiative
IDA:	International Development Agency
IDU:	Injecting drug users
IPRs:	Intellectual property rights
MSM:	Men who have sex with other men
NRA:	National regulatory authority
UNAIDS:	The Joint United Nations Programme on HIV/AIDS
UNICEF:	United Nations Children's Fund
WHO:	The World Health Organisation

Abstract:

As candidate HIV vaccines are now entering phase III efficacy trials, it is hopeful that a successful vaccine is only a few years away from being found. With around 40 million people living with HIV/AIDS, and an estimated 14,000 new infections every day, it is believed that such a scientific discovery is the best hope to control the pandemic. However, organisations such as the International AIDS Vaccine Initiative (IAVI) recognise that the availability of a medical technology does not automatically assure access to every person that needs it. The historical paradigm of pharmaceutical access shows that it typically takes a drug or vaccine 15-20 years from initial licensure, to when it reaches the developing world at a modest level. To break this paradigm, changes must be made in almost every aspect of immunisation deployment.

The key parties involved include governments of both industrialised and non-industrialised countries, potential vaccine producers, IAVI, UNAIDS, WHO and many other organisations. The various endeavours made by each of these groups to prepare for the arrival of an HIV vaccine are collected together from the relevant literature. This creates a more complete picture of the overall impact of efforts to date, than has otherwise been developed.

The world is still far from prepared to swiftly introduce an HIV vaccine to developing nations. Although delayed access to such a life-saving product raises questions regarding justice and equity, there are economic, political and social reasons for this. To overcome these barriers, the importance placed on disease prevention must be increased. HIV vaccination is a global health issue, thus all sectors of global society must join together to ensure worldwide access once it is ready.

Introduction:

In 2003, more than 3 million people were killed by the global AIDS pandemic, with an additional 5 million people becoming infected with HIV. This means that today, in total, there are around 40 million people in the world that are living with HIV/AIDS. However, the global distribution of the disease is not evenly spread, with over 95 percent of those infected living in developing nations,^α particularly sub-Saharan Africa, which has around 26.6 million infected people alone.¹ This makes HIV a threat to global development, as well as global health.

Today AIDS kills more people than any other infectious disease.² Although prevention programmes (such as education programmes, condom and clean needle distribution, and testing services) have slowed the spread of HIV, they have not stopped it. Advances in antiretroviral medicines (ARVs) have also been important, but their costs and complexity of use have made them unobtainable by most people living in developing nations. Also, side effects and increasing viral resistance have raised doubts about the long-term use of ARVs.³

It is believed that the best long-term hope for controlling the spread of HIV, the fourth leading cause of death worldwide, and leading cause of death in Africa, is to develop a safe and effective preventive vaccine⁴ to be used alongside existing treatment

^α The terms 'non-industrialised countries', 'poorer countries' and 'developing countries' will be interchanged with each other. Although the controversial nature of these terms are acknowledged, their use in this paper is a reflection of their use in the relevant literature.

¹ UNAIDS and WHO (December 2003) AIDS epidemic update, Geneva.

² IAVI website. <http://www.iavi.org/need/needs.htm> (23/01/04)

³ *ibid.*

⁴ Esparza, J. (2001) An HIV vaccine: how and when?, *Bulletin of the World Health Organization*, 79(12), p.1133.

strategies. Successful vaccines have proven to be amongst the cheapest and most effective public health interventions that have helped control infectious diseases such as polio, smallpox, measles, yellow fever and hepatitis B, to name a few. Finally, 23 years after AIDS was first discovered, candidate HIV vaccines are now reaching phase III (efficacy) trials, essential for determining whether the vaccine candidate has any effect in reducing the frequency or severity of HIV/AIDS in humans. With an estimated 14,000 new infections daily, there is much hope that a successful vaccine is only a few years away from being found.⁵ The scientific barriers of an HIV vaccine can be overcome, but the world must commit sufficient resources for this to happen.

If (and hopefully when) a successful HIV vaccine is developed, many important issues regarding future access to such a vaccine arise. Geeta Rao Gupta, President of the International Centre for Research on Women has made the acknowledgment:

We are now more aware than ever before that the availability of a biomedical option does not necessarily guarantee access and use by the people who need it most.⁶

History has shown that it typically takes 15-20 years from when a new vaccine or drug is initially licensed, to when it trickles down to reach the developing world at a modest level. The hepatitis B vaccine exemplifies this, as there are still around one million preventable deaths annually, despite the fact that the vaccine was licensed over two decades ago.⁷ With more relevance to the HIV epidemic, ARV medicines

⁵ *ibid*, p.1133.

⁶ IAVI website. <http://www.iavi.org/access.htm> (04/12/03)

⁷ Berkley, S. (1998) HIV vaccine development for the world: an idea whose time has come?, *AIDS Research & Human Retroviruses*. 14(Suppl 3), p.S191

are another, more striking example of this, where in sub-Saharan Africa, only 1 in 500 HIV positive people receive any ARV drugs, nearly a decade after their licensure.⁸

Not enough importance is being placed on disease prevention. The free market, when left to its own ‘business as usual’ devices, does not have the motivation to serve the needs of developing countries. At first, only developed countries are catered for, as they have the ability to pay for the product. It is over time, when efficiency rises, manufacturing costs decline, and production capacity increases, that the product becomes more affordable for poorer countries. For the case of an HIV vaccine, such a delay would be unacceptable. A delay of even five years between licensure and widespread delivery would mean up to 30 million preventable infections.⁹

For swift, simultaneous access to occur once an HIV vaccine is ready, a complete paradigm shift is required in the way immunisations are deployed. Ensuring future access is an issue of human rights. The 1975 Charter of Economic Rights and Duties of States stipulates that:

All States should facilitate the access of developing countries to the achievements of modern science and technology, [and] the transfer of technology...¹⁰

Worldwide access is recognised as an ethical imperative of justice and global beneficence that must be achieved. Although this may be open to argument, discussion of the matter is outside the scope of this paper. Therefore, it shall be presumed that the current paradigm of pharmaceutical and vaccine access is morally

⁸ UNAIDS and WHO (December 2003), pp.13, 37.

⁹ Brown, P. (2000) No more business as usual, *GAVI Immunization Focus*, p.7.

¹⁰ UN General Assembly (1975) Charter of Economic Rights and Duties of States, Chapter II, Article 13.

unacceptable, thus must be changed. The world could use future deployment of an HIV vaccine to exemplify the necessary changes that are required, and to show how all nations should benefit from the progressions of technology. To do this, however, the world needs to prepare now, *before* the vaccine is available. The global community must succeed where they have previously failed. Otherwise, millions of people will be sentenced to needless deaths, a tragedy which would overshadow any scientific achievement.

In 1996, the International AIDS Vaccine Initiative (IAVI) was created. Their purpose has been “To ensure the development of safe, effective, accessible, preventive HIV vaccines for use throughout the world”.¹¹ Much of their work to date has been on their newest programme: assuring global access. In July 2000, they produced the groundbreaking blueprint ‘AIDS Vaccines for the World: Preparing Now to Assure Access’, which is the first to fully acknowledge and suggest ways to tackle the fundamental economic, political and logistical barriers that are posed against an ethically just distribution of an HIV vaccine.¹² The recommendations made in this blueprint and the updated 2001 ‘IAVI Access Project White Paper’, will be used as a framework for this paper to discuss the changes that will need to take place in each aspect of immunisation deployment to prepare for the arrival of a successful vaccine.

This paper shall explore the main literature relevant to future HIV vaccine access. What has been written in the area, and the actions that have been taken so far will be analysed. The different voices and opinions involved shall be compiled together to

¹¹ Berkley, S. (1998), p.S195

¹² International AIDS Vaccine Initiative (2000) AIDS vaccines for the world: preparing now to assure access, New York.

provide the reader with a greater insight into the situation. How prepared the world is for introducing an HIV vaccine, and any barriers that still remain against an ethically just distribution shall be determined. The best way forwards from here shall be discussed.

Although many of the changes that shall be addressed may apply to any other drug or vaccine, the obstacles that are posed specifically by HIV/AIDS shall be emphasised and integrated into all sections. These include research and development issues such as dealing with multiple disease subtypes and immunologic diversity, social issues such as stigma and discrimination, the large number and nature of at-risk individuals, and the possibility of HIV vaccines with only partial efficacy.

Throughout all sections, the importance of the public-private partnerships that need to be formed will be emphasised, as well as the co-ordinating role of international organisations such as IAVI, the Global Alliance for Vaccines and Immunisations (GAVI), the Joint United Nations Programme on HIV/AIDS (UNAIDS), the World Health Organisation (WHO), the AIDS Vaccine Advocacy Coalition (AVAC), the World Bank and the Global Fund to Fight AIDS, Tuberculosis and Malaria. Although global access to HIV vaccines in the future is a common goal of all parties, each organisation has their own outlook as to how this can be achieved, what actions they are able to take, and what their responsibilities should be. The same applies to the other parties involved, such as governments of both industrialised and non-industrialised nations, and the private sector, especially the pharmaceutical and biotechnology industries.

This paper will provide an overview of the different agendas of, and actions taken by each of these key parties involved, to present a more holistic view of the current situation regarding HIV vaccine introduction, than has previously been developed. By searching the most up to date literature available, including journal articles, reports and websites, the actual changes that have occurred so far, more than three years after organisations such as IAVI made their recommendations, will be analysed. In doing this, areas that are being sufficiently addressed, as well as areas that are lacking in efforts will be identified. The difference between the changes that *need* to take place and what changes actually *have* taken place can then be compared and contrasted. Reasons for such discrepancies will be explained and accounted for by the surrounding economic, political and social factors that are contextually relevant.

This paper is divided into sections that will address the main aspects of deploying a new vaccine. These areas are:

- i. Financing vaccine purchase
- ii. Creating vaccine delivery systems
- iii. Estimating vaccine demand
- iv. Ensuring sufficient production capacity
- v. Improving regulatory processes

Financing vaccine purchase:

One of the most obvious and fundamental aspects of deploying a vaccine is the purchase of the vaccine itself. Although it is unknown what the exact price of the first AIDS vaccine will be, a conservative estimate of even US\$ 10 per course would exhaust the average annual health ministry budgets of most developing countries, as their budgets are already overstretched.¹³ In addition, HIV vaccination for these countries may not be considered as cost-effective to health budgets. In terms of avoided medical spending, a vaccine with an efficacy of 75% that lasts for 10 years would be worth US\$ 2.67 per adult male in sub-Saharan Africa, compared to US\$ 343 in Western Europe.¹⁴ From this narrow economic perspective, the benefits of vaccination are highest in developed countries. However, an HIV vaccine would be of far greater epidemiological benefit in developing nations, where 95% of people infected live. Profit motivations of the free market mean that attention is paid to a cost-effective allocation of resources, not an ethical allocation according to human rights. Therefore, economic models do not account for intangible costs such as human suffering. There is a mismatch between public health needs and market forces, and the need for the public sector to fill this gap to achieve global health equity.

Although government health ministries aim to maximise their population's health under a fixed budget, the financial restrictions of most developing nations are so great that external assistance will be required. Some low-income countries may be eligible for concessionary World Bank loans under International Development Agency (IDA)

¹³ Bishai, D., Lin, M.K. & Kiyonga, C.W. (2001) Modeling the economic benefits of an AIDS vaccine, *Vaccine.*, 20(3-4), p.530.

¹⁴ *ibid*, p.530.

conditions. A per capita annual income of less than US\$ 885 is usually required, with loans typically having a grace period of 10 years. However, eligible countries are likely to be reluctant to incur any additional debts.¹⁵ For regions such as sub-Saharan Africa to be able to afford the vaccine, additional external sources of financing will be required.

Vaccine purchase funds:

Assuming that the first HIV vaccine costs US\$ 10 per course, a purchase subsidy of around US\$ 9 would be needed per person to make the vaccine affordable to developing countries.¹⁶ The initial demand will be massive, to the order of hundreds of millions of people (discussed later in the section on estimating vaccine demand). This suggests that international donors will need to commit billions of dollars in assistance. IAVI documents have proposed the need for an AIDS vaccination fund to be created now for both the purchase and delivery (see next section on creating delivery systems) of an AIDS vaccine as soon as it is ready.¹⁷ Developed countries, especially the G-8 nations, foundations and charities are called to make nominal contributions now, as well as public statements to commit to financial support in the future. In terms of management, it is proposed that the fund could be organised by the World Bank, other international organisations such as UNAIDS, WHO, or act as a sub-account of GAVI.¹⁸

¹⁵ IAVI (2001) A new access paradigm: public sector actions to assure swift, global access to AIDS vaccines, New York, p.10.

¹⁶ Ainsworth, M. et al. (2001) Future access to HIV vaccines: report from a WHO-UNAIDS consultation, Geneva, 2-3 October 2000, *AIDS*, 15(7), p.W33.

¹⁷ IAVI (2001), p.12.

¹⁸ *ibid*, p.13.

Apart from grants from the fund, financial assistance could also be complemented by the World Bank loans mentioned. A leveraged grant may also be a possible option, which uses grant financing to pay off loan debts, allowing a low-income country to borrow significantly more money.¹⁹ The IAVI Access Project White Paper recognises that:

Substantial, credible financing creates a market for new products in developing countries that otherwise would not exist and can drive commercial producers to invest in research and development.²⁰

Not only would committed financing ensure that a vaccine could be purchased for all who need it, but it would also act as a pull strategy to encourage the vaccine industry to accelerate development of vaccines in the first place.²¹ This is especially needed for vaccines against the specific HIV subtypes of the developing world, as will be discussed later.

In January 2002, the Global Fund to Fight AIDS, Tuberculosis and Malaria was initiated to fight the three most devastating communicable diseases affecting the world.²² Forming partnerships between governments, the private sector and affected communities, it acts as a financing mechanism that reviews grant proposals, distributes funding, and monitors programme performances. Pledges have been primarily from governments of industrialised countries, but private contributions from foundations and pharmaceutical companies have also been made.²³ Up until March

¹⁹ *ibid*, pp.13-4.

²⁰ *ibid*, p.7.

²¹ Batson, A. & Ainsworth, M. (2001) Private investment in AIDS vaccine development: obstacles and solutions, *Bulletin of the World Health Organization.*, 79(8), pp. 725.

²² The Global Fund to Fight AIDS, Tuberculosis and Malaria (March 2004) Progress report, Geneva, p.1

²³ Walker, S. (2001) A global health fund: one step closer, *IAVI Report*, 5(7), p.1.

2004, grant approvals have totalled US\$ 2 billion over two years, with 60% of this committed to the prevention and treatment of HIV/AIDS.²⁴ However, although IAVI and a number of governments have called for the creation of a vaccine sub-account, there is no window specifically allocated for HIV vaccines.

As previously mentioned, GAVI would be another potential source to administer funding. However, they currently focus all of their efforts on funding current vaccines, through partnership with the Vaccine Fund, which endeavours to improve existing childhood immunisations. Since its launch in 1999, more than US\$ 1 billion has been donated to the Vaccine Fund's immunisation programmes, with \$750 million of this coming from the Bill & Melinda Gates Foundation.²⁵ As of 2003, however, there have been no commitments by anyone to purchase AIDS vaccines.²⁶ It will take time to mobilise the billions of dollars required to purchase an HIV vaccine for all who need it. Governments of developed nations, the World Bank, the Global Fund, GAVI, the Vaccine Fund, and private companies would need to establish such financing now, not later, to ensure the purchase of HIV vaccines for the entire world.

The creation of such a necessary fund seems feasible, especially when looking at commitments to purchase other medical products. In the face of bioterror threats, the US federal government has already authorised \$640 million for a Strategic National Stockpile of bioterror products such as anthrax and smallpox vaccines. In addition, with Project BioShield, the US President has proposed a commitment of \$6 billion

²⁴ The Global Fund (March 2004), p.1.

²⁵ The Vaccine Fund website.

http://www.vaccinefund.org/default.aspx?page=about_the_vaccine_fund.html&style=full&lang=en
(15/03/04)

²⁶ AIDS Vaccine Advocacy Coalition (2003) 4 years and counting, New York, p.17.

over ten years in purchase capacity for next generation bioterror countermeasures, to spur the private sector to research and develop such products.²⁷ A financial mechanism such as the BioShield purchase authority would be ideal for an HIV vaccine. In fact, the initial plans for BioShield included vaccines and other products to fight global infectious diseases such as AIDS. However, the Office of Management and Budget soon put this idea to rest,²⁸ most likely for reasons regarding financial constraints. Although the threat of bioterror is a global concern of today's world, it would be difficult to argue that it is a greater threat than that of AIDS. Perhaps in the US, a nation where HIV infection is relatively uncommon, the *perceived* threat of bioterror is greater due to terrorist events such as September 11. Most people living in developed nations are probably quite detached from the full impact of AIDS, thus may not fully appreciate the importance of halting the pandemic. Governments of such countries may then favour bioterror protection for reasons regarding public acceptance by their citizens. In the interest of global health, however, the full threat of AIDS should be acknowledged by all, with an HIV vaccine advance purchase mechanism given at least as much attention as that which bioterror receives.

Tiered pricing:

Estimating the first HIV vaccine at an initial price of US\$ 10 per course would be quite conservative. In 2000, the newest paediatric vaccine, the pneumococcal conjugate vaccine, was marketed in the US at \$262 for four doses.²⁹ Although unlikely to be this expensive, the financing mechanisms discussed may still have trouble with purchasing an AIDS vaccine for all who need it. Tiered pricing can be

²⁷ *ibid*, pp.16-17.

²⁸ *Ibid*, p17.

²⁹ IAVI (2000), p.14.

used to complement vaccine purchase mechanisms by making the product more affordable. Also known as differential pricing, the concept refers to governments and institutions creating an environment that supports price levels that reflect each country's ability to pay.³⁰ The higher price paid by industrialised countries covers research and development, and other overhead costs borne by the producer, which then allows the firm to charge lower prices to developing nations. Donor financial support then only has to subsidise the difference, if any, between the lower tiers and what the country is able to pay.

To do this successfully, the public sector needs to build both societal and political support, as consumers paying higher prices, especially those from middle-income countries, may believe the system to be unfair. In addition, governments must commit to ensuring market segmentation to prevent the importation of lower-priced vaccines from developing to developed countries.³¹ The private industry must be ensured a sufficient return on their investment, and their financial interests must be protected and carefully balanced with global health interests, otherwise they will not be willing to invest in an AIDS vaccine in the first place.

Tiered pricing already exists for some paediatric vaccines, with low-income countries paying as little as 1-5% of the price that high-income countries are paying for the same vaccine. International organisations such as UNICEF and GAVI have procurement systems that obtain favourable prices through large volume purchases.³²

Pharmaceutical giant GlaxoSmithKline (GSK) has employed differential pricing

³⁰ Canadian HIV/AIDS Legal Network (2002) HIV vaccines for developing countries: advancing research and access, Montreal, p.44.

³¹ IAVI (2001), p.17.

³² Canadian HIV/AIDS Legal Network (2002), p.45.

systems with vaccines for over 20 years, and with antiretrovirals since 1997.

However, this has been done with justified concerns regarding the political acceptance of charging different prices to different countries, and parallel trading, where market segmentation is breached, and the lower priced product is imported back to developed countries.³³ Such concerns are not just in the economic interests of the private industry, but also relate to the commercial viability that is required for such companies to fund further research into improving medicines. Thus it should be a concern of the public health sector as well.

In May 2000, GSK expanded their tiered pricing systems through the Accelerating Access Initiative (AAI), involving partnerships with organisations such as UNAIDS, developing countries, and other pharmaceutical companies. GSK offers HIV/AIDS medicines at up to a 90% discount to all countries in sub-Saharan Africa, all developing nations, as well as international organisations and health funds such as the Global Fund.³⁴ It is hopeful that a similar tiered pricing system will be adopted for an HIV vaccine in the future, so that the vaccine will be affordable for all. However, no commitments seem to have been made by the pharmaceutical or biotechnology industries so far.

Tax credits:

Another financial strategy to ensure vaccine purchase would be to give private companies tax credits for the sale of HIV vaccines to qualified international health organisations or governments in developing countries. This would make the vaccine market of low-income countries more attractive, as well as enhance the value of

³³ Laya, K. (2002) Pharmaceutical services: differential pricing, GlaxoSmithKline plc., p.1.

³⁴ *ibid*, p.3.

purchase funds.³⁵ In his January 2000 State of Union address, President Bill Clinton proposed tax credits of 100% for sales of vaccines for malaria, TB and HIV, with a US\$ 1 billion cap over eight years. This legislation formed part of the Vaccines for the New Millennium Act of 2000, which also proposed the establishment of a purchase fund of up to US\$ 100 million per year for ten years, administered by the US Treasury Secretary for the purchase and distribution of priority vaccines. However, the Act failed to pass the 106th US Congress.³⁶ Sales tax credit legislation was then incorporated into the Vaccines for the New Millennium Act of 2001, but again the bill was not passed.³⁷ Hopefully, commitments for sales tax credits will eventually be made, preferably before a vaccine is licensed.

In addition, governments can provide tax relief to companies that make appropriate donations of drugs, vaccines and medical equipment. Such donation tax credits are already being implemented by the United States, with recent progress being made in the United Kingdom as well.³⁸ One would expect that such credits could incorporate AIDS vaccines in the future. The international community has begun to recognise the moral imperative to ensure that an HIV vaccine is affordable by all who need it, as various proposals are well underway. However, for talk to be turned into action, governmental approval is required, and this is not always happening. It is the underlying lack of political commitment and will that desperately needs to be tackled for the implementation of these proposals to go ahead.

³⁵ Collins, C. (2001) AIDS vaccine tax legislation proposed in the US and UK, *IAVI Report*, 5(7), pp. 7-8.

³⁶ Collins, C. & Morin, S.F. (2001) The policy of AIDS vaccines: exploring legislative options for advancing AIDS vaccine research and delivery, *HIV InSite website*.
<http://hivinsite.ucsf.edu/InSite.jsp?page=pa-3098.0181> (17/03/04)

³⁷ Canadian HIV/AIDS Legal Network (2002), p.44.

³⁸ IAVI (2001), p.18.

Creation of vaccine delivery systems:

As previously mentioned, funding is required not only for the purchase, but for the delivery of the vaccine as well. These delivery costs can be the most expensive part of an immunisation programme, with factors such as transportation, cold-chain requirements, safe injection supplies, staff wages, and waste disposal accounting for around 70% of the total cost of an established programme.³⁹ In the case of the Expanded Programme on Immunisation (EPI), the average cost for its six basic vaccines is US\$ 1.50 for purchase, plus US\$ 20 for delivery per child.⁴⁰ Funding for delivery of an HIV vaccine could be mobilised through the same financial mechanisms discussed in the previous section regarding vaccine purchase, so it shall not be discussed further in this section.

Delivery infrastructure:

However, in order to deliver a vaccine, the relevant infrastructure must first be in place. The EPI and most other established vaccination services are primarily targeted towards infants. However, an AIDS vaccine will initially need to target adolescents, sexually active adults, and high-risk groups such as commercial sex workers (CSW), injecting drug users (IDU), transport workers and men who have sex with men (MSM).⁴¹ For developing nations especially, there are currently very few established pathways in place to deliver vaccines to these groups. Some vaccination campaigns for polio and measles have occasionally targeted adolescents and young adults, but

³⁹ Walker, S. (2002/2003) GAVI partners gather to assess progress, plan future activities, *IAVI Report*, 6(6), pp. 3-4.

⁴⁰ Ainsworth, M. et al. (2001), p. W34.

⁴¹ IAVI (2000) p.8.

coverage is still very low.⁴² All other efforts for a swift HIV vaccine deployment will be wasted unless significant investments are made in building the necessary infrastructure to deliver vaccines to the intended populations.

The exact specifications of the required delivery infrastructure cannot be determined until the nature of the first HIV vaccine is known, such as its efficacy, number of required doses, duration of protection, route of administration, cold-chain requirements and cost.⁴³ However, general health services to reach adults and high-risk populations should be enhanced now to improve other programmes regarding HIV prevention, treatment and care strategies. By building this infrastructure, HIV vaccine delivery strategies can then be added in later as part of an overall prevention effort, whatever the vaccine's characteristics may be.⁴⁴ In reaching adolescents, school-based programmes may prove effective, and could provide a means for more general health education, such as education on drugs, alcohol, reproductive health and pregnancy. However, globally around 25% of children are not enrolled in schools, and it would be these children that are likely to be at a higher risk of HIV infection in the future.⁴⁵

The IAVI blueprint highlights the need for existing health services in developing countries to be strengthened, such as reproductive health services, STD clinics, services for commercial sex work places, military health services, and family planning clinics.⁴⁶ In essence, the literature shows that strengthening of the health

⁴² *ibid*, p.19.

⁴³ Canadian HIV/AIDS Legal Network (2002), p.46.

⁴⁴ *ibid*, p.46.

⁴⁵ Chang, M.L. et al. (2003) Public health considerations for the use of a first generation HIV vaccine, *AIDS*, 17(15), p.W6.

⁴⁶ IAVI (2000), p.19.

sector in many different areas is required to ensure that population coverage rates are adequate for eventual distribution of an HIV vaccine. For this to occur, sustained political support and long term financing will be required. Strategies will need to be specifically tailored to each country, depending on their current HIV epidemiology, existing health delivery infrastructure, as well as social and cultural environment.⁴⁷ These changes alone would lead to many improved national health outcomes, not only regarding HIV/AIDS, but to other diseases as well, such as hepatitis B, a disease which the global community has failed to properly address, despite a vaccine being available for over two decades.⁴⁸

Many parallels can be drawn between hepatitis B and HIV, as both have similar routes of transmission, and thus the high-risk groups for each disease are overlapping. Therefore, both diseases can be tackled at the same time. Making such necessary improvements to the health systems of developing countries is, however, an extremely complicated undertaking. Much technical and financial support will be required from the developed world, and international organisations such as GAVI and The Global Fund. Creating the necessary vaccine delivery systems for an HIV vaccine, unlike the other aspects of vaccine deployment, is not an isolated task at all. It is an issue that is embedded within the status of world health in general, addressing the need to solve the greater problems of health inequalities.

Organisations such as GAVI have done much work on strengthening existing health systems to improve immunisation coverage. Since their launch in 2000, an estimated 500,000 lives have been saved, with more than 35.5 million additional children

⁴⁷ *ibid*, p.19.

⁴⁸ *ibid*, p.22.

immunised against hepatitis B in one of the most rapid international health scale-ups ever, and more than 8 million additional children receiving basic vaccinations.⁴⁹ 48 countries have received financial support to improve child health care infrastructure, and together with The Vaccine Fund, the goal is to save the lives of one million more children by 2006.⁵⁰ However, although GAVI say that their work is "...paving the way for delivery of new vaccines and better health care, including HIV/AIDS..."⁵¹ it may not be entirely appropriate for an HIV vaccine. For example, improving child and prenatal health services may have little effect in improving medical access to CSWs or IDUs. Strengthening health care to these groups would not be a major goal of GAVI, or any childhood immunisation programme, as this would do little to improve childhood vaccination coverage.

In addition, GAVI are focussing on nearly developed vaccines against diseases such as rotavirus and pneumococcal, and ensuring access of these to children of poorer countries as soon as they become available.⁵² Much could be learnt from this in terms of breaking the paradigm of vaccination introductions, but only of limited relevance with regards to an AIDS vaccine, again due to the differing delivery requirements. The work being done by GAVI and its partners is highly significant, built on international human rights law that all children should have access to basic health care. However, it must not be forgotten that basic health care is a human right of everyone, not only children, and that vaccination is a health tool that others can benefit from as well.

⁴⁹ Global Alliance for Vaccines and Immunisations (2004) Progress and challenges 2004, Geneva, p.2

⁵⁰ GAVI website. http://www.vaccinealliance.org/home/Media_Center/Press_Releases/27022004.php (13/03/04)

⁵¹ *ibid.*

⁵² GAVI (2004), p.3.

Since they started in January 2002, The Global Fund has approved US\$ 1.2 billion in grants for the prevention and treatment of HIV/AIDS.⁵³ Three-quarters of countries that have been given funds for HIV programmes will use some of their grant to provide antiretroviral medicines, with all AIDS grants including prevention activities,⁵⁴ such as sexual education and condom distribution, with a focus on young people. Other interventions include HIV voluntary counselling and testing. It can be seen how the infrastructure that these grants are financing would be more appropriate to allow delivery of an AIDS vaccine to be incorporated later, compared to the health services that need to be implemented for paediatric immunisations. Setting up an HIV screening programme would target those at risk of infection, and creating a path to access these people now would provide a route to deliver an AIDS vaccine in the future. Investments in education and condom distribution will always be valuable, even when a vaccine becomes available, as the first generation immunisations are likely to only be of partial efficacy. Also, such investments can have many additional health benefits regarding other sexually transmitted infections, as well as benefits regarding birth control.

In addition, last year US President George W. Bush announced a separate, five year US\$ 15 billion pledge to fight AIDS in sub-Saharan Africa and the Caribbean.⁵⁵ However, one-third of funds spent on prevention must go towards abstinence programmes, raising concerns regarding cultural acceptance and effectiveness of such programmes. There are also concerns that the promotion of abstinence will be at the expense of condoms. It is therefore essential that different organisations and funds are

⁵³ The Global Fund (March 2004), p.1

⁵⁴ The Global Fund website. <http://www.theglobalfund.org/en/about/how/> (23/12/03)

⁵⁵ Wise, J. (2003) Mixed reaction to US pledge of US\$ 15 billion to fight AIDS, *Bulletin of the World Health Organization*, 81(7), p. 547.

harmonised with one another, to avoid overlapping in some areas, whilst neglecting others. Although groups such as GAVI and The Global Fund have made much progress, existing vaccinations and antiretroviral medicines still remain desperately underused. If an HIV vaccine were to exist today, it too would follow the same fate. Coordinated efforts by all parties must be increased.

Vaccine acceptance:

To effectively deliver a vaccine, especially one for HIV/AIDS, the psychosocial perspective and needs of the user must also be considered. Universal acceptance of a vaccine cannot be assumed, even if there is global access to it. Social and attitudinal barriers to acceptance of an AIDS vaccination must be properly addressed. Firstly, characteristics of the vaccine will influence acceptability in all societies. A study amongst adolescents in the United States indicated that vaccine efficacy was the characteristic that had the strongest influence on acceptance, with a vaccine of 50% efficacy regarded as unacceptable by many.⁵⁶ This was because such a vaccine was perceived as having no advantages over condoms. This supports diffusion theory, the concept that a technological innovation will only be accepted if it is viewed as superior to existing, available technology.⁵⁷ However, the first generation immunisations, which are likely to be of limited efficacies, are not meant to be “magic bullets”, but rather part of an overall prevention effort, used in combination with other measures such as condom use, not as a replacement. Therefore, communities must be properly educated about the benefits of low-efficacy vaccines, when properly used.

⁵⁶ Zimet, G.D., Blythe, M.J. & Fortenberry, J.D. (2000) Vaccine characteristics and acceptability of HIV immunization among adolescents, *International Journal of STD & AIDS*, 11(3), pp. 143-149.

⁵⁷ Webb, P.M. et al. (1999) HIV immunization: acceptability and anticipated effects on sexual behavior among adolescents, *Journal of Adolescent Health*, 25(5), p.321.

Concerns regarding low vaccine efficacy relate not only to non-acceptance, but also to increased risk behaviour that may occur by those that do accept HIV immunisation. By giving false confidence to consumers, a low efficacy vaccine has the potential to have a paradoxical effect, and actually lead to increased incidence of HIV. Therefore, like adolescent vaccination against hepatitis B, all AIDS vaccine recipients will require intensive counselling to maintain, or improve protective behaviours.⁵⁸ This would work very well in conjunction with condom distribution: a health intervention that can be implemented today, thus allowing vaccination programmes to be later superimposed onto the same delivery infrastructure.

Vaccine characteristics are not the only factors that determine acceptance, however. Even high efficacy vaccines of low cost, which are easy to administer can have low acceptance. In the US acceptance of hepatitis B immunisations by surgeons has been recorded at only around 70%, and failure of children in industrialised nations to receive routine immunisations is commonly documented.⁵⁹ This is because health beliefs also play an important role in determining vaccine acceptance, and can be related to local vaccination cultures, and images of diseases. It is not always scientific facts about a technology that determine whether or not people accept it, but rather people's interpretation of these facts.⁶⁰ News about a new vaccine will most likely be simplified, and this information will be interpreted differently, according to people's past experiences and current knowledge. Anti-vaccine movements can be easily propagated, due to spreading rumours, and the sharing of negative vaccination

⁵⁸ IAVI (2000), p.9.

⁵⁹ Zimet, G.D. (1997) Health beliefs and intention to get immunised for HIV, *Journal of Adolescent Health*, 20(5), pp. 354-359.

⁶⁰ Streefland, P.H. (2003) Introduction of a HIV vaccine in developing countries: social and cultural dimensions, *Vaccine.*, 21(13-14), p.1306.

experiences. Another study of US college students indicates that perceived low susceptibility to HIV infection, doubts about the benefits of vaccination, and concerns about vaccine safety will be the strongest reasons relating to health beliefs for non-acceptance of HIV immunisation. These findings were consistent with other studies regarding acceptance of other vaccines such as for hepatitis B and influenza.⁶¹

It is imperative that public health programmes are aware of local community attitudes towards immunisations, so that they can effectively educate populations to overcome public misconceptions, thus allowing for informed decisions. For example, it must be emphasised that it is behaviour, not merely membership of a risk group, which leads to HIV infection. This social marketing, however, may only be useful for dealing with scientific misconceptions, and it will be more difficult to deal with non-acceptance due to cultural and social issues such as, for example, religious beliefs.⁶² Ultimately, participation must be non-coercive, even though promotive vaccination programmes will have their limitations. Although there will be an urgent need for swift uptake of a new vaccine, this need must not override any human rights.⁶³

As the unique stigma associated with HIV/AIDS already challenges all other methods of prevention and treatment, it could also be a very strong barrier against a country embracing an HIV vaccination programme. Some groups may be opposed to immunisation against AIDS, perhaps believing that it will encourage sexual promiscuity or illegal drug use. Due to such stigma, individuals at risk of infection may refrain from being vaccinated, even though they may desire to do so, in the fear

⁶¹ Zimet, G.D. (1997), p.357.

⁶² Chang, M.L. et al. (2003), p.W4.

⁶³ IAVI (2000), p.21.

of being labelled as promiscuous or addicted to drugs, and being rejected by society.⁶⁴ Stigma and discrimination have the power to undermine any public health programme, as well as create an environment that further propagates disease. Fear of discrimination discourages people from using HIV testing services, from taking preventative measures such as condom use, and from seeking counselling and treatment for AIDS. Even some people that seek care have been rejected by the health services that should be helping them. A survey conducted in 2002 found that one in ten Nigerian doctors and nurses admitted to having refused care for an HIV/AIDS patient. In addition, many people living with HIV/AIDS in nations such as India, Indonesia and Thailand have had their HIV status disclosed without their consent.⁶⁵ These examples of violations to human rights contribute to the feelings of shame, guilt and isolation from which many people living with the disease suffer.

Another factor that fuels HIV stigma in developing nations is the lack of treatment for the disease, meaning that patients are often viewed as unproductive and hopeless cases. UNAIDS and WHO have begun on an initiative to provide antiretroviral treatment to 3 million people by the end of 2005.⁶⁶ In addition, governments of countries such as Brazil have begun initiatives to provide HIV drugs to their people, with the developed infrastructure potentially useful for eventual distribution of an HIV vaccine.⁶⁷ Such treatment programmes contest the effects of stigma by providing incentive for HIV testing, as well as creating hope amongst communities for those that are infected and at risk.

⁶⁴ *ibid*, p.9.

⁶⁵ UNAIDS and WHO (December 2003) p.32.

⁶⁶ *ibid*, p.32.

⁶⁷ Ainsworth, M. et al. (2001), p.W35

Much of the stigma and discrimination surrounding HIV is due to ignorance about the virus, and how it is transmitted. It follows that community education is one of the best ways to combat such ignorance. In Zambia, chiefs in the district of Lundazi led by example and took HIV tests, encouraging the community to do the same. In the South African children's television programme *Talkalani Sesame*, one of the characters is HIV-positive, raising AIDS related issues for young children to understand.⁶⁸

If necessary, however, harsher means such as using the law can and should be used to protect people's human rights of privacy and non-discrimination. For example, Venezuela's 'Citizens' Action against AIDS' has done so effectively since the late 1980s, providing the country's people with free legal support regarding HIV related discrimination.⁶⁹ Overall to date, much work has been done, yet HIV/AIDS stigma and discrimination certainly still exists throughout the world, meaning that similar efforts must continue in order to achieve full acceptance of a future HIV vaccine.

Much of IAVI's work in advocating research and development, and vaccine trials in developing countries involves promoting acceptance of an HIV vaccine as a first step. Taking Kenya for example, their first collaboration, IAVI partnered with a local media company to communicate with leaders, church organisations and the community. By overcoming fears and gaining acceptance, phase II trials of a candidate vaccine are now underway, with phase III trials being planned.⁷⁰ Although IAVI is meeting many of their aims, and their work is highly credible, there are some concerns, however, that their activities are not always staffed properly. In Kenya, it was felt that there was insufficient field presence on the ground to sufficiently handle

⁶⁸ *ibid*, p.33.

⁶⁹ UNAIDS and WHO (December 2003), p.34.

⁷⁰ Skolnik, R. et al. (2003) Independent evaluation of the International AIDS Vaccine Initiative, p.31.

the workload, with concerns that the upcoming phase III trials will not be carried out properly. Other concerns were also raised that because IAVI is still a young organisation, and is so focussed on making quick changes, they have been insensitive to local customs and practices at times.⁷¹ However, much has been learnt from their experiences in Kenya, and as the organisation has grown and funding has increased, improved efforts are now underway in countries such as India, Uganda and South Africa. IAVI has also worked with WHO and UNAIDS to speed up the development of the African AIDS Vaccine Programme (AAVP), which aims to prepare African leaders and public health officials to be ready for a vaccine within their countries.⁷²

As IAVI's work has demonstrated, it is not only the general public's view of HIV vaccination that must be addressed. All other parties involved in allocating resources, such as finance and health ministers, policy makers and health care providers, must also be educated to understand the true value of immunisations in preventing disease and reducing mortality. GAVI Executive Secretary Tore Godal, emphasises that:

...vaccine expenditures should be considered investments rather than costs. In this respect...the world still greatly undervalues immunization as a tool for health and development.⁷³

Vaccines are one of the most cost-effective medical interventions available, with studies estimating that existing vaccines would still remain cost-effective even if their prices were 10-50 times higher.⁷⁴ This is why organisations such as IAVI and GAVI are building partnerships between the public and private sectors. Such alliances both

⁷¹ *ibid*, pp.33-34.

⁷² Weidle, P.J. et al. (2002) HIV/AIDS treatment and HIV vaccines for Africa, *The Lancet*, 359, p. 2261.

⁷³ Walker, S. (2002/2003), p.3.

⁷⁴ IAVI (2000), p.22.

encourage the world to fully accept existing vaccines, as well as set an example that paves the way for a future HIV vaccine.

The next section on “estimating vaccine demand” looks at the gap between those who need a vaccine and those who are actually likely to be immunised. The two cannot be assumed to be the same, and it must be appreciated that both acceptability, as well as accessibility issues must be dealt with.

Estimating vaccine demand:

Demand assessments are fundamental for any manufacturer that develops a product, for it is these estimates that will help dictate many major business decisions. IAVI recognise that forecasting what the demand will be for a future HIV vaccine is an essential step that is required to organise the other major aspects of immunisation deployment.⁷⁵ An understanding of exactly who will want the vaccine once it has been created is necessary for both creating the relevant infrastructure for delivery, as well as planning for enough financing to purchase the vaccine. In addition, companies can use these predictions to help ensure sufficient production capacity, so that vaccine shortages are avoided, or at least minimised.

The IAVI blueprint reported no current reliable estimates, or established methods of estimating demand in 2000, especially amongst the developing world, thus it proposed that a method be created.⁷⁶ However, as an HIV vaccine does not yet exist, its characteristics, such as efficacy, cost, duration of protection and ease of use, are not yet known. As these properties will influence demand, it is impossible to predict exact figures. Therefore, it is recognised that a range of estimates will be required, accounting for various scenarios of vaccine characteristics. It is also appreciated that estimating demand will be an evolving task, as increasing demand is a necessary component of improving vaccine access. As mentioned in the previous section, for example, public acceptance of AIDS vaccination will be required for effective delivery, which can be achieved through social marketing and fighting stigma and discrimination. These actions are likely to result in greater demand in the future.

⁷⁵ *ibid*, p.17.

⁷⁶ *ibid*, p.17.

Demand will change along with the world's response to the HIV/AIDS epidemic.⁷⁷

This must be accounted for in the assessment of global demand.

In 2001, a study was jointly implemented by WHO, UNAIDS and IAVI which looked at both the *need* and *probable uptake* for HIV/AIDS preventive vaccines. This was done through four regional workshops, which took place between April and June 2001 in Florianópolis, Brazil (for Latin America), Entebbe, Uganda (for Africa), Seoul, Republic of Korea (for Asia and the Pacific), and Geneva, Switzerland (for North America and Europe). Two hypothetical scenarios of vaccine efficacy were used, low/moderate (30-50%) and high (80-90%) efficacies.⁷⁸ Using epidemiological data, need (defined as the number of people who could benefit from the vaccine) was estimated to be 260 million courses (with one course per person) for a low-efficacy vaccine, and 690 million courses for a high-efficacy vaccine. The need was greatest in poorer regions such as sub-Saharan Africa, with 41% of the population aged 15-49 years needing the low-efficacy vaccine, and 69% able to benefit from the high-efficacy vaccine. Probable uptake, or demand in the context of this public health study, drawing on data regarding accessibility and acceptability, was estimated to be 49 million courses for a low-efficacy vaccine (19% of needs), and 260 million courses for a high-efficacy vaccine (38% of needs).⁷⁹

This study made several assumptions regarding the vaccine's other characteristics. It was assumed that the vaccine would be easy to administer, and affordability as a constraint to purchase was removed, but with costs of distribution the responsibility of

⁷⁷ Bass, E. (2002) The need to understand demand, *IAVI Report*, 6(5), pp. 1-2, 13-15.

⁷⁸ Esparza, J. et al. (2003) Estimation of "needs" and "probable uptake" for HIV/AIDS preventive vaccines based on possible policies and likely acceptance, *Vaccine*, 21(17-18), pp. 2032-2041.

⁷⁹ *ibid*, p.2032.

each country.⁸⁰ However, not all such assumptions should be made. In the past, a vaccine's cost has been one of the strongest indicators of whether or not it would be added to childhood immunisation programmes.⁸¹ If vaccine purchase is not assured, the same will apply for an HIV vaccine, and the target population (adolescents and sexually active at-risk adults) in developing nations may not be able to afford the vaccine for decades. The study does, however, acknowledge that some developing countries are likely to receive assistance with strengthening their delivery systems, which would allow the probable uptake to be greater than estimated.

It is also acknowledged that vaccines may not be broadly protective against all HIV strains, and that if the vaccines are only subtype specific, they will have to be used in combination in areas affected by multiple strains. This would lead to a higher total number of immunisation courses required.⁸² Also, although the IAVI blueprint recognises that immunologic responses to a vaccine can differ between populations, and that the various routes of exposure to HIV may be protected differently by the same vaccine, these important factors are not raised in the study. In addition, the workshops only addressed vaccine demand by the public sector. Although it was acknowledged that the potential private retail market was not explored, it should have been due to the fact that it is the highest source of marginal profit, and thus a driving force for the vaccine industry.⁸³ However, a new Demand Project is being developed at IAVI to collect more detailed data to better project both need and demand,⁸⁴ with results not yet available.

⁸⁰ *ibid.*

⁸¹ Bass, E. (2002), pp. 1-2.

⁸² Esparza, J. et al. (2003), p.2035-6.

⁸³ Canadian HIV/AIDS Legal Network (2002), p.43.

⁸⁴ Bass, E. (2002), p.15.

It must be pointed out that throughout almost all of the literature, an assumption seems to be made that the first successful HIV vaccine will be a *preventive* vaccine, where its prophylactic nature will prevent uninfected individuals from infection. There is very little, if any, discussion about preparing for a *therapeutic* vaccine, which would boost the immune response of people already infected by HIV, thus slowing their disease progression to AIDS. Although most researchers believe that developing a therapeutic vaccine is far more difficult, especially as no such thing yet exists for any infectious disease,⁸⁵ it cannot be disregarded as a possibility, especially as several candidates are undergoing trials. Only recently, Virax, a biotechnology company based in Melbourne, Australia, has shown evidence of the first candidate vaccine to restrict HIV levels in infected patients, thus assisting to block their disease progression.⁸⁶

In the event that a therapeutic HIV vaccine is developed, the recommendations made by IAVI, and actions that have been taken so far will not all be entirely relevant. In the case of estimating demand, figures will need to represent the infected population, not the at-risk uninfected population. This, in turn, will indicate a different manufacturing capacity, as well as a different sized purchase capacity to be required. In addition, the necessary delivery infrastructure will have to be geared differently, perhaps with a heavier focus on accessing infected individuals with ARV treatment now, so that they can be reached with the vaccine later.

⁸⁵ Noble, S. (Sept 2003-Jan 2004) Therapeutic AIDS vaccines, *IAVI Report*, 7(3), p.18.

⁸⁶ Pirani, C. (February 13, 2004) Aussie vaccine 'blocks out' HIV, *The Australian*

It must be appreciated that some preparation may be necessary to prepare the world for a therapeutic vaccine. However, current efforts to ready the world for a preventive vaccine must not diminish as a result. As research towards a preventive vaccine may also benefit research towards a therapeutic vaccine, and vice versa, the two should not necessarily be seen as distinct,⁸⁷ and efforts should be made to prepare for both, as all such efforts share the common goal of a world free of AIDS.^β

⁸⁷ Noble, S. (2003/2004), p.18.

^β Although the possibility of a therapeutic HIV vaccine is acknowledged here, further discussion on the matter is beyond the scope of this paper. Therefore, the remainder of this paper will refer only to preventive vaccines.

Ensuring sufficient production capacity:

Global demand for the first AIDS vaccine, even one of a modest efficacy, is likely to grow very quickly at the start to reach a catch-up level, but then gradually decline and then stabilise at a lower maintenance level.⁸⁸ However, all other actions to assure access will be to no avail unless there is sufficient supply to meet the initial high demand. The historical paradigm for vaccine production has shown that, initially, vaccines are produced in relatively small quantities, almost always exclusively for industrialised countries that have the ability to pay full price. It is only over time, that production processes become more efficient, making it economically feasible to increase manufacturing capacity to supply the vaccine to developing countries at a lower price.⁸⁹ To break the paradigm, and ensure global supply, production capacity will have to be sufficient by the time the first suitable vaccine is licensed.

Manufacturing plants:

However, vaccine production plants typically take four to five years to commission, design, and build, at a cost of US\$ 100 to \$200 million.⁹⁰ This means that the scale-up of manufacturing capacity must begin well in advance of the producer even receiving regulatory approval. As the majority of vaccine manufacturers are from private firms, mainly pharmaceutical companies (such as GSK and Merck) and sometimes biotechnology companies,⁹¹ any investment decisions made regarding vaccine supply are likely to be based on risk assessment, by comparing alternative options in terms of likely costs and returns. Therefore, under such conditions of uncertainty, the private

⁸⁸ IAVI (2001), p.24.

⁸⁹ World Economic Forum & IAVI (2002) Delivering an AIDS vaccine, New York, p.6.

⁹⁰ IAVI (2000), p.18.

⁹¹ *ibid*, p.42.

industry alone cannot and should not be expected to initially invest in production plants with the capacity to supply global needs, to the magnitude of hundreds of millions of people. This is especially so when the product in question does not yet exist. In addition, with more and more vaccine trials entering the pipeline, potential producers are more reluctant to make large investments in production capacity, due to the possibility that improved next generation vaccines will displace their product.⁹² Left to their own 'business as usual' devices, such financial risks will not be readily accepted by the private sector alone. As investments in AIDS vaccination could have many benefits to the public sector, such as reducing public health costs, it seems justified to expect the public sector to provide assistance. Therefore, public-private partnerships must be forged to share any risks involved, thus allowing the necessary steps to be undertaken.

Firstly, IAVI recognises that an international body should be set up to monitor and evaluate vaccine candidates that are undergoing trials to identify the potential producers who need to be included in negotiations.⁹³ This will help predict the type of production facilities that will need to be designed and constructed. To be on the cautious side, companies such as VaxGen designed their new manufacturing facilities to be as versatile and multi-purpose as possible, able to produce a range of vaccine products.⁹⁴ This precaution was worthwhile, as the phase III trials of their candidate AIDS VAX showed that the vaccine gave no overall protection.⁹⁵ However, common production technologies allow their completed plant in San Francisco, US, and

⁹² *ibid*, p.18.

⁹³ *ibid*.

⁹⁴ Bass, E. (2002), p.14.

⁹⁵ IAVI (2003) VaxGen releases results of Thai phase III trial, *Vax: An IAVI Report Bulletin*, 1(4), p.1.

unfinished facility in Incheon, South Korea to be utilised for different candidates in the future, as well as vaccines for other diseases, such as anthrax.⁹⁶

The public sector could encourage the private industry to expand their production capacity through a range of financial incentives, all of which effectively reduce the financial risks taken by private firms. Such possible actions include loans and credits by organisations such as the World Bank, tax incentives and subsidies from national governments of developed countries, or even construction of public facilities that could be contracted to manufacturers for the initial period where demand will be highest.⁹⁷ The free market is primarily motivated by profit, and is therefore not always designed to take ethical factors into consideration, thus it is left to the public sector to step in and ensure that it does. Otherwise, nobody else will and supply will fall short, neglecting the developing world. If increasing manufacturing capacity can become an economic interest of the private sector, as is the purpose of these proposed actions, then the required changes are likely to occur.

Production will be especially challenging if vaccines need to be subtype specific. There would be very little financial incentive for any private company to produce a vaccine that only provides protection from a viral strain such as HIV subtype C, for example. This is because the market would be restricted to countries of sub-Saharan Africa and India, the main areas affected by this particular strain.⁹⁸ It would be unlikely that these economically weaker nations would be able to even cover the manufacturer's overhead costs, thus significant private investment in this market

⁹⁶ Fink, S. (2004) Breaking the bottleneck, *IAVI Report*, 8(1), pp. 15.

⁹⁷ IAVI (2001), p.25.

⁹⁸ Kahn, P. (2002) Do clades matter for HIV vaccines?, *IAVI Report*, 7(2), p.1-2, 14-16.

would also be unlikely. Therefore, to produce sufficient quantities of vaccines for strains specific to developing nations, more public sector involvement will be essential, and it may prove worthwhile to consider supporting developing country manufacturers to produce HIV vaccines for their own country. Although there are an enormous number of such producers, only few meet global quality standards, and these only produce the more simple vaccines that currently exist for other diseases.⁹⁹ Candidate HIV vaccines are using complex and expensive technologies such as mammalian cell fermentation processes, compared to hepatitis B vaccines which are more simply produced in yeast.¹⁰⁰ Therefore, for developing nation manufacturers to utilise such state-of-the-art technology, a great amount of financial and technical support would be required.

Legal issues:

Any support, however, will have to respect legal frameworks regarding patents and the protection of intellectual property rights (IPRs), in accordance with the World Trade Organisation Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS Agreement), which states that IPRs should contribute to:

...the mutual advantage of producers and users of technological knowledge and in a manner conducive to social and economic welfare, and to a balance of rights and obligations.¹⁰¹

Such patent laws secure a company's ownership and profit from their product, thereby acting as an incentive for research and development of new technological innovations, as well as the manufacturing of their product. They are designed to find a balance

⁹⁹ IAVI (2000), p.19.

¹⁰⁰ Ainsworth, M. et al. (2001), p. W39.

¹⁰¹ Canadian HIV/AIDS Legal Network (2002), p.38.

between the economic interests of the private sector and the social interests of public health.

So far, IAVI has made agreements with some biotechnology companies, where the firm can retain development rights, as long as their future HIV vaccine is produced in reasonable quantities for developing countries, and at a reasonable cost (i.e. tiered pricing). However, if the company fails to do this, IAVI then has the right to step in and transfer the technology to other manufacturers.¹⁰² In the case of an HIV vaccine, IPRs may be more complicated if more than one technology is utilised by more than one manufacturer to produce the vaccine, leading to potential disputes between companies.¹⁰³ In addition, IAVI's negotiations seem to have mainly been with smaller biotechnology companies, rather than with large pharmaceutical companies, perhaps because negotiations with larger firms are more complex. However, it is important that such negotiations still go ahead, as there is a strong possibility that the first successful HIV vaccine will come from one of the pharmaceutical giants.

It is also important that liability concerns regarding HIV vaccine use are addressed now, so that manufacturing is not delayed further. In the past, vaccines have been associated with negative side effects, such as the measles vaccine being correlated with autism in children. Whether or not this, or other associations are true, future HIV vaccine manufacturers may see potential compensation claims as a disincentive to vaccine research, development and production. In the US, the Childhood Vaccine Compensation System, which is constantly under much political scrutiny, limits the

¹⁰² Wheeler, C. & Berkley, S. (2001) Initial lessons from public-private partnerships in drug and vaccine development, *Bulletin of the World Health Organization*, 79(8), p.731

¹⁰³ Canadian HIV/AIDS Legal Network (2002), p.39.

liability of manufacturers who are not negligent, but only for paediatric vaccines.¹⁰⁴ In weighing up the potential benefits and disadvantages of HIV vaccination on public health, it may be necessary to regulate liability to ensure that the benefits prevail. However, there are currently no systems in place to indemnify AIDS vaccine producers from liability due to future vaccine injury.¹⁰⁵

Uncertainty and commitment:

Although it is well recognised what needs to be done, with the roles of both public and private sectors defined, the available literature shows little actual progress regarding the establishment of sufficient productive capacity now, before an HIV vaccine is ready. The public sector does not seem to be giving enough financial incentives by way of subsidies, loans and credits, and the private industry is still facing much uncertainty. It is this very uncertainty that is contributing to progress being inhibited. IAVI has done its best to remove as much of the unknown as possible, through previously mentioned work such as their collaborative demand estimate projects. Yet estimates still span an extremely wide range as there remains much further speculation, most of which regards the future vaccine itself, and its associated properties. Many questions remain about how much the vaccine will cost, how it will need to be administered, how long it will provide immunity for, and how effective it will be against each of the various subtypes. With so many vital questions unanswered, it is extremely difficult to plan for exact solutions. Although these questions can only be fully answered once a suitable vaccine is ready, solutions still need to be considered now, using whatever information is available.

¹⁰⁴ AVAC (2003), pp.15-16.

¹⁰⁵ *ibid*, p.16.

IAVI has collaborated with a number of countries regarding tax incentives for investments in vaccine manufacturing,¹⁰⁶ but little action has occurred to date. It seems that there is not enough political commitment from developed nations, the countries that have the financing and power to make the necessary changes. As mentioned previously, this may be due to the threat of AIDS being underestimated by these countries. It may also be due to reasons pertaining to political acceptance, where government decisions that are perceived to have more direct and immediate benefits for the citizens of their country are favoured, such as actions against bioterror. IAVI and other organisations must continue their work in providing support and encouragement to gain the necessary financial assistance. Governments and international organisations need to act now towards ensuring adequate global supply in the future, otherwise the humanitarian disaster that is occurring today will worsen even further.

¹⁰⁶ *ibid*, p.29.

Improving regulatory processes:

Once an HIV vaccine has been proven to be safe and effective in human trials, it needs to be licensed by the national regulatory authority (NRA) of each country that it is to be used in. In essence, this is a risk-benefit analysis. Not only does this process influence the design of pre-clinical and clinical trials, but it also continues to be important after the product is widely available, through post-licensing studies.¹⁰⁷ National approaches to market approval can vary widely, as an AIDS vaccine that is licensed in one country may not be considered as appropriate for all other countries. This may be due to subtype specificity issues, or perhaps reasons relating to vaccine efficacy and disease prevalence rates in each country. Therefore, there cannot be one universal standard for all regulatory decisions.¹⁰⁸ However, variations in procedures and approaches result in delayed access, as producers need to perform additional studies, or repackage material to meet the needs of each authority.¹⁰⁹ Current systems are inadequately suited to make swift yet safe decisions about AIDS vaccines. If changes are not made to regulatory procedures, AIDS vaccine licensure will be a drawn out, country by country process that spans several years, maintaining the existing paradigm of vaccine access.

Further complicating the issue is that many AIDS vaccines in the pipeline, as previously mentioned, incorporate state-of-the-art technology that many regulators, especially those from developing countries, are unfamiliar with, making it difficult to assess them.¹¹⁰ In addition, it is not yet exactly known what types of responses an

¹⁰⁷ IAVI (2001), p.22.

¹⁰⁸ World Economic Forum & IAVI (2002) p.5.

¹⁰⁹ IAVI (2000), p.21.

¹¹⁰ IAVI website. <http://www.iavi.org/access/programdetails.htm> (04/12/03)

effective vaccine needs to elicit, due to the unique and complex nature of HIV infection. For most other viral vaccines that are currently licensed, serological responses (antibodies produced by B cells) correlate with vaccine efficacy. However, for HIV vaccines, it is believed by some experts that vaccine efficacy may only correlate with cellular (T cell) immune responses, or local immune responses at mucosal sites.¹¹¹ For therapeutic HIV vaccines, which would not prevent infection but rather block the progression to AIDS, surrogate markers of efficacy, such as viral load, may have to be used. However, the US Food and Drug Administration (FDA) has never licensed a vaccine primarily based on surrogate markers.¹¹² In March 2001, a WHO-UNAIDS consultation in Geneva, Switzerland, highlighted the need to identify the gaps in scientific understanding so that regulatory guidelines for an HIV vaccine can be developed.¹¹³

The IAVI Access Project White Paper (June 2001) identifies the need for a broad group of regulatory agencies, including those of developing nations, to focus on the key issues that need to be addressed regarding AIDS vaccine approval. Such issues include vaccine efficacy and safety, and balancing the need to protect the public from unsafe products with the need to deploy a new HIV vaccine as quickly as possible. The European Community (EC) has already committed itself to focus on such a dialogue, but other efforts are called forwards, with suggestions that WHO play a leading role.¹¹⁴ There is also a need for all national regulatory authorities to develop a

¹¹¹ WHO-UNAIDS (2002) Scientific considerations for the regulation and clinical evaluation of HIV/AIDS preventive vaccines: report from a WHO-UNAIDS consultation 13-15 March 2001, Geneva, Switzerland, *AIDS*, 16(10), p. W17.

¹¹² Berg, B. (2003) HIV/AIDS: Vexing virus poses challenge for vaccine testing, *Center News*, 9(17). Fred Hutchinson Cancer Research Center website. http://www.fhcrc.org/pubs/center_news/2003/sep4/sart4.html

¹¹³ WHO-UNAIDS (2002), pp. W16.

¹¹⁴ IAVI (2001) p.22.

fast-track, expedited review process (no longer than 6 months) for all life-saving products. The European Union and the United States already have such mechanisms in place.

In addition, the need to streamline submission processes to NRAs was identified. By doing this, countries with similar epidemiological characteristics could combine their regulatory experience together, which would permit simultaneous applications for approval. Through the International Commission on Harmonisation (ICH), industrialised nations of Europe, Japan and the US have already made some progress.¹¹⁵ However, there remains the need for developing nations to follow suit, with regulatory agencies that serve these countries requiring technical and financial support to improve their capacity.¹¹⁶

As US and European firms sponsor most vaccines that are currently in development, it is likely that FDA or the European Medicines Evaluation Agency (EMA) will review the first successful vaccines.¹¹⁷ Then the NRAs of developing countries can follow their lead. However, even such crucial organisations such as FDA are short staffed and under funded. The AIDS Vaccine Advocacy Coalition (AVAC) has therefore worked with FDA since July 2001 to make improvements in areas such as administration, information sharing, and scientific guidelines.¹¹⁸ In addition, in March 2002, US legislation was drafted to commit US\$ 2 million to FDA for technical assistance and partnerships with NRAs of developing nations to improve regulatory

¹¹⁵ AVAC (2001) 6 years and counting, New York, p.14.

¹¹⁶ World Economic Forum & IAVI (2002) p.5.

¹¹⁷ AVAC (2002) 5 years and counting, New York, p.27.

¹¹⁸ *ibid*, p.27

capacity for life-saving biomedical technologies, including HIV vaccines.¹¹⁹ IAVI has also commenced discussions with FDA.¹²⁰

However, it is possible that after assessing the risks and benefits of a vaccine, FDA and regulatory authorities of other industrialised countries may decide against its licensure, especially if it is of a low efficacy. Yet the vaccine may still be suitable for some developing nations, due to the community benefits of herd immunity, and because of the lack of access to other treatment options. Therefore, these countries must strengthen their own regulatory capacity to stand independently. In November 2002, nine countries: Brazil, China, Cuba, India, Indonesia, Korea, Russia, South Africa and Thailand, were invited to attend a WHO meeting in Geneva to set up a proposed NRA network. The main objective of this meeting was to increase the regulatory capacity of the developing world to assess future vaccines, including AIDS vaccines, and an agreement was reached to establish a network between the countries involved.¹²¹ In the same month, another meeting took place in Gaborone, Botswana, between regulators from 14 southern African countries and WHO officials. This was a workshop aimed at improving the regulatory capacity of both vaccines and microbicides in Africa. The need for regional harmonisation of common guidelines was discussed, and participants were urged to lobby their governments to prioritise and fund regulatory structures.¹²²

¹¹⁹ Canadian HIV/AIDS Legal Network (2002), p.40.

¹²⁰ IAVI (2003) Mid-year progress report, New York, p.26.

¹²¹ WHO (November 2002) Report on the meeting on national regulatory authority (NRA) networking for new regulatory pathways, Geneva.

¹²² Bing, A. (2002/2003) Gathering of regulators from southern Africa tackles vaccines and microbicides, *IAVI Report*, 6(6), pp. 7, 15.

To date, much has been done in improving regulatory processes for future HIV vaccines. IAVI has done much of their own work in exploring new regulatory pathways. In October 2002, they hosted a consultation of regulatory experts, which focussed on outlining a regulatory strategy for current vaccine candidates, to ensure swift licensure in the developing world.¹²³ To do this, they conducted a survey with major AIDS vaccine developers to look at the regulatory history of products that are currently in development. As of mid-2003, the proposed strategy was under review by IAVI's senior management team,¹²⁴ but the review is not yet available. It appears, however, that sufficient work is being done in removing regulatory bottlenecks as a barrier to accessing an HIV vaccine in the future.

¹²³ IAVI website. <http://www.iavi.org/highlights/nov/h20021114.asp> (27/02/04)

¹²⁴ IAVI (2003), p.26.

Conclusion:

The barriers that are standing in the way of an ethically just distribution of an HIV vaccine in the future have been identified, and ways to overcome these barriers have been suggested. This involves a complete changing of the historical paradigm of drug and vaccine introduction. In areas such as estimating vaccine demand, and improving regulatory processes, much progress has been made by organisations such as UNAIDS, WHO and IAVI. However, the literature shows that in the other areas regarding HIV vaccine introduction, not enough improvement has been made thus far. For financing vaccine purchase, no solid commitments have yet been made to establish financing mechanisms such as a vaccine purchase fund. Current delivery systems remain inadequate to supply vaccines to adolescents and at-risk adults living in developing nations. Should an effective HIV vaccine be developed today, current manufacturing capacity would fall far short of producing the number of required doses.

Looking at this pattern of what changes have and have not occurred, financial constraints become evident as a primary obstacle against worldwide access. Estimating demand and improving regulatory processes are relatively inexpensive goals, thus many of the necessary steps in these areas have been taken. The areas lacking in effort, financing vaccine purchase, creating delivery systems, and ensuring sufficient production capacity, all require substantial funding to come primarily from developed nations. Governments have not been willing to commit the necessary resources as yet, as these costs are not recognised to be in their best economic interests. Such expenditures should, however, be viewed as investments in global

health and development, rather than as costs. The changes that are required, and processes that could be employed have been outlined, and are feasible to achieve. However, advocacy efforts must be continued by IAVI and other organisations to gain the political commitment and will required to overcome any financial obstacles.

If an HIV vaccine were to exist today, the world would be better prepared than a few years ago, but still far from ready to introduce it rapidly to all who would need it. In reality, even if all the changes suggested in this paper were to occur, developed countries would still be likely to have access to the vaccine first. Actual simultaneous introduction could only occur if health care systems of developing countries were to match that of the developed world. This, however, is not foreseeable in the near future. The purpose of the suggested changes is to reduce the time between vaccine discovery and worldwide access by as much as possible. Realistically, reducing this time to less than 10 years, from the historical paradigm of 15-20 years would be a great achievement. For every month that the access timeline is compressed by, nearly half a million lives are saved.¹²⁵

It has been argued that the private sector, in particular the pharmaceutical and biotechnology industries, should receive a reasonable return on their investments, otherwise there will be no incentive to research and develop an HIV vaccine in the first place. Although the manufacturers can assist vaccine access through mechanisms such as tiered pricing, they cannot bear the full responsibility. James Wolfensohn, President of the World Bank, stated that:

¹²⁵ World Economic Forum & IAVI (2002), p.1.

An AIDS vaccine for low income countries is an international public good which is not likely to happen without innovative international public action...¹²⁶

HIV vaccination is a global health issue, thus it should be tackled as a joint effort by all sectors of global society. The importance of public-private partnerships has been highlighted, which combine the skills and tools of all parties involved to allocate resources efficiently and affordably to the developing world. This collaborative effort, led by organisations such as IAVI, has set a positive example for equitable access to new medical technologies. However, much work still remains ahead to ensure that worldwide access to an HIV vaccine in the future will be possible.

¹²⁶ IAVI (2000) World leaders speak out about the need for an affordable AIDS vaccine, *IAVI Fact Sheet*, New York, p.2.

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