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Developing Countries

A Force in the Global Fight against HIV/AIDS

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INTRODUCTION

Infectious diseases at the start of the 21st century are responsible for 13 million deaths annually, of which two thirds are children, mainly in the developing world. In 2002, AIDS, malaria, and tuberculosis were responsible for six million deaths, and the immune deficiency caused by HIV is accelerating the spread and pathogenicity of both malaria and tuberculosis (TB). The global estimates of HIV infections exceed 42 million people, and this pandemic is most advanced in sub-Saharan Africa. The average rate of HIV infection in southern African countries has reached at least 10% of the general population. In Botswana, the average life span has been reduced from 77 to 29 years because of HIV/AIDS (Stanecki and Walker, 2002). A UNAIDS report estimated that the chance a 15-year-old boy in Botswana would die of AIDS before he reached adulthood (30 years) was about 90% (Piot and Bartos, 2002). The African epidemic demonstrates the social and economic consequences incurred by the directional transmission of this lethal infection by sex and blood contact targeting the major workforce and child-rearing age segment of society. The social impact of the efficient extinction of the sexually active segment of society is the generation of 11 million orphans by 2002 and an expectation that this number will exceed 20 million by 2010. Moreover, the directed infection of the major workforce has profound economic consequences, together with the associated spiraling burden of their health care. Vaccine development for AIDS is a low priority for the major vaccine manufacturers in developed countries and currently early stage clinical evaluation of vaccine candidates is spearheaded by publicly funded non profit groups. This picture of HIV/AIDS in Africa will be repeated in other developing countries unless a coordinated, proactive international effort is organized.

In 1996, Weniger and Brown proposed that evidence suggested that Asia would

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become the new battle ground in the war between humanity and AIDS (Weniger and Brown, 1996). This prediction was accurate and currently Asia faces a crisis similar to that confronted by Sub Saharan Africa in the early 1990's. In 1997, China reported less than one thousand cases of HIV. In response the "Chinese National Medium- and Long-Term Strategic Plan for HIV/AIDS prevention and control (1998–2010)", was to limit the HIV/AIDS cases to 1 million by the year of 2010. However, by the end of 2003, the Chinese Ministry of Health (MOH) estimated that HIV-1 might have already infected 840,000 people in China (UNAIDS 2003). China, India and Indonesia comprise more than half the world's population and have considerable financial resources, expertise in high technology, preventative medicine and public health. To control this economic and socially devastating disease, it remains to be seen whether they will entrust the development of an effective vaccine to poorly motivated manufactures in the developed world or will they devote national resources and expertise to develop an HIV vaccine on their own timetable. It is difficult to imagine that countries that have thriving high technology industries, nuclear and space programs and undertake major hydroelectric programs cannot coordinate with international collaborators the development of an effective HIV vaccine.

This chapter investigates the requirements for developing countries to take a leadership role in solving major infectious disease problems, such as those posed by AIDS. This will be attempted by evaluating:

1. the capacity to develop and manufacture safe and effective vaccines;
2. the infrastructure required to evaluate and distribute vaccines; and
3. the long-term commitment of government and public health officials to the production of high quality vaccines.

This evaluation will focus on China since it is a developing country with an emerging AIDS epidemic and has the capacity to attempt the development of an AIDS vaccine.

The Capacity to Develop and Manufacture Safe and Effective Vaccines

Vaccine production was initiated in China in 1919 and significantly expanded in the 1950's by the establishment of six major vaccine development and production facilities throughout the country, which were directly affiliated with the MOH in Beijing. These new institutes developed and produced a number of vaccines, including the large-scale production of Tiantan strain of vaccinia virus as the vaccine against smallpox, large-scale production of BCG as the vaccine against TB, live attenuated *Brucella* vaccine, live attenuated anthrax vaccine, and live attenuated yellow fever vaccine. In 1950, the Chinese Government published "the temporary measures for vaccination." The most notable success of these measures was the smallpox vaccination program. Within a decade, public health workers in the newly established epidemics preventive stations throughout the country were able to implement an effective nationwide vaccination drive using the Tiantan vaccinia virus as the vaccine. Together with the establishment of the nationwide smallpox case reporting and control network during the same ten year period, the last case of smallpox infection in China was reported in 1959 and was claimed to be eradicated in the country after an examination by the World Health Organization (WHO) (Wang *et al.*, 2000).

Another achievement of the Chinese vaccine production and national immunization programs in the 1950s was the use of BCG as the vaccine against TB in China. In 1950, the Ministry of Health decided to provide the BCG vaccine in Chinese cities free of charge, which in fact became the prologue of the national immunization program that was expanded in the following five decades. Although many vaccine experts and public health officials consider that the real

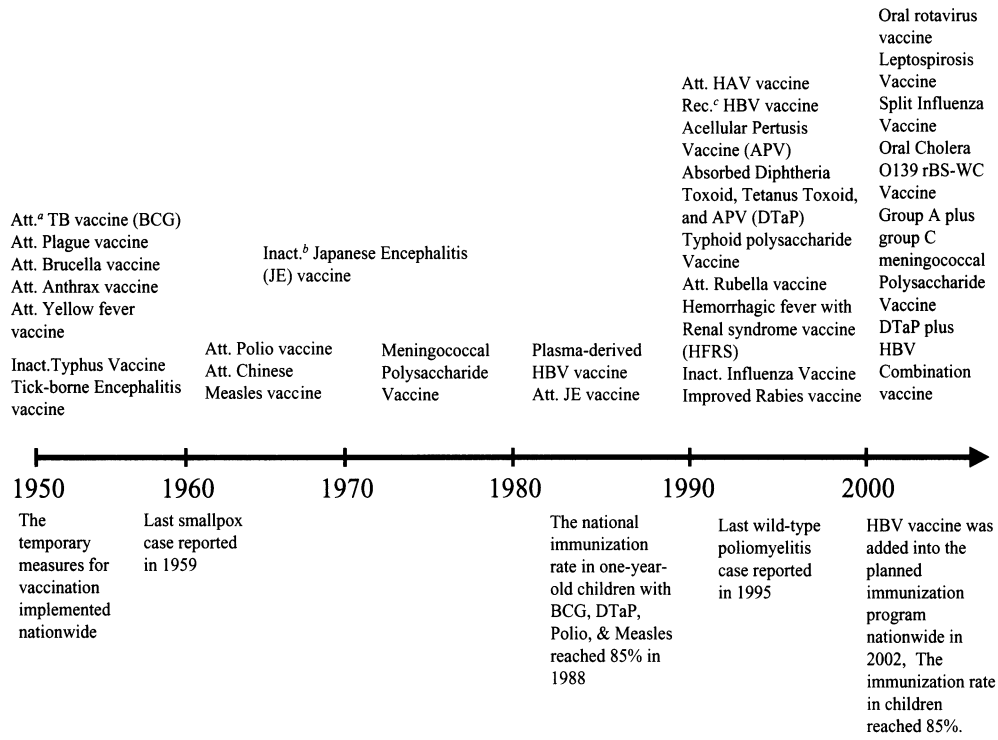

FIGURE 1. Vaccine production in developing countries: a case study (adapted from Lu *et al.*, 1995).
[a]live attenuated [b]inactivated [c]recombinant protein-based

effectiveness of BCG vaccination against TB is still scientifically questionable, the effort of the government trying to protect its people through a 50 year long national program should be commended.

In the 1960s, as shown in Figure 1, two notable new vaccine products were the vaccines against poliomyelitis and measles. The Beijing Institute for Biological Products introduced into China from the US the oral trivalent poliomyelitis vaccine (the Sabin strain). Within a short period of time, the Beijing Institute for Biological Products and the Kunming Biological Research Institute were able to achieve 1 hundred million doses per year, respectively. Like the successful eradication of smallpox in China through the nationwide vaccination program in the previous decade, the last case of poliomyelitis in China that was caused by wild strain virus infection was reported in 1995, and it has not been found since then (Wang *et al.*, 2000).

In 1965, the live attenuated measles vaccine of Chinese origin was developed (Lu *et al.*, 1995). The new live attenuated Chinese measles vaccine was soon proved to be safe and effective and used widely in the nationwide vaccination program. By 1987, the vaccination rate of this vaccine for children under age one reached about 77% nationwide, and the incidence rate for measles in the general population decreased 92% in comparison with that in 1980. By 2001, the Chinese vaccine industry was able to meet the need of vaccinating nearly 98% of all Chinese children under age five (MOH, 2002).

Since the early 1950s, China has managed to produce and supply a massive amount of childhood vaccines in a nationwide immunization program through its domestic vaccine manufacturers that are owned and operated by the government. As the Chinese vaccine industry has undertaken a self-sufficient proactive vaccination program that covers a

vastly populous nation of 1.3 billion people, it is conceivable that the industry may also enable China to play a significant role in the fight against AIDS. As shown in Figure 1, the Chinese vaccine industry entered into a rapid-growth period in the 1980s as a result of the country's economic reform. The production of the combination vaccine for prevention of diphtheria, tetanus, and pertussis (DTP) finally reached a massive scale that enabled the government to launch an initiative to immunize all newborns with four vaccines, including BCG, polio, measles, and DTP. The initiative later became known as the National Planned Vaccines in China. The immunization coverage rate of the planned vaccines in Chinese children under age one was 85% in 1988 for the first time. Two years later, the rate reached 90%. In 2001, the rate of the planned vaccination in children under age one was 97% nationwide (MOH, 2002). The annual production output by the Chinese vaccine industry is at average 110 million doses for each one of these four vaccines, respectively.

The Infrastructure Required to Evaluate and Distribute Vaccines

By 1997, there were 280,558 public health professionals working in 3619 Centers for Disease Control nationwide, plus 1893 special disease prevention and treatment centers in China (Wang *et al.*, 2000). These centers and their public health workers are mainly responsible for disease control and monitoring, sanitary inspection, health education and promotion, scientific research and personnel training, and annual immunization drives that inoculate millions of infants and children nationwide. It is worth noting that unlike many countries in the world, the vaccination program in China, including the vaccine production and planning, product distribution and pricing, and vaccine inoculation, has always been the responsibility of the government. Every year, the vaccine inoculation is conducted at the state-assigned hospitals and epidemic prevention centers, and various vaccines are purchased by local governmental health bureaus and distributed by their public health workers.

This huge and complex public health network in China has played an essential role in various national and local planned vaccination programs. After receiving vaccines from the state-owned vaccine manufacturers in their region (each of the six state-owned Institutes for Biological Products is assigned a number of neighboring provinces), the provincial CDC (Center for Disease Control, formerly known as the Disease Prevention Station) is responsible for proper storage of the vaccines and their distribution to the county and village level CDC. Each CDC, regardless of its level, must have designated public health workers responsible for individual tasks such as record-keeping, proper cold-chain storage and transportation, and safekeeping of the biological potencies of each vaccine according to the manufacturer's specific requirement.

The threat of Japanese Encephalitis (JE) virus infections in China lead to the development and field evaluation of an effective vaccine, SA14-14-2, which was used to stem the national epidemics of JE infections (Tsai *et al.*, 1999, Zhou *et al.*, 2001). The successful development of JE vaccine in China demonstrated a number of interesting features of the Chinese public health system and its vaccine industry. Firstly, it showed that when the country was threatened with a serious epidemic, it was capable of effectively mobilizing sufficient national resources to successfully combat the disease. Secondly, it showed that China has the scientific capability, the material resource, and the public health infrastructure to conduct large-scale vaccine efficacy trials with hundreds of thousands of participants.

Like in many other developing countries, the Chinese pubic health system lacks the ability and resources for the early detection and prevention of the epidemics that spread by chronic or "silent" infections. A devastating example is the wide spread of Hepatitis B infection in the country in the past three

to four decades. According to government statistics, as many as 58.1% of Chinese are infected with the Hepatitis B virus and 10.8% of Chinese are "carriers", who are at high risk of developing viral hepatitis disease in their lifetime (Lu *et al.*, 1995). An effective HBV vaccine (plasma-derived) was licensed in the US in 1982, and followed by the recombinant protein-based HBV vaccine (Mahoney and Kane, 1999). In 2002, the same recombinant protein-based HBV was listed as one of the planned vaccines for children nationwide in China, and the long-anticipated object of immunizing 90% of neonates in cities and towns was finally reached. In metropolitan areas such as Beijing and Shanghai, the HBV rate of infection in children under 5 years old for the first time has dipped below 1%. The development of the recombinant HBV vaccine in China was a slow process, yet it demonstrated the ability to transfer new technologies into the national vaccination program. It is anticipated that this and similar experiences will facilitate the transfer of new technologies that will be associated with the development of HIV vaccines.

The Long-Term Commitment of Government and Public Health Officials to the Production of High Quality Vaccines

Another example of infrastructure building in the Chinese public health system is the establishment of a functional system that regulates vaccines and other biological products. In the early 1960s, the government established the National Institute for the Control of Pharmaceutical and Biological Products (NICPBP) in Beijing in order to control the quality of pharmaceutical and biological products nationwide. In 1989, the Chinese Committee for the Standardization of Biological Products (CCSBP) was established, which has five branches with respective responsibility for virus products, bacterial products, blood products, bioengineering products, and diagnostic reagents. The main function of this new government agency was to establish a new set of regulatory standards known as *The Standards for Chinese Biological Products*, for all of biological products that were made or used in China. With regard to the vaccine industry, these standards are applied to the development of new products and the improvement of manufacturing technologies and quality control procedures. CCSBP amends *The Standards for Chinese Biological Products* every five years. For example, the latest edition of *The Standards for Chinese Biological Products* was published on October 1, 2000 and is still in effect.

In 1998, the State Drug Administration (SDA) was established, which published *The Regulations for Examination and Approval of New Biological Products* in order to differentiate biological products from chemical drugs and traditional Chinese medicines. In these regulations, biological products are defined as the products made from microorganisms (yeast, bacteria, viruses, etc.), cells, and various animal and human tissues and fluids. These include all vaccine products, blood-derived products, medicines, and diagnostic reagents. For example, the number of biological products listed in the year 2000 edition of *The Standards for Chinese Biological Products* was 137, which was divided into 36 preventive products, 39 therapeutic products, and 62 diagnostic products. However, this publication also listed ten preventive or therapeutic products that still need to be inspected due to unsatisfactory quality control standards and determination methods. If further improvement of these products by the manufacturers does not meet the deadline set up by the SDA, they will be deleted from the list in the next edition.

In July 1993, MOH issued The Management Rules of Biological Products, which stated that all of biological products were subject to governmental regulation and management, and principally listed the requirements for the ordering, supplying, cold-chain storage and abnormal reaction accident handling of biological products, especially preventive

vaccines. In the following year, the ministry further issued The Manufacture and Supply Management Rules of Preventive Biological Products, stating that preventive biological products are under the management system of the government-owned vaccine manufacturers and their supply chains. But, fitting the fifty-year-old Chinese public health system into the new market economy in China has been a real challenge to the Chinese political leadership. For example, the Chinese central government in 1989 created the China National Biological Products Company as an attempt to reorganize the national vaccine industry as a market-oriented business company instead of being just a government agency. Then in August 2003, this company was reorganized again as the China National Biotech Corporation (CNBC), a state-owned enterprise governed by the State-owned Assets Supervision and Administration Commission of the State Council (SASAC). This new corporation consists of the China National Scientific Instruments and Materials Import/Export Corporation (China Scientific), Beijing Tiantan Biological Products Company Ltd., and the six institutes of biological products. As aforementioned, these six institutes in Beijing, Changchun, Chengdu, Lanzhou, Shanghai and Wuhan were the backbone of the Chinese vaccine industry in the past fifty years. And they played major roles in the development and production of various vaccines that have protected hundreds millions of Chinese from several dreadful infectious diseases. As the largest corporation in the Chinese vaccine industry, CNBC aims at integrating vaccine development and production with marketing strategy. As a government-owned enterprise, CNBC also has the responsibility of producing and supplying various biological products, including vaccines, to meet the public health demands of the most populous nation in the world.

CNBC has more than 80 production lines that are in compliance with the national GMP (Good Manufacture Practice) and collectively produces more than 50 different vaccines with an annual output over three hundred million doses. The current vaccine product lines in CNBC are divided into three groups. The first group of vaccines are those that are listed in the national planned vaccination program, including BCG, polio vaccine, DTP, measles vaccine, and Hepatitis B Vaccine. These vaccines are mainly for newborns and children under school age and manufactured for the government with the pricing policy that is determined by the government. The second group of vaccines includes those that are listed or to-be-listed in the planned vaccination programs for children by each individual province in the country. These vaccines include the group A meningococcal polysaccharide vaccine, JE vaccine, and others. Unlike the vaccines in the national planned vaccine group, this group of vaccines has a more flexible price range, thus having possible profit margins. The vaccines in this group that are produced by CNBC has about 90% share of the Chinese domestic market. The third group is the so-called "market vaccines (shi-chang-miao)" such as Varicella, Rabies, Hepatitis A, Influenza, Pneumonia, epidemic hemorrhagic fever, and Typhoid. The vaccines in this group are profitable for the vaccine manufacturers. The price difference between a vaccine in the planned vaccination program and the others can be as much as 100 fold.

However, it became inevitable that the profound social and economic reforms in China since the early 1980s would change the monopoly status of the state-owned vaccine industry. By the year 2000, there were more than 200 private biotechnology companies that produced various biological products, including vaccines. Among these new companies, there were about 30 producing various vaccines as their main products. Because of their for-profit nature, these companies only focused on the profitable vaccines such as Rabies, Hepatitis A, Influenza and epidemic hemorrhagic fever. It is anticipated that the positive aspects of both the established CNBC and the new wave of for profit biotechnology companies can be exploited in

a concerted effort to produce an HIV vaccine. Moreover, during the evolution of the market driven economy, it would be desirable for the government to maintain its national planned vaccination program and expand it to include new vaccines for future generations of Chinese children.

Another essential component is that governments and public health officials adopt an open and honest approach to outbreaks of infectious diseases. In the past it was traditional for governments to try to conceal information on epidemics or deny the emergence of new diseases for reasons of pride or economy. Recent experience in both developed and developing countries has demonstrated the risks of such behavior, in particular with diseases like AIDS, that lead to the loss of the opportunity to control the disease before it becomes established and widespread in the society.

CONCLUSION

The challenge for China is how to immediately and proactively initiate a nationwide HIV vaccine research and development program, which will allow the Chinese vaccine industry to be on the front line of the international collaboration on the most advanced HIV vaccine development programs. In so doing, China may not only avoid becoming one of the biggest victims of this dreadful pandemic, but also play an important role in the global fight against AIDS. Following are some reasons why we believe that achieving such a goal is possible.

First of all, China has one of the biggest vaccine industries in the world in terms of the production capacity and capability of producing various classes of modern vaccines as illustrated in this chapter. Suppose that a future HIV/AIDS vaccine comes from those vaccine candidates currently in development around the world—the Chinese vaccine industry will have the capacity to produce several hundred million doses in compliance with GMP. These potential products include the DNA-based, recombinant vaccinia or other live viral vector-based, live bacterial vector-based, and recombinant protein-based, all of which can be made in China in a price range affordable for use in developing countries. Considering the future need for the international community to make hundreds of millions of high quality, affordable AIDS vaccines annually available to the vast majority of people at risk of being infected worldwide, producing enormous amounts of vaccine in China with low cost and acceptable quality standards is perhaps the ideal solution.

Proactively engaging in international HIV vaccine development will also help China to sustain its state-owned vaccine industry at the current level and provide a new public health model in the world market economy. The Chinese vaccine industry is currently at a crossroads. All of the state-owned vaccine manufacturers have been trying to readjust themselves in the new environment of a market economy and to become financially self-sufficient. The challenges for them are formidable. On one hand, they must fulfill their responsibility of producing hundreds of millions of vaccines for the national planned vaccination programs that have little or negative profit margins. On the other hand, they cannot continue to rely on government subsidies for the development cost of more profitable new vaccines or biological products. With an increasing loss of their most experienced and talented workforce to the private sector and foreign competitors, and a lack of the brightest young graduates to join the state enterprises like they used to, these state-owned manufacturers are gradually losing their competitive edge and their monopoly status. Some even worry about becoming financial burdens for the government if the current downward trend continues. One can imagine that through HIV vaccine development, the Chinese vaccine industry will become a significant part of the international vaccine industry and participate in international competitive bidding to provide

high-quality and low-price vaccines for millions of people in developing countries.

Secondly, China has one of the biggest functional public health networks in the world. Such a network is capable of conducting multiple large-scale vaccine efficacy trials, as illustrated in the development of JE vaccine in the past. Unlike other developing countries where the candidate HIV vaccines are to be tested, China has the infrastructure and workforce that can be mobilized rapidly for HIV vaccine development. With the increasing risk of HIV infection in many regions of China, it is conceivable that once China develops its own candidate vaccines for HIV, Chinese vaccine researchers will be able to test them effectively and expeditiously, thus facilitating the current international HIV vaccine development process. By adapting the international standard of GLP (Good Laboratory Practice) and GCP (Good Clinical Practice) for HIV vaccine testing, the current public health network will be able to improve itself for other vaccine tests that are urgently needed for China and the world. Moreover, with increasing cultural and economic globalization, the threats of global spread of newly emerging and re-emerging infectious diseases will undoubtedly increase in the 21st century. The world needs new vaccines, and research and development of new vaccines will become more and more important. Unlike drug development for medical treatment, vaccine development is unique in that it not only requires innovative basic and applied research, industrial capability to produce, and clinical infrastructure to test, it also needs populations in relative high risk of getting various infectious diseases. This is why many new preventive vaccines have to be tested in developing countries where the rate of infection for a particular disease is sufficiently high for demonstration of proposed vaccine efficacy.

Thirdly, there are thousands of qualified vaccine researchers in China who have advanced knowledge of molecular biology, virology, cell biology, immunology, and the state-of-art industrial biotechnology. In 1999, the newly established National Center for AIDS (NCAIDS) invited members of many of the key HIV vaccine research institutions and funding agencies in the world to attend the first international AIDS vaccine workshop in Beijing. The workshop focused on reviewing the development status of various candidate HIV vaccines in the advance stages of testing around the world, thus trying to formulate a national HIV vaccine development strategy that would be suitable for China. In the following year, an official delegation from the US National Institutes of Health (NIH) visited China to assess the possibilities of establishing a formal collaboration on the development of HIV vaccine in China. Afterwards, a team of American AIDS investigators was assembled by the NIH to collaborate with NCAIDS on preparation of a Comprehensive International Program for Research on AIDS (CIPRA), including plans that will launch an active international HIV vaccine collaboration in China. In the summer of 2001, a CIPRA working group was assembled with both Chinese and American principal investigators under the auspices of the MOH, and subsequently submitted a formal grant application to NIH. In May 2002, the governments of the US and China signed a memorandum of understanding on the governmental collaboration of HIV/AIDS in China and announced that NCAIDS was awarded $14.8 million as the first international recipient of the NIH's newly established CIPRA program. The significance of the Chinese CIPRA program is almost self-evident. It was built on the foundation of more than a decade of remarkable scientific research on HIV/AIDS in the US that included the most advanced knowledge in five key areas: epidemiology, behavior research, immunology and clinical laboratory assays, treatment, and vaccine development. Such a collaboration ensured that China, although a newcomer in the fight against AIDS, would begin its national AIDS program not from scratch, but in the frontier of the field with the most advanced

knowledge and the best expertise available in the world. This notion is further supported by the fact that the Chinese CIPRA was co-written by American investigators and awarded through the NIH's critical peer review system.

In order to help China proactively participate in the international collaboration of HIV vaccine research and development, many participants of the 1999 Beijing vaccine workshop suggested to jump-start the Chinese HIV vaccine effort by working closely together with various international collaborators. This strategy allowed Chinese vaccine investigators to take advantage of the success and lessons in vaccine basic research in the US and build their new programs with the most advanced knowledge and technology available. Since 1999, such a strategy has proved to be successful with the support of the international scientific community and the US government. The current HIV vaccine prototypes for China utilize the most advanced technologies and discoveries available in the world by collaborating with the best research institutions and individual investigators in the world. They indeed include all of the most hopeful approaches in the current field of HIV vaccine development.

The fourth reason why China can rapidly develop HIV vaccines is that unlike a typical developing country, China has sufficient national resources and wealth to finance such an initiative. Development of a new vaccine usually costs millions of dollars and takes many years by a vaccine company in the west. However, unlike the vaccine industry in the developed world where the expertise and resources for vaccine development are in the private sector, the Chinese vaccine industry is still owned by the government. It is possible, therefore, for the Chinese government to take the advantage of this structural difference and quickly put together a national HIV vaccine initiative. In fact, when governments in the world face continuing public health crises such as HIV/AIDS, malaria, tuberculosis, pandemic influenza, SARS, and the threat of bio-terrorism, many wonder if the task of developing new vaccines should be the responsibility of governments rather than the for-profit vaccine industry.

Finally, China has a functional and powerful central government that is capable of launching an effective national program to stop the spread of infectious diseases, if it really feels the threat. The SARS epidemic in China during the spring of 2003 was a perfect example. Unfortunately, China lacks the ability to detect the spread of chronic infections that hide their devastating effects for years. The spread of HBV in China was a painful example. As aforementioned, HIV/AIDS is much worse than HBV in terms of its lethality. If 2% of the Chinese population contract HIV, their treatment will overburden the Chinese health care system and destroy the fruits of the economic reforms of the past decades. The government of China can make a huge difference in the global fight against HIV/AIDS, as well as all other infectious diseases.

In conclusion, with the full commitment of the government, China is not only capable of developing HIV vaccines, but also has an opportunity to lead in the production of this essential vaccine.

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