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Transnational Factors and National Linkages: Indian Experience in Human Vaccines

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Abstract: This paper explores how transnational factors through international agendas/global policies determine and shape the indigenous technology development initiatives in the developing countries, using the case of vaccine development in India as an example. The institutionalization of vaccine research in India over a century and its trajectory of development reveal that the transnational factors shaped its research. In the post-independence period and during the post-biotechnology period, the policies of international agencies and the interests of transnational corporations directly or indirectly shaped the research and production pattern of vaccines to some extent. This study also reveals that in spite of the early institutionalization of vaccine R&D in India, inherent weaknesses in the national innovation system such as inadequate resources, weak in-house R&D, import dependency and inability to keep pace with modern technological developments made the Indian vaccine agenda vulnerable to international pulls and pressures.

Keywords: India, vaccine, policy, transnational, innovation system.

Introduction

Science and technology occupy an important place in the national policies of development in the modern world, especially in terms of contributing to improvement in the quality of human life. However, the mere existence of a strong science base does not necessarily guarantee technological competitiveness, nor does a success in technology development automatically guarantee production. This is much more likely to be true in a developing country context. Even in the West, simplistic assumptions regarding a unilinear relationship between science, technology and economic development forwarded by the pipe line theory have been replaced by more complex, multilayered, non-

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linear relationships as in the case of the chain linked model.[1] Moreover, the trajectory of technological development tends to be path dependent,[2] in the sense that the form and direction of technological changes in a developing country tend to be strongly influenced by the path established by the developed West. In such a situation, the development of indigenous capabilities gets complicated by the difficult choice between catching up with the developed countries on the one hand and concentrating on new frontiers on the other, and demands a certain degree of 'flexibility' and 'coherence' in the national innovation system.[3] The theory of capability requirements[4] provides a useful framework to model the entry of developing countries to catch up in any technology system. While several studies point out various key factors such as size of the firm and market characteristics,[5] institutional linkages,[6] interactive systems,[7] organizational environment,[8] etc., that shape the technological development, the present study focuses on how transnational factors and the institutions through which they are propagated shape the nationalist endeavours in the developing countries. Technological developments as well as socio-economic and political factors, across the countries that may influence the global and national endeavours have been referred to as transnational factors in this paper. While the above studies provide important leads that are contextual and geographical, this paper limits its focus to external influences on local capability building, without denying the importance of other determinants of innovation. The technological development determinants cited above were studied mostly in developed countries, that too in the core sectors.

This paper focuses on one of the social sectors (i.e. preventive medicine development in primary health care), and analyses the role of external factors in shaping the indigenous technological capability for improvement of the health of the population through vaccination.

Methodology

The study is based on personal interviews with the heads, scientific staff of R&D institutions and companies' executives by means of the structured interview schedule. This information is substantiated with published literature such as research papers and the annual reports of vaccine R&D institutions, vaccine companies and the Department of Biotechnology. This paper analyses the human vaccine development

in three periods. The focus of the study is on primary vaccines (TT, DT, DPT, BCG, OPV & Measles) that are included in the national immunization programmme. The attention on these vaccines would be discussed with a greater emphasis on the post-independence period as the focus on it coincides with the declaration of the WHO 'Health for All' in 1978 and the reorganization of institutional production priorities accordingly. However, the development of traditional vaccines such as cholera, smallpox, anti-rabies, typhoid, Diphtheria toxoid, tetanus toxoid and Triple antigen (DPT) were produced as per the demand during the pre-independence period. The three watershed periods are:

1. Pre-independence period (pre 1947),
2. Post-independence period (post 1947),
3. Post-biotechnology period (post 1980).

Pre-independence refers to the period before India became independent in the year 1947. Post-independence period is the time span after 1947. Though the Post-biotechnology period forms a part of the post-independence period, special reference to this period is made because that would enable us to compare the spectacular S&T developments in the field of vaccine internationally and nationally after the emergence of the new discipline of biotechnology in the 1980s. This paper defines the post-biotechnology period as the period beginning from the year 1980 onwards.

Early Developments and Institutionalization of Vaccine R&D and Production

Vaccines are widely regarded as extremely important in primary health care as preventive medicines against infectious diseases. While there are strong arguments contrary to this notion (for example, see Philips 1996), such challenges have not been posed in the Indian context. In any case, resolving this debate is beyond the scope of the present study, as its main purpose is to understand the external factors that shape the trajectories of development of self-reliance in vaccines. It is also important to mention that by no means does this study underestimate the importance of other preventive measures in public health, such as good sanitation, hygienic living conditions and safe drinking water.

Vaccines comprise only 2 per cent of the global pharmaceutical market representing a nearly US$ 8 billion global industry, which is

projected to grow to $10 billion in 2010. However, they are considered indispensable because of global immunization programmes. In 2001, worldwide spending on R&D for "biologicals", of which vaccines are the largest segment, was $1.1 billion (about 4 per cent of total private pharmaceutical R&D), dominated by a few large transnational corporations such as, Aventis Pasteur, Biocine Sclavo, GlaxoSmithKline Beecham, Chiron Behringer, Merck, Wyeth-Ledrle, etc. Many of these firms form a part of the global WHO-UNICEF vaccination programme (www.immunize.org). India is an attractive target for these companies due to its huge market. According to HAI News (1999), the pharmaceutical market in India is expected to grow to around 10 billion US dollars by 2010, maintaining a compound annual growth rate of 15 per cent with the increasing buying power of Indian consumers, especially the 200 million middle and upper middle class people, who are growing at a rate of 5-10 per cent per year. India's human vaccine market, estimated at over Rs.6800 million, is viewed as a gold mine by multinational and national manufacturing companies. Currently, the Indian vaccine market is estimated to be around $150 million. In 2002-2003, vaccines accounted for 57 per cent of the total Indian biopharmaceutical market with an estimated growth rate of 27 per cent in 2004. Tables 1 and 2 reflect that the number of private manufacturers have increased with new entrants in India in the post 1990s, in contrast to the shrinking number of global vaccine manufacturers. However, private manufacturers worldwide have shifted to the production of more new vaccines, leading to a demand-supply gap in primary vaccines. These recent trends that have major implications for the future of vaccine technology development, production, procurement and immunization strategies/policies in India are issues that are discussed in the current paper.

The Indian vaccine system offers an interesting and convenient example to study indigenous capability development for several reasons. The Indian government has identified vaccines as essential drugs, and is committed to expand the coverage of vaccination as a part of the global initiative towards achieving universal immunization. Moreover, it has adopted self-reliance in vaccine technology and self-sufficiency in vaccine production as a policy objective, and has taken the lead in encouraging indigenous technology development and production.

Table 1: Vaccine Manufacturers in India

Number of Vaccine Producers	Pre 1947		Post 1947		Post 1980		Latest (1995-2005)	
	Public sector	Private sector	Public sector	Private sector	Public sector	Private sector	Public sector	Private sector
All vaccines	15	5	18	10	23	8	**19	23
Primary Vaccine	#2+8	3	3	3	7	4	7*	10

Source: *Compiled* from Bhore Committee Report, Haiti Committee Report and Health Information of India, DGHS, MHFW, GOI, New Delhi.# Haffkine Institute & CRI Kasauli were the producers of DT, TT, DPT. However, there were 8 other companies that produced vaccines against plague, vaccine lymph, cholera and typhoid , as these diseases were rampant at that time.** 4 companies were closed down in post 1995. *3 companies were closed down by 2003-04.

Table 2: Number of Vaccine manufacturers in the world as on 1991

Country		Public sector		Private Sector	
		Primary Vaccines	New Vaccines	Primary Vaccines	New Vaccines
1.	USA	2	2	6	10
2.	UK	-	-	4	1
3.	Japan	-	-	2	2
4.	Korea	1	-	-	-
5.	Indonesia	2	1	-	-
6.	Czechoslovakia	1	-	-	-
7.	Yugoslavia	1	-	-	-
8.	Romania	1	-	-	-
9.	Russia	1	-	-	-
10.	Croatia	1	1	-	-
11.	Slovakia	1			
12.	Finland	1	1	1	-
13.	Italy	-	-	2	2
14.	France	-	-	1 (AVP monopoly)	1
15.	Switzerland	1	1	-	-
16.	Norway	1	-	-	-
17.	Denmark	2	-	-	-
18.	Germany	1	-	4	2
19.	Europe	1	-	2	1
20.	Spain	1	-	-	-
21.	Sweden				
22.	Belgium	-	-	1	2
23.	Australia	1			1
24.	Argentina	-	-	1 (AVP)	-
25.	Mexico	-	-	1	-
26.	Cuba	-	1	1	-
27.	Canada	1 (AVP monopoly)	1	-	-
28.	Brazil	2	-	-	-
29.	India	3	1		
30.	Egypt	1			

Source: Compiled from www.immunize.org

Pre-independence Period

The case study of vaccines is a unique and a very interesting example because vaccine research and development (R&D) and production in India are almost as old as the history of vaccine itself. Institutions for vaccine R&D and production evolved in India during the same period in history in which vaccination had gained importance and institutions were established for vaccine research in various parts of globe.[9] In fact, the organization of modern medical research in India started with

vaccine research during British India, primarily to protect the imperial army against infectious diseases, coupled with the enthusiasm shown by the British medical researchers in India. The prevailing infectious diseases of India were specific to tropical climate and were not understood by the researchers in the native country of the colonial government leading it to set up different institutions. Some of the important discoveries made in India during this period were the discovery of aetiological agents of plague by Haffkine and by Paul-Louis Simond (demonstrated transmission of plague by fleas in 1898) and the identification of the vector of kala-azar by Short and Swaminathan. Waldemar Haffkine developed a plague vaccine in India for the first time in the world. Works of Ross on malaria and others on insect-based transmission of disease and their lifecycles were also done during this period. These discoveries had led to the opening up of a promising field of microbiology for medical researchers in India. The first bacteriological institute in India was founded in 1892 in Agra, followed by the establishment of the King Institute of Preventive Medicine (KIPM) Chennai (then Madras) in 1898, Haffkine Institute (HI), Mumbai (then Bombay) in 1898; Central Research Institute, Kasauli (1905); and Pasteur Institute of India (PII), Coonoor (1907). Until these institutions came up, no regular organization existed to carry out medical research in India. By 1930, there were around 15 such institutions in India, which developed, produced and supplied vaccines and sera to defence organizations in the country.[10]

There were also a few private companies such as Bengal Chemicals and Pharmaceuticals Ltd. (BCPL), Bengal Immunity Ltd. (BI) and Smith Strainstreet & Co. Ltd., in Kolkatta (then) Calcutta that produced biologicals (vaccines & sera). Several firms that were set up during the war produced biologicals under much more satisfactory conditions than was formerly the case.[11] Though both state supported institutions and private companies served during critical times such as epidemics and during World Wars I and II, research was mainly carried out in public-sponsored institutions. These institutions developed indigenous vaccines & sera against rabies, tetanus, diphtheria, pertussis, cholera, smallpox, typhoid and anti-snake venom, which were rampant at that time.

The techniques of production were much simpler; either heat inactivated or attenuated crude preparations of disease-causing

organisms. The technology was not very well developed to produce entirely pure preparations and, therefore, could not ensure the safety and standardization of the dose all the time. Yet, these crude vaccines/sera were able to reduce the mortality to a large extent in the army and the native population during epidemics, though there were occasional controversies/conflicts due to the post-vaccination deaths. However, in the years that followed, increased demand for production/supply of vaccines & sera during the epidemics and World Wars I and II, have transformed these research institutions to mere production units, thus minimizing the research agenda to a limited activity of these institutes as several persons were transferred to do services for the army. After the war, the situation in many of these institutions was pathetic. These were run with a bare minimum of infrastructure, manpower, and resources. Coupled with after war effects, the socio-political and economic situation in British India was unstable with India's independence movement. Moreover, the colonial state's short sighted imperial interests of those times could not lay the foundation for a sustainable path for the technology development of vaccines and only short-term research and production needs were encouraged.[12] By the time India became independent these institutions actually reached some kind of a transition phase with the aftermath effects of war, where they required drive, direction and focus for restructuring of the organization and resources.

Post-independence Period

After independence, while the old institutions continue to exist without any radical transformation to foster R&D, at a time when the inter-disciplinary system began to gain importance in innovations elsewhere in the world, new institutions such as National Institute of Virology, Pune (the Poona) (in 1952 by partial support from the Rockefeller Foundation), Tuberculosis Research Centre, Madras (in 1956 under the joint auspices of Indian Council of Medical Research (ICMR), WHO, and British Medical Research Council), National Institute of Cholera and Enteric diseases, Calcutta (1962), Institute of Cytology and Preventive Oncology (1979), Rajendra Memorial Research Institute of Medical Sciences at Patna in 1981(to do research on kala-azar and other parasitic diseases), Enterovirus Research Centre (1981), Regional Medical Research Centre, Dibrugarh (1982, to study malaria, Japanese Encephalitis) were set up in India by the Indian Council of Medical Research (ICMR)[13]

and National Institute of Immunology (set up by DBT with partial support from the Population Council USA) dedicated to only R&D during the period 1950-1980.

India was at par with the world in vaccine technology development till the 1930s. After the 1940s, the technology development gap between the world and India increased so much so that even the introduction of improved techniques for known bacterial vaccines (Tetanus toxoid (TT), Diphtheria toxoid (DT), Diphtheria, pertussis and tetanus toxoid (DPT)) happened in India almost a decade after their introduction elsewhere in the world. By the time biotechnology revolution began, India was left far behind when compared to the technology development in the West (Madhavi 2005).

The first Committee on the Health Survey of India, pointed out in its report as far back as in 1946, that the mortality due to infectious diseases was very high in children, and that India needs to improve child health if it has to improve the health of the nation.[14] However, no clear strategies were adopted by independent India except in spurts as and when the demand was felt. For instance, A Bacillus Calmette-Guirin (BCG) vaccine Laboratory was set up in 1951 at Chennai (then Madras) with the help of United Nations Children's Fund (UNICEF) and its regular use was recommended. Accordingly, house-to-house BCG vaccination was carried out for some years. However, regular immunization of all children by BCG vaccine was articulated only in 1978, in alignment with the WHO's policy of 'Health for All' by AD 2000 (Annexure 2). In another instance, the Pasteur Institute of India (PII), Coonoor, which used to produce only the anti-rabies vaccine for South India, set up an Oral Polio Vaccine (OPV) production unit as a project in 1967 with support from WHO and the Government of India, based on the advice of Dr A. B. Sabin (who developed the oral polio vaccine) during his visit to India. The seed virus was obtained from the Institute of Poliomyelitis and Viral Encephalitis (IPVE), Moscow. The first batches of OPV were tested at the Medical Research Council laboratories, UK, through the good offices of WHO before it was used for immunization (Pasteur Institute Souvenir, 1907-1967). Since then, PII supplied OPV to the entire country till 1976, when one of the OPV batches was found to be reactogenic when tested at the Central Research Institute, Kasauli and the Haffkine Institute, Mumbai (then Bombay).

The government ordered PII to stop OPV production and prepare instead, for the production of bacterial vaccines (DT, TT, DPT) on a regular basis. Accordingly, the S&T personnel were trained at the Central Research Institute, Kasauli, and the production of bacterial vaccines started in 1978 (information based on personal interviews with PII staff at Coonoor). Strangely, there is no evidence of any attempt to rectify the problem in OPV either at PII or elsewhere. Equally strange is the fact that despite a few subsequent attempts, India could never master the technology to produce OPV indigenously in the public sector, as discussed in the later sections.

India launched an Expanded Programme on Immunization (EPI) in 1978, to meet the objectives of the "Alma Ata" Declaration of WHO in 1978. Accordingly, several state-supported old vaccine R&D institutions such as CRI Kasauli, HI Mumbai, PII Coonoor, Institute of Preventve Medicine, Hyderabad, etc., were restructured for the production of the DTP group of vaccines. With the declaration that India was smallpox free in 1976, institutions (for example, KIPM, Chennai, Vaccine Institute Belgaum, Pasteur Institute Shillong, etc.) that were producing the smallpox vaccine stopped production and started the manufacture of TT, DT and DTP. One more significant development that took place during this period was that the Indian government took over private companies such as BCPL (1980), BIL (1977), SSPL (1977), West Bengal Lab (1980) Calcutta, Vaccine Institute Baroda (1973), and Vaccine Institute Nagpur (1980). Thus, the public sector units that produced primary vaccines increased in number during this period (see Table 1).

The common factor that shaped vaccine technology development both in the old and new institutional structures (to some extent) has been the international health policy regime, besides the intrinsic problems associated with the institutional structures in post-independent India. India became a member country of the World Health Organization (WHO) soon after this was established in 1948 to control disease transmission across countries. WHO set up regional centres in its Member countries to monitor disease prevalence and co-ordinate their control. The regional centres in India were located in the existing (old) vaccine institutions which were already over-burdened with routine production and supply functions. Since monetary support was

available, epidemiological investigation became a research priority in these institutions, thus marginalizing other research activities for the development of new or improved vaccines. Similarly, vaccine R&D institutions that were set up in the post-independence period also largely conducted disease monitoring, post-immunization studies and clinical trials, as financial support was available to such investigations. Though some of these new institutions did develop vaccines (Japanese Encephalitis by National Institute of Virology, Pune and leprosy vaccine by National Institute of Immunology, New Delhi) very few have reached the market.

Vaccine Scenario in Post-Biotechnology Period in India

Scientific and technological developments in the life sciences were rapidly increasing in 1970s with the emergence of greater specialization and new disciplines such as molecular biology, immunology, biotechnology, etc. These advances contributed to new techniques of production and superior products for improving the quality of life and also impacted the economy. Using these new bio-techniques, several existing vaccines were improved in the West and new vaccines were developed that were safe and potent when compared to conventional vaccines. Biotechnology was also being increasingly viewed as a tool to enhance production and benefit the economy in the process. Several countries adopted policies to foster biotechnology and harness the fruits of biotechnology in their economies. In response to the S&T developments in the West, the Government of India set up the National Biotechnology Board in 1982, which was subsequently established as a separate Department of Biotechnology (DBT) under the Union Ministry of Science and Technology in 1986. The Government of India further intensified immunization efforts against vaccine-preventable diseases by launching the Universal Immunization Programme (UIP) in 1985 and a National Technology Mission on immunization in 1986. This was jointly implemented by the Ministry of Health and Family Welfare (MHFW) and DBT, with the former acting as a nodal agency. DBT was entrusted to fill the R&D gaps in vaccines to enable the country to achieve self-reliance.[15] UIP observed the existence of a gap between the supply and demand of vaccines, and that India was entirely import dependent for its measles and polio vaccine requirements due to the absence of a strong R&D base (DBT Annual Report 1987-88). DBT promoted research on vaccines by (1) sponsoring R&D projects to

develop vaccines in various institutions in India such as the National Institute of Immunology Delhi; Indian Institute of Science, Bangalore; All India Institute of Medical Sciences, Delhi; Central Drug Research Institute, Lucknow; National Institute of Virology, Pune, etc.[16] (2) DBT also signed a Memorandum of Understanding on an Indo-US Vaccine Action Programme (Indo-US VAP) to foster R&D in vaccines (Refer to Box 1). (3) DBT also attempted to foster the indigenous production of vaccines by setting up two public sector units for the indigenous production of OPV and the Measles vaccine. However, these objectives could not be achieved in the later years owing to the pressures of globalization and liberalization post 1990s. The following section discusses how transnational factors directly or indirectly influenced the indigenous vaccine development and production in India.

Box 1: Indo-US Vaccine Action Programme (VAP)

In 1987, the Government of India signed a memorandum of understanding (MOU) with United States of America (USA) to initiate a joint Indo-US Vaccine Action Programme (Indo-US VAP) to develop vaccines. This was a high profile agreement that involved the then Indian Prime Minister Rajiv Gandhi and the then US President Ronald Reagan, and was initiated during an earlier visit of the then US Secretary for health and human services, Dr. Otis R. Bowen. The objective of the MOU was 'to bring together Indian and US scientists to jointly develop and test new and improved vaccines for immunization against diseases and to focus upon vaccine production, quality control and delivery methodology', and US promised assistance of around $ 6 million through USAID for this purpose.

The following were the issues raised by the opponents of VAP.

- It has bypassed all the regular channels of decision-making including ICMR and high power biotechnology scientific committee to scrutinize the project if it concerns any biological warfare implications in the interest of national security and public health.[17] These concerns were based on the earlier experience of India with US scientists in 1974, when it was found that the information was leased out to an American leading defence organisation.[18]
- It was an unequal agreement, where US exercised much more control and India cannot review nor implement research programmes without US approval (Bidwai 1987, see notes in reference for details).

Box 1 continued

Box 1 continued

- Biotechnology firms in the West were under severe economic pressure to put their products on the market, and most of the US vaccines were under advanced stage of development waiting for clinical evaluation, Indian scientific community feared that India may become an experimental ground as stringent rules were either not in force or could not be enforced effectively.
- The clinical trials conducted under the Indo-US VAP would produce new vaccines by the US companies and will be sold back to India at exorbitant prices.[19]
- As a part of Indo-US VAP, USA allocated $1.62 million to establish an epidemiology research and training centre in Madras (now Chennai). This would make the most vital information regarding the Indian population would be made available to US which could be used in biological warfare.
- At that time it was agreed upon that within 90 days of signing of MoU, patent provisions will be developed and agreed upon to suit mutual interests. Fears were expressed that this may mean the replacing the Indian Patent Act of 1970 with strong US style system of patent protection, which is prevalent in the industrialised developed countries.[20]
- The Indo-US VAP agreement may come in the way of setting up Indian R&D centres in Vaccines (*Times of India*, 30 August 1987) to tackle local priorities.

External Factors and the Shaping of Technology Choices and Policy Options

The Indian government introduced six vaccines against childhood infectious diseases, i.e. tetanus, diphtheria, pertussis, tuberculosis, polio, and typhoid for regular immunization of children under the Expanded Programme of Immunization (EPI) in 1978, only after the global agenda for childhood vaccination was articulated by the WHO. Among these, the technologies for TT, DT, DPT, and BCG were known which were simpler and the existing vaccine production organizations could produce them in the country. In 1985, a vaccination against Measles was introduced under EPI. Even though the technologies for inactivated polio vaccine (IPV), oral polio vaccine (OPV) and Measles were introduced in the world in 1955, 1962 and 1963, respectively,[21] they

were not available in India for indigenous production. Since the launching of EPI in 1978, India was dependent entirely on imports for OPV and measles vaccine for two decades. This raises some pertinent questions: Why could India not achieve technological self-reliance in these two vaccines, despite an early start and fairly good institutionalization of vaccine research in the country? Why was technology choice between IPV vs. OPV not assessed and an appropriate course not adopted based on an assessment of the pros and cons? Though the Pasteur Institute of India, Coonoor, produced OPV indigenously for the entire country successfully for a decade (1967-1976), it was stopped due to reactogenicity. Why was the limitation never rectified? Instead, import of OPV was resorted to? Despite DBT's attempts, why could OPV never be produced in the Indian public sector thereafter?

The World Health Organization recommended the use of OPV in countries where polio was highly epidemic and endemic. Because of its easy administration, its ability to afford herd immunity (which occurs when the immunization of a population results in a decreased incidence of disease in the unimmunized remainder of that population) and low costs (one-tenth of IPV), this vaccine was recommended for mass immunization. However, since it was temperature sensitive, cold chain was a crucial factor in the success of OPV immunization, especially in the rural areas of tropical countries like India. The Indian government adopted it primarily because the WHO recommended it, and because it could be procured at a cheaper price through the United Nations (UN) procuring system. It is tempting to ask why WHO, which provided the technical know-how for indigenous production of the small pox vaccine in India at KIPM since 1965 (KIPM 1985), did not show a similar zeal in the case of OPV. Similarly, was the Indian Government's decision to launch the production of bacterial vaccines (after stopping OPV) at PII-Coonoor entirely based on indigenous considerations? Was it meant to fall in line with WHO's launch of the 'Health For All' programme in 1978, even prior to the launching of EPI in 1978 in India? IVCOL planned to produce vero cell culture based OPV instead of IPV as per the recommendations of WHO and MHFW (DBT Annual Report 1991-92). However, even this plan was also shelved as the company was closed in 1997. Why was OPV production not attempted again in any other national lab or vaccine institute for a long time? Was it due to any external influences? Were they prompted by the vested interest of

transnational companies that may have lobbied with the decision-makers in WHO or in the Indian Government to discourage indigenous production and ensure a captive market for their products? Alternatively, was the Indian Government genuinely concerned about the expected public fear/public acceptance of vaccination? If it was really concerned, why didn't it improve the standards of quality control such as good lab practices (GLP) and good manufacturing practices (GMP)? These questions have been addressed in the later sections, but the immediate issues relating to the choice between OPV and IPV are dealt with below.

There have been several newspaper reports about polio cases after OPV immunization using imported vaccines.[22] This could mean that either the imported vaccine was ineffective for some reasons, or maintenance of the cold chain was still a limiting factor in achieving the eradication of polio in India. However, even in the USA, where polio has been almost eradicated using OPV, cases of polio have been reported after vaccination, prompting the Action Committee on Immunisation Practice (ACIP) to shift towards the use of IPV in its national immunization programme in a phased manner-using a combination of IPV-OPV schedule initially, followed by a complete shift to IPV recently.[23] Similarly, European countries such as Sweden and Holland could successfully eliminate polio using only IPV. Some western countries as well as some African and Asian countries adopted a combination of IPV-OPV usage.[24] Apart from safety reasons, for a tropical country like India with erratic (if not total lack of) rural power supply and inadequate refrigeration facilities, use of IPV that was more stable at room temperature would have been a better choice. Alternatively, a cost benefit analysis of the available options would have given a better feedback for the choice of the right product/technology that suited Indian conditions. However, there is no evidence of any such official exercise being done. Unfortunately, unlike in western countries, which have a strong consumer awareness and strict enforcement of consumer/public interest laws and compensation policies[25], Indian officials acknowledged no such public concerns and did not face strong public pressure or litigation.

There is also no evidence for any objective basis for India's adherence to OPV as against IPV and its continued imports, other than that of falling in line with the WHO policies. Some argue that even though IPV in India was always effective OPV was recommended in developing

countries because international organizations were trying to find new markets for the US multinational corporations, since the market demand for OPV ceased to exist in the US and other developed countries by the end of twentieth century.[26] However, it is interesting to note that the Indian medical community is recently debating over the use of OPV in EPI and some recommend the use of IPV instead of OPV. The debate on this issue was spurred on after the United States decided to use IPV instead of OPV in their immunization programme (UN wire, 29 June 2000). Critics point out that the local field realities such as evaluation of actual protection levels achieved after the pulse polio immunization (OPV), recording of the actual number of vaccine-associated polio paralysis cases (VAPP), and an assessment of wild polio virus in the population, etc. were not taken into account while considering the policy of polio eradication in India. They point out that the nature of the polio virus transmission is such that it cannot be eradicated, but can only be controlled as the virus transmits silently over many years even if there are no paralytic polio cases. They emphasize that OPV is not effective in immunocompromised children and they recommend the use of IPV to tackle the cases of VAPP and the wild poliovirus transmission in the local population.[27]

The Case of OPV and Measles

An independent cost-benefit study in India revealed that indigenous production of OPV was more economical than importing it.[28] However, such studies did not receive due attention in the decision-making mechanism, and more often than not, the policy decisions seem to be guided by other considerations. After the formation of DBT in 1986, it took up an ambitious objective to make India self-reliant and self-sufficient in vaccines using new technologies of production for OPV, IPV, measles, DPT (with improved pertussis) and tissue culture-based anti-rabies vaccine, in addition to DT, TT and Hepatitis B. As a part of this effort, DBT set up two public sector units, the Indian Vaccine Corporation Ltd. (IVCOL) at Gurgaon and Bharat Immunological and Biologicals Corporation Ltd., (BIBCOL) at Bulandshar in 1987. The objective was to meet the growing demand for vaccines in the Indian market by repackaging these from imported bulk initially, and to absorb/develop the technology for indigenous production subsequently. However, the target date for the initiation of indigenous production was postponed each year, and repackaging and supply from the imported

bulk continued for OPV at BIBCOL and for the measles vaccine at IVCOL, till both the units were eventually declared sick. IVCOL was closed down for non-availability of the measles technology.[29] DBT had planned to transfer this technology from a French public sector company, which itself was privatized in the meantime, and the new owners refused to transfer the technology to the Indian joint venture.[30] Perhaps, selling technology was no longer an attractive option when direct access to the Indian market was becoming available to foreign companies under the Indian economy policies of liberalization and globalization, which were imposed on the country since 1991 as prescribed by the International Monetary Fund and World Bank. It is tempting to ask why the option of repackaging either from France or elsewhere, from imported bulk was not attempted at IVCOL, nor any efforts continued to find alternative means for indigenous manufacture.

The production of OPV in BIBCOL formed a part of the bilateral agreement between India and Russia for long-term integrated S&T co-operation, which was signed in 1987. As Russian industry did not have the resources to target global markets with its domestic technologies due to its sluggish economic condition at that time, Indian officials should have anticipated easier access to vaccine technology for the Indian industry. The project of OPV production in BIBCOL has no technology transfer from other countries. However, the Institute of Poliomyelitis and Viral Encephalitis (IPVE) at Moscow agreed to 'Technology Consultancy Co-operation' for OPV production at BIBCOL on the condition that India should import OPV in bulk from Russia in the first phase in its memorandum of understanding (MOU). According to the MOU, IPVE, Russia would provide the knowledge on basic know-how, supply of seed virus, training of S&T personnel, quality control of the first six batches and certification of first six batches according to WHO standards. The technology for indigenous production was to be utilized in the second phase, by which time the production facilities were established at BIBCOL. However, the first phase, which started in 1992 continued year after year, postponing the entry into the second phase for indigenous manufacture of OPV. Interestingly, BIBCOL's source for technology and bulk import was the same Russian institute (IPVE) from which PII obtained its technology two decades ago, but had stopped production after a decade due to objections over reactogenecity. This raises some important questions. Was BIBCOL obtaining a better

vaccine (or technology) than the OPV produced by PII earlier when using technology from the same Russian source? If not, was it free from the reactogenecity reported earlier, or was the earlier objection over reactogenecity not genuine? If the objection was genuine, was it really a problem of production at PII, or was it inherent in the technology sourced from IPVE?

In the meantime, BIBCOL's main customer, UNICEF, seems to have refused to purchase its repackaged vaccines of Russian origin. India's polio vaccination programme is supported by UNICEF, which procures the vaccines from the companies on behalf of its donor (predominantly Western) nations and makes them available for end users in India. As per the new procurement criteria introduced in 1998 (WHO/VSQ/98.05), all the vaccine suppliers to UNICEF had to have a mandatory GMP certification from WHO, which IPVE, the Russian partner of BIBCOL, did not have and perhaps had never even applied for one. This meant that BIBCOL would not be able to supply the OPV imported from Russia to UNICEF as long as BIBCOL and IPVE did not have a GMP certification. It would be difficult for BIBCOL to find other customers, as long as the Indian polio vaccination programme depended on UNICEF's support (and therefore its procurement criteria). Naturally, India's commitment to buy OPV in bulk from Russia was suspended in 1998 on the grounds that the supplier (IPVE) did not have the WHO accreditation based on GMP certification (Somasekhar 1998). During that year, BIBCOL sourced its OPV bulk from SmithKline Beecham (SKB), Belgium, and Biopharma, USA. Western drug multinationals such as SKB, Biopharma, Chrion and Pasteur Mereiux, France, are among the major WHO-approved, GMP-certified suppliers for UNICEF.

Curiously, it appears that soon after BIBCOL changed its import partners, its manufacturing infrastructure was certified as GMP compliant, following a visit by the WHO team in 1998-99. Within months, BIBCOL also obtained the approval of UNICEF as a supplier. From the bulk imported from its new partners, BIBCOL supplied 70 million doses of OPV to UNICEF and the company had a turnover of Rs. 552 crores with a net profit of Rs. 70-80 lakhs during 1999-2000.[31]

The above developments raise certain very pertinent questions: Was UNICEF unaware of its own procurement standards till 1998 or

were they made more stringent to suit some firms or keep out some others? In other words, was GMP certification a ploy of Western MNCs to end the Indo-Russian collaboration to access the Indian market? In that case, would India have got a GMP certification if it were to indigenize the OPV production before 1998? Going further, would it have made a difference (to obtain GMP certification) whether the indigenization of OPV production was based on Russian technology or locally developed technology or even perhaps some Western technology?

It is also pertinent to ask why the indigenous production of OPV was never started in BIBCOL? Though the S&T personnel of BIBCOL were trained at IPVE, Moscow, it was not very clear whether the seed virus was supplied to start the indigenous production in phase II according to MOU. Was it because of uncertainty over the GMP certification? In that case, was BIBCOL aware of the GMP requirement but was unsure of obtaining it if the manufacture was done indigenously? According to the managing director of BIBCOL, starting indigenous production of OPV at that juncture would have taken two and a half years, by which time indigenous production may no longer be commercially viable, as the projections were that polio may be eradicated in the next three years.[32] But then, it is not clear what prevented BIBCOL from indigenizing production much earlier to save on imports whether from Russia or elsewhere. With the continuing demand for OPV and no signs of total eradication of polio yet, the wisdom (if not motive) of BIBCOL's decision not to enter into the second phase in spite of having excellent infrastructure (pre 1998) and GMP certification (post-1999) becomes questionable.

In the meantime, competition from the entry of domestic private companies like Panacea Biotech pushed back BIBCOL even further. Eventually, BIBCOL was declared a sick unit in 2000 and handed over to the Board of Industrial and Financial Reconstruction (BIFR) for revival.[33] BIFR, based on a diversification plan submitted by the Industrial Development Bank of India (IDBI), recommended the production of BCG, measles and tetanus toxoid vaccines to generate additional revenue, which was approved recently. Interestingly, BIBCOL will continue to tie up with IPVE, Moscow for production of the BCG and measles vaccine. The company has also been exploring the options

of producing the Hepatitis B vaccine on a joint venture basis, with domestic companies such as Shanta Biotech, Cadila, etc. It is intriguing to note that a company which has virtually all 'immunologicals and biologicals' mentioned in its name had to go through BIFR for 'diversifying' its production from one vaccine (which was never produced) to the other. In the end, a public-sector company meant to bring about self-reliance in the production of primary vaccines, if revived at all, continues to depend on imports and foreign collaborations. The only vaccine that it may be able to produce using indigenous technology is Hepatitis B (though not developed in BIBCOL), which is not among the primary vaccines for which the company was originally established.

The failure of indigenous OPV production and the fall of BIBCOL is an example of how external factors such as international relations, the policies of WHO/UNICEF, and possibly of their donor nations or their companies, can define the fate of a perfectly legitimate policy objective of achieving self-sufficiency in vaccine production and self-reliance in vaccine technology. Walt (1994) observed that even though developing countries have a good voting strength in UN organizations such as WHO, this is a much weaker tool than the industrialized countries' potential of withdrawing their budgetary contributions, and moreover for practical reasons they are generally unwilling to oppose the donors who provide their countries with technical and financial assistance.

Private Sector's Role in Primary vaccines

Traditionally, the private sector's participation was negligible in primary vaccine R&D and production worldwide and in India. The vaccine market accounted for a meagre 0.3 per cent (USA) and 0.1 per cent (India) of the total pharmaceutical market (Anonymus 1985) (Indian drug statistics, 1985-87) even till the mid 1980s. Of the total human vaccine market in 1985, the private sector in the US accounted for sales of around US$ 170 million.[34] The number of private vaccine manufacturers that produced primary vaccines also came down in India (see Table 1) and other countries alike in the 1980s For instance, there were around 10 manufacturers in the mid-1970s and by mid-1980s there were only 3 companies (Connaught Laboratories, Wyeth Laboratories and Lederle Laboratories) in the US that produced primary vaccines, due to the impact of the stringent regulatory system on vaccine liability

issues coupled with a static product range and low profit margins in primary vaccines. However, this trend has changed the world over, especially during the post-biotechnology period in the 1990s where a few large private vaccine manufacturers have come to dominate a large share of the vaccine market with large investments in the development and production of new vaccines.

Similarly, in India too private sector participation increased in the post-biotechnology period, especially after the introduction of liberalization in India under the changed global trade regime. Though new technological developments coupled with the stringent Intellectual Property Rights regime provided the right background for entry of the private sector, the decline of the public sector and the liberalization policy have facilitated its easy entry to supply vaccines to EPI in India. For instance, Serum Institute of India, Pune, a private company, bought technology from London and has been supplying the entire measles requirement for the country since 1992.[35] Radicura Pharma, another private company in India, has been supplying OPV to EPI for a long time. However, this transition from the public sector era to the privatization and liberalization era was not smooth, and often led to tensions between the two sectors. For instance, in 1997, Haffkine Biopharmaceutical Ltd. (HBPCL), a public sector company started its indigenous production of OPV with the seed virus obtained from elsewhere.[36] However, its regular supply to EPI was discouraged by the government alleging that the OPV supplied by this company was not potent, but the company claimed that the allegation was false and that the government was supporting the private companies, whereas Haffkine Biopharmaceutical Ltd. would incur loses if the government does not buy the product from them.[37] It is ironical to note that private companies of the pre-independence period (BCPL, SSPL, BI), which were made public during post-independence period (1977-80) to meet the objectives of EPI, were declared sick (1993-94) and closed down owing to the pressures of liberalization. Also a hundred year old public sector institutions like IPM Hyderabad, State Vaccine Institute, Patwada Nagar were closed down during 2003-04, and in some institutions (The Pasteur Inst., Shillong; Government Vaccine Institute, Namkarim, Ranchi; Vaccine Institute, Baroda; Vaccine Institute, Nagpur; West Bengal Vaccine Lab, Calcutta; Public Health Institute, Patna; and State Health Vaccine Institute, Lucknow) the production of traditional vaccines (cholera,

anti-rabies, typhoid, TT) has been stopped since 1997-98, and it is likely that they might be closed down.

While the public sector focused on EPI vaccines, Indian private companies have largely focused on high value vaccines outside the EPI. For instance, Hoechst-Marion Roussell (India) and Cadila, Ahmadabad, India have been working on the development and import of an oral and injectable typhoid vaccine; Hoechst is producing an anti-rabies vaccine; and Cadila has a genetically engineered vaccine against Hepatitis B in the advanced stages of development. Glaxo, Biological Evans Ltd. and the Serum Institute of India account for a large share of the DTP vaccine production, but relatively few companies were working on Hepatitis B and OPV.[38] Thus, the attempts to achieve self-sufficiency in vaccine production and self-reliance in vaccine technology through the public sector got diluted over the years. Though private sector companies have filled the gap in some cases, the majority of them have been focusing their efforts on new vaccines and non-EPI vaccines. One of the main reasons for the growing gap between demand and supply of primary vaccines in India is that while the public sector production is on the decline, vaccine availability from the private sector or through the UNICEF procurement mechanism has not improved.[39] This trend is a worrisome global trend that has been acknowledged by UNICEF (http://www.unicef.org/supply/index_vaccine_security.htm). There is no guarantee that the private sector would provide primary vaccines at affordable prices, and especially when they are not worried by local competition or by the stringent price control regimes of the government. The last decade has witnessed a systematic dilution of the Drug Price Control Order by the removal of several drugs from price control.[40] Vaccines are so far still under price control, but going by the current trends, it may not be surprising if they are removed from price control in the future.

To add to the problems in primary vaccines used under the EPI, pressures have been building up to introduce some of the newly-developed vaccines into the EPI, such as those against Hepatitis B, Chickenpox, Rubella, Meningitis, Influenza type B, etc. being produced by private firms and transnational corporations. The case of Hepatitis B vaccine introduction in India is a good example. The big business in Hepatitis vaccines started with the introduction into the market of the

plasma-derived and recombinant Hepatitis B vaccine by Merck & Co., and Smithkline Beecham Ltd., fetching them millions of dollars in profit. Three new private companies were set up around the mid-1990s to produce the Hepatitis B vaccine and several private companies too created demand for the Hepatitis B market in India by various means. At the same time, this has led to increasing the pressure for including the Hepatitis B vaccine under the EPI. This has already triggered public debates, with several public health activists and non-governmental health organizations arguing that the prevalence of Hepatitis B in the Indian population is not uniform and the disease burden is far less when compared to other infectious diseases, and therefore, the costs and benefits of introducing such high cost vaccines in the EPI need to be weighed more carefully.[41] On the other hand, the Joint Working Group on the Indo-US Vaccine Action Programme has recommended the use of Hepatitis B in the EPI. Similarly, vero cell culture based rabies vaccine from PMSV, France was introduced in the Indian market through a tripartite agreement between PMSV (France), Alidac Genetics & Pharmaceuticals (Ahmedabad) and IVCOL (New Delhi) in India (DBT *Annual Report, 1991-92*). The growth of the vaccine industry in the private sector, especially in the non-EPI vaccines (dipththeria, pertussis, tetanus toxoid conjugated with IPV, oral typhoid, tissue culture based measles and anti-rabies, influenza type A and type B, rotavirus vaccine, rubella, mumps, meningitis, etc.), has fuelled the demand to include new vaccines in the EPI. EPI provides a huge captive market in a populous country like India, and the decline of the public sector and increasing influence of private sector and TNCs on international health agencies brings Indian mass vaccination policies under tremendous pressure.

New global alliances and their impact on developing countries

The 1990s witnessed new global alliances, which are formed to promote the development of vaccines through global net works and through bilateral/multilateral programmes (see Table 3). The background for the formation of global networks was prepared by organizing several international conferences on health research, stressing the fact that almost 90 per cent of the global disease burden is in developing countries (Murray and Lopez 1996) and their total investment in R&D amounts to only 4.4 per cent.[42] These conferences were also mostly spearheaded and sponsored by UN organizations and TNCs, ostensibly on behalf of the developing countries. However, it was argued that the research

Table 3: Transnational (Global) Alliances

Alliance	Year of launching	Objective	Sponsors	Remarks	Reference
Children Vaccine Initiative (CVI)	1990	To develop global strategies for development & utilization of vaccines	UNICEF, WB, UNDP, WHO, RF, Worlds largest manufacturers and the marketers		Fisher (2000), co-founder of National vaccine information Centre, www.nextcity.com
Global Programme on Vaccination (GPV)	1990	New vaccine development programme to purchase and supply vaccines to EPI	Sponsors of WHO	A superior policy making unit within the WHO	Greenouh and Streefland, Social Science Research Council, (1998), 52(1),1-16.
International AIDS Vaccine Initiative (IAVI)	1996	To develop antivirals against HIV for the world. Encourages industry participation and supports vaccine development partnerships.	Governments of UK, Netherlands and Canada, WB, the Bill and Melinda Gates Foundation, RF, Sloan Foundation and Starr foundation	More than 35 vaccine candidates undergoing trials at present	www.iavi.org www.dnavaccine.com HIV update, PR Newswire, South Africa, 11th July, 2000
Medicines for Malaria Venture (MMV), an entrepreneurial non-profit international organisation		To create incentives to develop new drugs & vaccines. To improve private sector participation and to eradicate malaria burden by 2010. To supply vaccines at cheaper prices to poor countries	RF, WB, SKB, Wellcome Trust, UK depart. for international development, IFPMA, the association of British Pharmaceutical industries, Philanthropic donations & foundations.	Any vaccine discovery may be patented, but the owner of the patents would be MMV, and Pharmaceutical companies can market the vaccine products	www.malariamedicines.org

Table 3 continued

Table 3 continued

Alliance	Year of launching	Objective	Sponsors	Remarks	Reference
Global alliance for Vaccines and Immunization (GAVI)	1999	Every child in the world would be protected against vaccine preventable diseases	Bill and Melinda Gates Foundation, IFPMA, Public health and research institutions, national governmenst, RF, UNICEF, WB, WHO.	Co-ordinates Immunization programmes at regional, national and international levels. Accelerates R&D, development and introduction of new vaccines to achieve sustainable immunizations.	www.vaccinealliance.org
Malaria Vaccine Initiative (MVI)	1999	To accelerate and develop vaccine candidates against malaria. To ensure their accessibility to developing world	Bill & Melinda Gates Foundation	MVI constituted with the scientists from NIH, NAID, Water Reed Army Institute, Hopkins University of Preventive Medicine and RAND corporation. MVI works with GAVI to explore commercialization, procurement and delivery of vaccines to primary health sector	www.malariavaccine.org

Source: Compiled from different sources.IFPMA: International Federation for Pharmaceutical Manufacturers Association, RF: Rockfeller Foundation, UK: United Kingdom, UNDP: United Nations Development Program, WB: World Bank, UNICEF: United Nations Children's Fund, SKB: SmithKline Beecham, WHO: World Health Organisation.

agendas are seldom developed with the active participation of developing country research leaders and communities.[43]

The structure of these global alliances reveal that the major players are transnational corporations, the UN system and the G7 countries (United States, Japan, Germany, France, Britain, Italy and Canada) that articulate the policies for the world (see Table 3). The rich industrialized countries also have significant influence on policies inside or outside UN agencies, as G7 countries are important funders of extra-budgetary programmes. Another major source for policy guidance on development and aid-related issues is the World Bank, whose prescriptions for a market-driven approach over the past decade proved to be an embarrassment.[44] It is a well-known fact that the TNCs are involved in almost every global industry and 90 per cent of all technology and the product patents worldwide are held by them. Scholars have cited that TNCs are among the most effective engines of development and also as one of the most powerful impediments to the third world development.[45] This is particularly true in the case of vaccines, as described earlier in this paper and by others in literature. As Greenough and Streefland (1998) put it,

> 'vaccine technology represents a biomedical intervention with truly global ramifications. Strategic policy formulations, target setting and prioritization in funding have become transnational process with a wide range of actors orchestered by global actors such as Child Vaccine Initiative. Though the implementation of vaccination programme is a national programme, the transnational decision-making have become an integral part of public sector health service delivery'.

The demand for vaccine markets is articulated through various means. For instance, developing countries are lured by the free donations of vaccines and large amounts of monetary aid by industrialized countries and TNCs, thus generating a preliminary demand. For instance, donation of vaccines by industry, founders and international organizations prompted by the US President in March 2000 who announced new partnerships to develop and deliver vaccines for diseases including human immunodeficiency virus (HIV)/acquired

immunodeficiency virus (AIDS), malaria and tuberculosis for developing countries (Table 4). It was announced that the US President would work with the G7 partners to ensure a future market for the critically needed vaccines (www.usinfo.stste.gov). Merck was to collaborate with Global Alliance for Vaccines and Immunization (GAVI) to identify countries that benefit from the Hepatitis B vaccine. Fisher (2000) pointed out that the proponents of mass vaccination and vaccine makers find ways to finance the delivery of newer and more expensive vaccines to poor countries by first making them as mandatory in rich countries. In some developed countries, vaccination was made mandatory for getting primary education.[46] On the one hand, the government-led vaccinations promoted the need for vaccine use, vaccine R&D and production. On the other hand, technology developments and government enforced vaccinations led to the burgeoning chemical/pharmaceutical industries in France, Germany and Britain. For instance, the Pasteur Institute founded in 1887 by the famed inventor of the rabies vaccine, eventually created Canada's largest vaccine manufacturer, Pasteur Merieux Connaught. Some argue that UNICEF launched a massive publicity drive to market the social product of child survival[47] and social marketing became the hallmark of the global child health programme.[48]

Table 4: Donation of Vaccines by Companies to Promote Vaccines and Vaccination

Manufacturer Objective	Vaccine Donated/	Donation worth $s
Merck & Co.	Recombivax	$100 million
American Home Products Corporation alliance for Vaccine Immunization (GAVI)	Hemophilus influenza type B to Global	100 million doses
Glaxo SmithKline Beecham	To eliminate lymphatic filariasis	1 billion
Aventis Pharma	Polio vaccine to Africa	50 million doses
Merck & Co	Announced projects	more than $150 million
United States President	Announced to GAVI	$50 million
World Bank	To expand immunization	$400 million
other multinational banks	To expand immunization	$900 Million
Bill and Melinda Gates Foundation	to GAVI	$750 million

Source: Times of India, 3 March 2000.

Impact of Global Alliances and Initiatives on Vaccine Development in India

As described earlier in this paper, Indian vaccine development and immunization policies have mostly been prompted by global or transnational initiative of some form or other. This is also true of the recent global initiatives mentioned above. India hosted one of the meetings of the global programme on vaccination meant to promote the concept of global coalition for vaccine development and immunization. The meeting was held in New Delhi in 1998 and had participants from India, Pakistan, Bangladesh, World Bank, WHO, UNICEF and Indian industries.[49] Other meetings were held in the United States, Europe and Africa in the same year. Following the global trend, the Indian government launched an ambitious project to develop and manufacture new 'home grown' vaccines against several communicable diseases (malaria, tuberculosis, cholera, rabies, Japanese encephalitis and acquired immune deficiency syndrome (AIDS) in 3 years for $4 million. Twelve basic research institutions and two private companies (Hyderabad-based Indian Immunologicals and Bharat Biotech) have been brought together in a collaborative effort to develop and manufacture vaccines.[50] For the first time, the Indian government has allocated funding specifically for vaccine R&D. It is to be seen if this public-private initiative would ensure availability/affordability of future vaccines in public health programmes.

The Government of India launched the National Jai Vigyan Mission on development of new generation vaccines through DBT five years back. The objective of the programme is to generate candidate vaccines. The programme has been grouped under three categories. Category A includes candidate vaccines that require clinical trials (e.g. cholera, rabies), B category includes those vaccines whose efficacy and immunogenicity need to be worked out (e.g. tissue culture based Japanese encephalitis vaccine, DNA (Deoxy-ribose nucleic acids) vaccines, synthetic candidate malaria vaccine) and category C includes these vaccines, requiring sustained R&D efforts with the possibility for the development of candidate vaccines (e.g. Anti-HIV and DNA vaccines for TB).

While the above examples reflect the government's efforts to step in line with global trends of shifting the focus on vaccines from public

sector to the private and transnational sector, the Indian industry has raised its pitch in asking for more. The All-India Biotechnology Association (AIBA), a forum of biotech companies, brought out a report in November 2000 after world wide consultation with experts from World Bank, Harvard University, etc., which was the first ever industry feedback on the Indian governments' biotechnology programme. The *All-India Biotechnology Association Report* alleged that the Indian biotech industry failed to deliver competitive biotech products due to the stringent regulatory system, lack of transparency that has stifled private sector investment, and this trend may dissuade foreign agencies from collaborating with Indian companies. It called for a fundamental restructuring of the regulatory system, as well as more resources for the private sector. The All-India Biotechnology Association approached the Technology Development Board of the Indian Union Ministry's Department of Science and Technology (DST), which was set up 5 years ago to provide loans to industries that have promising products to bring to the market. The Department of Science and Technology has applied for a loan of $ 100 million from the World Bank at the request of All India Biotechnology Association and $ 47.5 million would be used by the Department of Science and Technology to set up technology parks in India. The Finance Ministry was yet to approve of the World Bank loan.[51] This instance reveals how industry puts pressure on the governments to protect its own interest and how pressures from international organizations such as World Bank, etc., indirectly flow into national policies through the private industry.

Concluding Remarks

Vaccine R&D in India is as old as the history of vaccine itself, and India had the unique advantage of being one of the pioneers in developing vaccines against tropical diseases. However, the institutionalization of vaccine research in India and its trajectory of development over a century reveals that transnational factors shaped the research patterns, and very often, transnational interests had their impact on local factors and the national agenda. During the colonial period, the mercantile interests of the East India Company shaped the process of vaccine R&D and innovation in India.[52] Even though the institutions of the colonial period did R&D that led to the discovery of new vaccines and other important innovations in vaccines, increased demand for routine production functions with no division of labour

to focus on research activity, and the limitations associated with institutional procedures for recruitment and career growth could not lay a path for a sustainable innovation process[53] even after independence.

During the initial decades of the post-independence period, vaccine was not the mainstay of Indian public health policy agenda, and international initiatives often shaped the pattern of vaccine research, production and immunization policies (Annexure 2). Also the regular use of primary vaccines for large-scale immunization and efforts to promote vaccine R&D in independent India was mainly shaped by a global agenda and the declaration of 'Health for All by 2000 AD' by the World Health Organization in 1978. However, consistency in the effort to implement the policy objectives were not maintained by successive Indian governments and wavered according to the socio-political situations of times. In the 1970s, there was a massive drive for an increase in the public sector role during Indira Gandhi's prime ministership, resulting into the emergence of more public sector units. Several private sector units were converted into public sector units. However, during the 1990s owing to liberalization the same public sector units were closed down. These included the new public sector units that were specifically aimed to produce primary vaccines using new technologies.

Thus, by the time the biotechnology revolution began in the world and universal vaccination became a global agenda, the Indian vaccine system lost nearly all the advantages of its early institutionalization, and was not sufficiently prepared (nor supported) for a revival through biotechnology, thereby setting the stage for technological obsolescence and import dependence. In addition, during the post-biotechnology period, the interests of transnational corporations/international organizations shaped the research pattern and production pattern of vaccines in India through industrialized countries or through international agencies. Considering the fact that vaccination became a national slogan only as a part of the international slogan, the Indian efforts to promote vaccine R&D were also in line with the international trends, notwithstanding the occasional nationalist pronouncements towards 'achieving self-sufficiency in vaccine production and self-reliance in vaccine technology' by AD 2000. As global trends in the

post-biotech period increasingly led to shifting of the vaccine focus from the public sector to the private sector, India too was expected to follow suit. This seems to be the case with the failure of indigenous efforts to achieve self-reliance in OPV described earlier in this paper. The various questions raised in that context certainly provide some important links between international factors and the local policies, though there is no unambiguous evidence to establish a cause and effect relationship.

Similarly, the economic policies of liberalization and globalization promoted by the international agencies on the ground that they bring in investments and technology, seem to have achieved precisely the opposite result in the case of the measles vaccine at IVCOL: The closure of the Indian public sector company for non-availability of technology from its French public sector partner, due the privatization of the latter. The policies of liberalization and globalization implemented in India since 1991 under pressure from the World Bank and International Monetary Fund led to the marginalization of the public sector and allowed easy entry to foreign companies. It is no coincidence that around the same time, large TNCs in the West were seeking newer markets to release their biotech products. Moreover, markets for new vaccines were created through indirect means by lobbying for their inclusion in the national immunization programmes. Sometimes, the introduction of new vaccines in national immunization programmes was also articulated through bilateral R&D programmes, such as the Indo-US VAP. The case of Hepatitis B in India illustrates how its introduction in EPI overburdens the national governments and how the local realities such as disease incidence, endemicity and local priorities of vaccination have been over looked while considering the introduction of Hepatitis B into EPI.[54] Many western countries have included many other new vaccines (influenza type B, meningitis, influenza type b, MMR, chickenpox, etc.), in their regular immunization programmes.[55] In India too, soon there would be pressure to include many more vaccines in the EPI. Dr Plotkin who developed the vaccine against Rubella recommended that India should adopt this vaccine in the EPI.[56]

Moreover, dependence on the UN procuring system to meet the EPI requirements may also create a sense of dependency and act as a

disincentive to develop indigenous capabilities in developing countries, especially on the ground that they do not follow good manufacturing practices. The WHO encourages procurement of vaccines required for EPI through the UN system. In developing countries, most of the vaccines under the EPI are made available at cheaper prices through the UN procuring mechanism. At the same time, the UN procurement mechanisms reduce the competitiveness of vaccines produced in developing countries, and UN agencies have been openly discouraging indigenous development. The World Development Report 1993 suggests that it is more cost-effective for developing countries to continue to import vaccines through UN mechanisms than to invest in vaccine manufacturing plants, especially since quality control and regulatory mechanisms are sub optimal in many developing countries.[57] However, the problems that may arise from dependence on the developed countries should not be ignored.[58] It is also important to re-examine the whole issue of uniform global standards for quality control, namely, the GMP and GLP adopted by international agencies, and whether these are realistic, practical and truly objective and unbiased. Otherwise, they can be a convenient (and easily convincing) means of excluding new, especially developing country companies or those from politically unfavoured nations from supplying to the UN procuring system, which is presently monopolized by a handful of Western TNCs.

Thus, while international agencies determine the global agenda for vaccination and support developing countries in implementing their programmes, they do not support indigenous capability development for vaccine production, or in other forms of preventive health. The findings reported in this paper are in line with others, which indicate that the global initiatives tend to influence the priority setting in developing countries, as well as increase import dependence.[59] As argued by Banerjee (1996), the ruling classes in western industrialied countries have long used access to health services as a means of perpetuating their social and economic control over the peoples of the third world.

The Indo-US VAP was signed initially for five years, was later extended by five more years in 1992 and the programme continues till date (see annexure 1 for details). In the initial stages, the Indo-US VAP chose mutual interest research projects such as, viral hepatitis, hepatitis

Non A Non B, rotavirus diarrhoea, *E. coli* diarrhoea, typhoid, improved pertussis vaccine, canine rabies, respiratory syncytial virus and poliomyelitis. Initially, projects on Hepatitis Non A Non B, cholera, poliomyelitis and typhoid were approved. Tuberculosis, which was the top most killer among the vaccine preventable diseases was added only in 1995-96. Till 1998-1999 around 19 projects were approved and around 20 new proposals were under consideration. A new project was initiated on the development of edible vaccines in transgenic plants (tomato) against dairrhoea and cholera (DBT *Annual Report 1999-2000*). Thirteen years after launching the Indo-US VAP, the outcome of the projects revealed that, so far diagnostic kits for kala-azhar, hepatitis C and tuberculosis are being developed. Two candidate rotavirus vaccine strains were developed and patents were filed in the US by the Indian Institute of Science (IISC) Bangalore (1321 strain) and by All India Institute of Medical Sciences (AIIMS), New Delhi (116E). The rotavirus 116E strain was found to be immunogenic in newborn babies in AIIMS. Both candidate vaccines were tested in phase I trials in Cincinnati, US, and steps have been initiated to conduct phase I clinical trials in India.[60]

Diarrhoea is mainly caused by *E coli* in India (Brown et al. 1988, Ghosh et al. 1991) and rotaviral diarrhoea is not very significant, according to the ex-director of National Institute of Virology, Pune. However, candidate vaccines have been developed and are undergoing phase I trials (Annexure 1). While one does not underestimate the importance of development of diagnostic kits, it is interesting to note that under the Indo-US VAP, more diagnostic kits are being developed when compared to vaccine development. The development of diagnostic kits take a shorter time when compared to the development of vaccines and, therefore, reach the market early. An objective analysis of the prevalent disease pattern based on health surveillance information would have helped to identify more appropriate research priorities in India. However, owing to collapse of the surveillance system in India, this exercise may not be very meaningful. While the World Bank earlier gave funding to improve the Indian surveillance system, later it withdrew the same.[61] While the progress in research collaboration under the Indo-US VAP may be genuine, the real conflict may come up when ownership and patents of technology issues arise if it develops new vaccines and generates vaccine innovations.

Endnotes

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Annexure 1: Projects under Indo-US Vaccine Action Programme

Project	Approved in the year	Indian Collaborator	American Collaborator	Duration & Out come
Etiological & biological studies on enterically transmitted NANB hepatitis	1988-89	National Institute of Virology (NIV), Pune	Hepatitis virus section, National Institute of Health (NIH), Bethesda	5 years (New knowledge generated to develop a diagnostic kit)
Antigenic properties of *vibrio cholerae*	1988-89	Central Drug Research Institute, Lucknow	Centre for Vaccine Development, Baltimore, USA	3 years (molecular characterization confirm immunogenic properties of antigen)
Diagnosis of typhoid fever	1988-89	Christian Medical College (CMC), Vellore	Texas University Health Sciences, Texas	4 years (Field trials of ELISA based kit in CMC, Vellore was tested)
Neurovirulence & attenuation of poliovirus in primates	1988-89	Christian Medical College, Vellore	University of Colorado, Health science Centre, Denver	4 years (three mutant type-1 polio were developed and being tested for development of vaccine)
Molecular expression of human rotaviral genes	1989-90	Department of Microbiology and Cell Biology, IISC, Bangalore	School of Medicine, Stanford University, USA	5 years (neonatal rotaviral candidate vaccine 1321 was developed and conducted phase I trials in USA)
Characterization of AIIMS neonatal rotavirus strain as a vaccine candidate	1990-91	All India medical Institute (AIIMS), New Delhi	Viral Gastroenteritis unit, Centre for Disease Control (CDC), Atlanta	5 years (rotaviral candidate vaccine 116E was developed, tested in newborns in AIIMS and conducted phase I trials in USA)

Annexure 1 continued

Annexure 1 continued

Project	Approved in the year	Indian Collaborator	American Collaborator	Duration & Out come
Diagnosis of diarrohegenic *E coli* and development of ETEC vaccine against diarrhoea	1990-91	National Institute of Communicable and Enteric Diseases (NICED), Calcutta	John Hopkins University, United States of America (USA)	5 years (a diagnostic kit was developed for its use in India)
Etiology and diagnosis of NANB viral hepatitis	1990-91	All India Medical Institute (AIIMS), New Delhi	Hepatitis virus section, NIH, Bethesda	3 years (New finding: hepatitis E as the major cause of severe sporadic hepatitis in endemic area)
Molecular characterization and immunodiagnosis of Hepatitis C	1991-92	Osmania Medical College, Hyderabad	University of Colorado, Health science Centre, Denver	3 years (developed a method for detecting Hepatitis C virus by PCR technique)
Evaluation of ARI organisms to develop vaccines	1991-92	JIPMER, Pondicherry	John Hopkins University, USA	Diagnostic kit being prepared for some ARI organisms
Characterization of *E. coli* pathogen	1991-92	AIIMS, New Delhi	Pennsylvania State University	Molecular characterization being carried out
Plasma derived Hepatitis B vaccine Production	1992-93	BIBCOL, Bulandshar	CDC, Atlanta	Under progress
Site preparation evaluation vaccines for prevention of typhoid	1995-96	AIIMS, New Delhi, Tuberculosis Research Centre, Chennai	NIH, Bethesda	

Annexure 1 continued

Annexure 1 continued

Project	Approved in the year	Indian Collaborator	American Collaborator	Duration & Out come
The development of edible vaccines in transgenic plants (tomato)	1998-99	Delhi University, South campus, CBT, NII, New Delhi Delhi, IMTECH Chandigarh		
Diagnostic kit for hepatitis	1998-99	RGCB, Medical Deccan college, Trivandrum	University of Colorado	Commercial kit is being developed
Diagnostic kit for kala-azar	1998-99	JNU, New Delhi		A diagnostic kit is being developed
A diagnostic kit for TB	1998-99	AIIMS, New Delhi		A diagnostic kit is developed and a patent has been filed
20 more proposals are under consideration	1999-2000			

Source: DBT Annual Reports 1987-88 t0 1999-2000.
ARI: Acute respiratory infections, TB: Tuberculosis, PCR: Polymerage chain reaction, CBT: Centre for Biotechnology, JNU: Jawaharlal Nehru University, NII: National Institute of Immunology, IMTECH: Institute of Microbiol Technology, RGCB: Rajiv Gandhi Centre for Biotechnology, NANB: Hepatitis non A and non B, ELISA: Enzyme linked immuneabsorbant assay, IISc: Indian Institute of Sciences, JIMPER: Jawaharlal Nehru Institute of Post Graduate Medical Education and Research, BIBCOL: Bharat Immunologicals and Biologicals Ltd.

Annexure 2: Events related to Health Planning in India and in the World

1947	Ministries of Health were established at the centre and states in India. The posts of Director General, Indian Medical Science and of Public Health Commissioner with the Government of India were integrated in the post of Director General of Health Services, who is the principal adviser to the union government on both medical and public health matters.
1948	Formation of World Health Organisation (WHO) to establish a single worldwide intergovernmental health agency. India joined the World Health Organization as a member state.
1949	The South East Asia Regional office of the WHO was established in New Delhi. The Indian Research Fund Association was reconstituted into Indian Council of Medical Research (ICMR).
1950	The Planning Commission was set up by the Government of India.
1951	The beginning of the First Five Year Plan in which 5.9 per cent out of total outlay was allotted to health programmes.
	The BCG vaccination programme was launched in the country.
1953.	The National Malaria Control programme was commenced as part of the First Five Year Plan. A nationwide Family Planning programme was started.
1960	The School Health Committee was constituted by the Union Health Ministry to asses the standards of health and nutrition of school children and suggest ways and means to improve these.
1965	Direct BCG vaccination without prior tuberculin test, on a house-to-house basis was introduced.
1966	Ministry of Health, Government of India was constituted to look into the additional staff required for primary health centres and to maintain the work of malaria and smallpox control programmes.
1974	WHO established the Expanded Programme on Immunization (EPI) to protect children against tuberculosis, measles, diphtheria, whooping cough (pertussis), tetanus and polio.
1978	WHO adopted the goal of 'health for all' by AD 2000, challenged the countries of the world to provide immunization services to all children or UCI by year 1990.
	Expanded Programme on Immunization (EPI) was launched by Government of India. Declaration of Alma Ata underlined the primary health care approach.
1979	World Health Assembly endorsed the declaration of 'Alma Ata' on primary health care.

Annexure 2 continued

Annexure 2 continued

1980	World Health Assembly declared eradication of small pox from the entire world.
1981	WHO and Member countries adopted the Global Strategy for Health for All. Report of the Working Group on Health for All, setup by the Planning Commission was published.
1982	The Govt. of India announced its National Health Policy. A Biotechnology Board was formed. UNICEF launched Child Survival and Development Revolution-immunization along with other cost effective, high impact interventions in its 'GOBI-FFF' package.
1984.	Task Force for Child Survival' launched by UNICEF, WHO, UNDP, World Bank and Rockfeller Foundation for international coalition to increase international collaboration.
1985.	United Nations general assembly affirmed full support for the goal of UCI 1990 and 74 countries and 400 voluntary agencies pledged to achieve the goal by 40th Anniversary of United Nations.
	Technology Mission was launched by Ministry of Heath and Family Welfare and DBT was a nodal agency to implement EPI programme in vaccines in India.
1986	Department of Biotechnology (DBT) was established in India.
1987	A world wide "safe motherhood" campaign was launched by World Bank.
1990	The World Summit for children convened in New York announced ambitious goals for 1990s.
1992	Child survival and safe motherhood programme (CSSM) was launched on 20 August.
1995.	ICDS renamed as Integrated Mother and Child Development Services (IMCD)
1996.	Pulse polio immunization took place on 9 December and 20 January 1996. The second phase of PPI conducted on 7 December 1996 and 18 January 1997.

Source: Compiled from Park & Park (1997), Banarasidas Bhanot Publishers, Delhi, and "Vaccination and World Health" by Cutts, F.T. (1994) John Wiley & Sons Ltd., London.