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Cholera	NII, New Delhi; IISc., Bangalore; CDRI, Lucknow	R&D
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Source: Compiled from annual reports of DBT from 1987–88 to 1993–94.

typhoid and small pox. Since independence, four more public sector units and an equal number of private sector units came up to boost vaccine production in the country.

Thus, India gained an early entry into vaccinology and had every reason to become self-sufficient in vaccine production over the years. However, the situation today is exactly the reverse. Vaccine production in India is far from meeting the demand. While the demand for most vaccines is in the range of millions of doses, indigenous production is of the order of lakhs (Table 2). Moreover, the trends in the production pattern of various vaccines in the last 10 years indicate that the production has been erratic and inconsistent (Table 3). As a result, half a century after independence, India continues to import most vaccines (Table 4). In the case of polio, almost the entire requirement of oral polio vaccines (OPV) is being met through imports.

In addition to the primary vaccines, which are a part of the Universal Immunization Programme (polio, measles, DPT and TT), several other vaccines, such as those meant for TB (BCG), yellow fever, Japanese encephalitis, rabies, cholera and typhoid are being produced in India, many of which are also in short supply.

Indigenous research into vaccine development received the much-needed attention only after the Government of India launched a technology mission under the Department of Biotechnology (DBT) in 1986. Efforts to develop new or improved vaccines against leprosy, hepatitis B and C, TB, typhoid, polio, cholera, rotavirus, rabies, etc. are currently at different stages of R&D in various academic institutions in India (Table 5). Significantly, many of them are a part of the Indo-US joint Vaccine Action Programme. Very few of these projects have been able to develop candidate vaccines which reached the stage of clinical trials, and successful commercial production based on indigenous R&D has not been achieved for any vaccine so far, though it can be argued that it is too early to expect such results.

Technological gaps

An ideal vaccine should have the following properties: (a) single dose administration, (b) life-long protection, (c) safety from the risk of infections and side effects, (d) heat stability, (e) simple and cost-effective technology for mass production, (f) easy method of administration, such as, for example, oral instead of injectible preparation, and (g) multipotent hybrid vaccines or formulations such as DPT, so that a single preparation can offer protection from a range of diseases.

Unfortunately, there is not a single vaccine anywhere in the world that can qualify for being an ideal vaccine.

Table 2. Installed capacity and production of vaccines (Figures in lakh doses)

	Installed capacity						Actual production (1991–1992)					
Institutions	DPT	DT	TT	BCG	OPV	Measles	DPT	DT	TT	BCG	OPV	Measles
Public sector												
Central Research Institute, Kasauli	220.00	170.00	270.00				137.60	170.93	259.21			
Pasteur Institute, Coonoor	150.00	100.00	100.00				150.40	93.49	97.70			
Haffkine Biopharmaceutical Corporation Ltd, Bombay	60.00	60.00	120.00		420.00*		60.00	0.0	120.00		380.00	
Pasteur Institute, Shillong		50.00	50.00					0.0	0.0			
King Institute of Preventive Medicine, Madras		0.0	100.00	308.00				0.0	80.00	168.50		
SVI, Patwadanagar			20.00						50.00			
Bengal Immunity, Calcutta			60.00						4.20			
Bharat Immunologicals and Biologicals Corporation Ltd, Bulandshar					1000.00†						0.00	
IPM, Hyderabad			50.00						13.60			
Private sector												
Serum Institute, Pune	1140.00	400.00	1500.00			700.00	695.00	276.40	967.00			680.00
Biological Evans, Hyderabad	240.00	240.00	1000.00				150.00	110.00	400.00			
Glaxo, Bombay	52.00		52.00				77.30		18.00			
Bio Vaccine, Hyderabad			750.00						310.00			
Radicura Pharma, Delhi					2000.00*						570.50	0.00
Indian Vaccine Corporation Ltd, Gurgaon						200.00						0.00
Total	1862.00	1020.00	4072.00	308.00	3420.00	900.00	1270.30	650.82	2319.71	168.50	950.50	680.00
Requirement‡							1320.24	350.00	1190.00	500.60	1550.60	500.00

Source: Compiled from Health Information India, CGHS, New Delhi, 1995.
*Supplied after procuring finished product.
†Starting indigenous production.
‡Annual report of Ministry of Health and Family Welfare 1994–1995, GOI, New Delhi.

However, efforts are on to bring the currently available vaccines as close as possible to the ideal situation. For example, most vaccines available currently require several rounds of immunization to develop adequate immune protection. There are also problems related to safety, especially while using whole cell vaccines. The pertussis component of DPT vaccine, as well as typhoid and rabies vaccines are highly reactogenic and less efficacious. Similarly, BCG offers very little protection from TB among adults.

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production of any vaccine against polio is just not available in India. Indian Vaccines Corporation Limited (IVCOL), established in 1989 as a joint venture company between the DBT, IPCL (GOI) and the Institut Merieux (France) to produce OPV indigenously had to be closed down even before the transfer of technology materialized, as the ownership of the French company had changed in the meantime, and the new owner declined to honour the commitment to transfer technology to the Indian joint-venture project[3].

Non-availability of the latest technology from abroad is only one part of the problem associated with the present vaccine production strategy in India. There is no guarantee that the latest technology available abroad is necessarily the best in the Indian situation.

For example, the OPV technology currently being used abroad imposes a strict maintenance of the cold chain (–20°C), as the shelf life of the vaccine at 37°C is less than 2 days. Inability to maintain the cold chain is often cited as a reason for the limited success of Indian polio vaccination programme[4,5]. On the other hand, IPV technology, though older and less effective, renders the polio vaccine stable at room temperature, and thus preferable for Indian conditions, especially when vaccination has to be performed in remote villages.

Gaps in innovations

Technological edge comes only through continuous efforts towards innovations in process and product improvement. There is a tremendous scope for such innovation in vaccines for the simple reason that there are no ideal vaccines today, and improvements are possible for even what are considered to be the best candidates in the market.

For example, conventional preparation of vaccines involves the use of killed or attenuated microorganisms, the safety and efficacy of which are limited. With the advent of modern biology, a whole new generation of vaccines are becoming available which use genetic engineering and improved cell culture-based techniques. Some of the more recent preparations are subunit and recombinant vaccines.

These are examples of more complex innovations, which involve almost a complete replacement of existing products and processes. While there has been some success in introducing cell culture-based production in India (Tables 5 and 6), recombinant DNA-based technologies are still a far cry, because of our inability to build up our innovative capabilities in biochemical engineering, downstream processing, etc. at par with Indian strengths in genetic engineering skills[6].

On the other hand, there could be other smaller innovative inputs to optimize process performance, or to make the existing products more stable, more efficient, or less costly. Inputs are also required to ensure quality of vaccines to meet global standards. Unfortunately, the only vaccines in India which meet WHO standards of quality are the tetanus and measles vaccines, produced by a private firm, Serum Institute of India, Pune.

The measles vaccine that is currently in use worldwide works only in children above the age of 9 months,

Table 6. Contrasting features of the present vaccine technology situation in India and abroad and directions of future research

	Current vaccine technologies		
Vaccine	Global scenario	Indian scenario	R&D trends world-wide
IPV	Vero cell culture-based technology, requires 3–4 doses, thermostable, costly	Entire polio vaccine is being imported so far	Efforts to improve efficacy
OPV	Monkey kidney cell culture based technology, requires 3 doses, thermolabile, cheap	Almost entire polio vaccine is being imported so far	Efforts to enhance thermostability
DPT	Acellular pertussis component, requires 2 doses, efficient	Conventional preparation (live attenuated virus or human immunoglobulins)	Efforts to improve purity and pertussis component
Measles	Schwarts strain and chick embryo fibroblast cell culture technology, requires single dose	Human diploid cell culture technology, only manufactured by private sector (Serum Institute, Pune)	R&D efforts to vaccinate before 6 months in children. A new live vector vaccine is being tested and other 3 vaccine candidates are under R&D
Hepatitis-B	(1) rDNA technology (2) Plasma-derived technology	Production nil	R&D efforts to combine with DPT
Rabies	Vero cell micro carrier technology	Sheep brain BPL inactivation cell technology	Efforts to develop vaccinia recombinant rabies vaccine

Source: Compiled from DBT annual reports and WHO, 1995.

whereas the disease is most prevalent among children between 4 and 9 months of age. Moreover, the vaccine is highly contagious, and could prove to be fatal unless it is stored and handled under sterile conditions[7]. These are some of the problems associated with measles vaccine which require innovative solutions.

Improving the stability of vaccines is another challenging area in which even small improvements can lead to big advantages. For example, BCG, measles and yellow fever vaccines are more stable in freeze dried form than as liquid preparations. Similarly, most vaccines require a strict adherence to cold chain during storage, transport and delivery. This is practically impossible in the Indian situation, and therefore often leads to inadequate immune protection (if not a total lack of it) in spite of a good coverage.

In the case of polio vaccine, through IPV had the advantage of being stable at room temperature, its high cost (over 4-fold compared to OPV) and lesser efficiency made it a second choice after OPV. However, as has been mentioned earlier, deficiencies in OPV immunization were attributed, at least in part, to the failure in maintaining the cold chain.

Recent findings by Crainic of the Institut Pasteur, Paris, that preserving OPV in heavy water instead of magnesium chloride solution renders the vaccine stable even at 45°C, offers tremendous hope in breaking away from the cold chain[8]. In principle, this logic applies equally well for preserving all live virus vaccines. Though WHO has estimated that the use of heavy water increases the cost of live vaccines by about 20%, the savings made from refrigeration costs would more than offset this increase. India should use the surplus heavy water being produced indigenously to stabilize vaccines and augment its immunization programmes with a sense of urgency.

Thus, there is no dearth of avenues for innovations in vaccine technology, and India was in a reasonably comfortable position because of its early entry into this field. In fact, unlike most other sectors of the Indian manufacturing industry, vaccine-producing units in India had a very significant R&D component from the very beginning. This could have given India a tremendous lead in the field, if the in-house R&D component was strengthened and effectively harnessed to boost vaccine production. This could have helped not only in achieving self-sufficiency within the country, but also in aiming at the world market. However, this did not happen, and Indian in-house R&D establishments seem to be satisfied by 'catching up' with the more recent technologies, rather than taking the lead.

One of the reasons for this situation seems to be tendency on the part of the government to accord priority to imports rather than indigenous development and capability building. In fact, in most cases, the very order of priority in vaccine production has been: firstly to import finished products, secondly to import in bulk and reformulate in India, thirdly to import technology for local manufacture. In such a situation, it is difficult to expect a strong motivation and incentive for indigenous innovations. This is best exemplified by Bharat Immunologicals and Biological Corporation Limited (BIBCOL), which continues to produce OPV from imported bulk and has not been able to achieve its target of indigenous production so far. It is being hoped that the lessons from BIBCOL and IVCOL experiences will prompt a rethinking on the Indian strategy for vaccine production.

Gaps in linkages

A closer examination of the Indian vaccinology R&D scenario reveals that we have a strong base and basic infrastructure in microbiology, immunology, biochemistry, molecular biology, rDNA technology, animal cell culture and chemical engineering. Over the last decade, several ambitious projects have been initiated to produce new or improved vaccines in various research institutions in India. In addition, several vaccine-production units have their in-house R&D programmes. What seems to be lacking, however, is a mechanism that forges effective linkages between the various groups of actors from their diverse fields synergizing their strengths towards a common goal.

At the level of individual institutions such as Central Drug Research Institute (CDRI) and National Institute of Immunology (NII), there have been some examples of successful links with other institutions, hospitals, etc. But linkages with industries were comparatively weaker, one-sided, linear, and often hierarchical[9]. While this deficiency has been widely acknowledged in recent times[10], institutional mechanisms to improve the situation are yet to emerge in a concrete manner.

The Indo-US joint Vaccine Action Programme (VAP) was widely acclaimed to be an important step in forging effective linkages with the specific purpose of vaccine development. While there is no denying this fact, one would have liked to see similar enthusiasm in building similar linkages within the country, a step that was long overdue. Another important aspect of some of the foreign linkages has been the terms and conditions agreed to by the Indian side. Indian negotiations with respect to foreign joint venture projects have often met with criticism, whether it is VAP, BIBCOL or IVCOL. A thorough review of the Indian experiences with these projects needs to be undertaken in retrospect, and lessons drawn for the future.

National innovation strategy

The above discussion strongly underlines the need for

a national policy on vaccines. Shaping a national innovation strategy should be an integral part of this exercise. As a developing country located in the tropics, India is in a highly vulnerable situation with respect to infectious and parasitic diseases, and their increasing resistance to curative methods of control underscores the need for vaccines. The very fact that tropical diseases research accounts for a mere 5% of the global health-related R&D, even though they account for over 90% of the world's disease burden[1] strongly points to the need for indigenous efforts to fight them.

Thus, vaccines are indispensable preventive medicines against infectious diseases, and self-sufficiency in vaccine production and self-reliance in a vaccine technology are undoubtedly the important determinants of our national health security. Moreover, our experience with imported technologies and foreign joint ventures further emphasizes this point. In this context, the following aspects need to be emphasized: (a) A reliable information system on infectious and parasitic diseases based on regular surveillance should be the bottom line of any such effort; (b) Revitalizing the in-house R&D base in vaccinology; (c) Stress on indigenous manufacture and import substitution; (d) A national award and other incentives for innovations in vaccines; (e) Linking research institutions and in-house R&D around specific projects, and (f) A specially earmarked fund for R&D in vaccines.

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MEETINGS/SYMPOSIA/SEMINARS

Second Contact Programme on Molecular Biology and Crop Biotechnology (1997) for M Sc Ag. students

Date: 27 August to 10 September 1997
Place: Meerut

The programme aims to expose M Sc/M Sc Ag. students and fresh research students of Agricultural and Life Sciences to recent developments in Molecular Biology and to provide them basic training in the application of molecular biology techniques for crop improvement.

There will be laboratory exercises involving the following techniques: Isolation and purification of genomic and plasmid DNA, isolation of RNA, estimation of DNA and RNA, gel electrophoresis, restriction digestion of genomic and plasmid DNA, radiolabelling of probes, Southern and in-gel hybridization, Northern hybridization, PCR, DNA sequencing, etc.

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National Workshop on Environmental Pollution Control and Regulation Strategies

Date: 12–13 September 1997
Place: Calcutta

Topics include: Various aspects of pollution control and its regulation, the control strategies for abatement of air, water and food pollution and also to fulfil the zero pollution targets and ISO 14000 certification.

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XXVIII National Seminar on Crystallography

Date: 24–26 September 1997
Place: Kottayam

Subject categories include: A. Methods in crystal structure analysis and computational methods, B. Crystallography in biology, biochemistry and pharmacology, C. Materials sciences, D. Real and ideal crystals, E. Inorganic and mineralogical crystallography, F. Structures of organic, organometallic coordination compounds and polymers, G. Education, data retrieval and other topics in crystallography, H. Structure methods other than diffraction, I. Apparatus and techniques.

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