Review Article

Human Vaccines in India: Present and Future Perspectives

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Abstract

Vaccines are formulations that equip the human immune system to fight against a pathogen. All the vaccines approved for use are safe. On vaccination, the body produces enough clonal B and T cells to resist infection. Vaccines are the most cost-effective defense against infectious diseases. In India, there are at least 19 manufactures of vaccines. In addition, there are also a large number of companies that import specific vaccine formulations and sell these in India. These include two multinational companies that have also established repacking facilities. India has a well-established Universal Immunization Program (UIP) that targets vaccination of 30 million pregnant women and 27 million newborns annually. Indian vaccines are available at affordable prices to the private consumers but are supplied free of cost to the Indian beneficiaries through the UIP. Several kinds of vaccines technology are being researched all over the world. India has concentrated on the production and supply of conventional vaccines at cost-effective prices. India is also engaged in some level of research at manufacturing companies as well as at the institutional level. Effective vaccination of pregnant women and children would translate into a generally more healthy and productive society globally. India is poised to contribute in such an endeavor.

Keywords: Antigens, Bacille de Calmette et Guérin (BCG) vaccines, cholera vaccines, conjugate vaccines, DPT, *Haemophilus influenzae* type B (Hib) vaccine, hepatitis B vaccines, Indian vaccine manufacturers, influenza vaccines, measles–mumps–rubella (MMR), polio, rotavirus vaccine, typhoid fever vaccines, vaccines, yellow fever vaccine

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INTRODUCTION

A human vaccine is a formulation that is processed safely and contains substances that have features which match materials in part or in whole to pathogens (disease-causing microorganisms) against which bodily protection is sought. Infection is caused to the human when pathogenic microbes invade the body. The human body has lymphocytes or white blood cells to protect from pathogens. The human body protects itself from the attacks of invading pathogens by innate as well as acquired immune responses. Protective immunity is acquired by the body through vaccination. In these processes, mainly four kinds of white blood cells get involved, which include the T cells, B cells, the lymphocytes, and the macrophages. Dendritic cells that are monocytes and are a part of white blood cells assist in the presentation of antigens to the lymphocytes, which in turn activate the T cells and the B cells for the formation of the effector cells or clonal cells to fight against the pathogen.

Vaccination of individuals is a complex process of acquiring capabilities in them to produce essentially two

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types of immune cells, which are effector cells and memory cells. On vaccination, part of the T and B cells acquire capacities to have memories to remember the pathogen or its parts for getting activated at a later time to protect the vaccinated recipient. Effector B cells and effector T cells carry out different functions. Antibody molecules produced by B-lymphocytes in response to the vaccines are effector B cells that are also called plasma B cells and that secrete specific antibodies (also designated as clonal antibodies) that are capable of binding to toxins or to pathogens secreting the toxins most effectively. Formation of such binding complex arrests or inactivates the pathogen. The immunoglobulin-pathogen (or its parts) complex is cleared by the macrophages continuously from the system, keeping the body healthy and the vaccinated individuals protected from the pathogens. Activation of T cells to form clonal T cells is more complex. Effector T cells or T lymphocytes are of three main types: cytotoxic T cells, helper T cells, and regulatory T cells. The classification is based on the profile of cytokines these cells secrete and the roles the cells play in mediated immune response system. These cells arise from a series of subsets of T cells and are matured and selected in the thymus. The cells predominantly include cytotoxic CD8 + T cells and a wide range of helper CD4 +T cell; these cells execute mediated responses. Specific stimulus triggers a mediated response.

It was believed earlier that the $CD4^+$ T helper cells of two specific types, namely the $CD4^+$ T helper-1(Th1) and $CD4^+$ T helper-2(Th 2) cell types are generated as a consequence of vaccination response. On vaccination using appropriate adjuvants, the T cells expand rapidly through a complex process, on the basis of presentation of antigens by the lymphocytes and macrophages on the cell surface of resting T cells, which stimulate the differentiation into effector cells and into memory cells. The Th-1 cells would produce and activate the formation of effector and memory $CD4^+$ T cells, whereas the Th 2 cells would produce and activate the formation of effector and memory B cells.

It was gradually revealed later that these Th1 and Th2 cell types were closely linked to another a large number of subtype lymphocytes that possessed capacities to produce yet another large number of distinct cytokines and expanded homing capacities. Experimental evidence revealed that $CD4^+$ T helper cells differentiate into several lineages after vaccination, distinct among these are $CD4^+$ Th1, $CD4^+$ Th2, $CD4^+$ Th17, and CD8+T cells. Each lineage of these T cells plays a role in the protection process. The response manifestation varies among individuals but essentially these manifest similar broad patterns of biochemical activities in the body. The $CD4^+$ Th1 cells on activation differentiate into subsets that secrete interferon-gamma (INF-γ), interleukin-2 (IL-2), and tumor necrosis factor-beta (TNF-β) that destroy the viral pathogens; these differentiated T cells also provide assistance and support to cytotoxic T cells and macrophages. The $CD4^+$ Th2 cells manifest antimicrobial functions by secreting IL-4, IL-5, IL-6, IL-10, and IL-13; these cells also support B lymphocytes activities. The $CD4^+$ Th17 cells secrete several interleukin factors such as IL-17, IL-21, and IL-22; these lymphocytes protect the extracellular areas of the body from bacterial infection and colonization. The CD8+T cells are lymphocytes that acquire abilities to kill infected cells that need to be cleared from the infection site. These differentiated lymphocytes secrete excessive amounts of Perforin, Granzyme, TNF-α and IFN-γ that facilitate the killing of the infected cells.

All the vaccines approved for human use are safe as these are rigorously tested for safety and efficacy before licensing approvals is accorded for human use. Presently there are vaccines that are widely used worldwide to protect human from multiple infectious diseases but mainly 16 diseases that include vaccines for viral diseases such as chickenpox (varicella), measles, mumps, rubella, rotavirus, polio, hepatitis A, hepatitis B, human papilloma virus (HPV), herpes zoster, and viral influenza; and bacterial diseases such as diphtheria, tetanus, pertussis, *Haemophilus influenzae* type b, meningococcal vaccine type B multivalent vaccine, meningococcal polysaccharide vaccine as well as meningococcal conjugate vaccine.[1,2] Vaccines are either live-attenuated microbes or inactivated pathogens or antigens selected from portions of pathogenic microbial metabolites. Antigens that are selected from portions of pathogenic microbial metabolites can be microbial toxins that are converted into toxoids, subunits of pathogens, recombinant proteins resembling portions of the pathogenic microbes including virus-like particles (VLPs), peptides, and carbohydrates of various kinds emanating from the pathogens as well as conjugates thereof.

Attenuated microbes are more immunogenic than the inactivated pathogens or the protein-based antigens, selected from portions of pathogenic microbial metabolites. Antigens that are not protein-based especially certain carbohydrates, polysaccharides, oligosaccharides, small peptides, haptens, and others that are not sufficiently immunogenic need to be modified by conjugation with certain proteins that are then easily recognized by the immune cells. In general, all the conjugate vaccines are manufactured by linking certain proteins to the disease-specific antigens belonging to the classes of polysaccharides, oligosaccharides, peptides, haptens, and others in order to

enable and enhance the antigen presentation phenomenon to the immune cells to activate the immune system to produce the necessary clonal B and T cells to recognize the pathogens and to act against those to resist infection.

Development of vaccines against certain infectious diseases such as those caused by *H. influenza* type *b, Streptococcus pneumonia* and *Neisseria meningitides* requires enhancement of the polysaccharide-based antigens of these microbes to make those more immunogenic. Multiple kinds of proteins can be chosen for this purpose such as the diphtheria protein CRM, diphtheria toxoids, tetanus toxoids, *N. meningitides* outer membrane complex, and *H. influenza* protein D. Immunogenicity of the covalently conjugated polysaccharides in the process gets substantially enhanced. The best one needs to be chosen, taking into consider the overall property enhancement of the conjugate vaccine including ease of antigen presentation, induction of immunologic memory, reduction of nasopharyngeal colonization and herd immunity, antibody avidity, and avidity maturation as also cost consideration. Conjugation technology has paved[3] the way to develop more effective vaccines against certain infectious diseases.

The activities of several of the antigens are further enhanced by using these along with adjuvants that positively modulate their presentation to the antigen-presenting cells of the immune system. The aluminum compounds such as aluminum hydroxide and aluminum phosphate are widely used as adjuvants for a number of vaccines. Use of an effective adjuvant enables the development of acquired immunity in fewer numbers of vaccine applications. The concept and the benefits of adjuvants in vaccination process have been reviewed[4] with special focus toward the prospects of controlled release of antigens.

Presently, several vaccine formulations are marketed to protect from a single disease (one individual disease) or vaccine formulations of multiple antigens for protection in one shot from multiple diseases. Vaccination of people with greater coverage of children and other vulnerable subsets of individuals leads to healthier and more productive population.

Major Indian producers and suppliers of vaccines

India has made considerable progress in developing processes and technologies to combat diseases caused individually by eight bacterial pathogens such as diphtheria caused by *Corynebacterium diphtheria* (D); tetanus is caused by an anaerobic bacteria *Clostridium tetani* (T or TT); pertussis or whooping cough caused by *Bordetella pertussis* (P or wP, aP); *H. influenza* caused by multiple types of *H. influenza*, designated as types a, b, c, d, e, and f, of which type b (Hib) is known to be a major factor in manifesting greater virulence in disease syndrome in human especially in infants and young children; *Meningococcal* (Meningococcal) *meningitis* and septicemia infection caused by a variety of *N. meningitides* (e.g., caused by subtypes A, C, Y, and W-135); live-attenuated bacterial vaccines such as *Salmonella enterica* serovar Typhi Ty21a as well as naked *S. typhi* Vi capsular polysaccharide-based and also its conjugated antigen-based typhoid fever vaccines (typhoid); the live-attenuated *Bacille de Calmette et Guérin* (BCG) vaccine, which is derived from *Mycobacterium bovis* species; and a vaccine made up of killed whole-cell *Vibreocholerae* O1 antigen in combination with a recombinant B-subunit of cholera toxin (cholera).

Among the viral pathogens, vaccines are being produced by Indian manufacturers from the basic stage to protect the vaccinated individuals from 12 different kinds of viral infections that include live-*attenuated* viral vaccines such as measles vaccine; mumps vaccine; rubella vaccine; influenza nasal spray vaccine (the seasonal flu nasal spray and the 2009 H1N1 flu nasal spray); rotavirus vaccine; yellow fever (live attenuated) vaccine; and varicella or chickenpox vaccine. Formulations of live-attenuated chickenpox vaccine and oral polio vaccine (Sabin) are being marketed based on imported finished formulations or formulated from imported bulk as in polio vaccines. Hepatitis A vaccines are marketed in India by MNCs by importing the finished formulations; this vaccine is yet not manufactured by any Indian company. Injectable polio vaccines are produced in India based on imports of bulk vaccines. Injectable influenza vaccines based on killed influenza virus is manufactured locally. A number of *subunit viral vaccines* are also being manufactured using recombinant deoxyribonucleic acid (DNA) technologies, which include recombinant Hepatitis B (Hep-B) vaccine as well as viral influenza vaccine where VLPs are produced by rDNA technology in insect cells and are used as antigens for the manufacture of the vaccine formulation.

Formulated single-antigen-based vaccines marketed in India are against T or TT, D, BCG, Hib, typhoid, cholera, Hep-A, Hep-B, measles, monovalent oral poliovirus vaccine (m OPV), inactivated polio vaccine (IPV), H1N1, Japanese encephalitis (JE), rabies, rotavirus, yellow fever virus (YFV), and varicella. Formulated vaccines in combinations of multiple antigens are also available; major among these are DPT (generally meaning combinations of toxoids of D and T and whole-cell-inactivated P, also designated as DTwP), DTaP (contains acellular P), b OPV, DPT, t OPV, measles–mumps–rubella (MMR), meningococcal, Hep-A + Hep-B, DPT + Hib, DPT + Hep-B, DPT + Hib + Hep-B, and DPT + Hib + Hep-B + IPV.

Table 1: Names and addresses of Indian vaccines manufacturing companies and the sites of their production facilities[5,6]

Indian private companies
1. Bharat Biotech International Ltd (BBIL), Genome Valley, Turkapally (V), Shameerpet (Mandal), Hyderabad 500078, Telangana
2(a). Biological E. Limited, 18/1 & 3, Azamabad, Hyderabad 500020, Andhra Pradesh
2(b). Biological E. Limited, 7-4-114, Gaganpahad, Rajendranagar Mandal, Ranga Reddy District, Andhra Pradesh
2(c). Biological E. Limited, Plot No.1, S.P. Biotechnology Park, Phase-II, Kolthur Village, Shameerpet Mandal, Rangareddy District, Andhra Pradesh
3. Bio-Med Pvt. Ltd, C-96, Bulandshahr Road Industrial Area, Ghaziabad 201009, Uttar Pradesh
4(a). Cadila Healthcare, SarkhejBawala, NH No. 8-A, Moraiya, Sanand, Ahmedabad, Gujarat
4(b). Cadila Healthcare Limited, Survey No. 23,25/P, 37, 40/P, 42 to 47, Sarkhej-Bavla N.H. No. 8A, Changodar Road, Tal. Sanand, Ahmedabad, Gujarat.
5.Cadila Pharmaceuticals Ltd,1389, Trasad Road, Dholks, Ahmedabad 387810, Gujarat
6. Chiron Behering, Plot No. 3502, Post Box No. 136, GIDC, Estate, Ankleshwar, Bharuch 393001, Gujarat
7. Dano Vaccine & Biological Pvt. Ltd., Hyderabad, Telangana
8. Green Signal Bio Pharma Pvt Ltd., 49, Pappankuppan Village, Chennai 601201, Tamil Nadu
9(a). Panacea, Malpur, Baddi, PO Bhud, Tehsil, Nalagarh, Distt. Solan, Himachal Pradesh
9(b). Pan Era Biotech, Ambala, Chandigarh Highway, Lalru, District Mohali, Punjab
10. Ranbaxy Lab, Sy. No. 16, Ekarajapura, Siddlaghatta Road, Hasigila Post, Hoskote, Bengaluru 562114, Karnataka
11. Serum Institute of India Pvt Ltd., 212/2, Hadapsar, Pune 411028, Maharashtra
12(a). ShanthaBiotechnics Ltd., Survey No. 274, Athvelli Village, Medchal Mandal, Ranga Reddy, District 501401, Telangana
12(b). ShanthaBiotechnics Pvt Ltd., Survey No. 354, Muppireddypalli Village, Toorpan Mandal, Medak District 502236, Telangana
Multinational companies (having repacking facilities only)
13. GSK Asia Pvt. Ltd., Plot No. A-10/1, MIDC, Ambad-Pathardi Block, Nashik 422010, Maharashtra
14. Sanofi Pasteur India Pvt Ltd, EL-223, TTC Industrial Area MIDC, Mahape, Navi Mumbai 400710, Maharashtra.
Indian public sector undertakings
15. Bharat Immunologicals and Biologicals Corpn (BIBCOL), Village Chola, Bulandshahr, Uttar Pradesh
16. Haffkine Acharya Donde Marg, Parle, Mumbai 400012, Maharashtra
17(a). Human Biologicals Institute (HBI), Rakshapuram, Gaachibowli, Hyderabad 500032, Telangana
17(b). Human Biological Institute, Kozhipannai, Pudumund, P.O. Udhagamandalam 643007, Tamil Nadu
17(c). M/s Human Biol. Instt. Sy. No. 281- 284 and 321, Karakapatla Village, MuluguMandal, Medak Dist 502281, Telangana
Government-owned companies
18. BCG Vaccine, Guindy, Chennai, Tamil Nadu
19. CRIKasauli, District Solan, Himachal Pradesh
20. Pasteur Institute of India(PII), Nilgiris District, Coonoor 643103, Tamil Nadu
21. HLL Biotech Ltd (HBL). Integrated Vaccines Complex, SF No. 192 and 195, Thirumani Village, Chengalpattu 603001, Tamil Nadu

The vaccines manufactured in India by all the manufacturing units along with the addresses of their manufacturing facilities are presented in Table 1. All other manufacturers listed in Table 1 are engaged in the production of the vaccines from the basic stage except the two multinational companies (MNCs). Glaxo and Sanofi have repacking units but essentially these companies are importing and selling finished vaccines in this country.

Other major suppliers of vaccines in the Indian trade sale

A couple of other establishments also exist, both MNCs and Indian companies that do not manufacture vaccines nor even repack but procure the finished, saleable packs through imports or by teaming up with the local manufacturers and market those finished vaccines formulations to the consumers. MSD operates its vaccines business in India through MSD Pharmaceuticals Private Limited,[7] Gurugram and Mumbai; it markets through imports five vaccines, namely an HPV vaccine (GARDASIL), which helps to protect against four types (Types 6, 11, 16, and 18) of HPV to help prevent cervical cancer; a vaccine indicated for active immunization against 23 serotypes of pneumococcal bacteria to protect from the disease (PNEUMOVAX 23); a live, an oral pentavalent vaccine that contains five live rotaviruses (RotaTeq) to protect children against rotavirus diarrhea; a live-attenuated virus vaccine indicated for the prevention of herpes zoster (shingles) in middle-aged and older people (ZOSTAVAX); and lyophilized preparation of live-attenuated varicella virus vaccine using the Oka/Merck strain to protect children against varicella (VARIPED). The pneumococcal vaccine Prevenar13 is being imported by Pfizer[8] and sold in Indian private market. Many other Indian companies have teamed up with foreign companies and are selling some of these vaccines in the private market. Typhoid vaccine based on Vi capsular polysaccharide of *Salmonila Typhi*, which is a subunit vaccine is being imported and marketed by Cadila Newgen[9] (a sister concern of Cadila Pharmaceuticals, Ahmedabad) after being imported from Sanofi; TYPHIM Vi is the brand name of Sanofi.[10]

Indian strength in vaccines manufacture

India excels in the manufacturing and marketing of old-generation and conventional vaccines such as D, P, T, or TT, MMR, Hib, typhoid, and rabies vaccines adding a small number of modern vaccines such as Hep-B, rotavirus, cholera and off-late varicella vaccines. Indian manufacturers have shown their strength in their making available these vaccines at most affordable prices while maintaining

international quality standards. These vaccines are no more protected by Intellectual Property Rights (IPR).

Indian strength emanates from the availability of low-cost highly skilled manpower, availability of multiple starting materials including plastics and other packing materials locally, prefilled syringes at competitive prices, availability of small animals at competitive prices (which are used in quality assurance and quality control endeavor), efficiency in engineering capabilities including a production system that can handle sterile operations efficiently. In addition, India has developed profound capabilities in handling services facilities cost-effectively.

Consumption/sale of Indian vaccines

Indian vaccines industry has a large internal market to be serviced. The market includes the sale of vaccines for use in the Universal Immunization Program (UIP) of the government. The UIP of India is one of the largest public health programs in the world and the program targets 30 million pregnant women and 27 million newborn annually.[11] Although the Indian UIP has largely contributed to the reduction of vaccine preventable mortality rate under the age of 5 years in the country, the success of the program is being attributed to the deployment of the necessary funds for the purpose. Although the national exchequer has been contributing a major chunk of the money, praiseworthy monetary supports from multiple benevolent organizations such as the United States Agency for International Development (USAID); Centre for Disease Control, USA; Bill & Melinda Gates Foundation, USA; Rotary International, USA; Gavi, Switzerland; and many others were received from time to time.

The Indian private market (trade market) is comparatively smaller in terms of volumes of consumption of dosages units of vaccines but is large enough in terms of prices for sale of each unit of the vaccine. The trade market is expanding at faster rates, much faster than the expansion of the pharma trade sales. The vaccination cost per child up to the age of 2 years is calculated[12] based on the average existing prices charged by the retailer/practicing pediatrician. There are minor variations between and among the available brands. The IPR-protected vaccines are expensive. The attending doctors have their fees fixed, which vary but yet the variations are in the close price range and are location specific. The vaccination schedule is standardized and is usually as follows: at birth, the infant receives the first dose of BCG (average price Rs. 60.00 per dose) + one OPV (Rs. 230.00) + one dose of Hep-B (Rs. 175.00); at 6 weeks to 2 months, the second dose of vaccines is applied, which include the second OPV/first IPV (Rs. 230.00/Rs. 700.00) + Hep-B (Rs. 175.00) + DPwT/DPaT (Rs. 50.00/800.00) + rotavirus vaccine (Rs. 1500.00) + pneumococcal vaccine (PCV) (Rs. 1800.00: Synflorix [GlaxoSmithKline]/Rs. 3800.00: Prenavar [Pfizer]); at 10 weeks to 4 months, vaccines applied are OPV/IPV (Rs. 230.00/Rs. 700.00) + rota virus vaccine (Rs. 1500.00) + PCV (Rs. 1800.00: Synflorix [GlaxoSmithKline]/Rs. 3800.00: Prenavar [Pfizer]) + pentavalent DPwT with Hib and Hep-B/DPaT with Hib and Hep-B (Rs. 550.00/2495.00); and at 14 weeks to 6 months, vaccines applied are OPV/IPV-3rd (Rs. 230.00/Rs. 700.00) + rota virus vaccine (Rs.1500.00) + PCV (Rs. 1800.00: Synflorix [GlaxoSmithKline]/Rs. 3800.00: Prenavar [Pfizer]) + DPwT with Hib (Rs. 600.00). On 9th month, the child receives one MMR (Rs. 500.00); on 12th month the first Hep-A vaccine is applied. On 15th month, the second MMR (Rs. 500.00) dose + a chicken pox vaccine (Rs. 1900.00) + PCV booster dose (Rs. 1800.00 [GlaxoSmithKline]/Rs. 3800.00 [Pfizer]) is applied. On the 18th month, one DPwT (Rs. 50.00)/DPaT (Rs. 800.00) + one OPV/IPV + the second dose of Hep-A are applied. On the 24th month, the child receives a dose of typhoid vaccine (Rs. 300.00). The cost of vaccines calculated from above is over Rs. 20,000.00 using cheaper vaccines and over Rs. 33,000.00 using the expensive ones. The expensive ones are claimed to be less toxic; the cheaper version of PCV protects against less number of serotypes of pneumococcal antigens. To complete the schedule will require approximately 10 visits or more to the doctors which would cost another Rs. 10,000.00 to Rs. 20,000.00. The total vaccination cost up to the age of 2 years could, therefore, be from approximately Rs. 30, 000.00 to over Rs. 50,000.00 per child, which are considered substantial under the poor setting. However, the Indian middle class has the capacity to pay and this situation is beneficial to both the users and the suppliers.

Because of various other reasons including World Health Organization (WHO) certification of multiple numbers of Indian vaccines as also the manufacturing premises which maintain WHO compliant standards, Indian manufacturers are in a position of exporting a sizable quantum of their production annually. The exports are made in large quantum to the international procuring agencies such as the United Nations Children's Fund (UNICEF). Several benevolent organizations such as the Bill & Melinda Gates Foundation, USA and Gavi, Switzerland also procure sizeable quantities. Some traders from certain countries are also buying for sale in trade in those countries.

Estimated turnover of Indian vaccines in 2019 and its comparison with global vaccines industry

One analysis indicated[13] that during the recent past, the Indian vaccines industry grew to approximately $1 billion

in 2015 with a compound annual growth rate (CAGR) of 25% between 2011 and 2015; and the exports constituted a dominant 69% share in monetary value terms. The author estimates that by the end of 2019, Indian vaccines industry turnover would reach US$1.95 billion. The split of the turnover in 2019 is anticipated to comprise sale for UIP equivalent to US$545.00 million, followed by domestic trade sale equivalent to US$470.00 million and export turnover of US$935.00 million. Through the UPI, nearly 50% of the country's productions in physical terms representing only approximately 28% in value terms are consumed. The domestic sale of vaccines in the private market is estimated to be of the order of US$470.00 million at the end of 2019 and represents approximately 24% in terms of turnover but approximately 21% in terms of physical production quantities, whereas the exports turnover is estimated at $935.00 million, which is approximately 48% of the total turnover of the vaccines industry.

The global vaccines market at prices of 2016 was estimated[14] at the US$28.0 billion and was projected to grow to US$48.0 billion by 2025. In another estimate,[15] the market was considered to grow from $33.70 billion in 2018 to approximately $57.50 billion by 2025, registering a CAGR of 7.9%. Taking into consideration the lowest estimate among these the sets of figures and by projecting the 2016 figures to 2019 at a CAGR of 7.9%, the 2019 figure of the global turnover of vaccines would work out to approximately US$35.2 billion. Indian industry's turnover, in comparison, works out to approximately 5.5% of the global vaccines market.

The global markets serviced by the key players include GlaxoSmithKline, UK; Merck & Co, USA; Sanofi, France; Pfizer, USA; Emergent BioSolutions, USA; CSL, Australia; Inovia Pharmaceuticals, USA; Bavarian Nardoc, Denmark; and Mitsubishi Tanabe, Japan.

Research and development in India for vaccines innovation and invention

Several kinds of vaccines technology are being researched all over the world. These include the development of DNA vaccines where circular pieces of DNA called plasmids containing sequences of specific protein antigens are integrated into the chromosomes of specific cells/tissues and the DNA pieces express specific proteins encoded on the inserted DNA, and are available to the immune system for the stimulating it for acquiring adaptive immunity. Such DNA vaccines are not available in India. Other types of vaccines include the viral vector vaccines where live viruses disarmed from imparting a disease but containing DNA stretches that code for specific antigenic proteins are used to infect human cells. Once infected, the antigenic proteins are released; these get hold of the immune cells and activate the immune system for stimulating it to develop acquired immunity. These kinds of the viral vector, live viruses are also used to infect the defective cells to enable those to fight back and resist the disease. None of these live viral vaccines are available in India yet in clinical research.

In India, the types of vaccines majorly used in clinical research include the development of conventional inactivated (killed) and antigen-expression-specific bacteria or viruses, which are grown, inactivated, processed, and formulated as inactivated vaccines. Live-attenuated vaccines using disabled microbes of specific types are also used to some extent. Further, subunit vaccines of specific types that include the use of purified toxoids or recombinant proteins formulated to enhance the immunogenicity are also used. Different kinds of polysaccharides either as such or covalently conjugated with appropriate proteins to enhance the immunogenicity are also researched upon. Vaccine formulations manufactured by combining two or more of these antigens would result in multi-ingredient vaccines, use of which will ease the need for taking multiple single-ingredient vaccines. Development of such multi-ingredient multivalent vaccines is another area of active research.

Indian research is also focused on developing the vaccines that are available in India through imports but are not manufactured yet in the country, with the objective of import substitution. As the imported vaccines are already in use, substantial information on clinical efficacy is in the public domain. In cases where the vaccine is protected under IPR, the development for substitution can start in advance taking into consideration the expiry date of the IPR and becoming ready for market introduction soon after the expiration of the patent. The driving force is to beat on prices and capture the market share as the imported vaccines are very expensive. India can reduce the costs substantially because when an efficient technology is developed, the costs can be cut down sizably through savings in civil construction and capital goods costs, skilled-manpower costs, certain raw and packing materials costs, and costs of ancillaries. Moreover, there exists a local market. The development cost is also lower as highly skilled modern biologists including microbiologists, chemists, and chemical and biochemical engineers are abundantly available. Several hospital settings and patient population exist for high-quality clinical data generation at much cheaper costs. However, the existing infrastructure falls short when a totally new vaccine is not to be developed for the first time as the industry nor the institutional

infrastructure has the necessary resources. The risks of investment are enormous for such kinds of research work.

Among the existing vaccines manufactured by the Indian companies, the challenge for the development of acellular pertussis vaccine is an important milestone as such a vaccine is effective and at the same time is less toxic than the whole-cell inactivated pertussis vaccine. Among other reasons, the MNCs are in a position of capturing a major portion of the market for the DPT vaccines globally because of their having a less toxic acellular pertussis component in their DPT vaccine product portfolio. The acellular component is sufficiently immunogenic to elicit enough protective-antibody responses against Pertussis bacteria called Bordetella pertussis. There is also a need to have multiple numbers of less toxic but immunologically potent proteins and toxoids in the portfolio of Indian products for enabling to come out with more efficient conjugate vaccines. Presently, the tetanus toxoids are being extensively used by the Indian companies for this purpose.

Among the new approaches, there is an urgent need for Indian companies to develop certainly vaccines on a priority basis which include vaccines against pneumonia from *S. pneumonia*; dengue virus; HPV; chickenpox and herpes zoster virus; malaria: human immunodeficiency viruses (HIV); tuberculosis (TB); respiratory syncytial virus (RSV); enterotoxigenic *Escherichia coli* (ETEC); shigella; Norovirus; Zika virus; Chikungunya virus; and Nipah virus. Severe Acute Respiratory Syndrome (SARS) virus; Middle East Respiratory Syndrome (MARS) virus; and Ebola virus are becoming important issues for the protection of human health globally. The Corona virus infection in China is spreading very fast; prevention strategy and development of an effective vaccine against this disease also needs attention. India needs to intensify its research and development (R&D) efforts for developing vaccines against these diseases.

For the development of vaccines against pneumonia from *S. pneumonia*, the Indian company Serum Institute of India is working[16] on the development of a PCV (10-valent) vaccine in collaboration with PATH.[17] Two other Indian companies, namely Tergene Biotech, Hyderabad[18] and Biological E. Ltd, Hyderabad[19] are also working to develop multivalent pneumococcus vaccines. As regards dengue fever, which is the mosquito-borne viral disease, transmitted by the *Aedesaegypti* mosquito vector and where the disease is caused by four antigenically related dengue viruses (DENV), namely DENV-1 to DENV-4, the only one commercially available vaccine is presently sold by the trade name Dengvaxia (CYD-TDV).[20] This vaccine is a live-attenuated tetravalent chimera of DENV manufactured and marketed by Sanofi Pasteur, France. Certain Indian companies, namely Panacea Biotec, New Delhi in collaboration with the National Institutes of Health (NIH), USA, have claimed to have developed[21] a dengue vaccine and that the Drug Controller General of India (DCGI) had given permission for conducting early-phase clinical trials in humans (phases 1 and 2). Indian scientists are also experimenting on a recombinant DNA technological mode where a VLP platform[22] has been created and the VLPs of the relevant DENVs partly chimerized with hepatitis B virus surface antigen (HBsAg). The International Center for Genetic Engineering and Biotechnology (ICGEB) is working with Sun Pharma, Mumbai on this project.

On the development of HPV vaccines, currently three HPV vaccines are being marketed throughout the world, of which one is bivalent, the other a quadrivalent, and the third a 9-valent one. CERVARIX, a human bivalent HPV vaccine, is manufactured by GlaxoSmithKline Biologicals (GSK) Belgium; GARDASIL that is a human quadrivalent (Types 6, 11, 16, and 18) HPV vaccine and GARDASIL 9 that is a human 9-valent HPV vaccine, are both manufactured by Merck Sharp and Dohme, a subsidiary of Merck & Co (Merck). Bharat Biotech Ltd, Hyderabad[23] and Serum Institute of India, Pune [16] have claimed to be involved in the development of an HPV vaccine. As regards vaccines against either chickenpox or herpes zoster disease, Indian development is yet not significant. Malaria is caused by infection attributable to *Plasmodium vivax* (Pv), *P. falciparum* (Pf), *P. oval* (Po), and *P. malariae* (Pm), of which Pv is most widely distributed, Pf is the most dangerous, and the other two are not widespread. Indian research in the development of a malaria vaccine was pursued[24] at the ICGEB by a group to develop vaccines against Pv and Pf malaria. In small animals, the immunogenicity studies of the products developed were conducted and it was found that these recombinant proteins elicited high titer of invasion-inhibitory antibodies. It is, however, a long way to bring the research to a human-usable vaccine. On HIV vaccine development, Indian efforts[25] have been directed toward the design and evaluation of preventive HIV vaccines at the HIV Vaccine Translational Research (HVTR) Laboratory at the Translational Health Science and Technology Institute (THSTI), NCR Biotech Science Cluster, Faridabad, Haryana. On TB vaccine development, there is yet no vaccine against TB except the BCG vaccine. BCG vaccine has several limitations. It is not a universal vaccine against TB. The efforts to develop new TB vaccines for adolescents and adults in the global context have been discussed and described.[26] In this context, the Indian efforts in working on certain candidate vaccine are noteworthy. The safety and

immunogenicity of the candidate TB vaccine M72/AS01 in HIV-positive and HIV-negative Indian adults, which were carried out at the VHS-YRG Care Medical Centre, Chennai is significant. Indian efforts in the development of vaccines against other diseases caused by RSV, ETEC, shigella, noroviruses, Zika virus, chikungunya virus, and Ebola virus are yet at a rudimentary stage.

Bharat Biotech Ltd., Hyderabad is engaged in developing vaccines against Zika virus; the company has claimed to have two[27] Zika vaccine candidates, one of which is a recombinant vaccine and the other is an inactivated vaccine. In addition, Bharat Biotech claimed to have developed a vaccine composition[28] for prophylaxis and treatment of chikungunya infections.

Indian efforts for vaccines development through international collaborations

With a far-faced foresight, India had instituted international collaborations with certain countries such as the previous USSR (now Russia), France, USA, and the European Union (EU) with a view to develop technologies for the production of certain vaccines required for the country. The Indo–USSR collaboration culminated into the setting up of an oral polio vaccine production unit at Bulandshahr, Uttar Pradesh and in 1989 the company was registered by the name Bharat Immunologicals and Biologicals Corporation Limited (BIBCOL); however, the unit could not produce oral polio vaccines from the basic stages requiring the multiplication of the specific strains of the poliovirus through cell cultures. The unit produced the oral polio vaccines from imported bulk.

The Indian collaboration with France was to produce injectable polio vaccines at Manesar, Gurugram, Haryana. A unit was incorporated on 27 March 1989 by the name Indian Vaccine Corporation Ltd (IVCOL) and was to come up as an Indo–French joint venture. However, the collaboration did not proceed to fruition and the unit did not come up. The Indo–US collaboration made substantial progress in research as well as in applications as detailed below. The Indo–EU collaboration on vaccines was initiated only very recently.

The Indo–US Vaccine Action Program (VAP) was initiated in July 1987. Research projects under VAP currently include dengue fever, enteric diseases, influenza (including avian influenza), malaria, and TB, TB clinical research, human immunology, antimicrobial resistance, chikungunya vaccines, infant immunology, and RSV vaccine.[29,30] A rotavirus vaccine was developed through the VAP initiative. This is an oral vaccine based on the use of the 116E strain of rotavirus, which is a naturally available attenuated strain and is further multiplied in Vero cells for producing vaccines. The rotavirus strain of Indian origin obtained from All India Institute of Medical Sciences (AIIMS), New Delhi was characterized as genotype G9P10 in the USA, multiplied in Vero cells and tested in human. A large number of investigators had worked in multiple facets, which culminated in the development of the rotavirus vaccine, which is now being produced by Bharat Biotech Ltd., Hyderabad. The strain and the technology were obtained by Bharat Biotech from the National Institute of Allergy and Infectious Diseases (NIAID), USA, which is a part of NIH, USA, through a technology transfer agreement.

India also has a major Indo–EU initiative to develop effective vaccines against viral influenza. This project was chosen as seasonal influenza is considered a major health threat globally. The Department of Biotechnology, Ministry of Science and Technology, Government of India along with the EU had announced in 2018 their engagement on research and innovation to develop a next-generation influenza vaccine.[31]

Indian Institutional efforts in vaccines development

The DBT had established thus far 16 institutes in biotechnology in the country to promote biotechnology in its various facets. One of the institutes, namely the National Institute of Immunology, New Delhi, had developed a leprosy vaccine, which was also identified as an immunomodulator against leprosy disease. The leprosy immunomodulator is based on a heat-killed *Mycobacterium* spp. identified as *Mycobacterium w*, later renamed as *Mycobacterium indicuspranii* (MIP) was developed by the National Institute of Immunology, New Delhi. The strain and technology was transferred[32] to Cadila Laboratories, Ahmedabad in early 1990s. The formulated product of Cadila is marketed as Cadi-05 and is indicated to treat leprosy and non-small cell lung cancer.[33]

The institutions under the Indian Council for Medical Research (ICMR), which are presently 26 in numbers, are engaged in research in diverse areas of medical importance. Collectively, the ICMR institutions have made magnificent additions[34] toward a scientific understanding of various diseases of national importance such as TB, filariasis, leprosy, malaria, kala-azar, several diarrheal diseases, rabies, poliomyelitis, JE, acquired immunodeficiency syndrome (AIDS), and other viral diseases. ICMR institutions have also made noteworthy contributions in the areas of reproduction, maternal and child health, human nutrition especially for children and pregnant women as well as in occupational and environmental health areas. ICMR is the top body or institution in India for formulating, coordinating, and promoting development in all areas of

medical research. ICMR promotes medical research in India for the benefit of the country. Among different areas of medical research, ICMR also promotes the evaluation and development of vaccines for the prevention of pathogenic diseases. Through the India TB Research Consortium of the ICMR, efforts are being made to develop vaccines against TB. The National Institute of Cholera and Enteric Diseases (NICED), Kolkata is particularly involved in research for the development of vaccines against cholera, shigellosis, and typhoid fever. No vaccine has yet been commercialized.

Indian prospects and outlook on its expertise on vaccines

Use of vaccines makes an impact on the health of the people of all nations at the most cost-effective manner. In any country, of all the different kinds of human diseases falling within various segments such as communicable diseases, the noncommunicable disorders arising from defects in organs or tissues or cells or combinations of these including the chronic diseases; unusual mental health; maternal and child-health-related diseases and issues; and the geriatric diseases and ailments, the most important segment, namely the maternal and child-health-linked diseases, assumes one of utter importance and is apriority segment because the adequacy of the health of this segment is linked with the future health of the nation. This segment is also of paramount importance in the poor and developing economies where maintenance of health program among the citizen is yet suboptimal. In this segment, imparting immunization through vaccination plays the most cost-effective key role. India has profound strength in terms of technological abilities and its strength can be traced through capacity building, availability of skilled human resources, professional education, infrastructure, and supply of finished products. The post-2020 agenda of sustainable development goals across all nations would certainly have to be reframed and rationalized in the present word which is becoming more complex and multipolar. The future requirements are to emphasize, besides others, on the health needs especially in the developing and poorly setting regions where cheaper but effective quality vaccines would play a major role. India will continue to hold a leadership role in such endeavor because of an edge in skills, the advantage in costs and holds on the considerable spread in the availability spectra of vaccines to address multiple infectious diseases. Intelligent strategies on a cautious mode can be drawn in advance particularly to work together with international organizations such as the WHO, UNICEF, World Bank, and Asian Development Bank (ADB) as also with several giant private-sector resource-rich operators, as Indian strength in vaccines technology is enormous to service the health-care cause in this segment in a most professional and cost-effective manner.

DISCUSSIONS AND CONCLUDING REMARKS

The profound strength of the Indian vaccine manufacturers emanates from the availability of low-cost highly skilled manpower, availability of multiple starting materials including plastics and other packing materials locally, prefilled syringes at competitive prices, availability of small animals at competitive prices (which are used in quality assurance and quality control endeavor), and efficiency in engineering capabilities including production system that can handle sterile operations efficiently. In addition, India has developed strong capabilities of handling service facilities cost-effectively, which include among others capabilities to manage air and water showers, expertise in heating, ventilation, and air-conditioning (HVAC) system, chiller units, steam-handling system, system sterilization units, water-handling units for maintenance of right labels of minimum conductance of water for in-process use, Pass Box integrity maintenance, communication integrity, capability of efficient maintenance and integrity establishment of the high-efficiency particulate air (HEPA) filters and maintenance of predetermined minimum levels of microbial load at different points/rooms of the production units through air filters and multiples of such measures. The movement of personnel and materials also needs adequate restriction and control so as to minimize the chances of contamination; these aspects have also been mastered by the Indian operating executives.

Indian vaccines industry has a large internal market to be serviced. The market includes the sale of vaccines for use in the UIP of the government and the trade market. The UIP supplies need to be rationalized further with the more production-friendly endeavor to strengthen procurement of the infrastructure that benefits both the government and the industry. The vaccine trade market is expanding at faster rates, much faster than the expansion of the pharma trade sales, which are indicators of more awareness of the benefits of vaccination among the educated middle-class Indian population. This population class can also afford to buy the vaccines from the open market at whatever prices these are available, which is a situation benefitting the industry. The open-market prices are rationalized through statutory price control measures. Annually, while the majority of the 27 million new born receives vaccines through UIP, nearly over one million new born receive vaccines from the open market. Besides the benefits derived by the industry through trade sales at comparatively higher prices than the sale through UIP, a large number of others

also benefit from exports of their vaccines. This situation emanates from the fact that a multiple number of Indian vaccines are certified by the World Health Organization (WHO) to comply with the efficacy and safety standards of WHO. Further, WHO also certifies the manufacturing premises of such vaccines to be compliant with the current good manufacturing practice (c GMP) standards of the WHO. Indian manufacturers are therefore in a position of exporting a sizable quantum of their production annually.

Indian research needs to be intensified to work on the development of vaccines to protect people from the attack of multiple numbers of pathogens. There are certain diseases for which presently there are no vaccines. Certain infectious diseases previously found in specific regions are spreading elsewhere, thereby posing threats of outbreaks and therefore effective vaccines are required to be developed against those infections sooner. Although Indian efforts continue to intensify through international collaborations for vaccines development along with efforts made through local institutional efforts, such endeavor needs to be intensified with the allocation of more funds in order to make a faster global impact.

The future agenda of sustainable development goals of the world would certainly have to be framed on the health needs especially in the developing and poorly setting regions. India can play an important role in such an endeavor through the services that India can provide in the whole area of vaccines technology.

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