Science Diplomacy Case Studies

4

Indian Vaccines Industry Addressing Human Health Challenges

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Dr. Prasanta Kumar Ghosh, a master in Chemical Engineering & Chemical Technology followed by a PhD degree, from the University of Calcutta, is an eminent policy researcher and practitioner in the arena of biotechnology. He has held various key positions, while working with the Government of India; he served as the Advisor to the Department of Biotechnology, Ministry of Science & Technology. He was involved very closely with the Indian Drugs Policy and Drugs Pricing, in several facets during 1968 to 1980 and made significant contributions.

In biotechnology, his major contributions are recognized towards conceptualizing and implementing bio-safety issues related to the use of genetically modified organisms; facilitating intellectual property protection; transferring technologies from universities to industry and facilitating the creation of several centers of excellence and institutions in the country. Later, he also worked with some of the reputed firms in the Indian biotechnology sector, in developing biosimilars and subsequent commercialization. He has several scientific publications and has authored two books; he holds three US Patents on Polymeric Hydrophilic Nano-particles. He is a fellow of several learned societies including the Royal Society of Chemistry, UK; and the Institution of Engineers (India). He received several laurels including the UDYOGBONDHU award from the Chamber of Commerce & Industry.

Published in October 2019 by:

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CASE STUDY

Indian Vaccines Industry Addressing Human Health Challenges

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Introduction

A human vaccine is a pharmaceutical 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 human when pathogenic microbes invade the body. Human body has lymphocytes or white blood cells to protect from pathogens. 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 macrophages.

Vaccination of individuals is a process of imparting to acquire capabilities in them to produce both clonal B-cells and clonal T-cells that have memories to remember the pathogen or its parts; the clonal B-cells have in addition incessant capabilities of producing immunoglobulins that bind and neutralize the pathogens or their parts; further, the clonal T-cells produce cytotoxic T-lymphocytes which are capable of engulfing the pathogens or their parts for destruction. The immunoglobulin-pathogen (or its parts) complex is cleared by the macrophages continuously from the system, keeping the vaccinated individuals protected from the pathogens.

Theoretically, it is possible to conceive outlines of processes by which the immune system can be primed to acquire capabilities through vaccination to combat any pathogen or diseased/disordered cells to be eliminated from the ailing individuals. The complexities of the pathogens or of the diseased/disordered cells limit the human deployment of effective processes and therefore human endeavour continues to search for newer methods and capabilities for combating pathogens or diseased/disordered cells using immunological tools.

All the vaccines approved for human use are safe as these are rigorously tested for safety and efficacy before licensing approvals are accorded for human use. Presently there are vaccines which are widely used worldwide to protect human from mainly sixteen diseases which include vaccines for viral diseases such as chicken pox (varicella), measles, mumps, rubella, rotavirus, polio, hepatitis–A, hepatitis-B, human papilloma virus, 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]. The list of presently available vaccines in USA is more exhaustive[3]. Indeed, the beneficiaries from the developed countries including USA use more number of vaccines than those used for the beneficiaries in the developing and poor nations.

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.

Vaccines are either live-attenuated microbes or inactivated pathogens or antigens selected from portions of pathogenic microbial metabolites. Antigens which are selected from portions of pathogenic microbial metabolites can be microbial toxoids, subunits of pathogens, recombinant proteins resembling portions of the pathogenic microbes including virus–like particles (VLPs), carbohydrate of various kinds emanating from the pathogens as well as conjugates thereof.

Attenuated microbes are more immunogenic than the protein-based antigens, selected from portions of pathogenic microbial metabolites or inactivated pathogens. Antigens which are not protein-based especially certain carbohydrates, polysaccharides, oligosaccharides, small peptides, haptens and others which are not sufficiently immunogenic need to be modified by conjugation with certain proteins which 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 Haemophilus influenzae type b, Streptococcus pneumoniae and Neisseria meningitidis 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, Neisseria meningitidis outer membrane complex, and Haemophilus influenzae protein D. Immunogenicity of the covalently conjugated polysaccharides in the process gets substantially enhanced. The best one needs to be chosen, taking in to consideration 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[4] the way to develop more effective vaccines against certain infectious diseases.

The complexities of the pathogens or of the diseased/ disordered cells limit the human deployment of effective processes and therefore human endeavor continues to searching for newer methods and capabilities for combating pathogens or diseased/disordered cells using immunological tools.

The activity of several of the antigens for the development of effective vaccination is 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 less numbers of vaccine applications. The concept and the benefits of adjuvants in vaccination process have been reviewed[5] with special focus towards 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.

The theme of this paper is to take a stock of the Indian strength in terms of manufacturers of vaccines and future prospects of Indian capabilities in the global context. The paper is intended to be made useful and purposeful for easing science communication building between and among India and other countries and organizations. The strengths and opportunities of India for contributing to national and international public health arena in diverse aspects of vaccines manufacture and supply has been touched upon. Indian inadequacies and vulnerabilities in several high-tech and emerging areas of vaccines development have also been briefly discussed.

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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** like 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);** haemophilus influenzae caused by multiple types of *H. influenzae*, 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 septicaemia infection caused by a variety of *Neisseria meningitidis* (for example caused by subtypes A, C, Y, W 135 etc); live attenuated bacterial vaccines such as *Salmonella enterica* serovar Typhi Ty21a as well as naked *Salmonella typhi* Vi capsular polysaccharide based and also its conjugated antigen

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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 *Vibrio cholerae* O1 antigen in combination with a recombinant B-subunit of cholera toxin **(Cholera).**

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Among the **viral pathogens,** vaccines are being produced by Indian manufacturers from the basic stage to protect the vaccinated individuals from twelve different kinds of viruses which 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 (**Vericella)** or Chicken pox vaccine**.** Formulations of live attenuated **Chicken pox** vaccine and oral **Polio** vaccine (Sabin) are being marketed based on imported finished formulations or formulated from imported bulk as in Polio vaccines.

Inactivated (killed) viral vaccines include injectable Hepatitis A; injectable viral Influenza (whole multiple virus inactivated mass); Japanese encephalitis presented as inactivated vaccine **(JE)**; Rabies vaccine **(Rabies)** and injectable Polio (single or multiple inactivated strains). 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 are manufactured locally. A number of subunit vaccines are also being manufactured using recombinant DNA technologies which include recombinant Hepatitis B **(Hep B)** vaccine as well as viral influenza vaccine where virus-like particles (VLPs) are produced by rDNA technology in insect cells and are used as antigens for the manufacture of 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, m OPV, IPV, H1N1, JE, Rabies, Rotavirus, YFV and Vericella. 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, Meningococcal, Hep A +Hep B, , DPT + Hib, DPT +Hep B , DPT + Hib +Hep B and DPT + Hib +Hep B+ IPV.

The vaccines manufactured in India by all the manufacturing units along with the addresses of their manufacturing facilities as also the vaccines manufactured by them with trade names (where available) are presented in **Table-1**. It can be seen from

Table-1: Names and addresses of the Indian manufacturing units of vaccines along with the trade names of vaccines where available (in bold letters in brackets).

Name & address of manufacturing Unit	Vaccines licensed and manufactured with trade names(where available) in bold alphabets in brackets and remarks
PRIVATE SECTOR UNITS	
Bharat Biotech International Ltd (BBIL)[6] Genome Valley, Turka-pally (V), Shameerpet (Mandal) , Hyderabad 500 078	Hib (**Biohib**); Rabies (**Indirab**); b OPV (**Biopolio**); m OPV; Hep B (**Revac B+** and **Revac –B mcf)**); DTP (**Comvac3**); DTP+ Hep B (**Comvac4**) DTP+Hib+Hep B(**Comvac5)**; Vi capsular polysaccharide of *Salmonella typhi* Ty2. (**Typbar**); Vi capsular polysaccharide of *Salmonella typhi* Ty2 conjugated to tetanus toxoids (**Typbar TCV**) H1N1(**HNVAC**); Rotavirus vaccine (**ROTAVAC**); Inactivated JE vaccine (**JENVAC**); and DTP+Hep B+Hib (Liquid), DTP+Hib
(a) Biological[7] E. Ltd, 18/1 &3, Azamabad, Hyderabad,(AP) **(b)** Biological E.Ltd, 7- 4-114, Gaganpahad, Rajendranagar Mandal, Ranga Reddy District, (AP) **(c)** Biological E Ltd, Plot No.1, S.P. Biotechnology Park, Phase-II, Kolthur Village, Shameerpet Mandal, Rangareddy District, (A P)	Bulk toxoids of Diphtheria, Tetanus, Pertussis; Bulk JE vaccines; Other bulk vaccines Formulated and marketed vaccines are : Tetanus toxoids (**BE tt**); Toxoids of tetanus and diphtheria (**BE Td-**reduced antigen content and **DT-** adult dose); Hib-purified capsular polysaccharide covalently linked to purified tetanus toxoids (**HiBE**); DTP+ Hep B+ Hib -Liquid & Lyophilized (**Com BE Five);** JE inactivated purified virus strainSA_{14}-14-2 adsorbed on Aluminium hydroxide (**JEEV**); DTP(**TRIPVAC**); Hep B (**BEVAC-** Paediatric and Adult**)**); Measles and Rubella (**MRBEV);** Products in pipeline : Typhoid conjugate vaccine (TCV), Pneumococcal Polysaccharide Conjugate Vaccine –adsorbed (PCV), Inactivated Polio Vaccine (IPV), DTwP +r Hep B +Hib+IPV(Hexavalent) and Hepatitis A Vaccine
Biomed[8] Pvt. Ltd, C-96, B.S. Road, Industrial Ropad, Ghaziabad (UP).	b OPV ([**POLIOMYELITIS VACCINE, LIVE (ORAL) I.P. (DI-VALENT) (Bivalent/b-OPV) Type 1 & Type 3**]; Typhoid vaccines in one version is Vi capsular polysaccharide of *Salmonella typhi* (**Bio Typh**) and other version is Vi capsular polysaccharide of *Salmonella typhi* (Strain Ty2) conjugated with Tetanus toxoids (**Peda Typh**); Meningococcal polysaccharide -A & C (**Bi Meningo**); Meningococcal polysaccharide vaccine based on antigens from Group A, C, Y & W135 (**Quadri Meningo**); Hib is from capsular polysaccharide (polyribitol phosphate) covalently bonded to tetanus toxoids (**Peda Hib**); Rabies vaccine is Pitman Moore strain, multiplied in Vero cells and inactivated by ß-propiolactone (**Rabies Vaccine, Human I.P. Sure Rab);** Varicella vaccine is attenuated OKA strain of Varicella-Zooster virus multiplied in MRC-5 human diploid cell culture**.(BIO POX**)
(a) Cadila healthcare, SarkhejBawala, NH No. 8-A, Moraiya, Sanand, Ahmedabad (Gujarat). **(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).	Rabies vaccine human is Pitman Moore strain, propagated in chick embryo fibroblast cell culture and inactivated by beta-propiolactone (**Vaxi Rab N**)[9]; Influenza viral vaccine which in one version is a monovalent vaccine and is based on an inactivated (whole virion) monovalent (H1N1) 2009 influenza vaccine (**Vaxiflu-S**)[10]**;** another is a tetravalent one containing inactivated four whole virions namely H1N1, H3N2, Type B (Brisbane) and Type B (Phuket) (**VaxiFlu-4**)[11]**;** and a Typhoid vaccine based on purified Vi capsular polysaccharide of *S..typhi* conjugated with tetanus toxoids(**Zyvac-TCV**)[12].

Cadila Pharmaceuticals Ltd[13], 1389, Trasad Road, Dholks-387 810, Ahmedabad(Gujarat)	Producing H1N1 VLPs Vaccines. Production of vaccines undertaken at CPL Biologicals Pvt Ltd (CPL), Dholka; it is a joint-venture company established in 2009 by Cadila and Novavax Inc., USA. Through this collaboration, has access to VLPs technology; now producing influenza vaccines as monovalent (**CadiFlu)** and trivalent (**CadiFlu –S**) versions using VPL technology.
Chiron Behering, Plot No. 3502, Post Box No. 136, GIDC, Estate, Ankleshwar, Bharuch (Gujarat)	Rabies vaccine manufacture[14] by using Flury LEP rabies virus strain multiplied in primary chick embryo fibroblast cells using specific pathogen-free eggs. The multiplied virus is inactivated with beta-propiolactone, purified by high speed density-gradient centrifugation, formulated and freeze-dried in dosage forms (**Rabipur**).
Dano[15] Vaccine & Biological Pvt. Ltd., Hyderabad	Tetanus toxoids prepared by formalin inactivation using established methods (adsorbed on Aluminium phosphate gel)-(**DANO – TT)**
8.Green Signal BioPharma[16] Ltd., 49, Pappankuppan Village, Chennai–601201(TN)	BCG (Bacillus Calmette Guerin) vaccine is manufactured from a chosen strain of live attenuated tuberculosis bacilli *Mycobacterium Bovis*, obtained as a primary seed (Strain' Danish 1331). BCG also produced for Immunotherapy as a live freeze-dried preparation(**UROVAC - BCG**)
(a) Panacea, Malpur, Baddi, PO Bhud, Tehsil, Nalagarh, Distt. Solan, (H.P) **(b).** Pan Era Biotech, Ambala, Chandigarh highway, Lalru, District Mohali	Bulk bacterial vaccines are either sourced by Panacea from outside and formulations manufactured on loan licence or manufactured in its affiliate facilities. Pan Era Biotech is an affiliate company of Panacea Biotech for production of bulk vaccines. Licensed to manufacture DTP, HepB, DTP+Hep-B, DPT+Hep-B+Hib, IPV, Hib & H1N1, bOPV, DTP-Hib, DPT+HepB+Hib+IPV Manufacturers[17] a six antigens formulations of D, T, P, Hep B, Hib and injectable polio inactivated type-1, type-2 and type-3 (all three Vero-cell based polio bulk sourced from Bilthoven Biologicals B V, Netherlands) in the brand name (**Easy Six**).
Ranbaxy Lab, Sy. No. 16, Ekarajapura, Siddlaghatta Road, Hasigila Post, Hoskote, Bangalore-562114	Manufacturer of typhoid polysaccharide vaccines and haemophillus influenzae type b conjugated to tetanus toxoids produced by Biovel[18] Life Sciences (P) Limited, Bangalore a biotechnology company, which was acquired by Ranbaxy Laboratories Ltd; Ranbaxy has presently been acquired by Sun Pharmaceutical Industries, Mumbai
Serum Institute[19] of India, 212/2, Hadapsar, Pune-411028	Largest vaccine manufacturer in the world measured by the number of doses produced. Licensed to manufacture DTP, TT, DT, Hep-B, Hib (Vaccine & bulk), MMR, Measles, Rubella, B C G, Rabies, IPV, DTP+Hep B+Hib (Liquid +lyophilized), DTP +Hep B, DTP+Hib,H1N1, Meningococcal A conjugate (Freeze Dried), Mumps, MR, H1N1 (whole virion inactivated), Measles +Mumps, Measles+ Rubella, Influenza Vaccine seasonal, Diphtheria Vaccine (bulk), TT bulk, Pertussis bulk, Measles bulk, Mumps bulk, Rubella bulk & DT bulk & OPV vaccine, CRM 197 Bulk, DTP+ Hep B+ Hib Bulk. Marketed products include BCG Vaccine I.P.(**Tubervac**); Tetanus Vaccine (Adsorbed) I.P.(**Tetanus Vaccine**); Diphtheria and Tetanus Vaccine (Adsorbed) I.P.(**Dual Antigen**); Diphtheria, Tetanus and Pertussis Vaccine (Adsorbed) I.P.(**Triple Antigen**); Diphtheria and Tetanus Vaccine (Adsorbed) for Adults and Adolescents I.P.(**Sii Td-Vac**); Rabies Vaccine, Human I.P. -Freeze-dried (**Rabivax-S**); Measles Vaccine (Live) I.P. -Freeze-dried (**M-Vac**); Measles, Mumps and Rubella Vaccine (Live) I.P. -Freeze-dried (**Tresivac);** Measles & Rubella Vaccine (Live) I.P.**(MR-Vac);** Rubella Vaccine (Live) I.P. -Freeze-dried **(R-Vac);** Poliomyelitis Vaccine (Inactivated) I.P. (**Poliovac PFS/SD);** Rotavirus Vaccine (Live Attenuated Oral) I.P. -Freeze-Dried**(Rotasiil**); Diphtheria, Tetanus, Pertussis (Whole Cell), Hepatitis B (rDNA) and Haemophilus Type b Conjugate Vaccine (Adsorbed) I.P.**(Pentavac SD/PFS);** Diphtheria, Tetanus, Pertussis (Whole Cell) and Haemophilus Type b Conjugate Vaccine (Adsorbed) I.P.(**QUADROVAX SD/PFS)** (liquid); and Hepatitis B Vaccine (rDNA) I.P.(**GeneVac-B**);

(a) Shantha[20] Biotechnics Ltd., Survey No. 274, Athvelli Village, Medchal Mandal, Ranga Reddy, District-501401 **(b)**Shantha Biotechnics Pvt Ltd., Survey No. 354, Muppireddypalli Village, Toorpan Mandal, Medak District-502236	Licensed to manufacture bulk and formulations of tetanus toxoids, DT, DTP, DTaP Hep-B, Hib, DPT+Hep B , DTP+Hib, DTP+Hep B+Hib (Liquid), Oral cholera vaccine, IPV, Typhoid, Hep A, Pneumococcal, Yellow fever, Seasonal influenza, Rabies, Meningococcal, DTaP-IPV-Hib and Varicella. Shantha began in 1993 and in 1997 marketed rDNA based hepatitis B subunit vaccine (**Shanvac-B).** Other products marketed include a vaccine against tetanus (**ShanTT**); a bivalent oral cholera vaccine based on use of inactivated-whole-cell (**Shanchol**). Cholera vaccine was developed in collaboration with the International Vaccine Institute, Seoul, Korea. Also produces a liquid vaccine to protect against diphtheria, tetanus, pertussis, Hib and hepatitis B (**Shan 5).** Other product is inactivated polio vaccine (**ShanIPV**). Shantha obtained technology for manufacture of Typhoid vaccines from International Vaccines Institute[21], S. Korea and produced their formulation (**Shantyph**). Several other vaccines are imported and marketed. Shantha was acquired by Sanofi in July, 2009 and is presently a wholly owned subsidiary of Sanofi group.
GSK Asia Pvt. Ltd., Plot No. A-10/1, MIDC, Ambad-Pathardi Block, Nashik – 422 010	All vaccines are imported, which are either manufactured by: GSK Biologicals s.a. (GSKBsa) Belgium followed by relabeling and repacking done by GSK Asia P. Ltd, Chennai at GSK Asia Pvt. Ltd., A-10/1, M.I.D.C., Ambad, Nasik 422010; or imported vaccines manufactured by GlaxoSmithKline Biologicals SA, (GSKBSA) Rue de l'Institut, 89, B-1330, Rixensart, Belgium are marketed as such; marketing done in India by GlaxoSmithKline[22] Pharmaceuticals Limited, Dr. Annie Besant Road, Mumbai 400 030. Trademarks are owned by or licensed to the GSK group of companies. Vaccines marketed include Pneumococcal Polysachharide and Non-Typeable Haemophilus influenza vaccine and vaccines against hepatitis A, hepatitis B, DPT, DTwP-Hep b-Hib pentavalent, rotavirus, Varicella and human papilloma virus. GSKBsa vaccines are(**Havrix) 720** PFS vaccine[23] - Paediatric(Hepatitis A Virus antigen (HAV) HM 175 Strain, propagated in MRC5 human diploid cells); a DPT vaccine (**Boostrix)** [24] containing diphtheria, tetanus and Pertussis toxoids suspended in aluminium phosphate and aluminium hydroxide; paediatric purified HBV surface antigen- HBsAg (**Engerix B)** [25] vaccine, produced in recombinant *Saccharomyces cerevisiae*; pneumococcal polysaccharide conjugate vaccine **(Synflorix)**[26] derived from non-typeable *Haemophilus influenzae* where several serotypes are used and antigenic polysaccharides isolated and purified are conjugated to multiple proteins such as toxoids of T , D and protein D; **(Rotarix)**[27] , a rota virus vaccine containing live attenuated RIX-4414 strain; and (**Varilrix)**[28], a live virus vaccine for immunisation against varicella containing OKA strain propogated in MRC5 human diploid cell. GSKBSA products are an adult vaccine protecting against Hep A and Hep B and containing inactivated hepatitis A virus, multiplied in human diploid (MRC-5) cells and rDNA based antigen HBsAg of hepatitis B produced in recombinant *Saccharomyces cerevisiae* ((**Twinrix)** [29]; GSKBSA also produces a DPT vaccine (**Boostrix)** vaccine; and human papillomavirus vaccine (Types 16 and 18) presented as **(Cervarix)**[30] **.**

Sanofi Pasteur India[31] Pvt Ltd, EL-223, TTC Industrial Area MIDC, Mahape, Navi Mumbai – 400 710. (Relabeling & Stickering)	All vaccines are imported; has a relabeling and stickering facility only; Sanofi Pasteur SA Lyon, France is the manufacturer. Markets several vaccines including Hep A, Seasonal influenza, DTaP-IPV-Hib, IPV-Hib, DTaP, DTP-Hib-IPV, DPT-hep B-Hib, IPV, DPT-IPV-Hib, Typhoid,Yellow fever, Rabies and Varicella, The major marketed products are trivalent DPT vaccine (**Adacel**); hepatitis A vaccine is formaldehyde-inactivated GBM strain adsorbed on aluminium hydroxide (**Avaxim**); quadrivalent influenza vaccine ,an inactivated formulation with four influenza strains (**FluQuadri)** and another influenza vaccine based on 3 strains of influenza virus (**Vaxigrip**); an adsorbed suspension containing five antigens namely D,T and acellular component of pertussis plus a recombinant subunit HBsAg of Hep B plus inactivated poliomyelitis viruses and *Haemophilus influenzae* type b conjugate antigen forms the(**Hexaxim**); the inactivated sterile mixture of Type 1 (Mahoney strain) plus Type 2 (MEF-1 strain) plus Type 3 (Saukett strain), all multiplied on Vero cells, inactivated, purified and formulated is IPV (**Imovac Polio**); meningococcal vaccine (**Menactra**) contains N meningitidis serogroup 7 A, C, Y and W-135 capsular polysaccharide antigens individually conjugated to diphtheria toxoids and are the antigenic polysaccharides extracted from the N meningitidis cells and purified. The antigenic substances in (**Pentaxim**) are toxoids of D , T plus acellular components of pertussis toxoid along with inactivated poliomyelitis virus of type 1 (Mahoney strain) plus type 2 (MEF-1 strain) plus type 3 (Saukett strain), and polysaccharide of Haemophilus influenzae type b conjugated to the tetanus toxoids, all adsorbed on hydrated aluminium hydroxide; typhoid bacterial polysacharide-based vaccine is (**TYPHIM-Vi);** and Yellow fever vaccine (**Stamaril**) is a freeze-dried, live, attenuated Yellow fever virus1 17D-204 strain; rabies vaccine is based on the rabies virus WISTAR Rabies PM/WI 38 1503-3M strain, multiplied on human diploid cells, concentrated , inactivated (killed), purified and formulated(**IMOVAX Rabies).** Sanofi has access to Vericella vaccine manufactured by Merck Sharp & Dohme, USA (**VARIVAX**) for sale.
PUBLIC SECTOR UNITS	
Bharat Immunologicals[32] and Biologicals Corpn (BIBCOL), Village Chola, Bulandshahr, U.P	Produces oral polio vaccine (b-OPV) based on imported bulk and supplies to government. Presently, because of decline in procurement by government, company's scale of operations sharply declined. Established in 1989, went into production in 1994 based on imported bulk and assisted in elimination of Polio from India.
Haffkine[33], Acharya Donde Marg, Parle, Mumbai 400012	Producer of monovalent (m OPV) and bivalent (b OPV) oral Polio vaccine based on procured bulk material. Presently, because of decline in procurement by government, business is declining.
(a) Human Biologicals Institute[34] (HBI), Rakshapuram, Gaachibowli, Hyderabad 500032	HBI is a division of Indian Immunologicals Ltd (ILL). ILL at its facilities at Hyderabad produces DPT, DT, TT in single and multiple dosage forms. Also produces Hep- B and Rabies vaccines. Formulated DPT is marketed as (**Abhay-TAG).** TT is marketed as **(Abhay-TOX).** Based on its recombinant purified major surface antigen (H Bs Ag) of Hepatitis B, the formulation marketed is (**Elovac-B).** Rabies vaccine is an inactivated, purified and freeze-dried Rabies virus (L. Pasteur 2016/ Vero strain), multiplied in Vero cells. The bulk material is formulated and sold (**Avhayrab)**; a combination vaccine of DTwP-HepB-Hib (liquid) also sold (**Vaxtar-5**).
(b) Human Biological Institute, Kozhipannai, Pudumund, P.O. Udhagamandalam TN- 643 007	Anti rabies vaccine**(Avhayrab)**is manufactured as above in its cGMP plant at Udhagamandalam TamilNadu.
(c) Human Biol. Instt. Sy. No. 281- 284 and 321, Karakapatla Village, Mulugu Mandal, Medak Dist – 502 281, Telangana	Vero cell culture rabies vaccine **(Avhayrab**) is being manufactured as above in its plant at Medak Dist., (Telangana).

GOVERNMENT OWNED UNITS	
BCG Vaccine[35], Guindy, Chennai	The Laboratory, established in May, 1948 manufactures freeze dried BCG Vaccine; facilities transformed into c GMP compliant plant.
CRI[36], Kasauli, District Solan, HP	Licensed to manufacture DTP, TT, DT, Concentrated DTP, Yellow fever, JE, Manufactures mainly the bulk diphtheria, pertussis and tetanus vaccines, and mainly formulations of DPT and tetanus toxoids. Was supplying yellow fever vaccine from 1960 onwards; facility was later stopped; presently, the institute engaged in importing and distributing the vaccine to various authorized yellow fever centres.
Pasteur Institute of India (PII)[37], Coonor. Nilgiris District, Tamil Nadu-643103	Licensed to manufacture DTP, TT, DT & inactivated Rabies vaccine Manufactures DPT, DT and TT in cGMP facilities. PII has also established a tissue culture based anti rabies vaccine plant where presently PV-11strain of rabies adopted in BHK-21 cell lines are grown for the vaccine; after multiplication and concentration, virus is deactivated, formulated and presented in lyophilized form.
HLL Biotech Ltd[38] (HBL),. Integrated Vaccines Complex, SF No192 & 195, Thirumani Village, Chengalpattu, Tamilnadu–603001	Manufactures DTwP –HepB –Hib; Hep- B; BCG vaccine; *Haemophilus influenzae* type b (Hib); rabies ; measles and rubella (live attenuated); and Japanese Encephalitis(JE). HBL is a 100% subsidiary of HLL Lifecare Limited, Poojappura Thiruvananthapuram – 695 012 (Kerala), a GOI Enterprise under the Ministry of Health and Family Welfare. Building its cGMP compliant unit at Alapakkam Village at Chengalpattu, near Chennai, Tamil Nadu; would soon be the producer of pentavalent (DPT-HepB-Hib); BCG ; Haemophilus influenzae type b (Hib); and antiviral vaccines against rabies (inactivated); measles and rubella (live attenuated); Japanese Encephalitis (inactivated); and rDNA based hepatitis B.; would be major supplier to the Universal Immunization Programme of the Government of India

(***Note:*** **Hib**=Haemophilus influenzae type B vaccine; **b OPV**=Bivalent oral polio vaccine; **m OPV**= Monovalent oral polio vaccine; **DPT**=Triple vaccine for protection against diphtheria, pertussis and tetanus; **Hep-B**=Viral vaccine against hepatitis B; **H1N1 inactivated**=H1N1 influenza virus inactivated and given as a shot; also known as "swine flu" vaccine. **H1N1 live**=Vaccine formulation containing live virus, given as nasal drops. **JE**=Japanese encephalitis inactivated vaccine; **DT**=Combined diphtheria and tetanus bacterial vaccine; **TT**=Tetanus toxoid bacterial vaccine; **IPV**=Injectable viral polio inactivated vaccine; **RTF**=Ready to fill bulk vaccine supply. Names in bold letters within brackets under **Remarks column** for each company are the trade names of the formulations.)

Table-1 that except Glaxo and Sanofi, all other manufacturers are engaged in the production of the vaccines from the basic stage. Glaxo and Sanofi have repacking units but essentially these companies are importing and selling finished vaccines in this country.

A couple of other establishments also exist, both MNCs and Indian companies, which 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 vaccine formulations to the consumers. MSD operates its vaccines business in India through MSD[39] Pharmaceuticals Private Limited, Gurgaon and Mumbai; it markets through imports, five vaccines namely a human Papillomavirus (HPV) vaccine (**GARDASIL**)[40] which helps to protect against 4 types (Types 6, 11, 16, 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**)[41]; a live, oral

India excels in the manufacturing and marketing of old-generation and conventional vaccines. The strength Indian manufacturers have demonstrated lies in their making available these vaccines at most affordable prices while maintaining international quality standards.

The UIP of India is one of the largest public health programmes in the world and the programme targets 30 million pregnant women and about 27 million new born annually. In this country, UIP forms a strong action point towards achieving national development. In such an effort, several outside institutions and agencies have come forward to supplement the Indian government efforts. The contributions of UNICEF and Gavi among others require special mention in this context.

pentavalent vaccine that contains 5 live rotaviruses (**RotaTeq**)[42] ; to protect children against rotavirus diarrhoea; live attenuated virus vaccine indicated for prevention of herpes zoster (shingles) in middle-aged and older people (**ZOSTAVAX**)[43]; and a lyophilized preparation of live, attenuated Varicella virus vaccine using the Oka/Merck strain, to protect children against Varicella (**VARIPED**)[44]. The pneumococcal vaccine **Prevenar13** is being imported by Pfizer[68] 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 Salmonella Typhi, which is a subunit vaccine, is being imported and marketed by Cadila Newgen[45] (a sister concern of Cadila Pharmaceuticals, Ahmedabad) after being imported from Sanofi; **TYPHIM Vi** is the brand name[46] of Sanofi.

It is evident from Table-1 that India excels in the manufacturing and marketing of old-generation and conventional vaccines such as D, P, T or TT, Measles, Mumps, Rubella, Hib, Typhoid and Rabies vaccines adding a small number of modern vaccines such as Hep-B, Rotavirus, Cholera and Varicella vaccines, the strength Indian manufacturers have demonstrated lies in their making available these vaccines at most affordable prices while maintaining international quality standards. These vaccines are no more IPR protected.

Indian strength emanates from the availability of low cost highly skilled manpower, availability of multiple starting materials including plastics and other packing materials locally, pre-filled syringes at competitive prices, availability of small animals at competitive prices (which are used in quality assurance and quality control endeavour), efficiency in engineering capabilities including production system that can handle sterile operations efficiently. In addition India has developed profound capabilities in handling services facilities cost-effectively which include among others, capabilities to manage air and water showers, HVAC, 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, HEPA filters maintenance and integrity establishment, and maintenance of predetermined minimum levels of microbial load at different points/rooms of the production units through air filters, restricted movement management of personnel and materials etc. Compromising at any stage due to inadequate knowledge will jeopardize the integrity of good manufacturing practices. Indian manufacturers have also learnt to extensively document the integrity of the production system at every stage.

Indian vaccines industry is fortunate to have a large internal market to be serviced. The market includes the sale of vaccines for utilization in the Universal Immunization Program (UIP) of the government. UIP market is however tender application based and is not always certain to capture. Further, compliance of fulfillment of business terms requires maintenance of large stocks of vaccines (which have expiry dates) and therefore if companies are unable to secure a tender, the risks of disposing off such stocks become high. The Indian private market (trade market) is comparatively smaller in terms of volume of consumption of units of dosages of vaccines but is large enough in terms of prices for sale of each unit of vaccine. The trade market is expanding at faster rates, much faster than the expansion of the pharma trade sales. Because of various other reasons including WHO certification of multiple numbers of Indian vaccines as also the manufacturing premises which maintain WHO compliant standards (as discussed later), Indian manufacturers are in a position of exporting a sizable quantum of their production annually.

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Details of usage pattern of vaccines: beneficiaries through UIP and the private consumers in India

UIP

India has an extensive and dedicated Universal Immunization Programme (UIP) with a goal of increasing the coverage substantially to cater to the needs of vaccination for over 26 million new born and 30 million pregnant mothers every year. This huge program has a history.

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Government of India from the Ministry of Health & Family Welfare introduced its immunization programme in 1978 as Expanded Programme of Immunization (EPI) which gained momentum in 1985. This programme was expanded subsequently as the Universal Immunization Programme (UIP) with a goal of increasing the coverage to the beneficiary substantially by 1989-90. Over time, the program became a part of Child Survival and Safe Motherhood Programme in 1992. Later on, the immunization activities were further escalated to be an important component of National Reproductive and Child Health Programme from 1997 onwards. Presently, the UIP activities since 2005 are one of the key components of India's National Health Mission (NHM).

Presently, to successfully address the targeted beneficiaries and implement the program is indeed a surmountable national task which is being successfully implemented by the government. The vaccines used in the UIP are to protect the

beneficiaries from eleven vaccine preventable diseases namely severe forms of certain childhood tuberculosis, diphtheria, pertussis, tetanus, polio, measles, rubella, hepatitis B, pneumonia & meningitis caused by Haemophilus influenzae type b, Japanese encephalitis (in certain regions) and Rotavirus enteritis or rotaviral diarrhea. The majorly used vaccines include BCG (for TB); DPT (Diphtheria, Pertussis and Tetanus); OPV (Oral Polio Vaccine); Measles; Hepatitis B; TT (Tetanus Toxoid); JE vaccines (in selected high disease burden districts); and Hib, containing pentavalent vaccine (DPT +Hep B +Hib) in selected states[47]. All the vaccines given under the UIP are received by the beneficiaries free of cost. The beneficiaries get themselves vaccinated on fixed days at the nearest Government/Private health facility or at an immunization establishment such as the "anganwadi centers/ other identified sites" near to the locality of the recipients.

The vaccines have been embodied in the National List of Essential Drugs under the current Drugs (Prices Control) Order of the country. This ensures their sale even in the retail market at considerably 'Controlled Prices", thereby ensuring more affordable prices to the private consumers.

Indian vaccines are available at most affordable prices to the private consumers but are available free to the Indian beneficiaries through the UIP. The vaccines have been embodied in the National List of Essential Drugs[48] under the current Drugs (Prices Control) Order of the country. This ensures their sale even in the retail market at considerably 'Controlled Prices", thereby ensuring more affordable prices to the private consumers.

Free supply through UPI costs the exchequer an expenditure of substantial sum. The immunization budget was Rs 45.70 billion (US$ 762 million) in 2013 of which the cost of vaccines alone was Rs 5.106 billion (US$ 85.1 million). In the following years, the cost of vaccines only was Rs 6.328 billion (US$ 101.2 million) in 2014, Rs 14.551 billion (US$ 218.8million) in 2015 and Rs 17.699 billion (US$ 261.0 million) in 2016. The projected budget for the whole of 2017 UIP was estimated at Rs 94.51 billion (US$ 1.454 billion) .These figures[49] provide a flavour of the huge extent of expenditure incurred by the Indian government for its UIP.

A fully immunized child in the age of 12 months receives vaccine doses of one BCG, four Hep B, four oral polio doses, three doses of DPT, and three doses of Hib and one dose of measles. Only in selected areas, children also get a dose of JE. The vaccination schedule[50] can be seen at **Table-2**.

It would be interesting to know how much it costs the exchequer on each immunized child in terms of costs of vaccines only at current cost. In a recent study[51] based on a hierarchically graded and ordered study of the public health facilities carried out from 24 districts across seven Indian states for the fiscal year 2013-2014 and projecting the cost data at 2017 prices using unit price per dose, average wastage percentage of each category of

Table 2: Indian UIP Vaccination schedule

Vaccination schedule as per the plan of the Government of India under the UIP[50]				
Name of the Vaccine & numbers required	**When scheduled to apply**	**Dose quantity**	**Dosing route**	**Site of administration of the dose**
For Pregnant Women				
TT-1	Early in pregnancy	0.5 ml	Intra-muscular	Upper Arm
TT-2	Four weeks after TT-1*	0.5 ml	Intra-muscular	Upper Arm
TT- Booster dose	If received 2 TT doses in a pregnancy within the last 3 years	0.5 ml	Intra-muscular	Upper Arm
For Infants				
BCG	At birth or as early as possible till one year of age	0.1ml (0.05ml until 1 month of age)	Intra-dermal	Left Upper Arm
Hepatitis B Birth dose	At birth or as early as possible within 24 hours	0.5 ml	Intra-muscular	Antero-lateral side of mid-thigh
OPV Zero dose	At birth or as early as possible within the first 15 days	2 drops	Oral	Oral
OPV 1,2 & 3	At 6 weeks, 10 weeks & 14 weeks	2 drops	Oral	Oral
DPT1,2 & 3		0.5 ml	Intra-muscular	Antero-lateral side of mid-thigh
Hepatitis B 1,2 & 3		0.5 ml	Intra-muscular	Antero-lateral side of mid-thigh
HiB containing Pentavalent 1, 2 & 3**		0.5 ml	Intra-muscular	Antero-lateral side of mid-thigh
Measles 1st dose	9 completed months-12 months. (give up to 5 years if not received at 9-12 months age)	0.5 ml	Sub-cutaneous	Right upper Arm
JE 1st dose***	9 completed months	0.5 ml	Sub-cutaneous	Left Upper Arm
For Children and Adolescents				
DPT 1st booster	16-24 months	0.5 ml	Intra-muscular	Antero-lateral side of mid-thigh
OPV Booster	16-24 months	2 drops	Oral	Oral
Measles 2nd dose	16-24 Months	0.5 ml	Sub-cutaneous	Right upper Arm
JE 2nd dose	16-24 months with DPT/ OPV booster	0.5 ml	Sub-cutaneous	Left Upper Arm
DPT 2nd Booster	5-6 years	0.5 ml.	Intra-muscular	Upper Arm
TT	10 years & 16 years	0.5 ml	Intra-muscular	Upper Arm

Note: *TT-2 and Booster doses injected before 36 weeks of pregnancy; must be taken even if more than 36 weeks have passed. If a woman in labour did not receive TT previously, a dose has to be administered during labour.
**In Indian States where pentavalent DPT-HepB -Hib introduced, this will replace DPT 1, 2 & 3 and Hep B 1, 2 &3. The Hep B birth dose and DPT booster doses will continue.
*** JE Vaccine (SA 14-14-2) given in select endemic districts.

vaccines and USD to Indian rupees exchange rate of US$ 1.00 equal to Rs 64.00, the national estimated cost per child at 2017 prices was calculated at US$ 31.67 for a pentavalent 3 vaccination shots (containing DPT along with Hib and Hep B at 12 months age. Taking into consideration the schedule of vaccination as above in **Table-2** and using the data on unit price per dose of vaccines and the average wastage percentage of various forms from the work of Chatterjee[51] et al (average wastage ranged from 27per cent to 56 per cent depending on different types of vaccines), the vaccines cost per child at 2017 prices was worked out to US$ 32.887 for a fully immunized child of 2 years age where the child receives in addition to the vaccine dosages up to 12 months, one booster dose of DPT and one OPV dose and the second Measles dose. Cost of JE not considered as this vaccine is used in selected areas only. The Dollar to Rupee exchange rate correction takes the cost to US$ 35.42 in 2019 (February). On the basis of the demographic data [52] of 2017 it was found that nearly 23.4 million children become competent for vaccination annually during the period. This number is anticipated to rise to 24.83 million in 2019. The NFHS 2015-2016 data [53] shows that the full immunization of children was up to 62 per cent of the recipient children only. Assuming similar immunization coverage in 2019 and providing adjustments for the increase in the number of children competent for coverage during the year, the exchequer cost of vaccines only during the year 2019 would be about US$ 545.3 million. If the coverage would rise to 90 per cent as was the intent of the government [54], this cost would rise to US$ 791.6 million or over Rs 5540 crores! Interestingly, the average wastage of various vaccines worked out and reported by the authors [51] were 56 per cent for BCG, 37 per cent for measles, 36 per cent for OPV, 32 per cent for DPT, 30 per cent for recombinant hepatitis B and 27 per cent for pentavalent vaccine containing Hib. Such colossal wastes need to be done away with when there is so much resource constraint.

India has in the meantime began transitioning from Gavi support and is finding its own fund for this critically important program for building a more healthy population with increase in its coverage of more eligible children and to also induct additional vaccines in its UIP.

The UIP of India is one of the largest public health programmes in the world and the programme targets 30 million pregnant women and 27 million new born annually [55]. While the Indian UIP has largely contributed to reduction of vaccine preventable mortality rate under the age of 5 year in the country, the success of the program is being attributed to the deployment of the necessary funds for the purpose. While the national exchequer has been contributing to the major chunk of the money, Indian government had also explored the possibilities of outsourcing of funding for this huge project.

Development of a nation begins with the child and the welfare measures include, among others, providing good health so as to lead to all aspects of development of a nation in

economic, social and political arena. In this country, UIP forms a strong action point towards achieving national development. In such an effort, several outside institutions and agencies have come forward to supplement the Indian government efforts. The contributions of UNICEF and Gavi among others require special mention in this context.

UNICEF had been working closely with the Government of India since 1949 and had provided the country with the strain and technology for the basic production of Potassium Penicillin G to Hindustan Antibiotics Ltd [56], Pune, a public sector undertaking, based on which India produced the drug for the first time in 1954. UNICEF has been working closely with Indian government supporting its multiple priority areas of action plan that ensures that Indian children get best start in health after birth, thrive and develop to their full potential as they grow. These include enhanced immunization[57] coverage for the eligible children. The role of UNICEF in UIP is to assist in routine immunization and supplementary immunization, cold chain management, capacity building and evaluation of action plans in UIP, coordination with India-base partners for UIP and implementation through Immunization Action Group of UIP. UNICEF is also active to support policy development for enhanced immunization through UIP. The efforts of UNICEF are supported through contributions and efforts from multiple donors and well wishers which include various governments; the corporate partners; USAID; Centre for Disease Control, USA; Bill & Melinda Gates Foundation; Rotary International; Gavi; several celebrities; many Civil Society Organizations; and many others.

The Indian companies have been concentrating especially on the supply of conventional vaccines and recombinant DNA based hepatitis B vaccines.

The government of India entered into a partnership alliance with Gavi[58] (formerly known as the Global Alliance for Vaccines and Immunization) an international organization which is based in Geneva, Switzerland. Gavi brings together public and private sector establishments with the goal of creating equal access to vaccines for children. Gavi presently has vaccine support programs in 73 countries including India. The supplies of vaccines paid for by Gavi are negotiated through UNICEF. Presently, 60 per cent of the vaccines procured by Gavi are provided by the Indian manufacturers of vaccines. Gavi and the Indian government came into a partnership in the year 2000. Gavi has been supporting Indian UIP since 2002. Up to 2015, Gavi had provided [59] more than USD 240 million to help India in its UIP and has committed [60] to provide another US$ 500 million during 2016-2021 periods. India has in the meantime began transitioning from Gavi support and is finding its own fund for this critically important program for building a more healthy population with increase in its coverage of more eligible children and to also induct additional vaccines in its UIP.

Indian vaccines have substantially been procured by the UNICEF over the years. Other international procurement agencies such as Gavi and Bill & Melinda Gates Foundation etc have also been procuring Indian vaccines in sizable quantities. Besides, there have also been procurements by multiple private companies from around the glove to procure certain quantities of Indian vaccines for sale in those countries in trade.

Trade sale

Trade sale of vaccines in the Indian market is smaller when compared with the doses of vaccines consumed in UIP. However, the profitability through trade sale is more than what is made through UIP sale. However, the private Indian trade sale of vaccines is dominated by the MNCs namely GSK, Sanofi, Merck and Pfizer. GSK vaccines include a wide range of vaccines for the prevention of viral diseases such as hepatitis A, hepatitis B, chickenpox, rotavirus and cervical cancer caused by papilloma virus; among the bacterial diseases, the GSK vaccines include those against diphtheria, pertussis, tetanus, H. influenzae type b and streptococcus pneumonia. Besides supply of vaccines through its acquired company Shantha Biotechniques Hyderabad, the own vaccines of Sanofi include viral vaccines to prevent against hepatitis A, hepatitis B, viral Influenza, Polio and Yellow Fever. They also market antibacterial vaccines to prevent diseases against tetanus, diphtheria, pertussis, meningococcal (Groups A, C, Y and W-135) polysaccharide conjugate vaccine conjugated to diphtheria toxoids and haemophilus influenza type B conjugate vaccine. Merck import specialized IPR protected vaccines which include Gardasil (to protect against 4 types (Types 6, 11, 16, 18) of HPV to help prevent cervical cancer), Rota Teq (to protect against multiple rotavirus diseases and is a live, oral pentavalent vaccine that contains 5 live rotaviruses), Zostavax (live attenuated virus vaccine indicated for prevention of herpes zoster (shingles) in middle-aged and older people, Pneumovax 23 (a vaccine indicated for active immunization against 23 serotypes of pneumococcal bacteria to protect from pneumonia) and Variped (a lyophilized preparation of live, attenuated Varicella virus vaccine using the Oka/Merck strain, to protect children against Varicella virus. Pfizer[68] concentrates on the import and sale of vaccines to protect the recipient from pneumococcal and meningococcal diseases.

India stands on the top and that among the nine Indian companies, Serum Institute of India have the maximum number of such vaccines for supply. Indeed, because of the competence established through the rigors of evaluation by the WHO authorities, Indian vaccines have been well accepted by the international agencies.

All companies including the MNCs as well as the Indian private companies are active for maximizing their trade sale. However, the MNCs are dominating in trade sale compared to all other sectors. Even though the trade selling prices of vaccines are subjected to price control, there is adequate margin provided in the fixation of the maximum selling prices. Consequently, the trade market is attractive to all the suppliers of vaccines. From the past available data from multiple sources, the trade sales of vaccines has been estimated by the author to be about Rs 32900 million or US$ 470 million by the end of 2019. The trade sale percentage captured by the MNCs is estimated at 55 per cent while the remaining portion of 45 per cent is captured by the Indian private companies and others. Among the MNCs, the GSK share is the maximum, estimated

at about 35 per cent of the total followed by Sanofi, Pfizer and Merck. Both GSK and Sanofi are engaged in the supply of a wide range of paediatric vaccines including the conventional as well as certain specialized vaccines while Pfizer and Merck have specialized only in the supply of high tech vaccines to treat specific diseases as mentioned above. The turnover of meningococcal pneumonia by the end of 2019 by Pfizer is estimated to be over Rs 214 crores (US$ 30.6 million). The Indian companies have been concentrating especially on the supply of conventional vaccines and recombinant DNA based hepatitis B vaccines. The turnover of these companies by the end of 2019 is estimated at Rs 14800 million.

Exports of Indian Vaccines

Indian vaccines have substantially been procured by the UNICEF over the years. Other international procurement agencies such as Gavi and Bill & Melinda Gates Foundation etc have also been procuring Indian vaccines in sizable quantities. Besides, there have also been procurements by multiple private companies from around the globe of certain quantities of Indian vaccines for sale in those countries in trade.

The confidence built in the procurement of Indian vaccines by the international agencies emanates from the certification of the premises and the vaccines manufactured there from by the World Health Organization (WHO).

With the aim of providing universal health coverage to billions of people for better health and wellbeing, the World Health Organization (WHO) strives[61] to endeavor focusing on access to essential medicines and health products especially to the vulnerable, tackle health emergencies especially in fragile settings, promote programs on elimination of antimicrobial resistance and eradication of high-impact communicable diseases. In another significant endeavor, WHO caters and renders services to UNICEF and other UN agencies by evaluating the manufacturing establishments engaged in the production of vaccines including candidate vaccines through sound scientific and technological procedures so as to ease the procurement of quality vaccines by such procuring agencies. The design, purpose, intention and aim of rendering such services of WHO are to ensure that safe and effective vaccines that meet the potency, thermostability, presentation, labeling and shipping conditions are met and that the efficacy data of the vaccines are suitable, appropriate and fit for the target beneficiaries. The organization works with the relevant National Regulatory Authority (NRA) that is accountable and is obligated for the regulatory oversight of the vaccine. NRA has to be "functional" as per the indicators established by

In India, vaccines manufacturing companies have come up by utilizing cheap labor, chipper skills, and alternate cheaper raw materials as also cheaper packaging materials; these companies operate at lower margins to serve initially the local needs at affordable prices as the purchasing power is lower.

the WHO. The **Table-3** [62], prepared based on the WHO List of Prequalified Vaccines, depicts the country wise names of the companies, the vaccines manufactured by them and the facilities qualifying for the manufacture of quality vaccines in accordance with the WHO certification criteria.

It can be seen from the information in **Table-3** that among all countries competent for supply of quality vaccines for purchase by the international agencies as per the WHO criteria, India stands on the top and that among the nine Indian companies, Serum Institute of India have the maximum number of such vaccines for supply.

Indeed, because of the competence established through the rigours of evaluation by the WHO authorities, Indian vaccines have been well accepted by the international agencies.

The exports of vaccines from India at the end of 2019 is estimated at US$ 935 million, of which procurement by

Table-3: WHO Prequalified Vaccines available from Manufacturers[62].

AUSTRALIA	
Name of company	**WHO prequalified vaccines & commercial names in bold fonts**
Seqirus Ltd(A CSL Company, UK)	Influenza pandemicH1N1(**Panvax)**
BELGIUM	
Glaxo Smith Kline Biologicals SA, (operates as a subsidiary of GlaxoSmithKline, UK)	Hep A(**Harvix 1440 Adult** and **Harvix 720**));Hep B(**Engerix**); m OPV(**Polio Sabin Mono T 1** & **Polio Sabin Mono Two** & **Polio Sabin Mono Three**), b OPV (**Polio Sabin One and Three**); t OPV (**Polio Sabin**); Polio (inactivated)-(**Poliorix**); MMR(**Priorix**); Rotavirus (**Rotarix**); Human Papilloma (Bivalent)-**(Cervarix**); Pneumococcal -conjugate (**Synflox**);DTPa(**Boostrix**); Meningococcal conjugate vaccine-serotypeACYW-135(**Menveo**);
BRAZIL	
BioManguinhos/Fiocruz	Yellow fever (**Yellow Fever)**
CANADA	
Sanofi Pasteur Limited (a subsidiary of Sanofi, France)	DPTa (**Adacel**)
Seqirus Vaccines Ltd, Canada (A CSL Company,UK)	Influenza seasonal (**AGRIFLU)**
CHINA	
Chengdu Institute of Biological Products	JE (**Japanese Encephalitis Vaccine Live**)
Hualan Biological Bacterin Co. Ltd.	Influenza seasonal **Influenza Vaccine (split viron, inactivated**)
Sinovac Biotech Co Ltd.	Hepatitis AVaccine-inactivated (**HEALIVE**)
Beijing Bio-Institute Biological Products Co. Ltd., Beijing	b OPV (**Poliomyelitis Vaccine (live, oral attenuated. Human Diploid Cell) type 1 and 3)**
CUBA	
Centre for Genetic Engineering and Biotechnology	Hep B (**Heberbiovac HB**); Hib (**Quimi-Hib**)

DENMARK	
A J Vccines AS, Copenhagen	BCG (**BCG Vaccine SSI);** IPV **(IPV Vaccine SSI**)
FRANCE	
Sanofi Pasteur SA, Lyon (a subsidiary of Sanofi, France)	DPTa-Hep B-Hib-Polio (Inactivated) (**Hexaxim**); Meningococcal A+C(**POLYSACCHARIDE MENINGOCOCCAL A+C VACCINE**); m OPV(**ORAL MONOVALENT TYPE 1 POLIOMYELITIS VACCINE** and **ORAL MONOVALENT TYPE 2 POLIOMYELITIS VACCINE (m OPV 2)** and **ORAL MONOVALENT TYPE 3 POLIOMYELITIS VACCINE**); b OPV-Type 1&3 (No commercial name) Influenza pandemic H1N1(**Panenza**); Influenza seasonal (**Vaxigrip**); Typhoid0Polysaccharide (**Typhim Vi**);
GERMANY	
Seqirus GmbH, Germany (A CSL Company, UK)	Influenza pandemicH1N1 (**Celtura)**)
INDIA	
Biological E Ltd.	TT(**BEtt)**; DTwP-Hep B-Hib (**ComBEFive**); JE(**JEEV)**
Haffkine Bio Pharmaceutical Corpn., Mumbai	m OPV (**Monovalent type 1 Oral Poliomyelitis Vaccine IP**), b OPV (**Bivalent type 1&3OralPoliomyellitis Vaccine) I P**), t OPV (**Polioviral Vaccine**)
Serum Institute of India	TT (**Tetanus Toxoid Vaccine Adsorbed**), DT(**Diphtheria and Tetanus Vaccine Adsorbed**), Td(**Diphtheria and Tetanus Adsorbed for Adults and Adolescents**), DTwP (**Diphtheria -Tetanus-Pertussis Vaccine Adsorbed**, DTwP-Hep B (**Diphtheria – Tetanus-Pertussis and Hepatitis B Vaccine Adsorbed)**; DTwP-Hib, Hep B (**Hepatitis B Vaccine (r DNA) (Adult) and (Paediatric))**; BCG (**BCG Vaccine**); Hib (Haemophillus influenza type b Conjugate Vaccine), Measles (**Measles Vaccine ,Live, Attenuated**), Rubella (**Rubella Vaccine , Live, Attenuated**), MR (**Measles and Rubella Vaccine, Live, Attenuated**), MMR (**Measles , Mumps and Rubella Vaccine, Live, Attenuated**), Meningococcal conjugate vaccine-serotype A(**Meningococcal A Conjugate MenAfrVac**), H1N1 Pandemic Influenza (**NASOVAC Influenza Vaccine, Live Attenuated(Human**); Influenza seasonal (**Nasovac-S Influenza Vaccine, Live, Attenuated (Human)**; b OPV (**Poliomyelitis Vaccine (Oral), Bivalent types 1 and 3**); t OPV (**BIOPOLIO**); IPV (**Poliomyelitis Vaccine(Inactivated);** DTwP-Hep B-Hib (**Diphtheria, Tetanus, Pertussis, Hepatitis B and Haemophilus Influenza type b Conjugate Vaccine**); Rabies (**Rabies Vaccine Inactivated**); Rotavirus(**ROTASIL**)
Panacea Biotech	DTwP-Hep B-Hib (**Easyfive-TT);** b OPV (**Bivalent OPV Type 1 and 3PoliomyelitisVaccine, Live (Oral)**)
Chiron Behring Vaccines Pvt Ltd.	Rabies (**Rabipur).**
Shantha Biotechnica Pvt Ltd., (acquired by Sanofi , France)	TT (**Shan TT);** DPTw-Hep B-Hib **(Shan-5**); Cholera inactivated oral (**Shanchol);** IPV(**Shan IPV**); Typhoid conjugate (**Typbar-TCV**)
Bharat Biotech International Ltd., Hyderabad	tOPV(**BIOPOLIO**); b OPV (**BIOPOLIO B1/3);** Rotavirus**(Rotavac)**
Cadila Health Care Ltd., Ahmedabad	Rabies Vaccine lyophilized active (**VaxiRab N**)
Green Signal BioPharma Ltd.	BCG (**BCG vaccine(Freeze Dried)-Intradermal**);

INDONESIA	
PT Bio Farma (Persero)	TT (**TT Vaccine**); DT (**Adsorbed DT Vaccine**); DTwP (**DPT Vaccine**); Hep B (**Hepatitis B Vaccine Recombinant)**; DTwP-Hep B-Hib (**Pentabio**); Measles(**Measles Vaccine**); m OPV(**Monovalent Oral Poliomyelitis Vaccine**); b OPV (**Bivalent Oral Polio Vaccine Type 1&3**); t OPV (**Oral Polio**); and Yellow fever (**Yellow Fever**).
ITALY	
Novartis Vaccines and Diagnostics S. r. l.	Hib (**Vaxen HIB**),
Novartis Vaccines and Diagnostics S.r.l (a subsidiary of Novartis AG., Switzerland)	Hib (**Vaxem HIB**);
Seqirus Vaccines Ltd (A CSL Company, UK)	Influenza pandemicH1N1 (**Focetria**)
JAPAN	
Japan BCG Laboratory	BCG (**BCG Freeze Dried Glutamate Vaccine**)
THE NETHERLANDS	
Bilthoven Biologicals B.V., (acquired by Serum Institute of India)	IPV(**Poliomyelitis vaccine multidose, suspension for injection** and **Poliomyelitis vaccine**)
Abbott BiologicalsB V(operates as a subsidiary of Abbott Laboratories, USA)	Influenza seasonal **(Serinflu**)
REPUBLIC OF KOREA	
Green Cross Corp.,(Presently known as GC Pharma)	Influenza pandemic H1N1 (**Green Flu S**); Influenza seasonal-Inactivated(H1N1 +H3N2+antigen Type B)- (**GC FLU inj** and **GC FLU Multi inj**); and Inactivated quadrivalent vaccine (**GC FLU Quadrivalent)**
LG Chem Ltd.	DTwP-Hep B-Hib(**Eupenta**)
Janssen Vaccines Corp. (formerly, Berna Biotech Korea Corp)	DTwP-Hep B-Hib (**Quinvaxem)**
IL-YANG Pharmaceutical Co Ltd.	Influenza seasonal (**IL-YANG FLU Vaccine INJ.)**
Eu Biologics Co Ltd.	Cholera inactivated oral (**Euvichol** and **Eucol-Plus))**
RUSSIA	
Federal State Budgetary Scientific Institute	YE (No brand name)
SENEGAL	
Institut Pasteur de Dakar	YE (**Stabilized Yellow Fever Vaccine**)
SWEDEN	
Valneva Sweden AB, Sweden (a subsidiary of Valneva SE., Sweden)	Cholera inactivated oral (**Ducoral)**
THAILAND	
GPO-MBP Co Ltd. (Government Pharmaceutical Organization-Merieuk Biological Products Co.,Ltd.)	JE (**IMOJEV MD**)

UK	
Seqirus Vaccines Ltd (A CSL Company, UK)	Influenza seasonal & pandemicH1N1 (**Fluvirin** and **Fluvirin-H1N1**)
USA	
Sanofi Pasteur (an affiliate of Sanofi, France)	Meningococcal ACYW-135 conjugate vaccine (**Menveo** and **Menactra)**); Influenza seasonal including quadrivalent (**Fluzone** and **Fluzone Quadrivalent**); Influenza pandemic H1N1 (**Influenza A (H1N1) 2009 monovalent vaccine**);
Merck Vaccines, USA (an affiliate of Merck Co, USA)	Human Papillomavirus (quadrivalent and ninelvalent) vaccine **(Gardasil** and **Gardasi 9**); Varicella (**Varivax**); Rotavirus (**Rotateg**)
MedImmune, Maryland	Influenza pandemicH1N1 (**Influenza A (H1N1) 2009 monovalent**)
Pfizer	MeningococcalACYW-135-conjugate vaccine (**Nimenrix**); Pneumococcal (conjugate)-(**Prevenar 13**)

It can be seen from the information in **Table-3** above that among all countries competent for supply of quality vaccines for purchase by the international agencies as per the WHO criteria, India stands on the top and that among the nine companies, Serum Institute of India have the maximum number of such vaccines for supply.

UNICEF alone would be about US$800 million, up[63] from US$ 515 million in 2014.

Estimated Turnover of Indian vaccines in 2019

One analysis indicated [64] that during the recent past, the Indian vaccines industry grew to approximately US$ 1 billion in 2015 with a CAGR of 25 per cent between 2011 and 2015; and the exports constituted a dominant 69 per cent 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 per cent of the country's production in physical terms representing only about 28 per cent in value terms is 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 about 24 per cent in terms of turnover but about 21 per cent in terms of physical production quantities while the exports turnover is estimated at US$ 935.00 million which is about 48 per cent of the total turnover of the vaccines industry.

Comparison of Indian Vaccines Industry with the Global Players:

As has been stated earlier, the Indian vaccines industry is anticipated to reach a turnover of US$ 1.95 billion by the end of 2019.

The global vaccines market at prices of 2016 was estimated [65] at US$ 28.0 billion and was projected to grow to US$ 48.0

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 a substitution can start in advance taking in to consideration the expiry date of the IPR and becoming ready for market-introduction soon after the expiration of the patent.

billion by 2025. In another estimate [66], market was considered to grow from $33.70 billion in 2018 to about $57.50 billion by 2025, registering a CAGR of 7.9 per cent. In yet another estimate[67], the market turnover value was considered to US$ 65 billion by 2024, attributing the sharp rise in growth of vaccines industry due to rising support of the industry from the governments, invention of innovative technologies, increasing awareness towards benefits from vaccination, prevalence of infectious diseases in developing countries where the purchasing power is rising and further, the development of therapeutic vaccines against certain chronic diseases including cancer. 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 global turnover of vaccines work out to about US$ 35.2 billion. Indian industry's turnover works out to about 5.5 per cent of the global vaccines market.

The global market serviced by the key players include[68] Glaxo Smith Kline, UK and the top branded vaccines of the company are **Ambirix, Boostrix, Menjugate, Rabipur**, and **Varilix**.; Merck &Co, USA and the top-selling vaccines manufactured by the company are **GARDASIL, GARDASIL-9, RECOMBIVAX HB, RotaTeq, VARIVAX**, and **ZOSTAVAX;** Sanofi, France and the top-selling vaccines manufactured by the company are **Act-HIB, Adacel-Polio, Pediacel, ViVAXIM, Quadracel,** and **YF-VAX**; Pfizer, USA and the brands of vaccines owned by the company include **Prevnar 13, NeisVac-C, Mencevax, Nimenrix,** and **Trumenba**; Novamax, USA and list of vaccines manufactured by the company or in the pipeline are **RSV F, NanoFlu,** and **ResVa**; Emergent Biosolutions, USA and the list of vaccines manufactured include **BioThrax, ACAM2000, FLU-IGIV,** and **UNI-FLU**; CSL, Australia and the top-selling vaccines available from this company are **Fluvax, Panvax, Pneumovax, Tet-Tox,** and **Varivax**; Inovia Pharmaceuticals,USA and the vaccines manufactured by this company include **PENNVAX-B, VGX-3400,** and **INO-5401**; Bavarian Nardoc, Denmark and their list of top-selling vaccines include **IMVAMUNE, MVA-BN Filo, MVA-BN HPV,** and **MBA-BN RSV**; and finally, Mitsubishi Tanabe, Japan which specializes in the manufacture of **TETRABIK, JEBIK V, Mearubik**, and **Varicella vaccine**. The revenues generated worldwide by the top 10 global pharmaceutical companies individually[69] on vaccines sale in 2017, and a projection as has been published for each of these companies for the year 2024 are as under in **Table-4**.

It is apparent from the above information that the in 2017, the above ten companies were holding a share of nearly in excess of 85-88 per cent in value terms of the global vaccines market.

Table 4: Ten major global producers of vaccines & their revenues-2017 and 2024 (estd).

Serial No.	Name of Company	Revenue from sale of Vaccine: 2017 (USD million)	Projected revenue from sale of Vaccines :2024 (USD million)
1	Glaxo Smith Kline, UK	6652	10742
2	Merck & Co., USA	6546	9398
3	Sanofi, France	5764	8130
4	Pfizer, USA	6001	7256
5	Novamax, USA	Not available	2650
6	Emergent Biosolutions, USA	287	1119
7	CSL, Australia	835	1068
8	Inovio Pharmaceuticals Inc. , USA	Not available	671
9	Bavarian Nordic, Denmark	8	544
10	Mitsubishi Tanabe, Japan	407	501
Total		**26500**	**42079**

Presently, in India there are 19 vaccine producing companies with 24 vaccine manufacturing establishments (**Table-1**). Most of the vaccines produced by these companies are the conventional vaccines and some more including the recombinant DNA based hepatitis B vaccines and a couple of conjugate vaccines, where the IPR protection period is already exhausted. These companies are also operating profitably. Smaller companies with scientific and technological content get established in environments where the base line of scientific and technological development as also the scientific institutions and infrastructure are comparatively well-established and further, the government allocates considerable amounts of funds and encourages local development of technologies. Indian environment particularly provides enabling conditions in the current setting of societal and political structure for the comparatively smaller units to come up with in-house R&D as besides adequately meeting the congenial environment of setting up of such smaller industries, there also are a large number of people who are eager to receive and consume the produce. In India, vaccines manufacturing companies have come up by utilizing cheap labor, cheaper skills, and alternate cheaper raw materials as also cheaper packaging materials; these companies operate at lower margins to serve initially the local needs at affordable prices as the purchasing power is lower. It is interesting and worthwhile to surmise that such units survive by providing low cost but quality vaccines and serve a national cause of healthcare with competence. The contributions of certain international agencies like the WHO and UNICEF, and certain benevolent private organizations like Gavi, Bill & Melinda Gates Foundation etc in the strengthening of Indian vaccines industry are also significant.

The global majors including the MNCs produce the entire

There is an urgent need for the Indian companies to develop certain vaccines on a priority basis which include development of pneumococcal vaccine, vaccines against dengue fever, human papilloma virus vaccine, vaccines for prevention of genital warts and herpes (shingles), malaria vaccine and a few others against certain viral diseases such as Chikungunya, Zika etc.

range of conventional vaccines, many with additional product qualities imparted in to them. Additional product qualities include properties such as increased efficacy and/or reduced toxicity or both. Better product quality also includes novelty in the presentation which offers ease in applications. The companies sell their produce preferably in markets where the prices fetched by them are considerably higher, which happens due to various reasons .These aspects are beyond the scope of discussion in this paper. The companies also produce certain specialized vaccines emanating from their own research, such as the pneumococcal conjugate vaccine of Pfizer protecting against 13 different types of pneumococcal bacteria (**Prevnar 13);** the HPV vaccine (**GARDASIL and GARDASIL-9**) of Merck& Co used to protect women from anal or cervical or vaginal cancers or genital warts caused by certain types of HPV; the live attenuated virus vaccine (**ZOSTAVAX**) indicated for prevention of herpes zoster (shingles) in individuals 50 years or above sold by Merck & Co; the vaccine (**BioThrax**) indicated for the active immunization for the prevention of disease caused by *Bacillus anthracis* and marketed by Emergent BioSolutions; the non-replicating smallpox vaccine (**IMVAMUNE)** and the proprietary vaccine platform technology based on Vaccinia Ankara - Bavarian Nordic (**MVA-BN Filo, MVA-BN HPV,** and **MBA-BN RSV**) of Bavarian Nordic, which are not being produced or marketed in India. These are proprietary products of individual companies which enable them to fetch much higher prices. The global vaccine majors derive higher turnover and higher returns on their vaccines because of novelty in their products. Increased novelty arises from intensive R&D resulting in not only innovations in existing products but also developing new products for the first time in the world.

Research and Development in India for vaccines innovation and invention:

Several kinds of vaccines technology are being researched upon the world over. 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 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 the stimulating it to develop acquired immunity. These kinds of 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 utilized and used in clinical research include development of conventional inactivated (killed), 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 which include 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. Combinations of several of these are also areas of active research to broad-band the immunization process.

Development of a safe and successful dengue vaccine is complicated for various reasons especially because the adaptive immune responses to DENV upon subsequent infection after vaccination can be both protective and pathogenic and the exact mechanism and contours for these features are unknown.

Indian research is also focused on developing the vaccines which 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 a substitution can start in advance taking in to 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 since highly skilled modern biologists including microbiologists, chemists, 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 on 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. Among other reasons, the MNCs are in a position of capture a major portion of DPT vaccines market globally is because of their having

acellular pertussis vaccine in their product portfolio. 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 the Indian companies to develop certain vaccines on a priority basis which include development of pneumococcal vaccine, vaccines against dengue fever, human papilloma virus vaccine, vaccines for prevention of genital warts and herpes (shingles), malaria vaccine and a few others against certain viral diseases such as Chikungunya, Zika etc. In **Table-5**, the names of the diseases against which development of vaccines are emerging issues have been listed.

The following is a brief on certain extremely important vaccines and the current Indian developments on these.

Table 5: Names of the vaccines to be developed by the Indian companies to address emerging issues in diseases.

1.	Vaccines against Pneumonia from Streptococcus pneumonia:
2.	Dengue virus vaccine
3.	Human Papilloma virus (HPV) vaccine
4.	Chicken Pox and Herpes Zoster vaccine:
5.	Malaria vaccine:
6.	HIV vaccine
7.	TUBERCULOSIS vaccine
8.	RSV vaccine
9.	Enterotoxigenic Escherichia coli (ETEC) vaccine
10.	SHIGELLA disease vaccine
11.	NOROVIRUS disease vaccine
12.	ZIKA virus disease vaccine
13.	CHIKUNGUNYA virus disease vaccine
14.	EBOLA virus disease vaccine

Streptococcus pneumonia vaccine

Indian efforts are fragmented on the development of certain vaccines only. The utility of *Streptococcus pneumonia* vaccine for protecting children of such age group is considered very high. According to WHO estimate[70] in 2000 more than 50 per cent of pneumonia deaths among children aged 1 month to 5 years were due to infection from Hib and pneumococcal infection together. Presently, vaccines against Hib are being deployed in UIP but not any for infection from pneumococcal bacteria. The need for such a Pneumococcal vaccine (PCV) for inclusion in UIP

is inevitable. In India, Serum Institute of India is working [71] on the development of a PCV (10-valent) vaccine in collaboration with PATH[72]. Two other Indian companies namely Tergene Biotech[73], Hyderabad, and Biological[74] E Ltd, Hyderabad are also working to develop multivalent Pneumococcus vaccines.

Dengue Vaccine

Dengue fever is mosquito-borne viral disease transmitted by the *Aedes aegypti* mosquito vector. The disease is caused by four antigenically related dengue viruses (DENV) namely DENV-1 to DENV-4. The only one commercially available presently is sold by the trade name Dengvaxia[75] **(CYD-TDV)** and is a live attenuated tetravalent chimera of dengue viruses manufactured and marketed by Sanofi Pasteur. Development of a safe and successful dengue vaccine is complicated for various reasons especially because the adaptive immune responses to DENV upon subsequent infection after vaccination can be both protective and pathogenic and the exact mechanism and contours for these features are unknown.[76] Certain Indian companies namely Panacea Biotec, New Delhi in collaboration with the National Institutes of Health (NIH), US, has claimed to have developed[77] a dengue vaccine and that the Drug Controller General of India (DCGI) had given permission for conducting early phase clinical trials in humans (phase 1 & 2); the Technology Development Board[78] (TDB), New Delhi had provided financial support to the project. The latest progress of clinical evaluation is not available. Serum Institute of India, Pune also aims to launch a dengue vaccine candidate which is understood to be licensed from the US National Institutes of Health[79]. Further details of the project are not available. An Indian version India is experimenting on a recombinant DNA technological mode where on a virus-like particle (VLP) platform has been created and the VLPs of the relevant DENVs partly chimerized with hepatitis B virus surface antigen (HBsAg) are being expressed in recombinant methylotrophic yeast Pichia pastoris, isolated, purified and converted into vaccine formulations[80,81,82] . ICGEB is working with Sun Pharma, Mumbai on this project.

Human Papilloma virus

There are more than 100 types of Human Papilloma virus (HPV) of which at least 14 are identified to be cancer-causing. Certain types of HPV cause cervical cancer and about 70 per cent of the cases are caused due to infection from HPV types[111] 16 and 18. In 2012, nearly 85 per cent of the global burden of cervical cancer occurred in poor countries [83]. Presently, three HPV vaccines are being marketed throughout the world of which one is bivalent, the other a quadrivalent, and the third

There is yet no vaccine against tuberculosis except the BCG vaccine. BCG vaccine has several limitations is not a universal vaccine against tuberculosis. The efforts to develop new TB vaccines for adolescents and adults in the global context have been discussed and described

a 9-valent one. **CERVARIX**, a human bivalent HPV vaccine, is manufactured by GlaxoSmithKline Biologicals, (GSK) Belgium; **GARDASIL** which is a human quadrivalent (Types 6, 11, 16, and 18) HPV vaccine and **GARDASIL 9** which is a human 9-valent vaccine HPV vaccine are both manufactured by Merck Sharp and Dohme, a subsidiary of Merck & Co (Merck), USA. All the three vaccines, one of GSK and two of Merck are based on synthesis of virus-like particles (VLP) of HPV capsid proteins L 1 or both L1 and L2, by recombinant DNA technology. Development of a HPV vaccine by recombinant DNA technology is complex. India has expertise in evolving and developing recombinant hosts especially in a varied range of yeasts. However, the recombinant HPV proteins are of recent origin and are IPR protected materials. Therefore, in immediate future India would not be able to get in to the technology even though R&D can be pursued. Bharat[84] Biotech Ltd., Hyderabad and Serum[85] Institute of India, Pune have claimed to be involved in the development of a HPV vaccine; the details of their program are not known.

Chicken pox

Chickenpox is a disease of temperate region and occurs throughout the year in children between the ages of one year to 14 years but infect people of higher ages too. In higher ages, the disease can be more severe. In India chickenpox vaccine is not included in the UIP. The incidence rate in India is not precisely available. The vaccines namely VARILRIX of GSK and VARIVAX of Merck are available in Indian market. These are imported and sold. In addition, several other vaccine formulations are being sold in India by brand names such as BIOVAC V[86], marketed by Wockhardt, Mumbai; and NEXIPOX [87], marketed by NOVO Medi Sciences Pvt. Ltd, Mumbai; all these vaccines are of Chinese origin, manufactured by Changchun[88], China. Basic and applied research in India is yet not adequate for developing vaccines against either chickenpox or herpes zoster disease.

Malaria

Malaria is caused by infection attributable to *Plasmodium vivax* (Pv), *Plasmodium falciparum* (Pf), *Plasmodium ovale* (Po) and *Plasmodium 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[89] at the International Center for Genetic Engineering and Biotechnology by a group to develop vaccines against *P. vivax* (Pv) and *P. falciparum* (Pf) malaria. The group identified the cysteine-rich region II (Pv R II) at the N-terminal conserved region as the receptor binding sites of P. vivax Duffy

binding protein. Antibodies raised against this domain were expected to block the capability of invation of erythrocytes by the parasite. Recombinant proteins PvR II were developed and multiplied in *E.coli*. For P. *falciparum* malaria, recombinant Pf MSP-119 and PfF2 proteins were also multiplied in *E. coli*. In small animals the immunogenicity studies 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.

HIV

HIV vaccine development strategy has to have simultaneously both antibody mediated immunity and cell mediated immunity. The largest vaccination trial named as RV144 vaccine trial conducted in Thailand138 used a combination of two vaccines in a heterogeneous prime-boost paradigm has shown lower infection rates of HIV in the vaccinated individuals than the group receiving placebo but the protection was not considered adequate. More work is to be done therefore. Indian efforts[90] have been directed towards 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 in Faridabad, Haryana.

Tuberculosis

There is yet no vaccine against tuberculosis except the BCG vaccine. BCG vaccine has several limitations is not a universal vaccine against tuberculosis. The efforts to develop new TB vaccines for adolescents and adults in the global context have been discussed and described[91]. In this context the Indian efforts in working on certain candidate vaccines is noteworthy. The safety and immunogenicity of the candidate tuberculosis 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.

Vaccines against other pathogens

Indian efforts in the development of vaccines against other diseases caused by **RSV, Enterotoxigenic Escherichia coli,** Shigella, Noroviruses, **ZIKA virus,** Chikungunya virus and Ebola virus are yet at rudimentary stage. Bharat Biotech Ltd., Hyderabad is engaged in developing vaccines against Zika virus; the company has claimed to have two[92] 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[93] 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 like the previous USSR (now Russia), France, USA and the European Union 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 Bulandshahar, Uttar Pradesh and in 1989 a company was registered by the name[94] 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 polio virus 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, Gurgaon (Haryana). A unit was incorporated on 27 March 1989 by the name Indian Vaccine Corporation Ltd (IVCOL)[95]and was to come up as an Indo-French joint venture. However, 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.

Indo-US Programme

India had been receiving financial support and assistance through the United States Agency for International Development[96] (USAID) from the decade of 1980-1990 and later to handle the health problems emanating from tuberculosis, leprosy, malaria, HIV/AIDS and cataract blindness. Besides, financial assistance had also been received from USAID during the decade, supporting nutrition programmes for the children in India. USAID is an independent agency of the federal government of United States. USAID provides civilian foreign aid and development assistance to various countries the world over. In mid 1980s, a bilateral discussion was initiated between the two countries following the efforts of the two leaders of the two countries namely Prime Minister Mrs. Indira Gandhi and US President Ronald Reagan and in 1983 the India-US Science and Technology Initiative (STI) was established. Later, after the visit of Dr. Fred Robbins in 1984 to India, the initiatives took further roots. Dr. Fred Robbins was a Nobel Laureate in Medicine along with others, for their discovery of the ability of poliomyelitis viruses to grow in cultures of various types of tissue. These initiatives culminated to the initiation of the Indo-U.S. Vaccine Action Program (VAP) in July 1987 when a

Memorandum of Understanding (MOU) was signed between USA and India; the MOU was signed by the Director, National Institute of Allergy and Infectious Diseases (NIAID) Dr Anthony S. Fauci, MD from the USA side and by Secretary, Department of Biotechnology (DBT) Dr S Ramachandran, Ph D. The MOU is renewed every five years. Research projects under VAP currently include dengue fever, enteric diseases, influenza (including avian influenza), malaria, and tuberculosis (TB), TB clinical research, human immunology, antimicrobial resistance, chikungunya vaccines, infant immunology and respiratory syncytial virus (RSV) vaccine[97,98]. 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 rotaviral strain of Indian origin, obtained from All India Institute of Medical Sciences, New Delhi was characterized as genotype G9P10 in 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 candidate[99] vaccine. The strain 116E and all the techniques for identification, characterization and multiplication methods of the virus in Vero cells were transferred[100] to Bharat Biotech Ltd., Hyderabad in 2000 by the National Institute of Allergy and Infectious Diseases (NIAID), USA, which is a part of NIH, USA, through a technology transfer agreement. NIAID also assisted in the absorption of the techniques for the multiplication of the virus in Vero cells. Bharat Biotech adapted the strain and produced the investigational vaccines for human clinical studies and finally the vaccine was approved for use in India. The funds for the development were by DBT, the Bill & Melinda Gates Foundation, the Research Council of Norway, and the UK Department for International Development; and Bharat Biotech invested important technical, manufacturing, and financial resources towards the development[101] of the vaccine.The last phase of trial conducted involving 6,799 infants at three sites in Delhi, Pune and Vellore demonstrated 55-60 per cent efficacy, which was considered as satisfactory; the results were published[102] in Lancet in June 2014 issue. Based on these results, the vaccine[103] was approved for use in 2015 and later from 2017, this vaccine was included[104] in Indian UIP. Interestingly, it was calculated that the total cost of the vaccine project[4] was less than US $50 million which cost is considered to be substantially less and was assessed to be about one tenth of the cost of bringing a similar live attenuated viral vaccine to market in a developed country environment.

Major Indo-EU initiative has been to develop effective vaccines against viral influenza. This project was chosen, as seasonal influenza is considered a major health threat globally.

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Major Indo-EU initiative has been to develop effective vaccines against viral influenza. This project was chosen as seasonal influenza is considered a major health threat globally.

All the Influenza viruses namely Influenza virus A, Influenza virus B, Influenza virus C and Influenza virus D are negative stranded RNA viruses causing influenza in human and other vertebrates. Influenza viruses found in swine are known as swine influenza viruses (SIVs), which include influenza C and the subtypes of influenza A known as H1N1, H1N2, H3N1, H3N2 and H2N3. Human infection from Influenza virus A subtypes are causes of greatest concern as the viruses mutate and evolve rapidly into newer subtypes which limit the efficacy of the already used vaccines as well as the antiretroviral drugs against the virus.

With a far faced foresight India had instituted international collaborations with certain countries like the previous USSR (now Russia), France, USA and the European Union with a view to develop technologies for the production of certain vaccines required for the country.

A recent estimate places the death of between 291,000 and 646,000 people each year globally from seasonal influenza-related respiratory illnesses. These estimates are based on analysis[105] of data collected from 47 countries between 1999 and 2015. Added to this is the threat from the non-seasonal emergence of new strains; such strains also have the potential of spreading the disease.

The Department of Biotechnology(DBT) of the Indian Ministry of Science & Technology along with the European Union(EU) had announced in 2018, their engagement on research & innovation to develop a Next Generation Influenza Vaccine[106] A sum of EUR 30 million (or approximately INR 240crs.) had been earmarked for research and innovation actions of which both DBT and EU has committed to share the developmental costs equally. Jointly, these efforts aim to develop cost-effective & affordable influenza vaccine rapidly without compromising on quality.

Indian Institutional efforts in vaccines development

DBT Institutional efforts

The DBT had established thus far sixteen[107] 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 indicus pranii* (MIP) was developed by the National Institute of Immunology, New Delhi. The strain and technology was transferred[108] to

Cadila laboratories, Ahmedabad in early 1990s and was to be used in the National Leprosy Eradication Program run by the Ministry of Health and Family Welfare, Govt. of India. However, this vaccine was not used in the national program. After purchase of the technology, the scientists of Cadila had modified the formulation by enhancing the suspension characteristics using certain suspending agents, which improved the antigen presentation characteristics. A team at Cadila from the biotechnology division headed by the author (who was then working at Cadila, initially as the Consultant and later as the President- Biotechnology) successfully carried out the developmental work. The improved formulation acts as desmocollin modulators; immunostimulants; P38 mitogen-activated protein kinase inhibitors; and Toll-like receptor agonists[109]. The formulated product of Cadila is marketed as Cadi-05 and is indicated to treat Leprosy and Non-small cell lung cancer[110].

ICMR Institutional efforts

Presently, there are 26 National Institutions under the Indian Council for Medical Research (ICMR). These Institutes are engaged in research in diverse areas of medical importance. Collectively, the ICMR institutions have made magnificent additions[111] towards scientific understanding of various diseases of national importance such as tuberculosis, filariasis, leprosy, malaria, Kala-azar, several diarrheal diseases, rabies, poliomyelitis, Japanese encephalitis, 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 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 tuberculosis. 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.

Attempts are made to develop clonal cytotoxic T cells that acquire the abilities of destroying the pathogens directly or destroying the pathogen- infected cells. Several strategies and procedures have been developed for this purpose. The science of precise understanding of protection from each infectious microbial disease continues to evolve further with time as human kind encounters newer pathogens.

Discussions and concluding remarks

Vaccines impart adaptive immunity in the vaccinated individuals through complex cellular interactions. The broad understanding of the pluripotent hematopoietic stem cells

originating from the bone marrow, transforming into common progenitors of lymphoid cells and further dividing into the mature T cells and B cells, which lineages are responsible for adaptive immunity, is in place. Eliciting and elaborating strong neutralizing antibody response through clonal B cells against a pathogen is the main strategy in developing a vaccine. Concurrently, attempts are made to develop clonal cytotoxic T cells that acquire the abilities of destroying the pathogens directly or destroying the pathogen-infected cells. Several strategies and procedures have been developed for this purpose. The science of precise understanding of protection from each infectious microbial disease continues to evolve further with time as human kind encounters newer pathogens.

In recent years competition from producers from China and South Korea has affected the exports of Indian vaccines to some extent. This is a challenge that will have to be faced by the industry and the Indian government.

Vaccines are manufactured in India by companies that belong to any of the three sectors namely the Indian private sector, the Public sector units and those belonging to the government. A large number of other companies import specific vaccine-formulations and sell these in India. Besides, a number of companies have teamed up with the Indian manufacturers for selling/marketing specific brands to the Indian consumers. The MNCs are dominating in the sale of vaccines in the Indian trade market. The progress made by the Indian companies is also praiseworthy. The Indian companies are manufacturing mainly the conventional vaccines. Certain recombinant DNA based vaccines have also been added to the skills of Indian companies. Indian companies are also concentrating for the production of multiple numbers of conjugate vaccines. Knowledge gap in Indian companies exists in the development of multiple numbers of viral vaccines, authentication of the purity of mammalian cell lines used in the multiplication of viral entities such as absence from mycoplasma infection etc. Indian vaccines industry has however strength in multiple facets of production.

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, pre-filled syringes at competitive prices, availability of small animals at competitive prices (which are used in quality assurance and quality control endeavour), efficiency in engineering capabilities including production system that can handle sterile operations efficiently. In addition India has developed strong capabilities of handling services facilities cost-effectively which include among others, capabilities to manage air and water showers, HVAC, 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,

HEPA filters maintenance and integrity establishment and maintenance of predetermined minimum levels of microbial load at different points/rooms of the production units through air filters, restricted movement management of personnel and materials etc. Compromising at any stage due to inadequate knowledge will jeopardize the integrity of good manufacturing practices. Indian manufacturers have also learnt to extensively document the integrity of the production system at every stage.

Indian vaccines industry has a large internal market to be serviced. The market includes the sale of vaccines for utilization in the Universal Immunization Program (UIP) of the government and the trade market. The UIP supplies need to be rationalized further with more production-friendly endeavour to strengthen procurement infrastructure that benefits both the government and the industry. The 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 which situation emanates from awareness and rise in the income of certain section of Indian population. Because of various other reasons including 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.

There is scope for joint scientific cooperation between Asian countries such as India and other countries to advance vaccine development for treating neglected tropical diseases. Another possibility is for innovative financing mechanisms to make research and development of such vaccines more attractive to the global industry.

Presently, most of the vaccines used to protect the pregnant women and the children in developed world are also being made available in the developing world. The coverage of vaccinated women and the children in developed world is more than those in the developing world. This situation emanates primarily from the constraints in the availability of adequate funds. Interestingly, in the developing world besides the government, several benevolent organizations have come forward to assist in the endeavour to enlarge and increase the vaccinated beneficiaries. The example of Indian UIP is worth mentioning where every beneficiary receives vaccines free of cost. Another one point also requires to be flagged while dealing with such mega-projects as the Indian UIP. It has come out from one study elaborated in the text that a substantial portion of the procured vaccines for the program gets wasted, which ranges from 27 per cent to 56per cent. Steps need to be taken to bring down such colossal losses.

Internationally, only a handful of companies generate huge revenue from the sale of vaccines. The revenues generated worldwide by the top 10 global vaccine producing companies accounted for nearly 85-88 per cent of the global vaccines market in value terms. At present, the four companies namely, GSK, Sanofi, Pfizer and Merck continue to hold over 80 per

cent of the market share in terms of revenue. The author is of the opinion that smaller but innovative companies cannot stand the market competition even with an innovative new product in competition with these MNC giants. New products developed by small companies would have to solve the issues of logistics and market distribution fast enough to make an impact on the global context. This is not easy. It is the view of the author that in the present day world, innovative but small companies cannot remain independent with their comparatively smaller resources and therefore new products developed elsewhere are often acquired by the large MNCs. Teaming up with the MNCs is therefore considered a plausible and feasible better option for success for the small innovators. In Indian context, this implies that as the Indian companies are smaller in terms of investment, technological capabilities and market capture, these companies should explore to team up with MNCs and international institutions when they have developed new products of increased potentials and in this context Indian government assistance directly or indirectly are considered avenues for strengthening the Indian vaccines industry. Science diplomacy policies need to be evolved to tackle these issues.

Though the global monopoly in the production of vaccines is held within a few hands, the contributions of medium, small and tiny units operating from different corners of the world, producing and selling more cost-effective vaccines cannot be belittled. The vaccines produced by these 'Rest of the World' companies are consumed mostly at the developing and underdeveloped settings and constitute sizable numbers to protect human from a large number of vaccine-preventable infectious diseases.

The World Health Organization provides[112] a service to the vaccines procuring agencies of the United Nations such as the UNICEF as also to other vaccine procurement agencies like Gavi, the Vaccine Alliance and the Global Fund so as to facilitate such organizations with information, that are used and required for the purchase of vaccines matching the safety, efficacy and other technical needs of the programme. The service of vaccines prequalification programme was established[113] by the WHO in 1987 and continues up to the present time. Procurement of Indian vaccines through UNICEF and other agencies mentioned above had boosted the exports from India and also helped developing countries. In recent years competition from producers from China and South Korea has affected the exports of Indian vaccines to some extent. This is a challenge that will have to be faced by the industry and the Indian government. There exist scopes for coming out with innovative procedures and measures to beat the competition.

India has been able to introduce newer vaccines such as the rotavirus vaccines using international collaboration with institutions in the USA. In the process India had acquired additional skills in handling and maintaining authentic animal cell lines used for the multiplication of viral particles. International collaborations with other agencies like EU are also anticipated to benefit India substantially.

Although more than one billion people suffer from neglected tropical diseases (NTDs), the development and use of vaccines against such diseases do not attract the leading multinational companies as these have limited commercial market. The NTDs manifest primarily in people living in poorer socioeconomic conditions. Vaccines developmental supports come from public–funded institutions and certain benevolent non-profit product development organizations such as the Bill & Melinda Gates Foundation. There is scope for joint scientific cooperation between Asian countries such as India and other countries to advance vaccine development for treating neglected tropical diseases. Another possibility is for innovative financing mechanisms to make research and development of such vaccines more attractive to the global industry. Countries such as India could take the initiative in this field. In addition the problem of new and re-emerging diseases for which much more rapid vaccine development and production will be required poses a challenge to the international community.

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.

Several developing countries have made substantial progress in being able to produce cost-effective quality vaccines at affordable prices and India certainly leads the race. But because of a sizable shortfall in the access of vaccines to the beneficiaries, the infectious diseases in certain poor countries continue to infect people comparatively in larger numbers especially in the developing countries. There is a need for coming out with more innovative international treaty to expand the coverage of vaccines in developing countries.

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. While Indian efforts continue to intensify through international collaborations for vaccines development along with efforts made through local institutional efforts, such endeavour needs to be intensified with allocation of more funds in order to make 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 endeavour through the services that India can provide in the whole area of vaccines technology.

In conclusion, it can be said that while India recognizes that human vaccines are the most cost-effective defense against infectious diseases and that in the country there are at least nineteen manufactures of vaccines producing a sizable number including majorly the conventional vaccines against a wide range of diseases and having regard to the fact that India has a well-established Universal Immunization Program (UIP) that targets annually the vaccination of 30 million pregnant women and 27 million new born, and that Indian manufacturers produce maximum number of WHO certified vaccines, the country is poised for playing a leadership role on the major aspects of human healthcare especially in the less developed settings of the world in a most professional and cost-effective manner.

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Acknowledgements

The author acknowledges Ms. Deepali Ghosh, the other partner of **Sompradip Publishers and Consultants**, New Delhi for encouraging and providing all the financial support to complete the manuscript. The author has no conflict of interest regarding the content of this article.

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