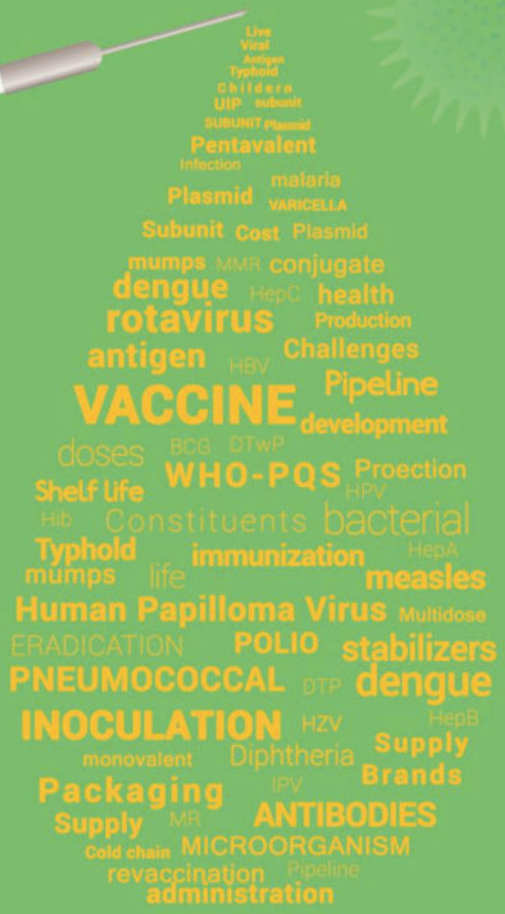
MARKET ASSESSMENT OF NEW VACCINES



Confidential Document

September 2015

ITSU
IMMUNIZATION
TECHNICAL SUPPORT UNIT
Ministry of Health & Family Welfare

KNOWLEDGE TO ACTION
phfi

Immunization Technical Support Unit,
Public Health Foundation of India

MARKET ASSESSMENT OF NEW VACCINES

Study Conducted by
Sathguru Management Consultants
on behalf of **Immunization Technical Support Unit,**
Public Health Foundation of India

Table of Contents

Abbreviations

Abbreviations

2vHPV	**Bivalent HPV vaccine (Cervarix®)**	**4vHPV**	**Quadrivalent HPV vaccine (Gardasil®)**
9vHPV	9-valent HPV vaccine (Gardasil®)	**AMC**	Advanced Market Commitment
BCG	Bacille Calmette-Guérin (Tuberculosis) Vaccine	**CDIBP**	Chengdu Institute of Biological Products
DALYs	Disability-adjusted life years	**DT**	Diphtheria and tetanus toxoids, pediatric formulation
DTaP	Diphtheria and tetanus toxoids and acellular pertussis vaccine, pediatric formulation	**DTP or (DTwP)**	Diphtheria and tetanus toxoids and whole-cell pertussis vaccine, pediatric formulation
eIPV	Enhanced inactivated polio vaccine	**FIOCRUZ**	Oswaldo Cruz Foundation
GAVI	The Global Alliance for Vaccines and Immunizations	**GSK**	Glaxo Smith Kline
HbOC	Haemophilus b Oligosaccharide Conjugate (Hib) Vaccine	**HBV**	Hepatitis B Virus
HepA	Hepatitis A Vaccine	**HepB**	Hepatitis B Vaccine
Hib	Haemophilus influenzae type b	**HPV**	Human Papillomavirus
HPV2	Human Papillomavirus vaccine, bivalent (Cervarix®)	**HPV4**	Human Papillomavirus vaccine, quadrivalent (Gardasil®)

HZV	Herpes Zoster (Shingles) Vaccine (formerly called ZOS)	**ICGEB**	International Centre for Genetic Engineering and Biotechnology
IIL	Indian Immunological Ltd	**IPV**	Inactivated Poliovirus Vaccine
JE	Japanese Encephalitis	**JE-MB**	Inactivated, mouse brain-derived Japanese encephalitis vaccine (JE-Vax®)
JEV	Japanese Encephalitis Virus	**JE-VC**	Inactivated, Vero cell culture-derived Japanese encephalitis vaccine (Ixiaro®)
MCV	Measles antigen-containing vaccines	**MMR**	Measles, Mumps & Rubella Vaccine
MMRV	Measles, Mumps, Rubella & Varicella Vaccine	**MR**	Measles-Rubella Vaccine
MSD	Merck, Sharpe and Dohme	**OPV**	Oral Polio Vaccine
PAHO	Pan-American Health Organization	**PCV13**	Pneumococcal Conjugate Vaccine (13-valent) (replaced PCV7)
PCV7 (or PCV)	Pneumococcal Conjugate Vaccine (7-valent)	**PPSV23**	Pneumococcal Polysaccharide Vaccine (23-valent) (formerly called PPV or PPV23)
PRP-T	Polyribosylribitol Phosphate-Tetanus Conjugate (Hib) Vaccine	**PRV**	Pentavalent Rotavirus Vaccine (i.e., RotaTeq®) (replaced by the term ROTA, then by RV5)
ROTA	Rotavirus Vaccine (replaced by the terms RV1 and RV5)	**RRV-TV**	Live, tetravalent rotavirus vaccine (RotaShield™) (no longer available)
RV1	Rotavirus Vaccine, monovalent (Rotarix®) (formerly called ROTA)	**RV5**	Rotavirus Vaccine, pentavalent (RotaTeq®) (formerly called ROTA)

RVGE	Rotavirus Gastroenteritis	**Td**	Tetanus & diphtheria Vaccine, adult/adolescent formulation
Tdap	Tetanus, diphtheria & acellular pertussis vaccine, adult/adolescent formulation	**TT**	Tetanus Toxoid
Ty21a	Live Oral Typhoid Vaccine	**UNICEF**	United Nations' Children's Fund
VAR	Varicella Vaccine	**ViCPS**	Vi Capsular Polysaccharide (Inactivated Typhoid) Vaccine
WHO	World Health Organization	**WRAIR**	Walter Reed Army Institute of Research

Executive Summary

Executive Summary

Vaccines where both MNCs and Indian companies hold marketing registrations in India

For six vaccines namely pentavalent, rotavirus, measles-rubella (MR), Japanese encephalitis (JE), typhoid and inactivated polio vaccine (IPV) there are multiple Indian manufacturers in addition to major global vaccine manufacturers with marketing license in India.

Pentavalent Vaccine: The pentavalent vaccine is a natural successor to the DTP vaccine, incorporating Hepatitis B (HepB) and Haemophilus influenzae type b (Hib) antigens; and was developed by industry primarily for the public health market. Most of the commercialized vaccines have the Hib component coupled with tetanus toxoid (PRP-TT), with only Berna Biotech's Quinvaxem incorporating a Hib component conjugated to the CRM 197 carrier protein. Currently, there are six domestic manufacturers and three MNCs selling imported vaccines in India. Pentavalent vaccine manufacturing capacity with Indian manufacturers exceeds 700 million dosesand Indian manufacturers accounted for 20% of the total global supply of pentavalent vaccines in 2014 and this is expected to rise to 25% by 2020. Additionally, their entry into the public health supply market, along with other regional players has contributed to a significant drop in pentavalent vaccine prices with Biological E's vaccine being procured by GAVI at the lowest price (US$ 1.19/dose). On the development landscape, there are not too many efforts concentrated at pentavalent vaccine, as GAVI, the largest procurer of pentavalent vaccines has indicated surplus supply. However, owing to its planned introduction into India's national immunization program, public enterprise HLL Lifecare has acquired technology from Biological E and developed capacity to manufacture this vaccine. Additionally, another public enterprise, Indian Immunologicals is developing a pentavalent vaccine and is aiming to launch it in 2017.

Rotavirus Vaccine: There are 2 types of currently commercialized Rotavirus vaccines - Human Monovalent Vaccines (currently manufactured by GSK and Bharat Biotech) and Animal Re-assortant vaccine (currently manufactured by Merck). Both these type of vaccines are administered orally and show significant cross-protection among predominant strains of rotavirus. However, a common challenge in both these types of vaccines is that these oral vaccines elicit diminished immune response and have lower efficacy in developing countries than in developed countries (drop from 85-96% to as low as 41% efficacy). GSK's Rotarix and Merck's Rotateq, both WHO pre-qualified vaccines, are imported into India and sold in the private market. Bharat Biotech's Rotavac, is an indigenously developed vaccine which was launched in March 2015 is currently being rolled out into the Indian private market. It is projected to be 40% cheaper than either of GSK and Merck's vaccines, based on its announced price of US$ 1 /dose for public health procurement. Bharat has established an installed capacity of 300 million doses annually for this vaccine. There are several rotavirus vaccines under development in India and globally. Shanta Biotech's (Sanofi) tetravalent bovine re-

assortant candidate and Serum Institute of India (along with PATH) pentavalent bovine re-assortant candidate, both undergoing Phase 3 trials, are two notable candidates from India. Hilleman Labs in India is developing a heat-stable formulation of Merck's Rotateq vaccine. There are efforts underway to develop rotavirus vaccine candidates utilizing non-replicating viruses by NIH and PATH.

Japanese encephalitis: Currently, there are four different types of JE vaccines. The first generation inactivated mouse brain-derived (IMB) JE vaccine by Green Cross Corporation (JenceVax) has now been commonly replaced by cell culture-based inactivated vaccines (cultured in PHK cells or Vero Cells). Inactivated vaccines CD.JEVAX by Chengdu Institute of Biological Products (CDIBP), JEEV by Biological E and JENVAC by Bharat Biotech are WHO-prequalified. The supply volumes for these vaccines to GAVI are currently unknown. Two Indian manufacturers Bharat Biotech and Biological E have India license for JE vaccines and currently have production capacities of 30 million doses and 20 million doses respectively. CD.JEVAX from Chengdu Institute of Biological Products (CDIBP) is imported into the country by HLL Lifecare Ltd. We do not note any significant developments globally on next generation products.

Typhoid: There have been two types of typhoid vaccines, Vi Polysaccharide and Ty21a oral. Both these vaccine types are safe and moderately efficacious and are licensed for use in individuals two years and above. More recently, a conjugate typhoid vaccine has been developed for pediatric use in children below two. Currently there are several manufacturers with commercialized typhoid vaccines (oral and polysaccharide) in the market, with Bharat Biotech and Bio-Med Pvt. Ltd manufacturing in India, with production capacities of 30 million and 4 million doses respectively. Sanofi's polysaccharide vaccine Typhim-Vi is the only WHO pre-qualified typhoid vaccine in the world, and is imported and marketed in India by Cadila Pharmaceuticals. Bharat and Bio-Med are also the only two companies globally with a licensed typhoid conjugate vaccine. There are about five typhoid conjugate vaccine candidates currently under various stages of development per Coalition against Typhoid. Technology source for majority of them has been IVI, NIH and Novartis Vaccines Institute for Global Health.

MR: In countries where Mumps vaccination is discontinued from their National Immunization Programme, MR vaccines are used instead of MMR vaccines. The only vaccine marketed in India and the only WHO prequalified MR vaccine globally is MR-VAC produced by Serum Institute of India and it was launched in the year 2002. The MR-VAC contains Edmonston-Zagreb strain for Measles virus and Wistar RA 27/3 strain of Rubella virus which are propagated on human diploid cells (HDC). The price of Serum Institute's vaccine is gradually increasing due to increase in demand and their advantageous position as the sole supplier. Serum'sannual manufacturing capacity is 150 million doses[1] and the retail MR-VAC price in private market ranges from INR 95-128. GAVI negotiated price for MR-VAC for 2014 is US $0.57/dose for a 10 dose presentation. As per GAVI, there are about three pipeline vaccines that are expected to gain pre-qualification between 2017 and 2019.

IPV: The First IPV was developed and licensed in 1955. All IPV vaccines are trivalent providing protection against type1, type 2, type3 wild polio virus strains. Currently there are five IPV vaccines available globally out of which three are WHO-prequalified i.e. Inactivated Poliomyelitis vaccine of Bilthoven Biologicals B.V., Poliorix of GlaxoSmithKline and IMOVAX/IPOL of Sanofi Pasteur. The other two vaccines which are not WHO prequalified, are Poliovac-PFS of Serum Institute of India and Polprotec of Panacea Biotec. Except GSK's Poliorix, all other four IPV vaccines have marketing license in India and their retail prices are between INR 375-450.

Vaccines where only MNCs are currently marketing products in India

For Human Papillomavirus Vaccine and Pneumococcal Vaccine, there are currently no Indian manufacturers and entire supply in India is dependent on global vaccine manufacturers.

Pneumococcal Vaccine: There are currently 2 types of vaccines available for pneumococcal infections- the pneumococcal polysaccharide vaccine (PPSV) which can only be administered to adults (≥ 2 years) and the pneumococcal conjugate vaccines (PCV) which can be administered to infants as well (≥ 6 weeks). PCVs are complex and expensive to produce, hence, there are only 3 vaccines licensed globally, with Prevenar 13 (Pfizer) the most popular and broadest in terms of serotype coverage. To ensure adequate supply at accessible prices in developing countries, GAVI has initiated an Advanced Market Commitment (AMC) mechanism from 2010 under which PCV manufacturers Pfizer and GSK have pledged a cumulative supply of 1.46 billion doses up to 2023-2024 at a fixed l price of US$ 3.50 per dose (with an additional $3.50 being paid to companies from donor funding for approximately 20% of the doses)[2]. Despite this, the PCV is significantly more expensive than other traditional vaccines and accounts for 39.2% in value but only 3% in volume of all UNICEF's vaccine procurement. There is currently no manufacturing of PCV vaccines in India, however Serum Institute of India has a candidate in Clinical Phase 1/2 which is expected to be launched in 2019. Tergene, a Hyderabad based company also has a PCV candidate in pre-clinical stages also expected to be launched by 2019 and Panacea Biotech also has a vaccine under clinical development the current status of which was not confirmed by the company. Globally, Merck has a 15 valent PCV candidate in Phase 2 (in collaboration with Serum Institute of India), while GSK has a PCV + protein vaccine candidate also in Phase 2.

HPV: There are currently three FDA approved HPV vaccines i.e. Cervarix of GSK, Gardasil and Gardasil 9 of Merck. Cervarix and Gardasil are WHO prequalified and are marketed globally including India. Gardasil is a quadrivalent vaccine while Cervarix is a bivalent vaccine. Gardasil 9 is a recently approved 9-valent vaccine that protects against infection with HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58. While there are no Indian manufacturers for HPV, there are pipeline candidates from Indian companies including Zydus, Serum Institute and Indian Immunologicals but the current status of these has not been confirmed. The current GAVI negotiated price for HPV vaccine is US $4.50/dose.

Vaccines yet to be launched in India

Recently, first Dengue vaccine, Sanofi's Dengvaxia® got approved for use in three countries – Mexico, Phillipines and Brazil. The only approved vaccine for Malaria is the Mosquirix developed by GSK that was approved by EMA in July 2015. However, there are several pipeline candidates with one Phase 3 Dengue candidate from Sanofi.

Dengue: The first Dengue vaccineto get approval for use is the yellow fever/dengue chimeric, live, attenuated, tetravalent vaccine (CYD-TDV), developed Sanofi Pasteur under the brand name Dengvaxia®. Dengue vaccine's phase 2 clinical pipeline includes candidates from National Institute of Health (NIH), Brazil's Instituto Butantan and GlaxoSmith Kline (GSK). GSK is developing the vaccine in collaboration with Oswaldo Cruz Foundation (FIOCRUZ) and Walter Reed Army Institute of Research (WRAIR). Brazil's Instituto Butantan is collaborating with National Institute of Health (NIH) for its vaccine pipeline. Several promising dengue vaccine candidates are in early to preclinical development in India. The three noticeable candidates are from Biological E (live, attenuated), Panacea Biotec (live, attenuated, and chimeric) and ICGEB India (Virus like Particle-VLP).

Malaria: The complexity of the malaria parasite makes development of a malaria vaccine a very difficult task. Three main strategies have been adopted for developing malaria vaccines by either pre-erythrocytic stage, blood stage or blocking transmission of infection. GSK's malaria vaccine 'Mosquirix' that was developed in partnership with PATH's Malaria Vaccine Initiative has recently received approval from EMEA regulatory agency on July 25th 2015. Key pipeline programs are from organizations including Oxford University, Crucell and Seattle BioMed collaboration, National Institute of Health (NIH) and these are in Phase 2 clinical trials. ICGEB India has malaria vaccine candidates under pre-clinical development stage. Additionally, Bharat Biotech has a research program on the malaria vaccine.

Summary Table

Vaccine Type	India Licensed	India Import Licensed	WHO pre-qualified	India Pipeline
Rotavirus	Bharat Biotech (Rotavac)	GSK (Rotarix), MSD (Rotateq)	GSK (Rotarix), MSD (Rotateq)	Shantha Biotech, Sanofi; Serum Institute
DTwP-HepB-Hib Pentavalent	Shantha Biotech (Shan 5); Serum Institute (Pentavac); Biological E (ComBEfive); Panacea Biotec (Easyfive-TT); Bharat Biotech (Comvac 5); HLL Biotech (Pentahil)	Berna Biotech, Novartis, GSK (Quinvaxem)	GSK (Trinatrix-HB + Hib); Shantha Biotech (Shan 5); Serum Institute (Pentavac); Biological E (ComBEfive); Panacea Biotec (Easyfive-TT)	Indian Immunologicals
Typhoid	Bharat Biotech (Typbar and Typbar TCV); Bio-Med Pvt Ltd (Bio-Typh and Peda-Typh)	Sanofi (Typhim-Vi); GSK (Typherix)	Sanofi (Typhim-Vi)	Biological E, Novartis; Cadila Healthcare
Japanese Encephalitis	Biological E (JEEV); Bharat Biotech (JENVAC)	Chengdu Institute - Imported by HLL Lifecare	Biological E (JEEV); Sanofi (IMOJEV MD); Chengdu (SA14-14-2 JE)	Indian Immunologicals; Panacea Biotec
IPV	Serum Institute (Poliovac PFS); Panacea Biotec (Polprotec)	Sanofi (IMOVAX POLIO); Bilthoven Biologicals (iPV)	GSK (Poliorix); Sanofi (IMOVAX POLIO); Bilthoven Biologicals (iPV)	Panacea Biotec; Bharat Biotech; Indian Immunologicals
MR Vaccine	Serum Institute (MR-VAC)	-	-	Zydus Cadila
Pneumococcal Vaccine	-	Pfizer (Prevenar 13 and Prevenar); GSK (Synflorix); MSD (Pneumovax 23)	Pfizer (Prevenar 13 and Prevenar); GSK (Synflorix)	Serum Institute, Panacea Biotec; Tergene
Human Papilloma Virus Vaccine	-	GSK (Cervarix); Merck (Gardasil)	GSK (Cervarix); Merck (Gardasil)	Serum Institute; Shantha Biotech; Indian Immunologicals
Vaccines yet to be globally launched				
Malaria Vaccine	-	-	-	ICGEB
Dengue Vaccine	-	-	-	Biological E; Panacea Biotec; ICGEB

Approach and Methodology

Approach and methodology

The overall methodology adopted for this study comprised of primary and secondary research for landscaping of commercialized and late stage pipeline vaccines covered under the scope of our study. Our analysis covered commercialized vaccines and late stage vaccine pipeline from all Indian vaccine manufacturers and ex-India vaccine manufacturers who have at least one vaccine licensed in India.

Beyond this mandated scope, we have proactively included information available from secondary sources for regionally (excluding India) commercialized vaccines having WHO prequalification and all early stage clinical pipeline from Indian vaccine companies/institutions. More specifically, for Malaria and Dengue vaccines, we have made efforts to assimilate global late stage pipeline information from secondary sources along with various research institutions having no India market presence which was beyond the study scope. For early stage vaccine pipeline from Indian manufacturers, we have made best efforts to obtain information by directly reaching out to them.

For the mandated scope, we have made best/extensive efforts on both secondary research and primary research. We would like to point out that the report is lean on certain information elements specifically sought in the scope (such as product wise capacity, committed prices and volumes and pipeline status, production plans etc.) due to lack of willingness of companies to disclose given the sensitive nature of such information. Information in our report is limited to the extent disclosed by companies in response to our survey requests and any additional information traces available in the public domain.

Our secondary research information sources include web portals such as vaccine manufacturers' website, WHO, GAVI, UNICEF, MSF, CDSCO, Central Bureau of Health Intelligence (CBHI), PATH, Reputed scientific journals, vaccine/disease specific recognized health initiatives/societies (e.g. 'Malaria Vaccine Initiative', 'Coalition Against Typhoid', Dengue Vaccine Initiative etc.) and other trusted domains wherever possible. Vaccine brand specific information was collated from sources including Company portals, Online pharmacy portals (e.g. Medplus, Apollo Pharmacy), product inserts available online, WHO etc. Such obtained information includes brand name, vaccine type, vaccine constituents, mode of administration, age of administration, doses, packaging, temperature for storage and transportation, shelf life, retail market price per dose in various packing options (wherever available). GAVI portal provided certain publicly disclosed relevant information including GAVI negotiated prices, GAVI's global demand estimations, GAVI's long term supply arrangements with certain WHO Prequalified vaccine manufacturers. WHO portal provided publicly disclosed relevant information including WHO prequalification status, cold chain volume

requirement, clinical information etc. CDSCO provided licensure status information related to manufacturing and import licenses issued to vaccine manufacturers. CBHI India publishes National Health Profile (NHP) of India annually. In their last published report (2015), they have provided relevant vaccine wise manufacturing capacity information for India based vaccine manufacturers. Vaccine specific clinical pipeline information/status was obtained from sources such as Clinical Trials Registry India (CTRI), ClinicalTrials.gov, CDSCO, company portals and reputed research reviews.

Our primary research included outreach to Indian vaccine manufactures, multinational vaccine manufacturers having license to market in India for at least one vaccine, public health funders such as the Bill and Melinda Gates Foundation (India Country Office), PATH, Wellcome Trust, Biotechnology Industry Research Assistance Council (DBT) and Indian research institutions where any vaccine candidates included in the study scope where identified (through secondary research) as being advanced through preclinical stages or later or were referred to by other primary research respondents. Outreach efforts for primary research include developing customized questionnaires, scheduling, traveling and information consolidation and analysis. By leveraging Sathguru Management Consultants' existing industry linkages, we scheduled interactions with most manufactures, and other organizations within India as indicated above. We also made visits to hospital linked pharmacies to validate vaccine brand specific product information.

Primary research was designed to collect critical details on vaccine launches, pricing for various packaging options, vaccine specific market experience in India and other Asian countries, cold chain volume requirement, long term agreements with any country/organization. Information related to production duration from bulk to final product, production capacities, and pipeline specific critical information (unpublished) were mostly denied by the vaccine manufacturers due to confidentiality reasons. Wherever possible during our primary interactions, we also validated most other product specific commercial, clinical, technical information earlier collated through secondary research.

Pneumococcal Vaccine

Pneumococcal Vaccine

Overview

Every year, 2.58 million episodes of severe pneumonia caused by *Streptococcus pneumoniae* occur globally in children aged under five, accounting for 18% of all episodes of severe pneumonia and 33% of all pneumonia-related deaths. Most of this burden is disproportionately borne by low and middle-income countries[3]. The WHO recommends the inclusion of the pneumococcal conjugate vaccines (PCV) in national immunization programs.

Marketed products – technical overview

Currently there are two types of multivalent vaccines available for the prevention of pneumococcal infections, the pneumococcal polysaccharide vaccine (PPSV) and the pneumococcal conjugate vaccines (PCV). The commonly used PPSV vaccine contains polysaccharide from 23 serotypes (PPSV23). The commonly used PCV vaccine contains polysaccharide from 13 serotypes (PCV13) and conjugated to a carrier protein that is a non-toxic mutant of diphtheria toxin (CRM197). The conjugation with CRM197 in PCV vaccines contributes to excellent immunogenicity in infants and toddlers. The table alongside highlights the currently marketed products and their serotype coverage. Both PCV and PPSVvaccines confer protection for only the serotypes contained in the vaccines and do not offer cross-protection for other serotypes. There are more than 90 serotypes identified till date and the quest for broader coverage continues with broader or region specific serotype combinations and the next generation protein vaccines that could offer universal coverage.

BrandName	Type	Manufacturer	Serotypes	% Serotype Coverage	
				Africa	Asia
Prevenar 13	13- Valent PCV	Pfizer (erstwhile Wyeth)	1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F	77%	74%
Synflorix	10- Valent PCV	GSK	1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F	63%	66%
Prevenar	7- Valent PCV	Pfizer (erstwhile Wyeth)	4, 6B, 9V, 14, 18C, 19F, and 23F	40%	48%
Pneumovax 23	23- Valent PPSV	Merck Sharpe and Dohme	1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F	Not comparable	

The Pneumococcal polysaccharide vaccine (PPSV23 or Pneumovax 23) consists of capsular material from 23 pneumococcal types which have historically caused approximately 85 to 90% of cases of pneumococcal disease globally. This vaccine administered intramuscularly or subcutaneously, and has been administered in adults for decades but not in infants or toddlers below 2yrs of age since polysaccharide antigens are poorly immunogenic in such infants/toddlers.

The Pneumococcal conjugate vaccine (PCV, initially marketed as a 7-valent vaccine, PCV7 (Prevnar), now replaced by PCV13 (Prevnar 13) consists of capsular polysaccharides from the 13 most common types that cause disease, covalently linked to the carrier protein CRM197. This covalent linking to the CRM197 carrier protein renders the polysaccharide antigenic in infants and toddlers. Due to its excellent immunogenicity in infants and toddlers, PCV7 was adopted for universal use in this age group beginning in year 2000. Since year 2010, PCV13 has been recommended for infants and children by WHO. Starting in year 2012, PCV13 began to be recommended for use in selected high-risk adults and, in year 2014, PCV13 began to be recommended for all adults ≥65 years of age[4]. Amongst the PCV vaccines, Prevenar 13 shows the most serotype coverage particularly for Asia (74%) and Africa (77%) compared to Synflorix (63% for Africa, 66% for Asia)[5]. This vaccine is administered intramuscularly.

Marketed products – commercial overview

Prevenar-13 (Pfizer), a 13-valent PCV is currently the most widely used vaccine, with the earlier Prevenar-7 (Pfizer), a 7-valent PCV being gradually phased out in its favor. GSK's 10-valent PCV 'Synflorix' is also widely used, particularly in the public health system.

Brand Name	Manufacturer	India Retail Price
Prevenar 13	Pfizer	INR 3,801/dose (1 dose vial)
Synflorix	GSK	INR 2,190 (0.5 ml injection)
Pneumovax 23	MSD	INR 1,155/dose (for single dose vial); INR 1,245 (0.5 ml injection)

India Market: Both Pfizer's Prevenar-13 and GSK's Synflorix are imported into India, as there is no local manufacturing for either of these vaccines. Merck's PPSV-23 is marketed in India by Lupin along with Merck, but is not WHO pre-qualified and as such not procured by public health bodies globally. There are currently no Indian manufacturers for PCV.

Global Public Health Procurement: The PCV vaccine is significantly more expensive than other traditional vaccines and accounts for 39.2% of overall procurement cost but only 3% of overall procured vaccine volume of all UNICEF's vaccine procurement[6].

Company	Vaccine	Duration	Doses
GSK	PCV 10	2010-2024	720,000,000
Pfizer	PCV 13	2010-2023	740,000,000
		Total	**1,460,000,000**

UNICEF, GAVI have multiple long-term PCV supply agreements with two manufacturers (Pfizer, GSK) for 1.46 billion doses covering a total duration from 2010 through 2023 / 2024 under an Advanced Market Commitment (AMC) mechanism. Under the Pneumococcal AMC, firms sign legally-binding agreements to supply their vaccines at a price no higher than US$3.50 for 10 years to be paid by GAVI and the developing country governments that introduce the vaccines. For approximately 20% of the doses, companies also receive an additional payment of US$ 3.50 for each dose they provide, which is paid out of the US$ 1.5 billion of donor commitments. This is more than a 90% reduction from the current private market pricing in industrialized countries. A total of 103.4 million doses of pneumococcal conjugate vaccine (PCV) were procured through the AMC in 2014 alone, a 40% increase from 2013[7]. As the AMC pilot encourages production from multiple manufacturers, it is expected that competition will drive the price lower over time.

Pipeline Review

Indian pipeline

While there are no Indian companies manufacturing PCV today, there are three candidates currently being advanced into or through clinical validation. Serum Institute of India is developing its own PCV candidate, a 10-valent vaccine in partnership with PATH, focusing on serotypes prevalent in developing countries of Asia, Africa and in India[8]. Tergene, a Hyderabad based company is developing a 15-valent PCV candidate utilizing a novel process for synthesizing the carrier protein and is expected to be a low cost vaccine as a result, along with broader serotype coverage (78% for Asia, 81% for Africa) when compared to other PCV vaccines.

Global developments

There are several PCV candidates being developed incorporating additional or more regionally prevalent serotypes. Merck is developing a 15-valent PCV candidate in partnership with Serum Institute of India while GSK is developing a 12-valent PCV candidate, an improvement on its existing 10-valent PCV product.

In addition to PCV candidates, there are several new approaches being evaluated that involve targeting proteins such as pneumolysin, pneumococcal surface protein A (PspA), pneumococcal surface protein C (PspC), pneumococcal surface antigen A (PsaA), neuraminidase enzymes, and histidine-triad proteins with the aim to induce greater cross-serotype protection and immunogenicity. Sanofi and GSK's protein-based vaccine candidates target these proteins and are currently in Phase 2 and Phase 1/2 respectively[9,10].

Development of inactivated whole cell vaccines and vaccines that combine protein and conjugate vaccine technologies to protect against a broader range of pneumococcal disease than existing licensed vaccines is also underway. GSK Biologicals has developed a combined PCV/pneumococcal recombinant protein vaccine, containing PCV10 (Synflorix™ with serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F conjugated to PD) with additional pneumococcal proteins dPly and PhtD[11,12] and is currently in Phase 2.

Pneumococcal Vaccines-Commercial Details

Type of Vaccine	Brand Name	Manufacturer	India Licensure Status	WHO Pre-qualification Status	India Private Retail Price	GAVI/WHO cost	India Production Capacity (doses/year)
Pneumococcal Conjugate Vaccine (PCV)	Prevenar 13	Pfizer (erstwhile Wyeth)	Import License *(Valid up to: Mar 2018)*	Pre-qualified in 2010	INR 3,801 for 3 doses (1 dose vial)	US$ 3.10/dose for 4 dose vial	Not applicable
	Synflorix	GSK	Import License *(Valid up to: Dec 2017)*	Pre-qualified in 2009	INR 2,190 (0.5 ml injection)	US$ 3.40/dose for 2 dose vial	Not applicable
	Prevenar	Pfizer (erstwhile Wyeth)	Not Licensed	Pre-qualified in 2009	Not applicable	Not applicable (Discontinued)	Not applicable
Pneumococcal Polysaccharide Vaccine (PPSV)	Pneumovax 23	Merck, Sharpe and Dohme (Marketed by Merck, Lupin and Sanofi Aventis in India)	Import License *(Valid up to: June 2017)*	Not Pre-qualified	INR 1,155/dose for single dose vial INR 1,245 (0.5 ml injection)	Not applicable	Not applicable

Pneumococcal Vaccines-Technical Details

Type of Vaccine	Brand Name	Manufacturer	Serotype Coverage	Vaccine Constituents (per dose)	Presentation/Form
Pneumococcal Conjugate Vaccine (PCV)	Prevenar 13	Pfizer (erstwhile Wyeth)	1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F	Pneumococcal polysaccharide for serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F & 23F: 2.2 µg each; for serotype 6B: 4.4 µg; Diphtheria protein CRM197: ~34 µg; Aluminum as aluminum phosphate adjuvant: 0.125 mg; Succinate buffer: 295 µg; Polysorbate 80: 100 µg	Liquid
	Synflorix	GSK	1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F	Pneumococcal polysaccharide for serotypes 1, 4, 5, 6B, 7F, 9V, 14, 23F: 1 µg each; for serotype 18C, 19F: 3 µg each; aluminum phosphate, sodium chloride, water for injections	Liquid
	Prevenar	Pfizer (erstwhile Wyeth)	4, 6B, 9V, 14, 18C, 19F, and 23F	Pneumococcal polysaccharide for serotypes 4, 9V, 14, 18C, 19F, & 23F: 2 µg each; for serotype 6B: 4 µg; Diphtheria protein CRM197: ~20 µg; Aluminum as aluminum phosphate adjuvant: 0.125 mg; Sodium chloride, Water-for-injection	Liquid
Pneumococcal Polysaccharide Vaccine (PPSV)	Pneumovax 23	Merck, Sharpe and Dohme	1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F	25 µg of each polysaccharide ; phenol; sodium chloride solution; thiomersal added as preservative	Liquid

Pneumococcal Vaccines-Clinical Prescribing Details

Type of Vaccine	Brand Name	Manufacturer	Mode of Administration	Age of Administration	Dose and Administration Schedule	Special Exclusion Criteria
Pneumococcal Conjugate Vaccine (PCV)	Prevenar 13	Pfizer (erstwhile Wyeth)	Intramuscular Injection	6 weeks-17 years; Adults ≥ 50 years	**Infants:** 4 doses at 2, 4, 6, and 12–15 months ; **Unvaccinated Children 7 Months- 5 Years of Age:** *7–11 months of age-3 doses*: first 2 doses 4 weeks apart, 3rd dose at least 2 months apart from 2nd dose; *12–23 months of age- 2 doses*: 2 doses at least 2 months apart; *24 months through 5 years of age:* 1 dose; **For all ages 6 years and above**: 1 dose	Hypersensitivity to constituents; Immunocompromised individuals
	Synflorix	GSK	Intramuscular Injection	6 weeks-5 years	**3-dose primary series:** 1st dose after 6 weeks up to 2 months age, 2 subsequent doses at least 1 month apart. 1 booster dose at least 6 months after last primary dose. **2-dose primary series** (infant immunization program): 1st dose after 6 weeks up to 2 months age, 1 subsequent dose after 2 month interval. 1 booster dose at least 6 months after last primary dose.	Hypersensitivity to constituents; postponed in acute severe febrile illness patients

Type of Vaccine	Brand Name	Manufacturer	Mode of Administration	Age of Administration	Dose and Administration Schedule	Special Exclusion Criteria
Pneumococcal Conjugate Vaccine (PCV)	Prevenar	Pfizer (erstwhile Wyeth)	Intramuscular Injection	6 weeks- 9 years	**Infants:** 3 primary doses every 2 months+1 booster dose at 12-15 months; **Previously Unvaccinated Older Children:** *7-11 month olds:* 3 doses total- first 2 doses 4 weeks apart, 3rd dose at least 2 months apart from 2nd dose; *12-23 month olds:* 2 doses total at least 2 months apart; *24 months to 9 years:* 1 dose total	Hypersensitivity to constituents
Pneumococcal Polysaccharide Vaccine (PPSV)	Pneumovax 23	Merck, Sharpe and Dohme	Intramuscular or Subcutaneous Injection	≥ 2 years	Primary: 1 dose post 2 years age Re-immunization every 3-5 years recommended for children under 10 years of age with nephrotic syndrome, asplenia or sickle cell disease	Hypersensitivity to constituents; Compromised cardiovascular or pulmonary function; Altered immuno-competence; Chronic Cerebrospinal Fluid Leakage; Children below 2 years

Pneumococcal Vaccines-Packaging and Logistics Details

Type of Vaccine	Brand Name	Manufacturer	Packaging Information	Cold Chain Volume (cm^3/dose)	Storage and Transportation Temperature	Shelf Life
Pneumococcal Conjugate Vaccine (PCV)	Prevenar 13	Pfizer (erstwhile Wyeth)	• 1dose (0.5ml) vial- Secondary packaging: carton of 50 vials, carton of 25 vials • 1 dose (0.5 ml) in pre-filled syringe • New 4 dose vial (2ml)- to be introduced	**1 dose vial:** 12 (in 50 vial carton) 15.7 (in 25 vial carton)	2 - 8 °C	24 months
	Synflorix	GSK	• 1 dose (0.5 ml) vial- Secondary packaging: 1, 10, 100 vial cartons • 2 dose (1 ml) vial- Secondary packaging: 100 vial carton • 1 dose (0.5 ml) pre-filled syringe- Secondary packaging: 10 pre-filled syringes carton	**1 dose vial:** 1 vial carton: 58 10 vial carton: 11.5 100 vial carton:10 **2 dose vial:** 100 vial carton: 4.8	2 - 8 °C	36 months
	Prevenar	Pfizer (erstwhile Wyeth)	• 1 dose (0.5 ml) vial- Secondary packaging: 5 vial carton	**1 dose vial:** 5 vial carton: 21	2 - 8 °C	24 months
Pneumococcal Polysaccharide Vaccine (PPSV)	Pneumovax 23	Merck, Sharpe and Dohme	• 1 dose (0.5 ml) vial • 5-dose (2.5 ml) vial • 1 dose (0.5 ml) pre-filled syringe	Not available	2 - 8 °C	24 months

Pneumococcal Vaccines-Pipeline Information

Type of Vaccine	Vaccine Name	Originator(s), Collaborator(s)	Vaccine Information	Development Stage	Clinical Trial Location	Expected Launch
Pneumococcal Conjugate Vaccine (PCV)	V114	Merck, Serum Institute of India	15-valent PCV- Conjugate (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, 33F serotypes covered) with CRM197 as carrier	Phase 2	US	2017
	GSK2189242A	GSK	12-valent PCV	Phase 2	US, EU	2018
	SIILPCV10	Serum Institute of India, PATH	10-valent PCV focusing on serotypes prevalent in 70.4% of the affected population (Asia, Africa, LAC, India)	Phase 1/2	India	2019
	-	Tergene	15-valent PCV Expected coverage of 85% in Asia and 81% in Africa	Pre-clinical	India	2018
Protein-based Vaccines	-	Sanofi Pasteur	PhtD/pneumolysoid (dPly)/PcpA common protein vaccine with broad coverage	Phase 2	US, EU	-
	-	GSK	PhtD monovalent protein vaccine with broad coverage	Phase 1/2	US, EU	-
PCVs incorporating Common Proteins	-	GSK, PATH, Medical Research Council Unit in The Gambia, London School of Hygiene & Tropical Medicine	PCV-10 + PhtD/pneumolysoid common protein vaccine (Conjugate with protein D, diphtheria and tetanus toxoids as carriers with added PlyD1 and PhtD) with broad coverage	Phase 2 completed	EU, Gambia	-

Rotavirus Vaccine

Rotavirus Vaccine:

Overview

The WHO estimates that 453,000 rotavirus gastroenteritis (RVGE)-associated deaths occur annually in children aged under five years[13] and to counter this it recommends rotavirus vaccination in all national immunization programs. There are 2 types of Rotavirus vaccines that have been commercialized to date- Human Monovalent Vaccines, which are currently manufactured by GSK and Bharat Biotech and Animal Reassortant vaccine, which is currently manufactured by Merck. Both these vaccine types are orally administered.

Marketed products – technical overview

VP7 and VP4 are two structural proteins in the rotavirus that are of most significance in vaccine development and serotypes determined by each of these proteins are called G serotypes and P serotypes respectively. These twoproteins are targets for neutralizing antibodies and can provide both serotype specific and in some cases cross-reactive protection[14]. Rotavirus has at least 12 different G-type and 15 different P-type viral particle antigens[15].

Type of Vaccine	Brand Name	Manufacturer	Strain/Subunit/ Serotype Coverage
Human Monovalent	Rotarix	GSK	G1P[8] subunit RIX4414 strain Coverage for G1, G3, G4, G9 serotypes
	Rotavac	Bharat Biotech	G9P[11] 116E strain
Human-Bovine Reassortant Vaccine (BRV-PV)	Rotateq	Merck, Sharpe and Dohme (MSD)	P1A[8], Human G1, G2, G3, G4; P7 from parent rotavirus bovine strain

GSK's ROTARIX® (human monovalent) and Merck's ROTATEQ® (human-bovine reassortant) are the two widely used rotavirus vaccines and both are licensed for sale in India. Both these vaccines show significant cross-protection among predominant strains of rotavirus[16,17]. GSK's ROTARIX® vaccine incorporates the G1P[8] strain, which although globally most common, shows significant diversity in its demographic distribution in developing countries in Asia and Africa. Bharat's vaccine ROTAVAC®, launched recently in 2015, incorporates a rotavirus strain of Indian origin- 116E- G9P[11], a naturally occurring reassortant containing one

bovine rotavirusgene P[11] and ten human rotavirus genes. Merck's ROTATEQ®, a bovine reassortant vaccine, contains rotavirus parent strains isolated from human and bovine hosts with capsid proteins expressed by human strains and attachment protein(s) expressed by animal strains.

Both the currently marketed oral vaccines elicit diminished immune response and have lower efficacy in developing countries than in developed countries. ROTARIX® shows 98% efficacy against severe rotavirus diarrhea in children below 1 year in high income countries[18], while showing only 59% efficacy in low and middle income countries[19]. ROTATEQ® shows a similar efficacy of 85-96% in high income countries[20]with reduced efficacy of 51-64% in low and middle income countries[21]. Bharat's ROTAVAC® has been shown to have a similar efficacy profile of 56.3% against severe rotavirus diarrhea[22], with more post-licensure safety studies planned. Additionally, these vaccines carry a risk of intussusception, a medical condition in which a part of the intestine folds into another section of the intestine, associated with rotavirus vaccines. The WHO estimates the incidence of rotavirus vaccine-induced intussusception to be one to two cases per 100,000 infants vaccinated.[23]Recent studies indicate that the relative risk of intussusception for GSK's human monovalent ROTARIX® exceeds 8.1 while the Merck's ROTATEQ® has a significantly lower relative risk of 1.1.[24]

Marketed products – commercial overview

India Market

GSK's ROTARIX and Merck's ROTATEQ are imported into India and sold in the private market. Although, ROTARIX is more expensive per dose, its 2 dose schedule renders it more cost effective than ROTATEQ, a 3-dose vaccine. Bharat Biotech's low cost rotavirus vaccine ROTAVAC was recently launched in India and is being rolled out to the private market currently. Bharat Biotech clarified during primary research that while ROTAVAC was being initially supplied with an antacid buffer, this has been discontinued as clinical trials have shown that

Brand Name	Manufacturer	No. of doses per schedule	India Private Retail Price	GAVI/WHO cost
Rotarix	GSK	2 doses	INR 1,099/dose for 1 dose vial Total cost: INR 2,198 (2 doses)	US$ 2.09/dose
Rotavac	Bharat Biotech	3 doses	INR 800/dose	US$ 1/dose (projected)
Rotateq	MSD	3 doses	INR 900/dose for 1 dose vial Total cost: INR 2,700 (3 doses)	US$ 3.50/dose

efficacy of the vaccine is at par with existing commercialized vaccines even without the antacid buffer. Bharat has indicated a manufacturing capacity of 300 million doses per year for this vaccine.

Global Public Health

Both GSK and Merck's vaccines are WHO pre-qualified and are extensively procured by GAVI/UNICEF and PAHO. UNICEF procured 30.1 million doses in 2014 for GAVI as part of an existing long term arrangement with GSK and Merck, to procure a cumulative of 152.5 million doses from 2012 to 2016 out of which GSK's vaccine accounts for 136.2 million doses and Merck's vaccine accounts for 16.3 million doses[25]. GSK's ROTARIX has significantly lower cost given the advantage of following a two-dose schedule while three doses are necessary to complete the schedule for Merck's ROTATEQ. Additionally, even the committed price to GAVI of $2.09 per dose for GSK's ROTARIX is significantly cheaper than the $3.5 per dose committed for Merck's ROTATEQ. Bharat's ROTAVAC is also a 3-dose vaccine but is touted to be approximately 40% cheaper[26]in the public health system than either of GSK and Merck vaccines (based on their lowest price) at an announced price of US$ 1 per dose[27].

Pipeline review

India Pipeline

There are several rotavirus vaccines under development from both large MNCs and regional players. The most notable ones include Shanta Biotech and Sanofi's tetravalent bovine reassortant candidate, currently under Phase 3 trials, and Serum Institute of India and PATH's pentavalent bovine reassortant candidate, which is also undergoing Phase 3 trials. Serum is expecting the supply for their rotavirus vaccine to be 10 million doses in the first year of the vaccine's launchwhich is expected around 2016-2017.

Global Development

In addition to these animal reassortant vaccines, Biofarma (Indonesia) and Murdoch Children's Research Institute (MCRI) (Australia) are developing a human monovalent vaccine, isolated from a neonatal rotavirus strain (G3P[6]) and is currently in Phase 3. In an alternative strategy developed, NIH and PATH are developing multiple vaccine candidates which utilize non-replicating viruses administered by

intramuscular injection. This approach is expected to overcome the reduced efficacy of existing live, oral vaccines in low-income settings which may be due to elevated maternal antibodies, potential interference by other oral vaccines, and co-infections of the digestive system[28,29,30].

The overall rotavirus vaccine research landscape is not only limited to alternative vaccine constituent strategies, but also includes extensive formulation research to develop more efficient vaccine forms. Hilleman Laboratories, formed through a joint venture partnership between Merck Sharp & Dohme Corp and Wellcome Trust in India, is currently developing a novel heat-stable formulation along with a suitable delivery mechanism and packaging for vaccine supplied by Merck. This is aimed towards limiting vaccine wastage and reducing dependence on cold storage, two major issues encountered when handling vaccines in developing countries. Hilleman Laboratories is aiming to commence clinical trials in 2015-16 in India for this heat-stable formulation and are exploring options for receiving an accelerated approval from the Drugs Controller General of India.

Rotavirus Vaccines- Commercial Details

Type of Vaccine	Brand Name	Manufacturer	India Licensure Status	WHO Pre-qualification Status	India Private Retail Price	GAVI/WHO cost*	India Prod^{n} Capacity (doses/year)
Human Monovalent	Rotarix	GSK	Import License *(Valid up to: Nov 2016)*	Pre-qualified in 2009	INR 1,270/dose for 1 ml dose vial	US$ 2.09/dose for 1 dose liquid vial	Not applicable
	Rotavac	Bharat Biotech	Licensed *(Valid up to: Dec 2016)*	Not pre-qualified (Expected to be pre-qualified in 2015)	INR 800/dose for 1 ml dose vial	US$ 1/dose (projected)	300 million
Human-Bovine Re-assortant Vaccine (BRV-PV)	Rotateq	Merck, Sharpe and Dohme (MSD)	Import License *(Valid up to: May 2016)*	Pre-qualified in 2008	INR 900/dose for 1 dose vial Total cost: INR 2,700 (3 doses)	US$ 3.50/dose for 1 dose liquid vial	Not applicable

Rotavirus Vaccines- Technical Details:

Type of Vaccine	Brand Name	Manufacturer	Strain/Subunit/ Serotype Coverage	Vaccine Constituents (per dose)	Presentation/Form
Human Monovalent	Rotarix	GSK	G1P[8] subunit RIX4414 strain Coverage for G1, G3, G4, G9 serotypes	Suspension of at least 10^6.0 median Cell Culture Infective Dose (CCID50) of live, attenuated human G1P[8] rotavirus after reconstitution; Excipients: Sucrose, Di-sodium Adipate, Dulbeccoís Modified Eagle Medium (DMEM), sterile water	Liquid + Lyophilized
	Rotavac	Bharat Biotech	P[11]+G9 116E strain	Bovine-human, neonatal, naturally reassorted, asymptomatic strain of Indian origin. Antacid is required as a buffer to address issue of potential inactivation rotaviruses in the stomach. Exact composition not available	Liquid + Lyophilized
Human-Bovine Re-assortant Vaccine (BRV-PV)	Rotateq	Merck, Sharpe and Dohme (MSD)	P1A[8], Human G1, G2, G3, G4; P7 from parent rotavirus bovine strain	Reassortant G1 2.2 X 10^6 infectious units; Reassortant G2 2.8 X 10^6 infectious units; Reassortant G3 2.2 X 10^6 infectious units; Reassortant G4 2.0 X 106 infectious units; Reassortant P1[8] 2.3 X 106 infectious units; Stabilizer: Sucrose (NF) 1080 mg; Stabilizer: Sodium Citrate Dihydrate (USP) 127 mg; Stabilizer: Sodium Phosphate Monobasic Monohydrate (USP) 29.8 mg; pH adjustment: Sodium Hydroxide (NF) 2.75 mg; Stabilizer: Polysorbate-80 (NF) 0.17-0.86 mg	Liquid

Rotavirus Vaccines- Clinical Details:

Type of Vaccine	Brand Name	Manufacturer	Mode of Administration	Age of Administration	Dose and Administration Schedule	Special Exclusion Criteria
Human Monovalent	Rotarix	GSK	Oral	≥6 weeks ≤24 weeks	1ml/dose 2 doses at 1 month intervals	Hypersensitivity to constituents, Gastrointestinal tract congenital malformation, SCID, history of Intussusception
	Rotavac	Bharat Biotech	Oral	≥6 weeks ≤16 weeks	2ml/dose 3 doses at 1 month intervals. First dose before 8 weeks, last dose before 16 weeks	Hypersensitivity to constituents, history of Intussusception, immunocompromised infants
Human-Bovine Re-assortant Vaccine (BRV-PV)	Rotateq	Merck, Sharpe and Dohme (MSD)	Oral	≥6 weeks ≤32 weeks	2ml/dose 3 doses- starting at 6 to 12 weeks of age, with the subsequent doses administered at 4- to 10-week intervals. The third dose should not be given after 32 week	Hypersensitivity to constituents, Immunocompromised infants

Rotavirus Vaccine- Packaging and Logistics Details:

Type of Vaccine	Brand Name	Manufacturer	Packaging Information	Cold Chain Volume (cm^3/dose)	Storage and Transportation Temperature	Shelf Life
Human Monovalent	Rotarix	GSK	**1 dose plastic squeezable tube** 1, 10 or 50 doses/carton **1 dose applicator-** 1, 10 doses/carton	**1 dose plastic squeezable tube-** 115.3 in 1 dose carton; 43.3 in 10 dose carton; 17.1 in 50 dose carton **1 dose applicator-** 134 in 1 dose carton; 85.3 in 10 dose carton	2-8°C	36 months
	Rotavac	Bharat Biotech	**Liquid stable frozen vaccine (0.5ml)+ 2.5 ml antacid separated:** 10 dose (5 ml) vial- Carton with 30 vials 4 dose (2 ml) vial- Carton with 30 vials *(This packaging has been discontinued)*	Not available	-20 ± 5°C (frozen);	36 months at -20 ± 5°C, 6 months at 2-8°C
			Liquid Buffered vaccine (2ml): 1 dose vial (2 ml)- Carton with 30 vials, 30 doses/carton	Not available	2-8°C	24 months
Human-Bovine Re-assortant Vaccine (BRV-PV)	Rotateq	Merck, Sharpe and Dohme (MSD)	**1 dose squeezable tube** 10 or 25 doses per carton	75.3 in 10 dose carton 46.33 in 25 dose carton	2-8°C	24 months

Rotavirus Vaccine- Pipeline Summary

Type of Vaccine	Vaccine Name	Originator(s), Collaborator(s)	Vaccine Information	Development Stage	Clinical Trial Location	Expected Launch
Human Bovine Re-assortment Vaccine		NIH, Shantha Biotech, Sanofi Pasteur	Tetravalent- G1, G2, G3, G4	Phase 3 completed	India	2015
	SIIL Rota Vaccine	NIH, Serum Institute of India, PATH	Pentavalent- Bovine (G6P[7]) + G1,G2,G3,G4, G9 reassortants	Phase 3	India, Niger (Africa)	2017

DTwP-HepB-Hib Prntavalent Vaccine

DTwP-HepB-Hib Pentavalent Vaccine

Overview

Annually across the world, diphtheria accounts for an average of 2,500 deaths[31], pertussis for 89,000 deaths[32], and tetanus for 72,600 deaths among children aged under five years[33]. Hepatitis B (HepB) alone accounts for between 500,000 and 700,000 deaths per year with most cases occurring in developing countries. Most cases of liver cancer across the world (60–80%) are also attributable to infection with the Hep B virus[34] Haemophilus influenzae type b (Hib) accounts for 200,000 annual deaths, with a disease incidence of two to three million cases; the most serious cases occur in children aged 6 to 12 months[35]. The pentavalent vaccine combines diphtheria, tetanus, whole cell pertussis, Hepatitis B and Haemophilus influenzae type b (DTwP-HepB-Hib) vaccines to prevent all five diseases. DTwP had been in use for decades and was the most common vaccine administered as part of routine immunization to children globally. The pentavalent combination vaccine is its natural successor in order to boost coverage of Hep B and Hib vaccines by including them as part of routine immunization while reducing the number of shots that would be required to immunize against each of the five diseases- 3 doses compared to 9 (3 each for DTP, Hep B and Hib). The whole-cell pertussis containing pentavalent (wP-pentavalent) vaccine was developed and targeted by industry primarily for the 'GAVI' market, thus profits are not being made in high income countries, and only to a limited degree in middle income countries[36].

Currently marketed products- Technical Review:

Brand Name	Manufacturer	Subunit
Quinvaxem	Berna Biotech (Crucell), Novartis, GSK	Hib conjugated to CRM 197 protein
Shan 5	Shantha Bio, Sanofi	HiB- Polyribosylribitol Phosphate-Tetanus Conjugate
Pentavac	Serum Institute of India	HiB- Polyribosylribitol Phosphate-Tetanus Conjugate
ComBEfive	Biological E	HiB- Polyribosylribitol Phosphate-Tetanus Conjugate
Pentahil	HLL Biotech Ltd	HiB- Polyribosylribitol Phosphate-Tetanus Conjugate
Easyfive-TT	Panacea Biotech	HiB- Polyribosylribitol Phosphate-Tetanus Conjugate
Comvac 5	Bharat Biotech	HiB- Polyribosylribitol Phosphate-Tetanus Conjugate
Tritanrix-HB+Hib	GSK	HiB- Polyribosylribitol Phosphate-Tetanus Conjugate

Commercialized pentavalent vaccines combining diphtheria, tetanus, whole cell pertussis, hepatitis B and Haemophilus influenzae type b (DTwP-HepB-Hib) vaccines mainly differ in the carrier proteins used for conjugation of their Hib components. In Quinvaxem (Crucell, Novartis, GSK), the Hib component is made of purified capsular oligosaccharides conjugated to CRM 197 (Cross Reacting Material), a non-toxic mutant of diphtheria toxin, prepared from *C. diphtheriae* cultures.

In other commercialized pentavalent vaccines, the Hib component is derived from highly purified capsular polysaccharide isolated from *Haemophilus influenza* type b coupled with Tetanus toxoid (Polyribosylribitol Phosphate-Tetanus Conjugate, PRP-TT). Both types of vaccines are administered intramuscularly with the immunization schedule consisting of 3 primary doses administered 4 weeks apart from 6 weeks after birth, along with a booster dose administered 12-24 months after birth.

Currently marketed products- Commercial Review:

India landscape

There are six manufacturers producing the pentavalent vaccine in India, with a total annual production capacity exceeding 700 million doses and is expected to rise with the inclusion of this vaccine in India's national immunization programme. However, most of this is sold in the public health system with 4 out of those 6 having a pre-qualified vaccine (except Bharat's Comvac 5 and HLL's newly launched Pentahil).

Six Indian manufacturers accounted for 20% of the global supply for pentavalent vaccine (~28 million doses) in 2014, which is expected to rise to approximately 25% in the next 5 years. The vaccine introductions by multiple Indian and other regional pentavalent vaccine manufacturers has created a competitive supply landscape, and in conjunction with the introduction of vaccines in 10-dose vials, has driven the cheapest public procurement price down from US$ 3.50/dose in 2001 to US$ 1.19/dose (10 dose vial of ComBEfive by Biological E) in 2014. Country presentation preferences have led to an increase in the 10-dose vial market share to approximately 70%, which is expected to rise up to roughly 80% by 2017[37].

Brand Name	Manufacturer	GAVI/WHO cost*	India Prod^{n} Capacity (doses/year)
Shan 5	Shantha Biotec, Sanofi	US$ 1.65/dose for liquid 10 dose vial	100 million
Pentavac	Serum Institute of India	US$ 2.7 /dose for single dose vial US$ 1.95-2.10/dose for 10 dose vial	200 million
ComBEfive	Biological E	Liquid+ lyophilized: US$ 1.80 (10-dose vial); Fully liquid: US$ 1.19 (10-dose vial) US$ 2.35 (1-dose vial)	130 million
Pentahil	HLL Biotech Ltd	Not applicable	100 million
Easyfive-TT	Panacea Biotech	US$ 1.94/dose for 10 dose liquid vial	86million
Comvac 5	Bharat Biotech	Not applicable	130 million

Despite these positives, some challenges, particularly from the Indian manufacturer's perspective remain. Shantha Biotechnics (Now part of Sanofi), previously had a WHO prequalified fully liquid, pentavalent vaccine – Shan5. Shan5 vaccine was withdrawn from WHO prequalified list for a period of four years, due to quality concerns. It has only regained WHO pre-qualification in year 2014. In 2011, Panacea Biotec had their pentavalent vaccine's (Easyfive-TT) WHO pre-qualification withdrawn due to inadequate quality control processes, but regained pre-qualification in 2013.

Recently, HLL Biological Ltd (a subsidiary of HLL Lifecare- Govt. of India) has forayed into manufacturing pentavalent vaccines through a licensing and tech transfer agreement with Biological E, and has established a capacity of 100 million doses per year.

Global public health

This is the first vaccine to be rolled out to all GAVI eligible countries and the global demand for pentavalent vaccine has grown significantly since 2009 and is expected to relatively stabilize from 2015 at ~300 million doses per year. Currently, GAVI procurement accounts for 85% of

the global market volume, and GAVI countries are expected to be the world's largest market for pentavalent vaccines through 2020[38]. There are several global and Indian companies involved in manufacturing the pentavalent vaccine.

Pipeline Review:

Theoretical global supply of prequalified 1- and 10-dose wP-pentavalent vaccines now likely exceeds 400 million doses per year and is expected to remain greater than demand over the long term (2020 and beyond). However, due to country specific supply uncertainties, particularly in India, public enterprises are developing capabilities to manufacture this vaccine. HLL Lifecare's recent technology transfer agreement with Biological E and significant capacity development to manufacture this vaccine is one such indicator. Another public enterprise, India Immunologicals Ltd is developing a DTwP-HepB-Hib pentavalent vaccine, which is currently in Phase 2 of clinical evaluation.

Pentavalent vaccine- Commercial Details

Type of Vaccine	Brand Name	Manufacturer	India Licensure Status	WHO Pre-qualification Status	India Private Retail Price	GAVI/WHO cost*	India Prod^{n} Capacity (doses/yr)
DTP-HepB-HiB Pentavalent Vaccine	Quinvaxem	Berna Biotech (Crucell), Novartis, GSK	Import License *(Valid up to: Dec 2016)*	Pre-qualified in 2006	INR 1,645/dose for 1 dose vial	US$ 2.40-2.60 for 1 dose vial	Not applicable
	Shan 5	Shantha Bio, Sanofi	Licensed *(Valid up to: Aug 2019)*	Pre-qualified in 2014	Not available	US$ 1.65/dose for liquid 10 dose vial	100 million
	Pentavac	Serum Inst. of India	Licensed *(Valid up to: Dec 2016)*	Pre-qualified in 2010	INR 585/dose for 1 dose vial	US$ 2.7 /dose for single dose vial US$ 1.95-2.10/dose for 10 dose vial	200 million
	ComBEfive	Biological E	Licensed *(Valid up to: Apr 2016)*	Pre-qualified in 2011	INR 580/dose for 1 dose vial	Liquid+ lyophilized: US$ 1.80 (10-dose vial); Fully liquid: US$ 1.19 (10-dose vial) US$ 2.35 (1-dose vial)	130 million
	Pentahil	HLL Biotech Ltd	Licensed	Not pre-qualified	Not available	Not applicable	100 million
	Easyfive-TT	Panacea Biotech	Licensed *(Valid up to: Sep 2017)*	Pre-qualified in 2013	INR 600/dose for 1 dose vial	US$ 1.94/dose for 10 dose liquid vial	86million
	Comvac 5	Bharat Biotech	Licensed *(Valid up to: Dec 2016)*	Not pre-qualified	INR 600/dose for 1 dose vial	Not applicable	130 million
	Tritanrix-HB+Hib	GSK	Not Licensed	Pre-qualified in 2003	Not applicable	US$ 2.95/dose for two dose lyophilized presentation	Not applicable

Pentavalent vaccine- Technical Details

Type of Vaccine	Brand Name	Manufacturer	Subunit	Vaccine Constituents (per dose)	Presentation
DTP-HepB-HiB Pentavalent Vaccine	Quinvaxem	Berna Biotech (Crucell), Novartis, GSK	Hib conjugated to CRM 197 protein	≥30 IU purified diphtheria toxoid; ≥60 IU purified tetanus toxoid; ≥4 IU inactivated B. pertussis whole-cell suspension; 10 µg HBsAg; 10 µg Hib oligosaccharide conjugated to approximately 25 µg of CRM197 protein and Aluminium phosphate (0.3mg Al3+) as adjuvant	Liquid
	Shan 5	Shantha Biotec, Sanofi Pasteur	HiB-Polyribosylribitol Phosphate-Tetanus Conjugate	Diphtheria Toxoid: ≥ 30 IU; Tetanus Toxoid: ≥ 60 IU; B. pertussis (Whole cell): ≥ 4 IU; Hepatitis B Surface Antigen (rDNA): 10 µg; Purified capsular polysaccharide of Hib conjugated to 20 – 40 µg of Tetanus Toxoid (carrier protein): 10 µg; Thiomersal I.P 0.05 mg; Aluminium Phosphate equivalent to Al+++ 0.625 mg; Sodium Chloride I.P 4.5 mg; Water for Injection I.P q.s. to 0.5 mL	Liquid
	Pentavac	Serum Inst. of India	HiB-Polyribosylribitol Phosphate-Tetanus Conjugate	Diphtheria Toxoid: ≤ 25 Lf (≥30 IU); Tetanus Toxoid ≥5 Lf (≥40 IU) B. pertussis (whole cell) ≤ 16 OU (≥ 4 IU) HBsAg (rDNA)≥ 10 µg; Purified Capsular Polysaccharide (PRP) 10 µg; Tetanus Toxoid (carrier protein) 19 to 33 µg; Adsorbed onto AluminiumPhosphate: ≤ 1.25 mg; Preservative: Thiomersal 0.005%	Liquid+ Lyophilized
				Diphtheria Toxoid: ≤ 25 Lf (≥30 IU); Tetanus Toxoid ≥ 2.5 Lf (≥ 40 IU); B. pertussis (whole cell) ≤ 16 OU (≥ 4 IU); HBsAg (rDNA)≥ 10 µg; Purified capsular Hib Polysaccharide (PRP) Conjugated to Tetanus Toxoid (carrier protein): 10 µg; Adsorbed on Aluminium Phosphate: ≤ 1.25 mg; Preservative: Thiomersal 0.005 %	Liquid

DTP-HepB-HiB Pentavalent Vaccine	ComBEfive	Biological E	HiB-Polyribosylribitol Phosphate-Tetanus Conjugate	Diphtheria Toxoid : > 30 IU; Tetanus Toxoid : > 60 IU; B.Pertussis(Whole cell) : > 4 IU; r-HBs Ag : 10 µg; Purified Capsular Polysaccharide (PRP): 10 µg Tetanus Toxoid (Carrier protein) 19 to 33 µg; Al+++ (as AlPO4) : < 1.25 mg; Preservative : Thiomersal BP 0.01%	Liquid + Lyophilized
				Diphtheria Formol Toxoid : >30 IU; Tetanus Formol Toxoid : > 60 IU; Bordetella Pertussis (Whole cell, Killed) > 4 IU; r-HBsAg :11 µg; Al+++ (as AlPO4) : < 1.25 mg; Preservative : Thiomersal : 0.01% w/v	Liquid
	Pentahil	HLL Biotech Ltd	HiB-Polyribosylribitol Phosphate-Tetanus Conjugate	Diphtheria Formol Toxoid: >30 IU; Tetanus Formol Toxoid : > 60 IU; Bordetella Pertussis (Whole cell, Killed) > 4 IU; r-HBsAg :11 µg; Al+++ (as AlPO4) : < 1.25 mg; Preservative : Thiomersal : 0.01% w/v	Liquid
	Easyfive-TT	Panacea Biotech	HiB-Polyribosylribitol Phosphate-Tetanus Conjugate	Diphtheria Toxoid: ≥ 30 IU; Tetanus Toxoid: ≥ 60 IU; Inactivated B. pertussis (Whole cell): ≥ 4 IU; Hepatitis B Surface Antigen (rDNA): 10 µg; Hib PRP-TT Conjugate:10 µg; Thiomersal I.P 0.025 mg; Aluminum Phosphate equivalent to Al+++ 0.25 mg; Physiological saline: q.s.	Liquid
	Comvac 5	Bharat Biotech	HiB-Polyribosylribitol Phosphate-Tetanus Conjugate	Diphtheria Toxoid: 30 IU; Tetanus Toxoid: 60 IU; Inactivated w-B. pertussis: 4 IU; HBsAg (rDNA): 10µg; Hib PRP-TT Conjugate: 10 µg; Aluminium Phosphate Gel as Aluminum (Al+++): 0.3 mg; Thiomersal (as Preservative) :0.025 mg	Liquid
	Tritanrix-HB+Hib	GSK	HiB-Polyribosylribitol Phosphate-Tetanus Conjugate	Diphtheria Toxoid: 30 IU; Tetanus Toxoid: 60 IU; Inactivated w-B. pertussis: 4 IU; HBsAg (rDNA): 10µg; Aluminum Hydroxide, hydrated: 0.26 mg; Aluminum Phosphate: 0.37 mg; Thiomersal, Sodium Chloride; Water for injections	Liquid + Lyophilized

Pentavalent Vaccine-Clinical Prescribing Details

Type of Vaccine	Brand Name	Manufacturer	Mode of Administration	Age of Administration	Dose and Administration Schedule	Special Exclusion Criteria
DTP-HepB-HiB Pentavalent Vaccine	Quinvaxem	Berna Biotech (Crucell), Novartis, GSK	Intramuscular Injection	Primary: ≥ 6 weeks Booster: 13-24 months	3 dose vaccine- 0.5 ml/dose Primary: 3 doses 1 month apart Booster: 1 dose	Hypersensitivity, acute febrile illness
	Shan 5	Shantha Bio, Sanofi	Intramuscular Injection	Primary: ≥ 6 weeks Booster: 13-24 months	3 dose vaccine- 0.5 ml/dose Primary: 3 doses 1 month apart Booster: 1 dose	Hypersensitivity, acute febrile illness, encephalopathy
	Pentavac	Serum Inst. of India	Intramuscular Injection	Primary: ≥ 6 weeks Booster: 15-18 months Reinforcing shot: 5 yrs	3 dose vaccine- 0.5ml/dose Primary: 3 doses 1 month apart Booster: 1 dose; Reinforcing shot: 1 dose	Hypersensitivity, acute febrile illness, abnormal cerebral signs
	ComBEfive	Biological E	Intramuscular Injection	Primary: ≥ 6 weeks	3 dose vaccine- 0.5ml/dose Primary: 3 doses 1 month apart	Hypersensitivity, acute febrile illness, abnormal cerebral signs
	Pentahil	HLL Biotech Ltd	Intramuscular Injection	Primary: ≥ 6 weeks	3 dose vaccine- 0.5ml/dose Primary: 3 doses 1 month apart	Hypersensitivity, acute febrile illness, abnormal cerebral signs
	Easyfive-TT	Panacea Biotech	Intramuscular Injection	Primary: ≥ 6 weeks	3 dose vaccine- 0.5ml/dose Primary: 3 doses 1 month apart	Hypersensitivity, acute febrile illness, abnormal cerebral signs
	Comvac 5	Bharat Biotech	Intramuscular Injection	Primary: ≥ 6 weeks Booster: 15-18 months Reinforcing shot: 4-6 yrs	3 dose vaccine- 0.5ml/dose Primary: 3 doses 1 month apart Booster: 1 dose; Reinforcing shot: 1 dose	Hypersensitivity, acute febrile illness, abnormal cerebral signs
	Tritanrix-HB+Hib	GSK	Intramuscular Injection	Primary: ≥ 6 weeks Booster: 12-24 months	3 dose vaccine- 0.5 ml/dose Primary: 3 doses 1 month apart; Booster: 1 dose	Hypersensitivity, acute febrile illness, encephalopathy. Subcutaneous administration for thrombocytopenia or bleeding disorder patients

Pentavalent Vaccines- Packaging and Logistics Details

Type of Vaccine	Brand Name	Manufacturer	Packaging Information	Cold Chain Volume (cm^3/dose)	Storage and Transport Temperature	Shelf Life
DTP-HepB-HiB Pentavalent Vaccine	Quinvaxem	Berna Biotech (Crucell), Novartis, GSK	• 1 dose vial- 1 carton with 50 vials • 1 dose pre-filled auto-disable device-1 carton with 240	• 10.28 for 1 dose vial carton • 15.2 for 1 dose device carton	2 - 8 °C	36 months
	Shan 5	Shantha Biotechnics, Sanofi Pasteur	• 1 dose vial (0.5 ml)-carton of 35 vials • 10 dose vial (5 ml)- carton of 30 vials	• 16.8 for 1 dose vial carton • 4.36 for 10 dose vial carton	2 - 8 °C	24 months
	Pentavac	Serum Institute of India	**Liquid + Lyophilized** • 1 dose ampoule DTPw-HepB (liquid) + 1 dose vial Hib (lyophilised)- 1 carton with 200 vial/ampoules each • 2 dose ampoule DTPw-HepB (liquid) + 2 dose vial Hib (lyophilised)- 1 carton with 200 vial/ampoules each • 10 dose vial DTPw-HepB (liquid) + 10 dose vial Hib (lyophilised)- 1 carton with 150 vial/ampoules each	**Liquid + Lyophilized** • 39.2 for 1 carton with 1+1 • 19.6 for 1 carton with 2+2 • 5.1 for 1 carton with 10+10	2 - 8 °C	24 months * 10 dose liquid vial can be kept for 28 days after opening
			Fully Liquid • 1 dose vial of 0.5 ml- 1 carton with 50 vials • 2 dose vial of 1 ml- 1 carton with 50 vials • 10 dose vial* of 5 ml- 1 carton with 50 vials	**Fully Liquid** • 26.1 for 1 carton of 1 dose vial • 13.1 for 1 carton of 2 dose vials • 2.6 for 1 carton of 10 dose vials		

Type of Vaccine	Brand Name	Manufacturer	Packaging Information	Cold Chain Volume (cm^3/dose)	Storage and Transport Temperature	Shelf Life
DTP-HepB-HiB Pentavalent Vaccine	ComBEfive	Biological E	**Liquid + Lyophilized:** • 1 dose vial DTP-HepB (liquid) + 1 dose vial Hib (lyophilized)- 1 carton with 24 1-dose vials of each • 10 dose vial DTP-HepB (liquid) + 10 dose vial Hib (lyophilized)- 1 carton with 15 10-dose vials of each	• 29.36 for 1 carton with 1+1 • 7.8 for 1 carton with 10+10	2 - 8 °C	24 months
			Fully Liquid: • 1 dose liquid vial- 1 carton of 48 vials • 2 dose liquid vial- 1 carton of 48 vials • 5 dose liquid vial- 1 carton of 48 vials • 10 dose liquid vial- 1 carton of 24 vials	• 14.6 for 1 dose vial carton • 7.3 for 2 dose vial carton • 2.9 for 5 dose vial carton • 2.9 for 10 dose vial carton		
	Pentahil	HLL Biotech Ltd	• 1 dose liquid vial, 10 dose liquid vial	Not available	2 - 8 °C	24 months
	Easyfive-TT	Panacea Biotech	• 1 dose vial- 1 carton of 800 vials • 10 dose vial- 1 carton of 600 vials	• 18.05 for 1 dose vial carton • 4.30 for 10 dose vial carton	2 - 8 °C	24 months
	Comvac 5	Bharat Biotech	• 1 dose, 5 dose and 10 dose vial • 1 dose pre-filled syringe	Not available	2 - 8 °C	24 months
	Tritanrix-HB+Hib	GSK	• 1 dose liquid Trinatrix HB + 1 dose lyophilized Hib • 2 dose liquid Trinatrix HB + 2 dose lyophilized Hib	Not available	2 - 8 °C	36 months

Pentavalent Vaccine- Pipeline Details

Type of Vaccine	Vaccine Name	Originator(s), Collaborator(s)	Vaccine Information	Development Stage	Clinical Trial Location	Expected Launch
DTP-HepB-HiB Pentavalent Vaccine	-	Human Biologicals Institute (Indian Immunologicals Ltd.)	-	Phase1/2	India	2016-2017

Typhoid Vaccine

Typhoid Vaccine:

Overview

Typhoid fever is an infectious disease endemic to South and Central America, the Middle East, South East Asia and India. It is estimated that more than 33 million cases of typhoid fever occur annually causing more than 500,000 deaths[39]. An estimated 90% of these deaths occur in Asia. *Salmonella enterica* serotype *typhi* causes typhoid fever, which is characterized by fever, headache, abdominal pains, diarrhea, paradoxical bradycardia and various other symptoms. The disease is transmitted through the fecal-oral route and is most common in areas with poor water and sanitation systems and practices. The emergence of multi drug resistant to *S.typhi* (MDRST), reduces the effective treatment options, increases treatment costs and results in higher rates of serious complications and deaths[40].

Type of Vaccine	Brand Name	Manufacturer	Doses/Regimen
Vi Capsular Polysaccharide Vaccine	TYPHIM-Vi	Sanofi- Pasteur (Cadila Pharma markets in India)	1
	Bio-Typh	Bio-Med Pvt. Ltd.	1
	Typbar	Bharat Biotech	1
	Typherix	GSK	1
Vi Conjugate Vaccine	Peda-Typh	Bio-Med Pvt. Ltd.	1
	Typbar TCV	Bharat Biotech	1
Ty21O ral	Typhoral	Sanofi Pasteur	4

Marketed Products- Technical Overview

Two new-generation typhoid vaccine typesnamely injectable Vi Polysaccharide and live oral Ty21a have replaced the old, reactogenic inactivated whole-cell vaccines. These new-generation vaccines types have been shown in large-scale clinical trials to be safe and moderately efficacious and are internationally licensed for two years and olderindividuals. The single-dose injectable Vi vaccine provides around 70% protection, and protection lasts at least three years[41]. The liquid formulation of Ty21a – the formulation most likely to be used in developing countries– is given in 3-4 doses, each spaced two days apart and provides 53-78% protection, and protection has been documented for at least five years[42].

Injectable Vi polysaccharide and Ty21 oral vaccines have not been backed by any of the major international funders due to the fact that they are not effective in young children (under age two) and only provide a moderate duration of protection before re-vaccination is required, and have a high cost per dose. In recent years another class of vaccines, the typhoid conjugate vaccine has been approved for pediatric use. The main advantage of vaccines conjugated to proteins is the stimulation of T-cell dependent immune response. The implication of this is that infants with relatively less mature immune systems respond to this vaccine type. There are two typhoid conjugate vaccines licensed in India (produced by Bharat Biotech- Typbar TCV and Bio-med- Peda-typh) and about five in the pipeline globally (including one Indian company Biological-E).

Marketed Products - Commercial Overview

India landscape

Currently there are several manufacturers with commercialized typhoid vaccines in the market, with Bharat Biotech and Bio-Med Pvt. Ltd manufacturing in India. All of them manufacture the Vi Capsular Polysaccharide vaccine type, with Bharat Biotech and Bio-Med Pvt. Ltd additionally marketing the Vi-conjugate (Vi-TT) vaccine. This type of vaccine is only licensed in India and is available in the private market. Sanofi's Typhim-Vi is the only WHO pre-qualified typhoid vaccine in the world, and is imported and marketed in India by Cadila Pharmaceuticals. Crucell's (J&J) oral, live attenuated vaccine Vivotif is not licensed for use in India.

Type of Vaccine	Brand Name	Manufacturer	India Private Retail Price	India Prod^{n} Capacity (doses/year)
Vi Capsular Polysaccharide Vaccine	TYPHIM-Vi	Sanofi- Pasteur (Cadila Pharma markets in India)	INR 300/dose for 1 dose vial	Not applicable (Product Imported)
	Bio-Typh	Bio-Med Pvt. Ltd.	Not available	4 million
	Typbar	Bharat Biotech	INR 175/dose for 1 dose vial; INR 105/dose for 5 dose vial	30 million
	Typherix	GSK	Not available	Not applicable (Product Imported)
Vi Conjugate Vaccine	Peda-Typh	Bio-Med Pvt. Ltd.	Not available	Not available
	Typbar TCV	Bharat Biotech	Not available	Not available

Global public health

As highlighted in the technical overview above, the typhoid polysaccharide vaccines have not been funded by any international funders. However, with the emergence of the typhoid conjugate vaccines that could be administered to children below 2 years of age. The 'Coalition Against Typhoid' has been advocating for its adoption in public health programs and the GAVI expects to start funding it in the latter half of the 2016-2020 funding window as and when WHO prequalified vaccines become available. Routine and campaign vaccination with typhoid conjugate vaccine are currently projected to start in year 2018 in GAVI supported countries. Total required supply of the typhoid conjugate vaccine is forecast to reach approximately 30 million doses at a steady state for 73 GAVI typhoid-endemic countries. It is projected that, by 2020, 16 countries will introduce typhoid conjugate vaccination with Alliance support and GAVI-eligible demand is projected to peak in 2021 at 78 million doses/year.[43]

Pipeline Review

India

Biological E entered into a technology transfer arrangement with Novartis Vaccine Institute for Global Health (NVGH) in 2013 for a typhoid conjugate vaccine candidate[44]. The candidate is a Vi-CRM 197 glycol-conjugated vaccine with the Vi polysaccharide of S.Typhi and O polysaccharide of S. Paratyphi A conjugated to the carrier protein CRM-197. NVGH had completed Phase 2 trial prior to the technology transfer. Additionally, we understand Cadila Healthcare is also a developing a typhoid conjugate vaccine with tetanus toxoid as the carrier protein but no additional information on the program is available in the secondary domain. Additionally, Shantha Biotechnics also had a pipeline candidate that was licensed from the International Vaccine Institute, Korea (and had received NIH development support as well). However, we secondary sources indicate that the program has been halted.

Global pipeline

There are about five typhoid conjugate vaccine candidates currently under development per Coalition against Typhoid. Technology source for majority of them has been IVI, NIH and Novartis Vaccines Institute for Global Health.

Typhoid Vaccines-Commercial Details

Type of Vaccine	Brand Name	Manufacturer	India Licensure Status	WHO Pre-qualification Status	India Private Retail Price	GAVI/WHO cost*	India Prod^{n} Capacity (doses/year)
Vi Capsular Polysaccharide Vaccine	TYPHIM-Vi	Sanofi- Pasteur (Cadila Pharma markets in India)	Import License (*Valid up to: Dec 2017)*	Pre-qualified in 2011	INR 300/dose for 1 dose vial	Not applicable	Not applicable
	Bio-Typh	Bio-Med Pvt. Ltd.	Licensed (*Valid up to: Dec 2016)*	Not pre-qualified	INR 160/dose for 1 dose vial	Not applicable	4 million
	Typbar	Bharat Biotech	Licensed (*Valid up to: Dec 2016)*	Not pre-qualified	INR 175/dose for 1 dose vial INR 105/dose for 5 dose vial	Not applicable	30 million
	Typherix	GSK	Import License (*Valid up to: Dec 2016)*	Not pre-qualified	INR 250/dose for 1 dose vial	Not applicable	Not applicable
Vi Conjugate Vaccine	Peda-Typh	Bio-Med Pvt. Ltd.	Licensed	Not pre-qualified	Not available	Not applicable	Not available
	Typbar TCV	Bharat Biotech	Licensed	Not pre-qualified	INR 1,799/dose for 1 dose pre-filled syringe	Not applicable	Not available
Live Attenuated Vaccine	Vivotif	Crucell (J&J)	Not Licensed	Not pre-qualified	Not applicable	Not applicable	Not applicable

Typhoid Vaccines-Technical Details

Type of Vaccine	Brand Name	Manufacturer	Strain	Vaccine Constituents (per dose)	Presentation/Form
Vi Capsular Polysaccharide Vaccine	TYPHIM-Vi	Sanofi- Pasteur	Salmonella typhi-Ty2 strain	Polysaccharides of Salmonella typhi (Ty2 strain): 25 µg; Phenol, sodium chloride, disodium phosphate dihydrate, sodium dihydrogen phosphate dihydrate and water for injections	Liquid
	Bio-Typh	Bio-Med Pvt. Ltd.	Salmonella typhi-Ty2 strain	Vi polysaccharide of Salmonella typhi: 25 µg; Phenol (I.P.) (preservative) max.: 0.25%; Isotonic saline q.s.: 0.5 ml	Liquid
	Typbar	Bharat Biotech	Salmonella typhi-Ty2 strain	Vi Capsular polysaccharide of Salmonella typhi (Ty2 strain)-25µg; Phenol and buffer solution containing sodium chloride; Disodium phosphate; Monosodium phosphate; Water for injection	Liquid
	Typherix	GSK	Salmonella typhi-Ty2 strain	Typhoid Vaccine Vi Polysaccharide- 25 µg; Sodium phosphate dehydrate; Disodium phosphate dehydrate; Sodium chloride; Phenol; Water for injection	Liquid
Vi Conjugate Vaccine	Peda-Typh	Bio-Med Pvt. Ltd.	Salmonella typhi-Ty2 strain conjugated to tetanus toxoid	Vi polysaccharide of Salmonella typhi 5 µg conjugated to 5 µg of Tetanus toxoid protein in isotonic saline	Liquid
	Typbar TCV	Bharat Biotech	Salmonella typhi-Ty2 strain conjugated to tetanus toxoid	Purified Vi-capsular polysaccharide of S. typhi Ty2 conjugated to Tetanus toxoid- 25 µg; Sodium chloride- 4.5 mg; Water for injection (WFI)- q.s. to 0.5 ml	Liquid
Live Attenuated Vaccine	Vivotif	Crucell	Salmonella typhi-Ty21a strain	Viable *S. typhi* Ty21a 2.0–10.0x109 colony-forming units*; Non-viable *S. typhi* Ty21a 5–50x109 bacterial cells; Sucrose 3.3 – 34.2 mg; Ascorbic acid 0.2 – 2.4 mg; Amino acid mixture 0.3 – 3.0 mg; Lactose up to 180 - 200 mg; Magnesium stearate 3.6–4.0 mg	Capsule

Typhoid Vaccines-Clinical Details

Type of Vaccine	Brand Name	Manufacturer	Mode of Administration	Age of Administration	Dose and Administration Schedule	Special Exclusion Criteria
Vi Capsular Polysaccharide Vaccine	TYPHIM-Vi	Sanofi- Pasteur	Intramuscular/ Subcutaneous Injection	≥ 2 years	1 dose (0.5ml) vaccine; Revaccination performed every 3 years if risk of exposure continues	Hypersensitivity to constituents; fever, an acute disease, a progressive chronic disease; pregnancy; age below 2 years
	Bio-Typh	Bio-Med Pvt. Ltd.	Intramuscular/ Subcutaneous Injection	≥ 2 years	1 dose (0.5ml) vaccine; Revaccination performed every 3 years if risk of exposure continues	Hypersensitivity to any constituent; Pregnant and lactating women; fever or severe infection; age below 2 years
	Typbar	Bharat Biotech	Intramuscular Injection	≥ 2 years	1 dose (0.5ml) vaccine; Revaccination performed every 3 years if risk of exposure continues	Hypersensitivity; Not to be administered intravascular under any circumstances
	Typherix	GSK	Intramuscular Injection	≥ 2 years	1 dose (0.5 ml) vaccine, 2 weeks before travel to endemic region	Hypersensitivity to constituents

Vi Conjugate Vaccine	Peda-Typh	Bio-Med Pvt. Ltd.	Intramuscular or Subcutaneous Injection	≥ 3 months	**Between 3 months to 2 years:** 2 injections of one dose each at interval of 4-8 weeks, followed by booster at 2 to 2.5 years age; Re-vaccination every 10 years; **Above 2 years :** 2 injections of one dose each at interval of 4-8 weeks. Booster vaccination every 10 years.	Hypersensitivity to any constituent; Pregnant and lactating women; fever or severe infection
	Typbar TCV	Bharat Biotech	Intramuscular Injection	>=6 months	1 dose (0.5ml) vaccine; Revaccination performed every 3 years if risk of exposure continues	Hypersensitivity; Not to be administered intravascular under any circumstances
Live Attenuated Vaccine	Vivotif	Crucell	Oral	>= 6 years	Primary: 4 doses (capsules taken alternate days) Booster**:** given at an interval of not more than 5 years	Hypersensitivity to constituents

Typhoid Vaccines- Packaging and logistics Details

Type of Vaccine	Brand Name	Manufacturer	Packaging Information	Cold Chain Volume (cm^3/dose)	Storage and Transportation Temperature	Shelf Life
Vi Capsular Polysaccharide Vaccine	TYPHIM-Vi	Sanofi- Pasteur	20 dose vial (10 ml)- 1 box of 10 vials	1.58 (in 10 vial carton)	2 - 8 °C	36 months
	Bio-Typh	Bio-Med Pvt. Ltd.	1 dose vial (0.5 ml); 5 dose vial (2.5 ml)	Not available	2 - 8 °C	Not available
	Typbar	Bharat Biotech	1 dose (0.5 ml), 5 dose (2.5 ml), 10 dose (5 ml) vials; 1 dose (0.5ml) Pre-filled syringe	Not available	2-8°C	36 months
	Typherix	GSK	1 dose (0.5 ml) pre-filled syringe in packages of 1,10,50 and 100 syringes	Not available	2-8°C	Not available
Vi Conjugate Vaccine	Peda-Typh	Bio-Med Pvt. Ltd.	1 dose vial (0.5 ml)	Not available	2 - 8 °C	Not available
	Typbar TCV	Bharat Biotech	1 dose (0.5 ml), 5 dose (2.5 ml) vial; 1 dose (0.5 ml) pre-filled syringe	Not available	2 - 8 °C	24 months
Live Attenuated Vaccine	Vivotif	Crucell	A single foil blister contains 4 doses of vaccine in a single package	Not available	2-8°C	Not available

Typhoid Vaccines- Pipeline Details

Type of Vaccine	Vaccine Name	Originator(s), Collaborator(s)	Vaccine Information	Development Stage	Clinical Trial Location	Expected Launch
Vi Conjugate Vaccine	-	Biological E, Novartis Vaccine Institute for Global Health (NVGH)	Vi-CRM 197 glycol-conjugated vaccine; Vi polysaccharide of S.Typhi and O polysaccharide of S. Paratyphi A to the carrier protein CRM-197	Phase 2 completed	US	-
Vi Conjugate Vaccine	-	Cadila Healthcare[45] (Zydus-Cadila)	Conjugate vaccine (Vi-TT)	Phase 1	India	-

Japanese Encephalitis Vaccine

Japanese Encephalitis Vaccine

Overview

Japanese encephalitis (JE) is a vector-borne viral disease that occurs in South Asia, Southeast Asia, East Asia, and the Pacific. There are about 3 billion people living in regions endemic to JE virus with annual incidence of the disease being 30,000- 50,000 cases[46]. The disease can cause irreversible neurologic damage. The JE virus (JEV) is mainly transmitted by the mosquito *Culex tritaeniorhynchus*, which prefers to breed in irrigated rice paddies. JE virus is maintained in a cycle involving mosquitoes and vertebrate hosts, mainly pigs and wading birds. Humans can be infected when bitten by an infected mosquito. Most human infections are asymptomatic or result in only mild symptoms. The annual number of human deaths is 10,000–15,000, and the estimated global impact from JE in 2002 was 709,000 disability-adjusted life years (DALYs)[47]. Steps to prevent JE include using personal protective measures to prevent mosquito bites and vaccination.

Currently marketed products - Technical Overview

JE vaccines first became available in 1950's. Currently, there are four different types of JE vaccines.

1. Inactivated mouse brain-derived vaccines (first generation vaccines)
2. Inactivated Vero cell vaccines
3. Live attenuated vaccines
4. Chimeric vaccines

The first generation inactivated mouse brain-derived (IMB) JE vaccine by Green Cross Corporation (JenceVax) has now been commonly replaced by cell culture-based vaccines. A live attenuated vaccine cultured in Primary Hamster Kidney (PHK) cells manufactured by Chengdu Institute of Biological Products, is based on the SA_{14}-14-2 strain of the JE virus and is widely used in China and in an increasing number of countries within the Asian region, including India (licensed by HLL Lifecare Ltd.), the Republic of Korea, Sri Lanka, and Thailand. The other

vaccine commonly used is Vero cell-derived, inactivated and alum-adjuvanted JE vaccine based on the SA $_{14}$-14-2 strain that was approved in 2009 in North America,

Vaccine type	Brand name	Manufacturer	Strain type
Inactivated (mouse brain cells)	JenceVax	Green Cross Corporation	Nakayama
Inactivated (PHK cells)	SA_{14}-14-2 JE CD.JEVAX	Chengdu Institute of Biological Products (CDIBP)	SA_{14}-14-2
Inactivated (Vero cells)	IXIARO IC51/JE-VC/JESPECT	Intercell/ Valneva	SA_{14}-14-2
Inactivated (Vero cells)	JEEV	Biological E	SA_{14}-14-2
Inactivated (Vero cells)	JENVAC	Bharat Biotech	JEV 821564-XY (Kolar strain)
Live chimeric (Vero cells)	IMOJEV MD (JE-CV/ChimeriVax-JE)	Sanofi Pasteur	SA14-14-2/Yellow Fever 17D

Australia and various European countries. The vaccine was developed by Intercell/Valneva, a European vaccine manufacturing company and is marketed as IXIARO in the USA and JESPECT in Australia and New Zealand. This vaccine is licensed in India and available under the brand name JEEV by Biological E. Another Indian vaccine manufacturer, Bharat Biotech has developed a JE vaccine based on a local JEV 821564-XY strain (Kolar strain) and markets it in India under the brand name JENVAC. In addition, a new live attenuated, JE–yellow fever chimeric vaccine IMOJEV MD (JE-CV/ChimeriVax-JE) has recently been licensed in Australia and Thailand by Sanofi Pasteur (as described in the table on left). A single dose of this chimeric JE vaccine was found to be safe, highly immunogenic and capable of inducing long-lasting immunity in both preclinical and clinical trials[48].

Type of vaccines and their dosing schedules

1. **Live attenuated vaccine (SA $_{14}$-14-2 strain)**, the first dose is given subcutaneously at age 8 months, followed by a booster dose at 2 years of age. In some areas, an additional booster is offered at 6–7 years of age. However, protection for several years may be achieved with a single dose of this vaccine, and in many countries one dose without subsequent boosters is recommended.

2. **Inactivated, Vero cell-derived (SA_{14}- 14-2 strain),** alum-adjuvant vaccine consists of two intramuscular primary doses, 4 weeks apart. A booster is recommended after 1 year.

3. **Inactivated Vero cell-derived vaccines (Beijing-1)** strain consists of three doses at days given at 0, 7 and 28, or two doses given preferably 4 weeks apart (0.25 ml for children <3 years, 0.5 ml for all other ages). One booster is recommended 12–14 months after completion of the primary immunization and thereafter every 3 years.

4. **Live chimeric vaccine (with yellow fever 17D as backbone)**, a single dose is recommended; the need for and timing of a possible booster dose have not yet been determined. (Please refer to the table below for more clinical details)

Currently marketed products- Commercial Overview

India landscape

Four new vaccines have been introduced into the country's Universal Immunization Program (UIP), including Japanese Encephalitis in 2014. To control JE, the Government of India has decided to introduce and expand JE vaccination to the JE endemic districts of the country in a phased manner and Japanese Encephalitis (JE) will be rolled out in 179 endemic districts in 9 states in the country as per announcements made by Government of India in 2014[49]. India has procured between 13–33 million doses of JE vaccine annually from Chengdu Institute of Biological Products, China (CDIBP) to support its rolling campaigns in targeted districts as a single-dose intervention, and subsequent use in routine immunization programs in districts in the years following campaign completion. Routine immunization in India will likely transition from a one-dose to a two-dose series in 2014 to increase coverage in targeted populations, potentially doubling demand to approximately 17 million doses of vaccine annually[50]. Currently, there are two Indian companies Biological E and Bharat Biotec (as mentioned in table), manufacturing JE vaccine in the country today.

Manufacturer	Vaccine Brand	Production capacity
Biological E	JEEV (WHO pre-qualified)	20 million
Bharat Biotec	JENVAC	30 million
Total volume		**50 million**

Manufacturer	Vaccine Brand	Price/dose in Indian retail market
Biological E	JEEV	INR 985
Bharat Biotec	JENVAC	INR 160
Chengdu Institute of Biological Products (CDBIP)	JE-CD.JEVAX	Not available (direct govt. procurement through HLL)

The total volume manufactured is 50 million doses annually[51]. Two vaccines JEEV by Biological E and JENVAC by Bharat Biotech are licensed in India at a retail price of INR 985/dose and INR 160/dose respectively. Chengdu Institute of Biological Products (CDBIP) also has import license and is procured by HLL Lifecare Ltd. for usage in national vaccination program (Refer table alongside).During primary research, Biological E's management confirmedthat the company has conductedadditional clinical trials to strengthen already available clinical data for their brand JEEV,it is now licensed for sale in India and is expected to receive WHO prequalified soon. Bharat Biotech indicated that the company intends to apply for WHO prequalification for JENVAC in the near future.

Global public health

Brand name	Manufacturer	WHO pre-qualification	Price commitment
SA_{14}-14-2 JE CD.JEVAX	Chengdu Institute of Biological Products (CDIBP)	Pre-qualified	1 million vials- $0.4220 1 million vials < Order <= 3 million vials- $0.4180 3 million vials < Order <= 5 million vials- $0.41405M vials- $0.4100
JEEV	Biological E	Pre-qualified	Not available
IMOJEV MD (JE-CV/ChimeriVax-JE)	Sanofi Pasteur	Pre-qualified	Not available

The GAVI Alliance supports JE vaccination campaigns in endemiccountries with the objective of reducing JE cases in targeted GAVI countries and to impact the JE market in such a way that countries continue to benefit from improved supply and sustainable prices after GAVI funding of catch-up campaigns ends and GAVI is no longer purchasing JE vaccines. The global demand for JE vaccine is currently estimated at approximately 75-100 million doses annually[52]. The majority of demand is steady and driven by routine immunization in large countries, including China (~50 million doses annually), Japan and South Korea. Smaller but still significant markets such as Thailand, Malaysia and the Philippines also contribute to global demand. Several non-GAVI countries also have routine immunization programs driving demand for JE vaccines. A small amount of global demand - probably less

than 5 million doses - is driven by travel immunization, military use, outbreak response, and private market purchases in India and 5 to 10 developed markets. The GAVI Alliance is forecast to support mass preventive campaigns of Japanese encephalitis vaccines in 5 endemic countries by 2020. GAVI demand for these vaccines is projected to peak above 30 million doses in 2017 and 2018[5]. The vaccines listed below are prequalified by WHO:

1. Live attenuated vaccine based on the SA 14-14-2 strain (Chengdu Institute of Biological Products [CDIBP], China)
2. Inactivated vaccine based on the SA 14-14-2 strain for adult use (Biological E. Ltd, India)
3. Live chimeric vaccine based on yellow fever backbone (Sanofi Pasteur)

Pipeline Review

Currently, the development pipeline for new JE vaccines in India is not dense. There are two candidates in preclinical and R&D stages from Indian Immunologicals Ltd. (live vaccine) and Panacea Biotec (inactivated vaccine). We donot note any global developments on next generation products globally.

Type of Vaccine	Vaccine Name	Originator(s), Collaborator(s)	Vaccine Information	Development Stage	Expected Launch
Live	-	Indian Immunologicals Ltd	-	Preclinical/R&D	-
Inactivated	-	Panacea Biotec	-	R&D	-

Japanese encephalitis Vaccines-Commercial Details

Type of Vaccine	Brand Name	Manufacturer	India Licensure Status	WHO pre-qualification status	India Retail Price	GAVI/WHO cost	India Production Capacity (doses/year)
Inactivated (Mouse Brain)	JenceVax	Green Cross Corporation	Not Licensed	Not pre-qualified	INR 750/dose for (5 dose vial)	Not applicable	Not applicable
Inactivated (Vero Cell)	IXIARO IC51/JE-VC/JESPECT	Intercell, Valneva	Not Licensed	Not pre-qualified	Not applicable	Not applicable	Not applicable
	JEEV	Biological E	Licensed *(Valid up to: Apr 2016)*	Pre-qualified in 2013	INR 985/dose	Not available (Not procured till now)	20 million
	JENVAC	Bharat Biotech	Licensed *(Valid up to: Dec 2016)*	Not pre-qualified	INR 160/dose	Not applicable	30 million
Live attenuated (PHK)	SA14-14-2 JE CD.JEVAX	Chengdu Institute of Biological Products (Imported by HLL Lifecare Ltd.)	Import License *(Valid up to: May 2018)*	Pre-qualified	Not applicable (Govt. procurement only)	**2015:** 1 million vials- $0.4220 1 million vials < Order <= 3 million vials- $0.4180 3 million vials < Order <= 5 million vials- $0.4140 5 million vials- $0.4100	Not applicable
Live Chimeric (Vero)	IMOJEV MD (JE-CV/ChimeriVax-JE)	Sanofi Pasteur	Not Licensed	Pre-qualified	Not applicable	Not available (Not procured till now)	Not applicable

Japanese encephalitis Vaccines-Technical Details

Type of Vaccine	Brand Name	Manufacturer	Strain/Serotype Information	Vaccine Constituents (per dose)	Presentation/Form
Inactivated (Mouse Brain)	JenceVax	Green Cross Corporation	Nakayama strain	Inactivated JE virus suspension (Nakayama strain)-1 ml, Potassium phosphate monobasic (buffer)- q.s., Sodium phosphate, dibasic (buffer)-q.s., Sodium chloride (isotonic agent)-q.s., Purified gelatin (stabilizer)- q.s., Polysorbate 80 (stabilizer)- q.s., Thimerosal (preservative)- 0.0015 w/v%, Water for injection- q.s.	Liquid
Inactivated (Vero Cell)	IXIARO IC51/JE-VC/JESPECT	Intercell/Valneva	SA_{14}-14-2 strain	JE virus strain SA_{14}-14-2 (inactivated)1,2 6 µg corresponding to a potency of ≤ 460 ng ED_{50} produced in Vero cells adsorbed on aluminium hydroxide, hydrated (approx. 0.25 mg Al^{3+}) total protein **Excipients:** Potassium < 1mmol, sodium <1mmol, Phosphate Buffered Saline 0.0067 M (in PO4) has the following saline composition- NaCl – 9mg/ml, KH2PO4 – 0.144 mg/ml, Na2HPO4 – 0.795 mg/ml	Liquid
	JEEV	Biological E	SA_{14}-14-2 strain	**Adult:** JE virus strain SA_{14}-14-2 JE (inactivated)- 6 µg corresponding to potency of <90 ng ID_{50} **Pediatric:** JE virus strain SA_{14}-14-2 JE (inactivated)- 3 µg corresponding to potency of <90 ID_{50} (adsorbed on aluminum hydroxide, hydrated 0.25 mg Al^{3+}) **Excipients:** Phosphate buffered saline with Sodium chloride, Potassium dihydrogen phosphate, Disodium hydrogen phosphate, Water for injection, Aluminum as aluminum hydroxide hydrate	Liquid
	JENVAC	Bharat Biotech	Kolar strain JEV 821564-XY strain	Purified, inactivated JE virus protein-NLT 5.0 µg, Adjuvant- Aluminium hydroxide gel; 0.25 mg, Preservative- Thiomersal; 0.025 mg, Diluent- Phosphate buffered saline; q.s. to 0.5 ml (sodium chloride, potassium dihydrogen phosphate, disodium hydrogen phosphate)	Liquid

Live attenuated (PHK)	SA14-14-2 JE CD.JEVAX	Chengdu Institute of Biological Products (CDIBP)	SA_{14}-14-2 strain	Live attenuated virus- not less than 5.4 lg PFU, Gelatin- 1.28 mg, Sucrose- 5.6 mg, Lactose- 5.6 mg, Carbamide- 0.64 mg, Human Serum Albumin- 0.48 mg, Residual antibiotic: gentamicin- not more than 50 ng, Diluent composition- sterile phosphate buffered saline (PBS)	Lyophilized
Live Chimeric (Vero)	IMOJEV MD (JE-CV/ChimeriVax-JE)	Sanofi Pasteur	SA14-14-2 strain /Yellow Fever 17D	Live, attenuated, recombinant JE virus- 4.0-5.8 log Plague Forming Unit (PFU) per dose (0.5 ml) **Excipients:** Mannitol, lactose, glutamic acid, potassium hydroxide, human serum, albumin, sodium chloride, water for injection No adjuvant or antimicrobial preservative is added	Lyophilized

Japanese encephalitis Vaccines-Clinical Details

Type of Vaccine	Brand Name	Manufacturer	Mode of Administration	Age of Administration	Dose and Administration Schedule	Special Exclusion Criteria
Inactivated (Mouse Brain)	JenceVax	Green Cross Corporation	Injection	12-23 months	**Primary:** 3 doses (0/7-30 days/>6 months) **Booster:** 2 doses Ages 6 years and 12 years	Fever or severe dystrophy; Cardiovascular, renal or hepatic diseases with acute or active phase; Hypersensitivity; Individuals who have experienced convulsions within 1 year prior to vaccination; Pregnant women
Inactivated (Vero Cell)	IXIARO IC51/JE-VC/JESPECT	Intercell/Valneva	Intramuscular injection	>=17 years (>=2 months in US)	**Primary:** 2 doses (0/28 days) **Booster:** 1 dose 1 year	Not to be administered intravascular; Hypersensitivity; Should not be administered intramuscularly to persons with bleeding disorders
	JEEV	Biological E	Intramuscular injection	>=18 years, <=49 years (In India 1-3 years)	**Primary:** 2 doses (0/28 days) **Adults**- 0.5 ml **Pediatric**- 0.25 ml	Hypersensitivity; Postponed administration in persons with severe febrile conditions; Not be given intravenously under any circumstance; Not to be administered in patients with bleeding disorders
	JENVAC	Bharat Biotech	Intramuscular injection	>=1 years	**Primary:** 2 doses (0/28 days) **Booster:** 1 dose >1 years	Not to be administered intravascular, intradermal or subcutaneous under any circumstances; Hypersensitivity

Live attenuated (PHK)	SA14-14-2 JE CD.JEVAX	Chengdu Institute of Biological Products (CDIBP)	Subcutaneous injection	>= 8 months	**Primary**: 1 dose **Booster**: 9-12 months, or age 2 year in some countries	Hypersensitivity
Live Chimeric (Vero)	IMOJEV MD (JE-CV/ChimeriVax-JE)	Sanofi Pasteur	Subcutaneous injection	>1 year	**Primary:** 1 dose **Booster** (pediatric): Age 2 year	Hypersensitivity; Postpone vaccination in case of febrile or acute disease; Congenital or acquired immune deficiency impairing cellular immunity including immunosuppressive therapies; Not to be administered in patients with asymptomatic HIV infection accompanied by impaired immune function; Pregnancy and lactation

Japanese encephalitis Vaccines-Packaging and logistics Details

Type of Vaccine	Brand Name	Manufacturer	Packaging Information	Cold Chain Volume (cm^3/dose)	Temperature for Storage and Transportation	Shelf Life
Inactivated (Mouse Brain)	JenceVax	Green Cross Corporation	Not available	Not available	2°-8°C	18 months
Inactivated (Vero Cell)	IXIARO IC51/JE-VC/JESPECT	Intercell/Valneva	0.5 ml of sterile suspension in a pre-filled syringe (Type I glass) with a plunger stopper Pack size of 1 syringe with or without a separate needle	Not available	2°-8°C	24 months
	JEEV	Biological E	**1 dose-** 0.5 ml per vial **Secondary Packaging:** carton of 48 vials (Adults- 48 doses; Pediatric-96 doses) **Tertiary Packaging:** 24 cartons with a total 1152 vials (adults- 1152 doses; pediatric- 2304 doses)	1 dose vial-14.7 (7.4 for pediatrics)	2°-8°C	24 months
	JENVAC	Bharat Biotech	Single dose- 2 ml glass vial Multi dose- 3 ml glass vials 1 ml glass syringe containing inactivated JE vaccine (0.5 ml dose injected)	Not available	2°-8°C	24 months

Live attenuated (PHK)	SA14-14-2 JE CD.JEVAX	Chengdu Institute of Biological Products (CDIBP)	1 dose vial (0.5 ml)- secondary packaging: 100 vial carton 5 dose vial (2.5 ml)- secondary packaging: 100 vial carton	1 dose vial- 21.2 (in 100 vial carton) 5 dose vial- 4.2 (100 vial carton)	2°-8°C	18 months
Live Chimeric (Vero)	IMOJEV MD (JE-CV/ChimeriVax-JE)	Sanofi Pasteur	4 dose vial (2 ml)- Secondary Packaging: 10 vial carton+ separate carton of the same size of 10 vials of diluent Tertiary Packaging: 20 cartons of 10 vials each in tertiary carton. 18 tertiary cartons (i.e. 14400 doses)	4 dose vial : 2.5 (in 10 vial carton + 10 vial diluent)	2°-8°C	36 months

Human Papilloma Virus Vaccine (HPV)

Human Papilloma Virus Vaccine (HPV)

Overview

Human papilloma virus (HPV) are known to cause cervical cancer, genital warts, and other cancers. The World Health Organization (WHO), as well as other public health organizations in Australia, Canada, Europe, and United States etc. have recommend vaccination of young women against HPV. HPV vaccination is also effective for males to protect their partners from HPV infections, as well as themselves from anal cancer, genital warts, and other HPV associated cancers.

Currently marketed products – technical overview

There are over 100 different types of HPV[53] and more than 40 HPV types can be spread through direct sexual contact.Human papilloma viruses belong to the family Papillomaviridae. The virions are non-enveloped and contain a double-stranded DNA genome. The genomic material is enclosed by an icosahedral capsid composed of major and minor structural proteins, L1 and L2, respectively. These viruses are highly tissue-specific and infect both cutaneous and mucosal epithelium.

Type of Vaccine	Brand Name	Manufacturer	Strain/Subunit/ Serotype Coverage
Recombinant –VLP (Virus like Particle)	Cervarix	GSK	L1 protein of HPV type 16 and 18
	Gardasil	Merck Sharp & Dohme Corp	L1 protein of HPV type 6, 11, 16 and 18
	Gardasil – 9	Merck Sharp & Dohme Corp	L1 protein of HPV type 6, 11, 16, 18, 31, 33, 45, 52, and 58

Based on the genomic sequence of L1, the gene that encodes the principal capsid protein, over 190 types of HPV have been identified and characterized by molecular analysis. These HPVs are classified according to their potential to induce cancer into high- and low-risk groups. The International Agency for Research on Cancercurrently defines 12 high-risk HPV types that are associated with cancers in humans (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59) with additional types for which there is limited evidence of carcinogenicity (HPV types 68 and 73)[54]. Persistent infection with the high risk types can cause cellular changes that may progress to cancer, including cervical, anal, penile, vaginal, vulvar and oropharyngeal cancers. HPV types 16 and 18 are responsible for approximately 70% of all cervical cancers and HPV types 31, 33, 45, 52, and 58 are responsible for another 20% of cervical cancers. Types 6 and 11 are low-risk types that do not cause cancer but can cause warts on or around the genitals, anus, mouth, or throat[55].The median time from HPV infection to sero-conversion is approximately 8–12 months, although immunological response varies by individual and HPV type.

Till date, there are three FDA approved vaccines to protect against HPV infection i.e. Cervarix of GlaxoSmithKline, Gardasil and Gardasil 9 of Merck. Whereas, there are two WHO prequalified vaccines which are currently available and marketed in many countries worldwide for the prevention of HPV-related disease: a quadrivalent vaccine and a bivalent vaccine, both of which are directed against oncogenic genotypes. Gardasil 9 is a newly approved 9-valent vaccine that protects against infection with HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58.

Using recombinant technology, vaccines are prepared from purified L1 structural proteins that self-assemble to form HPV type-specific empty shells or virus-like particles. The vaccines are intended to be administered if possible before the onset of sexual activity, i.e. before first exposure to HPV infection.

The HPV vaccine can be administered in 3 dose and 2 dose schedule. Vaccines are originally licensed, marketed and recommended to administer in 3 dose schedule with no booster doses though results of a systematic review indicate that 2 doses of HPV vaccine in girls aged 9−14 years are non-inferior to 3 doses in terms of immunogenicity when compared to 3 doses in girls aged 9−14 years or 3 doses in women aged 15−24 years. When administered in 3-dose schedules, Cervarix and Gardasil vaccines provide some cross-protection against HPV genotypes that are not included in the vaccines. The bivalent vaccine induces strong neutralizing antibody responses (>50% seropositivity) to HPV-31, HPV- 33, HPV-45, and HPV-52. The quadrivalent vaccine induces neutralizing antibody responses to HPV-31, HPV- 33 and HPV-52. Serum-neutralizing antibody responses against non-vaccine HPV types have been reported to be broader and of a higher magnitude in the bivalent versus quadrivalent vaccine recipients. The clinical significance and longevity of this cross-protection are unclear.

The 3-dose schedules of bivalent and quadrivalent vaccines from literature reviews concluded that the serum antibodies reach their peak soon after the third dose and plateau at approximately 2 years and remain stable for at least 5 years after vaccination. For the bivalent vaccine, immunogenicity and efficacy of a 3-dose schedule against infection and cervical lesions associated with HPV-16/18 have been demonstrated up to 8.4 and 9.4 years respectively.

Currently marketed products – commercial overview

India landscape

The MNCs GlaxoSmithKline and Merck Sharp & Dohme Corp currently sell in India and they don't have any manufacturing facility in India. Though presently there are no Indian company selling HPV vaccines but there are Indian companies who have HPV vaccines in their pipeline. Cervarix of GSK and Gardasil of Merck have India import license and have validity up to December 2016 and June 2018 respectively (Source CDSCO).

Global public health

Depending on a country's demonstrated ability to deliver vaccines to adolescent girls, the GAVI Alliance is providing support to 37 countries by 2020 under National introduction support and to 19 countries by 2020 under Small-scale demonstration projects. Three countries (Rwanda, Uganda, and Uzbekistan) have been approved to nationally introduce the vaccine in 2013. By 2020, the Alliance estimates more than 30 million girls in 40 countries will be vaccinated against HPV. By 2020, demand is projected to reach 48 million doses and by 2025, the HPV demand is forecasted to be approximately 66 million doses per year in the GAVI 73[56].

Brand Name	Manufacturer	No. of doses per schedule	India Private Retail Price	GAVI/WHO cost*
Cervarix	GSK	3 doses	INR 2,190/dose for a 1 dose vial	US$4.60/dose (1 dose vial)
Gardasil	Merck Sharp & Dohme	3 doses	INR 2,990/dose for a 1 dose vial	US $4.50/dose (1 dose vial)

By August 2014, 58 countries (30%) had introduced HPV vaccine in their national immunization programme for girls, and in some countries also for boys. Most of the countries that have introduced HPV vaccine are from the WHO regions AMR, EUR and WPR.

MedImmune and GSK had alliance for Cervarix vaccine against HPV since Dec 1997 and still the alliance between them continues after Astra Zeneca acquired Medimmune. Companies collaborate on research and development activities. MedImmune conducted Phase I and Phase II clinical trials and manufactured clinical material for the studies, GSK obtained worldwide marketing rights.

Pipeline Review

Serum Institute of India, is developing a tetravalent HPV vaccine that includes L1 VLPs of serotypes 6,11,16,18, which is expected to give a coverage of approximately 90% against papilloma virus prevalent in the developing world.We note news articleindicating the launch of HPV vaccine in late 2018 at almost one-third the price of Gardasil, where it has also been mentioned that Serum Institute will conduct clinical trials in India and Africa starting from year 2015[57]. Another news article indicates that Zydus Cadila also has HPV vaccines in their pipeline and planning to launch in India market by 2015 or 2016[58]. Indian Immunologicals Ltd has an oral HPV vaccine whose toxicology study had been completed in 2013 and is seeking approval for further studies[59].

We do not observe any significant technical developments on next generation products in the global pipeline.

HPV Vaccine- Commercial Details

Type of Vaccine	Brand Name	Manufacturer	India Licensure Status	WHO pre-qualification status	India Retail Price	GAVI/WHO cost	India Production Capacity (doses/year)
Recombinant –VLP (Virus Like Proteins)	Cervarix	GlaxoSmithKline	Import License *(Valid up to: Dec 2016)*	Pre-qualified in 2009	INR 6,000 / 3-dose regimen (1 dose vial)	US $4.60/dose (1 dose vial)	Not applicable
	Gardasil	Merck Sharp & Dohme Corp	Import License *(Valid up to: June 2018)*	Pre-qualified in 2009	INR 8,400 / 3-dose regimen (1 dose vial)	US $4.50/dose (1 dose vial)	Not applicable
	Gardasil – 9	Merck Sharp & Dohme Corp	Not Licensed	Not Pre-qualified	Not applicable	Not applicable	Not applicable

HPV Vaccine- Technical Details

Type of Vaccine	Brand Name	Manufacturer	Serotype Information	Vaccine Constituents (Per dose)	Presentation / Form
Recombinant – VLP	Cervarix	GSK	HPV type 16 HPV type 18	L1 protein of 20 mcg of HPV type 16 & 18, 50 mcg of the 3-O-desacyl-4'-monophosphoryl lipid A (MPL), 0.5 mg of aluminum hydroxide, 4.4 mg of sodium chloride and 0.624 mg of sodium dihydrogen phosphate dihydrate.	Liquid
	Gardasil	Merck Sharp & Dohme Corp	HPV type 6 HPV type 11 HPV type 16 HPV type 18	L1 protein of 20 mcg of HPV type 6 & 18, 40 mcg of HPV type 11 & 16, 225 mcg of aluminum (as Amorphous Aluminum Hydroxyphosphate Sulfate adjuvant), 9.56 mg of sodium chloride, 0.78 mg of L-histidine, 50 mcg of polysorbate 80, 35 mcg of sodium borate,<7 mcg yeast protein/dose, and water for injection. The product does not contain a preservative or antibiotics.	Liquid
	Gardasil – 9	Merck Sharp & Dohme Corp	HPV-6, HPV-11, HPV-16, HPV-18, HPV-31, HPV-33, HPV-45, HPV-52, and HPV-58	L1 protein of 30 mcg of HPV Type 6, 40 mcg of HPV Type 11 & 18, 60 mcg of HPV Type 16, 20 mcg each of HPV Type 31, HPV Type 33, HPV Type 45, HPV Type 52 L1 protein, HPV Type 58 500 mcg of aluminum (provided as AAHS), 9.56 mg of sodium chloride, 0.78 mg of L-histidine, 50 mcg of polysorbate 80, 35 mcg of sodium borate, <7 mcg yeast protein, and water for injection. The product does not contain a preservative or antibiotics.	Liquid

HPV Vaccine- Clinical Details

Type of Vaccine	Brand Name	Manufacturer	Mode of Administration	Age of Administration	Dose and Administration Schedule	Special Exclusion Criteria
Recombinant – VLP	Cervarix	GSK	Intramuscular injection	Females: 9 – 25 years	Primary: 3 doses (0; 1 month; and 6 month)	• Hypersensitive to any components • Latex allergic people
	Gardasil	Merck Sharp & Dohme Corp	Intramuscular injection	Females: 9 – 26 years Males: 9 – 15 years	Primary: 3 doses (0; 2 month; and 6 month)	• Hypersensitive, including severe allergic reactions to yeast
	Gardasil – 9	Merck Sharp & Dohme Corp	Intramuscular injection	Females: 9 – 26 years Males: 9 – 15 years	Primary: 3 doses (0; 2 month; and 6 month)	• Hypersensitive, including severe allergic reactions to yeast

HPV Vaccine- Packaging and Logistics Details

Type of Vaccine	Brand Name	Manufacturer	Packaging Information	Cold Chain Volume (cm^3/dose)	Temperature for Storage and Transportation	Shelf Life
Recombinant – VLP	Cervarix	GSK	• **1 dose vial (0.5ml)** Secondary packaging: Carton of 1 vial, 10 vials and 100 vials • **2 dose vial (1ml)** Secondary packaging: Carton of 1 vial, 10 vials and 100 vials • **Prefilled syringes (0.5ml)**	**1 dose vial:** Carton of 1 vial : 57.7 Carton of 10 vials : 11.5 Carton of 100 vials : 9.7 **2 dose vial:** Carton of 1 vial : 28.8 Carton of 10 vials : 5.7 Carton of 100 vials : 4.8	2-8°C	48 months
	Gardasil	Merck Sharp & Dohme Corp	• **1 dose vial (0.5ml)** Secondary packaging: Carton of 1 vial, 10 vials • **Prefilled syringes (0.5-ml)**	**1 dose vial:** carton of 1 vial: 75 carton of 10 vials: 15	2-8°C	36 months
	Gardasil – 9	Merck Sharp & Dohme Corp	• **1 dose vial** Secondary packaging: Carton of 1 vial, 10 vials • **Prefilled syringes (0.5 ml)** Secondary packaging: Carton of 10 prefilled syringes	Not available	2-8°C	Not available

HPV Vaccine- Pipeline Details

Type of Vaccine	Vaccine Name	Originator(s), Collaborator(s)	Vaccine Information	Development Stage	Clinical Trial Location	Expected Launch
Recombinant – VLP	--	Serum Institute of India	Tetravalent Vaccine (L1 protein of HPV type 6, HPV type 11, HPV type 16, HPV type 18)	--	--	2018
Live Attenuated (Oral)	--	Shantha	Tetravalent Vaccine	--	--	--
	--	Indian Immunologicals Ltd.	--	Phase I Completed	--	--

Inactivated Polio Vaccine (IPV)

Inactivated Polio Vaccine (IPV)

Overview

India is no longer a country where polio is endemic. Wild poliovirus has not been found in India since 13 January 2011 and thus India has been certified as polio freeby WHO. This does not mean that the virus cannot reemerge within any of the countries or within the endemic regions. There is no room for complacency with ongoing polio vaccination work. High immunity levels must continue in order to protect those in the region and as newer, more comprehensive interventions are developed, these too need to be rolled out. Furthermore, whilst no new cases of wild polio have been recorded recently, the disease in different forms can be brought in to the Region via those who have contracted it in other parts of the world and then travel[60]. Poliomyelitis is an acute communicable viral disease causedby any 1 of 3 wild poliovirus (WPV) serotypes (types 1, 2 or 3). The injectable IPV is used in countries, which have already won the battle against the incurable crippling disease, as a protective wall against resurfacing of the virus. In the remaining polio infected countries, substantive progress has been made in implementing polio emergency action plans by introducing at least one dose of inactivated poliomyelitis vaccine (IPV) in the routine immunization programmes globally, after which trivalent oral polio vaccines (OPV) will be replaced with bivalent OPV in all OPV-using countries – setting the stage for eventually ending OPV use.[61]

In an effort to accelerate the global eradication of polio and help prevent a resurgence of the disease, Nepal introduced IPV on 18 September 2014 into its routine immunization programme. Nepal was the first country in South Asia and the first GAVI-eligible country to launch IPV as part of the global roll-out of the vaccine.[62] India has achieved polio free status and is all set to make the transition from oral polio drops to injectable vaccine. IPV is expected to be introduced in the routine immunization programme and rolled out across the country around September 2015.[63]

Currently marketed products – technical overview

The First IPV was developed and licensed in 1955.It is only available in the trivalent form and is usually made from selected WPV strains – Mahoney or Brunhilde (type 1), MEF-1 (type2) andSaukett (type3) – that are now grown in Vero cell cultureor in human diploid cells. IPV based on the attenuatedSabin virus strain (sIPV) was more recently developed andlicensed in Japan, with the aim of reducing the numberof

manufacturing sites generating large volumes of hightiterWPVs for traditional IPV production. Sabin poliovirusespose a lesser threat in the event of a release (intentionalor unintentional) from the production facility[64]. As an injectable vaccine, it can be administered alone or in combination with other vaccines (e.g. diphtheria, tetanus, pertussis, hepatitis B, and *Haemophilus influenza*). The IPV technology is very established and we do not note any significant strain differences amongst all the currently marketed products all of which are trivalent IPVs.

Type of Vaccine	Brand Name	Manufacturer	Strain Information
Inactivated Polio Vaccine (IPV)	Poliomyelitis vaccine	Bilthoven Biologicals B.V.	IPV type 1 (Mahoney)* 40 D – AU IPV type 2 (MEF 1)* 8 D – AU IPV type 3 (Saukett)* 32 D – AU
	Poliovac®- PFS	Serum Institute of India	IPV type 1 (Mahoney)* 40 D – AU IPV type 2 (MEF 1)* 8 D – AU IPV type 3 (Saukett)* 32 D – AU
	Poliorix	GSK	IPV type 1 (Mahoney)* 40 D – AU IPV type 2 (MEF 1)* 8 D – AU IPV type 3 (Saukett)* 32 D – AU
	IMOVAX POLIO / IPOL - US	Sanofi Pasteur	IPV type 1 (Mahoney)* 40 D – AU IPV type 2 (MEF 1)* 8 D – AU IPV type 3 (Saukett)* 32 D – AU
	Polprotec	Panacea Biotech	IPV type 1 (Mahoney)* 40 D – AU IPV type 2 (MEF 1)* 8 D – AU IPV type 3 (Saukett)* 32 D – AU

IPV is being manufactured by Indian companies as well as multinational companies. Till date we have five IPV vaccines available in the market out of which three are WHO-prequalified. Apart from GlaxoSmithKline's IPV vaccines, Poliorix all other IPV vaccines have marketing license in India. Usually, three doses of IPV is recommended to children of age 2 - 18 months with a booster dose at age of 4-6 years. IPV can also be given along with OPV in children. IPV can be injected to adults as well who were not earlier administered with the polio vaccines.

Currently marketed products –commercial overview

India landscape

Earlier Biological E used to import IPV bulk from Bilthoven Biologicals and market the packaged product in India under the brand name Erapol. However, the product has not been marketed for the last couple of years since the bulk supply has been terminated after the acquisition of Bilthoven Biologicals by Serum Institute of India in 2012. Consequently, Serum Institute of India now imports the product into India and has license to sell in India. Serum Institute of India also has its own prefilled IPV vaccine, Poliovac – PFS which is not WHO prequalified along with Panacea Biotech's IPV vaccine, Polprotec which is also not WHO prequalified. Panacea sources the bulk from the The Nederlands Vaccin Instituut (NVI)) and fills the product domestically in India.

Significant capacity challenge on account lack of access to wtIPV: The WHO global action plan to minimize poliovirus facility associated risks (GAP-III) highlights the biosafety risks of facilities handling the wild type poliovirus (wtIPV). The reintroduction of wtIPV from a poliovirus facility risks the potentially serious consequences of unrecognized virus transmission, reversion to cVDPV and again reestablishing poliovirus transmission. The GAP-III containment safeguards include population immunity in country hosting the facility as well as require location of facilities in areas with low transmission potential for wild polioviruses[65]. Hence, they restrict IPV production in India to only Sabin IPV (sIPV) and for wtIPV Indian companies are dependent on the limited number of global suppliers for sourcing bulk and then fill the product in India. Companies have indicated this as a capacity challenge during our primary research interactions and some of them are focused on developing the sIPV to address this challenge.

Demand uncertainty on hexavalent vs IPV: While Biological-E has not marketed the Erapol IPV for last couple of years due to constraints on bulk procurement, the company as a collaboration with GSK for supply of IPV for Biological-E's hexavalent vaccine (pentavalent with IPV). During our primary research, certain companies have also indicated hesitance to invest in creation of production capacity for hexavalent and IPV given the demand uncertainty for both of these vaccines since there is visibility on countries adopting one vs the other. Given visibility on demand and procurement possibilities, companies are willing to make the required investment in infrastructure. Serum Institute of India has also indicated during the primary research that they are working on Hexavalent vaccine with one of the component of the vaccine as IPV.

Global public health

Till date there are four WHO pre-qualified IPV vaccines which are available in market, they are being manufactured by Bilthoven Biologicals B.V., GlaxoSmithKline, Sanofi Pasteur and Statens Serum Institut. Statens Serum Institutes' IPV vaccine VeroPol is not licensed for sale in India. The Global Polio Eradication Initiative (GPEI) is a public-private partnership led by national governments and spearheaded by the World Health Organization (WHO), Rotary International, the US Centers for Disease Control and Prevention (CDC), and UNICEF. Its goal is to eradicate polio worldwide. It was launched in year 1988. With the GPEI efforts and vaccination, polio cases have decreased by 99%. But as long as a child anywhere remains infected with polio, children in all countries are at risk. In May 2013, the World Health Assembly endorsed the new Polio Eradication & Endgame Strategic Plan 2013-2018, calling on countries to introduce at least one dose of the inactivated polio vaccine (IPV) and begin the phased removal of oral polio vaccines.Removing the live-attenuated oral polio vaccines (OPV) will eliminate the risk of vaccine-associated polio outbreaks. Introducing IPV is a critical step to manage any risks associated with this phased removal. Adding IPV to routine immunization programmes will also improve immunity and help prevent further any emergence of VDPVs[66]

Brand Name	Manufacturer	No. of doses	India Retail Price	GAVI/WHO cost
Inactivated Poliomyelitis vaccine	Bilthoven Biologicals B.V.	Children: 3 doses + Booster Adults: 1 dose (Endemic regions)	Not Applicable	US $2.80/dose (For 1 dose vial) US $1.90/dose (For 5 dose vial)
Poliovac®- PFS	Serum Institute of India	Children: 3 doses + Booster Adults Unimmunized: 3 doses	INR 385/dose for 1 dose injection	Not applicable
Poliorix	GSK	Children: 2-dose or 3-dose	Not Applicable	Not Applicable
IMOVAX POLIO / IPOL	Sanofi Pasteur	IMOVAX POLIO: Children: 3 doses Adults: 2 doses IPOL: Children: 4 dose + Booster Adults: 3 doses	INR 440/ dose (1 dose vial)	73 GAVI countries: US $0.83/dose (For 10 dose vial) INR 440 / dose (1 dose vial)
Polprotec	Panacea Biotech	Children: 3 doses + Booster Adults: 2 doses + Booster	INR 375.00 / dose (1 dose vial)	Not Applicable

Pipeline review

To address the current bulk supply challenge, Panacea, Bharat Biotech and Indian Immunologicals are focused on developing the sIPV. There is limited information available in the secondary domain on the status of development.

We do not observe any significant technical developments on next generations' products in the global pipeline.

IPV - Commercial Details

Type of Vaccine	Brand Name	Manufacturer	India Licensure Status	WHO pre-qualification status	India Retail Price	GAVI/WHO cost	India Production Capacity (doses/year)
Inactivated Polio Vaccine (IPV)	Inactivated Poliomyelitis vaccine	Bilthoven Biologicals B.V. (Imported by Serum Institute India)	Import License *(Valid up to: Jan 2018)*	Pre-qualified in 2010	Not Applicable	US$2.80/dose (For 1 dose vial) US$1.90/dose (For 5 dose vial)	Not applicable
	Poliovac®-PFS	Serum Institute of India	Licensed *(Valid up to: Dec 2016)*	Not qualified	Not available	Not applicable	Not available
	Poliorix	GSK	Not Licensed	Pre-qualified in 2010	Not Applicable	Not Applicable	Not applicable
	IMOVAX POLIO IPOL (IPV-1955) – (IPOL in US)	Sanofi Pasteur	Import License *(Valid up to: Dec 2017)*	Pre-qualified in 2005	INR 365 / dose (1 dose vial)	73 GAVI countries: US$0.83/dose (For 10 dose vial)	Not applicable
	Polprotec	Panacea Biotech	Licensed *(Valid up to: Sep 2017)*	Not qualified	INR 375 / dose (1 dose vial)	Not Applicable	Not available

IPV- Technical Details

Type of Vaccine	Brand Name	Manufacturer	Strain Information	Vaccine Constituents (Per dose)	Presentation / Form
Inactivated Polio Vaccine (IPV)	Poliomyelitis vaccine	Bilthoven Biologicals B.V.	IPV type 1 (Mahoney)* 40 D – AU IPV type 2 (MEF 1)* 8 D – AU IPV type 3 (Saukett)* 32 D – AU	**Active Ingredients:** IPV type 1, IPV type2 & IPV type 3 **Excipients:** Formaldehyde, 2-phenoxyethanol, Medium 199 primarily consisting of amino acids, minerals and vitamins, disodium hydrogenphosphate dehydrate, potassium chloride, sodium chloride, potassium dihydrogen phosphate, polysorbate 80, calcium chloride and water for injection.	Liquid
	Poliovac®- PFS	Serum Institute of India	IPV type 1 (Mahoney)* 40 D – AU IPV type 2 (MEF 1)* 8 D – AU IPV type 3 (Saukett)* 32 D – AU	**Active Ingredients:** IPV type 1, IPV type2 & IPV type 3 **Excipients:** 2-phenoxyethanol, Traces of Formaldehyde, Neomycin, streptomycin, polymyxin B	Liquid
	Poliorix	GSK	IPV type 1 (Mahoney)* 40 D – AU IPV type 2 (MEF 1)* 8 D – AU IPV type 3 (Saukett)* 32 D – AU	**Active Ingredients:** IPV type 1, IPV type2 & IPV type 3 **Excipients:** 2-phenoxyethanol, Formaldehyde, Medium 199 including amino acids, Polysorbate 80, Water for injections and traces of Neomycin & Polymyxin B	Liquid
	IMOVAX POLIO - Finland, Hong-Kong, Israel IPOL - US	Sanofi Pasteur	IPV type 1 (Mahoney)* 40 D – AU IPV type 2 (MEF 1)* 8 D – AU IPV type 3 (Saukett)* 32 D – AU	**Active Ingredients:** IPV type 1, IPV type2 & IPV type 3 **Excipients:** 2-phenoxyethanol, Formaldehyde, ethanol, Medium 199 Hanks and hydrochloric acid or sodium hydroxide for pH adjustment. Traces of Neomycin, Streptomycin & Polymyxin B.	Liquid
	Polprotec	Panacea Biotech	IPV type 1 (Mahoney)* 40 D – AU IPV type 2 (MEF 1)* 8 D – AU IPV type 3 (Saukett)* 32 D – AU	**Active Ingredients:** IPV type 1, IPV type2 & IPV type 3 **Excipients:** 2-phenoxyethanol, Phosphate buffer, Dilution fluid, Water, Phenol red as pH indicator	Liquid

IPV- Clinical Details

Type of Vaccine	Brand Name	Manufacturer	Mode of Administration	Age of Administration	Dose and Administration Schedule	Special Exclusion Criteria
Inactivated Polio Vaccine (IPV)	Poliomyelitis vaccine	Bilthoven Biologicals B.V.	Intramuscular or Subcutaneous	Children: 2 – 6 months Adults: >18 years	**Children:** Primary: 3 doses (within first 6 months) Booster: Min 6 months after first dose If administered <2 months: 3 doses (interval < 8 weeks) Booster: => 9 months **Adults:** 1 dose (Endemic regions)	Hypersensitivity to any constituents
	Poliovac®-PFS	Serum Institute of India	Intramuscular or Subcutaneous	Children: 2 – 6 months Adults: >18 years	**Children:** Primary: 3 doses (6, 10, 14 weeks) Booster: 15-18 months **Adults:** Unimmunized: 3 doses (2 doses 1-2 month interval and 3 dose 6-12 month later). If 1-2 month available, 2 doses - 1 month apart. If <1 month available, 1 dose	Febrile illness, Immunocompromised
	Poliorix	GSK	Intramuscular	Children: 2 – 6 months	**Children:** 2-dose schedule: 2-4/ 3-4 ½/ 3-5/ 4-6 months 3-dose schedule: 3-4-5/ 3-4 ½-6 months	Hypersensitivity to any constituents

Inactivated Polio Vaccine (IPV)	IMOVAX POLIO - Finland, Hong-Kong, Israel IPOL - US	Sanofi Pasteur	Intramuscular or Subcutaneous	Children: 2 – 6 months Adults: >18 years	IMOVAX POLIO Children: 3 doses (6, 10, 14 weeks) Adults: 2 doses (0, 2 months) IPOL Children: 4 doses (2, 4, 6 to 18 month) Booster: 4-6 years Adults: 3 doses (0, 1/2, 6/12 months)	Hypersensitivity to any constituents Fever / acute illness
	Polprotec	Panacea Biotech	Intramuscular	Children: 2 – 6 months Adults: >18 years	Children: 3 doses (6, 10, 14 weeks) Booster: >6 months Adults: 2 doses (0, 1 months) Booster: 8-12 months	Hypersensitivity to any constituents

IPV- Packaging and Logistics Details

Type of Vaccine	Brand Name	Manufacturer	Packaging Information	Cold Chain Volume (cm^3/dose)	Temperature for Storage and Transportation	Shelf Life
Inactivated Polio Vaccine (IPV)	Poliomyelitis vaccine	Bilthoven Biologicals B.V. (Acquired by Serum Institute of India)	Primary packaging: Filled in vials (type 1 hydrolytic glass) - sealed with a rubber stopper (free of latex) and an aluminium flip-off cap (1 dose & 5 dose) • **1 dose vial** Secondary packaging: Akylux tray of 360 vials • **5 dose vial** Secondary packaging: Akylux tray of 280 vials Tertiary Packaging: Insulated shipper with 220 Akylux trays and with 4 Akylux trays	**1 dose vial:** 15.7 (in akylux tray of 360 vials) **5 dose vial:** 4.0 (in akylux tray of 280 vials)	2-8°C	36 months
	Poliovac®- PFS	Serum Institute of India	• **Prefilled syringe (1 dose)**	Not available	2-8°C	Not available
	Poliorix	GlaxoSmithKline	• **1 dose vial** Secondary Packaging: carton of 1 vial, 10 or 100 vials • **2 dose vial** Secondary Packaging: carton of 1 vial, 10 or 100 vials • **Prefilled syringe (1 dose)**	Not available	2-8°C	36 months
	IMOVAX POLIO - IPOL - US	Sanofi Pasteur	• **10 dose vial** Secondary packaging: 10 vials of 10 doses (IMOVAX) • **Prefilled syringe (1 dose)**	**10 dose vials:** 2.46 (in 10 vials)	2-8°C	36 months
	Polprotec	Panacea Biotech	• **Prefilled syringe (1 dose)**	Not available	2-8°C	36 months

IPV- Pipeline Details

Type of Vaccine	Vaccine Name	Originator(s), Collaborator(s)	Vaccine Information	Development Stage	Clinical Trial Location	Expected Launch
Inactivated Polio Vaccine (IPV)	Sabin IPV (sIPV)	Panacea Biotech	IPV type 1 (Mahoney)* 40 D – AU IPV type 2 (MEF 1)* 8 D – AU IPV type 3 (Saukett)* 32 D – AU	Pre-clinical completed	India	--
	Sabin IPV	Bharat Biotech	IPV type 1 (Mahoney)* 40 D – AU IPV type 2 (MEF 1)* 8 D – AU IPV type 3 (Saukett)* 32 D – AU	R&D	India	2018
	--	Indian Immunological Ltd	IPV type 1 (Mahoney)* 40 D – AU IPV type 2 (MEF 1)* 8 D – AU IPV type 3 (Saukett)* 32 D – AU	R&D	India	--

Measles-Rubella Vaccine

Measles-Rubella Vaccine (MR)

Overview

Measles is a highly contagious, serious disease caused by a virus. The disease remains one of the leading causes of death among young children globally, despite the availability of a safe and effective vaccine. Approximately 145,700 people died from measles in 2013 – mostly children under the age of 5. Measles is caused by a virus in the paramyxovirus family and it is normally passed through direct contact and through the air. The virus infects the mucous membranes, then spreads throughout the body. Accelerated immunization activities have had a major impact on reducing measles deaths. During 2000-2013, measles vaccination prevented an estimated 15.6 million deaths. Global measles deaths have decreased by 75% from an estimated 544,200 in 2000 to 145,700 in 2013[67].

The rubella virus, a togavirus of the genus Rubivirus, is an enveloped single stranded RNA virus with a single serotype that does not cross-react with other togaviruses. Humans are the only known host, with seasonal epidemics occurring every 59 years over a worldwide distribution[68]. Rubella, transmitted through airborne droplets, is generally a mild illness. But when a pregnant woman becomes infected, particularly during the first trimester of pregnancy, serious consequences can occur including miscarriages, still births, and infants born with birth defects known as Congenital Rubella Syndrome (CRS). The most common congenital defects include lifelong heart problems, deafness or blindness (cataracts). An estimated 112,000 cases of CRS occur each year and are preventable through vaccination[69].

Currently marketed products – technical overview

Both the MMR and MR vaccines are live attenuated vaccines. There are three types of strains of Measles i.e. Edmonston-Zagreb, AIK-C and Schwarz which are commonly used in MMR or MR vaccines. It has been also evidenced from the Seroconversion rate that the administration of AIK-C and high-dose Edmonston-Zagreb strains at 4-5 months is at least as effective as vaccination with the standard strains at 8-10 months.[70] For Rubella the most common strain used in MMR or MR vaccine is Wistar RA 27/3. Other attenuated rubella vaccine strains include the Matsuba, DCRB19, Takahashi, Matsuura and TO-336 strains used primarily in Japan, and the BRD-2 strain used primarily in China. Vaccination results in high (>95%) seroconversion rates and protection is generally assumed to be lifelong, although rubella antibodies may fall below detectable levels.[71] Currently only one MR vaccine i.e. MR VAC which is WHO pre-qualified and present widely in the market. There are few other MR vaccines commercialized but they are present in specific locations only. Usually 2 doses of MR vaccine is recommended at the age of 9 months and 15 months, along with a booster dose at age of 4-6 years.

Type of Vaccine	Brand Name	Manufacturer	Strain Information
Live Attenuated Vaccines	MR-VAC	Serum Institute of India	Measles virus: Strains of Edmonston-Zagreb Rubella virus: Wistar RA 27/3 propagated on human diploid cells (HDC)

Currently marketed products – commercial overview

India market

The MR-VAC is produced by Serum Institute of India and it was launched in year 2002. The vaccine has India licensure validity till December 2016. The MR-VAC contains Edmonston-Zagreb strain for Measles virus and Wistar RA 27/3 strain of Rubella virus propagated on human diploid cells (HDC).From primary research it has been indicated by Serum that they can increase their capacity to 50-60 million if there is a need for the vaccine in the near term.

Brand Name	Manufacturer	No. of doses per schedule	India Private Retail Price	GAVI/WHO cost*
MR-VAC	Serum institute of India	2 doses + Booster	INR 95-128 / dose (For 1 dose vial)	US $0.57 / dose (For 10 dose vial)

Global public health

The Measles & Rubella Initiative is a global partnership committed to ensuring no child dies from measles or is born with congenital rubella syndrome. Founded originally as the Measles Initiative in 2001, it's led by the American Red Cross, the United Nations Foundation, the U.S. Centers for Disease Control and Prevention, UNICEF and the World Health Organization.Since 2001, the Initiative has supported 80 countries to deliver more than one billion doses of measles vaccine, helped to raise measles vaccination coverage to 85% globally, and reduced measles deaths by 74%.

Global demand for MR vaccines in 2013 is expected to reach approximately 100 million doses.The demand will increase to 330 million doses at peak expected in 2016/17, followed by a long term demand of 150 to 250 million doses per year from 2018/19 onwards. This increase is mostly driven by GAVI-supported countries' catch-up campaigns 2013 to 2017 and the demand is maintained long term, mostly by the country-funded development of MR routine and follow-up immunizations. Demand will be variable from one year to another beyond 2018 as a function of periodic follow-up campaigns.Over the period 2013–2018, demand from GAVI-supported countries is expected to reach approximately 640 million doses, representing a 59% share of volume from low and lower-middle income countries. Few other countries will use MR vaccines and their supply does not interfere with the GAVI market.Up to three pipeline MR vaccines are expected to gain pre-qualification between 2017 and 2019[72].

Pipeline review

India Pipeline

Zydus Cadila has an MR vaccine in its pipeline which has completed phase I clinical trial. Strains used in the vaccine were Edmonston-Zagreb (1000 CCID50) for Measles virus and Wistar RA 27/3 (1000 CCID50) for Rubella virus, which were propagated on human diploid cells (HDC). In 2013, Biological E received a commercial grant for this vaccine from Bill and Melinda Gates Foundation. For MR vaccine production, Bharat Immunologicals and Biologicals Corporation Ltd (BIBCOL) has a MoU with Translational Vaccinology (INTERVACC), a govt. based institute in Netherland. The INTERVACC of Netherlands will provide technical support for vaccine's development to BIBCOL.[73]

Global Development

No significant technical developments on next generation products have been noted.

MR Vaccine- Commercial Details

Type of Vaccine	Brand Name	Manufacturer	India Licensure Status	WHO pre-qualification status	India Retail Price	GAVI/WHO cost	India Production Capacity (doses/year)
Live Attenuated Vaccines	MR-VAC	Serum Institute of India	Licensed *(Valid up to: Dec 2016)*	Pre-qualified in 2000	Rs. 95 / dose (For 1 dose vial)	US $0.57 / dose (For 10 dose vial)	150 million

MR Vaccine- Technical Details

Type of Vaccine	Brand Name	Manufacturer	Strain Information	Vaccine Constituents (Per dose)	Presentation / Form
Live Attenuated Vaccines	MR-VAC	Serum Institute of India	Measles virus: Strains of Edmonston-Zagreb Rubella virus: Wistar RA 27/3 propagated on human diploid cells (HDC)	1000 CCID50 of Measles virus 1000 CCID50 of Rubella virus (CCID50: 50% cell culture infective dose (CCID50) from a virus stock)	Lyophilized + water for injection diluent

MR- Clinical Prescribing Details

Type of Vaccine	Brand Name	Manufacturer	Mode of Administration	Age of Administration	Dose and Administration Schedule	Special Exclusion Criteria
Live Attenuated Vaccines	MR-VAC	Serum Institute of India	Subcutaneous	9 months – 10 years Also indicated for >10 years	Primary: 2 doses (9, 15 months) Booster: 1 dose (4-6 months)	Should not be given in febrile states, pregnancy, acute infectious diseases, leukemia, severe anemia and other severe diseases of the blood system, severe impairment of the renal function, decompensated heart diseases, following administration of gamma-globulin or blood transfusions or to subjects with potential allergies to vaccine components.

MR- Packaging and Logistics Details

Type of Vaccine	Brand Name	Manufacturer	Packaging Information	Cold Chain Volume (cm^3/dose)	Temperature for Storage and Transportation	Shelf Life
Live Attenuated Vaccines	MR-VAC	Serum Institute of India	**1 dose vial** + 0.5ml diluent Secondary Packaging: carton of 50 vials (active) + carton of 50 ampoules of diluent **2 dose vial** + 0.5ml diluent Secondary Packaging: carton of 50 vials (active) + carton of 50 ampoules of diluent **5 dose vial** + 0.5ml diluent Secondary Packaging: carton of 50 vials (active) + carton of 50 ampoules of diluent **10 dose vial** + 0.5ml diluent Secondary Packaging: carton of 50 vials (active) + carton of 50 ampoules of diluent	1 **dose vial:** 26.11 in **C**arton of 50 vials (active) + carton of 50 ampoules of diluent **2 dose vial:** 13.1 in **C**arton of 50 vials (active) + carton of 50 ampoules of diluent **5 dose vial:** 5.22 in **C**arton of 50 vials (active) + carton of 50 ampoules of diluent **10 dose vial:** 2.611 in **C**arton of 50 vials (active) + carton of 50 ampoules of diluent	2-8°C (-20°C for long term storage)	24 months

MR- Pipeline Details

Type of Vaccine	Vaccine Name	Originator(s), Collaborator(s)	Vaccine Information	Development Stage	Clinical Trial Location	Expected Launch
Live Attenuated Vaccines	-	Zydus Cadila	Measles virus: Strains of Edmonston-Zagreb (1000 CCID50) Rubella virus: Wistar RA 27/3 (1000 CCID50) propagated on human diploid cells (HDC)	Phase 1	India	--
	-	Biological E	Not available	-	-	-

Mumps-Measles-Rubella Vaccine (MMR)

Mumps-Measles-Rubella Vaccine (MMR)

Overview

UNICEF projected ~326M doses demand for MCV in 2015. UNICEF anticipates 2016 MCV demand to reach ~400M doses to meet country demands (due to Rubella catch up vaccination)[74].Currently, most countriesuse Measles only vaccines (MV),However as per WHO SAGE recommendations, countries are switching from MV to either MR or MMR. Developed countries have already acquired MMR in their schedule. 94% of MCV supply is sourced from Serum Institute of India. Serum has common production facilities for MV and MR vaccines with total production capacity of 350M doses/ year.

MMR Vaccine- Commercial Details

Type of Vaccine	Brand Name	Manufacturer	India Licensure Status	WHO pre-qualification status	India Retail Price	GAVI/WHO cost	India Production Capacity (doses/year)
Live Attenuated Vaccines	Priorix	GlaxoSmithKline	Licensed *(Valid up to: 2016 (Bulk)*	Pre-qualified in 2001	Rs. 545 / dose (For 1 dose vial)	US $3.25 / dose (For 2 dose vial)	Not available
	M-M-R II	Merck Sharp & Dohme Corp	Not licensed	Pre-qualified in 2009	Not applicable	Not available	Not applicable
	TRIMOVAX MÉRIEUX	Sanofi Pasteur (Exited market)	Not licensed	Pre-qualified in 2002	Not applicable	US $1.985 / dose (For 10 dose vial)	Not applicable
	MMR / TRESIVAC®	Serum Institute of India Ltd	Licensed	Pre-qualified in 2003	Rs. 128 / dose (For 1 dose vial)	US $2.25 / dose (For 1 dose vial) US $1.09 / dose (For 5 dose vial) US $1.077 / dose (For 10 dose vial)	50 million

MMR Vaccine- Technical Details

Type of Vaccine	Brand Name	Manufacturer	Strain Information	Vaccine Constituents (Per dose)	Presentation / Form
Live Attenuated Vaccines	Priorix	GSK	**Measles virus:** Schwarz strain **Mumps virus:** RIT 4385 strainderived from Jeryl Lynn strain (Measles virus& Mumps viruses are produced in chick embryo cells) **Rubella virus:** Wistar RA 27/3 strain (produced in human diploid (MRC-5))	Active Ingredients: Measles virus - 103.0 CCID50, Mumps virus - 103.7 CCID50, Rubella virus2 - 103.0 CCID50. Cell culture infectious dose 50% Excipients:Amino acids, lactose, mannitol, neomycin sulphate (traces), sorbitol. Diluent: Water for injections	Lyophilized + WFI diluent
	M-M-R II	Merck Sharp & Dohme Corp	**Measles virus:** Enders' attenuated Edmonston strain **Mumps virus:** Jeryl Lynn strain (Measles virus& Mumps viruses are propagated in chick embryo cell culture) **Rubella virus:** Wistar RA 27/3 strain, propagated in WI-38 human diploid lung fibroblasts.	Active Ingredients: Quantity/Dose Measles virus ≥1000 CCID50, Mumps virus ≥20,000 CCID50, Rubella virus ≥1000 CCID50 Inactive Ingredients: Sodium Phosphate - Monobasic 3.1 mg, Sodium Phosphate Dibasic 2.2 mg, Sodium Bicarbonate 0.5 mg, Medium 199 3.3 mg, Minimum Essential Medium Eagle 0.1 mg, Neomycin 25.0 µg, Phenol Red 3.4 µg, Sorbitol 14.5 mg, Potassium Phosphate Monobasic 20.0 µg, Potassium Phosphate Dibasic 30.0 µg, Gelatin (Porcine) Hydrolyzed 14.5 mg, Sucrose 1.9 mg and Monosodium L-Glutamate 20.0 µg Diluent Composition Water for Injection	Lyophilized + Diluent
	MMR / TRESIVAC	Serum Institute of India Ltd	**Measles virus:** Edmonston-Zagreb strain **Mumps virus:** Leningrad-Zagreb strain **Rubella virus:** Wistar RA 27/3 strain The measles and rubella viruses are propagated on human diploid cells (HDC) and the mumps virus is grown on chick fibroblasts from SPF eggs (Specific pathogen free eggs)	Measles virus ≥ 1000 CCID50, Mumps virus ≥ 5000 CCID50, Rubella virus ≥ 1000 CCID50.	Lyophilized + Water for Injection diluent

MMR- Clinical Prescribing Details

Type of Vaccine	Brand Name	Manufacturer	Mode of Administration	Age of Administration	Dose and Administration Schedule	Special Exclusion Criteria
Live Attenuated Vaccines	Priorix	GlaxoSmithKline	subcutaneous or intramuscular	9 months – 10years	Primary: 2 doses (12-15 months / 9 months in high incidence countries), 2nd dose in routine or supplemental activities.	Acute severe febrile illness
	M-M-R II	Merck Sharp & Dohme Corp	subcutaneous or intramuscular	9 months – 10 years	Primary: 2 doses (12-15 months / 9 months in high incidence countries), 2nd dose in routine or supplemental activities.	History of cerebral injury, convulsions, or any other condition like stress due to fever, allergic to egg proteins, Hypersensitivity to any of the constituents
	MMR / TRESIVAC	Serum Institute of India Ltd	subcutaneous or intramuscular	12 months – 10 years	Primary: 2 doses (12-15 months, 4-6 years)	Febrile states, pregnancy, acute infectious diseases, leukemia, severe anemia and other severe diseases of the blood system, severe impairment of the renal function, decompensated heart diseases, following administration of gamma-globulin or blood transfusions or to subjects with potential allergies to vaccine components

MMR- Packaging and Logistics Details

Type of Vaccine	Brand Name	Manufacturer	Packaging Information	Cold Chain Volume (cm^3/dose)	Temperature for Storage and Transportation	Shelf Life
Live Attenuated Vaccines	Priorix	GlaxoSmithKline	**1 dose vial (active) + diluent** **2 dose vial (active) + ampoule (diluent)** Secondary Packaging: carton of 100 vials of vaccine and cartons of 100 ampoules of diluent.	**1 dose vial:** Cold Chain volume per dose (cm3): vaccine vial: 9.6; diluent ampoule: 25.6 [diluent can be stored at 25 °C] **2 dose vial:** Cold Chain volume per dose (cm3): vaccine vial: 4.8; diluent ampoule: 12.8 [diluent can be stored at 25 °C]	2-8°C	24 months
	M-M-R II	Merck Sharp & Dohme Corp	**1 dose vial:** Package A: Secondary Packaging: carton of 10 vials (a box of 10 single-dose vials of lyophilized vaccine) Package B: A box of 10 vials of diluent	**1 dose vial:** 15 in **C**arton of 10 vials (active)	2-8°C	24 months
	MMR / TRESIVAC	Serum Institute of India Ltd	**1 dose vial (active) + ampoule of diluent** Secondary Packaging: carton of 50 vials + carton of 50 ampoules of diluent 50 **2 dose vial (active) + ampoule of diluent** Secondary Packaging: carton of 50 vials (active) + carton of 50 ampoules of diluent **5 dose vial (active) + ampoule of diluent** Secondary Packaging: carton of 50 vials (active) + carton of 50 ampoules of diluent **10 dose vial (active) + ampoule of diluent** Secondary Packaging: carton of 50 vials (active) + carton of 50 ampoules of diluent	**1 dose vial:** 26.11 in **C**arton of 50 vials (active) **2dose vial:** 13.1 in **C**arton of 50 vials (active) **5dose vial:** 5.22 in **C**arton of 50 vials (active) **10 dose vial:** 2.611 in **C**arton of 50 vials (active)	2-8°C	24 months

Dengue Vaccine

Denguevaccine

Overview

Dengue is a viral disease transmitted by the mosquito vector *Aedes aegypti* and is caused by antigenically related Flaviviruses (dengue virus serotypes one through four (DENV-1-4). Dengue is endemic in large parts of Americas, Africa and Asia with 2.5 billion people at high risk.[75] Unplanned urbanization, increase and migration of population and ineffective vector control efforts have led to further spread of the vector. There is an increase of dengue in its more severe forms, such as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS), for reasons that are not fully understood, leading to increased morbidity and mortality. The disease is mainly observed in children and is a leading cause of pediatric hospitalization[76].

Dengue vaccine development landscape – global landscape

Even after 60 years after the discovery of the virus and active research for dengue vaccines, there is only one commercially available vaccine today. The following overview table focuses on dengue candidate vaccines that are in late stages of clinical development globally or have been recently approved.Table also includes pipeline candidates in all stages of clinical development in India. Due to global threat of Dengue and the economic burden, the development of an effective vaccine is an international health priority. Vaccine development programs in academic laboratories and pharmaceutical companies have investigated a variety of technologies, including live, attenuated vaccines, recombinant vaccines, proteins and DNA vaccines. Vaccine development efforts have made remarkable progress in recent years, hencethe current dengue vaccine pipeline is advanced, diverse, and overall promising.

The only vaccine approved for use is the yellow fever/dengue chimeric, live, attenuated, tetravalent vaccineDengvaxia® (CYD-TDV), initially developed by Acambis and further advanced by Sanofi Pasteur. Dengvaxia® has all four dengue serotypes (DEN-1: PUO-359/TVP-1140 Thai strain, DEN-2: PUO-218 Thai strain, DEN-3: PaH881/88 Thai strain, DEN-4: TVP-980 Indonesian strain) with pre-membrane and envelope proteins from a wild type dengue virus substituted into the yellow fever (YF) 17D vaccine backbone. Three doses of the vaccine is given over a course of one year. This vaccine completed Phase III clinical trials in Latin America, Asia and Australia in 2015 and has an overall efficacy of 60.8%[7778].

Another vaccine candidate'Denvax' by Inviragen Inc. (recently acquired by Takeda) has been developed in collaboration with the U.S. CDC, University of Wisconsin, and Universidad de Antioquia in Colombia. This vaccine is a live, attenuated, tetravalent chimeric candidate, undergoing phase 2 clinical trials in Puerto Rico, Colombia, Singapore, and Thailand. The vaccine willbe given as two doses at three months interval.

The other global vaccine candidate in Phase 2 clinical trials includes TV003 from National Institute of Health (NIH). TV003 is a chimeric tetravalent candidate that involves combinations of gene mutations and deletions and currently undergoing clinical trials in Thailand and Brazil.

Collaboration between GlaxoSmith Kline (GSK), Oswaldo Cruz Foundation (FIOCRUZ) and Walter Reed Army Institute of Research (WRAIR) have a dengue vaccine candidate in development. Also, Brazil's Instituto Butantan and National Institute of Health (NIH) have Dengue vaccine candidates in clinical Phase 2 testing globally.

Dengue vaccine development landscape – Indian landscape

Several promising dengue vaccine candidates are in preclinical development in India. The three noticeable candidates are from Biological E (live, attenuated), Panacea Biotec (live, attenuated, and chimeric) and International Centre for Genetic Engineering and Biotechnology (ICGEB) (Virus like Particle-VLP). The ICGEB Dengue vaccine program, a project initially nurtured under the Indo-US Vaccine Action Program,has been advanced into preclinical validation with fundingfrom Wellcome Trust. The vaccine candidate is a Virus Like Particle (VLP) produced in yeast with parts of all serotypes (DEN1-4) of dengue virus used as immunogen. Alum hydrogel is used as adjuvant to enhance immunogenicity of this candidate. The vaccine candidate has undergone pre-clinical studies in Rhesus monkeys and ICGEB is looking to collaborate with industry for further development of this vaccine.

Challenges in development of Dengue vaccine

1. **Complexity of Dengue disease**- The disease is caused by four dengue virus serotypes (DEN 1-4) adding to the complexity of disease pattern across endemic regions of globe**.** While infection with one virus serotype confers lasting protection against reinfection and disease by the same serotype, the same is not true for infection with a heterologous virus serotype. In fact, secondary and tertiary infection is associated with more severe disease such as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS).

2. **Lack of animal models for research purposes**- There is no suitable animal model for studying dengue or its severe forms. Genetic variations for viral virulence are not fully understood yet,genotypic-phenotypic relationship of phenotypic attenuation of virus and its behavior in humans and animals is also unclear.

Type of vaccine	Vaccine Name	Originator(s), Collaborator(s)	Vaccine Information	Development Stage	Clinical Trial/development location	Expected Launch
Live, attenuated, chimeric	Dengvaxia® (CYD-TDV)	Sanofi Pasteur	Tetravalent, YF17D/DEN chimeric viruses	Phase 3-Completed Approved for use in Mexico, Phillipines and Brazil	Latin America, Asia, Australia	Launched in 2015
Live, attenuated, chimeric	DenVax	Takeda (Inviragen)	Tetravalent, Attenuated DEN2 PDK-53 virus and DEN/DEN intertypic chimeric viruses	Phase 2	Puerto Rico, Colombia, Singapore, Thailand	-
Chimeric	TV003	National Institute of Health (NIH)	Tetravalent, Combinations of defined mutations/deletions and chimeras	Phase 2	Thailand, Brazil	-
Live, attenuated	-	Biological E	Tetravalent candidate	Preclinical	India	-
Live, attenuated, chimeric	-	Panacea Biotec	Tetravalent candidate	Preclinical	India	-
VLP (Virus like Particle)	-	International Centre for Genetic Engineering and Biotechnology (ICGEB)	Monovalent, EDIII-HBs Ag VLPs or ectoE-based VLPs expressed in E.Coli	Preclinical	India	-

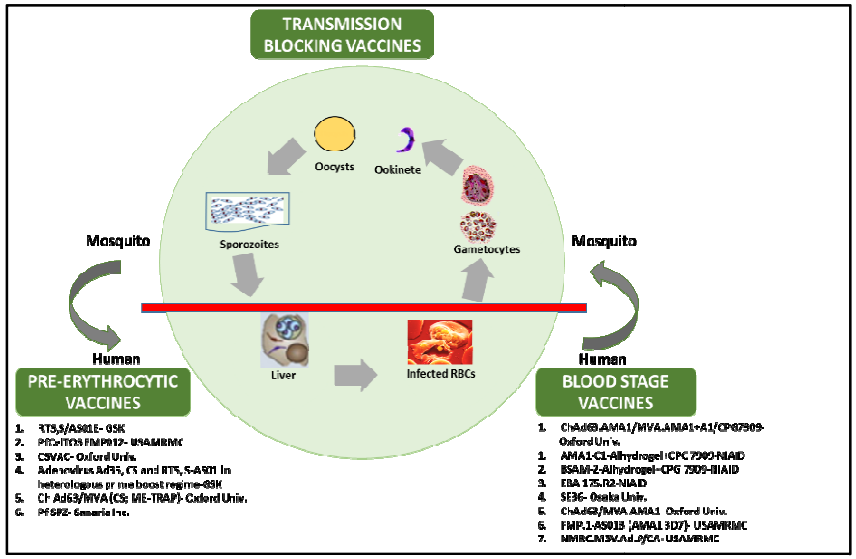
Malaria Vaccine

Malaria vaccine

Malaria is a major public health threat, especially among children and pregnant women in Africa.The parasite that causes the most deadly form of malaria, Plasmodium falciparum, is spread by highly prevalent mosquitoes *Anopheles gambiae* and *An. funestus*. Malaria causes more death than any other parasitic disease and it is estimated that every 30 seconds one child in Africa dies from Malaria[79]. There are about 4 billion people in approximately 90 different countries around the globe who are at constant risk of developing the disease with 500 million cases of malaria reported every year[80]. Most number of cases including deaths is caused by *Plasmodium falciparum, although Plasmodium vivax* is also an important contributorin Asia and Latin America.

Malaria vaccine development – global landscape

The complexity of the malaria parasite makes development of a malaria vaccine a very difficult task. Given this, there are different approaches being adopted for development of malaria vaccine around the globe by scientists that arrest the growth of malaria parasite at different lifecycle stages as described in the figure alongside.



Lifecycle of malaria parasite *P.falciparum* and candidate vaccines in clinical development globally

Three main strategies have been adopted for developing malaria vaccines. The first involves neutralization of sporozoites as they enter blood stream, rendering them incapable of infecting liver, thus preventing infection completely. The second strategy involves production of vaccines against blood stages of the parasite, thereby, preventing erythrocytic infection. The last strategy involves blocking the transmission of infection by stimulating antibodies production against sexual stages of the parasite, thereby, rendering the mosquito from transmitting infection to humans.

July 2015 has been a landmark date in the history of malaria vaccine development since Mosquirix developed by GSKwas approved by EMA. Despite many decades of intense research and development effort this is

the only approved product as on date. Over 20 subunit vaccine constructs are currently being evaluated in clinical trials or are in advanced preclinical development using the above described approaches.

Pre-erythrocytic stage immunity is not acquired naturally and is developed in clinically immune adults infected with blood stage parasite. This forms the basis for vaccine development and has been captured by GlaxoSmithKline (GSK) and Walter Reed Army Institute of Research (WRAIR). This research has led to the development of the first vaccine candidate to be globally approved, 'RTS, S/AS01' against the most deadly form of malaria by *P.falciparum*. RTS, S/AS01 vaccine (Brand name-Mosquirix) consists of hepatitis B surface antigen (HBs Ag) fused with thrombospondin domain of CircumSporozoite Protein (CSP) formulated in adjuvant AS01. Phase III trials were conducted in seven countries in sub-Saharan Africa: Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique, and the United Republic of Tanzania with two groups in the trial, first group included children aged 5-17 months at first dose receiving only the RTS,S/AS01 vaccine; and second group included children aged 6-12 weeks at first dose who received the same malaria vaccine co-administered with pentavalent vaccines in the routine immunization schedule. Both groups received 3 doses of RTS, S/AS01 vaccine at 1 month intervals. The vaccination with RTS,S, followed by a booster dose of RTS,S administered 18 months after the primary schedule, reduced the number of cases of clinical malaria in children (aged 5-17 months at first vaccination) by 36% to the end of the study[1] (over an average follow-up of 48 months across trial sites) and in infants (aged 6-12 weeks at first vaccination) by 26% to the end of the study (over an average follow-up of 38 months across trial sites)[81]

Several promising malaria vaccine candidates are in preclinical and clinical development around the globe. Key pipeline programs are from organizations including Oxford University, Crucell and Seattle BioMed collaboration, National Institute of Health (NIH) and others and are in Phase 2 clinical trials around the globe.

Malaria vaccine development – Indian landscape

International Centre for Genetic Engineering and Biotechnology (ICGEB) from India also has malaria vaccine candidates under pre-clinical development stage. This was supported under the Indo-US Vaccine Action Program and is the most advanced research program in India on the malaria vaccine. However, we have not been able to confirm the current status of the same with the Principal Investigator. Additionally, Bharat Biotech has a research program on the malaria vaccine which has been stalled due to lack of appropriate adjuvants.These adjuvants are currently available with multinationals only. Bharat Biotech has recently started upstream adjuvants research to further support their Malaria research.

Type of vaccine	Vaccine Name	Originator(s), Collaborator(s)	Vaccine Information	Development Stage	Clinical Trial/development location	Expected Launch
Recombinant (pre-erythrocytic)	RTS,S-AS01	GSK	Sequences of the circumsporozoite protein and the hepatitis B surface antigen (HBs Ag)	Phase 3-Completed	Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique, Nigeria, and Tanzania	2015
Recombinant	PvDBPII	ICGEB India/ Malaria Vaccine Development Program (MVDP)	-	Preclinical	India	-

Challenges in development of Malaria vaccine[82]

1. **Lack of immunity correlation-** there is a lack of immunity correlation in malaria, making it difficult for vaccines candidates to have a benchmark. The vaccine's efficacy, toxicology can only be validated in clinical trials making it an expensive process.
2. **Lack of diverse target antigens and delivery platforms-** very few antigens have been added to malaria vaccine candidate pool over the past decade. The field would benefit from the availability of diverse target antigens that are capable of inducing a variety of immune responses.
3. **Accessibility to immune-enhancing adjuvants-** there are very few adjuvants available today and the ones available are mostly controlled by few for-profit entities, which limits the scope for newer candidates for further research.

Experiences of Vaccine Manufacturers in other Markets and other Primary Research Findings

Experiences of vaccine manufacturers in other markets and other primary research findings

We have summarized below key findings from primary research covering experiences in other geographic markets,overall challenges constraining the manufacturers and focus of public health funders:

1. **Manufacturers' experience especially in other Asian countries of introduction of the vaccine in their national immunization program including challenges and learning**

India's leading vaccine manufacturers have indicated that their focus geographic markets are India and global public health procurement programs managed by GAVI and UNICEF. Most of them supply vaccines to public immunization programs of Asian and African countries via GAVI. The larger Indian companies have one or more vaccines in their portfolio that are WHO pre-qualified and they have been able to obtain high volume procurement commitments from GAVI and UNICEF. This has allowed them to extend their presence into the public health programs of many countries.

While the GAVI model of large volume commitment for longer duration has encouraged some of the Indian companies to establish large production capacity in certain vaccines, it has also made the market unattractive for potential late entrants into the same vaccines.

Apart from GAVI public procurement, vaccines manufacturers have indicated very limited experience in directly supplying to national immunization programs of countries where respective government procurement is prevalent. Manufacturers only referred to few examples such as bulk supplies for Typhoid to Pakistan and some other South East Asian countries.

2. **Manufacturers' experience on use of vaccine in India and other countries in the private sector**

All major Indian vaccines manufacturers have indicated that they supply vaccines for the private markets in various South East Asian and Middle Eastern countries. Commonly explored markets include Pakistan, Sri Lanka, Indonesia, Nepal, Philippines, Bangladesh etc.. The basic criteria required to cater to private Asian markets is WHO pre-qualification for these vaccines. Vaccine brands are registered in respective countries for private markets. For example, Panacea's Proprotec is registered in Thailand, Nigeria, Philippines, Bangladesh, Peru, Uganda, Chile, Kenya etc. EasyFive TT is registered in Thailand and Pakistan and so forth. Bharat Biotech and Biological E supply vaccines to South East Asian markets and Panacea Biotech caters to Thailand and Philippines. Most of the companies are not exploring African private markets yet and don't find them very attractive. However, majority of the African markets are covered by public health procurement programs discussed above.

3. Regulatory challenges

Regulatory issues are involved in nearly every aspect of vaccine development, manufacturing, and marketing approval. Regulations come into play from the time of vaccine design and clinical testing, through manufacturing, to when the final product is distributed for widespread use. Manufacturers catering to private markets in South East Asia and countries in Middle East face challenges in obtaining import licenses for their vaccines pertaining to handling, storage of vaccine in transit, labeling adherence with regulatory body standards etc.

4. Demand unpredictability hinders capacity planning

A significant challenge that manufacturers face today is unpredictability in demand of vaccines in various developing countries in Asia and Africa. Such unpredictability results in inefficient planning of production timelines and eventually timely supply. Unpredictability arises due to under reporting of disease incidences by countries, inability and hesitance of underdeveloped and developing countries to allocate national funding on vaccination programs and the consequent dependence on funding support and unreliable demand forecasts.

In addition to the above mentioned reasons for unpredictability of demand, the gap between anticipated timelines and actual adoption of vaccines in national immunization programs is very unpredictable and often very long. This challenge has been sighted by most companies as one of the foremost detriments of investment in infrastructure since they are always unsure about when the demand will actually arise.

The case of IPV and pentavalent is a poignant case of demand uncertainty holding back production and development investment. IPV has already been a challenging vaccine for suppliers since there is limited access today to wtIPV bulk. Per WHO's GAP-III guidelines, IPV production in India is restricted to only Sabin IPV (sIPV) and for wtIPV Indian companies are dependent on the limited number of global suppliers for sourcing bulk. To further complicate the demand-supply landscape, companies are uncertain about future demand of IPV and potential hexavalent combinations that could include IPV. Hence, the investment in IPV capacity in India and several other countries is observed to be slow given lack of clarity on future demand.

Companies have emphatically indicated willingness to investment in expanded capacity and desire to serve as strong suppliers of vaccine to the world and will be able to do so if such demand uncertainty in domestic as well as global markets is addressed.

5. Current Engagement of Global Public health funders in product development and capacity building in vaccines in India

Our discussions with funders has helped clarify their current funding priorities and confirm programs they are currently supporting in India.
Wellcome Trust is currently looking to fund programs for Polio (inactivated), Rotavirus, Dengue, Typhoid and Japanese Encephalitis vaccines primarily in addition to their ongoing funding of Hilleman Labs in India. Representatives from the Bill and Melinda Gates Foundation have indicated a willingness to fund vaccine programs for Polio (inactivated), Rotavirus and Pneumococcal disease (PCV), in addition to extending further support to existing programs for Dengue and Malaria vaccines. BIRAC, with a more India focused approach to funding, is prioritizing support to Indian programs for HPV, Influenza, Pneumococcal disease and TB vaccines. Representatives from BIRAC also indicated that through their grants, they extend funding to upstream research programs as well clinical trials for vaccines in India.
All of them have supported major vaccine development efforts in India - Wellcome Trust is supporting ICGEB's dengue vaccine program, BIRAC has supported Tergene Biotech's PCV development effort and the Bill and Melinda Gates Foundation is supporting several development and post development efforts (such as surveillance) across rotavirus, PCV and more recently, IPV.

Appendix

Appendix

Scope of the project

Detailed assessment of the aspects listed below:

1. Product profiles of above mentioned new vaccines:
    - Brand Name
    - Type of vaccine
    - Constituents of vaccine
    - Age of administration
    - Mode of administration
    - Any special requirement or exclusion criteria
    - Doses
    - Packaging
    - WHO-PQS status, including proposing to seek WHO-PQS
    - Temperature for storage and transportation
    - Shelf life
    - Production duration from bulk to final product
    - Cost per dose in various packing options

- Cost per dose for public health program, if supplied
- Cost per dose in retail market
- Manufacturers' experience on use of vaccine in India and other countries in the private sector*
- Manufacturers' experience especially in other Asian countries of introduction of the vaccine in their national immunization program including challenges and learning**
- Cold chain volume requirement***
- Any other relevant information

2. Production capacity of each manufacturer for individual vaccine.
3. Long term agreements with any country/organization
4. Licensure status
5. Similar product under development or licensure
6. Supply timelines****

*Manufacturers refused to reveal vaccine specific experience information for each vaccine brand

**Manufacturers refused to reveal vaccine specific experience information in Asian countries for each vaccine type

*** Manufacturers refused to reveal vaccine specific cold chain requirements for each vaccine brand not present in the public health system (not WHO pre-qualified)

****Manufacturers were not willing to share information on supply timelines

About Sathguru Management Consultants Private Limited

Founded in 1985, Sathguru is a multi-disciplinary consulting firm with expertise across corporate advisory (strategy, corporate finance, M&A), innovation advisory, public policy and regulatory and international development. Sathguru is differentiated by its deep entrenchment in innovation advancement and the consequent techno-commercial perspective; and has led several landmark efforts across cross-border licensing of intellectual property and public-private partnerships across the spectrum of Lifesciences. Sathguru works with leading Indian and global companies on market entry, corporate footprint expansion, and innovation access and commercialization in the Indian context. Sathguru has offices in India, USA, Bangladesh and Malawi and with a team strength of around 150 people.

Immunization Technical Support Unit, Public Health Foundation of India

Founded in 2006, the Public Health Foundation of India (PHFI) is a public private independent foundation to help build institutional and systems capacity in India for strengthening education, training, research and policy development in public health. PHFI works on broad areas in public health that encompasses promotive, preventive and therapeutic services.

Immunization Technical Support Unit (ITSU) was established by Ministry of Health and Family Welfare, Government of India and the Public Health Foundation of India (PHFI) to augment and support ongoing efforts around immunization. ITSU provides techno-managerial support for scaling up the Universal Immunization Program (UIP), enabling system strengthening for providing quality services and supporting implementation of MoHFW's Multi-Year Strategic Plan for Immunization. ITSU has a multi-disciplinary technical team of thematic experts and advisors with expertise in program design and management, policy research, advocacy and communications.

References

References

[1] 2015 National Health Profile published by Central Bureau of Health Intelligence

[2] GAVI Website – Pneumococcal Vaccine Support page. Available from http://www.gavi.org/support/nvs/pneumococcal/ Accessed on: July 23 2015

[3]Walker CLF, Rudan I, Liu L, Nair H, Theodoratou E, Bhutta Z A, et al. Global burden of childhood pneumonia and diarrhea. The Lancet 2013 Apr;381(9875):1405-16

[4] Musher DM. Pneumococcal vaccination in adults. Up-to-date (www.uptodate.com) December 2013. Accessed on: July 23, 2015

[5] Pneumococcal Regional Serotype Distribution for Pneumococcal AMC TPP. GAVI's PneumoADIP. Available from: www.gavi.org/library/gavi-documents/amc/tpp-codebook/

[6] UNICEF Supply Division. Historical Vaccine Procurement [Internet]. UNICEF Supplies and Logistics. 2013 [cited 2014 May 1]. Available from: http://www.unicef.org/supply/index_38554.html

[7] ADVANCE MARKET COMMITMENT FOR PNEUMOCOCCAL VACCINES Annual Report 2015. Secretariat of Gavi, the Vaccine Alliance.

[8] Serum Institute of India. Product Pipeline [Internet]. Research & Development. Available from: http://www.seruminstitute.com/content/research.htm

[9] PATH. Accelerating new vaccine development against pneumonia and other pneumococcal diseases [Internet]. Seattle; 2013. Available from: http://www.path.org/publications/files/VAC_pvp_fs.pdf

[10] PATH. Developing new vaccines against pneumonia and other pneumococcal diseases [Internet]. Seattle; 2014. Available from: http://www.path.org/publications/files/VAC_pvp_tech_fs.pdf

[11] Ginsburg AS, Alderson MR. New conjugate vaccines for the prevention of pneumococcal disease in developing countries. Drugs Today 2011;47:207-14.

[12] Hausdorff W, Godfroid F, Fierens F, Verlant V. Need for and development of a protein-based pneumococcal vaccine. http://www.meningitis.org.assets/x/53980

[13] WHO. Rotavirus Vaccine - WHO position paper. Wkly Epidemiol Rec [Internet]. 2013 Jan; 5(88):49–64. Available from: http:// www.who.int/wer/2013/wer8805.pdf. Accessed on: July 23, 2015

[14] Penelope H Dennehy, Rotavirus Vaccines: An Overview. Clinical Microbiology Reviews [Internet] 2008 January; Available from http://cmr.asm.org/content/21/1/198.full

[15] WHO. Rotavirus Vaccine - WHO position paper. Wkly Epidemiol Rec [Internet]. 2013 Jan; 5(88):49–64. Available from: http://www.who.int/wer/2013/wer8805.pdf

[16] Leshem E, Lopman B, Glass R, Gentsch J, Bányai K, Parashar U, et al. Distribution of rotavirus strains and strain-specific effectiveness of the rotavirus vaccine after its introduction: a systematic review and meta-analysis. Lancet Infect Dis [Internet]. 2014 Jul [cited 2014 Aug 6]; Available from: http://linkinghub.elsevier.com/retrieve/pii/S1473309914708321

[17] Steele A, Neuzil KM, Cunliffe NA, Madhi SA, Bos P, Ngwira B, et al. Human rotavirus vaccine RotarixTM provides protection against diverse circulating rotavirus strains in African infants: a randomized controlled trial. BMC Infect Dis [Internet]. 2012 [cited 2014 Aug 6];12(1):213. Available from: http://www.biomedcentral.com/1471-2334/12/213.

[18]Ruiz-Palacios NEJM, 2006 et al. Safety and Efficacy of an Attenuated Vaccine against Severe Rotavirus Gastroenteritis.

[19] Vesikari et al. NEJM, 2006. Safety and Efficacy of a Pentavalent Human–Bovine (WC3) Reassortant Rotavirus Vaccine.

[20] Madhi and Cunliffe et al. NEJM, 2010. Effect of Human Rotavirus Vaccine on Severe Diarrhea in African Infants.

[21] Armah et al., Lancet, 2010. Efficacy of pentavalent rotavirus vaccine against severe rotavirus gastroenteritis in infants in developing countries in sub-Saharan Africa: a randomised, double-blind, placebo-controlled trial.

[22] Bhandari et al. Lancet, 2014. Efficacy of a monovalent human-bovine (116E) rotavirus vaccine in Indian infants: a randomised, double-blind, placebo-controlled trial.

[23] WHO. Rotavirus Vaccine - WHO position paper. Wkly Epidemiol Rec [Internet]. 2013 Jan; 5(88):49–64. Available from: http:// www.who.int/wer/2013/wer8805.pdf . Accessed on : July 23, 2015

[24] Weintraub ES, Baggs J, Duffy J, Vellozzi C, Belongia EA, Irving S, et al. Risk of Intussusception after Monovalent Rotavirus Vaccination. N Engl J Med [Internet]. 2014 Feb 6 [cited 2014 Jul 16];370(6):513–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24422678

[25] Rotavirus Vaccine: Supply & Demand Update UNICEF Supply Division. July 2014. Available from: http://www.unicef.org/supply/files/Rotavirus_Update_Note_July_2014.pdf Accessed on: July 23, 2015

[26]Robert Roos. Phase 3 results boost rotavirus vaccine developed in India [Internet]. CIDRAP. 2014 [cited 2014 May 15]. Available from: http://www.cidrap. umn.edu/news-perspective/2014/03/ phase-3-results-boost-rotavirus-vaccinedeveloped- India

[27] Prime Minister of India launches Made in India ROTAVAC® Vaccine for the world. Mar 09, 2015. Bharat Biotech Press-release. Available from: http://www.bharatbiotech.com/wp-content/plugins/prs/pdf/BBIL-ROTAVAC-Launch-09Mar2015.pdf . Accessed on: July 23, 2015

[28]Madhi SA, Cunliffe NA, Steele D, et al. Effect of human rotavirus vaccine on severe diarrhea in African infants. New England Journal of Medicine. 2010;362(4):289-298.

[29]Armah GE, Sow SO, Breiman RF, et al. Efficacy of pentavalent rotavirus vaccine against severe rotavirus gastroenteritis in infants in developing countries in sub-Saharan Africa: a randomised, doubleblind, placebo-controlled trial. The Lancet. 2010;376(9741):606-614.

[30]Zaman K, Dang DA, Victor JC, et al. Efficacy of pentavalent rotavirus vaccine against severe rotavirus gastroenteritis in infants in developing countries in Asia: a randomised, double-blind, placebocontrolled trial. The Lancet. 2010;376(9741):568-570.

[31] WHO. Diphtheria [Internet]. WHO Department of Immunization, Vaccines and Biologicals. 2014. Available from: http://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/passive/diphtheria/en/

[32] WHO. Pertussis [Internet]. WHO Department of Immunization, Vaccines and Biologicals. 2013. Available from: http://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/passive/pertussis/en/

[33] WHO. Tetanus [Internet]. WHO Department of Immunization, Vaccines and Biologicals. 2013. Available from: http://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/passive/tetanus/en/

[34] PATH. PATH Vaccine Resource Library: Hepatitis B [Internet]. Vaccine Resource Library. 2014 [cited 2014 Apr 22]. Available from: http://www.path.org/vaccineresource

[35] WHO. Estimated Hib and pneumococcal deaths for children under 5 years of age, 2008 [Internet]. World Health Organization- Immunization,Vaccines and Biologicals: Monitoring and Surveillance. Available from: http://www.who.int/immunization/monitoring_surveillance/burden/estimates/Pneumo_hib/en/

[34]Gavi Supply and Procurement Roadmap Pentavalent (DTwP-hepB-Hib). June 2014. Available from: Roadmap Pentavalent (DTwP-hepB-Hib). June 2014. Available from

[37] PATH. PATH Vaccine Resource Library: Hepatitis B [Internet]. Vaccine Resource Library. 2014 [cited 2014 Apr 22]. Available from: http://www.path.org/vaccineresource

[37] WHO. Estimated Hib and pneumococcal deaths for children under 5 years of age, 2008 [Internet]. World Health Organization- Immunization,Vaccines and Biologicals: Monitoring and Surveillance. Available from: http://www.who.int/immunization/monitoring_surveillance/burden/estimates/Pneumo_hib/en/

[6] Gavi Supply and Procurement Roadmap Pentavalent (DTwP-hepB-Hib). June 2014. Available from: Roadmap Pentavalent (DTwP-hepB-Hib). June 2014. Available from

[37] Gavi Supply and Procurement Roadmap Pentavalent (DTwP-hepB-Hib). June 2014. Available from: Roadmap Pentavalent (DTwP-hepB-Hib). June 2014. Available from:

[38] Gavi Supply and Procurement Roadmap Pentavalent (DTwP-hepB-Hib). June 2014

[39] Recent advancement in typhoid research- a review, Khan et al, Advanced Biotech, 2008, 35

[40] Weekly epidemiological record, WHO 2008

[41] Coalition against Typhoid, Available on: http://www.coalitionagainsttyphoid.org/vaccines/available-vaccines/, Accessed on 27 July 2015

[42] Recent advancement in Typhoid research- a review, Khan et al, Advanced Biotech, 2008

[43] GAVI Strategic Demand Forecast. 2014. Available from

[44] Biological E Website. Link: www.biologicale.com . Accessed on July 25, 2015

[45] CTRI/2015/04/005710 Available from: www.ctri.nic.in Accessed on 25 July 2015

[46] Solomon T Control of Japanese encephalitis–within our grasp? N Engl J Med 2006;355:869–71 10.1056/NEJMp058263

[47]World Health Organization World health report. (for years 2000–2004) [Cited 2008 Oct 14]. Available fromhttp://www.who.int/whr/en

[48]http://www.who.int/ith/vaccines/japanese_encephalitis/en/ Accessed on- 25 July 2015

[49]Operational Guide Japanese Encephalitis Vaccination in India, September 2010

[50]JE Supply and Procurement Roadmap, GAVI Alliance, April 2014

[51] National Health Profile of India. Central Bureau of Health Intelligence Available from: www.cbhidghs.nic.in Accessed on 27 July 2015

[52] Strategic Demand Forecast, GAVI Alliance, 2014

[53]HPV vaccine – NHS – Accessed on 27 July 2015

[54]Human papillomavirus vaccines: WHO position paper, October 2014position paper - Weekly Epidemiological Record – Accessed on 27 July 2015

[55]Gardasil 9 Vaccine Protects against Additional HPV Types – National Cancer Institute – Accessed on 27 July 2015

[56] 2014 GAVI Strategic Demand Forecast – Accessed on 22 July, 2015

[57]Serum Institute of India poses challenge to Merck HPV vaccine **–** Fierce Vaccine – 27 January, 2015 – Accessed on 23 July 2015**.**

[58]Zydus Cadila preps for big splash into India's vaccines market **–** Fierce Vaccine – 21 May, 2015 – Accessed on 23 July 2015.

[59]Indian Immunologicals' Raksha Ovac became the largest selling veterinary brand in India with sales exceeding `125 crore – Socially conscious – BioSpectrum – 27 July, 2013 – Accessed on 23 July 2015.

[60]**India three years polio-free** – WHO – Accessed on 27 July 2015

[61]Poliomyelitis – WHO – Accessed on 23 July, 2015

[62]Lessons learned and experiences from IPV introduction – WHO – Accessed on 23 July, 2015

[63]Polio-free India to Introduce Injectable Vaccine Soon – Indian Express – 15 Dec-2014 – Accessed on 23 July 2015

[64] Polio vaccines: WHO position paper – January 2014 – Accessed on 27 July 2015

[65] WHO Global Action Plan to minimize Poliovirus facility associated risk (GAP-III) Accessed on 28 July 2015

[66]Inactivated Polio vaccine support – GAVI – Accessed on 27 July 2015

[67]Measles – WHO – Accessed on 27 July 2015

[68]Rubella (German Measles) – WHO – Accessed on 24 July 2015

[69]Global partners launch new plan to control and eliminate measles and rubella – WHO – Accessed on 27 July 2015

[70]Serological effects of Edmonston-Zagreb, Schwarz, and AIK-C measles vaccine strains given at ages 4-5 or 8-10 months – NCBI – 9 Dec 1989 – Accessed on 24 July 2015

[71]Rubella (German Measles) – WHO – Accessed on 24 July 2015

[72]MR Supply and Procurement Roadmap – January 2014 – Accessed on 27 July 2015

[73]Netherlands to help India develop, mass produce measles-rubella vaccine – BioPharma – 10 Jun 2015 – Accessed on 24 July 2015

[74]. UNICEF – Measles Containing Vaccine supply & demand outlook (http://www.unicef.org/supply/files/Measles_Containing_Vaccines_Supply_Update_July_2015.pdf)

[75]Latest developments and future directions in dengue vaccines, Thisyakorn et al, Therapeutic Advances in Vaccines, Jan 2014

[76]Vaccines against dengue: a review of current candidate vaccines at advanced development stages, Hombach, World Health Organization, Initiative for Vaccine Research, 2007

[77] Efficacy of a Tetravalent Dengue Vaccine in Children in Latin America, Villar et al, The New England Journal of Medicine, 2014

[78]http://kff.org/news-summary/brazil-joins-philippines-mexico-in-approving-sanofis-dengue-vaccine/. Accessed on 28th January 2016.

[79] Prospect and progress of malaria vaccine development, Adeyeba et al, Americal Journal of clinical and experimental Biology, 2005

[80]Safety and immunogenicity of DNA/modified vaccine virus Ankara malaria vaccination in African adults, Moorthy et al, Journal of Infectious disease, 2003,188, 1239-1241

[81] Malaria Vaccine Initiative, From: http://www.malariavaccine.org/pr2015Apr24-RTSS.php, Accessed on, 28 July 2015

[82] Editorial- Malaria and the Challenges of Vaccine Development, University of Benin, Tropical Journal of Pharmaceutical Research, December 2007; 6 (4): 801-802

ITSU
IMMUNIZATION
TECHNICAL SUPPORT UNIT
Ministry of Health & Family Welfare

KNOWLEDGE TO ACTION
phfi
PUBLIC
HEALTH
FOUNDATION
OF INDIA

B-28, Qutub Institutional Area, Near Rockland Hospital, New Delhi -110016, Ph.: +91-11-41213100