

*Review Article*

## Medical Microbiology in India: The Recent Developments in the Basic Research, Diagnostics and Vaccines

JUGSHARAN SINGH VIRDI<sup>1,#,\*</sup>, NEELJA SINGHAL<sup>1,#</sup>, ANAY KUMAR MAURYA<sup>1</sup>, THANDAVARAYAN RAMAMURTHY<sup>2</sup>, PRIYA SINGH<sup>3</sup> and NIRJARA SINGHVI<sup>3</sup>

<sup>1</sup>*Microbial Pathogenicity Laboratory, Department of Microbiology, University of Delhi South Campus, New Delhi 110 021, India*

<sup>2</sup>*Translational Health Science and Technology Institute, Faridabad 121 001, Haryana, India*

<sup>3</sup>*Department of Zoology, University of Delhi, Delhi 110 007, India*

(Received on 03 April 2019; Accepted on 04 November 2019)

Medical microbiology being the largest subset under microbiology brings out the benefits of the research in the field of microbiology for the welfare of the masses through applied medical science. Researchers around the globe are working tirelessly in this field in order to prevent, diagnose and treat infectious diseases well in time. India being a tropical country with poor socio-economic conditions and slack healthcare schemes has wide range and burden of the infectious diseases. This has led to the researchers here to take up the challenging tasks of medical microbiology research, they are actively working and the present article reviews the exemplary contribution of these researchers from India in the last decade. This enlists the basic research carried to assess the infections caused by Rotavirus, Human Immunodeficiency Virus (HIV), Pathogenic *Vibrios*, *Mycobacterium tuberculosis*, *M. leprae*, *Salmonella enterica* serovar *typhi*, *Helicobacter pylori*, *Yersinia enterocolitica*, *Leptospire*s, *Leishmania*, *Plasmodium falciparum*, *P. vivax*, *Wuchereria bancrofti*, *Entamoeba histolytica* and some other pathogens. The knowledge gathered through the basic research has been applied for the development of certain vaccines and diagnostic tools and/or techniques to tackle infectious diseases. Notably, *Mycobacterium Indicus Prani* vaccine (against certain Mycobacterial infections), Rotavac (against rotavirus), JENVAC (against Japanese encephalitis), recombinant vaccine DENVs (against dengue virus) etc. have been developed by Indian research groups and have found wide application. The present article briefly reviews such breakthrough developments in the field of applied microbiology along with a concise account of the infectious diseases outbreaks that resulted from inadequate containments of the vectors.

**Keywords:** Epidemicity; Pathogens; Gastroenteritis; Genotypes; Serovars

### Introduction

India with its variety of climatic conditions, demography, rich flora and fauna and wide socioeconomic spectrum constitute an ideal niche for the emergence and spread of infectious diseases caused by pathogenic microorganisms. Consequently, microbiologists from India have contributed significantly in understanding the epidemiology, basic and applied aspects on biology of infectious agents. This article covers the recent research outcomes of important pathogens.

### Basic Research

#### *Rotavirus*

Rotavirus is the most common cause of gastroenteritis (vomiting and severe diarrhea) among infants and young children. Rotavirus infections can cause mild to severe disease characterised by vomiting, watery diarrhoea and low-grade fever. The genotypes of the human and animal rotaviruses circulating in India have been extensively studied (Saluja *et al.*, 2017). The human and bovine-human re-assortment rotaviruses in children with gastroenteritis in hospitals, the neonatal nurseries and in community settings (Babji *et al.*, 2014;

\*Author for Correspondence: E-mail: virdi\_dusc@rediffmail.com; #Contributed equally

John *et al.*, 2014; Kang *et al.*, 2015) have brought new understanding about this virus.

### **Human Immunodeficiency Virus (HIV)**

HIV is a lentivirus that causes the viral infection and over time acquired immunodeficiency syndrome (AIDS). AIDS in turn causes the progressive failure of the immune system allowing life-threatening opportunistic infections and cancers to thrive. The genetic heterogeneity of HIV-1 strains circulating in different parts of India has been investigated (Khan *et al.*, 2007; Seth 2010). More than 95% isolates circulating in India belonged to the subtype-C. This information was instrumental in undertaking research for designing an HIV vaccine for Indian population. A new subtype; Thai-B was identified in Manipur, which was different from the subtype B, the most prevalent HIV-1 strain in the US and Europe (Sarkar *et al.*, 2011).

### **Pathogenic Vibrios**

Vibrios are the Gram-negative bacteria and few of the species can cause foodborne infection, usually associated with eating undercooked food or untreated/unsafe water. Several species of vibrios were associated with acute diarrhoea and other systemic infections. The epidemicity and endemicity of cholera caused by *V. cholerae* serogroups O1 and O139 are well investigated in several findings (Kanungo *et al.*, 2010; Ramamurthy and Sharma, 2014; Chowdhury *et al.*, 2016; Sharma *et al.*, 2017). The genome of *V. cholerae* is continuously changing, as evidenced by variation in the biotype encoding and cholera toxin encoding genes (Mukhopadhyay *et al.*, 2014; Das *et al.*, 2016). The importance of other serovars (other than O1 and O139) of *V. cholerae* in causing the cholera-like diarrhoea has been emphasized in a study from Kolkata (Dutta *et al.*, 2013). Emergence of *V. fluvialis* associated with hospitalized acute diarrhoea cases has also been reported from Kolkata (Chowdhury *et al.*, 2012). The appearance and global spread of *V. parahaemolyticus* O3:K6 and other serovars had several epidemiological implications (Nair *et al.*, 2007). In fact, this event was the first to demonstrate the emergence of pandemic clones in this species.

### ***Mycobacterium tuberculosis***

Tuberculosis has been a rampant health threat worldwide and has been the most devastating in the under-developed and developing countries around the world. India has a substantial burden of patients suffering from tuberculosis caused by *Mycobacterium tuberculosis*. Several studies helped to identify new genotypes, dynamics and dissemination of this pathogen (Chauhan *et al.*, 2007; Haldar *et al.*, 2007; Lavania *et al.*, 2007; Sharma *et al.*, 2008; Gupta *et al.*, 2010, Chauhan *et al.*, 2011; Gautam *et al.*, 2014; Sikri *et al.*, 2015; Kaur *et al.*, 2016). Using genetic typing of *M. tuberculosis* isolates from India, presence of ancestral isolates as the predominant form circulating in India has been shown which could explain the lack of concordance between bacterial load and disease burden in the Indian population (Rao *et al.*, 2006; Ahmed *et al.*, 2009; Ahmed and Hasnain, 2011; Thomas *et al.*, 2012). Studies on functional characterization of *M. tuberculosis* hypothetical PE/PPE protein family revealed their importance in diagnostics, as vaccine candidates and as drug targets (Akhter *et al.*, 2012; Kohli *et al.*, 2012; Parsa and Hasnain, 2015). The genetic diversity and drug susceptibility profile of *M. tuberculosis* isolated from different regions, safety and tolerability profiles of anti-tubercular medications have also been studied in detail (Swaminathan, 2014; Ramachandran and Swaminathan, 2014). Additionally, there was a study from the Indian subcontinent that took into account the shift in the bacterial community of gut and the functional implications of microbes on the gut-lung axis, especially during tuberculosis (Maji *et al.*, 2018; Sood *et al.*, 2018).

### ***Mycobacterium leprae***

Data obtained from the National Leprosy Eradication Programme (NLEP) has shown the reduction in cases from 57.8/10,000 in 1983 to 0.66/10,000 in 2016. Globally, India continues to account for 60% of new cases and from 2007 to 2016, the number remained the same with almost 1.35 lakh new cases (Rao and Suneetha, 2018). Several other works have been done on the detection of *M. leprae*, its drug resistance and vaccines (Lavania *et al.*, 2015)

### ***Salmonella enterica* serovar typhi**

Enteric fever is an important public-health problem

in India. The clinical presentation of typhoid fever caused by *Salmonella enterica* serovar *typhi* was found to be highly variable. The estimated prevalence of *S. typhi* detected through culture or serology across all hospital-based studies in the random effects model was 9.7% (John *et al.*, 2016). The meta-regression revealed a significant decline in laboratory confirmed typhoid among patients with fever or suspected typhoid. Apart from causing typhoid fever, *S. typhi* was found to be significantly associated with gallbladder cancer (Tewari *et al.*, 2010). A diverse population of *S. typhi* with H58 haplotypes was detected with multidrug and quinolone resistance (Holt *et al.*, 2012). Variable number tandem repeat-PCR analysis also showed high genetic variability within the *S. typhi* strains (Sankar *et al.*, 2013). Ciprofloxacin has become the first-line drug of choice for the treatment of typhoid due to the widespread emergence and spread of strains resistant to chloramphenicol, ampicillin and trimethoprim. Recently, there is also increase in the occurrence of strains resistant to ciprofloxacin (Harish *et al.*, 2011; Patel *et al.*, 2017).

### *Helicobacter pylori*

Cytotoxic *H. pylori* were isolated more frequently from patients with peptic ulcers, than from patients suffering from gastritis, the milder form of the disease (Shanjana and Ayyagari, 2003). Exaggerated apoptosis was found to play an important role in *H. pylori*-mediated gastric diseases, including carcinogenesis (Tiwari *et al.*, 2008). The frequency of *H. pylori* infection in patients suffering from gastric neoplasms was detected more by endoscopy than serology.

DNA sequence information has helped in understanding the evolution of *H. pylori*, its survival and adaptation through genomic changes (Devi *et al.*, 2010; Avasthi *et al.*, 2011). This study also helped to understand the natural history of *H. pylori* in the context of human anthropology (Ahmed *et al.*, 2008; Devi *et al.*, 2006; Alvi *et al.*, 2007). Whole genome microarrays, pan-island sequencing and full genome sequencing revealed that though parts of the pathogenicity islands were seen to rearrange over time, these rearrangements did not bring about significant change in severity of pathology of the disease (Prouzet-Mauleon *et al.*, 2005; Alvi *et al.*, 2007).

### *Yersinia enterocolitica*

*Y. enterocolitica* is an important food and waterborne zoonotic enteropathogen. The first outbreak of gastroenteritis due to this bacterium was reported in 1996. The organism has been isolated from wastewater, pork, pigs and the stools of the diarrhoeic patients. These strains belonged to several serotypes. Genotyping using REP- and ERIC-PCRs showed that the strains belonged to two clonal groups indicating their narrow genetic heterogeneity (Sachdeva and Viridi, 2004). Similar results were inferred from genotyping based on *rrn* and *gyrB* loci. Sequencing of  $\beta$ -lactamase genes (*blaA*, *blaB*) also discerned two clonal groups (A and B) as based on repetitive extragenic palindrome- and enterobacterial repetitive intergenic consensus-PCR genotyping (Sharma *et al.*, 2006; Singhal *et al.*, 2014; Singhal *et al.*, 2015). These studies also showed that the serotypes 6,30-6,31 isolated from wastewater were genotypically different from the serotype 6,30-6,31 isolated from diarrhoeal patients (Mallik and Viridi, 2010).

The detection of a large number of virulence-associated genes (*inv*, *ail*, *virF*, *ystA*, *ystB*, *ystC*, *myfA*, *fepA*, *fepD*, *fes*, *hreP*, *ymoA*, *tccC*, *sat*) showed that the *Y. enterocolitica* strains belonged to low virulence biotype 1A group (Bhagat and Viridi, 2007). Multilocus variable number tandem repeat analysis (MLVA), multilocus enzyme electrophoresis (MLEE) and multilocus restriction typing (MLRT) and their analysis by minimum spanning tree and e-BURST suggested that the clinical strains probably originated from environmental strains by host adaptation and genetic change (Mallik and Viridi, 2010). It has also been reported that the interaction of these bacteria with cultured cell depends on characteristics of the individual strains and not the clonal groups. Interestingly, some functional parameters did not reflect the two clonal groups. A variety of studies have reported the presence of virulence factors in these bacterial strains. One of the reported factors is presence of iron-acquisition system and well-regulated iron homeostasis. Suppression subtractive hybridization between clinical and environmental strains and proteomic analysis indicated the presence of several iron-acquisition and storage genes showed up-regulation or down-regulation during conditions of iron depletion or iron repletion (Kanaujia *et al.*, 2015).

## Leptospire

Leptospirosis is primarily a zoonotic disease, which may be transmitted to human beings. It is caused by a pathogenic spirochete of the genus *Leptospira* that traditionally consist of two species, *Leptospira interrogans* (the pathogenic serovars) and *Leptospira biflexa* (the saprophytic serovars). The *Leptospira* serovars predominantly identified include *L. andamana*, *L. pomona*, *L. grippityphosa*, *L. hebdomadis*, *L. semoranga*, *L. javanica*, *L. autumnalis*, *L. canicola* (<https://www.ncdc.gov.in/>). Most outbreaks of leptospirosis have been reported from the coastal regions of Gujarat, Maharashtra, Orissa, West Bengal, Kerala, Tamil Nadu, Karnataka and the Andaman Islands (Divya *et al.*, 2017). Outbreaks have also occurred in the recent years in different parts of the country, including the 2007 outbreak in Karnataka (<http://www.gideononline.com>), 2011 and 2012 outbreak in Gujarat (<http://www.healthmap.org>).

Leptospire from patients suffering from Andaman hemorrhagic fever was associated with high fatality in Andaman Islands (Sharma *et al.*, 2006; Lall *et al.*, 2016). Valbuzzi is a common infective serovar of leptospire responsible for pulmonary complications in Andaman Islands (Vijaychari *et al.*, 2003).

## Leishmania

Visceral leishmaniasis (VL, also known as kala-azar), is caused by intracellular protozoan, *Leishmania*. India has reported the largest number of VL cases, accounting for 40%-50% of the world's disease burden (Agarwal *et al.*, 2017). Most of the research is focused largely on the clinical and epidemiological aspects of the disease. To date, there is no effective vaccine available. However, treatment of VL is based only on chemotherapy *i.e.* a single dose of liposomal amphotericin B (L-AmB) and multidrug therapy [L-AmB+miltefosine, L-AmB+paromomycin (PM), or miltefosine+PM] (Singh *et al.*, 2016). National Vector Borne Disease Control Program (NVBDCP) of India recommends sodium stibo gluconate or miltefosine for the treatment of VL and post kala-azar dermal leishmaniasis (PKDL) (Saha *et al.*, 2017).

## *Plasmodium falciparum* and *P. vivax*

Malaria in India is mainly caused by *P. vivax* with

53% of the estimated cases. In 2014 alone, about 380,000 malaria cases were recorded, which is nearly a sixth of total cases reported globally (Anvikar *et al.*, 2016). Chloroquine resistant *P. falciparum* has emerged since 1973. Sulfa-pyrimethamine is a new first-line drug for treatment of this pathogen (Shah *et al.*, 2011). The epidemiology of *P. vivax* is very complex, including multiple relapse phenotypes with varying latencies and resistant to control measures. Calcium-dependent protein kinases (CDPKs) were found to play a critical role in different life cycle of *Plasmodium* including secretion of adhesions, cell invasion, gamete maturation, and motility (Kadian *et al.*, 2017).

## *Wuchereria bancrofti*

Lymphatic filariasis is mainly caused by the parasite *W. bancrofti*. India contributes to 41% of global lymphatic filariasis (Agarwal and Sashindran, 2011). Data collected in 2006 exhibited the prevalence of 31 million microfilaraemics, 23 million cases of symptomatic filariasis, and about 473 million individuals potentially at risk of infection in the country (Agrawal *et al.*, 2006). Annual single-dose treatment with diethylcarbamazine along and albendazole for three consecutive years has shown significant reduction in the lymphatic filariasis (Kshirsagar *et al.*, 2017). Therapeutic prospects of biopolymer functionalized gold nanoparticles against filarial parasite has been established through nuclear factor erythroid-derived Nrf2. These nanoparticles induced oxidative stress and apoptotic cell death in filarial parasites is mediated through mitochondria. A new 70-kDa microfilarial protein that binds to macrophage-Toll-like receptor 4 and triggers nuclear factor kappa beta activation that upregulates secretion of proinflammatory cytokines has been discovered (Mukherjee *et al.*, 2017). Functional analysis of this protein would help in understanding the host-parasite relationship and immunopathogenesis of filarial infection. Genetic polymorphism studies revealed the existence of three variant *W. bancrofti* glutathione S-transferase (Wb-GST) alleles in the four filarial endemic regions. Mutational impact on the functions of Wb-GST highlights the mechanisms of parasite survival against the host oxidative stress environment (Sakthidevi *et al.*, 2013).

### ***Entamoeba histolytica***

Amoebiasis still remains one of the major public health problems for developing countries like India. People's access to clean water, hygienic food and proper sanitation is limited to certain places and because of this most people get exposed to deadly diseases like amoebiasis. It is caused by enteric protozoan parasite *Entamoeba histolytica*. Indian researchers have contributed variously to check the infection, its rapid detection and treatment (Anwar *et al.*, 2018; Mukhopadhyay *et al.*, 2002; Nath *et al.*, 2015; Pandey *et al.*, 2018; Zaman *et al.*, 2018). The work has been carried out in order to manage the disease in best possible manner as this infectious organism is here to stay pertaining to unhygienic conditions. The prevalence of this disease is more in developing countries due to lack of advanced diagnostic methodologies. Diagnosis of the disease is based on various techniques like microscopy, culture and serology based techniques. RT-PCR has been reported to be one of the best and most sensitive method to confirm the tests, also confirmed by WHO. But due to its expensive equipment and cumbersome routine diagnostic, this technique has not been successfully employed in limited resources nations (Dhanalakshami and Parija, 2016).

### ***Other Pathogens***

Many studies pertaining to the respiratory syncytial virus, their genetic variability, molecular detection of human caliciviruses with special emphasis to Norwalk-like viruses (NLVs) and Sapporo-like viruses (SLVs), molecular epidemiology, genotyping and viral load assays of Polioviruses, the study of genetic variability of other respiratory viruses have demonstrated the role of some other viral pathogens (Banarjee *et al.*, 2007; Rachakonda *et al.*, 2008; Bharaj *et al.*, 2009; Mir *et al.*, 2012; Broor *et al.*, 2014; Raghuram *et al.*, 2015). Several pathogens associated with diphtheria (2000), plague (1994-2004), H1N1 (2009), Chandipura virus (2003), chikungunya virus (2005) and Congo haemorrhagic virus (2011) were found to be emerged/re-emerged in the country (Dikid *et al.*, 2013).

### ***Diagnostics***

In the last two-decade or so, with the introduction of state-of-art scientific infrastructure and facilities in

several laboratories and support from the funding agencies like Department of Biotechnology (DBT) and its associated Biotechnology Industry Research Assistance Council (BIRAC), many scientists have undertaken research and development related to the diagnosis of infectious diseases. This development has been further aided by the establishment of a large number of Technology Based Incubators (TBIs) in several states of the country.

A test kit for the on-site detection of HIV antibodies (HIV-1 and HIV-2) in two minutes has been developed using a drop of blood (Gupta and Chaudhary, 2003). Recently, an indigenously developed technology for dengue NS1 antigen detection has been successfully transferred for commercial production and use. Since then, a large number of dengue NS1 Antigen tests have been carried out by the laboratories in India to detect and diagnose dengue infection in the country (<http://www.icgeb.org/navin-khanna.html>).

A rapid test for identification and confirmation of TB has also been developed. The test is based on the detection of two *M. tuberculosis* specific antigens using high affinity monoclonal antibodies. The research carried out at the Defence Research and Development Establishment (Gwalior) has resulted in the development of kits for rapid and real-time detection of emerging viruses of public health importance. The diagnostic kits have made use of several newer techniques like RT-PCR, Multiplex PCR, Real-Time PCR and RT-LAMP (Parida *et al.*, 2011; Sharma *et al.*, 2011; Kumar *et al.*, 2012; Parida *et al.*, 2016).

Blood culture remains gold standard for diagnosis. Widal test has low sensitivity and specificity, but may be used in second week to support the diagnosis. Salivary anti-*Salmonella typhi* lipopolysaccharide IgA antibody-based ELISA has been developed and tested in children with typhoid fever (Zaka-ur-Rab *et al.*, 2012). An immunoassay using Ag-labeled nano-conjugated antigen was developed for the rapid detection of *S. typhi* and *S. paratyphi* antibodies in serum samples (Chattopadhyay *et al.*, 2014).

A nested multiplex PCR based diagnosis was developed for the detection of virulent *S. typhi* from the patient's blood samples (Prabakaran *et al.*, 2017). This M-PCR targets first the flagellin gene (*fliC*)

followed by the detection of Via B operon of *Salmonella* Pathogenicity Island-7 (PI-7) that comprises *tviA* and *tviB* genes. This M-PCR can be used to detect Vi-negative Typhi serovar in typhoid endemic regions, where the Vi vaccine has been administered. Additional cases of *Salmonella* Paratyphi A and non-typhoidal *Salmonella* can be detected with the PCR screen made with *fliC* and *iroB* that encodes glycosyl transferases (Ganesan *et al.*, 2014).

Molecular and serological tests for analysis and diagnosis of *Leptospira* species prevalent in India have also been developed (Ahmed *et al.*, 2006; Natarajaseenivasan *et al.*, 2008). Several different simple and rapid tests such as Lepto-dipstick, Lepto-lateral flow, Leptodri-dot, Linnodee etc. for the diagnosis of leptospirosis (Vijayachari and Sehgal, 2006; Sehgal *et al.*, 1999). Microscopic examination of tissue smears is a gold standard for the definitive diagnosis of VL and PKDL. Loop-mediated isothermal amplification (LAMP) assay with DNA from biological samples, immunochromatographic test with anti-rK-39 antibodies and latex agglutination test using serum samples were successfully evaluated (Boelaert *et al.*, 2014).

Ziehl-Neelsen (ZN) staining technique using smears from ear lobe, skin lesion, and normal skin and histopathology of specimens stained with hematoxylin and eosin and Wade-Fite stain are clinically used for the detection of *M. leprae*. In addition, serum anti-PGL1 levels, fine needle aspiration cytology from the affected nerve, and *M. leprae*-specific multiplex PCR were also used in the routine practice. Fluorescent staining method was found to be more sensitive than modified fite-faraco and ZN staining techniques (Adiga *et al.*, 2016). *M. leprae*-specific repetitive element PCR was found to be superior compared to other PCR targetting the *rpoT*, *SodA* and 16S rRNA genes (Turankar *et al.*, 2015).

Apart from direct microscopy, several useful protein antigens were targeted in the rapid diagnosis of malaria (Patankar *et al.*, 2017).

Based on WbSXP-1, the chimeric peptides for the detection of anti-SXP antibody was found to be reactive, specifically with microfilaremic sera by ELISA. These peptide-based ELISA is useful in the

diagnosis of lymphatic filariasis (Pandiaraja *et al.*, 2010). Monoclonal antibodies against recombinant WbSXP-1 has also been tested in the rapid-antibody-flow-through diagnostic kit for filariasis (Janardhan *et al.*, 2011).

### Vaccines

The live oral vaccine VA 1.4 was developed for the first-time using *V. cholerae* O1 El Tor strain that was genetically engineered to contain only the immunogenic subunit of the cholera toxin (Thungapathra *et al.*, 1999). In field trials, this vaccine was found to be highly safe and immunogenic (Mahalanabis *et al.*, 2009). Many potential candidate vaccine strains for typhoid have been prepared. In animal studies, the recombinant Omp-28 protein elicited strong protection against virulent *Salmonella typhi* (Saxena *et al.*, 2017). OmpR attenuated strains of *S. typhi* may be used as good candidate strains for the development of live attenuated vaccine against salmonellosis (Senthilkumar *et al.*, 2014).

A rotavirus vaccine containing a G9P(11) human strain (116E) isolated from an Indian child was developed as part of the Indo-US Vaccine Action Program. This vaccine (now Rotavac) is well tolerated and immunogenic in several clinical trials. Mw is an immunoprophylactic and an immunotherapeutic vaccine, developed in India, for multibacillary leprosy. The vaccine is based on a non-pathogenic *Mycobacterium*, now named as *Mycobacterium indicus pranii* (MiP) (Talwar *et al.*, 2016). The National Leprosy Eradication Programme has initiated the *Mycobacterium Indicus prani* vaccine in 2016. This vaccine has both immunotherapeutic and immune-prophylactic effects (Rao and Suneetha, 2018).

Japanese encephalitis, a mosquito-borne viral infection, is the most common cause of viral encephalitis in certain parts of India, especially eastern Uttar Pradesh, Bihar and Bengal, claiming several lives every year (Tiwari *et al.*, 2012). Mortality is higher among children and many individuals who were inflicted by this infection have been disabled for life by its sequelae. Scientists have developed a method for growing the Japanese encephalitis virus (Jev) in cell lines and its inactivation (Kalia *et al.*, 2013). This simple and inexpensive method of growing Jev was

transferred to M/s Panacea Biotech for the development of India's first indigenous vaccine against Japanese encephalitis called JENVAC (Singh *et al.*, 2015). This vaccine is to be manufactured in the public-private partnership between the Indian Council of Medical Research (ICMR) and M/s Bharat Biotech (<http://pib.nic.in/newsite/erelease.aspx?relid=99873>). The vaccine provides increased immunity and long-term protection due to its unique manufacturing technologies. A recombinant vaccine made from the major 'envelope proteins' of dengue viruses, which protects against four closely related dengue viruses (DENVs) has also been developed.

Scientists have developed a genetically engineered vaccine against anthrax, a disease caused by *Bacillus anthracis* which has the potential to be used as an agent of bioterrorism (Goel, 2015; Dhasmana *et al.*, 2014; Singh *et al.*, 1999; Singh *et al.*, 1998; Kaur *et al.*, 2013). The technology of recombinant anthrax vaccine was transferred to M/s Panacea Biotech Ltd. (<https://www.panacea-biotech.com/>).

A collaboration between Indian scientists have developed a DNA vaccine which is targeted to be used both for veterinary and human use (Kumar *et al.*, 2013). This is a combination rabies vaccine (CRV) in which both a DNA vaccine and a conventional cell culture grown attenuated rabies vaccine have been combined (Garg *et al.*, 2014; Bharati *et al.*, 2013). Once the efficacy and the safety of the vaccine has been proved in the veterinary use its further development for use in humans are on the agenda (Biswas *et al.*, 2001; Kumar *et al.*, 2006; Kumar *et al.*, 2013). Several studies have also been carried out

for the development of vaccine for *Mycobacterium tuberculosis*, including identification of possible drug targets (Jain *et al.*, 2008; Dey *et al.*, 2010; Khare *et al.*, 2011; Dey *et al.*, 2011; Jatana *et al.*, 2011).

A DNA vaccine encoding the Indian subtype C sequences and using an attenuated vaccinia virus as a vector has been developed by the scientists. The prototype MVA (vector)-based potential AIDS vaccine (TBC-M4), is currently undergoing trials. A detailed investigation into HIV have been provided by the scientists working in India (Khan *et al.*, 2007; Seth, 2010).

A subunit vaccine formulation based on recombinant envelope proteins of Chikungunya virus has also been developed (Khan *et al.*, 2012). Several *P. falciparum* transmission blocking vaccines are now under trial stage (Chaturvedi *et al.*, 2016). Prophylactic efficacy of the chimeric epitope vaccine with a filarial epitope protein (FEP) has been successfully tested in a murine model (Anugraha *et al.*, 2015). This FEP has generated multiple types of protective immune responses with effective obliteration of the parasite.

### Outbreak Investigations

India has developed several initiatives for investigating and containment of outbreaks caused by infectious agents. Integrated Disease Surveillance Programme (IDSP) was initiated in 2004 to strengthen the disease surveillance system and to investigate and respond to disease outbreaks promptly. Through a network system ([www.idsp.nic.in](http://www.idsp.nic.in)), IDSP receives disease outbreak reports from all the States/UTs on a weekly basis.

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