Chapter 9
Veterinary Type Cultures and Their Preservation: Status and Challenges

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Abstract Microbial repositories are seminal to the development of biotechnology and its myriad applications in animal and agriculture bio-economy. These are the specialized storehouses of authenticated microbial cultures and accessory products needed for research and development in the animal agriculture. The public fund managed microbial culture collections like National Centre for Veterinary Type Cultures (NCVTC) and National Bureau of Agriculturally Important Microorganisms (NBAIM), initiated by the Indian Council of Agricultural Research (ICAR), are the future of the emerging agriculture bio-economy as they cement their positions as premier sources of authenticated microbial resources from ex situ preserved biodiversity of microbial strains of veterinary, dairy, rumen, and agriculture origins. Apart from this, they can fuel the development of taxonomy and exploration of animal microbial biodiversity and act as source of new knowledge, data, and skill in the field of microbiology. Their role as managers and disseminators of IPR issues is related to safekeeping of various categories of strain deposits. Although the demands and expectations from repositories are increasing, the challenges faced in the day-to-day functioning and maintenance of culture collection are also enormous.

9.1 Microbe Resource Centers: Bedrock of Modern Bio-economy

Culture collections (CC) or microbial resource centers (MRC) are needed for preservation and provision of biological resources for scientific, industrial, agricultural, environmental, and veterinary-medical research and development (R&D) applications. The essential functions of such centers consist of doing research on these biological resources with an aim for ex situ conservation of biodiversity and authentication and characterization of strains in order to make them available for

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S. K. Sharma, A. Varma (eds.), *Microbial Resource Conservation*, Soil Biology 54,
https://doi.org/10.1007/978-3-319-96971-8_9

future application in biotechnology and enhancing food security (Sly 2010). These centers act as repositories of critical microbial reference materials in laboratory research, testing, and diagnosis (Stackebrandt 2010). The creation of new knowledge of genetic engineering and molecular biology in the last century is giving way to modern omic sciences including genomics, proteomics, and transcriptomics, the tools which hold promise to unlock the useful information inherent in versatile microbial genetic resources (MGR). In order to capture and utilize such benefits of developing bio-economy, culture collections provide the well-described living resources (OECD 2001). They also function as repositories of microbial resources for protection of intellectual property. These will act as resources for public information and policy formulation also. The governments world over are actively establishing, nurturing, and sustaining MRCs because by making available microbes, their products and information of guaranteed identity and quality, a MRC will serve an essential infrastructural function for scientific investigation and R&D (Sasson and Malpica 2017).

It is conventional wisdom that a scientific research experiment requires reproducibility with statistical robustness. Scientific experiments, products, and vaccines must be able to replicate the responses and results from one geographical setting to another (McCluskey et al. 2017). Similarly, it is important that the microbial resources are also purified, properly authenticated, and genetically stable as is required of the purity of chemical reagents and the precision of equipments used to conduct scientific research (Prakash et al. 2013). The availability of known, validated, and precisely identified microbial resources is essential for biomedical and biotechnological research (Overmann 2015). Molecular-based assays like PCR, qPCR which are used to target specific genes of virulence factor or taxonomic indicator gene (*rpo*B) from a given microbial analyte, need to be demonstrating a diagnostic validity, for the target pathogen, for which positive and negative control strains are required (USFDA 2015).

Antimicrobial sensitivity testing is a routine procedure in clinical laboratories. The emergence of antimicrobial-resistant organisms and multidrug-resistant strains (MDR) makes it important for a more judicious use of antimicrobials, as newer drugs are rare to come by (May 2014). Therefore, antimicrobial drug testing is an important part of treatment for proper guidance to clinician in selection of an antimicrobial agent; however, a quality-controlled drug testing requires reference strains for different group of infections and antibiotics (CLSI 2008). Microbial strains collected in different space and time are useful resources for evaluation of temporal and spatial trend studies of their drug susceptibility profile, as evaluated by measurement of minimal inhibitory concentrations (MIC) against given antimicrobials (Jorgensen and Ferraro 2009). Moreover, as the discovery of novel antibiotics by Waksman platform method, which requires screening and evaluation of a large number of potential strains, is tapering off (Lewis 2012), the genomic tools are offering innovative ways to produce novel antibiotics by synthetic biology techniques. For instance, the sequence of *Streptomyces coelicolor* revealed many clusters of genes which if manipulated can lead to production of novel antimicrobial products (Bentley et al. 2002; Braff et al. 2016).

9.2 Wider Veterinary Research and Withered Microbial Germplasm

The history of establishment of research infrastructure in the field of veterinary sciences in India starts in 1893 with the establishment of Imperial Veterinary Research Institute (IVRI) by British colonial rulers at Himalayan hilly location of Mukteshwar and Gangetic plains of Izzatnagar near Bareilly, in United Provinces, the present Uttar Pradesh (UP) (Sinha 2010). In order to prepare vaccine and hyperimmune sera for use in prophylaxis of cattle plague or rinderpest (RP), the additional facility was created in 1901 in the plain region of Izzatnagar, Bareilly. The preparation of sera for bacterial diseases like anthrax and hemorrhagic septicemia (HS), vaccine for black quarter (BQ), and mallein reagent was started in the first decade of the twentieth century. The research ambit of IVRI has, since its inception, gradually increased from doing investigation and treatment of domestic animals to research and technological development on all animal endemic diseases of India. However, a systematic repository of the microbial strains, which might have been isolated in late eighteenth century and in early nineteenth century up to 1947, when Imperial Veterinary Research Institute was rechristened Indian Veterinary Research Institute, was either not created or was probably lost. Old Indian origin cultures, NCTC 3708 (mule isolate, 1932, India) and NCTC 3709 (horse isolate, 1932, India), of *Burkholderia mallei*, a highly pathogenic zoonotic bacteria causing glanders in equines, a disease still endemic in India, are part of National Centre for Type Cultures (NCTC), UK, but such or other strains are sadly not available in India. These and other cultures of Indian origin are being utilized for studying their biology (Gee et al. 2003). Similarly, another *B. mallei* strain (Genome Online database ID Go0000225; NCBI taxonomy ID 320388), which is identified as a strain (SAVP1) "that had previously caused disease in a mule (in India)," lacks in information on isolation metadata (Schutzer et al. 2008).

Although, Civil Veterinary Departments were created in the provinces in 1889, veterinary colleges were started at Babugarh (1877), Lahore (1882), Bombay (1890), and Madras and Calcutta (1893), and investigation of the diseases of the animals in India began in 1889–1890 with appointment of Dr. Alfred Lingard as imperial bacteriologist at the College of Science at Poona; however, any initiation to curation of cultures of veterinary-medical significance isolated during that period, or subsequently, has been lost in time. Meanwhile, National Collection of Type Cultures, UK, was established in 1920 (Russell 2014) and the American Type Culture Collection (ATCC) took its root in 1925 (Buchanan 1966), which are presently functional and cover a wide variety of reference microbes for use by industry. Similar facilities, however, were lacking in India, especially in the agricultural and livestock sectors, until recently. The Convention on Biological Diversity (CBD), which came into force from December, 1993, prompted signatory national governments to establish and maintain facilities for the ex situ conservation of different facets of biological diversity in the country of origin, considering that microbes are integral part of biodiversity.

9.3 Culture Collection for Value Addition

Enormous sums have continuously been spent in veterinary science institutions of teaching and research in our country toward isolation of microbes and their genes from nature. The elucidation of the genetic and functional molecular elements of microbes is capital intensive (OECD 2011). It is not only essential for these veterinary microbial resources to be preserved but also to be used further, so that research findings can be strengthened and corroborated. Without such a microbial repository, every user would have to reinvent the wheel and invest innumerable hours and money in the recovery of organisms and genes and their characterization, again and again. International studies which elucidate the impact of MRCs have categorically shown that microbial repositories and other biological resource centers (BRCs) significantly increase the value of research if the research materials are deposited and thus shared (Furman and Stern 2011).

The MRCs are safe heavens where researchers can deposit their well-characterized strains so that these are available for further research. It will also foster a culture of utilization of deposited strains for research work. The impact of publications increases if well-curated cultures are utilized in studies (Furman and Stern 2011). Moreover, as the cultures are isolated, identified, characterized, and preserved ex situ, they gain in value as compared to the in situ clone, which is considered to be of negligible monetary value (WFCC 1997). Although it is not always possible to ascertain the true value of a given microbial isolate, many factors, such as time and expertise needed to grow and catalogue a strain, its fastidiousness on culture media, and its level of characterization and preservation, all add value to a cultured strain. Consequently, it has been calculated that a microbial strain, which has been isolated and deposited in a European CC, attains a value of approximately 1000 €, which is roughly equal to 752,528 ₹, whereas same strain will be of 5042 €, approximately equal to 379,424 ₹ (2017 prices) in India (Overmann 2015). It thus implies that by ex situ isolation, characterization, and preservation of veterinary microbial resources, we can look forward to development of animal agriculture bio-economy through various value additions, in contrast to uncharacterized wild isolates remaining in situ.

The value added to a characterized isolate also indirectly indicates the quantum of economic loss incurred by our nation when researchers either do not deposit or fail to deposit their isolated cultures in public repositories. Internationally also, the deposition of "microbial strains cited in publications" into microbial repositories for their smoother publication is poor (Stackebrandt 2010). In a cursory back of the page survey done on Indian Journal of Animal Sciences publications related to the microbes, it was observed that out of total number of 16 papers published in 12 issues (2016–2017), in which research related to various aspects of microbes was reported, only 2 articles utilized authenticated reference or accredited accessioned cultures, and none of the papers indicated deposition of the cultures in any of the public-funded microbial collections (unpublished data). This loss can be reversed if public-funded institutions, funding agencies, and journals can formulate their own coherent

policy regarding the mandatory deposition of microbial cultures isolated in a research in a MRC. In addition to serve as repository of such strains as deposited by principal investigators (PIs) of projects and authors, a veterinary MRC will have opportunities to carry out R&D on the microbial resources they house including research on identification, characterization, and preservation of biological resources. Their R&D activities can contribute to the advancement of the veterinary-medical life sciences. However, MRC need to balance their R&D function with their culture distribution service function, providing and preserving microbial resources for the wider scientific communities.

The Bureau of Animal Industry of the USA in the decades of 1920–1940 embarked upon an ambitious program to control brucellosis, a dreaded zoonotic disease, which is caused by pathogen *Brucella abortus* in cattle. Research was conducted with one of the specific aims to formulate an effective vaccine. Incidentally, the bureau veterinarian, Dr. John M. Buck, had maintained a group of *B. abortus* cultures for "well over a year" on his desk at room temperature. In a subsequent evaluation of "stored cultures" for immunogenicity and stability, the 19th culture evaluated was found to be significantly less pathogenic. It was also stable even after many animal transmission studies, thus eventually becoming an optimal vaccine strain (Graves 1943). This live, attenuated strain S19 had been in use all over the world including India since the early 1930s as an effective vaccine to prevent brucellosis in cattle (Nicoletti 1990).

The anecdote illustrates the importance of well-documented microbial strains as a tool of biology. Microbial strains or MGRs obtained from animals, such as bacteria, pathogenic or commensal strains, viruses including bacteriophages, fungi and their genes, plasmids, nuclear material, cDNAs, and the related information are the essential raw materials for the advancement of animal biotechnology, veterinary and human health, and research and development in the life sciences in general and veterinary-medical sciences and public health in particular. Clinical microbial strains of bacteria, viruses, and fungi isolated from disease outbreaks and preserved with relevant epidemiological metadata are useful tools for analysis and understanding of patterns of pathogen transmission and modes of dispersion and taxonomical studies (Holmes et al. 1978; Plainvert et al. 2014). The data attached to strains can give information about time and location of the host from which the pathogen was isolated.

Culture collections are the custodians of microbial diversity and play a key role in storage and supply of authentic reference material for research and development. The importance of collection of biological specimens has always held its forte. However, the recent past has witnessed a new increased awareness of the value of culture collections. This has been partly due to emergence of new genomic and proteomic level molecular technological breakthroughs and also due to the realization of the value of conservation of genetic resources and maintenance of biodiversity, especially after the comity of consenting nations signed CBD. The breakthrough in the science of sequencing and gene hunting has opened up a new and exciting field of discovery. It is thus imperative to understand and nurture MRCs

or CC which are going to be the support source houses for scientific development in the field of agriculture, health, and environment biotechnology.

9.4 Overview of the National Centre for Veterinary Type Cultures

The National Centre for Veterinary Type Cultures (NCVTC) was established as a microbial repository for the collection, characterization, and distribution of animal microbes at ICAR-NRCE, Hisar. The NCVTC was sanctioned in April 2004 and its actual functioning began in 2006. The National Agriculturally Important Microbial Culture Collection (NAIMCC), dedicated to the microbes in agriculture, was established at NBAIM, Maunath Bhanjan, in Uttar Pradesh by ICAR in agriculture sector and with a similar mandate applicable in microbes of plant origin.

The activities of NCVTC comprise of acquisition, authentication, preservation, documentation, and repository database management system of microbes of animal origin, so that resource generated can be utilized for application in control and prevention of animal disease, application in dairy science, and in understanding the rumen function. Apart from these functions, NCVTC also caters to requests of taxonomic identification of culture isolates of veterinary background. In order to rapidly develop the repository for representation of microbial strains from different animal species and environments, a plan of carrying forward the collection work was mooted by formation of a Network of State Agricultural Universities and ICAR throughout the country. As India is a large country, so initially the states of Haryana, Rajasthan, Uttar Pradesh, Himachal Pradesh, Assam, Jammu and Kashmir, Tamil Nadu, Gujarat, Uttarakhand, Karnataka, Arunachal Pradesh, and Nagaland were included in Network.

A culture collection must meet the high standards of quality and expertise expected from a researcher for the delivery of biological information and materials. A veterinary type culture setup has to provide access to microbial resources on which R&D in the veterinary-medical sciences, animal sciences, and the advancement of animal biotechnology depends. Precisely in this direction, the DARE, Indian Council of Agricultural Research, New Delhi, had sanctioned this new activity of veterinary type culture, during the tenth plan period with the following mandate and objectives.

9.4.1 Mandate

- National repository of veterinary, dairy, and rumen microorganisms and their identification, characterization, and documentation.

- Distribution of microbes for teaching, research, and development of new technologies.

9.4.2 Objectives

(a) Veterinary Microbes

- Exploration and collection of microbes of veterinary origin/significance/relevance
- To identify and characterize the isolated/collected microbial pathogens (viruses, bacteria, fungi, mollicutes, protozoa, etc.) isolated from different disease conditions and carrier animals by conventional and molecular techniques
- Collection and central storage of animal microbes from existing culture collection centers, institutions, and universities
- To clone and sequence important genes to generate epidemiological information and to understand disease pathogenesis
- To create a genome/gene bank of different microbes by storing genomic DNA/RNA, recombinant plasmid clones, transfected cell lines, transformed bacteria, etc. for conservation of microbial biodiversity

(b) Rumen Microbes

- To isolate cellulolytic rumen bacteria from Indian cattle, sheep, goats, and buffaloes
- To isolate rumen fungi from domesticated and wild animals
- To determine the best fibre digesting organism

(c) Dairy Microbes

- To isolate indigenous strains of lactic acid bacteria including the ones with probiotic attributes from ethnic fermented milk and other foods prepared in various parts of India
- To identify and characterize the isolated strains using conventional and molecular techniques
- To analyze the plasmid pool encoding commercially important traits of selected cultures and their characterization at molecular level
- To identify the commercial potential of these diversified strains for designing novel starter cultures with functional/probiotic properties
- To conserve these strains and their germplasm ex situ and create a well-catalogued collection

To date, 726 culture collections from 75 countries have been registered in World Federation of Culture Collection (WFCC 2017). However, out of these, only a small percentage caters to animal and human pathogenic microbe culture collection.

Although the number of veterinary and animal microbe-related CC is unknown, a cursory survey of WFCC data indicates that more than 20 repositories are listed in World Data Center for Microbes (WDCM) (Table 9.1). There are many specialized bacteria culture collections also, and at least ten of these are dedicated to collection and research on strains of *Leptospira*, *Brucella*, *Salmonella*, *Yersinia*, and even antimicrobial-resistant bacteria (Table 9.2).

Table 9.1 International culture collections dedicated to veterinary microbes, dairy and related strains

Culture collection/ (status)	Acronym	WDCM number	Category of cultures	Date of institution	Number of cultures
Centro de Investigaciones en Ciencias Veterinarias, Buenos Aires, Argentina	CICV	WDCM33	Animal bacteria, protozoa, hybridoma, viruses, plant viruses	1981	200–500
Center for Veterinary Culture Collection, Beijing, China	CVCC	WDCM129 WDCM876	Veterinary bacteria, cell lines and viruses	1985	1300
Pusat Veterinaria Farma, Surabaya, Indonesia	PVF	WDCM628	Veterinary and industrial cultures	1989	NA
Korean Veterinary Culture Collection, Gyeongsangbuk-do, South Korea	KVCC	WDCM954	Veterinary bacteria, viruses	2009	>6000
Veterinary Branch of National Strain Collection, Pulawy, Poland	DMVB	WDCM194	Bacteria	1981	450
Thai Collection of Medical Microorganism, Chulalongkorn University, Bangkok, Thailand	TCMM	WDCM661	Bacteria	1981	NA
Animal Health Division Culture Collection, Perth, Australia	AHLDA	WDCM334	Bacteria	1981	1350
Rumen Yeast Collection of Animal Science Institute, Mayabeque, Cuba	RYCASI	WDCM980	Yeast	2011	NA
Collection of Animal Pathogenic Microorganisms, Brno, Czech	CAPM	WDCM181	Veterinary bacteria/Viruses	1962	900
Collection of Animal Viruses, Baranya, Hungary	RCAT	WDCM425	Veterinary Viruses	1981	~50
Regional Collection of Animal Viruses and Tissue Cultures, Szeged, Hungary	IMMH	WDCM427	Animal Viruses	1981	36
National Institute of Animal Health, Ibaraki, Japan	NIAH	WDCM638	Veterinary microbes	1990	100

(continued)

Table 9.1 (continued)

Culture collection/ (status)	Acronym	WDCM number	Category of cultures	Date of institution	Number of cultures
Culture Collection of Animal Cells, Foot and Mouth Disease Institute, Ankara, Turkey	HUKUK	WDCM756	Animal cells and hybridoma	2008	100
Rumen Microorganisms, Grassland Research Centre, New Zealand	RM	WDCM764	Rumen microbes	1995	150
Culture Collection of Dairy Microorganisms Laktoflora, Tabor, Czech	CCDM	WDCM878	Dairy bacteria, yeasts and fungi	2005	1000
New Zealand Reference Culture Collection of Microorganisms, Dairy Section	NZRD	WDCM318	Bacteria, virus	1968	3000
Centro de Referencia para Lactobacilos, Argentina	CERELA	WDCM614	*Lactobacillus, Propionibacteria and Bifidobacteria*	1981	900
Greek Aquaculture Bacteria, Veterinary Medicine, University of Thessaloniki, Greece	GAB	–	Aquaculture	2006	100

Table 9.2 International culture collections dedicated to specific pathogenic microorganisms

Culture collection/(Status)	Acronym	WDCM number	Cultures	Date of institution	Number of cultures
Brucella ANSES Culture Collection, Maisons-Alfort, France	BACC	WDCM789	*Brucella*	1998	>3000
WHO/FAO/OIE Collaborating Centre for Reference and Research on Leptospirosis, Queensland, Australia	CPHS	WDCM14	*Leptospira*	1981	213
Leptospirotheque, Paris, France	LIPP	WDCM345	*Leptospira*	1981	1020
Collection of Leptospira Strains, Instituto Superiore di Sanita, Rome, Italy	RV	WDCM421	*Leptospira*	1981	600

(continued)

Table 9.2 (continued)

Culture collection/(Status)	Acronym	WDCM number	Cultures	Date of institution	Number of cultures
W.H.O./F.A.O. Collaborating Centre for Reference and Research on Leptospirosis, Royal Tropical Institute, Amsterdam, Netherlands	ITH	WDCM196	*Leptospira*	1981	250
Salmonella Genetic Stock Centre, Department of Biology Sciences, University of Calgary, Canada	SGSC	WDCM338	*Salmonella*	1981	10,000
International Salmonella Centre (W.H.O.), Paris, France	ISC	WDCM63	*Salmonella*	–	–
Collection of Salmonella Microorganisms, Medical University of Gdańsk, Poland	KOS	WDCM784	*Salmonella*	1998	2000
Centre des Yersinia, CCOMS Reference and Research Center for Yersinia, Pasteur Institute, France	CY	WDCM7	*Yersinia*	–	–
Collection de Champignons et Actinomycetes Pathogenes, Pasteur Institute France	PCC	WDCM481	Actinomycetes	–	–
Culture Collection of Antimicrobial Resistant Microorganisms, Seoul, S. Korea	CCARM	WDCM847	Antibiotic Resistant Microbes	1999	20,226
Colecao de Trypanosoma de Mamiferos Silvestres, Domesticos e Vetores, Avenida, Rio de Janeiro, Brazil	ColTryp	WDCM 949	*Trypanosoma* of Wild and Domestic Mammals and Vectors	2009	700–800

9.5 NCVTC and Its Role in Research and Development

9.5.1 Conservation of Biodiversity

Ex situ microbial culture collections help preserve biodiversity, which is threatened by unsustainable economic development, natural disasters, and global change. The benefits of the conservation of biological resources are emphasized by the CBD, which highlights the need for creation of ex situ conservatories of biodiversity for its

uses and conservation. Repository should strive to be a source of certified, stable, and validated microbial materials.

Several collections, called International Depository Authorities (IDAs) in the Budapest Treaty (Budapest Treaty on the International Recognition of the Deposit of Micro-organisms for the Purposes of Patent Procedures), serve as repositories of biological resources for the purpose of implementing intellectual property rights (IPRs). A veterinary MRC should strive to attain the competency to act as IDA in relevant field; however, MRC functions are a set of many complex activities. Apart from the basic work of populating a collection through isolation of clinical outbreak strains, cultures of various taxa received from depositors need subsequent purification, identification, characterization, and long-term preservation. In addition to characterization of bacteria, viruses, fungi, protozoa, and cell lines of animal relevance/significance, development and evaluation of assays and techniques for validating research resources and preserving and distributing microbial biological materials to the public and private sector research communities need to be done in a quality-conscious and timely manner. In order to rise to the level of expertise inherent in the definition of a biological resource center (BRC) (OECD 2009), emphasis of NCVTC is needed on value addition of microbial cultures by advanced molecular characterization, economic operations, and competitive benchmarking for all areas of the MRC. In order to develop expertise on collection, preservation, and distribution in a quality-conscious standardized manner, it is imperative to establish the repository with standard set of protocols (like collection of microbes, collection of information on microbes from depositors, storage conditions of cultures of different type, inventory management of liquid nitrogen with backup, location and retrieval system of samples/cultures, power backup system, media and chemical quality control, security of collection, access to collection. etc.) and documentation of various nature (such as various data/deposit forms, declaration, identity proofs). Apart from serving as a bio-repository and distributor, NCVTC envisages to provide specialized services related to its overall mission as a MRC, for example, HRD in the area of biological repository management services. However, the plans of NCVTC to develop into a worthy leader in R&D expertise for identifying, characterizing, preserving, and distributing a wide range of microbes have its own set of challenges.

9.6 Animals and Microbial Life: What to Preserve?

For most people, microbes are out of sight and thus out of mind. However, the biodiversity of plants and animals is largely known to us. In this genetic biodiversity lie mines of precious genetic information (Fraser and Dujon 2000). Among the variety of environmental niches, the animals are also one of the important locations of microbial life. Animals harbor various forms of microorganisms in and on their body in different role of associations, which can be described as commensals, opportunists, mutualistic, beneficial, or pathogenic. The close association between humans and animals also leads to transmission of pathogenic bacteria directly or

indirectly through animal products as zoonoses. Taylor et al. (2001) catalogued 1415 known human pathogens, out of which 62% were of zoonotic origin. Intermingling of commensals with pathogens has also led to emergence of pathogens as a result of horizontal gene transfer (Ochman and Moran 2001).

The term microorganisms comprise all prokaryotes (archaea and bacteria), some eukaryotic organisms (fungi, yeasts, algae, protozoa), noncellular entities (e.g., viruses), their replicable parts, and other derived materials, e.g., genomes, plasmids, cDNA, etc. In the veterinary-medical health and production systems, the diversity of microbial life forms, which have an economic impact on health and production of animal and public health, is enormous and wide ranging. The horizon of microflora ranges from a variety of bacteria with different growth and environment requirements. This ranges from aerobic facultative organisms to microaerophilic and strict anaerobes on one side and fastidious pathogens like *Mycobacterium* spp., *Leptospira* spp., *Chlamydiales*, Rickettsiae (*Rickettsia rickettsii*), *Anaplasmataceae*, and *Coxiella burnetii* on the other. The *Mycoplasma* of class Mollicutes are the smallest prokaryotes capable of replicating on their own. This taxonomic group with five out of eight genera found in animals and humans are important agents to warrant research on their disease aspects and as persistent contaminants of cell lines (Corral-Vázquez et al. 2017). *Mycoplasma* cause significant disease in domestic and companion animals with about 35 species recorded taxonomically to be involved in infections of poultry, pigs, cattle, goats, sheep, horses, dogs, cats, and laboratory animals. Each one of the myriad microbial forms, including categories of bacteria, fungi, and viruses, requires separate laboratory setup, biosafety environments, growth and preservation necessities, human expertise, and handling requirements.

India is the seventh largest country in the world, with a variety of geo-climatic zones and landforms. The two broad climatic regions, viz., temperate or continental zone in the north and tropical zone in the south, are further divided into 11 regions depending upon the amount of rainfall and temperature. The variety of climatic and physiographical features leads to a complex ecology of diseases in Indian subcontinent. National Institute of Veterinary Epidemiology and Disease Informatics (2014–2015) report indicates that common bacterial diseases prevalent in India are hemorrhagic septicemia (HS), black quarter (BQ), enterotoxemia (ET), brucellosis, anthrax, leptospirosis, and salmonellosis, and among viral disease, peste de petits ruminants (PPR), foot and mouth disease (FMD), classical swine fever (CSF), goat pox, sheep pox, orf, blue tongue, swine pox, and rabies are prevalent in domestic animal population (AICRP-ADMAS Annual Report 2014–2015) (Table 9.3). Among these, most of the diseases are vaccine preventable, and for devising robust prevention and control measures, an inventory of spatially and temporally indexed isolates for long-term preservation with serum samples in all categories of domestic animals would be an effective tool in future control of disease. It would lead to a better understanding of disease ecology and agent biology for effective control and diagnostic reagent development.

Table 9.3 Summary of animal diseases prevalent in some Indian States

State	Bacterial disease	Animals	Viral disease	Animals
Andaman and Nicobar Islands	Leptospirosis	–	Goat pox (GP), Classical Swine Fever (CSF)	Goat, pigs
Andhra Pradesh	Anthrax, Haemorrhagic septicaemia (HS), Enterotoxaemia (ET), Black Quarter (BQ)	Cattle, sheep, goat, buffalo	Ranikhet disease (RD), Pesti des petits Ruminants (PPR), Sheep-pox, Goat-pox	Poultry, sheep, goat
Telangana	HS, BQ, ET, Anthrax, Brucellosis	Goat, sheep, cattle, buffalo	PPR, CSF, goat-pox, sheep-pox	Sheep, goat, pig
Assam	BQ, HS, ET, Swine Erysipelas	Cattle, goat, pig	CSF, RD, PPR	Pig, poultry, goat
Gujarat	HS	–	Sheep-pox, rabies, PPR	Sheep
Jammu and Kashmir	Foot Rot, BQ	Sheep	FMD, sheep and Goat pox, PPR, RD, contagious ecthyma	Cattle, sheep, goat, poultry
Jharkhand	HS, Anthrax	Cattle	FMD, PPR, CSF, avian influenza (AI)	Cattle, sheep, pig, poultry
Karnataka	BQ, HS, ET, Anthrax	Cattle, buffalo, sheep, goat	Sheep and goat-pox, PPR, BT, FMD	Sheep, goat
Kerala	HS, Anthrax, ET, CCPP	Cattle, sheep, goat	CSF, PPR, swine-pox, rabies (in cattle), Orf, Kyasanur forest disease (KFD), AI (In ducks and turkeys)	Pig, sheep, cattle, monkey,
Punjab	HS, BQ, Anthrax	Cattle	FMD, PPR, rabies	Cattle
Maharashtra	HS, Fowl typhoid,	Cattle, poultry	PPR	Small ruminant
Manipur	BQ, HS, Brucellosis, CRD, Salmonellosis, Colibacillosis	Cattle, sheep	Blue tongue (BT), CSF, goat pox, rabies, RD, IBD, fowl-pox	Sheep, goat, dogs
West Bengal	Anthrax, BQ, HS	–	CSF, PPR, FMD, sheep and goat-pox	Pig, sheep, goat
Rajasthan	HS, ET	–	Rabies, PPR	–

Adapted from Annual Report, AICRP on ADMAS 2014–2015

9.7 Costly Endemic Diseases Need Strategic Collection

An important aspect of our understanding of host-microbe interaction is the ability to detect, identify, and isolate microorganisms and to recognize diseases caused by them. Our abilities and achievements in this aspect have so far been limited. This has been due to use of conventional methods of pathogen research like dependence on microbial propagation methods, nonspecific clinical and epidemiological indicators, insensitive imprecise and sometimes cross-reacting serological tests, and an almost nil understanding of the microbial "background" in the external and internal host environment. In order to control diseases in animals and humans, molecular understanding of pathogens and pathogenesis is imperative. Colibacillosis, for example, caused by various strains of *Escherichia coli* takes a heavy toll of domestic animal neonates. These bacteria also spread through water and food to community causing diarrhea (Vaid et al. 2003). Further, there are many strains of *E. coli*; among them are those not causing any disease and those causing high mortality in humans due to verocytotoxins. These are emerging pathogens like *E. coli* O157:H7 strains (Besser et al. 1999). The neonatal diarrhea causing enterotoxigenic strains of *E. coli* (ETEC) are an economic drain on animal industry as they lead to undermining of fresh animal crop by high mortality (Bandyopadhyay et al. 2011). It will, however, be a boost to the research on ETEC, if scientists working in this field can deposit the ETEC strains, which can serve as positive control strains for future research. Availability of such strains (e.g., K88 variants, K99 and 987P fimbrial antigen-positive strains) has been difficult, as, in author's experience, many efforts to locate standard control strains for ETEC research from public health institutions like AIHPH, Kolkata; NICED, Kolkata, and Central Research Institute, Kasauli, have in the past been unsuccessful, probably due to differences in institutional mandates. The NCVTC and other MRCs have the sacred duty as well as obligation to make a concerted effort with all stakeholders, funding agencies, and publishers of research findings to start a dialogue within a timeline to make sure that important microbial strains, which are a component of funded/published research, are available to all contemporary and future generations by their deposition, in order to optimize and economize on government-funded research output.

Pasteurella multocida is a heterogeneous species that produces septicemic or respiratory diseases in domesticated and wild large and small ruminants (Rimler and Rhoades 1989). Considerable variation has been observed among strains with respect to host predilection, pathogenicity, carbohydrate fermentation, colonial morphology, and antigenic specificity (Carter and Chengappa 1981). It is also an important economic disease of buffalo, goat, sheep, rabbits, and pigs and has zoonotic links also (Donnio et al. 1991; Vaid et al. 2012). The taxonomy of *Pasteurell*a has undergone many changes since its first isolation from domestic animals and it continues to change as new characterization procedures are used (Jaworski et al. 1998). A systematic collection, preservation, and characterization of pathogens of this group are imperative to understand the molecular virulence factors and pathogenicity mechanism in order to conceptualize novel vaccines. NCVTC has

been instrumental in obtaining *P. multocida* isolates from various geographical locations for preservation and distribution. In a recent outbreak investigation in buffaloes in N. India (Kumar et al. 2014), we have isolated a strain of *Mannheimia varigena* from pneumonic buffalo for the first time in India (NRCE Annual Report 2013–2014). This isolation is an indication for the need of fresh taxonomic investigation of *Pasteurellaceae* family members in domestic and wild ruminants of India as these constitute an important group of pathogens causing respiratory diseases in largest group of food animals.

Similarly, mastitis is one of the costliest diseases affecting the dairy industry. Mastitis as a disease may be caused by *Staphylococcus* spp., *Streptococcus* spp., *Mycoplasma* spp., *Corynebacterium* spp., and several Gram-negative bacteria (Nickesrson et al. 1995). The subclinical form of mastitis leads to maximum damage. *Staphylococcus aureus* is the most frequent infectious agent in subclinical manifestations representing an economic problem for the milk industry the world over (Baumgartner et al. 1984). During growth in milk, enterotoxigenic *S. aureus* strains are able to produce thermostable enterotoxins that, when ingested, cause nausea, vomiting, and diarrhea in humans (Jablonsky and Bohach 1997). In this way, *Staphylococcus* spp. become critical pathogens in causing mastitis, food-borne zoonoses, and clinical nosocomial infection in humans, especially by emerging antibiotic-resistant strains. Not much comparable investigations, however, have been initiated in *S. aureus* of mastitis origin. Workers have also isolated a new species of staphylococci, *Staphylococcus nepalensis* sp. nov. from goats of Himalayan region in Nepal (Spergser et al. 2003); however no such reports of isolation of any novel staphylococci or other veterinary pathogenic strains have been reported in India. As the microbial repositories are the central point for thorough characterization of strains, exploration of biodiversity by isolation, identification, and description of novel strains is facilitated in such scientific institutions. It is thus imperative that capacity for polyphasic characterization is accommodated in NCVTC.

The science of microbial systematic and approaches to the classification and identification of veterinary microorganisms is also, as in other prokaryotes, based on complete phenotypic and genotypic characterization of microbes which is based on collection and comparison of microbe's biochemical and molecular attributes with type strains (polyphasic characterization) (Rosselló-Móra and Amann 2015). Polyphasic characterization, apart from phenotypic and chemotaxonomic data, also includes results obtained from 16S rRNA gene sequence pair similarity and phylogenetic analysis, DNA-DNA hybridization, and DNA G + C content. Due to recent advancements in next-generation sequencing (NGS) platforms and reduction in cost of sequencing, now whole genome sequence (WGS) comparison is leading to rapid polyphasic characterization by replacing DNA-DNA hybridization techniques (Chun and Rainey 2014). Polyphasic characterization not only leads to identification of novel species but is also instrumental in further strain-level differentiation of established species. Workers in Spain were able to delineate a novel subspecies *Streptococcus phocae* subsp. *salmonis* on the basis of polyphasic characterization (Avendaño-Herrera et al. 2014). However, the discipline of taxonomy, which is

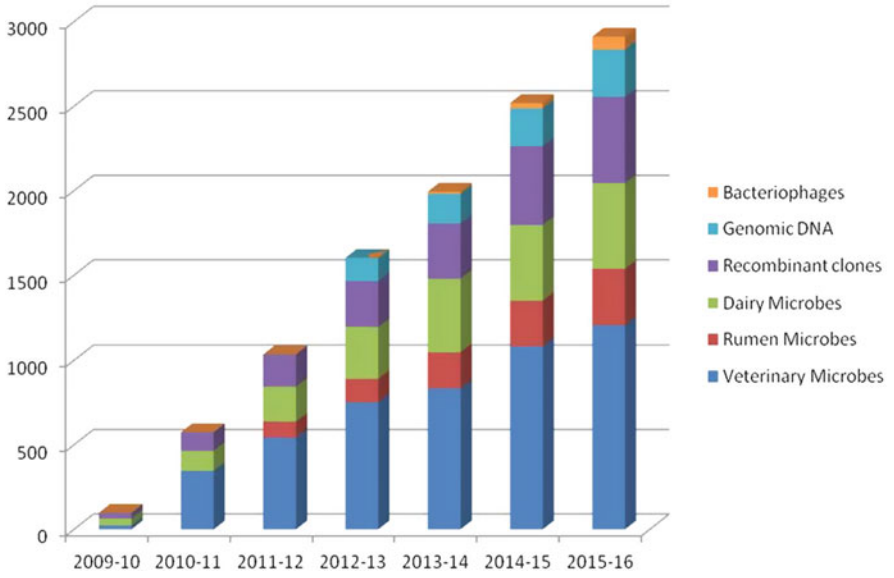

Fig. 9.1 The NCVTC repository has shown a steady progress in collection of different microbes

advancing at molecular level, also requires type strains as reference strains for comparison with under investigation novel strains for nomenclatural research and publications (Stackebrandt 2010; Tindall et al. 2010). However, such resources, especially the type strains of taxa relevant to veterinary-medical isolates, are hardly available in India, and efforts to get these strains get entangled in host of biodiversity regulations and administrative approvals (Overmann and Scholz 2017).

At present the NCVTC, with its limited scientific strength, initiated its CC activities in the field of aerobic, facultative anaerobic microbes and anaerobes, viruses, and bacteriophages. The biodiversity of taxa belonging to this category of microbes itself is huge. Within the ambit of this biodiversity, the available human resource capacity, capability, and aspirations are presently stretched. In spite of constraints, the NCVTC has, since its inception, reached a veterinary bacterial collection of more than 1000 strains representing greater than 50 genera. Apart from veterinary bacteria, numbers of various taxa of viruses, bacteriophages, dairy microbes, rumen bacteria and archaea, and recombinant clones preserved in NCVTC have shown a steady increase (Fig. 9.1). The facilities and funding requirements for enhancing and maturing the authentication and characterization skills need further appreciation. As the number of strains increases, the biodiversity, both at the species level and at higher taxa level, also increases. In order to aspire for a quality benchmark of BRC, a further investment in characterization technologies, automated preservation system, strain data management systems, and identification and nurturing of new talent in taxonomy of additional category of microbes, e.g., fungi, is urgently required. In addition, the NCVTC has also started distribution of bacterial

strains to researchers in government and private network. Consequently, availability of technical staff is a very critical aspect in maintenance of cultures, distribution to customers, routine subculturing from seed repository, lyophilization, file work, packaging of strains, postage, and maintenance of records.

The establishment of NCVTC may also lead to progress in exploration of biodiversity of microbial cultures of animal origin in India and discovery of novel strains. However, the genetic studies can only take place if, after isolation, we develop a long-term preservation environment which includes methods of cataloguing the isolates, their DNA isolation, and preliminary 16S rRNA-based identification and classification (Woese et al. 1985, 2000; Harmsen and Karch 2004). Methods for rapid amplification of specific known sequences or the amplification of broad-range group sequences giving genus level information have improved our understanding of real state of etiology, detection, and exploration of microbial diversity. Among these approaches are BioLog MicroLog automated system based on metabolic characterization, ribotyping of isolates by RiboPrinter, and targeting of microbial small molecules such as fatty acid profile (Sherlock microbial identification system) of bacterial cell wall (Srinivasan et al. 2001). The characterization of accessioned isolates however is challenging without recourse to modern technologies utilized in the polyphasic characterization of isolates. Technologies such as Sanger sequencing platform to sequence smaller genetic elements such as 16S rRNA, and various housekeeping genes for particular taxa identification viz., *rpo*B, *inv*A, and NGS for quick measurement of Average Nucleotide Identity (ANI) (Kim et al. 2014) are instrumental in measurements of genomic identity comparison between strains, which is indispensable in the prokaryotic taxonomy.

Comparison of genome sequence (comparative genomics) of closely related pathogens and or non-pathogens (commensals/opportunistic pathogens) e.g., *E. coli* from goat/sheep/cattle/buffalo and environmental isolates has the potential to provide a rapid and effective method for understanding pathogenesis (Strauss and Falkow 1997). The enormous database of prokaryotic genomes now getting sequenced will prove a cornerstone of genome-based microbiology. The analysis of the entire available microbial sequences is already opening innovative research ideas and insights. What will be the potential impact of this database on human society when the projected database of over 2000 small genomes of each species will be available to the comity of scientists by the end of 2020? Certainly, NCVTC will be able to provide the pivot point from where suitable, critical bacterial isolates can be recognized for WGS work. It will be useful, because the cultures will be backed up by its disease metadata information. NCVTC has already embarked upon ambitious attempt to WGS some important pathogenic isolates (Vaid et al. 2014, 2015) (Table 9.4). However, bioinformatic analysis of curated genome data needs expertise in high-end genome data hosting, application of window-based analytical software, software skills in installation, and running of Linux OS platforms and computational analysis. The NCVTC needs to be either collaborating with expert bioinformatic institutions or achieve its goals of bioinformatic analysis by getting a human resource placed.

Table 9.4 Details of NCVTC accessioned strains with WGS

ACC.	DID	ID	Source	Genome size
BAA1	Eq24E	*Bordetella bronchiseptica*	Nasal swab	5,264,383 bp
BAA267	Bu5	*Trueperella pyogenes*	Buffalo pus	2,407,500 bp
BAA264	Bu1	*Pasteurella multocida*	Buffalo intestine	2,073,865 bp
BAA445	Eq28B	*Actinobacillus equilli*	Nasal swab foal	2,295,342 bp
BAA614	Sal40	*Salmonella gallinarum*	Poultry fowl typhoid	4,809,037 bp

The metadata collected during the collection of samples from which pathogens are isolated constitutes all the information concerned about the circumstances of isolation of pathogen thus providing a real epidemiological backdrop of the pathogen (Field et al. 2005). Example of such information is information on host, environment including meteorological data and type of samples. However, the epidemiological context of genes and organisms will be threaded only by an information system, which can give quick access to metadata based on key search criteria. Furthermore, information management is also important in day-to-day operation and use of culture collection (Casaregola et al. 2016). The information systems like Microbial Information Network Europe (MINE), which has been integrated across the networks of European collections and has evolved into recently developed Microbial Resource Research Infrastructure (MIRRI), encompass key feature of common minimal microbial metadata sets including taxonomy, growth, and biochemical and hazard information, among others (Stalpers et al. 1990; Smith et al. 2016). These are highly advanced online integrated systems networking the European BRCs. The optimal utilization and expansion of activities in collections like NCVTC and NBAIM will require advanced interactive websites, searchable electronic catalogue system, and tools of information system for curation of strain data. An interactive user interface for structured data dissemination and communication systems between users and staff and in between staff is important for operational efficiency. For optimization of utilization of microbial resources available in regional collections, the communication system's interoperability between collections, controls on regulatory issues and restrictions on data, ability to conduct simple searches within and across databases and to mine databases, etc. are some of the essential requisites that need to be developed.

9.8 Conclusion

The vision of our nation developing in leaps and bounds in the realm of bio-economy is very ambitious. That there is no dearth of competent human resource and biodiversity is well documented. However, biodiversity aspect of microbial variety can only be better utilized, if it is conserved ex situ, where its value can be enhanced by characterization and value addition. The current repositories of veterinary culture collection resources, including ex situ culture collections of veterinary pathogens,

are inadequate to meet our needs for veterinary microbial resources because of the issues of standards, quality, and reliability. Microbial resource centers like NCVTC are the important institutions which act as source of biological material for reference and biological and biotechnological research, and they act as rallying point for development of taxonomy of microbes of animal origin. The effort of national government in responding to need for various biodiversity capturing institutions is timely and noteworthy, as historically, private participation in such endeavors is hardly feasible. Indian Council of Agricultural Research also embarked upon nurturing of various institutes, among which NCVTC caters to ex situ preservation of veterinary, dairy, and rumen microbes.

Isolation, preservation, and conservation of veterinary pathogens and use of molecular tools for their identification and their genomic and proteomic level characterization work can give impetus in the direction of combating newly emerging and reemerging veterinary pathogens, majority of which also cross-species barrier. This will also give impetus for strengthening taxonomic base and work in the fields of functional and comparative genomics. NCVTC is working toward becoming a veterinary MGR center to fulfill a long-felt resource gap in the fast developing knowledge-based society facing new challenges in the field of agriculture, health, and environment. Requirements such as new communication standards, technologies, Internet services, database and information management system, and web interfaces with efficient integration of veterinary microbial resources information in the bioinformatic network are needed. In the given limited resources, in which to carry out essential research and work to enhance the value and applications of strains and provide metadata information, the requirement and application of new technologies to aid in identifying and characterizing microbial diversity is a continuous challenge.

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