



UNDERSTANDING MICROBIAL NETWORKS OF FARM ANIMALS THROUGH GENOMICS, METAGENOMICS AND OTHER META-OMIC APPROACHES FOR LIVESTOCK WELLNESS AND SUSTAINABILITY – A REVIEW

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Abstract

The association of microorganisms with livestock as endosymbionts, opportunists, and pathogens has been a matter of debate for a long time. Several livestock-associated bacterial and other microbial species have been identified and characterized through traditional culture-dependent genomic approaches. However, it is imperative to understand the comprehensive microbial network of domestic animals for their wellness, disease management, and disease transmission control. Since it is strenuous to provide a niche replica to any microorganisms while culturing them, thus a substantial number of microbial communities remain obscure. Metagenomics has laid out a powerful lens for gaining insight into the hidden microbial diversity by allowing the direct sequencing of the DNA isolated from any livestock sample like the gastrointestinal tract, udder, or genital system. Through metatranscriptomics and metabolomics, understanding gene expression profiles of the microorganisms and their molecular phenotype has become unchallenging. With large data sets emerging out of the genomic, metagenomic, and other meta-omics methods, several computational tools have also been developed for curation, assembly, gene prediction, and taxonomic profiling of the microorganisms. This review provides a detailed account of the beneficial and pathogenic organisms that dwell within or on farm animals. Besides, it highlights the role of meta-omics and computational tools in a comprehensive analysis of livestock-associated microorganisms.

Key words: livestock, metagenomics, meta-omics, bioinformatics, livestock sustainability

The existence of more than 3 billion ruminants is essential for sustainable farming practices and food security; therefore, understanding their microbial networks is imperative for sustainable agricultural practices and food security. Animal microbiome studies are widely regarded as a new discipline with the advent of novel sequencing approaches. The animal microbiome is the aggregation of complete microbiota present in the animal tissues, biofluids (salivary, seminal fluids, and vaginal and uterine discharges), and other anatomical sites, such as mammary glands, oral cavity, and biliary tract (Amin et al., 2021; Matthews et al., 2018). Microorganisms may have a specific role and typically harbor at particular sites in the animal body to perform a certain function. For example, ruminants largely depend on the rumen microbiome to convert dietary fibers, mainly cellulose, into volatile

fatty acids and microbial proteins (Sha et al., 2020). The digestion in the reticulorumen occurs by the fermentation process with structural carbohydrates (cellulose and hemicellulose) and non-structural carbohydrates (pectin, sugar and starch) as the primary substrates (Murphy, 2011). Rumenal space harbors diverse microbiota, including bacteria (Bacteroidetes and Firmicutes), fungi (*Neocallimastix*, *Piromyces*, *Orpinomyces*, *Cyellamyces* and *Caecomyces*) and archaea (*Methanosphaera stadtmanae*, *Methanobrevibacter smithii*) (Petri et al., 2013). The rumen's reductive environment is established by the action of microorganisms like *Ruminococcus*, *Butyrivibrio* and *Prevotella* (Huang et al., 2018). The rumen-fungi (*Piromyces*, *Cyellamyces*, *Orpinomyces*), anaerobic microorganisms making 10% of the biomass, are imperative during fiber digestion (Hess et al., 2020). In many

organs/systems, eubiosis of microorganisms is crucial to maintain these systems' health status and function. The prevalence of stress in animals can increase the chances of infection, which can subsequently alter the eubiosis of the microbiome of the animals (Hulbert and Moisé, 2016). In such conditions, probiotics, beneficial microorganisms, have proved helpful by avoiding the excess secretion of cortisol that reduces the chances of infections and, therefore, improves performance (Uyeno et al., 2015). The applicability of probiotic *Lactobacillus reuteri* helps in immunomodulation, diarrhea prevention, and elevation in milk production (Markowiak and Ślizewska, 2018). One of the studies has reported the reduction of postweaning diarrhea in piglets using *Bacillus cereus* and *Enterococcus faecium* (Scharek et al., 2007). Microbial communities also produce specific metabolites like organic acids, bacteriocins, and lysozyme-1,2 and 3 that are anti-microbial in nature (Chikindas et al., 2018; Oyama et al., 2017; Reis et al., 2012). They are helpful in the prevention of meat contamination occurring with *Campylobacter* and *Salmonella* (Thames and Theradiyil Sukumaran, 2020). The reduction of *Listeria monocytogenes*, the causative agent of listeriosis, by using bacteriocins has also been reported (Quereda et al., 2017). Another critical example of the role of microbial eubiosis in maintaining good health status and functions is the reproductive tract. Several microorganisms normally colonize the reproductive tract. Some of them exist as commensals (co-exist without harming the host), mutualistic (beneficial for both), and pathogenic (disease-causing) (Wang et al., 2013). Uterine diseases like endometritis and metritis occur due to the interaction between the host and the pathogens like *Trueperella pyrogens* and/or *Fusobacterium necrophorum* (Rzewuska et al., 2019). A shred of strong evidence suggests that the infiltration of the microorganisms into the reproductive tract of female bovines occurs during mating or calving and interrupts the commensal microflora (Underwood et al., 2015). The continuous presence of pathogenic microorganisms can damage the pregnancy pattern of bovines that can also transmit to the fetus leading to birth abnormalities, abortion, or death (Khodakaram-Tafti and Ikede, 2005).

Even though the livestock-microorganism relationship is important, before disease control and sustainable use, conventional culture-dependent microbial methods have proven insufficient for in-depth analysis. Metagenomics, also known as ecogenomics, involves the study of the genetic material obtained directly from the samples in a culture-independent manner. Metagenomics offers the advantage of characterizing the previously unknown microorganisms dwelling in different environments, including the biological environment of domestic animals (Berini et al., 2017). The metatranscriptomics provides more insight into the role of microorganisms within their natural environments. It ensures easy analysis of microbial gene expression by creating gene expression profiles of the microbial communities (Aguilar-Pulido et

al., 2016). Thus, metagenomics is concerned about the genomic content and identification of complete microbiota of a particular niche, whereas metatranscriptomics focuses on the active genes present in such microbial communities. Accordingly, this review paper highlights the importance of metagenomics and related meta-omics approaches in understanding the microbial networks of farm animals and their possible role in tracking and treating the diseases for sustainable use.

Culture-dependent methods for the exploration of animal microbiomes

Culture-dependent microbiological strategy ensures the multiplication of microorganisms in predetermined laboratory conditions. This helps to determine the microbial density, type of microorganism, and degree of pathogenicity associated with different microbial members of the sample. Matsumoto et al. (2008) isolated coliform bacilli and *Campylobacter jejuni* from liver and bile of the slaughtered cattle in Japan following the culture-dependent strategy. *Streptococcus pyrogens*, causing strep throat, is isolated by a culture-based method by scraping the throat tissue lining of a cow followed by its blotting onto a suitable medium like nutrient agar, Muller-Hinton agar etc. (Schmidt et al., 1987). It is imperative to isolate an axenic population of microorganisms to understand the molecular dynamics of isolated microorganisms using agar or guar gum. For instance, *Mycobacterium* species (spp.) are known to cause disease in livestock animals, but their ubiquitous molecular nature makes them difficult to track using independent microbiological techniques. The use of culture-dependent and culture-independent procedures in synergy has helped characterize and understand several mycobacterium reservoirs. In one study, *Mycobacterium* (*M.*) spp. from cattle and pigs in Uganda has been classified into 37 *M. avium* subsp. hominissuis using both culture-dependent and culture-independent methods (Muwonge et al., 2014). The microbial culture collection repositories have been developed for authentication, preservation, cataloging, production, and distribution of viable microbial culture as reference microorganisms, which is vital in studying microbial systematics. Some culture collection repositories include American Type Culture Collection (ATCC) in Virginia, the Culture Collection University of Gothenburg in Sweden, Japan Collection of Microorganisms in Tsukuba Japan, and the National Collection of Type cultures (NCTC) in London (Uruburu, 2003). Even though culturomics helps identify species or strains from any sample obtained from environment or animal tissues, it leaves a significant number of microorganisms "untouched." The main drawback of culturomics remains the growth conditions of microbial species, which are challenging to provide in controlled laboratory conditions. Metagenomics was conceived as an alternative to the culturomics approach depending on the homologous sequences for identifying novel microbial species (Chang et al., 2019; Rinke et al., 2013).

Metagenomics (culture-independent) and microbial networks in farm animals

The development of sequencing techniques has ensured easy and high-resolution revelation of culturable and non-culturable microbial communities synchronously (Handelsman, 2004). In animal-microbe interaction, the obtained information through metagenomics has been an important advancement in decoding the interplay between microbes and hosts (Singh et al., 2008). Metagenomic studies through function-based and/or sequence-based approaches unveil the impact of complete metagenome in establishing pathogenicity of microbes, susceptibility of the host and infection outcomes (Bashir et al., 2014). The role of microorganisms and their secreted biomolecules in digestion, excretion, pregnancy, and fitness of livestock is a well-established fact (Hanning and Diaz-Sanchez, 2015; Hashem and Shehata, 2021). The secreted molecules can be easily characterized with the help of metatranscriptomics and metabolomics (Aguilar-Pulido et al., 2016). In the next section, the role of microorganisms isolated from different body parts of farm animals in the health and performance of farm animals by using culture or non-culturable techniques has been discussed.

Skin microbiota

As shown by the studies presented in Table 1, the presence of commensal microbiota on the skin of farm animals may play a role in innate immunity and safeguards animals from the attack of disease-causing microorganisms (Belkaid and Hand, 2014). The physiological properties of the skin, like lower temperature, moisture, pH, and high salt concentrations, fluctuate the microbial diversity, which is estimated to be more than 10^7 microorganisms/cm² on cow skin (Dean et al., 2021). A study that used both culturable and non-culturable techniques to evaluate the microbial diversity of the teat skin of cows, identified 29 and 27 microbial species using culture-dependent and culture-independent approaches,

respectively (Verdier-Metz et al., 2012). *Staphylococcus* and *Micrococcus* are dominant in cattle, pigs, sheep, and raccoons (Ross et al., 2019). Interestingly, almost all pigs and cows harbor *Staphylococcus* irrespective of the geographical location (Lakhundi and Zhang, 2018). Microbes such as *Staphylococcus* spp. and *Escherichia coli* which grow on the teat skin and udder can be responsible for causing mastitis in cattle (Kasa et al., 2020). Dermatophilosis, also known as rain rot or rain scald, is a dermatological bacterial disease caused by *Dermatophilus congolensis* affecting cattle (Underwood et al., 2015). Besides being treated with 1% potash alum, povidone-iodine or chlorhexidine, it can heal on its own by the action of native microorganisms (Hamid and Musa, 2009). Sorge et al. carried out the metagenomic evaluation of skin biopsies (udder sores) in dairy cows and suggested that sores are associated with the increased population of *Helococcus*, *Trueperella*, *Prevotella*, *Anaerococcus*, *Fusobacterium*, and *Porphyromonas* (Sorge et al., 2019). Using different metagenomics approaches, various microbes have been separated from the skin of other body parts from farm animals. These microbes that are part of the skin microbiome of farm animals have been reported to cause skin damage, mastitis, wounds and inflammation in the animals (Table 1). Apart from the pathogenic effects of the skin microbiome, they can also help in cheese making (Verdier-Metz et al., 2012). In culture-dependent microbiome analysis of cow teat skin, several bacteria belonging to *Aerococcus*, *Staphylococcus*, *Pediococcus*, *Pantoea*, *Enterobacter*, *Enterococcus* genus commonly found in raw milk were identified (Verdier-Metz et al., 2012). Some of the nonstarter lactic acid bacteria belonging to *Actinobacteria* and *Staphylococcus* present on the cow teat skin can be responsible for the generation of sensory properties of cheese while ripening (Verdier-Metz et al., 2012). Furthermore, *Enterococcus* species which are part of skin microbiota have been reported to have probiotic effect and protect animals from diarrhea (Hanchi et al., 2018).

Table 1. List of beneficial and pathogenic microorganisms isolated from skin of farm animals using culture and non-culturable techniques

Microorganisms	Animal	Niche	Action	Isolation technique	References
1	2	3	4	5	6
Beneficial microorganisms					
<i>Staphylococcus</i> spp., <i>Enterococcus</i> spp., <i>Pediococcus</i> spp.	Cow	Teat skin	Cheese making	Combination of both culture driven and transcriptomic approaches	(Verdier-Metz et al., 2012)
<i>Enterococcus</i> spp.	Cattle	Epidermis	Has probiotic to prevent or treat farm animals from diarrhea	Culture driven	(Hanchi et al., 2018)
Pathogenic microorganisms					
<i>Staphylococcus intermedius</i> and <i>S. aureus</i>	Cattle	Skin and teats	Damages epidermis	Culture driven	(Nagasawa et al., 2020)
<i>Staphylococcus aureus</i> and <i>Staphylococcus agalactiae</i>	Cattle	Teat skin	Intramammary infection	Culture driven	(Svennesen et al., 2019)
<i>Clostridium tetani</i>	Cattle	Toes	Bloating and muscular spasticity	Sequence driven metagenomics	(Brüggemann and Gottschalk, 2004)

Table 1 – contd.

1	2	3	4	5	6
<i>Staphylococcus</i> spp., <i>Stomococcus</i> spp., <i>Enterococcus</i> spp., <i>Corynebacterium</i> spp., <i>Micrococcus</i> spp.	Sheep	Skin	Damages to dermis and epidermis layers	Culture driven	(Mohamed et al., 2016)
<i>Staphylococcus aureus</i> and <i>Pseudomonas aeruginosa</i>	Cattle, sheep and goat	Skin	Wounds	Culture driven	(Saha et al., 2019)
<i>Streptococcus</i> spp., <i>Staphylococcus</i> spp., <i>E. coli</i> , <i>Proteus</i> spp.	Cow	Udder and teat skin	Mastitis	Culture driven	(Kasa et al., 2020)
<i>Staphylococcus</i> spp.	Dairy cows	Mammary glands	Mastitis (inflammation and abscess formation)	Sequence driven metagenomics	(Bianchi et al., 2019)
<i>E. coli</i>	Cow and buffaloes	Teat skin	Intramammary infections	Culture driven	(Fahim et al., 2019)
<i>Staphylococcus aureus</i>	Cows	Teat skin	Mastitis	Culture driven	(Costa et al., 2019)
<i>Dichelobacter nosodus</i>	Ovines	Interdigital skin	Footrot	16S rRNA driven	(Calvo-Bado et al., 2011)

Table 2. List of beneficial and pathogenic microorganisms isolated from digestive system of farm animals using culture and non-culturable techniques

Microorganisms	Animal	Niche	Action	Isolation technique	References
1	2	3	4	5	6
Beneficial microorganisms					
<i>Neocallimastix californiae</i>	Dairy cows	Rumen	Fatty acid oxidation	Sequence driven metagen- omics	(Neelakanta and Sultana, 2013; Peng et al., 2021)
<i>Methanobrevibacter</i> spp., <i>Prevotella</i> spp., <i>Bacteroi- detes</i>	Cattle	Rumen	Improve feed efficiency and ru- men fermentation	Sequence driven metagen- omics	(Li et al., 2019)
<i>Prevotella ruminicola</i>	Buffalo	Rumen	Identification of BT-01 protein which can be used as animal feed supplement	Function driven metagenomics	(Nguyen et al., 2012)
<i>Methanobrevibacter</i> spp., <i>Prevotella</i> spp., <i>Bacteroides</i> spp., <i>Ruminococcus</i> spp., <i>Eubacterium</i> spp., <i>Roseburia</i> spp.	Black Bengal goats	Rumen	Identification of enzymes that can be used in food and pharmaceutical industries	Sequence driven metagenomics	(Suryawanshi et al., 2019)
<i>Prevotella</i> spp.	Pigs	Gut, and oral cavity	Lipopolysaccharide production useful for mucus and cytokine synthesis	Culture driven	(Amat et al., 2020)
<i>Lactobacillus reuteri</i>	Cattle	Ruminal fluid	Suppresses <i>E. coli</i> to improve food safety	Function driven metagenomics	(Bertin et al., 2017)
<i>Selenomonas ruminantium</i>	Rumi- nants	Rumen	Fermentation of lactate and succinate	Sequence driven metagenomics	(Nathani et al., 2013)
<i>Lachnospira multipara</i>	Cow and camel	Intestine	Help in absorption	Culture-based	(Cornick and Stanton, 2015; Redington et al., 2016)
<i>Megasphaera elsdenii</i>	Sheep	Gut	Lactate degradation	Culture-based	(Chen et al., 2019)
<i>Butyrivibrio</i> spp., <i>Ruminococcus</i> spp., <i>Campylobacter</i> spp., <i>Desulfobulbus</i> spp.	Cattle	Gastrointestinal tract	Amino acid and carbohydrate metabolism	Function driven metagenomics	(Mao et al., 2015)
Pathogenic Microorganisms					
<i>Actinobacillus lignieressi</i>	Cattle	Gastrointestinal tracts	Lymph-node swelling	Function driven metagenomics	(Caffarena et al., 2018)
<i>Arcanobacterium bovis</i>	Sheep and goats	Oral cavity	Mandibular lesions	Culture-based	(Delano et al., 2002)

Table 2. contd.

1	2	3	4	5	6
<i>Brucella melitensis</i>	Goats	Rumen	Brucellosis (Inflammation of epididymis and abortion)	Sequence driven metagenomics	(Samadi et al., 2010)
<i>Campylobacter intestinalis</i> and <i>C. jejuni</i>	Goats	Intestinal tract	Diarrhoea	Culture driven	(Underwood et al., 2015 b)
<i>Clostridium perfringens</i>	Ruminants	Gastrointestinal tracts	Produces toxins leading to enterocolitis	Culture driven	(Uzal et al., 2010)
<i>Pseudomonas aeruginosa</i> and <i>Fusobacterium</i> spp.	Bovine	Esophagus, omasum and tongue	Esophagitis, omasitis, and glossitis	Culture driven	(Tosaki et al., 2018)

Rumen microbiome

A list of beneficial and pathogenic microorganisms isolated from the digestive system of farm animals using culture and non-culturable techniques is shown in Table 2. The microbial diversity of the ruminants' digestive system has been thoroughly studied owing to its importance in producing methane, a vital greenhouse gas (Black et al., 2021). The microbial communities perform fundamental metabolic processes inside the gut by helping in the digestion of plant feed. The conversion of hemicellulose and cellulose into nutritional components is an integral part of the ruminants' digestive system (Merchen et al., 1997). The cellulose-degrading microorganisms characterized by culture-dependent and/or culture-independent techniques include *Ruminococcus albus*, *Ruminococcus flavefaciens*, and *Fibrobacter succinogenes* whereas, the hemicellulose degraders mainly belong to the *Pseudobutyrvibrio*, *Prevotella* and *Butyrivibrio* (Morais and Mizrahi, 2019). Rumen also harbors microorganisms, such as *Selenomonas ruminatum*, that consume the secondary products of other microbial communities (Petri et al., 2013). Xue et al. (2020) studied the impact of the rumen microbiome on the performance of dairy cows by metagenomic analysis. They revealed a higher population of *Prevotella* species in the rumen of high-milk protein-yielding cows. They also reported a comparatively lower population of microorganisms with methanogenesis function (Xue et al., 2020). However, it is imperative to understand that less-abundant microorganisms are not less important. *Fibrobacter succinogenes*, a cellulolytic bacterium occupying 0.5% of the core microbiome, is key bacterial species that metabolizes cellulose and produces succinate and soluble sugars (Neumann et al., 2018). Geographical location and food habits have been studied to alter the gut microbiome, particularly farm animals' methanogenic community, mainly ruminants (Conlon and Bird, 2014). In a sequence-driven metagenomics study of the gastrointestinal tract of goats and sheep of the same age, there are no significant differences in their microbial communities at the phylum level (Shabana et al., 2021). The microbes isolated from the rumen and gastrointestinal parts of the farm animals

using various metagenomics approaches have been reported to show beneficial effects on the performance and health of farm animals. They have improved feed efficiency, amino acid and carbohydrate metabolism, fatty acid oxidation, and rumen fermentation (Table 2). Furthermore, these metagenomics studies have also helped in identification of enzymes and proteins that can be used as animal feed supplements and/or important for food and pharmaceutical industries (Table 2).

Even though the gut microbiota is beneficial for both the host and the surrounding environments, it can be harmful to animal health. Hemorrhagic bowel syndrome (HBS), a sporadic disease, is believed to occur due to *Clostridium perfringens* (Owaki et al., 2015). Animals that are closely stocked, stressed, older, exposed to contaminated water and feed are prone to diarrhea, dysentery and toxemia with *Salmonella* spp. infection (Carslake et al., 2011). The presence of *Escherichia coli*, *Campylobacter jejuni*, and *Yersinia enterocolitica* in the intestines of cattle is non-pathogenic in action. Still, it can very well be transmitted to humans via fecal contamination of milk, leading to gastroenteritis in people if milk is not pasteurized (Rahimi et al., 2014). Different metagenomic studies focusing on the rumen and gastrointestinal parts have shown that the microbes present in these parts can be responsible for diarrhea, inflammation, esophagitis, lesions in the farm animals (Table 2).

Reproductive-tract microbiome

The percentage of healthy offspring born and raised in a particular breeding cycle is vital for sustainable beef and dairy production. Therefore, an optimal level of reproduction is the top priority in livestock farming systems (Crowe et al., 2018). The reproductive tract microbiome can affect all reproductive events in females, including folliculogenesis, ovulation, fertilization, embryo survival and development, pregnancy establishment, and parturition (Molina et al., 2020) (Table 3). The dysbiosis of the reproductive tract is associated with several reproductive disorders such as the arrest of ovarian follicle development, endometritis, vaginitis, preterm delivery and abortion, endocrine disorders in human and animal models (Sirota et al., 2014;

Caffarena et al., 2018; Qi et al., 2021). Similarly, the disbiosis of the male reproductive tract microbiome can obstruct genital ducts, a certain inflammation of tissues, epididymitis, orchitis, poor semen quality, prostatitis, and infertility (Altmäe et al., 2019). The reproductive performance of domestic animals is influenced by factors like nutrition, environment, fertility and microbiome (Lucy, 2007; Sirota et al., 2014). The persistence of infectious agents in different sites of the reproductive tract can lead to inflammation (Sheldon et al., 2014), which ultimately reduces the conception rate, increases the risk of abortion and stillbirth, and extends the calving interval (Moore et al., 2021). Microorganisms can gain entry into the reproductive tract from different anatomical sites (Clemmons et al., 2017; Peric et al., 2019). For example, the cervical barrier is crossed, allowing the microbial entry from the vagina or environment or skin into the genital tract (Ochiel et al., 2008). *Porphyromonas*, *Bacteroidetes*, and *Fusobacterium* inhabiting rumen are excreted but also add to the possibilities of uterus infection leading to metritis (Hassan et al., 2020; Wang et al., 2013). The prevalence of microbes in livestock environments can easily cross the host's defense system and establish a niche in the uterus (Baker et al., 2018). Cattle have been studied for their ability to decontaminate their uterus by involution, discharging of cervix and uterus content, supported by its immune system within the first few weeks post-calving (Lin et al., 2021; Silvestre et al., 2009; Stephen et al., 2019). The persistence of opportunistic pathogens in the reproductive organs of the cattle largely perturbs the hormonal balance (Sheldon et al., 2009). For example, bacterial lipopolysaccharide causes problems in the regulation of luteinizing and prostaglandin hormones, which ultimately causes changes in the uterine environment leading to embryonic loss (Herath et al., 2009). The occurrence of microorganisms in the beef and dairy cattle reproductive parts is not only due to external colonization but can also be due to hematogenous transmission (Holschbach and Peek, 2018; Moore et al., 2021). Galvão et al. established that *Trueperella pyogenes* and

Fusobacterium necrophorum isolated from the uterus are responsible for liver abscess, whereas *Helcococcus ovis* cause endocarditis (Galvão et al., 2019). A small number of microorganisms have been characterized from farm animals' reproductive samples using culture-dependent microbiological techniques, but with the advent of metagenomics and next-generation sequencing methods, several microorganisms present in a lesser number have been identified. A metagenomic study revealed the presence of similar microbial communities in Fleckvieh, Holstein, and Nellore, which comprised *Proteobacteria*, *Firmicutes*, and *Bacteroidetes* microbial species (Thoetkiattikul et al., 2013). The microbial community in reproductive tract parts identified by different metagenomics approaches has been reported to have beneficial and harmful effects on farm animals. Microbes identified in these parts by metagenomics approaches have been reported to improve immune response in gilts (Table 3).

Excreta and milk microbiome

Other than the rumen, reproductive tract, and skin of the farm animals, their excreta and milk can also be sources of some pathogenic and beneficial microbes. In piglets where *Prevotella* genera were abundant in their feces, it was reported that the *Prevotella* species were correlated with higher average body weight, average daily gain after weaning and luminal secretory immunoglobulin A (IgA) levels in piglets (Mach et al., 2015). Furthermore, a metagenomics study has reported a higher abundance of bacteria belonging to the *Veillonellaceae* family in feces of sheep and cows, which were transitioning from milk to solid food, suggesting the role of these bacteria in solid food digestion and fermentation (Ahlborn et al., 2020). Microbes belonging to *Shigella* and *Salmonella* species isolated from compost made of dairy cow and beef manure have been reported to secrete bacteriocin-like substances and inhibit the growth of various food spoilage and food-borne pathogenic bacteria, suggesting that the farm animal excreta can be a source of novel antimicrobial compounds (Abdel-Mohsein et al., 2010). De-

Table 3. List of beneficial and pathogenic microorganisms isolated from reproductive system of farm animals using culture and non-culturable techniques

Microorganisms	Animal	Niche	Action	Isolation technique	References
Beneficial microorganisms					
<i>Streptococcus</i> spp., <i>Fusobacterium</i> , Gilts		Vagina	Affects immune response	Sequence driven metagenomics	(Sanglard et al., 2020)
<i>Campylobacter</i> spp., <i>Kurthia</i> spp.,					
<i>Lactobacillus reuteri</i>	Bullock	Testicular tissue	Increases in testosterone levels	Sequence driven metagenomics	(Poutahidis et al., 2014)
Pathogenic microorganisms					
<i>Actinobacillus lignieressi</i>	Cattle	Reproductive tract	Lymph-node swelling	Function driven metagenomics	(Caffarena et al., 2018)
<i>Brucella melitensis</i>	Goats	Reproductive tract	Brucellosis (inflammation of epididymis and abortion)	Sequence driven metagenomics	(Samadi et al., 2010)
<i>Taylorella equigenitalis</i>	Equine	Reproductive tract	Contagious metritis	Culture driven	(Kristula, 2014)

spite beneficial effects, harmful effects of the microbes isolated from excreta and milk of farm animals have been reported. In a study where the authors compared the core microbiota of milk from healthy sheep and sheep with subclinical mastitis (SM), it was reported that milk from SM sheep had a higher number of bacteria belonging to *Staphylococcus* and *Streptococcus* species in comparison to milk from healthy sheep (Esteban-Blanco et al., 2020). Furthermore, the milk of SM sheep had bacteria belonging to *Alloiococcus* species, *Jeotgalicoccus* species, *Pseudomonas* and *Clostridium* species which were absent in the milk of healthy sheep (Esteban-Blanco et al., 2020). These bacteria, whose number was increased in the milk of SM sheep, have been associated with clinical, subclinical mastitis (Esteban-Blanco et al., 2020). The importance of other bacteria identified from the milk and excreta of farm animals has been listed in Table 4.

tuberculosis caused by *Mycobacterium bovis* in the Hook Lake Wood Bison breeding herd with a total of 140,000 infections (Himsworth et al., 2010). Pleuropneumonia, also called lung plague, is another transmissible bacterial disease caused by *Mycoplasma mycoides*, resulting in the inflammation and pneumonia of the lungs. During 1879–1892 it affected the herds of the United States, which promoted a ban on the U.S. cattle exports by several countries like Canada and Britain (Jaja et al., 2016). The recently emerged severe acute respiratory syndrome Coronavirus-2 (SARS-CoV-2) has also negatively affected animal agriculture globally (Gauly et al., 2021; Hashem et al., 2021). The ongoing pandemic due to SARS-CoV-2 has also affected the availability of feed and management of diseases among cattle (Hashem et al., 2020; Obese et al., 2021). Considering the overall damage and economic repercussions, the need for disease control, management,

Table 4. List of beneficial and pathogenic microorganisms isolated from excreta and milk of farm animals using culture and non-culturable techniques

Microorganisms	Animal	Niche	Action	Isolation technique	References
Beneficial microorganisms					
<i>Methanomicrobium mobile</i>	Swine	Faeces	Methane production through reduction of carbon dioxide with formate or hydrogen	Sequence driven metagenomics	(Lee et al., 2010)
<i>Veillonella parvula</i>	Sheep	Faeces	Help in transition of infants animals from milk based diet to solid diet	Function driven metagenomics	(Ahlborn et al., 2020)
<i>Prevotella</i> spp.	Piglets	Faeces	Improve immunity and body weight	Sequence driven metagenomics	(Mach et al., 2015)
<i>Salmonella</i> spp.	Cattle	Manure	Synthesis of bacteriocin like substances	Culture driven	(Abdel-Mohsein et al., 2010)
Pathogenic microorganisms					
<i>Staphylococcus</i> spp., <i>Sterptococcus</i> spp., <i>Shigella</i> spp., <i>Corynebacterium</i> spp., <i>Escherichia</i> spp., <i>Pseudomonas aeruginosa</i> , <i>Clostridium perfringens</i> , <i>Alloiococcus</i>	Ewes	Milk	Mastitis	Sequence driven metagenomics	(Esteban-Blanco et al., 2020)
<i>Yersinia enterocolitica</i>	Hog	Manure	Diarrhea	Culture driven	(Holley et al., 2008)
<i>Escherichia coli</i> 0157:H7	Cattle	Manure	Diarrhea	Culture driven	(Ronner and Cliver, 1990)

Disease management and surveillance using metagenomics in farm animals

The comprehensive metagenomic analysis in cattle is rapidly growing in importance for sustainable and safe domestic livestock. Metagenomic next-generation sequencing (mNGS) helps to identify rare and novel pathogens and to characterize the microbial diversity in different animals like ruminants, monogastric (pigs and rabbits), and poultry (Kwok et al., 2020; Li et al., 2018). To meet the demands of the growing human population, livestock intensification is widely practiced, which increases the livestock density and, therefore, the chances of zoonotic disease outbreak and transmission are very susceptible (Hashem et al., 2020). A significant animal health challenge that occurred in March 2005 was bovine

and surveillance is essential. Figure 1 illustrates the general procedure of metagenomics for pathogen identification and disease control.

Controlling the disease outbreak

Early detection of outbreaks in cattle is always crucial in minimizing the damage. Conventional testing generally involves polymerase chain reaction (PCR), enabling timely detection of a pathogen only (Yang and Rothman, 2004). However, metagenomics ensures complete genetic examination of microbial communities present within a particular sample associated with domestic animals by comparing with the genomic databases (Chen et al., 2021). This helps in identifying new genetic signatures like sensitivity and copy number. Xu et al. (2015) identi-

fied genomic signatures and revealed new pieces of evidence for the selection of valuable genetic traits in cattle. Depending on the allele frequency, they identified known and unknown genes under positive selection among Holstein, Brahman, Charolais, and Angus (Xu et al., 2015). The increased globalization and subsequent human-animal contacts make the pathogenic diffusion into the world non-stop. Metagenomics offers an advantage in this regard because prior knowledge about a particular pathogen is not required; hence it is a faster tool to detect and control the evolving pathogens.

Metagenomic screening can be applied to both bacterial as well as viral pathogens. One of the virome-metagenomic studies carried out on the feces of 24 healthy and 12 pigs with diarrhea reported the shedding of 4.2 viruses by healthy pigs and 5.4 by diarrheic pigs (Shan et al., 2011). Using the metagenomics approach, several known and previously uncharacterized viruses associated with bovine respiratory disease in cattle were identified (Ng et al., 2015). The metagenomics studies were recently carried out on mosquitoes collected from different animal farms in China to investigate their virome, which can be potential sources of viral diseases to humans and animals (Hameed et al., 2021). Similarly, metagenomics technology has also been implemented to identify avian viruses, lethal to poul-

try farming (Qiu et al., 2019). Apart from viruses, various pathogenic bacteria have also been identified using metagenomics analysis from different animals. *Anaplasma bovis* and *Anaplasma phagocytophilum*, which cause hemolytic damage in ruminants and other animals, have been identified from rodents in Northern Thailand using the metagenomics approach (Takhampunya et al., 2019). Since zoonotic outbreaks are common among humans and non-human animals, early sequencing data is essential to develop a combatting strategy. The metagenomics analysis of different microbiomes can help monitor various pathogens, which can aid in the early and timely detection of pathogens infecting animals and poultry. The regular check-up of the hot spots and places with higher human-animal contact can help in minimizing the damage and ensure safe and sustainable livestock. MiSeq and HiSeq developed by Illumina, are helpful and cheap tool kits for this purpose with a slight difference in reading lengths (Gupta and Verma, 2019). MiSeq is a generation benchtop sequencer that can be used for metagenomics and gene expression analysis (Liu et al., 2012; Ravi et al., 2018). HiSeq, which uses sequencing by synthesis method, is another next-generation sequencing tool that can be used for the metagenome analysis of animals (Liu et al., 2012).

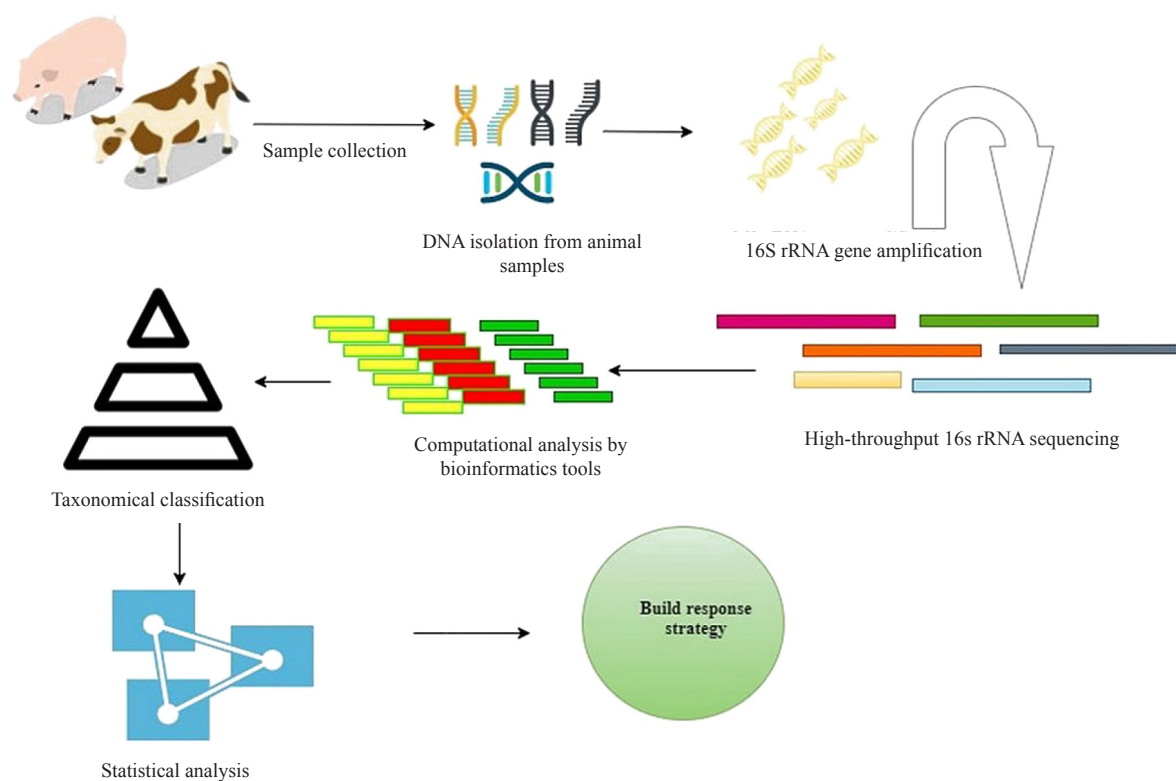


Figure 1. Metagenomic-approach for pathogen detection and response strategy

Function-driven metagenomic studies

Function-driven metagenomics starts with the microbial DNA isolation from an animal sample or any other environmental sample to study the function of genetically encoded proteins. The fragments of DNA are cloned, expressed and then screened for enzyme activities. This allows the discovery of new enzymes, which is impossible by DNA sequencing only (Mullany, 2014; Ngara and Zhang, 2018). In another study, sulfatase enzyme was isolated from the rumen of bovines by function-driven metagenomics (Colin et al., 2015). A similar approach was followed by other scientists for amylase and cysteine protease isolation from the animal feces and ovine rumen, respectively (Brock et al., 1982; Seura and Fukuwatari,

2020). In another function-driven metagenomics study, the *Umcel-1* gene was identified from the ruminal content of gayals (semi-wild bovine native to Indo-China) (Li et al., 2016). The recombinant Umcel-1 protein was reported to have cellulase activity as it hydrolyzed carboxymethyl cellulose (Li et al., 2016). Another protein, Umcel5B29, which also possesses cellulase activity, was identified from the rumen of swap buffalo using the same approach (Cheema et al., 2012). As these function-driven metagenomics studies help in identification of various proteins from the animal microbiome, this strategy can be useful in early detection of pathogens and their secreted toxins, which can lead to severe animal health crisis if left unchecked.

Table 5. Meta-omics findings in livestock for sustainability

Animals	Aims	Consequence/implication	References
Cow	Identification of hippuric acid as biomarker responsible for low production of milk in corn stover fed cows.	Improving milk production	(Xue et al., 2020)
Livestock and poultry	Prediction of male reproductive traits effecting fertility.	Improving male fertility	(Long, 2020)
Pigs	Identification of pathways and genes (TPH2, FAR2) for feed conversion.	Improving feed conversion and feed utilization	(Miao et al., 2021)
Dromedary camels	Analysis of rumen microbiota under varying dietary conditions with special focus on taxonomic and carbohydrate active enzyme (CAZyme) profiles.	Detection of carbohydrate enzymes and improving fiber digestion	(Hinsu et al., 2021)
Jaffarabadi buffalo	Analysis of microbial role in polysaccharide breakdown.	Improvement of plant polysaccharide breakdown	(Nathani et al., 2015)
Chicken	Identification of quantitative trait locus forming basis of the functional studies of the genes regulating fat deposition and body weight.	Improvement of body weight and feed efficiency	(Moreira et al., 2019)
Holstein dairy cows	Multifunctional redundancy during feed degradation by rumen microbiome assessment.	Improvement of plant biomass degradation and mitigation of methane emission	(Söllinger et al., 2018)
Sheep	Studying role of rumen microbiome in methane production and lactate pathways.	Mitigation of methane emission	(Kamke et al., 2016)
Swine	Analysis of gut microbiome revealed 17,237,052 complete genes from 787 gut metagenomes which included 28% of unknown proteins.	Act as resource for swine gut microbiome research	(Chen et al., 2021)
Livestock	Composted manure contains the low microbial density and antibiotic resistance genes than the manure treated with precipitation and mechanical drying.	Controlling the spread of anti-microbial resistance gene	(Zhang et al., 2020)
Pigs	Gut microbiota metabolome is influenced by the herbicide glyphosate.	Determines the effect of herbicide glyphosate on the metabolome of pigs	(Krause et al., 2020)
Beef cattle	Rumen metagenome are more clustered more closely than metatranscriptomes indicating higher functional variation at RNA level than the DNA level.	The breed of beef cattle affects the rumen microbiome and feed efficiency	(Li et al., 2019)
Angus bull	Discovery of signature bacterial taxa and their role in feed conversion. In Black Angus <i>Chitinophaga pinesis</i> and <i>Clostridium stercorarium</i> were identified, whereas <i>Oscillibacter valericigenes</i> was characterized in Red Angus.	Improvement of feed conversion efficiency	(Neves et al., 2020)
Gir cattle (<i>Bos indicus</i>)	Identification of less explored transcriptionally active genera like <i>Paludibacter</i> and <i>Caldicellulosiruptor</i> from the rumen.	Identifying bacteria that can help in degradation and metabolism of fiber	(Pandit et al., 2018)
Hens	Roles of cecal microbiota of laying hens in hydrogen sulfide production and increase in methionine concentration in laying hens.	Help in breeding hens in environment friendly way by reducing hydrogen sulfide emission	(Xing et al., 2021)
Heifer cow	Studying the role of ruminal microbiome alters in the transcripts expression for biochemical pathways involving fiber degradation and fatty acids production.	Determine the effect of pH on fiber degradation and fermentation in cows	(Li et al., 2021)

Sequence-driven metagenomic sequencing

In a sequence-driven metagenomic approach, the isolated DNA from animals or other environmental samples is subjected to sequencing to establish a phylogenetic relationship (Berini et al., 2017; Handelsman, 2004). Several bioinformatics tools analyze the obtained sequence data for sequence pre-filtering, assembly, gene prediction, species diversity, data integration and comparative analysis (Hiraoka et al., 2016). This approach offers an advantage in establishing early phylogenetic relationships over the functional approach. Several fibrolytic enzymes have been characterized from the rumen that exhibits a rich diversity of microbial communities. Various enzymes belonging to glycosyltransferases, polysaccharide lyases, glycoside hydrolases and carbohydrate-binding modules were also identified. Their results showed the complexity of cattle rumen microbiome harboring bacteria of the genera *Bacteroides*, *Ruminococcus*, *Clostridium*, *Fibrobacter*, and *Prevotella* (Jose et al., 2017). In another sequence-driven metagenomics study, various carbohydrate-active enzymes such as glycoside hydrolases, carbohydrate esterases and glycosyl transferases were identified from the goat rumen metagenome (Suryawanshi et al., 2019). These enzymes can have broad applications in the pharmaceutical and food industries (Suryawanshi et al., 2019). This strategy can be useful in timely identification of animal-borne pathogenic microbes and viruses that can be harmful to animals and humans.

Other meta-omics approaches for livestock sustainability

Meta-omics approaches have revolutionized our perspective about the animal microbiome, structure, and metabolism (Table 5). Culture-independent metagenom-

ics focuses mainly on identifying new microorganisms in animals or any other environment sample using genomic content. On the other hand, metatranscriptomics evaluates the functional gene diversity within that community (Bashiardes et al., 2016). This helps to analyze the gene expression levels and further monitors fluctuations in expression levels in changing pathological and physiological conditions of an organism (Aguilar-Pulido et al., 2016). Metatranscriptomics offers an advantage in providing information about the contrast in active functioning of microbial networks within a particular microbiota. Microarrays have been utilized in metatranscriptomic studies, but mNGS and third-generation sequencing are favored techniques in metatranscriptomics (Shakya et al., 2019). Li et al. carried out a comparative metagenomic and metatranscriptomic analysis on the rumen microbiome of beef cattle (Li et al., 2019 a). They reported that the breed of beef cattle affected the rumen microbiome and feed efficiency (Li et al., 2019 a). They observed differences in microbial composition (metagenomic level) and functional potentials (metatranscriptomic level). They concluded that interaction between rumen microbiome and host breed genotype significantly contributes to the changes in feed efficiency (Li et al., 2019 a), thus opening the new gateway for engineering particular rumen microbiome through selective breeding.

Metabolomics involves the quantitative measurement of metabolites and metabolic responses of animal systems. It gives a detailed account of the small biomolecules present within a particular sample. The obtained metabolic profile provides an instant snapshot of the specific microbial community or a cell, thus giving a functional readout of an organism's physiological state (Aguilar-Pulido et al., 2016; Boersma et al., 2001; Emwas

Table 6. Computational tools for metagenome and other meta-omics data analysis

Computational tool	Significance	Link
MEGAN (MEtaGenome Analyzer)	Correlation of DNA reads with known sequences	http://www-ab.informatik.uni-tuebingen.de/software/megan .
MG-RAST (Metagenomic Rapid Annotations using Subsystems Technology)	Phylogenetic analysis	http://metagenomics.anl.gov/ .
SmashCommunity	Assembly of reads	http://www.bork.embl.de/software/smash
IMG/M (Integrated Microbial Genomes and Microbiomes)	Genome annotation and curation	http://img.jgi.doe.gov/
MetaVelvet	Metagenome contig assembly	http://metavelvet.dna.bio.keio.ac.jp/
MetaclusterTA	Binning of sequence reads for annotation and taxonomic analysis	http://i.cs.hku.hk/~alse/MetaCluster
METAGENassist	Phenotype mapping by comparative metagenome analysis	http://www.metagenassist.ca/METAGENassist/faces/Home.jsp
MEGAHIT	Metagenome data assembly	https://hku-bal.github.io/megabox
Metaphlan 2.0 (Metagenomic Phylogenetic Analysis)	Strain identification by metagenome profiling	http://segatalab.cibio.unitn.it/tools/metaphlan2/
MetaPath	Analysis of Metabolic pathways	https://www.cbcb.umd.edu/software/metapath
MetaSort	Mini-metagenome sorting based on single-cell sequence approach	https://sourceforge.net/projects/metasort/

et al., 2019). In another study, comprehensive metabolomic results of several bovine fluids (ruminal fluid, serum) and tissues (testis, semimembranosus muscle) were described. They were able to characterize nearly 150 metabolites using liquid chromatography, nuclear magnetic spectroscopy and mass spectrometry (Foroutan et al., 2020). Metabolomic studies are widely used in diseases diagnosis, trait selection and function evaluation in domesticated animals. This also ensures the determination of genotype caused by gene manipulation (Blakebrough-Hall et al., 2020). This offers an advantage in predicting the activity of unknown genes. One recent research on metabolomics helped identify N-acyltaurines from mammalian systems as previously unknown endogenous monoalkylglycerol ethers and amide hydrolases.

Computational tools for metagenomic and meta-omics data analysis

Metagenomics and other meta-omics approaches discussed above provide an in-depth analytical understanding of the microbial communities and their gene products for the sustainability and wellness of livestock. However, to predict the gene function in a complex environment like rumen and reproductive tract, it is essential to have databases for the previously discovered similar microorganism to evaluate and understand the multiple functional roles within the microbial niche. Several computational tools (Table 6) have been developed for easy evaluation and interpretation of metagenome data analyses. In a study, deep metagenomic sequencing was carried out, which revealed the association of microbiome signature in bovine mastitis with functional biases (Hoque et al., 2019). They used several computational tools like MG-RAST (Metagenomic Rapid Annotations using Subsystems Technology) and Pathoscope, which resulted in the generation of 483.38 million reads. They observed definite shifts and differences between healthy milk and clinical mastitis microbiome. They performed functional annotation of metagenomic sequences and reported several metabolic pathways related to immune diseases, oxidative stress, bacterial colonization, heavy metal resistance, and cell signaling (Hoque et al., 2019).

Conclusion and the way forward

There is an urgent need to apply novel microbial techniques like metagenomics and other meta-omics approaches for livestock sustainability and wellness. Of late, there has been an increase in bacterial, fungal, and viral diseases in domestic animals, which has subsequently led to significant economic loss and strongly hits the resilience of the food chain. Since microbes tend to change their way of life by different adaptive strategies, surveillance is an essential tool of disease control and management. Together with other meta-omics approaches, metagenomics can be utilized in microbial community monitoring, disease control, and building robust and precision response strategies. As shown in this review, several reports/studies highlighted the significance of the

culture-independent metagenomic approach for the early detection of diseases for controlling transmission to human populations. Besides, abundant data and metagenome-used computational tools present important cues to understand the importance of microbes in the normal and abnormal functioning of different animal cells, tissues, and organs. Microbiota is pivotal to the normal functioning of animals regarding defense, digestion, excretion, and other biochemical processes, making microbial analysis imperative for sustainable livestock. Metagenomics and other meta-omics strategies as a replacement to conventional microbiological methods have expanded the animal microbiota understanding. Still, scientists are unable to keep pace with human microbiome exploration. Nowadays, animal microbiota studies are more or less confined to ruminal spaces, and focus needs to be shifted towards other animals' tissues like the uterus, sebaceous glands etc. as well to mitigate the pathogenic nature of microorganisms.

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Conflict of interest

All the authors hereby declare no conflict of interest.

Author contribution

All the listed authors have made a substantial, direct, and intellectual contribution to the work. All the authors approved the manuscript.

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