Chapter

Introductory Chapter: Understanding Bovine Science - An Emerging and Re-emerging Menace in the Growing Epoch

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1. Introduction

Agricultural sector plays an inevitable role for the economy of most Asian and African countries and is the greatest source of domestic income. In addition, it manipulates 70–90% of the gross working population. Sustainably feeding the world is the crucial challenge in the forthcoming years. Surprisingly, the agricultural sector meets the food needs of 50% families besides income [1]. Livestock animals are important source of food to billions of the world's population. It is also agricultural backbone in developing countries because it adds about half of the value to agricultural output [2]. Livestock contribution to agriculture is 56% among which 11% is imparted to GDP. This escalation is due to increasing demand for livestock product which in turn is driven by growing population size, income, lifestyle change and industrialization in economically developing nations. The need for livestock products is estimated to get doubled by 2030 in unindustrialized countries. However, in technologically advanced countries, the need for such products is comparatively lower and is expected to grow slowly over a specified period of time [3]. Despite the demand variability, livestock dichotomy exists between industrializing and industrialized countries in terms of meat and milk production which are the major commodities obtained from dairy animals globally. Meat is an important source of proteins (myosin, myoglobin and collagen), vitamins (thiamine, niacin riboflavin), iron and zinc etc. Annually, 340 million tonnes meat is produced and the quantity is three times more from the past 50 years. The United States of America (USA) is the world's largest cattle and buffalo meat producing country accounting for 12 million tonnes of meat [2]. Milk, on the other hand is produced by 150 million householders in rural, urban and peri-urban areas and contributes to food security, income and nutrition. The world annual milk production has risen from 530 million tonnes in 1988 to 843 million tonnes in 2018. India is the world's largest milk producing country followed by USA, China, Pakistan and Brazil [4].

Everyone is aware with the importance of agricultural subsector (dairy and livestock industry) in the country's economy; still this sector is prone to variety of emerging and re-emerging threats. The threats associated with ungoverned livestock farming in the form of nutritional deficiencies, metabolic disorders, changing environmental conditions, diseases (either infectious or non-infectious) and antimicrobial resistance has led to the importance of understanding bovine

science. Therefore, in this chapter we will learn about the impact of different kinds of re-emerging and emerging threats on bovine community.

2. Potential constraints to bovine science

Animal health, nutrition, diseases and limited access to available vaccination are the major threats to dairy productivity. Animal diseases directly pose negative effects on economy in the form of reduced milk and meat production, trade restrictions, mortality and animal health issues or indirectly in the form of public health [5]. Livestock bovine is prone to major infectious diseases particularly Foot and mouth disease (FMD), Rinderpest and Brucellosis which has caused previous outbreaks worldwide [6]. Fortunately, by 2010, rinderpest eradication at global level is praise worthy [7]. However, the other diseases are currently endemic in many South-Asian countries including Pakistan. FMD is placed in the list of notifiable diseases by OIE. FMD has also caused epidemics globally and is associated with high morbidity and is a major constraint to economic development in terms of production loss due to changing serotypes [8]. In Pakistan, 200 million dollar loss annually has been reported due to FMD. In India, the loss is even bigger i.e. 430 million dollar. These losses are attributed to poor disease diagnosis and surveillance, lack of reporting and limited data availability on the dynamics and distribution of livestock diseases in South-Asian countries [9].

Several factors are considered as major threats to animal health and livestock sectors. The introduction of new animal in the resident population which has not been vaccinated previously before transportation, is likely to carry infectious agent and cause disease in herd animals. In addition to the factors discussed above, there is a range of threats which could pose dilemmic situation over the livestock herd. If the barriers are removed, then animal's productivity could be improved [10].

Some of the emerging and re-emerging threats are discussed below in detail:

2.1 Nutrition

Various energy proteins, enzymes, vitamins and minerals are needed by animals for their better performance. Nutrients deficiency can have a devastating effect on bovine health [11]. Diet rich in starch concentrates is required by beef cattle for high gains. Besides this, small amount of rough fibrous material should also be included in their diet to ensure efficient rumination.

Gastric or peptic disorders due to heavy rumen acidosis and nurturing of acidogenic products are responsible for 30–42% of cyclic death rates in the feedlots where the overall mortality rates ranges from 0.17% to 0.42% [12]. Moreover, feeding high concentrate diets to livestock bovine has been related with the formation of pyogenic liver abscess and laminitis [10].

Minerals are although required by cattle in a very small amount although, its deficiency might lead to reduced immunity and reproduction of animals. Therefore, for better animal performance and productivity, it is important to improve herd management by increasing the amount and quality of feed produced on cropland, also using feed supplements is suggestive [13].

2.2 Emerging and re-emerging diseases

Emerging diseases can be defined as "any disease which has increased incidence during past couple of decades or is likely to escalate in the forthcoming years". The emerging diseases are fundamentally very important because they are the key players of demographic or social changes alongside encumbrance of illness [14]. Major

epidemics of re-emerging and emerging diseases have been recorded in recent years, most of them are caused by viruses [15].

Re-emerging diseases are those disease which have been managed in the past but there is a chance of their reversal in near times. Different factors play role in the emergence of disease but most likely it is due to host factors, environmental conditions or pathogen adaptation [16]. The emergence and re-emergence of diseases like brucellosis, FMD and antimicrobial resistance can render huge impact on national and international economy, animal and human health [14].

2.2.1 Metabolic diseases

Cattle metabolic disorders are the group of diseases affecting cattle, right after parturition. Different metabolic diseases have been identified in dairy cattle. These include ketosis, udder edema, downer cow syndrome and milk fever. Although these diseases are non-infectious but still they cause heavy economic loss in the form of reduced milk yield and impairment of reproductive system [17]. The impact of these diseases on animal milk production, survival and fertility is of paramount importance to evaluate diagnosis and treatment regimens and prevention strategies because the economic loss caused by these metabolic disorders in dairy farming is poorly addressed [18].

Ketosis refers to the elevated levels of ketone bodies without any clinical signs. Ketosis causes huge economic losses through reduced milk production and other associated pre-parturient disorders [19].

Downer cow syndrome is a cow disease with milk fever in which the cow did not recover from the early recumbence within first 24 hours after intravenous administration of calcium. This disease is also known as 'fat cow syndrome', 'creeper cows' or 'downers'. Downers is characterized by disease complex including milk fever and tendon, nerve or muscle injuries [20].

Milk fever is a metabolic disorder of dairy cows occurring during parturition and lactation period. The disease is also known as eclampsia, parturition paresis, parturient apoplexy and paresis peurperalis. The increasing milk production after calving increases the demand for minerals and glucose at that time when the intake of food have not reached its peak leading to the drainage of calcium and glucose from blood rendering the animal under stress with decrease metabolic activity. Reduced calcium levels are observed before, after or during calving. Accordingly, management of eclampsia is very important economically as it not only results in reduced milk production, but also death of animal [17].

Udder edema is an emerging threat to dairy cow because it has the potential to effect animal welfare and farm's profit. Udder edema may be the result of stress, physiological condition, genetics or nutrition. The disease is characterized by the accretion of lymphoid fluid in the interstitial spaces of mammary gland and their adjacent tissues [21]. Prevalence of udder edema is high in dairy cattle affecting their life negatively. The supporting framework of udder may be broken down due to tissue necrosis [22]. The teats get swollen making their attachment to milking unit difficult resulting in decreased milk production and other secondary infections such as mastitis and udder cleft dermatitis [22]. Severe cases may also lead to farm culling. However, edema can be managed by feeding formulated feed rich in anionic salt, vitamin C, vitamin E, flavonoids and carotenoids (for the management of oxidative stress) [23].

2.2.2 Bovine diseases

The advent of "old-new" animal diseases in the last few years have challenged veterinarians and animal health workers. The list of animal diseases enlarges as

the livestock and dairy industry grows up with adding new research tools and techniques and rapid point of care detection. Consequently, large number of new disease causing agents have been gifted by the veterinary science [24]. They comprise the genetic evolution and emergence of foot and mouth disease virus, bovine brucellosis, bovine viral diarrhea virus and bovine papilloma virus [25]. The reason behind the appearance of these animal disease is difficult to interpret however different molecular factors, genetic evolution, environmental condition and host factors are implicated for playing role in the re-emergence of these diseases. On the contrary, it is implicated that most of the animal disease causing agents are not truly the new agents rather they are the old agents that have been recognized with new technological tools i.e. genomic sequencing. Thus the modern era will keep us bringing robust animal diseases and their associated pathogens [26].

2.2.2.1 Foot and mouth disease

Foot and mouth disease virus (FMDV); an evolving pathogen is an apthovirus belongs to the family picornaviridae. It is a positive-sense, single stranded RNA virus responsible for causing foot and mouth disease in livestock rendering huge economic impact. The disease is prevalent in ungulated animals i.e. cattle, buffalo, sheep, swine and goat [27]. Seven different serotypes (A, O, C, Asia-1, SAT-1, SAT-2 and SAT-3) of FMD are reported from different countries worldwide. It is circulating in about 77% of the livestock population of Africa, Asia and Middle East and is an important transboundary animal disease (TAD). Therefore it can largely disrupt the national and international trade of animals and animal's products and is the leading bottleneck [28]. Disease is characterized by high fever, appearance of blisters (vesicles) in oral cavity (gums, tongue) hooves and teats. The virus initially replicates in the lymphoid tissue of respiratory tract, from there it enters the bloodstream causing viremia. The virus causes death of young animals however it only causes morbidity in infected adult animals and impact can be seen in the form of reduced meat and milk production [29]. Transmission of virus occurs directly through respiratory droplets or it can also occur via mechanical route i.e. fomites [30]. Diagnosis is carried out either by serology (detecting FMD antigen and antibodies) and molecular assay (Real-time PCR) [29]. The FMD is an economically devastating disease, it was initially reported in early 1960s and is still prevalent and endemic in many developing countries. It is estimated that about 75% of the annual cost of low and middle income countries (LMIC) is attributed to FMD prevention and control. The prevention of FMD is based on timely surveillance and implementation of early vaccination programs [31].

2.2.2.2 Bovine viral diarrhea virus

Bovine viral diarrhea virus (BVDV) is a positive-sense, single stranded RNA virus, lying within the genus pestivirus and family flaviviridae. The two predominant species of BVDV is BVDV1 (which possess 21 genotypes) and BVD2 (which possess 3 genotypes) prevailing worldwide [32]. The BVDV subgenotypes BVDV-1a and BVDV-1b and BVDV-1c are distributed widely around the world affecting bovine cattle population and causing severe economic loss in the form of gastrointestinal and respiratory diseases, reproductive disorders, immunosuppressive distress and decreased milk production [33]. The virus has also the ability to cross the placental barrier and cause fetal death andabortion. It can also lead to persistent infection whereby the infected animals can shed virus for the rest of their life [34].

The BVD virus exists in two forms cytopathogenic and non-cytopathogenic based on its ability to produce cytopathic effect in cell culture. BVDV has a high

mutation rate [35]. The occurrence of large number of subgenotypes of BVDV hinder the prevention and mitigation regimes because a vaccine effective in one locality against certain strain is unable to provide immune protection against another strain in another locality [33]. Therefore investigating the number and frequency of subgenotypes of BVDV can be used to study virus evolution which may play role in future vaccination design [36].

2.2.2.3 Bovine papillomavirus (BPV)

Bovine papillomavirus (BPV) is positive sense, non-enveloped, double stranded DNA virus having 8 kb genome and icosahedral symmetry [37]. Virus replicates in the epithelial cells squamous nuclei affecting skin and mucosal surfaces causing malignant or benign tumor. The virus was initially characterized in cattle from where it has got its name [38]. Uptil now, 26 types of BPV has been identified among which three are unclassified and the rest 23 have been characterized into 5 genera: the deltapapillomavirus contain 4 types (BPV-1, 2, 13 and 14). The genus Xipapillomavirus has further 2 species: Xipapillomavirus 1 (BPV-3, BPV-4, BPV-6, BVP-9, BPV-10, BPV-11, and BPV-15) and Xipapillomavirus 2 (BPV-12). Epsilonpapillomavirus 1 contains (BPV-8 and BPV-5) and the last Dyoxypapillomavirus 1 includes (BPV-7). Among the species described, the members of deltapapillomavirus (BPV-1, BPV-2 and BPV-13) has the ability to infect bovine cattle causing bovine papillomatosis [39]. Bovine papillomatosis is characterized by the formation of papilloma or cutaneous warts that is the representative of proliferative lesions ranging from minute lesion to rough, spiny cauliflower shaped warts, often black and gray in color [40]. The virus has caused considerable economic losses previously and currently is causing damage to dairy industry and cattle hides. BPV infects teats and udder of milking cows, and can also cause udder and gastrointestinal cancer. The milking process of young calves is also affected predisposing these animals to secondary bacterial infections. Transmission occurs due to contaminated milking equipment, or animals rubbing them on uncleaned objects (wire fences). Sexual transmission of virus in venereal warts is also recorded [41]. The virus affect cattle of all ages. In the past, detection of virus was carried out using isothermal loop-mediated amplification process but with the advances in the field of science and technology, the in-point of care detection has been replaced by sensitive, fast and reliable molecular techniques i.e. polymerase chain reaction (PCR) [42].

2.2.2.4 Bovine brucellosis

Brucellosis is the disease of cattle, goats, sheep and pigs caused by bacteria, *Brucella melitensis* and *Brucella abortus*. It can spread after having direct contact with the infected animal or animal product [43]. It is classified as category B pathogen by CDC because of its potential to be used as bioweapon in biowar. Although, the disease is prevalent worldwide but its distribution is changing due to newly emerging and re-emerging focuses. This bacteria has the ability to immediately adapt itself to the new environmental conditions and spread after having direct contact with the infected animal or animal product [44]. *Brucella* in animals can cause huge economic damages in the form of spontaneous abortions which in extreme situations are known as *abortion storms*. Pastoralism of cattle, goat, sheep and buffalo have aggravated the occurrence of brucellosis because of the broad spectrum of its transmission in different species [45]. Rose Bengal test, indirect ELISA assay and molecular diagnostics procedures (PCR) are the proposed tests for sensitive detection of *Brucella* in livestock [46]. Effective management

and surveillance strategies, mass vaccination and animal husbandry practices can prevent the transmission of infection [47].

3. Antimicrobial resistance (AMR)

A microbe is known as human's best friend but at the same time is his worst enemy. Antibiotics are known as magic bullets because of its magic in the previous era [48]. Antimicrobial resistance (AMR) can be defined as "the ability of any microbe to become resistant to available antimicrobial therapy to which it was previously found susceptible" [49]. AMR is a problem prevailing worldwide in both veterinary medicine and human sector where antibiotics are used mainly for treating diseases and animal growth promotion [50]. AMR is complex and multifactorial process and is the result of antimicrobial usage (AMU) in animal, human and agriculture sector. The rapid dissemination and spread of resistant bacteria and their associated genes are responsible for increased mortality and morbidity in animals, reduced production and diminished food security [48]. The overuse and misuse of antimicrobial agents has resulted in the appearance of resistance, threatening the prevention and treatment regimens [51]. Antibiotics are also added as food supplements in animal feed which also give rise to resistant bacteria. The usage of many of the growth supplements have been banned in most of the countries especially colistin, because it is the last resort antibiotic and it is also a resurgent drug therefore it can pose great risk of AMR [52]. The WHO (World Health Organization) identified potential antimicrobial resistant agent to which urgent antibiotics are needed [53]. Among the top priority pathogen; extended spectrum beta-lactamase (ESBLs producing *Escherichia coli*) have been recognized as emerging universal dilemma due to their increasing occurrence in livestock sector [54].

Among food-producing animals, cattle are the important reservoir of bacteria capable of producing ESBLs [55]. ESBLs are beta-lactamases that have the ability to degrade ceftazidime, ceftriaxone, cefotaxime, cefepime and monobactam antibiotics. The important variants of ESBLs are TEM, SHV, OXA and CTX-M. Of these variants, TEM and SHV were initially identified in *E. coli* and *Klebsiella pneumoniae*. *Pseudomonas* specie carries TEM, SHV and CTX-M. It is implicated that CTX-M has

Method	Description
Use of eubiotics instead of antibiotics as growth supplements	Eubiotics include prebiotics, probiotics, oil, herbs and enzymes which can be used in animal feed instead of antibiotics. Eubiotics are known for improving performance and health of animals.
CRISPR-Cas 9 system	Gene editing via CRISPR-Cas9 technology can target antibiotic resistant gene and ultimately kill the microbe.
Antimicrobial peptides	Synthetic antimicrobial peptides have broad spectrum of activity against gram positive and gram negative bacteria because they are amphipathic, and rapidly kill the pathogen by depicting lower propensity and toxicity compared to antibiotic.
Bacteriophages	Virulent phages have the ability to disrupt the cell membrane and eliminate the bacteria carrying resistant genes.
Use of conjugated antibiotics	Toxicity, bioavailability, short activity and efficacy are the major shortcomings of naturally occurring antibiotics. Use of conjugated antibiotics can eliminate the resistance forming pathways and can effectively deliver antibiotics to their target portion.

Table 1.
Procedures and their details for combating antimicrobial resistance [57].

been originated from the *Kluyvera* specie persisting in the environment. Most of the bacteria carry the ESBLs on their plasmid facilitating horizontal gene transfer while CTX-M is encoded on bacterial chromosome [56].

AMR is a challenging problem and tackling it is hard however, advances in the field of biotechnology and nano-technology have resulted in procedures which not only target resistant genes but can also be used for treating microbe associated diseases in animals [57]. Many of these procedures are described in **Table 1** given below:

4. Vaccination

Vaccination is an important component for the constructive management of cattle diseases. In-order to ensure effective vaccination of animals, knowledge about the pathogen, its disease-causing ability, host factors, immune status, stress and optimal vaccination timings should be taken into considerations [58].

For the management of respiratory diseases in cattle, modified live-virus vaccines are generally recommended. The live vaccines were available commercially since 1970s. Vaccination is considered to be effective considering it should be biologically active and stimulate active immunity against the pathogenic agent present in the vaccine. It should reduce the clinical illness, improve animal weight and should be economical with long-lasting immunity in commercial setting. However, the existing data suggests that the vaccine immunity gets compromised because during the transportation of animals, the release of pro-inflammatory factors put the animal under stress. Therefore, it would be beneficial to administer vaccine before animal shipment [58].

Excellent animal based surveillance studies along with vaccination might play a crucial role in the management of *Brucella* infection. In case of *B. meletensis*, the two commonly used vaccines are Rev1 and RB51. These vaccines do not interfere with the result of serodiagnosis and therefore can be used in the susceptible animal population for controlling *Brucella*-induced infection and relative abortions [47].

In veterinary virology, both live and killed vaccines are used for controlling livestock diseases, however their efficacy have been compromised due to new and re-emerging virus infections. Therefore, it is necessary to develop new vaccines containing prevailing serotypes and subtypes. Nano-particles have gained considerable fame in veterinary science due to their small size, large surface area and their ability to act as carrier vehicle for antigen delivery and immunogenicity [13]. In case of FMD infection, inactivated vaccines are used mostly but in order to initiate a protective immune response, a time period of almost 7 days is required. Therefore, in order to avoid such situation, silver nanoparticles were used as an adjuvant for the polyvalent inactivated FMD vaccines. Silver nano-particles have been shown to induce a much stronger humoral and mucosal immunity by enhancing interleukin production. Therefore, for long-lasting immunity, silver nanoparticles can be used as adjuvant in vaccine subunits [59]. Further, understanding the molecular mechanism of pathogen and their interaction with host and environment might also be beneficial for future vaccination studies.

5. Conclusion

Management is key to disease prevention and is utmost necessary for global and national food security and animal wellbeing. Dairy cattle and buffaloes play important role in economic development because of their milk and meat production

ability. However, livestock and dairy animals are vulnerable to variety of metabolic and infectious diseases, the introduction of new animal in the herd increases the likelihood of disease. Besides this, antimicrobial resistant strains are also circulating in the environment. The dissemination of antibiotics resistant genes in animals from the surrounding environment poses threat to animal in the form of abortion and reproductive disorder. Procedures to reduce the risk seem plausible. Many live and inactivated vaccines are administered to animals to protect them from diseases. However, these vaccines may not provide lifelong immunity Therefore, a comprehensive surveillance system and mass vaccination programs are needed in light of current dilemma to cope with the scenario.

Conflict of interest

The authors declare no conflict of interest.

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