REVIEW ARTICLE

The contribution of bovines to human health against viral infections

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Abstract

In the last 40 years, novel viruses have evolved at a much faster pace than other pathogens. Viral diseases pose a significant threat to public health around the world. Bovines have a longstanding history of significant contributions to human nutrition, agricultural, industrial purposes, medical research, drug and vaccine development, and livelihood. The life cycle, genomic structures, viral proteins, and pathophysiology of bovine viruses studied in vitro paved the way for understanding the human counterparts. Calf model has been used for testing vaccines against RSV, papillomavirus vaccines and anti-HCV agents were principally developed after using the BPV and BVDV model, respectively. Some bovine viruses-based vaccines (BPIV-3 and bovine rotaviruses) were successfully developed, clinically tried, and commercially produced. Cows, immunized with HIV envelope glycoprotein, produced effective broadly neutralizing antibodies in their serum and colostrum against HIV. Here, we have summarized a few examples of human viral infections for which the use of bovines has contributed to the acquisition of new knowledge to improve human health against viral infections covering the convergence between some human and bovine viruses and using bovines as disease models. Additionally, the production of vaccines and drugs, bovine-based products were covered, and the precautions in dealing with bovines and bovine-based materials.

Keywords Bovines · Bovine-based products · Contribution · COVID-19 · Human viruses · One medicine · Transchromosomic bovines

Introduction

Cattle belong to the *Cetartiodactyla* order of eutherian mammals, which is phylogenetically distinct from humans, the primates order (Murphy et al. 2004). Although cows aren't the closest animal to

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humans, human and cow DNA sequences are nearly identical (Zimin et al. 2009). Constructing a cattle–human comparative map using radiation hybrid (RH) mapping, a genetic technique for mapping mammalian chromosomes, revealed approximately 91% of the comparative coverage of the human genome sequence (Everts-van der Wind et al. 2005).

Bovines have significant contributions to human foods, industry, livelihood, medical research, and pharmaceutical development. Although there are differences between humans and bovines, the similarities between them are not tiny such as, but not limited to, a) the same approximate gestation period of 280 days between bovine and human (Schultz et al. 1973); b) the similar timing of the immune system development and fetal placentation (Baldwin and Telfer 2015), c) bovines respond in the same way, to a large extent, as humans to the viral infections such as respiratory syncytial virus (RSV) (McCluskey 2003); d) the factors of disease outbreaks in bovine populations and human settings are very similar such as poor hygiene, crowding, a high rate of individuals turnover in the facility, contaminated fomites, close contact, and compromised skin integrity (Lanzas et al. 2010); e) bovines and humans share many similar pathogens such as coronaviruses, papillomaviruses, babesiosis, tuberculosis and brucellosis (Haydon et al. 2002).

In the eighteenth century, the amazing work of Edward Jenner, the father of immunology, to vaccinate a boy with cowpox, as a prior infection, against smallpox rendered the boy immune to smallpox infection and paved the way for the vaccination in its current form (Kues and Niemann 2004). The development of the BCG vaccine (Waters et al. 2012), the tuberculin skin test and the interferon-gamma test (Wood et al. 1990), which were first introduced in cattle to prevent and diagnose bovine tuberculosis and later extended to humans, reflect the related accomplishments and discoveries in bovine and human immunology (Baldwin and Telfer 2015). Cattle and humans share various immune-physiological characteristics, including the in utero development of the immune system, which makes cattle an excellent model for human immunology (Baldwin and Telfer 2015). Unlike rodent models, cattle models have answers that improved our understanding of the immune system such as gamma delta ($\gamma\delta$)-T cells (Baldwin and Telfer 2015), but they also contributed to human health through beneficial clinical outcome (Hein and Griebel 2003). $\gamma\delta$ T cells are a special type of T cells that is found in many peripheral tissues such as lungs, but is uncommon in secondary lymphoid organs (Ribot et al. 2020). Animal models are central in the production and testing of vaccines and therapeutic drugs (Colby et al. 2017) and laboratory animals are the main animal models for studying specific aspects of human pathogenesis and immunity, especially mice (Lanzas et al. 2010). However, for the pathogen under study, mice are more often surrogate model than natural model. Additionally, laboratory animals are commonly used as organism-level models, but not to fix population-level issues. Bovines are considered excellent candidates, coupled with mathematical models, for population-level studies of infectious disease dynamics (Lanzas et al. 2010), and that is attributed to that humans and bovines share pathogens (Woolhouse and Gowtage-Sequeria 2005), in addition, as bovines are natural reservoir hosts/natural animal model for some human pathogens (Cleaveland et al. 2001; Kues and Niemann 2004; Buddle et al. 2005; Lanzas et al. 2010; Bem et al. 2011). Their advantage lies in their very complexity, which mimics the biologically relevant situation (of human disease) (Wiles et al. 2006) in addition to, as previously mentioned, the similar factors of disease outbreaks. Therefore, bovine populations as farm animals are able to provide experimental models (Lanzas et al. 2010), which is suitable for explaining the transmission of human infectious agents at the population level, their disease pathogenesis and the triggered immune response. In addition, the biological information can be gained at the level of organ or tissue from biopsies and autopsies samples, which can be carried out easily and regularly (Lanzas et al. 2010).

The movements of infected animals are considered a crucial factor in spreading cattle diseases (Gilbert et al. 2005), such as Foot-and-mouth disease (Gibbens et al. 2001; Bouma et al. 2003; Ortiz-Pelaez et al. 2006; Martínez-López

et al. 2008) and bovine virus diarrhea (Meyling et al. 1990; Gethmann et al. 2015). Cattle trade between cattle farmers occurs at a relatively high frequency creating a complicated network (Brzoska et al. 2020). Some European countries have built livestock movement databases, such as the Cattle Tracing System (CTS) data archive in Great Britain (England, Wales, and Scotland) (Gilbert et al. 2005), after bovine spongiform encephalopathy (BSE), commonly known as mad cow disease, investigations (Dubé et al. 2009). These data give richer information about pathogens dynamics and the benefits of these data exceed over than is typically available in wildlife or human systems (Lanzas et al. 2010).

To understand various diseases related to human health, bovines have been used as models for infectious (Hein and Griebel 2003; Lanzas et al. 2010) and non-infectious diseases, such as Niemann-Pick type C disease (Woolley et al. 2020). Cattle are one of the most used large animal models for acute respiratory distress syndrome (ARDS) (Ballard-Croft et al. 2012) and useful animal model for human respiratory pathogens such as Tuberculosis (Hewinson et al. 2003), *Chlamydia psittaci* infection (Reinhold et al. 2012; Ostermann et al. 2014), Human respiratory syncytial virus (Bem et al. 2011; Jordan et al. 2015), through studying pathophysiology and functional host-pathogen interactions in the mammalian lung and even developing immune-based approaches such as diagnostic tests and vaccines (Pollock et al. 2001, 2006), i.e., vaccines against human tuberculosis and RSV (Gershwin et al. 1998; Hewinson et al. 2003; Buddle et al. 2005; Taylor 2013; Gerdts et al. 2015). Cancer of the upper gastrointestinal tract in cattle (bovine papillomavirus (BPV)-4 and bracken fern) could act as models for the study of oncogenesis of papillomaviruses (Misdorp 1996), their molecular mechanisms (Cotchin 1962, 1976) and discovering novel therapeutics against (Misdorp 1996). The life cycle, genomic structures, viral proteins, and pathophysiology of bovine viruses studied in vitro paved the way for understanding the human counterparts such as Hepatitis C virus (HCV) that could not grow in cell culture (Buckwold et al. 2003).

Endemic stability is defined as the epidemiological condition of a population, despite high levels of infection in the population, clinical disease prevalence is low because immunity is acquired at a young age when the disease has milder manifestations (Coleman et al. 2001). Endemic stability has been developed previously to characterize tick-borne disease patterns in cattle (babesiosis and theileriosis in Australian and African cattle, respectively). Recently, the control procedures introduced for dengue virus (a viral disease spread by mosquitoes) were based on endemic stability (Egger et al. 2008).

Using oncolytic viruses for treating human cancers become one of the most interesting areas of research. Oncolytic bovine viruses such as Bovine herpesvirus type 1 (BHV-1) (Rodrigues et al. 2010), type 4 (BHV-4) (Farzani et al. 2021), and BVD (Marchica et al. 2020), could play a

promising role in this trend due to their tropism, selective replication only in tumor cells, and possible synergic interaction with other therapeutics. Other significant contributions of bovines to human health (Kues and Niemann 2004; Redwan 2009) are using (A) bovine insulin for treating diabetes mellitus; (B) bovine glucagon to prevent hyperglycemia; (C) Aprotinin, a bovine protein-based drug, during complex surgery such as heart and liver surgery for reducing bleeding; (D) bovine heparin in the treatment of thrombotic conditions in both medical and surgical indications; (E) gelatin extracted from bovines, worldwide approved, in several pharmaceutical products such as vaccines and drugs; (F) bovine hyaluronidase (Wydase= Amphadase) as an adjuvant (spreading agent) to increase the absorption and dispersion of the injected drug and (G) Pancreatin (food grade), commercial mixtures of amylase, lipase, and protease extracted from bovine pancreas, to treat malabsorption syndrome due to certain pancreatic problems (Redwan 2009).

Here we review some examples of human viruses and their bovine counterparts, elucidating the contribution of bovine virology and immunity to human virus research and human health in addition to the use of bovines as disease models (Table 1).

DNA viruses in bovines and humans

Bovine and human papillomaviruses (BPV and HPV)

BPV and HPV are members of the *Papillomaviridae* family, non-enveloped icosahedral structures, small circular ds DNA, 55–60 nm in diameter, 8000 base pairs, and are able to infect all vertebrates (Crawford and Crawford 1963; Campo 1988; Bernard et al. 2010). Their genome is made up of three different regions; long control region (LCR) or upstream regulatory region (URR) without ORFs, and the other two regions are responsible for encoding early (E1–E8 ORFs) and late (L1 and L2 ORFs) genes (Borzacchiello 2007; Alberti et al. 2010). Replication and transformation are regulated by the early genes (E1, E2, and E4). Capsid proteins are encoded by the two late genes (L1 and L2), and LCR has the origin of replication (ori) (Bogaert et al. 2007; Van Doorslaer 2013; Bocaneti et al. 2016) (Table 2). Expression of early and late genes occurs in epithelial cells in early maturation and differentiated keratinocytes, respectively.

Papillomaviruses (PVs) are one of the world's oldest viral families (Rector and Van Ranst 2013) that infect a wide range of hosts. They are originated in Africa then spread to all continents over one million years (Bernard 1994). Over 280 types of PV are categorized into 35 genera (de Villiers 2013; Rector and Van Ranst 2013). To date, roughly 170 types of HPV have been categorized and classified into five genera; *Alpha*, *Beta*, *Gamma*, *Mu*, and *Nu*-papillomavirus (Rector and Van Ranst 2013), and around 24 pathotypes of BPV have been described and categorized into four genera; *Xi*, *Delta-*, *Epsilon*, and *Dyoxi*-papillomavirus (Roperto et al. 2019). Although the actual numbers of HPV and BPV types may exceed 200 and 30, respectively. Most PV infections are asymptomatic without visible clinical signs. PVs are commonly found on the clinical normal skin of humans (Doorbar et al. 2012).

In 1981, Zur Hausen et al. explained that the etiologic agent of most cervical cancers is papillomavirus (zur Hausen et al. 1981). Cervical cancer is a serious malignancy that is considered the major cause of mortality among women (Bosch et al. 2002). Around 500,000 patients and 250,000 deaths globally occur per year with cervical cancer (Arbyn et al. 2011) and 85% of cervical cancer cases occur in developing countries where 75% of the world's population lives (Marrazzo and Holmes 2013). The HPV is suspected that is the possible etiologic agent of other human cancers as oropharyngeal, anal,

Table 1 Bovine contribution to the scientific research field

Human viruses	Contributions (Outputs)
Human papillomavirus (**HPV**)	- Transformation
	- Latency mechanisms
	- Vaccine development
Human lymphotropic T cell virus (**HLTV-1**)	- Leukemogenesis
	- Antiviral drugs
Hepatitis virus C (**HCV**)	- Antiviral drugs
Human immunodeficiency virus (**HIV**)	- Broadly neutralizing antibodies
Human parainfluenza virus 3 (**HPI3**)	- Vaccine development
Human rotaviruses	- Vaccine development
Human respiratory syncytial virus (**HRSV**)	- Pathophysiology and immunobiology
	- Vaccine development
Human coronaviruses (**HCoV**)	- Bovine-derived human polyclonal IgG
	- Immune milk

Table 2   Summary of PV proteins

Replication proteins

E1   - Recognition of origin of replication (ori).
     - binds to E2 protein, resulting in E1-E2 complex.
     - participates in the recruitment of host cell replication proteins.
     - exhibits intrinsic ATPase/helicase activity.

E2   - Acts as E6 and E7 transcriptional regulator.
     - participates in the maintenance of the viral genome in its episomal form by promoting binding between these genomes and mitotic chromosomes during cell division.

E4   - The most expressed protein of PVs and an important hallmark of PVs' pathogenic activity.
     - occurs abundantly in the cytoplasm of the differentiated keratinocytes of papillomas.
     - Unlike E1 & E2, E4 is produced later in the differentiation process.
     HPV16 E4 has also been associated with the collapse of cytokeratin filaments, which thus suggests an auxiliary function in the process of viral exit from cells.

Oncoproteins

E5   - Can induce both *in vivo* and *in vitro* transformation.

     - The major BPV oncoprotein.
     - Disrupt the Golgi complex leading to Inhibiting the expression of MHC-I and cyclooxygenase (COX). (An evolutionary mechanism of immune evasion).
     - Bind to PDGFR ending with promoting cell cycle deregulation, stimulating angiogenesis.
     - interferes with normal gap junctions.
     - disturbs the actin cytoskeleton.
     - increases the motility of transformed cells.
     - Disrupting the cell cycle during a productive BPV infection.
     These mechanisms contribute to viral infection persistence
     - Most of the tumors of cattle affected by enzootic hematuria express BPV2 E5.
     - **HPV E5** has weak transforming activity, in contrast to its bovine counterpart, BPV1 E5, which shows strong transforming activity.

E6   - A small oncoprotein without enzymatic activity.
     - Characterized by the presence of a class I PDZ domain, (found in BPV and high-risk HPVs).
     - BPV and HPV E6 oncoprotein promotes p53 downregulation.
     - Inducing cell transformation and immortalization due to the up-regulation of telomerases.
     - BPV E6 protein binds paxillin, which correlates with its transformation function.
     - prevents apoptosis by degrading p53.
     - prolongs cell life by telomerase activation.
     - binds to PDZ domains within several proteins involved in cell polarity, proliferation, and signaling.

E7   - binds to proteins of the retinoblastoma family (RB),
     - regulate the expression of genes during the S-phase of the cell cycle.
     - binds and degrades key regulators of cell cycling, including retinoblastoma protein (pRb), p107, and p130.

Capsid proteins

L1   - used in PVs virus classification into different types (able to self-organize in pentameric structures that compose the viral capsid).
     - Allowing the capsid anchorage to heparin sulfate receptors present in the cell membrane.
     - L1 immunodetection has been considered the main evidence of productive infection, (the virus assembly).
     - C-terminal of L1 plays a cardinal part in BPV's infection and immunogenicity.
     - produce VLPs that identical to that of intact viral particles.
     - Strongly immunogenic inducing production of neutralizing antibodies.

L2   Component of the viral capsid.

Virus-like particles (VLPs) can be produced using prokaryotic and eukaryotic systems to express a combination of L1 and L2 or L1 alone

L3   A third structural protein (L3).
     Present exclusively in BPV-4. However, its function remains unclear.

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penile (Parkin 2006), lung, breast, bladder (Tolstov et al. 2014), and esophageal cancers (Dillner et al. 1995; Lagergren et al. 1999; Syrjänen 2002; Lyronis et al. 2005; Vieira et al. 2013). Therefore, it can be said that 30% of all human cancers are caused by HPV (Bravo et al. 2010). In 1982, Syrjänen was the first who explained that there is a relationship between HPV and esophageal cancer (Syrjänen 1982). Esophageal cancer is the world's sixth cancer that causes death (Antonsson et al. 2010; Herbster et al. 2012), and its mortality rate is 25% greater than that of cervical cancer (Han et al. 1996).

Although majority of BPVs were detected in cutaneous papillomas hitherto (Daudt et al. 2018), BPV also causes esophageal, gastrointestinal, and bladder cancers. Death may be the inevitable end of these cancers (Borzacchiello and Roperto 2008; Kumar et al. 2015). In 1959, Olson, et al. (Olson et al. 1959) were able to induce urinary bladder cancer in calves by injecting bovine wart extracts. In 1992, it was reported that bladder cancers consistently developed in cattle that were fed bracken fern (Campo et al. 1992), leading to enzootic hematuria, and the role of E5 oncoprotein of BPV-1, 2, 13, and 14 was detected in bladder cancers (Wosiacki et al. 2006; Balcos et al. 2008; Roperto et al. 2016; Russo et al. 2016). Consumption of bracken fern also predisposes the incidence of esophageal carcinoma (Masuda et al. 2011), which is directly associated with BPV-4 infection (Borzacchiello et al. 2003; Masuda et al. 2011). The clinical signs of esophageal carcinoma in humans (Felin et al. 2008; Haster and Owyang 2013) are similar to those in bovines (Borzacchiello et al. 2003). Immunosuppression is the most common identified cofactor for HPV–induced cancers (Chaturvedi et al. 2009). Also, BPV causes papillomas (Fig. 1) that can transform into cancers due to enhancing cofactors (biological, immunological, environmental, and genetic) (Roperto et al. 2008). These cofactors delay the infection clearance and subsequently promoting malignancy. Although PVs are species-specific, cross-species infection by BPV1 and 2 was recorded in equine species (Campo 2006), giraffe, sable antelope, buffaloes, and yaks (Pangty et al. 2010; Van Dyk et al. 2011; Bam et al. 2013). BPV-5, besides BPV-1, and -2, were found in ruminal wart-like lesions in buffaloes and cattle (Kumar et al. 2015). Feline sarcoid-associated papillomavirus DNA was also amplified from four bovine fibropapillomas and five inflammatory skin lesions that are homologous to BPV-2 with non-productive infection (Teifke et al. 2003; Munday and Knight 2010). All the previous cross-species infections by BPV confirm the hypothesis that cattle may be the natural host of feline sarcoid-associated papillomavirus (Munday and Knight 2010).

The similarities between BPV and HPV were reported based upon the phylogenetic analyses (García-Vallvé et al. 2005). BPV1 virion has a very similar structure to HPV1 (Baker et al. 1991). Unlike the two early proteins in HPV E6 and E7, E5 is expressed during BPV replication in cattle (Campos et al. 2013). The possibility of using HPV E6 and
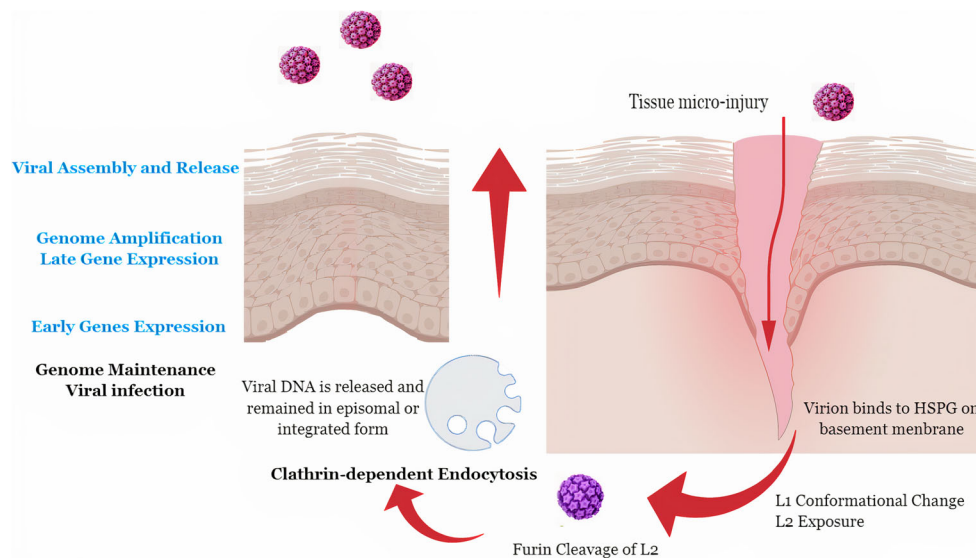

Fig. 1 Papillomavirus life cycle. Viral lodgment starts from tissue micro-injury (because these viruses cannot actively penetrate the skin of their host), but other routes were reported as infected lymphocytes (viral hematogenous infection to the skin or urinary bladder), infected semen, and infected milk. After tissue micro-injury, heparin sulfate proteoglycan (HSPG) receptors that present on the basement membrane (BM) provides access to the basal keratinocytes, are exposed to L1 binding leading to conformational changes in capsid icosahedral structure, exposing the L2 N-terminal to be cleaved by extracellular furin protein that presents in the cell membrane inducing a second capsid conformational change, allowing L2 to bind to different receptors, such as integrin 24. Viral entry; virions internalization by clathrin-dependent endocytosis mechanism, resulting in cytoplasmic vesicles that associate to lysosomes, the lysosomal acid content release promotes pH alterations in capsid proteins, resulting in viral DNA release. BPV genome is found in episomal form and HPV genome can integrate into fragile sites of the host genome. Differentiation triggers the production of the PV early proteins that force the suprabasal cell to reenter the S-phase of the cell cycle resulting in cell cycle continuation. Amplification process: PVs induce the S-phase entry because they do not codify polymerase, stimulating cell proliferation, and inducing mitotic stress. As a result, many cell cycle checkpoints are abrogated. Consequently, an accumulation of mutations resulting in cytogenetic aberrations and progression into cancer occurs in cells that are persistently infected by these viruses. The productive infection occurs within the terminal differentiation and keratinization of an infected cell. PV late genes expression and viral assembly occur close to the cell surface and viral particles are released only after the epithelial cell sloughing from the epithelial surface and not by causing cell lysis. Thus, the viral life cycle is completed without directly causing cell death and without systemic viremia

E7 in humans as a vaccine has been discussed (Borysiewicz et al. 1996; He et al. 2000; Yao et al. 2013), based on the therapeutic action of BPV E6 and E7 (Campo 1997). The single skin lesion in cattle could contain different BPV types (Claus et al. 2009; Carvalho et al. 2012; Kumar et al. 2013) as in human skin lesions, co-infection by different HPV types have been frequently detected (Antonsson et al. 2000). BPV plays a pivotal role as a model for HPV studies and vaccine development (Borzacchiello and Roperto 2008). Understanding the complicated interaction between HPV and human cancer has been shown by studies of BPV-associated lesions and BPV-infected cell lines. Based upon the ability of BPV to transform cells (Meischke 1979), it facilitates understanding the pathogenic mechanisms that lead to cancer (Araldi et al. 2016) and subsequent development of protective HPV vaccines and vaccine biotechnology (Munday 2014). Immunity to PV infection was principally studied using the BPV model (Dvoretzky et al. 1980), but developing a HPV vaccine followed the HPV16 and BPV1 L1 expression in insect cells (Zhou et al. 1991). The most important feature of L1 alone is having the intrinsic capacity for the assembly of virus-like particles (Kirnbauer et al. 1992). Not only for L1-based vaccine but also, L2-based vaccine demonstrated its protective effect in cattle, reinforcing the use of L2 in the future as a second vaccine against HPV infections (Lunardi et al. 2013), and may be used as a prophylactic and multivalent vaccine due to its cross-neutralizing epitope (Campo and Roden 2010).

Cervarix and Gardasil are the available prophylactic virus-like particles (VLP) vaccines against HPV with acceptable safety and tolerance (Ribeiro-Müller and Müller 2014). L1 VLP vaccine is a prophylactic vaccine and has no therapeutic effect in humans (Koutsky et al. 2002; Vandepapelière et al. 2005; Hildesheim et al. 2007). The immunity produced by L1 or L2 VLP-based vaccines can be mediated only by neutralizing antibodies (Gambhira et al. 2007; Day et al. 2008, 2010; Schiller et al. 2010) or with an extra contribution by T cell–mediated response (Jarrett et al. 1991). The disadvantages of PV vaccines are the limited protection for certain PV types and the high cost of production. An alternative way to yeast and insect-cell is using *Escherichia coli* for expression of recombinant protein for vaccine production because *E. coli* do not require L1 VLP and is more stable (Ribeiro-Müller and Müller 2014). Another trend is using prostate cancer antigen, BPV VLP vaccines in transgenic adenocarcinoma of the mouse prostate (TRAMP), which showed safety and efficacy exceed over other vaccines. This vaccine is nominated to be used for patients in active-surveillance or patients with a high-risk of localized prostate cancer (Simons et al. 2020).

RNA viruses in bovines and humans

Bovine leukemia virus (BLV) and human T cell leukemia virus type-1 (HTLV-1)

A century passed between the discovery of bovine leukemia virus (BLV) and human T cell leukemia virus type 1 (HTLV-1) (Leisering 1871; Gallo 2005). In 1979 and 1980, HTLV-1 was recovered from many people who suffered from adult T cell leukemia (ATL) (Poiesz et al. 1980a, b). HTLV-1 was established as the first retrovirus directly relevant to malignancy in humans (reviewed in (Matsuoka and Jeang 2007)). Worldwide, HTLV-1 infected 10–20 million people (Proietti et al. 2005), and it is endemic to some areas in Africa, Japan, and the Caribbean (Watanabe 2011).

Although enzootic bovine leukosis (EBL) was first reported in 1871 (Leisering 1871), most BLV infections in cattle are asymptomatic. Typical bovine leukemia has two forms; sporadic bovine leukosis and EBL (Gillet et al. 2007). The only route of BLV transmission is contact with infected cells through wet proboscis of insects because the free viral particles are unstable and inefficient in the infection phase (Cuesta et al. 2018). BLV-infected cattle are typically infected for life due to viral maintenance through clonal expansion of infected lymphocytes (Lezin et al. 2009). One of the common features of BLV-induced leukemogenesis is p53 mutation that occurs within the host genome and consequently, the essential p53 functions are disturbed (Ishiguro et al. 1997; Zhuang et al. 1997; Tajima et al. 1998). BLV may pass with a self-attenuating process to escape from immunosurveillance (Gillet et al. 2007) so, no direct detection of BLV viruses or proteins in peripheral blood (Lagarias and Radke 1989; Jensen et al. 1991).

Gag, pro, pol, and env are basic retrovirus genes (Fig. 2) that used to produce infectious virions and are flanked by two identical Long terminal repeats (LTRs) (Aida et al. 2013). The two identical LTRs are responsible for viral replication (Aida et al. 2013). The pX is a unique sequence present in both BLV and HTLV-1 genome between the env gene and 3′ LTR. pX is neither a host cell nor an oncogene. In vitro immortalization of primary cells has been confirmed for both viruses (Grassmann et al. 1989; Willems et al. 1990). For both viruses, the surface unit (SU) and transmembrane unit (TM) proteins are encoded by env gene and their functions are accomplishing binding and attachment to cellular membrane receptors during viral entry (Lairmore 2014). Due to the common features in their structure, BLV and HTLV-1 viruses were grouped into a new single group (genus *Deltaretrovirus*) in the retroviruses family (Gillet et al. 2007). Both viruses share genomic similarities, routes of transmission, and similar pathogenesis (Lairmore 2014) (Fig. 3). In the pX region, two regulatory proteins, Tax and Rex, are encoded (Aida et al. 2013). The BLV pX region encodes R3 and G4 proteins and the HTLV-1 pX
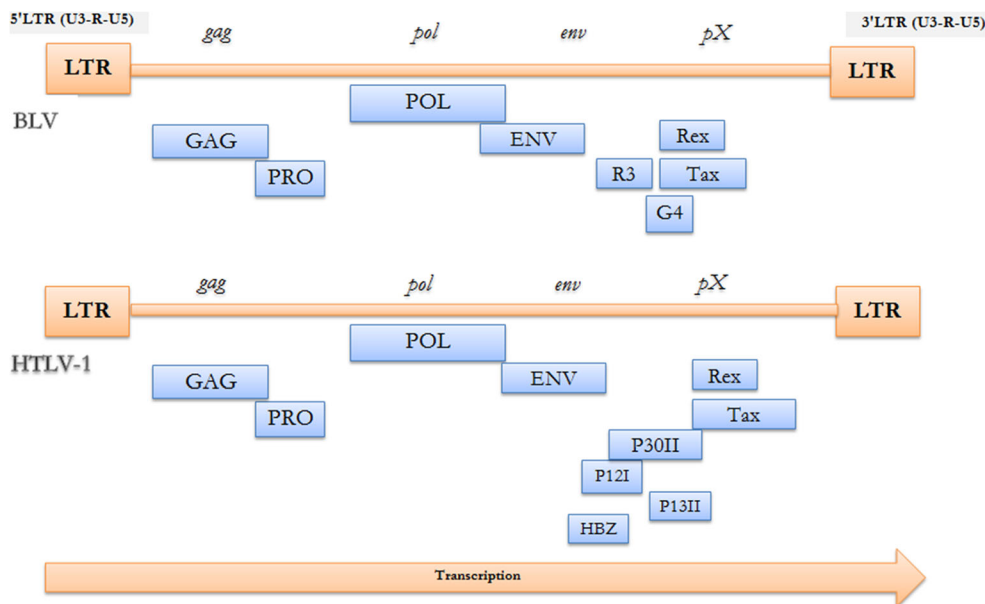
Fig. 2 Summary of BLV and HTLV-1 genes and their precursors and proteins produced (structural and enzymatic). Gene: Gag, Precursor: Pr44gag, Proteins: P15/MA (bind the genomic viral RNA - interact with the lipid bilayer of the viral membrane - proteolytically processed to generate three fragments: p10, a seven amino acids product, and p4) - P12/NC (Tightly bind to the packaged genomic RNA) - P24/CA (The major constituent of the capsid (CA) of BLV virions - The major target for the host immune response). Gene: Pro (Prt), Precursor: pr66gag-prt, Proteins: p14/Prt (Protease). Gene: Pol, Precursor: Pr145, Proteins: P80/RT+IN (contains all of the tryptic peptides of the gag-protease precursor - encodes reverse transcriptase (RT), (RNA dependent DNA polymerase). Gene: Env, Precursor: Pr72env, Proteins: Gp51/SU (The extracellular SU is very immunogenic, a useful tool for diagnostics and vaccine development) - Gp30/TM (The TM transmembrane protein is a key factor in cell fusion during transmission and is involved in signal transduction via immunoreceptor tyrosine-based activation motifs (ITAM) present in the cytoplasmic tail). Gene: pX, Precursor: Tax ORF, Proteins: Tax (p34) (Transcriptional activator of viral expression - target of the host immune response with T and B epitopes - Oncogenic potential - Activation of NF-kappa B (NF-κB) pathway - Inhibition of DNA repair of oxidative damage, increase accumulation of mutations in cellular DNA - Induction of DNA damage, cellular senescence and apoptosis - directly binds to tristetraprolin (TTP), a post-transcriptional modulator of TNFα expression – regulate many cellular proteins by direct binding) - Rex (p18) (Nuclear export of viral mRNAs - post-transcriptional regulation) - R3 (p5) (The maintenance of high viral load) - p12I (Maintenance of viral infectivity - Activation of nuclear factor of activated T cells (NFAT) pathway) - G4 (p11) like p13II (The maintenance of high viral load - Oncogenic potential) - p13II (Suppression of viral replication - Interaction with farnesyl pyrophosphate synthetase - Activation of Ras-mediated apoptosis) - p30II (Suppression of viral replication - Regulation of gene transcription by binding with p300 - Enhancement of Myc transforming potential) - HBZ (Inhibition of HTLV-1 transcription - suppression of the classical pathway of NF-κB - Enhancement of TGF-β signaling - Oncogenic potential)

region encodes p12I, p13II, and p30II (Sagata et al. 1984; Franchini et al. 2003). Unlike BLV genome, the HTLV-1 genome encodes a unique gene HBZ by the minus strand chain for basic leucine zipper factor (Gaudray et al. 2002), suggesting that the Tax protein has a crucial role in inducing the BLV leukemogenesis. In oncogenesis, the Tax protein affects the repair mechanisms for damaged DNA that contribute to an accumulation of mutations (Aida et al. 2013). So, BLV or HTLV-induced tumors take many years to appear after the first contact with these viruses.

Recently, Tax protein gained the attention of most researchers because of the belief in its key role in leukemogenesis for both BLV and HTLV-1 (Katoh et al. 1989; Tanaka et al. 1990; Willems et al. 1990). In addition, it is the key protein involved in viral replication (Aida et al. 2013). Tax is structurally distinguished by the presence of amino-terminal zinc finger and by a leucine-rich activation domain (Chen et al. 1989; Tajima and Aida 2000), and any alterations or substitutions entirely in them stop tax's transactivation

activity. For both BLV and HTLV-1, the Tax gene is also highly conserved indicating the importance of the encoded Tax protein for virus replication and spread (Lairmore 2014). VLP were generated in mammalian cells by gag polyprotein overexpression (Callahan et al. 1976; Wang et al. 2004) providing a way to produce VLP-based vaccines similar to PVs vaccines.

The cross-reactivity between BLV and HTLV-1 capsid antigens (CA) is based on the common epitope BLV p24 (Morgan et al. 1983; Zandomeni et al. 1991), suggesting an evolutionary relationship between BLV and HTLV-1. BLV p24 and viral DNA were discovered in bovine mammary tissue, in which researchers have looked into the possibility of the presence of BLV in humans in the same tissue (Buehring et al. 1994). Also, an immune cross-reaction was found between the nucleocapsid (NC) proteins of BLV and feline leukemia virus (FeLV) (Morgan et al. 1983), suggesting that the bovine is the natural host of this virus (Lairmore 2014) and transmitted to human afterward. Viral expression in cultured
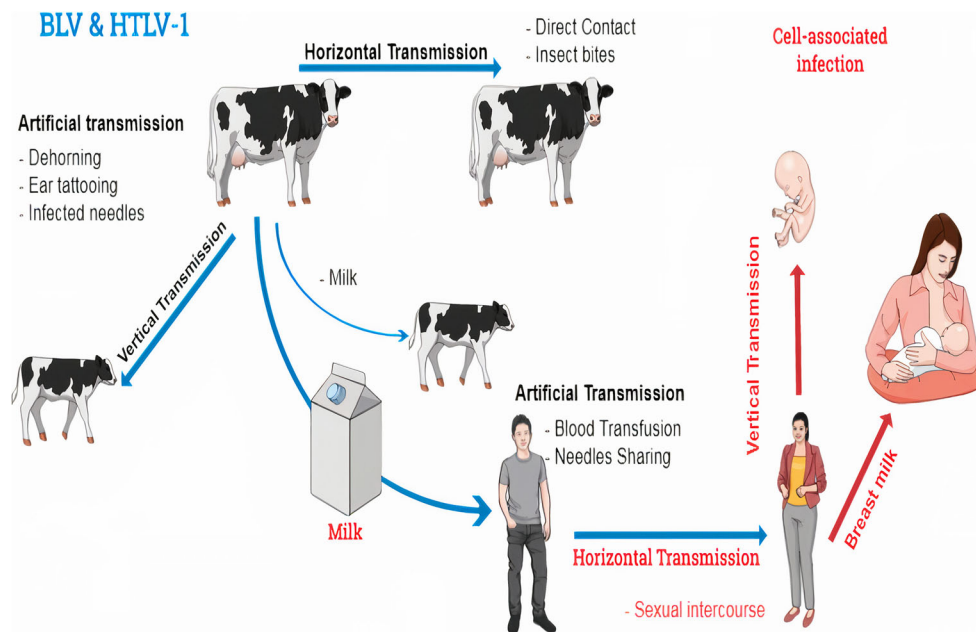
Fig. 3 BLV life cycle. BLV can be transmitted between bovines via horizontal and vertical transmission. Milk and insects play a role in BLV transmission. As well, HTLV-1 could be transmitted via horizontal and vertical transmission. Milk, sexual intercourse, and blood transfusion are routes of HTLV-1 transmission. Transfer of infected maternal lymphocytes to offspring is a natural transmission route of both BLV and HTLV-1. So, efficient transmission for both BLV and HTLV-1 requires cell-associated infection. The anti-BLV antibodies were clearly identified in the human serum. That is awakened the idea of a possible zoonotic disease. BLV might be transmitted to humans through unpasteurized milk or undercooked meat when bovine products were uncontrolled. Then, BLV had transmitted from person to person, like HTLV in body fluids once the virus was integrated into the human host genome. Both BLV and HTLV-1 infections are prevalent throughout the world. BLV was isolated from breast tissues. Designing eradication plans and improving preventive strategies are mandatory when the link between BLV and breast cancer is confirmed

BLV-infected B-lymphocytes increased through deacetylation inhibition by histone deacetylase inhibitors in vitro (Achachi et al. 2005). This observation has served as a basis for increasing the virus-infected cells in HTLV-1 patients using histone deacetylase inhibitors to create targets for immune-mediated elimination. In vitro antibodies from some leukemic cattle can inhibit the reverse transcriptase activity (Gillet et al. 2007). Although nucleoside triphosphate analogs are potent inhibitors against human immunodeficiency virus reverse transcriptase (HIV-RT), they are ineffective against reverse transcriptase of BLV (Perach and Hizi 1999). The BLV model has also recently shed light on novel possibilities for HTLV-induced disease treatments (Gillet et al. 2007).

Bovine viral diarrhea virus (BVDV) and hepatitis C virus (HCV)

HCV is the world's most common cause of chronic hepatitis that progresses to end-stage liver diseases, such as cirrhosis and carcinoma (Liang et al. 2000). HCV is a *Flaviviridae* virus that belongs to the genus *Hepacivirus*. It was first identified in 1989 (Choo et al. 1990; Houghton 2009). Although HCV infection is often asymptomatic, it is estimated that 150 million chronic HCV infections, and over 350,000 deaths each year from HCV-associated liver disease (Choo et al. 1990; Liang et al. 2000; Houghton 2009). It is worth mentioning that numbers of HCV infections increase by millions every year worldwide (Mohd Hanafiah et al. 2013). So, the need for finding a therapy for HCV is most urgent than a vaccine. Most patients in developing countries are devoid of new medicines, and safe vaccines are still not available (Drummer 2014; Pawlotsky 2014). BVDV belongs to the genus *Pestivirus* from the *Flaviviridae* family. Many clinical diseases in bovine species are caused by BVDV including respiratory, digestive, and reproductive manifestations (Baker 1995). Cytopathogenic and non-cytopathogenic biotypes of BVDV were identified based on their impact on host cells (Mendez et al. 1998).

BVDV and HCV are small, enveloped, positive-stranded RNA viruses encoding a single polyprotein precursor that is subsequently translated into ten different proteins by proteases from both the host and the virus. All proteins are encoded in a single, long ORF flanked by 5′ and 3′ untranslated regions with the structural proteins in the N-terminal end and the nonstructural proteins at the C-terminal end (Poole et al. 1995; Popescu et al. 2011). The 5′ terminus of the BVDV genome is not capped as in the HCV genome, and the start of translation is regulated by an internal ribosomal entry site (Poole et al. 1995). In the region encoding for the two heterodimer-forming envelope proteins gp25 (E1) and gp53 (E2) of BVDV polyprotein, there are six potential N-glycosylation

sites and in the region encoding for gp48 (E0) (a hydrophilic secreted protein of unknown function), there are eight potential N-glycosylation sites (Zitzmann et al. 1999).

BVDV utilizes the low-density lipoprotein (LDL) receptor to enter cells like HCV. Both viruses use a functionally identical internal ribosome entry site (IRES) for translation and an NS4A cofactor with its homologous NS3 serine protease. Both have a similar NS3 helicase/NTPase, a mechanistically similar NS5B RNA-dependent RNA polymerase, and a seemingly equivalent mechanism of virion maturation, assembly and egress (Buckwold et al. 2003).

Due to the high degree of similarity (Isken et al. 2007), BVDV has been most widely used in vitro as a surrogate model for understanding HCV replication (Weiskircher et al. 2009) and the discovery and development of anti-HCV agents because HCV does not replicate efficiently in cell cultures (Henzler and Kaiser 1998; Bhattacharyya et al. 2003; Buckwold et al. 2003; Yanagida et al. 2004; Romero et al. 2006; Zhang et al. 2010). To date, no HCV vaccine is available. Of the anti-HCV drugs, Interferon (IFN) and Ribavirin are available, but a combination of both is an expensive therapy and also induces several side effects (Bhattacharyya et al. 2003; Yanagida et al. 2004). The nonstructural protein 5B (NS5B) of BVDV has been formally validated as a target for antiviral drug discovery against HCV (De Clercq 2007). Consequently, HCV NS5B RNA-dependent RNA-polymerase (RdRp) is currently the most studied and used as a target for developing safe anti-HCV drugs. HCV NS5B RdRp is attractive for drug discovery due to its vital role in viral replication and the lack of RdRps in humans (Baginski et al. 2000; Paeshuyse et al. 2006; Puerstinger et al. 2007). The HCV p7 protein is necessary for HCV infectivity (Sakai et al. 2003) and is considered a pivotal target for anti-HCV therapy. Long-alkyl-chain iminosugar derivatives with antiviral activity against BVDV could inhibit the ion channel role of the p7 protein (Pavlović et al. 2003). Similarly, the small molecule BIT225 inhibits BVDV in vitro (Luscombe et al. 2010). 2′-C-methyl-cytidine showed an inhibitory activity against BVDV, and later showed to inhibit HCV RNA replication in the replicon assay (De Francesco and Migliaccio 2005). NM-283 (Valopicitabine) is an oral prodrug of 2′-C-methyl-cytidine, was synthesized for obtaining a molecule with higher oral bioavailability than its parent molecule, 20-C-methyl-cytidine (Pierra et al. 2006). NM-283 is now being evaluated in phase II clinical trials for the treatment of chronic HCV infection (Tian et al. 2021).

BVDV, as a non-human pathogen virus, can interact with human CD46 and can cause apoptosis to human myeloma cells showing its specific oncolytic activity for multiple myeloma (MM) cells and is a possible alternative to the human viruses, such as measles virus and adenovirus, for an oncolytic approach in MM treatment (Marchica et al. 2020).

Discovery of novel HCV-like viruses in many hosts began after 2011, indicating the widespread of *Hepaciviruses* (Kapoor et al. 2011; Baechlein et al. 2015; Scheel et al. 2015; Hartlage et al. 2016). In 2015, Ghana and Germany reported the first cases of bovine *Hepacivirus* (BovHepV) (Baechlein et al. 2015; Corman et al. 2015). BovHepV is a hepatotropic virus such as HCV without an obvious zoonotic risk (Baechlein et al. 2015). Establishment of BovHepV as a novel HCV model (Baechlein et al. 2015) is based on the chronicity and high viral loads in the liver of infected cattle. More interest is demanded in investigating the zoonotic potential of BovHepV and its impact on human health (Baechlein et al. 2015).

Bovine and human immunodeficiency viruses (BIV and HIV)

HIV was discovered in 1983. It was identified as the cause of acquired immunodeficiency syndrome (AIDS) after being isolated (Barré-Sinoussi et al. 1983; Gallo et al. 1983). After a period of the belief that the human oncovirus HTLV-III was the causative virus of AIDS (Popovic et al. 1984), it was eventually renamed HIV-1 and taxonomically separated from HTLV. HIV killed over than 35 million since epidemic (Vemuri et al. 2020).

In 1969 during research on bovine leukosis in Louisiana, USA, bovine immunodeficiency virus (BIV), first designated bovine visna-like virus, was accidentally detected and isolated from infected Holstein cow (Van Der Maaten et al. 1972). BIV is a member of the *lentivirus genus*, subfamily *Orthoretrovirinae* from the *Retroviridae* family (King et al. 2011). BIV triggers a chronic infection in buffalo and cattle. BIV does not cause a specific disease, but it may cause immunosuppression in calves (Zhang et al. 1997). BIV infects the immune system cells mainly, monocytes/macrophages and lymphocytes (Gonda et al. 1987).

BIV is morphologically, genetically, and antigenically closely related to HIV-1 (Gonda et al. 1987). BIV R-29 isolate was demonstrated that it is very similar to HIV (Gonda et al. 1985, 1986, 1987). Both BIV and HIV-1 genomes contain the structural genes *gag*, *pol*, *env*, and several accessory genes, including *tat*, *rev*, *vif*, *vpw*, *vpy*, and *tmx* (Avidan et al. 2006). The genes *vif, Tat*, *gag*, *pol*, and *env*, of BIV and HIV-1 have some sequence similarity (Bhatia et al. 2013). BIV causes chronic inflammatory disease compared to HIV-1 that causes severe immunodeficiency (Bhatia et al. 2013). Moreover, in certain cases, BIV may be used as a surrogate animal model for HIV research (Bhatia et al. 2013).

Calves experimentally infected with BIV R-29 isolates displayed intermittent lymphocytosis and lymphadenopathy without any obvious clinical indications (Carpenter et al. 1992; Onuma et al. 1992; Suarez et al. 1993). Virus-specific antibodies found in calves against BIV R-29 strain (Whetstone et al. 1990) were primarily to p26, which is the most immunodominant

protein of BIV (Abed et al. 1999). Also, cattle infected with BLV produced antibodies that can inhibit HIV-1 reverse transcriptase activity in vitro (Gillet et al. 2007).

Advances in understanding the viral life cycle are focused on endeavors to discover and develop anti-HIV drugs (De Clercq 2007). The key activator of viral gene expression is the Tat protein, which mediates a strong induction of the development of all viral transcripts by binding specifically to its cognate site, the transactivator response factor (TAR). Previous research on BIV Tat peptidomimetics contributed to the discovery of BIV2, a highly effective BIV Tat-TAR inhibitor. Using NMR techniques, the structure of BIV2 complex with BIV TAR was determined. Furthermore, the BIV Tat-TAR interaction was used as a model in discovering related peptidomimetic inhibitors of the Tat-TAR interaction in HIV-1 via exploiting the important information about RNA recognition, derived from the BIV Tat-TAR interaction (Athanassiou et al. 2007).

Since they can deliver the new gene by infecting the cell, viruses are often used as vectors. When used in humans, the viruses have been modified so that they do not cause disease. Vectors derived from BIV are an appealing alternative to those derived from HIV-1 (Matukonis et al. 2002) as virus-based gene transfer system.

Recombinant virus-like particles (VLPs) have been developed as a safe substitute to live or inactivated viruses for immunological, virological, and vaccine studies such as influenza virus-like particles (Bright et al. 2007; Pushko et al. 2007; Quan et al. 2010; Lua et al. 2014). Influenza VLPs comprised of hemagglutinin (HA), neuraminidase (NA), and matrix (M1) proteins. The gag of BIV (Bgag), in place of M1, can be used to prepare VLPs for several influenza subtypes (Tretyakova et al. 2016). Quadri-subtype H5/H7/H9/H10 VLPs were prepared using Bgag, which may be used as a first line of defense in the event of an outbreak involving H5, H7, H9, or H10 avian influenza viruses while a new vaccine against the culprit virus is being developed (Tretyakova et al. 2016).

Interestingly, Cows were immunized with HIV env produced potent broad neutralizing antibodies with long heavy-chain complementarity-determining region 3 (HCDR3), which can easily attack the CD4-binding site (CD4bs) on the Env trimer, but the situation in humans is different. Also, the pace of developing a broadly neutralizing antibody (bnAb) to the CD4bs of HIV Env in cows is noteworthy when compared with the length of time taken to generate equivalent antibodies in humans by natural infection (over five years) (Sok et al. 2017).

Bovine and human parainfluenza viruses 3 (BPIV-3 and HPIV-3)

HPIV-3 is the etiologic agent of lower respiratory tract diseases. It belongs to genus the *Respirovirus* from the *Retroviridae* family and is closely related to BPIV-3

(Welliver et al. 1986). Currently, no vaccine or drug was developed for the treatment of HPIV-3 (Hall 2001; Durbin and Karron 2003; Bartlett et al. 2007). BPIV-3 is one of the reasons for bovine respiratory disease complex (BRDC) (Snowder et al. 2006), whose immunosuppressive action results in severe bronchopneumonia due to bacterial co-infection, especially in stressed animals (Haanes et al. 1997). BPIV-3 belongs to genus the *Respirovirus* of *Paramyxoviridae* family (Adams et al. 2016). Approximately 25 % of both viruses are antigenically related by cross-neutralization (van Wyke Coelingh et al. 1988). The hemagglutinin–neuraminidase (HN) and fusion (F) proteins of BPIV-3 and HPIV-3 share more than 75% of their amino acid sequences. (Bailly et al. 2000), and the two viruses share at least five neutralization epitopes on the HN and F proteins (Coelingh et al. 1986; Klippmark et al. 1990). Furthermore, between BPIV-3 and HPIV-3, the major viral nonglycoproteins N, M, and L are greater than 85 % related (Pennathur et al. 2003).

Attenuated BPIV3 is utilized as a virus vector backbone to produce a safe, effective RSV vaccine (Haller et al. 2003). BPIV-3 is used to enhance both humoral and cellular immunity as a live virus vaccine in human beings against HPIV-3 disease based on the similarity between the two viruses. Neutralizing antibodies against HN and F play a key role in resistance to HPIV-3. In phase 2 clinical trials, a live-attenuated BPIV-3 vaccine was intranasally administered simultaneously with other routine vaccines (Greenberg et al. 1999; Lee et al. 2001) to infants aged 2, 4, and 6 months, a booster immunization at 12–15 months of age showed safety and well tolerance of BPIV-3 in infants.

In human clinical studies, another live-attenuated HPIV-3 vaccine candidate was developed by reverse genetics that yielded a recombinant BPIV-3 (rBPIV-3), phenotypically similar to the bioderived BPIV-3 (Haller et al. 2000, 2001). Furthermore, the growth in serum-free (SF) Vero cells of BPIV-3, r-BPIV-3, or B/HPIV-3, chimeric bovine/human parainfluenza virus type 3, did not affect vaccine yield, viral replication, immunogenicity, or efficacy in primates (Pennathur et al. 2003).

Bovine and human rotaviruses (BRV & HRV)

In 1969, rotavirus (RV) had been discovered in diarrheic cattle (Mebus et al. 1969). Rotavirus multiplies in the intestinal epithelium leading to malabsorption, which causes severe diarrhea and toxemia (Organization 2009). Rotaviral diarrheas are common in calves and could cause death due to severe dehydration or secondary bacterial infections (Holland 1990; Saif 1990; Chauhan and Singh 1996). BRV is considered economically important and zoonotic pathogens (Parashar et al. 2006). In 1973, RVs were first identified as a significant cause of acute gastroenteritis in babies and young children (Bishop et al. 1973; Flewett et al.

1973). Every year, RV cause around one hundred million cases of hospitalizations and deaths of children less than 5 years of age worldwide (Parashar et al. 2003, 2006).

Developing countries are likely to have the largest share of RV-caused deaths for socioeconomic and epidemiological reasons (Angel et al. 2007). Rotavirus-specific serum IgA levels typically correlate with intestinal IgA levels following natural infection in children (Franco et al. 2006), and rotavirus T cell responses are associated with the development of protective antibodies (Offit et al. 1993).

Rotaviruses are a member of the *Reoviridae* family, which is an 11-segment, double-stranded RNA genome with non-enveloped, icosahedral symmetry (Estes and Cohen 1989; Pesavento et al. 2006). Six structural proteins are present, which constitute three concentric layers. The viral genome is surrounded by the inner layer and contains the scaffolding protein VP2, the RNA-dependent RNA polymerase VP1 and VP3 (a guanylyl transferase and methylase). The intermediate layer, which is a major structural protein, is made of VP6. The neutralizing antibodies are the targets of two virus surface proteins, VP4 and VP7, and either antibody can mediate defense. Six nonstructural proteins (NSP1–6) are formed in infected cells. Once VP4 is cleaved by intestinal trypsin, VP5* and VP8* are formed (an asterisk is to denote post-translational product), and interact with cellular receptors inducing infection.

Gene reassortment occurs at high frequency when two rotaviruses co-infect the same cell producing progeny viruses with mixed genes from both parental strains (Greenberg et al. 1981), with evidence for the zoonotic potential of animal rotaviruses to humans, leading either to a reassortment between animal and human rotaviruses circulating in humans (Gentsch et al. 2005) or causing disease (Martella et al. 2006; Matthijnssens et al. 2006). The generation of RV group A genomic diversity principally is caused by the reassortment (Estes and Greenberg 2013). The same evolutionary origin was proposed for bovine strains A5-10 and A5-13, and human DS-1-like strains (Komoto et al. 2016). Reassortment events between bovine and human RV group A strains may have produced the bovine strains A5-10 and A5-13 (Komoto et al. 2016).

In addition, rotaviruses generally exhibit substantial host-range restriction (HRR), in which most human rotaviruses are highly attenuated in 'heterologous' animal hosts and vice versa (Angel et al. 2007). Based on gene reassortment and HRR, RotaShield and RotaTeq vaccines were developed (Angel et al. 2007). Both vaccines have been licensed in many countries.

RotaTeq vaccine has been designed to contain various serotypes to which a child could be exposed. It is a pentavalent vaccine consisting of five rotavirus strains, which are all derived from a parental WC3 bovine rotavirus strain and carry a gene from rotaviruses of human origin (a gene encoding VP4 or VP7) (Perez-Schael et al. 1997; Vesikari et al. 2006). The WC3 bovine virus grows well in vitro, but in contrast to Rotarix, the human rotavirus, is excreted by less than 6% of children (Vesikari et al.

2006). Induction of neutralizing serotype-specific antibodies was the gold standard for measuring immunogenicity to the RotaTeq vaccine (Clark et al. 2006).

Bovine and human respiratory syncytial viruses (BRSV and HRSV)

In 1970, BRSV disease was described in cattle for the first time (Paccaud and Jacquier 1970). BRSV causes a major respiratory disease in young calves resulting from seasonal outbreaks globally (Valarcher and Taylor 2007; Gershwin 2007). Cattle could be infected with HRSV (Thomas et al. 1984). In most veterinary researches, BRSV has been discussed in the context of bovine respiratory disease rather than from a human-centered perspective (Bem et al. 2011).

HRSV is considered an important cause of respiratory tract disease in humans (Ruuskanen and Ogra 1993). HRSV causes community outbreaks due to its stable transmission all the year-round reaching the peak during the winter months (Yusuf et al. 2007). The disease affects children under six months of age, frequently leads to hospitalization, often in intensive care for mechanical ventilation (Everard and Milner 1992), or causes the death of neonates and children in the presence of risk factors such as congenital heart defects and asthma. Also, more than 33 million infections, more than 3 million hospitalizations, and almost 200,000 deaths are in children under the age of 5 years per year (Nair et al. 2010). Not only children, but the elderly and adults could also be infected with HRSV (Falsey et al. 2005). HRSV infection in children is an immunologic process (interaction between the virus and the serum antibody). So, vaccine-induced serum antibody without local respiratory antibody does not protect against HRSV illness (Kim et al. 1969).

BRSV and HRSV are members of the genus *Pneumovirus*, the family *Paramyxoviridae*, are enveloped viruses with a negative-sense, non-segmented RNA genome and a length of 15,000 nucleotides. Virions have the same structure as each other, consisting of a nucleocapsid enclosed in a lipid envelope. The viral genome encodes eight structural proteins; the surface glycoproteins G, the fusion proteins F, the small hydrophobic SH protein (three viral transmembrane proteins), the nucleoprotein N, the phosphoprotein P, the transcription processivity factor M2-1, and the large polymerase subunit L (four nucleocapsids/polymerase proteins), and the matrix protein that presents on the inner face of the envelope (M). Two unique nonstructural proteins (NS1 and NS2) are present in high levels in infected cells (Easton et al. 2004). SH protein acts as a strong antiapoptotic protein and the function of G and F proteins is the binding and entry of HRSV and BRSV (Fuentes et al. 2007) into the host cell. Both viruses are genetically and antigenically closely related. Bovines play a dual role in HRSV researches as an animal model or alternative animal pneumovirus model, i.e., BRSV (Bem et al. 2011).

Animal models are heavily used in the search for new medicines and vaccines for HRSV disease, in vivo pathophysiological and preclinical efficacy tests for potential therapies and vaccines. Animals are a significant link between studies of tissue culture and human phase I trials (Bem et al. 2011). Due to ethical and practical reasons besides, the scare in autopsy and biopsy findings with severe HRSV disease in humans make our knowledge about pathogenesis in humans is minimal. BRSV in calves could be used as a model to study the pathogenesis and immunity of RSV because calves are large animals allowing screening of the immune response by body fluids' collection and analysis of mucosal immune responses. Vaccines against RSV are available in cattle but not in humans till now (Meyer et al. 2008). To date, no HRSV vaccine is available for infants because of the absence of an animal model, the need for immunization of young infants, the risks in use of live vaccines, and the risk of vaccine-associated disease (Meyer et al. 2008). The subunit vaccines were yielded after intensive research on the HRSV vaccine which has been evaluated in animal models, such as calves (Blodörn et al. 2014; Taylor et al. 2014), and under clinical trials in humans (Green et al. 2015; Taylor et al. 2015; August et al. 2017; Beran et al. 2018). Studies conducted on laboratory animals generally, not refer to or extend to humans and cattle (Siegrist 2001; Rudd et al. 2005; Murawski et al. 2009; Willcocks et al. 2013). The RSV vaccines seemed to be efficacious in rodents, but they have not worked in humans (Guzman and Taylor 2015).

In contrast to infection that occurs without prior vaccination, vaccine-enhanced disease (VED) occurs when a person who has received a vaccine develops a more severe type of the disease when exposed to the virus afterward. VED phenomenon is also reported with other viruses (Huisman et al. 2009) such as measles and SARS-CoV-1.

In the 1960s, vaccination trials of children with formalin-inactivated RSV (FI-RSV) vaccine not only elicit protection against RSV infection but also provoke enhanced morbidity and mortality in vaccines (Knudson et al. 2015) and termed as enhanced respiratory syncytial virus disease (ERD). Surprisingly, ~80% of the vaccinated children experienced serious disease and were hospitalized after acquiring a natural RSV infection, as compared to only ~5% of a control group (Fulginiti et al. 1969; Kapikian et al. 1969; Belshe et al. 1982). RSV infection in children who have previously received a FI-RSV vaccine is linked to increased disease and pulmonary eosinophilia, which is thought to be caused by an overactive memory Th2 response (Castilow et al. 2007). To date, no only single mechanism is responsible for VED, the potential mechanisms involved in this phenomenon are humoral ADE, cellular CD4 activation, DC/trans, and aberrant T-cell response (reviewed in (Huisman et al. 2009)).

The same scenario that occurred in calves when vaccinated with FI-BRSV vaccine showed that the vaccine-induced disease phenomenon is due to enhancing a Th2 mediated immune response (Gershwin et al. 1998; Kalina et al. 2004). So, calf vaccinated with FI-BRSV vaccine was used as a model of vaccine enhanced respiratory syncytial virus pathophysiology (Gershwin et al. 1998) in children. This model enabled researchers to produce RSV vaccines besides understanding RSV immunobiology (Gershwin et al. 1998). The innate immune response in calves is activated by RSV infection, which results in the production of pro-inflammatory cytokines and chemokines (Das et al. 2005; Valarcher and Taylor 2007; Sacco et al. 2012; Gershwin 2012). BRSV- and HRSV-infected macrophages and epithelial cells produce Interleukin 1 beta (IL-1β) (Werling et al. 2002; Bermejo-Martin et al. 2008; Fach et al. 2010; Taylor et al. 2014), which orchestrates the pro-inflammatory response enhancing interferon-gamma (IFN γ) production.

RSV infection is detected by various pattern recognition receptors (PRR) such as RIG-I receptors, Toll-like receptors (TLR), and nucleotide oligomerization domain (NOD)-like receptors, inducing the production of type I IFN that in turn have antiviral effects on neighboring non-infected cells (Saminathan et al. 2019). RSV, on the other hand, is more resistant to type I IFN's antiviral effects than other paramyxoviruses (Atreya and Kulkarni 1999; Schlender et al. 2000). Both the cellular antiviral responses and IFN induction are suppressed by the action of NS1 and NS2 of both human and bovine RSV (Schlender et al. 2000; Bossert et al. 2003; Ling et al. 2009). In calves, tumor necrosis factor-alpha (TNF-α) production differs according to the age (Antonis et al. 2010) besides the deficiency in TNF-α production by monocytes in newborns in response to TLR agonists, indicating the less serious RSV disease in babies and calves under a month of age (Levy 2007).

It is suggested that BRSV and HRSV NS proteins possess common mechanisms and cellular targets, and the NS proteins of both viruses showed a protective activity (Bossert and Conzelmann 2002). The two viral nonstructural proteins, NS1 and NS2, enable BRSV to escape from the cellular responses to IFN-α/β. A chimeric BRSV with HRSV NS genes (BRSV h1/2) showed a differential IFN escape capacity in cells from different hosts, providing a basis for the rational development of live-attenuated RSV vaccines (Bossert and Conzelmann 2002).

HRSV and BRSV infection does not cause life-long immunity, and re-infection is usually subclinical (Van der Poel et al. 1994). HRSV and BRSV diseases share many features, such as similarity in disease development depends on age (Van der Poel et al. 1994; Grell et al. 2005; Antonis et al. 2010), unique lung histopathology (Bennett et al. 2007), BRSV co-infection with bacteria, such as *Mannheimia* and *Haemophilus* species (BRDC) (Srikumaran et al. 2007). It was also recorded that the significant similarities in the lung structural features with the overlapping clinical symptoms of respiratory disease

(Kirschvink and Reinhold 2008). In temperate climates, both viruses cause annual winter respiratory disease outbreaks (Stott and Taylor 1985). The highest incidence of serious disease is in infants and calves under six months of age, and the majority of infections are to those 1–2 years of age (Stott and Taylor 1985). BRSV and HRSV replicate primarily in ciliated airway epithelial cells and type II pneumocytes (Viuff et al. 1996; Johnson et al. 2007; Welliver et al. 2008), and stimulate a variety of pro-inflammatory cytokines and chemokines (Valarcher and Taylor 2007; Bermejo-Martin et al. 2008; Rosenberg and Domachowske 2012), which direct the expression of cellular adhesion molecules and recruitment of neutrophils beside lymphocytes to the lung, resulting in bronchiolitis and interstitial pneumonia.

Bovine and human coronaviruses (BCoV/HCoV)

Coronaviruses (CoV) are single-stranded positive-sense RNA, 26 to 32 kb, enveloped, pleomorphic, 60 to 220 nm in diameter viruses, containing the spike (S) glycoproteins, approximately 12 to 25 nm in length (Saif et al. 2019). The subfamily *Coronavirinae* contains the four genera *Alpha-*, *Beta-*, *Gamma-*, and *Deltacoronavirus* (Corman et al. 2018). Coronaviruses (CoV) are common human and bovine pathogens, cause many infections such as enteric, respiratory, and neural infections. BCoV causes respiratory and enteric infections in cattle (Clark 1993) while HCoV isolate OC43 the causative agent of common cold in humans. In 1937, avian infectious bronchitis (IB) was the first characterized coronavirus (El-Sayed and Kamel 2021). Human coronaviruses (HCoV) were identified in the 1960s and later, the bovine coronavirus (BCoV) in the 1970s (El-Sayed and Kamel 2021). To date, seven different CoVs have been identified in humans. HCoV-OC43 (McIntosh et al. 1967) and -229E (Hamre and Procknow 1966) were isolated for the first time in the 1960s. HCoV-NL63 (Van Der Hoek et al. 2004) and -HKU1(Woo et al. 2005) were discovered only in 2004 and 2005, respectively. Three epidemic CoVs have emerged in humans in the last 2 decades, severe acute respiratory syndrome (SARS)-CoV, the Middle East respiratory syndrome (MERS)-CoV and severe acute respiratory syndrome 2 (SARS)-CoV-2 discovered in 2003, 2012 and 2019, respectively (Drosten et al. 2003; Zaki et al. 2012; Zhou et al. 2020).

Bovine coronaviruses (BCoV) and human coronavirus OC43 (HCoV-OC43) belong to the family *Coronaviridae*, order *Nidovirales,* subfamily *Coronavirinae*. O-acetylated sialic acid or similar derivative are recognized by HCoV-OC43 and BCoV as cell receptors (Vlasak et al. 1988) for viral binding and entry, and they are usually transmitted through the fecal-oral or respiratory route. On the contrary, SARS coronavirus and human coronavirus 229E (Matrosovich et al. 2015). BCoV is closely related to respiratory HCoV isolate OC43, they shared 95% genetic identity, suggesting that BCoV is an ancestor of human CoV-OC43 (Vijgen et al. 2005), or alternatively, they might have arisen from a common ancestor (Hasoksuz et al. 2007). Molecular clock analysis of genome sequences suggested that HCoV-OC43 originated from a zoonotic transmission event of a bovine coronavirus (BCoV) and dated their most recent common ancestor between the 1890s (Vijgen et al. 2005, 2006) and the 1950s (Lau et al. 2011). That is what led Vijgen et al. to theorize that the 1889-1890 "Russian flu" pandemic may have resulted in SARS-like interspecies transmission event, owing to the extensive depopulation of cattle herds between 1870 and 1890, which was associated with the highly pathogenic bovine respiratory disease (Greger 2007). BCoV, as a useful virus model, is paradigmatic of how CoVs are able to cross the interspecies barriers, establishing its derivatives as separate viral lineages affecting the respiratory and/or enteric tract of humans (HCoV-OC43), swine (Porcine Hemagglutinating Encephalomyelitis Virus; PHEV), horses (equine coronavirus, ECoV), and dogs (canine respiratory coronavirus, CRCoV) (Decaro and Lorusso 2020), and that may be attributed to the accumulated genetic diversity of BCoVs (Zhang et al. 2007).

The global pandemic of Coronavirus Disease 2019 (COVID-19) has now infected nearly 160 million people worldwide, resulting in over 3.3 million deaths (WHO, 2021). Since its etiologic agent, SARS-CoV-2, was isolated and identified in early January 2020, the entire scientific community has been hardly working to find an effective cure and develop a vaccine to control the pandemic (Dhama et al. 2020a; Izda et al. 2020). Animal spillover and cross-species jumping events of SARS-CoV-2 have been identified, and zoonosis is being investigated (Dhama et al. 2020b; Tiwari et al. 2020; Sharun et al. 2021). Respiratory BCoV shares some common features with SARS-CoV and SARS-CoV-2, such as BCoV has a broad host-range (interspecies transmission) including wild ruminants, zoonotic potential, and respiratory and gastrointestinal tropisms (Saif and Jung 2020). Passive immunity in humans via the consumption of bovine immune milk (bovine immunoglobulins) has been studied for tens of years. Short-term protection against COVID-19 could be provided in humans as a result of drinking microfiltered immune milk from cows that were immunized against SARS-CoV-2 (Jawhara 2020). Colostrum or antibodies-rich milk from cows can be used to treat human diseases caused by viruses and bacteria (Hurley and Theil 2011; Saied and Metwally 2019), such as SARS-CoV-2 (Jawhara 2020; Batista da Silva Galdino et al. 2021).

Transchromosomic bovines (TcB) offer a promising platform for the production of rapidly-produced fully human polyclonal immunoglobulin G (IgG) in large amounts for inhibition of Middle East Respiratory Syndrome coronavirus (MERS-CoV) in vivo (Luke et al. 2016). Only one MERS-CoV neutralizing antibody (nAb) isolated from Tc has been evaluated in phase I trials (SAB-301) (Zhou et al. 2019),

which showed safety and well tolerability in humans (Beigel et al. 2018). Interestingly, in a recent study, TcB was used to produce a polyclonal, fully human, anti-SARS-CoV-2 immunoglobulin (Liu et al. 2021) after hyperimmunization of TcB twice with plasmid DNA encoding the SARS-CoV-2 Wuhan-Hu-1 strain Spike strain S gene (Wu et al. 2020), then repeatedly immunized with S protein purified from insect cells. The resultant anti-SARS-CoV-2 immunoglobulin was termed SAB-185 and efficiently neutralized SARS-CoV-2, and vesicular stomatitis virus (VSV) SARS-CoV-2 chimeras in vitro (Liu et al. 2021).

Bovine-derived products

Antibodies have been used in the therapy of infectious diseases since the late nineteenth century, in which von Behring and Kitasato have worked on using serum therapy for treating diphtheria and tetanus (Behring 1890). For more than a century, polyclonal immunoglobulin-based medicinal products have been used successfully to treat virus-caused illnesses. Many components in bovine milk have immunomodulatory and antimicrobial properties (Ulfman et al. 2018). For viral pathogens, immunized bovines give polyclonal IgG molecules which were shown to be effective in prophylaxis for human viruses such as HIV, human simplex virus (HSV), and SARS-CoV-2.

Cows that were immunized by a single Env trimer immunogen, generated bovine broadly neutralizing antibodies (bnAbs) with the characteristic long heavy-chain CDR3 loops to HIV (Sok et al. 2017). it has been suggested that bovines have the advantageous ability to generate super-antibodies against other human pathogens (Walker and Burton 2018). Colostrum from cows vaccinated with conventional bovine rotavirus vaccine, displayed antibodies with in vitro anti-human rotavirus activity (Civra et al. 2019). bIgG promotes adaptive antiviral T cell responses and protects against RSV infection in vitro and in vivo. Therefore, purified bIgG can be added to infant formulas to pass some of the beneficial effects of raw bovine milk to microbiologically stable infant formulas (Nederend et al. 2020), which not undergo heat treatment to avoid reducing the protective effect of bovine milk (Mainer et al. 1997; Loss et al. 2015). Bovine lactoferrin (BL), protein found in cow milk, indirectly reduces human norovirus infection via inducing the innate interferon responses (Oda et al. 2021) and has a therapeutic potential against SARS-CoV-2 (Batista da Silva Galdino et al. 2021). Additionally, BL is an effective modality against Zika and Chikungunya viruses (Carvalho et al. 2017). Lactoferrin may be useful in reducing the cytokine storm associated with severe COVID-19 infection (Kell et al. 2020), inhibiting the SARS-CoV-2 binding to the host cells (Kell et al. 2020).

In 1998, transgenic cattle were produced (Chan et al. 1998; Cibelli et al. 1998), and in 2002, transchromosomal cattle were used to produce human polyclonal antibodies (hPABs) as useful therapeutic agents (Kuroiwa et al. 2002) via introducing human artificial chromosome (HAC) vector into bovine primary fetal fibroblasts using a microcell-mediated chromosome transfer (MMCT) approach. Human albumin serum (HAS), a human plasma protein, was produced in the mammary gland of transgenic cattle (Kues and Niemann 2004) and entered phase I trials for production of recombinant human serum albumin (rHSA) in humans. When transchromosomic bovines (TcB) were vaccinated, fully human IgG produced that does not need enzymatic treatment to prevent anaphylactic reaction and serum sickness associated with heterologous species IgG. Furthermore, human IgG from TcB has a longer half-life and retains the effector functions associated with the Fc, removed by enzyme treatment. Human IgG from TcB also provides medical products based on polyclonal immunoglobulin without the need for human donors or inactivated/attenuated vaccine antigens (Hooper et al. 2014). Transchromosomal cows have also been used to rapidly generate fully polyclonal neutralizing antibodies to MERS-CoV, Hantavirus, Venezuelan equine encephalitis virus, and Ebola virus (Hooper et al. 2014; Dye et al. 2016; Luke et al. 2016; Gardner et al. 2017; Beigel et al. 2018), showing the feasibility of using this platform to develop therapeutics to tackle emerging viral threats. Perhaps the first step in the road to mAb isolation from TcB has been done through yielding both polyclonal (SAB-100) and monoclonal (53C10) antibodies produced from the transchromosomic (Tc) cattle platform against influenza viruses. 53C10 mAb was capable of neutralizing diverse clades of the hemagglutinin-1 (H1) subtype indicating its potential role in treating H1 influenza virus infection in humans (Gao et al. 2020). The transgenic technology in bovines would solve many disadvantages of biopharmaceutical products such as immunogenicity, biosafety, cost-competitive (Redwan 2009), and production of therapeutic antibodies on a large scale. Transgenic cattle act as a novel model for infectious and non-infectious diseases. A novel glycosylated anti-CD20 monoclonal antibody was produced in the milk of transgenic cattle demonstrated superior efficacy over Rituxan, the first therapeutic recombinant monoclonal antibodies (mAb) to treat non-Hodgkin lymphoma (Grillo-López et al. 1999), against B-cell lymphomas in severe combined immunodeficiency mice (Zhang et al. 2018). Antibodies produced in TcB could solve the respiratory viruses-associated antibody-dependent enhancement (ADE) phenomena (Weingartl et al. 2004; Tseng et al. 2012). Recent studies showed that the anti-SARS-CoV-2 antibodies (antibody-based vaccines) could increase the severity of COVID-19 (Arvin et al. 2020; Lee et al. 2020) and multiple viral infections such as RSV (Graham 2016) and measles (Polack 2007) through ADE, which results in failed vaccine trials.

Concerns and precautions

Pathogens infecting livestock can come from wild animals as an infection or re-infection (Gortázar et al. 2007; Conner et al. 2008) and viruses, in particular, few RNA viruses such as MERS-CoV and Hendra virus (Cunningham et al. 2017), are the main and the most recently emerged pathogens of wildlife (Dobson and Foufopoulos 2001; Pedersen et al. 2007) (Fig. 4). Many newly identified human virus species have been found in humans for a considerable time but have only recently been recognized (Woolhouse and Gaunt 2007). Viruses undergo a biological evolution according to the evolutionary history of life. But, at the time of their discovery, an interesting question will arise: where these viruses firstly originated in animals or humans? More than half of pathogens that infect humans can infect other hosts (Woolhouse and Gowtage-Sequeria 2005), and most pathogens in farm animal populations are in human communities (Pearce-Duvet 2006; Lanzas et al. 2010). The high population densities of farm animals result in increased rates of pathogen transmission, acting as sources for emerging viruses for humans (Cleaveland et al. 2001; Morse et al. 2012). Human pathogens (189 (13.5%) of 1399) are viruses (~81% RNA viruses and ~19% DNA viruses), but in the last 40 years, there is an increase in the novel viruses much faster than other pathogens (Woolhouse and Gaunt 2007) especially in presence of new technologies (Morales-Sánchez and Fuentes-Pananá 2014). Twenty-three percent of all malignancies in humans are associated with pathogenic organisms (Organization 2003; zur Hausen 2009;

Brücher and Jamall 2014), mostly viruses (Ewald and Swain Ewald 2015). Bovines are one of the most common animal species that are directly or indirectly responsible for transmitting infections from animals to humans (Baechlein et al. 2015). In addition to being an important food source, this is due to their high population density and diversity in communication with humans and other species (Lu et al. 2018). Most non-human milk consumed by humans comes from cows, as this animal is used extensively in commercial production. Bovine meat consumption comes in the third rank after pig meat and poultry, respectively. Antimicrobial-resistant pathogens through food intake (meat or milk), direct contact with patient animals, waste management, and the use of manure as fertilizer, can be transmitted from cattle to humans (Marshall and Levy 2011). Interestingly and according to the phylogenetic studies, cattle were also recipients of parasites and microbes that spread from humans (Morand et al. 2014).

Concerns about using bovine materials from infected with bovine spongiform encephalopathy-infected cattle (BSE), such as bone, serum, and tissue of the nervous system, which could transmit the infectious agent to people, where Creutzfeldt-Jakob (CJD) disease could be caused. The benefit of vaccination outweighs the potential risk of vaccine contamination (Marwick 2000). Also, the same concerns are about using of vaccines, produced on allogeneic cell lines in humans (Benedictus and Bell 2017), and colostrum-containing dietary supplements (Kasonta et al. 2014) from PregSure-treated cows, PregSure is an inactivated BVD vaccine for cattle, but their risk for the reaction of transmitting alloantibodies, that
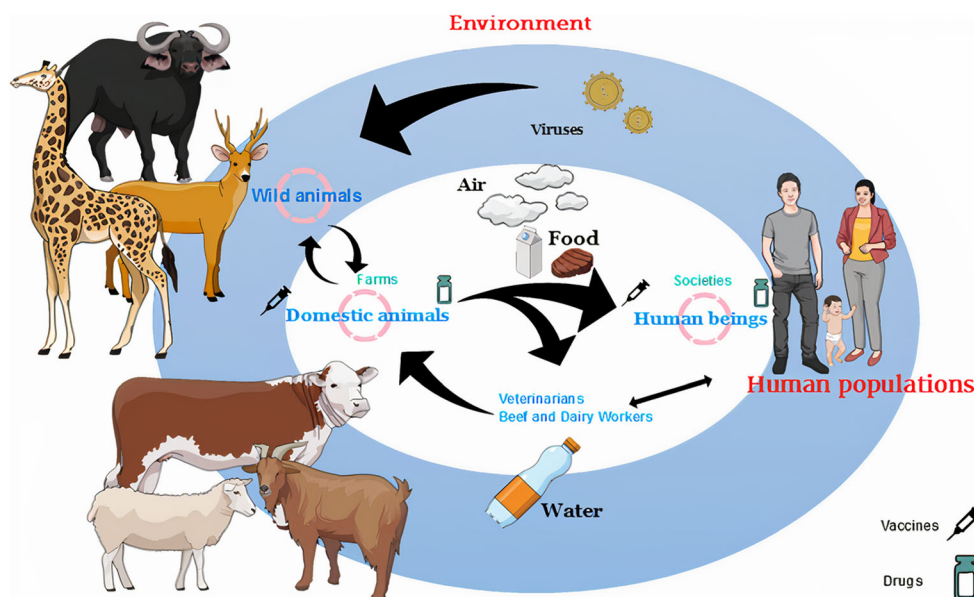

Fig. 4 The possible ways of transmission of viruses. Viruses are present around in the environment as inactive microbes where the life cycle of viruses begins after entering the living body. Wild animals are reservoir hosts for many emerging viruses, and bovines play an important role in the spread of viruses from wildlife to a human directly or indirectly. Furthermore, the air, water, and food are other routes of transmission of viruses besides the anthropogenic activities leading to pathogen spillover. Vaccination of farm animals, including bovines, is the strategy for improving animal health and protecting human health, and medicines are valuable and urgent against diseases that do not possess vaccines until now

responsible for developing bovine neonatal pancytopenia (BNP) in cattle, to human lymphoblasts is not totally scientifically confirmed.

Conclusion

"And there is no creature on (or inside) the earth or a bird that flies with its wings except (that they are) nations like you." (Cattle 38), the Noble Quran (Saied and Metwally 2019). Although there are differences between bovines and humans, the similarities are not tiny or far. The convergence of human health with animal health, under the concept of One Health, opens a new dimension in this era for solving and controlling many urgent topics. The idea of exploiting certain bovine characteristics to learn about human viral infections is gaining widespread application. Bovines can make significant, rapid contributions to better understand and improve therapies for human viral infections. "In our battle with microbes, we have a number of weapons in our armamentarium" Dr. Anthony S. Fauci said, is one of the world's leading experts on infectious diseases. Viral diseases are an important challenge to the health of the public worldwide. Unfortunately, most viral diseases are often asymptomatic in humans and cattle; the need for survey by using advanced technologies in diagnosis is a prompt need. All that suggested the presence of zoonotic diseases but in a hidden mask. Scientists are striving to find out drugs and vaccines due to the urgent need to combat viral diseases, especially in their speed pace.

Bovine could be used for, via their immunization with a specific human virus, the production of broadly neutralizing antibodies, in serum and colostrum of bovines, against human viruses such as HIV, MERS-CoV, and Hantavirus (reviewed in (Saied and Metwally 2019)) besides using transchromosomic (TcB) bovines as a platform for producing human polyclonal and monoclonal antibodies as a therapeutic modality to combat emerging viral threats such as MERS-CoV, Hantavirus, Venezuelan equine encephalitis virus, influenza virus, and Ebola virus, and provides a possible strategy for developing passive immunotherapy against coronaviruses such as SARS-CoV-2. Bovine viruses-based vaccines such as RotaTeq vaccine and a live-attenuated BPIV-3 vaccine were showed their safety and well tolerance in humans and infants at the age of 12-18 months. Other human vaccines that are based on bovine viruses have shown promising results. As well recent studies reported using bovine viruses-based therapies such as BVD in treating MM and BPV in treating prostate cancers.

Prevention of transmission of zoonotic pathogens from the bovine-derived products into the clinical application into human health is a crucial aspect that requires sensitive and reliable screening methods. Associated with the somatic cloning technology, conditional gene expression, and gene targeting will make cattle non-susceptible to spongiform encephalopathy (BSE), and give the scientists the chance to create useful bovine models for human diseases and as preclinical testing for vaccines. Exclusion of colostrum collected from PregSure-treated cows for colostrum powder manufacturing should be taken into account (Kasonta et al. 2014). Overall, bovines and their products showed promising outputs that warrant further research to clarify their contribution to this field and against other viruses such as influenza viruses and COVID-19. Future work including bovine viruses for vaccine development and TcB as a platform for the generation of human poly and mono antibodies against human viruses is crucial. This review is the first of its type that describes some human viruses for which bovines have contributed to their combating, offering different aspects of benefits from using bovines against human viral infections. We are sure the review topic will reshape the recent future.

Data availability All data related to this publication are made available in the article.

Declarations

Ethics approval This manuscript does not contain any studies with animals performed by any of the authors.

Consent for publication This manuscript does not contain any studies with human participants performed by any of the authors.

Consent to publish This article has the consent of all the authors and authors have no conflicts of interest.

Competing interests The authors declare no competing interests.

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