Human Viruses: Infection, Prevention and Potential Target(s) for Therapy – A Comprehensive Review

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Abstract It is well known that most pathogenic viruses cause acute, chronic and co-infections that lead to pathogenesis and progression and manifestated as various human diseases. Viral diseases mainly AIDS, Zika, Ebola, severe acute respiratory syndrome (SARS), Middle east respiratory syndrome (MERS), influenza and pneumonia of various forms are the biggest cause of mortality and disability in both developed and developing countries. Also certain infectious viruses have the potential to cause cancers in humans. Taken together, the known, unknown and novel viral diseases associated with cancers represent a major global public health challange for social well-being, economic stability, quality human health, productivity and progress. The threats posed by viral diseases mainly depend on the continued emergence, re-emergence of new and novel pathogenic viruses with varied pathogenecity and severity. Chronic infections contribute to as high as 26% of cancer cases in developing countries, only about 11 out of millions of microbes and chemical agents around us have been declared as human carcinogens. In the past few years, several new and highly pathogenic viral infections, that affect humans, have emerged and majority are of zoonotic origin. Thus, monitoring these zoonoses and other novel viruses with unidentified origins required, advanced efforts for increased awarness and the efficient global research co-ordination for

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pursuance of effective approaches for prevention and the control of diseases remains crucial. This chapter presents an update on emerging and re-emerging viruses and viral diseases, highlights their role in causing human diseases including cancer as well as their potential targets for development of new therapeutics and vaccines.

Keywords Infection · DNA virus · RNA virus · HPV · HIV · Influenza · Coronavirus · Covid-19 · Community transmission · Human diseases · SARS · MERS · Pathogenesis · Carcinogenesis · Therapy and vaccine

Abbreviations

AIDS	Acquired immune deficiency syndrome
AP-1	Activator protein 1
ACE2	Angiotensin-converting enzyme 2
ARDS	Acute respiratory distress syndrome
CaCx	Cervical cancer
COVID-19	Coronavirus disease
CRISPR	Clustered regularly interspaced short palindromic repeats
CAS9	CRISPR associated protein 9
CDC	Centres for disease control and prevention
CDK	Cyclin-dependent kinases
CD	Cluster of differentiation
CYD-TDV	CYD-tétravalent dengue vaccine
CFR	Case fatality rate
CT	Computed tomography
CMV	Cytomegalovirus
DENV	Dengue virus
dsDNA	Double-strand DNA
EBV	Epstein-Barr virus
ER	Endoplasmicreticulum
ELISA	Enzyme-linked immunosorbent assay
FDA	Food and drug administration
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
HR-HPV	High-risk human papillomavirus
HPyV	Human polyomaviruses
HSV	Herpes simplex virus
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HCQ	Hydroxychloroquine
HCC	Hepatocellular carcinoma
HTLV-1	Human T-cell lymphotropic virus type 1
IFN	Interferon
IL-12	Inter lukin-12

IARC	International agency for research on cancer
ICTV	International committee on taxonomy of viruses
JNK	c-Jun N-terminal kinases
KHSV	Kaposi sarcoma-associated herpesvirus
LR-HPV	Low-risk human papillomavirus
LMIC	Low-middle-income country
MERS-CoV	Middle east respiratory syndrome coronavirus
MCC	Merkel cell carcinomas
MCpyV	Merkel cell polyomavirus
mTOR	Mammalian target of rapamycin
NAAT	Nucleic acid amplification testing
NS1	Non-structural protein 1
NF-kB	Nuclear factor kappa-light-chain-enhancer of activated B cells
ORF	Open reading frame
PML	Progressive multifocal leukoencephalopathy
PIKFYVE	FYVE finger-containing phosphoinositide kinase
PCR	Polymerase chain reaction
R_0	Reproductive number
RT-PCR	Real-time reverse transcription PCR
RSV	Rous sarcoma virus
SARS	Severe acute respiratory syndrome
SARS-CoV-1	Severe acute respiratory syndrome conronavirus-1
SARS-CoV-2	Severe acute respiratory syndrome conronavirus-2
SiRNA	Small interfering RNA
STI	Sexually transmitted infection
STV	Sexually transmitted virus
STD	Sexually transmitted disease
ssDNA	Single-strand DNA
sgRNA	Single guide RNA
STAT3	Signal transducer and activator of transcription 3
TMPRSS2	Transmembrane protease, serine 2
VEGF	Vascular endothelial growth factor
VIA	Visual inspections with acetic acid
WHO	World health organization

1 Introduction

If we think we have greater knowledge of the infectious agents that occupy our planet and affect our health, nature reminds us that our understanding about infectious pathogens is too limited. In the last few decades, several kinds of pathogenic microbes had been discovered to cause various types of human diseases

and killed millions of people from almost every continent. The growing challenges to global public health and economic stability to a greater extent can be attributed to various infectious agents including viruses, bacteria, fungi and parasites. These infectious agents can be transmitted indirectly or directly, from human-to-human or animal-to-human or human-to-animal. Though a lot has been done by global health systems to protect and promote human health against infectious diseases, yet its menace is further deepened by the sustained emergence and re-emergence of novel, unrecognized, neglected and long standing infectious agents. At least 28.3% (17 million) of around 60 million deaths that occur globally every year are projected to be due to infectious diseases. Some of these infections (such as pneumonia, AIDS, tuberculosis, diarrhoea, measles and malaria) are more severe and deadly with high incidence and fatality rates (https://www.who.int/healthinfo/global_burden_disease/GBD_report_2004update_part2.pdf). The threats vary extensively in terms of severity, infectivity, morbidity and mortality, as well as their effects on social and global health and economy (https://www.who.int/healthinfo/global_burden_disease/GBD_report_2004update_part2.pdf). Regardless of high morbidity and mortality associated with many of these infections, the attempts in understanding them are restricted to a remarkably small group of biomedical and public health researchers. Whether the global health system as of today can provide effective safety and protection against huge array of infectious diseases is doubtful and this is very clear from by recent outbreaks of SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2) including previous epidemics of Ebola, HIV, Zika, influenza, SARS-CoV-1 and MERS-CoV (Middle East respiratory syndrome coronavirus) along-with looming threat of their increasing resistance (Kim et al. 2017; McNeil and Shetty 2017; https://www.worldometers.info/coronavirus/#countries; Feldmann et al. 2020; Ksiazek et al. 2003; Memish et al. 2020). The concern is magnified by rapid population growth in areas with weak healthcare systems, globalization, urbanization, environmental/cultural variations, ecological factors, civil conflict, global travel along with trade and the altered natural behaviour of pathogens and accelerated spread not only from human-to-human but also from animal-to-human. Human-created epidemics/pandemics originating from laboratory accidents or less possible but planned biological outbreaks are also of increasing concern. These infectious diseases caused by pathogens obviously do not respect human emotions, political and financial boundaries.

Thus, the global research communities have responsibilities to direct adequate attention to studying these diseases, their etiologic agents, and natural history with creating constant awareness and advanced efforts and effective strategies for closly monitoring infectious diseases and their future emergence and re-emergence. In this chapter, we sheds light on infectious agents particularly emerging and re-emerging pathogenic viruses, and briefly introduce its association with human diseases as well as their potential targets for development of new drug therapies and/or vaccines.

2 Infections: Acute and Chronic

Latent or Acute, chronic, recurrent and co-infections may involve in disease pathogenesis and play a serious role in manifestation of disease. It is essential to make a distinction between acute and chronic infections, as they play a different role in the genesis of several diseases. Several acute infections may play a protective role for the development of some diseases while chronic infections appear to be a predisposing factor for the onset of disease.

Acute infections are usually associated with an acute phase reaction with a local inflammatory response, fever and an increased hepatic acute phase protein synthesis. The acute process is characterized by the massive presence of activated monocytes and macrophages in the inflammation area. These inflammatory cells may promote angiogenesis (Corliss et al. 2015) by producing pro-angiogenic factors, such as VEGF (Zhang and Daaka 2011) and prostaglandin E2. Nevertheless, acute infections do not involve new vessel growth. The variety of infection-induced factors (TNF-α, IFN-α/β/γ, IL-12, TGF-β and the acute phase proteins) represent a critical regulator of acute inflammation that could prevent neo-angiogenesis. The observations of spontaneous cancer regression in patients with acute infections, pave the way for studies on the effects of infection and inflammation on cancer (Kucerova and Cervinkova 2016). Acute inflammation can lead to cancer regression as shown by early experiments that artificially infected tumors with erysipelas bacteria cause regression in some cases of incurable cancer (Zhang and Daaka 2011). It is also important to note, that acute infections occurring in childhood, adulthood or old age have different features. Some studies examined the acute infectious disease of childhood and underlined that these infections were associated to a reduced risk of future development of melanoma, ovarian cancer and multiple tumors (Oikonomopoulou et al. 2013). The cancer risk reduction may also be the effect and consequence of acute infectious diseases in childhood. These may provide protection against cancer, but will decrease with age, with the alteration of the immune system. It seems also that acute infections after the infancy may give an important protection against cancer (Jacqueline et al. 2017).

Chronic infections last for many years and are not associated with fever and present variable symptoms. In addition, these kinds of infections can be a consequence of a failed or deficient immune response. In chronic inflammation the active tissue destruction and repair process occur simultaneously with the help of angiogenesis and fibrosis (Kataoka et al. 2003). Chronic infections are a leading public health issue in high-income countries, and they cause a significant toll in low or middle-income countries as well. The onset of the infection and, subsequently, the establishment of the infectious disease and its possible chronic evolution basically depend on host and pathogen factors. These factors depend on biological characteristics of pathogen in terms of pathogenecity, virulence, tenacity, toxinogenesis, infection load, contagiousness and vitality. Instead, the factors inherent the host are

represented by sex, age, nutritional state, economic status, social, hygienic cultural and conditions, presence of metabolic disorders and the state of the immune system.

3 Infectious Agents that Can Cause Human Diseases

There are various infectious microbes such as viruses, bacteria, fungi and even parasites have the ability to spread infection from animal-to-human or human-to-human and transmit diseases directly or indirectly from one person to another. Generally, several microorganisms are harmless and live in and on human bodies but under certain conditions, some of them may purport to cause variety of human diseases ranging from acute to chronic including cancers.

Persistent infection of certain pathogenic microorganisms can cause variety of human diseases including cancers (cervical cancer, gastric cancer, liver cancer, oral cancer etc.) in both developing (26%) and developed (8%) countries (IARC 2012; Parkin 2006). Currently, more than 20% of the human malignancies are directly or indirectly caused by pathogenic microbes of which more than 50% of infection associated human malignancies are caused by different strains of human papillomavirus (HPV) (Parkin 2006; zur Hausen 2000). A series of studies showed links between infectious agents and cancer in the last 60 years. Worldwide, it has been estimated that 2.2 million (13%) infection-attributable malignancies (excluding non-melanoma skin cancers) were diagnosed in 2018 alone (de Martel et al. 2019). As per International Agency for Research in Cancer (IARC), about 11 infectious agents that have been classified as group-1 carcinogens, are responsible for more than 90% of infection-associated human cancers globally. These are Helicobacter pylori, high-risk human papillomaviruses (HR-HPVs), hepatitis B and C virus (HBV/HCV), Epstein–Barr virus (EBV), Kaposi sarcoma-associated herpesvirus (KHSV), human T-cell lymphotropic virus type 1 (HTLV-1), Schistosoma haematobium, Opisthorchis viverrini and Clonorchis sinensis. Out of these, *Helicobacter pylori*, HR-HPVs, HBV, and HCV are the most important pathogens which caused $\geq 90\%$ of infection-associated human malignancies world over (Plummer et al. 2016).

In the 21st century, while the world contineus to fight and contain existing diseaases (plague, AIDS/HIV, tuberculosis, hepatitis, Influenza etc.) and newly emerging (Dengue, SARS, MERS, Ebola, Zika, and SARS-CoV-2) the newly emerging agents are infectious wreaking havoc in both developed and developing countries alike when an outbreak as an epidemic or a pandemic occurs. To date, pathogenic diseases and associated fatalities have remained a significant menace throughout the globe. In spite of current advances highlighting the role of infectious agents in human diseases, the global incidence of infection associated diseases is still high, thus an a strong and flexible global health system and focused research on infectious disease surveillance, prevention, control and treatment strategies are required.

4 Viruses and Human Diseases

Viruses are a mystery and can quickly spread explosively around the world. They are "obligate intracellular parasite" that can replicate inside the host cell (Summers 2009). These intracellular parasites can be found in all living organisms such as bacteria, fungi, protozoans, plants, animals and humans. These are mainly those microorganisms that have small genomes, insufficient to encode their own proteins and every step of viral life cycle depends on the host machinery for almost all essential functions. Viruses also can affect human health and cause a wide range of acute to fatal human diseases including variety of cancers.

The World Health Organization (WHO) has reported various human diseases caused by different types of viral infections, and that millions of individuals are at risk globally (https://www.who.int/healthinfo/global_burden_disease/GBD_report_2004update_part2.pdf). The best example is of the recent global pandemic of coronavirus and COVID-19. Though, our understanding of the mechanisms of pathogenic virus -induced diseases has significantly advanced but we are still lacking in-depth knowledge of several existing, emerging and re-emerging viruses that cause severe diseases in humans. Thus, a better in-depth understanding of what types of viruses in which situation pose the highest risk to human health would enable evidence-based targeting of surveillance, treatment and management of these viral diseases.

5 Virus Infection Can Lead to Cancer

Currently, about 15–20% of all human malignancies are associated with persistent infection of several DNA and RNA viruses (Liu and Richardson 2013). There are six major families of animal viruses which have the ability to cause cancer in both humans and animals. Tumor viruses fall into 2 categories; DNA-containing tumor viruses (hepatitis B virus, papillomaviruses, Epstein-Barr virus, Herpesviruses, polyomavirus and Adenoviruses) and RNA-containing tumor viruses (Retroviruses and Hepatitis C virus). Viruses are unable to cause cancer directly, as several other co-factors including host cell factors besides additional exposure to various carcinogenic agents and immune impairment that can influence tumor development and progression.

Originally, tumor causing viruses were identified in animals but in 1964 onwards several human carcinogenic viruses were discovered. In 1911, Francis Peyton Rous showed that it is possible to transmit the tumour by injecting a solution made from extracts of cancer, thus opening the way for studies on the association between virus infections and cancer. Rous Sarcoma Virus (RSV) was the first carcinogenic virus identified; the studies on RSV had a major role in the development of current understanding on cancer. Nowadays, it is well known that infections caused by certain viruses play key roles in the pathogenesis of several cancers. Viruses can

subvert the functions of host cell purturting the pathways regulation of growth arrest and apoptosis (Bagga and Bouchard 2014). Viral particles can induce tumor as some of them have oncogenes while others can cause the transformation of a proto-oncogene to oncogene in the host cell. The viral oncogene is a mutated, hyperactive and homologue gene involved in cell proliferation, so it works rapidly in all infected cells. Moreover, the over-expression of the proto-oncogene, responsible for uncontrolled cell proliferation, is caused by the viral promoter or by other factors that regulate the transcription. The carcinogenesis process requires multiple steps, but it seems that virus-associated tumors may have common pathways; it could be, for viruses such as HBV, HPV and EBV, the functional inactivation of p53 by virally encoded oncoproteins (Jiang and Yue 2014; Ko 2015; Kordestani et al. 2014). The viruses associated with tumors are characterized by the capacity of causing a persistent infection, but they are not exclusively carcinogenetic agents; so cancer development may be considered as an accidental event in the course of the infection. Obviously, the host immune status may influence the evolution of the disease. Between the initial infection and the onset of cancer could take several years, and carcinogenesis process in virus associated cancer, can be promoted by direct and indirect mechanisms. The viral carcinogenesis also depends on genome type; therefore, it is necessary to consider the main differences between DNA viruses and RNA viruses and their implications on human cancers (Table 1) and other diseases (Tables 2 and 3).

A. **Pathogenic DNA viruses**

DNA viruses are obligate intracellular parasites and important human pathogens that have the ability to cause several acute and chronic diseases in humans. Their DNA is replicated either by host or virally encoded DNA polymerases (Fig. 1). Viruses lack the internal machinery to synthesize their proteins and their lytic cycle is totally dependent on their capability to control/command host cell genome and thus regulate different signalling pathways. Viruses essentially "hijack" the host cell and its mRNA is translated into proteins and these early proteins are accountable for changing normal cellular actions which in some cases permit the infected lysogenic cells to escape the host restriction systems. The genomes size of DNA viruses varies between 5 and 375 kb. During viral infection, majority of these viruses stimulate host-cell DNA replication, or at least in the early stages of DNA replication, it creates a suitable atmosphere for their own DNA replication.

Currently, 91 human DNA virus species have been identified with 22 genera and 8 families, many of them are associated with human diseases including cancer and are of immense public health importance worldover (Woolhouse and Adair 2013). According to International Committee on Taxonomy of Viruses (ICTV) (Kuhn et al. 2019a) DNA viruses are divided into 3 major categories (i) single-strand DNA (ssDNA) viruses, double-strand DNA (dsDNA) viruses and (iii) para-retroviruses (that replicate their genome through an RNA intermediate; e.g. Hepadnaviruses) (Katakura et al. 2005). There are 22 families of dsDNA viruses and 5 families of ssDNA viruses which have been recognized by ICTV. There are six distinct members of DNA virus families, Hepadnaviridae, Polyomaviridae,

Table 1 Estimated number of different virus-attributable human malignancies in 2018

Virus types	Associated new cases of malignancies in 2018	Total number of new cases due to infectious agents
DNA tumour viruses Human papillomaviruses (HPV)	Cervical (570000), Oropharyngeal (42000), Anal (29000), Penile (18000), Vagina (14000), Vulvar (11000), Oral cavity (5900) and Laryngeal (4100) Carcinoma	694,000 (de Martel et al. 2019)
Hepatitis B virus (HBV)	Hepatocellular carcinoma (HCC) (150000)	360000 (de Martel et al. 2019)
Epstein Barr virus (EBV)	Hodgkin lymphoma (40000), Burkitt's lymphoma (6600) and Nasopharyngeal Carcinoma (110000)	156,600 (de Martel et al. 2019)
Kaposi's sarcoma herpesvirus (KHSV/HHV-8)	Kaposi's sarcoma and primary effusion Lymphoma (12000)	42000 (de Martel et al. 2019)
Merkel cell polyomavirus (MCpyV)	Merkel cell carcinoma (MCC) (United States) (1972)	19,722 (de Martel et al. 2019)
RNA tumourviruses	**Associated malignancies**	
Hepatitis C virus (HCV)	Hepatocellular carcinoma (140000) and Other non-Hodgkin lymphomas (16000)	156,000 (de Martel et al. 2019)
Human immunodeficiency virus (HIV)	AIDS-related Kaposi's sarcoma (KS) (14000)	41,799 (Dalla Pria et al. 2019)
Human T-cell leukemia virus-1 (HTLV-1)	Adult T-cell leukaemia and lymphoma (ATL) (1900)	3600 (de Martel et al. 2019)

Table 2 List of human herpesvirus types and family

Herpes viruses types	Alternate name/Abbreviations	Sub-family
Human herpesvirus 1	Herpes simplex-1 (HSV-1/HHV-1)	α
Human herpesvirus 2	Herpes simplex-2 (HSV-2/HHV-2)	α
Human herpesvirus 3	Varicella-zoster (VZV/HHV-3)	α
Human herpesvirus 4	Epstein-Barr (EBV/HSV-4)	γ
Human herpesvirus 5	Cytomegalovirus (CMV/HHV-5)	β
Human herpesvirus 6	HHV-6	β
Human herpesvirus 7	HHV-7	β
Human herpesvirus 8	KSHV/HHV-8	γ

Table 3 Modes of transmission of most common sexually transmitted viruses (STV) in human and their key features

Common sexually transmitted viruses 	Human Papilloma Virus (HPV) 	Human Immunodeficiency Virus (HIV) 	Epstein-Barr virus (EBV) 	Herpes Simplex Virus (HSV1 and 2) 	Hepatitis B Virus (HBV) 
Disease(s)	Genital and skin warts, Cervical, Vaginal, Vulva, Anal, Penile and head and neck cancers	Acquired Immunodeficiency Syndrome (AIDS)	Infectious mononucleosis (glandular fever) Nasopharyngeal carcinoma and Lymphoma	Oral-Herpes and Genital Herpes	Acute and chronic hepatitis, liver cirrhosis and hepatocellular carcinoma
Genomic material	Double stranded DNA	Single-stranded RNA	Double-stranded DNA	Double-stranded DNA	Double-stranded DNA
Incubation period	1–20 months for warts to development. HR-HPV can take 10 years or more to develop cancer	2 weeks to 3 months	~4–6 weeks after initial infection	Symptoms tend to develop 2–20 days after exposure to the virus	~4–24 weeks
Transmission	Transmitted sexually or skin-to-skin contact	Blood, semen, rectal fluid, vaginal fluid, blood transfusion, breast feeding	Body fluids, Saliva, blood and semen during sexual contact, blood transfusions and organ transplantations	Oral-to-oral contact and genital-to-genital contact during sexual intercourse	Transmitted by person-to-person through blood, semen or other body fluids
Common symptoms	Wart; discomfort or pain, though they may itch or feel tender. Cancer;	Systemic disease, rapid weight loss, recurring fever, swollen glands,	Fatigue, fever, sore throat, swollen lymph nodes in the neck and	Mostly asymptomatic or unrecognized but can cause painful blisters or ulcers at	Abdominal pain, Dark urine, Fever, Joint pain, Loss of

(continued)

Table 3 (continued)

Common sexually transmitted viruses 	Human Papilloma Virus (HPV) 	Human Immunodeficiency Virus (HIV) 	Epstein-Barr virus (EBV) 	Herpes Simplex Virus (HSV1 and 2) 	Hepatitis B Virus (HBV) 
	chronic pain, bleeding, itching, discharge, burning, irritation, changes in color/ thickness of the skin	sores in mouth, anus, genital area, memory loss, depression, pink or purplish blotches on skin	armpits, head and body aches, rash, swollen liver or spleen or both	the site of infection, ranging from mild to moderate to severe	appetite, Nausea and vomiting, Weakness, fatigue and Jaundice
Prevention	Adolescent HPV vaccination, curcumin, neem	PEP, ART	Avoiding radiation exposure, healthy diets	Use of condom, Vitamin C, antioxidant	HBV vaccination of infants & adults
Diagnosis/ testing methods	Pap smear, Colposcopy and acetic acid test, Biopsy, PCR-based HPV DNA test, Southern Blot	ELISA Test, RT-PCR-based DNA test	Physical examination, Blood test; Antibody tests	Clinical evaluation, PCR of cerebrospinal fluid (CSF) and MRI for HSV encephalitis	Blood tests, Liver ultrasound, Liver biopsy
Treatment/ vaccine	FDA approved Vaccines; Cervarix, Gardasil-4 and 9 valent Imiquimod, Podofillox for warts & Surgery, Chemo-radiotherapy for cancerous lesions	No specific treatment and vaccine Supportive treatment-Antiretovirals (AZT, etc.)	No vaccine to protect against infectious mononucleosis, penicillin antibiotics like ampicillin or amoxicillin	No vaccine available, Acyclovir, valacyclovir, famciclovir are commonly used.	Vaccines-Energix B, RecombivaxHB, Drugs-Lamivudine, tenofovir and Interferon alpha

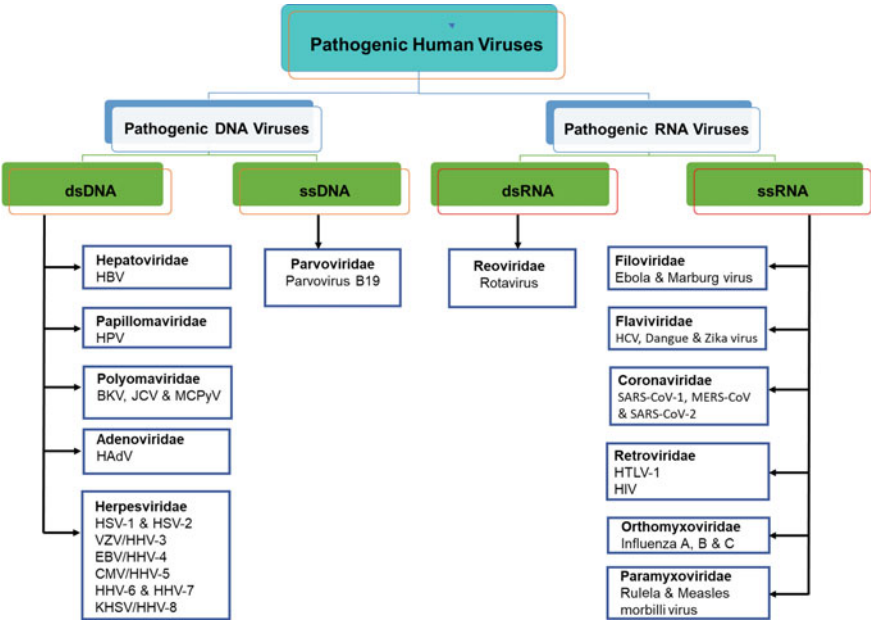

Fig. 1 Classification of most common pathogenic human DNA and RNA viruses

Papillomaviridae, Herpesviridae, Adenoviridae and Poxviridae; they are capable of infecting and causing various acute and chronic diseases in humans. Persistent infections of majority of these DNA viruses are linked with cellular transformation and carcinogenesis.

I. Hepatitis viruses

Viral hepatitis is caused by 5 different types of hepatotropic viruses (HAV, HBV, HCV, HDV and HEV). Both, acute and chronic Hepatitis B (Cho et al. 1973) is caused by the Hepatitis B virus (HBV). HBV is a non-cytopathic, partially (full length negative-sense, partial positive-sense) double stranded with circular DNA belongs to the family *Hepadnaviridae* (Hirschman et al. 1969). Chronic infections caused by HBV represent the main etiological factor for the development of liver diseases and hepatocellular carcinoma (Table 2). HBV infection remains to be a major public health concern globally and in the last two decades the chronically infected people ranged from 240 to 350 million (Lavanchy 2004; Ott et al. 2012), and 8,870,00 deaths were reported in 2015 worldwide (Lozano et al. 2012). It is an endemic in Southeast Asia and Sub-Saharan Africa and more than 8% African and Asian population are chronic carriers of HBV (Maddrey 2001). HBV seropositivity has been estimated to be 3.6%, with the greatest endemicity in Africa (8.8%) and Asia (5.3%). Since India is the second largest populated country in the world, it accounts for a large proportion of the global HBV infection and has about 40–50 million (10–15%) of the entire pool of HBV carriers (Ray 2017).

HBV is mainly found in secretions of semen, vagina, saliva, blood, and menstrual blood of infected persons and transmitted by parenteral, sexual or perinatal mode. HBV infected individuals generally remain asymptomatic or lead to an acute hepatitis after which the infection is cleared by the immune response (Guidotti et al. 1999). However, if HBV infection fails to get cleared, it can lead to chronic infection in a large number of individuals comprising young children and a good percentage of adults.

There are eight HBV genotypes and four serotypes (adv, ayw, adr and ayr) which are characterized by distinct geographic distribution and are clinically important. Several reports about HBV infection showed that genetic characteristics of virus, including genotypes and specific genetic mutations, may lead to the development of hepatocellular carcinoma (HCC) through direct and indirect pathways. The ability of the virus to integrate into the host cell genome leading to alteration of cellular signalling and tumorigenic growth control, assumes a great importance (Chu 2000; Farazi and DePinho 2006). It is interesting to note that integrated HBV DNA in human genome does not replicate independently but can do so along with the human genome and can persist indefinitely. Certain disease status of chronic HBV infection poses a higher risk of liver cancer and the risk is increased in patients with active hepatitis (Farazi and DePinho 2006) and in cirrhotic patients. HBV can cause cancer by integrations into the human genome, even in the absence of cirrhosis. The continuous injury and regeneration of cirrhotic liver lead to increased liver cells turnover, favouring critical genomic mutations, chromosomal rearrangements, activation of oncogenes and inactivation of tumour suppressor genes. The T-cell immune response elicited to combat infection, contributes to hepatocyte necrosis, inflammation and consequently regeneration (Katakura et al. 2005). HBV-induced hepatocellular carcinogenesis, like other malignancies, is considered a multi-step process involving several genetic alterations that ultimately lead to malignant transformation of the hepatocytes. Moreover, an association has been observed between past exposure to HBV and the risk for pancreatic cancer development. This is not surprising, because HBV can replicate within the pancreas and because elevations of serum and urinary level of pancreatic enzymes are often noted in patients with HBV chronic infection (Berrington de Gonzalez et al. 2008).

The HBV vaccine was developed in the late 1970s. This vaccine has provided an effective means to prevent and decrease HBV infection and eventually reduced chronic liver diseases and HBV-associated HCCs, which can therefore be considered the first anti-cancer vaccine against HBV (Hessel and West 2002). Various novel strategies (CRISPR/Cas9, siRNA, entry and secretion inhibitors and immunotherapy) are now being developed that could potentially be used to combat and eliminate HBV infections and prevent virus rebound on therapy discontinuation.

II. Human Polyomavirus infection

At present, 14 human polyomavirus (HPyV) species have been identified and some of which are known to cause infection in humans. These viruses are small, non-enveloped circular, dsDNA viruses that belong to the family *Polyomaviridae*. These HPyVs infect a wide range of tissues including skin, kidney, and respiratory tract, usually resulting in a persistent, asymptomatic infection. However, in immunocompromised hosts, HPyVs can cause serious diseases including fatal infection of the brain, kidney and can cause cancer. Recent works identified 8 novel species, MCV, HPyV6, HPyV7, KIPyV, WUPyV, HPyV9, and MW PyV/HPyV10 (Allander et al. 2007; Feltkamp et al. 2013; Feng et al. 2008; Gaynor et al. 2007; Schowalter et al. 2010; Scuda et al. 2011; Siebrasse et al. 2012). Studies have also shown that the JC virus (JCV) and BK virus (BKV), both belonging to HPyVs were discovered in 1971 in patients who were immunosuppressed (Gardner 1971). Evidence suggest that BKV persistently is linked with tissue injury, salivary gland diseases and sclerosis in HIV-positive patients, nephropathy in kidney transplant patients, haemorrhagic cystitis in recipients of bone marrow transplantation and oncogenesis in transplant recipients. JCV causes progressive multifocal leukoencephalopathy (PML) and in immunocompromised/AIDS patients it causes haemorrhagic cystitis and haematological malignancies.

MCPyV is the first polyomavirus directly implicated in more than 80% of aggressive Merkel Cell Carcinomas (MCCs), the second most deadly form of skin cancer after melanoma in elderly white patients. This rare and aggressive neuroectodermal cancer shares clinico-epidemiological features and other aspects with Kaposi sarcoma. MCPyV is an emerging, non-enveloped, fifth tumour polyomavirus virus, which was first described in January 2008 in Pittsburgh, Pennsylvania. About 1,500 new MCC cases are recorded annually in the United States (US), representing a relatively low prevalence compared to other skin cancers; however, its incidence has tripled in the past two decades (Agelli and Clegg 2003; Calder and Smoller 2010; Hodgson 2005).

III. Human Herpesvirus and associated diseases

Human herpesviruses (HHVs) are potential human pathogens that belong to the family *Herpesviridae*. There are eight distinct types of herpesviruses (Table 2) and their family is divided in3 subfamilies: Alphaherpesvirinae (α-herpesvirinae), Betaherpesvirinae (β-herpesvirinae) and Gammaherpesvirinae (γ-herpesvirinae). These viruses can cause variety of human diseases including genital or oral herpes, infectious mononucleosis, encephalitis, meningitis, herpes keratitis, neonatal herpes and Kaposi's sarcoma. These viruses are transmitted from the infected area of skin or mucous membrane and as a result of direct contact with the lesions. The distinct types of herpesviruses that infect humans and their key features are summarized in Tables 1 and 3.

HSV-1 and HSV-2: These are the two most common viruses which are generally associated with human oro-facial or genital herpes, encephalitis and conjunctivitis. However, genital herpes may be a consequence of HSV-1 infection and cold sores

may also be caused by HSV-2. Once the individual has been infected, reactivation is extremely common in both clinical forms: oral or genital (Whitley 1996; Wilck et al. 2013). HSV infection is untreatable and about 90% of global population is infected with one or both HSVs (Boppana and Fowler 2007). If HSV-encephalitis is left untreated, it can cause >70% mortality (Jereb et al. 2005).

Varicella-zoster virus (HHV-3): It is an exclusively human neurotropic alpha-herpesvirus that causes chickenpox (Varicella) especially in children (1–9 years of age) and reactivation of the dormant virus leading to herpes zoster (shingles) in elderly and immunosuppressed persons (Pergam et al. 2019). In the US, more than 90% of adults suffer from this disease in their childhood, whereas the remaining children and young adults get vaccinated (Gnann 2002).

Epstein-Barr virus (EBV/HSV-4): EBV was identified and fully sequenced for the first time in Burkitt lymphoma biopsy by Denis Burkitt in 1964 in Uganda (Zhang and Daaka 2011). Later it was considered, along-with other genetic and environmental factors (Yu and Zelterman 2002) responsible for the development of benign lesions, infectious mononucleosis, Burkitt lymphoma and other human malignancies, such as nasopharyngeal carcinoma and a series of other human infections and diseases particularly in immunocompromised patients. It also causes Hodgkin and non-Hodgkin lymphoma (NHL), thymic lympho-epithelioma, salivary gland and urogenital carcinoma (Parkin 2006; Javier and Butel 2008). Based on geographical regions, EBV infection alone accounts for 0.5–2% of human cancers (Epstein et al. 1964; Khan and Hashim 2014) and recent epidemiological studies indicate that 1.8% of all cancer-related mortalities were associated with EBV infection in 2010 (Khan and Hashim 2014). Globally, EBV is highly prevalent and more than 90% of younger population are infected with EBV (Young et al. 2008).

Two major types of EBV (EBV-1 and EBV-2) have been identified (Cho et al. 1973) and it has been revealed that the genomes of both the EBV types are very similar except for the regions of the EBV-nuclear antigen (EBNA) genes that have greater ability of type 1 EBV infection to induce B cell proliferation (Tzellos et al. 2014). EBV-2 infection is prevalent in Africa and mostly among homosexual men (Gratama and Ernberg 1995; Higgins et al. 2007; van Baarle et al. 2000). Markedly, percentage of EBV infection differs in different diseases and may have consequences toward the aggressivity of the associated diseases (Jha et al. 2016). Moreover, the presence of autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, and primary Sjögren's syndrome, the condition of transplanted and the consequent iatrogenic immunosuppression and HIV infection are all circumstances in which the EBV infection is strongly associated to leiomyomas, leiomyosarcomas and other smooth muscle neoplasms (Sousa et al. 2008) (Table 3).

Human cytomegalovirus (HCMV/HHV-5): It is a ubiquitous HSV-5 virus with the high morbidity and mortality rates compared to other HSVs worldwide. Infection of this virus inflicts "mononucleosis-like syndrome" (cytomegaly or "cytomegalic inclusion disease) (Davison and Bhella 2007; Liu and Zhou 2007).

Infection risk is higher among young, elderly, immunocompromised, HIV-infected and transplant recipient individuals. It may also cause encephalitis, retinitis, hepatitis, colitis, esophagitis, pneumonia and neonatal infection sequelae. In developed countries, the infection burden of HCMV increases progressively with age, reaching over 70% prevalence by the age 70. The seropositivity rates are higher ($\geq$90%) among lower socioeconomic groups, homosexual men, and in low-income countries (Beam and Razonable 2012; Cannon 2009; Ho 1990; Pass 1985; Razonable 2005; Stagno and Cloud 1990). Clinical management of HCMV infection is challenging due to the absence of 100% protective vaccine or anti-viral drugs against the virus (Griffiths and Boeckh 2007; Heineman 2007; Plotkin and Boppana 2019). The majority of studies have been focusing on the immune response of viral pathogenesis. However, studies on host-genetic interaction of virus may help in identifying molecular pathways that may lead to the discovery of new therapeutics.

HHV-6 and HHV-7: These are ubiquitous viruses and have been linked with lichen planus, pityriasis rosea, hypersensitivity reactions, roseola infantum, graft-vs-host disease, and early febrile infectious syndrome. A large number of adult population ($\geq$95%) is found seropositive to both HHV-6 and HHV-7 infection worldwide. Primary infection commonly occurs in children during infancy. HHV-6 was first identified in 1986 in patients with lymphoproliferative diseases. HHV-7 is one of the causative agents of exanthem subitum (ES) (Tanaka et al. 1994). The peak of HHV-7 seroconversion (Tanaka-Taya et al. 1996) takes place later than seroconversion for HHV-6 (Okuno et al. 1989) and mature CD4 positive T-lymphocytes and epithelial cells of salivary glands seem to be the principal target cells for both the viruses (Dockrell and Paya 2001; Caserta et al. 2001). Further studies on diagnostic techniques and therapy will lead to better detection and targeted anti-viral treatment.

Kaposi's sarcoma herpes virus (**KSHV/HHV-8**): KHSV is known cause of various Kaposi's sarcoma (KSHV) forms (AIDS-associated, classic, endemic, African, iatrogenic) also known as Human Herpes Virus 8 (HHV8) encodes for several cytokines and their receptors (Cesarman et al. 1995; Soulier et al. 1995). There are four forms of KHSV that have been described; the classic KS, identified by Moritz Kaposi, is found in elderly men of Mediterranean and Eastern European descent (DiGiovanna and Safai 1981). The second type is lymphadenopathic and AIDS associated form of KS present as African endemic KS, which occurs in Eastern and Central African countries (Friedman-Kien and Farthing 1990; Stein et al. 1994). Currently KS is the most common malignancy associated with HIV infection (Table 1). The fourth type of KS is iatrogenic/post-transplant KS, which is associated with the use of immunosuppressive therapy for the prevention of organ transplant rejection (Andreoni et al. 2001; Marcelin et al. 2007). In addition to Kaposi's sarcoma, the viral genome has been found in primary effusion lymphoma (PEL), Castleman disease, angioimmunoblastic lymphadenopathy and in certain

cases of reactive lymphadenopathies. Moreover, it is also considered a cause of body-cavity-based lymphomas.

IV. **Parvovirus B19 infection**

Parvovirus B19 infection may play a role in the pathogenesis of rheumatic diseases (Yaghoobi et al. 2015) and acute lymphoblastic and myeloblastic leukaemia (Kerr 2000). Even if Parvovirus B19 is an aetiological agent for certain diseases (Kerr et al. 2003), there is limited literature on Parvovirus B19 involvement in solid tumours. However, a correlation with papillary thyroid carcinoma (PTC) has been hypothesized. In fact, studies have demonstrated the presence of viral DNA and viral proteins in neoplastic epithelium of patients with PTC (Li et al. 2012). The possible role of B19 in pathogenesis of thyroid neoplasm is also suggested by involvement of immune system involving NF-kB, IL-6 and viral proteins. The rapidly activated NF-kB, by tax and tat protein, can play a pivotal role in the HTLV-1-induced acute leukaemia and HIV-induced KS which is also significantly increased and co-localized with the virus DNA in papillary thyroid carcinoma tissues (Chan et al. 2017). Moreover, one of the non-structural protein (NS1) encoded by viral genome is cytotoxic to host cells and linked to NF-kB and IL6. The correlation is probably due to the fact that the non-structural viral protein resembles tax protein of HTLV-1 and tat protein of type 1- HIV. They all play a part in viral propagation and activation of IL6 production through the NF-kB-binding site in the IL6 promoter (Yaghoobi et al. 2015). These findings also reveal a novel link between parvovirus B19 and thyroid carcinoma (Li et al. 2012).

V. **Human adenoviruses (HAdV)**

Human adenoviruses (HAdV) are ubiquitous, non-enveloped, dsDNA virus with $\sim$35 kb of genome size belongs to the Adenoviridae family. HAdV are the first respiratory viruses which were isolated in tissue culture. These viruses are well-recognized as an important human pathogen of upper respiratory tract infections including common cold in children and adults. Presently, $\geq$70 HAdV serotypes are known and these are further divided into 7 species (HAdV-A to HAdV-G). In humans, over fifty adenoviral serotypes have been identified that can cause widespread infections, from mild to life-threatening respiratory infections in young children and in immunocompromised persons (Sun et al. 2018). Severe HAdV infection in young children can be complicated, leading to acute respiratory distress syndrome (Hung and Lin 2015; Stebbing et al. 2020), pleural effusions (Cho et al. 1973), myocarditis (Treacy et al. 2010), respiratory failure (Lai et al. 2013) and central nervous system (CNS) dysfunction (Huang et al. 2013). However, HAdV also can cause variety of lesions of the conjunctiva and gastrointestinal, bladder, central nervous system and genitals. HAdV are tolerant to interferon treatments and only Cidofovir is a choice of drug which gives anti-adenoviral activity in severe disseminated disorders. Unfortunately, no effective vaccine for children and specific anti-adenovirus drugs against HAdV diseases is available (Fu et al. 2019). Majority of viral infections are self-limited but in immunocompromised patients, the burden and of the disease outcome is potentially

fatal. This has paved the way for additional work to work identifying novel avenues for immunotherapy and pharmacotherapy.

VI. The Human papillomaviruses (HPVs)

HPV being epitheliotropic virus it exclusively infects both, the skin and basalmucosal epithelial tissues of genital, head and neck area and infection can lead to the transformation of basal epithelial cells (Gupta et al. 2012). HPV have been classified into five genera (alpha, beta, gamma, mu and nu (de Villiers 2013; Gupta et al. 2018b). Mucosal HPV infection can cause various human diseases including condyloma acuminata, focal epithelial hyperplasia, cervical neoplasia and cervical and other anogenital and head and neck carcinomas (Table 3). Cutaneous HPVs which infect cutaneous epithelia can cause various types of benign warts (Plantar, and Filiform which may be pigmented), epidermoid cysts and skin cancers (Doorbar et al. 2015). To date >200 HPV genotypes have been discovered and majority of them (~40 HPV genotypes) infect the anogenital tract (Kocjan et al. 2015). HPVs have been categorized into two main types; (i) high-risk (HR-) and low-risk (LR-); these types are based on their potential to induce malignant lesions. Of these, 15 mucosal HR-HPV types (HPV type 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, 73 and 82) have been identified as oncogenic HPV types and are associated with more than 99% of cervical and other anogenital cancers (de Villiers 2013; Chen and Chou 2019) HR-HPV types 16/18 are considered as the most dominant types and are responsible for >80% of all cervical cancer (CaCx) cases, and 6 other HR-types (HPV 31, 33, 35, 45, 52, and 58) are responsible for an additional 20% (Bosch et al. 1995; de Sanjose et al. 2010).

HPV is considered as one of the most common sexually transmitted virus (STV) and globally ~12% females and 1% males are infected (Chu 2000). It is strongly associated with the pathogenesis of several types of human cancers and accounts for ~10–20% of total human tumors (Table 3). HPV infection transmission is considered through sexual contact, mostly during the vaginal, anal, oral sex, or genital-to-genital contact (Steben and Duarte-Franco 2007). In fact, most of the sexually active partners are exposed at least one strain of HPV at some point in their life-time. Therefore, the difference in the capability of virus to induce malignant transformation is totally depended on oncogenic HPV genotypes and host immune susceptibility. HPV infection is a necessary causative agent for cervical cancers (CaCx), which is one of the leading cause of death in women particularly in low or middle-income countries mainly due to lack of early screening program for CaCx. Other than CaCx, HPV infection also induce cancers of anal (88%), vaginal (78%), penile (50%), vulvar (25%), oropharynx (20–31%), tongue (30%), laryngeal (2.4%), oral cavity (2.2%) and also breast and stomach (Gupta et al. 2018b; Boda et al. 2018; Dunne et al. 2007; Pereira et al. 2015; zur Hausen 2002). Despite available effective prophylactic HPV vaccines, protecting against most prevalent HR- and LR-HPVs, the HPV-associated tumors still remain a major global health problem particularly in low-middle income countries (LMICs). Understanding molecular, mechanisms and conducting large-scale clinico-

demiological studies along-with organized HPV screening and vaccination are crucial to completely eradicate HPV-associated disease burden globally.

Genome structure and functions of HPVs. They are non-enveloped, small, circular dsDNA viruses with about 8 kb genomes (Fig. 2). HPV belongs to the family '*Papillomaviridae*'. The viral genome contains three major regions: (i) the early genes (E1, E2, E4, E5, E6 and E7) involved in viral replication, transcription and tumorigenic transformation, (ii) the late genes (L1 and L2) encodes two structural capsid proteins and (iii) the long control region (LCR), a non-coding upstream regulatory region (URR) (Dalla Pria et al. 2019) that controls viral transcription and replication (Fig. 2) (de Villiers 2013; Das et al. 2008). The HPV E6 and E7, which encode oncoproteins consisting of 151 and 98 amino acids, respectively, are largely responsible for the onset and persistence of the malignant phenotype in both anogenital and head and neck cancers (Fig. 2).

Emergence of HPVs as the key human carcinogens for cervical cancer. The existing data highlights that oncogenic HPV infections are the important etiological agents in the genesis of majority of cervical cancers (CaCx). It causes almost all cases of cervical cancer but being an epitheliotropic virus, it also induces a significant variable percentage of certain non-cervical carcinomas. CaCx is a deadly disease among women and a big challenge to the society, as it kills one woman in

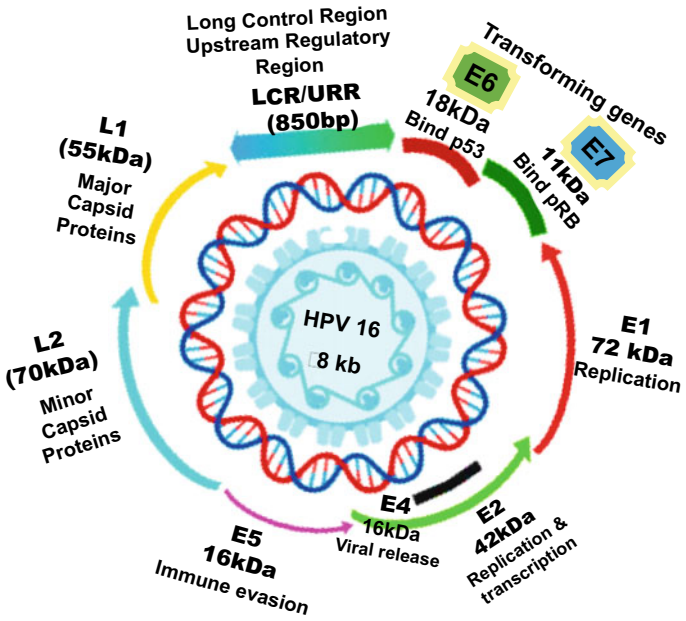

Fig. 2 Genomic organization of HR-HPV type 16. First the early region (E1–E7), second is late capsid (L1–L2) and third is non-coding upstream regulatory region (URR). Most Papillomavirus genomes resemble HPV16 organization in general

every two minutes around the globe (Bray et al. 2015). Globally, CaCx is most frequent gynaecologic cancer with an estimated 570,000 new cases and 311,365 cervical cancer-related deaths recorded in 2018, of which about 90% (9 out of 10) cancer-related deaths were recorded in low-middle income countries (LMIC) (Bray et al. 2015; Ferlay et al. 2018). CaCx is the 3rd most prevalent malignancy among females globally and 2nd leading cause of death in Indian females. Worldwide, it accounts for about 3.3% of all cancer-associated mortalities (Bray et al. 2018).

One-forth of all global cervical cancer cases are diagnosed in LMIC which harbour greater than 21.3% of world's population (Kumar et al. 2019). The substantial differences in CaCx incidence exist within the states, most prominently between urban and rural populations. These figures suggest that there is an urgent need for better prevention and treatment solutions regarding HPV-induced cancers in women. Ironically, regardless of the fact that a cancer control programs being an essential part of the national health strategy, there have been disappointing improvements on HPV-mediated cancer prevention strategies. However, the scenerio in interstingly changing with GAVI and UNDP implementing HPV vaccination programmes in India. More than 90% of all CaCx cases are caused by persistent infections with HR-HPVs which can lead to the genesis of precancer lesions and, eventually, invasive carcinoma (Ferlay et al. 2014). However, the possibility of HPV-DNA persistence and development to lesions is increased by a number of host and environmental factors. The risk of HR-HPV persistence and developing into high-grade cervical lesions increases 5–10 folds due to the host immune impairment (Birkeland et al. 1995). In addition, the relative risk of developing CaCx is increased by several other epidemeological factors such as types of STIs (Smith et al. 2002), continuous use of contraceptives (Moreno et al. 2002), multiple partners, early age marriage (<18 years), poor genital hygiene (Das et al. 2008), high parity, smoking, certain religious practices and ethnicity (Bharti et al. 2009; Wyatt et al. 2001). In majority of the cases, HPV infections are asymptomatic and cleared by host immune system, however, in few cases, persistent infections with specific strains of oncogenic HPVs can develop into invasive cancer (Gupta et al. 2018b). Nevertheless, persistent HR-HPVs are principal cause for more than 90% of CaCx. However, it clearly indicates that CaCx is a preventable disease through regular screening and HPV vaccination. Thus, with these primary and secondary prevention approaches such as HPV vaccination, different cervical screening methods along-with HPV DNA testing in the general population in LMIC will remarkably reduce the risk of HPV-induced cervical cancers as well as will help towards global elimination of cervical cancer in all groups of women (Gupta et al. 2012, 2018b; Bharti et al. 2009).

HPV: molecular mechanism of oncogenesis and target(s) for therapy.

HPV is an epitheliotropic virus that infects stratified squamocolumnar epithelial mucosa at the transformation zone (TZ) of the cervix through micro-abrasions caused during sexual intercourse. Thus, early age of first sexual intercourse, multiple sexual partners and other STIs enhance virus entry, progression of infections and development of lesions in women and progress through a variety of

pre-malignant and malignant lesions (Stokley et al. 2014). In majority of patients (~90%) immune system clears HPV infection thus remaining asymptomatic (Steben and Duarte-Franco 2007), cases of about ~10–12% HR-HPV infections that persist make the differentiating epithelial cells to reach a DNA-synthesis competent state leading to tumorigenic transformation mostly due to up-regulated transcription of E6 and E7 oncoproteins. Therefore, persistent or chronic HR-HPV infection for at least one year or more along-with other endogenous and/or exogenous factors are prerequisite for the development of cellular changes which can lead to aberrant viral oncogene expression and serve as the key factor for the genesis of HPV-induced cancers (Das et al. 2008; Bharti et al. 2009). During productive HPV infection, viral genomes remain in the episomal state in the basal undifferentiated epithelial cells and replicates together with the cellular genome. Apart from genomic predisposition, acute and chronic localized inflammatory co-infections, persistence of HR-HPVs triggers the integration of viral DNA into the host genome. Following this it makes nearly impossible for the premalignant lesions to return back to normal (Bharti et al. 2009; Moody and Laimins 2010), thus considered as a crucial step in the development of high-grade cervical lesions (Cullen et al. 1991; Das et al. 1992a, b; Pirami et al. 1997; Shukla et al. 2010).

HPV-induced tumorigenesis is a complex and multistage process associated with the occurrence of genomic alteration and/or tumorigenic transformation of the cells. Genomic alterations are the hallmark of tumorigenic transformation (Senapati et al. 2016). The molecular mechanism of HPV-induced tumorigenesis can be regulated by two key viral oncoproteins; E6 and E7 that are consistently overexpressed and are critical to the induction and maintenance of the malignant phenotype (IARC 2007; May and May 1999). These oncoproteins are also able to disrupt innate immunity by inhibiting type 1 interferon and alter functioning of several important molecular regulatory signaling pathways such as p53, Rb, EGFR, Notch1, Wnt, JNK, mTOR, STAT, AP-1 and NF-kB-mediated pathways, that are known to play critical role in regulating normal cell growth, differentiation, apoptosis and immune functions (Gupta et al. 2015, 2018a; Kuguyo et al. 2018; Olusola et al. 2019; Tyagi et al. 2017).

For maintenance of tumorigenicity and activation of replication machinery, HR-HPV-E6/E7 oncoprotein interact and bind to two key tumour suppressor proteins, p53 and retinoblastoma (pRb) respectively leading to inactivation of these two essential cell growth regulators and induction of S phase and cell cycle progression (Fig. 3). Furthermore, the E6 oncoprotein binds more efficiently to the p53 leading to the formation of a ternary complex with E6-associated protein (E6AP) causing inactivation of p53 and PDZprotein (post synaptic density protein of Drosophila disk large tumour suppressor-zonula occludens-1 proteins) while stimulating phosphoinositides 3-kinase (PI3K)/protein kinase B (Akt), Wnt/β-catenin and Notch signalling pathways (Gupta et al. 2018b; May and May 1999).

Similarly, E7 binds to unphosphorylated pRb and disrupts phosphorylated state of pRb which ultimately induces the degradation of retinoblastoma (pRb) family members (pRb1, p107 and pRb2). Thereby release of the E2F transcription factor to bind with promoters of cell cycle regulatory genes to translate cell cycle regulatory

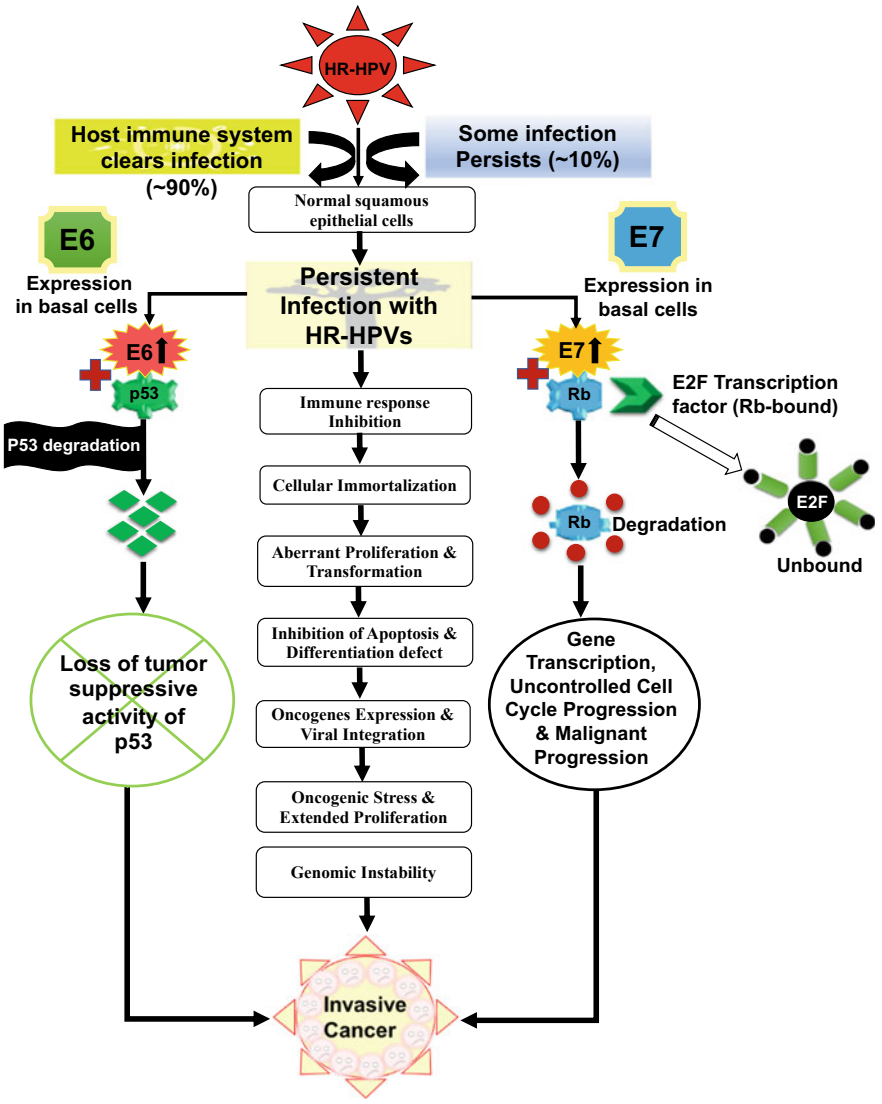

Fig. 3 Schematic diagram of molecular mechanisms of HPV-induced genomic instability and oncogenesis. Viral oncoproteins; E6 & E7 bind to p53 and Rb, respectively and induce their degradation and inactivation leading to uncontrolled cell cycle progression and growth causing genomic instability and chromosome aberrations following HR-HPV infection.

proteins and polymerases required for cell growth and cell cycle progression (Fig. 3). HR-HPV/E7 has ability to induce cell cycle progression by suppressing the activity of p21 and p27 cyclin-dependent kinase (CDK) inhibitors that is induced once p53 is stimulated in response to DNA damage (Cho et al. 2002; Helt et al.

2002; Helt and Galloway 2001). E7 also disrupts p16/pRb pathway and induces cellular immortalization. HR-HPV oncogenes specifically E5, E6 and E7 can abrogate DNA damage responses which may lead to the accumulation of several genomic alterations and activation of diverse signalling pathways and inhibit cancer suppressor genes during HPV-induced tumorigenesis (Demers et al. 1996; Slebos et al. 1994). Further, alterations in regulatory signalling pathways result cell growth, proliferation, inhibition of cell apoptosis and drug resistance. Hence, HR-HPV oncogenes and altered molecular signalling pathways may be excellent molecular biomarkers for developing effective targeted therapeutic approaches for the treatment of HPV-induced cancers (Oikonomopoulou et al. 2013; Parkin 2006). Since transcription of two essential HR-HPV oncogenes E6/E7 is tightly regulated by a host cell transcription factor, activator protein-1 (AP-1) as AP-1 binding to its URR is indispensable for overexpression of E6/E7, AP-1 especially its two-family proteins c-Fos and Fra-1 have been shown to be the potential targets for therapy (Gupta et al. 2018b; Tyagi et al. 2017).

Detection, Diagnosis and treatment of HPV-associated diseases. The comprehensive control of HPV-induced diseases can be achieved by primary prevention (HPV vaccination), secondary prevention (screening and treatment of benign lesions) and tertiary prevention (diagnosis and therapy of invasive HPV-associated cancers) (Gupta et al. 2012; Bharti et al. 2010). It has been established that organised HPV screening programmes or widespread good quality cytology can reduce both incidence and mortality of HPV-infected patients. The introduction of HPV vaccination, development of DNA-based testing for early screening, monitoring and diagnosis of HPV could also effectively reduce the burden of HPV-induced diseases in the next few decades.

HPV-induced tumorigenesis is a multistep, multistage (premalignant lesion to invasive cancer) and complex process which takes 15–20 years to develop invasive cancer thus providing a unique opportunity and an excellent window period for early detection, diagnosis, prevention and treatment of the disease through vaccination, conventional cytology or other methods including cellular and molecular testing and standard treatment approaches. Currently, three FDA-approved prophylactic HPV vaccines including bivalent Cervarix (for HPV types16 and 18), tetravalent Gardasil (for HPV type 6, 11, 16 and 18) and nonavalent Gardasil-9 (for HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58) are commercially available which provide protection against the most common HR- and LR- types of HPVs. All three vaccines are based on recombinant DNA technology and highly effective and induce high titre of specific antibodies. Further, Pap smear test, visual inspection with acetic acid can also be preferred and employed for early detection of HPV lesions which are suitable for low resource settings (Das et al. 2008). Initially, most of the HPV infected lesions are benign or asymptomatic, and are undetectable by Pap test or VIA, thus molecular HPV-DNA testing can be preferred which provides unequivocal results and are the most reliable methods for early HPV detection (Gupta et al. 2012, 2018b). When premalignant lesions are recognized, cryotherapy, loop electrosurgical excision procedure or cold knife conization can be done

depending upon the grade of lesion. However, in-spite of several preventive and treatments methods such as screening, vaccination, surgery, chemo and radiotherapy, the burden of HPV-induced diseases remains high world over. Existing HPV vaccines are providing limited results to eliminate pre-existing HPV infections and having many challenges in its widespread use in developing countries including India. Therefore, new approaches should be made for the development of therapeutic HPV vaccines which can regress pre-existing HPV-associated lesions and will facilitate better control and management of HPV-induced diseases.

B. **Human-infective RNA viruses**

RNA viruses, also referred to as retroviruses, are most common pathogens inducing new human diseases, and 1 to 3 novel RNA viruses are being discovered every year (Rosenberg et al. 2015). Retroviruses exist as more genetically diversified populations than the DNA viruses in that their genetic material is single-stranded or a double stranded RNA and also they have few similar notable features to DNA viruses. Depending on their genome polarities, RNA viruses are divided into 3 groups; (i) positive-strand RNA virus, (Liu and Richardson 2013) (ii) negative-strand RNA virus and (iii) double-strand RNA virus. Presently more than 158 species of human RNA viruses have been discovered which comprise 47 genera and 17 families, only few of them cause human diseases (Parvez et al. 2019). Among all potential pathogenic viruses, RNA viruses are special human etiological agents in particular these have become important zoonotic agents emerging and transmitting from wild animals, occupying about 25–44% of all emerging human infectious diseases (Jones et al. 2009; Morens et al. 2004; Woolhouse and Gowtage-Sequeria 2005). Notably, variant viruses are more often generated in RNA viruses due to their high mutation rate than DNA viruses. Due to this property, RNA viruses are difficult and challenging to treat and control using antiviral therapies. RNA viruses that can cause variety of acute to chronic human disorders involving retroviruses, flaviviruses, filoviruses, orthomyxoviruses, paramyxoviruses and coronaviruses (Fig. 1).

I. **Human retroviruses**

Retroviruses are pathogens that belong to Retroviridae family. Poiesz and colleagues (1980) had isolated the first human retrovirus in a cutaneous T-cell lymphoma patient (Poiesz et al. 1980). These viruses are enveloped and contain about 7–10 kb RNA as their genetic material. Upon infection, their complex replication strategy is characterized by its own enzyme ‘reverse transcriptase’, which converts their RNA genetic information into a DNA intermediate and produces a double-stranded DNA within a host. Retroviruses can cause several human diseases including AIDS, cancer, auto-immune and neurologic diseases. The Retroviridae family is consisting of 7 subfamilies. Two most pathogenic viruses; human T cell lymphotropic virus (HTLV) type 1 and human immunodeficiency virus (HIV) of which HIV1 are most important pathogens for humans and they have also the ability to induce cancers (zur Hausen 2002; Robertson and Levin 1999).

a. **Human immunodeficiency virus (HIV)**. HIV is a RNA virus of the *lentivirus* genus classified into two strains: HIV-1 and HIV-2, belong to different locations. HIV-1 is a main agent of HIV/AIDS pandemic globally and found in chimpanzees and gorillas living in western Africa, whereas the geographical location of HIV-2 strain is endemic in sooty mangabeys, species of monkey living in western and central Africa (Chen et al. 1996; Gao et al. 1992). The viral infection causes the Acquired Immune Deficiency Syndrome (AIDS), a disease defined as a set of events due to the depletion of T lymphocyte, even if HIV is able to productively infect other cell types such as lymphocytes, macrophages, microglia and dendritic cells. In patients with HIV infections, there is an increased risk to developing cancers such as Kaposi's sarcoma, non-Hodgkin's lymphoma B-cell, primitive brain lymphoma B cells and invasive carcinoma of the uterine cervix (Tables 1 and 3). Other AIDS-related cancers include Hodgkin disease and cancers of the lung, mouth and digestive system; the observation of all these cancers in people who are HIV-positive is so relevant, compared to normal population that it could be considered as an index for AIDS definition. In patients affected by AIDS, the most important causes of death are the opportunistic secondary infections, provoked in majority of cases by viruses, bacteria, fungi and parasites. These microorganisms rarely cause a disease in people with an efficient immune system but in subjects affected by AIDS, they may cause severe diseases which are usually disseminated, difficult to treat and often have relapses. So, HIV infection exposes to a number of opportunistic malignancies and other subsequent infections, some of which in turn are potentially carcinogenic. The chance that an opportunistic infection could develop depends on the deterioration of the immune system and, in the same way, the onset of cancer can be related to the status of patient's immunity. Nowadays, due to the modern and efficient HAART therapy (Highly Active Antiretroviral Therapy), we can observe an increase in survival of patients affected by AIDS. The therapy leads to an enhancement in life expectancy but ironically it can sustain an increased risk of contracting cancers not necessarily linked to HIV infection. Among "no-HIV related" cancers, there are pulmonary, digestive system and liver cancers (Bellan et al. 2003).
b. **Human T-cell leukemia virus type 1 (HTLV-1)**. HTLV-1 is predominantly associated to adult T-cell leukemia (ATL) (Hristov et al. 2010), a disease characterized by uncontrolled growth of CD4+ T-lymphocytes, lymphadenopathy, hypercalcemia, immunodeficiency and weak prognosis (Goncalves et al. 2010). After infection, HTLV-1 has a very long latency period that can last for several decades, but once cancer begins, the progression is rapid (Table 1). Mechanisms leading to ATL are not well understood, but it is possible that a multistep leukemogenic process, in which the main roles are played by viral genes and their products and host immune status (Goncalves et al. 2010). Besides, NF-kB has been reported in ATL cells and is known that it has a regulatory function of immune response to infection and is strongly associated with oncogenesis.

II. Human flaviviruses

Flaviviruses belong to the family *Flaviviridae*, which are associated with variety of distinct mosquitoes-transmitted human diseases including dengue, yellow fever, Japanese encephalitis (JE), tick-borne encephalitis (TBE) etc. Flaviviruses are small, enveloped, positive-sense single-stranded vector-borne RNA viruses with approximately 9–12 kb in genome length which share a common genome organization and replication strategy. Viral replication takes place in both the vertebrate host and the insect vector. Flavivirus infections vary from asymptomatic, mild fever, body aches, head-aches, nausea, vomiting joint pain and arthralgia to life threatening and haemorrhagic (Messaoudi et al. 2015). Flaviviruses are also able to persist in patients and may cause long-term morbidities. To date, there is no specific treatment for flaviviruses infections are available (Dovih et al. 2019).

a. **Dengue viruses**. Dengue fever is caused by one of the mosquito-borne virus, called Dengue virus (DENV). The disease is mainly transmitted by biting of Aedes aegypti/or Aedes albopictus mosquitoes. Globally, more than 50 million dengue virus infections have been reported annually in tropical and subtropical regions. More than 0.5 million peoples are hospitalised and more than 3 billion peoples live in dengue endemic regions of the globe (Sanyaolu et al. 2017). DENV is consisting four distinct serotypes; DENV-1, DENV-2, DENV-3 and DENV-4. Exposure to one serotype provides lifelong homologous herd immunity against all other virus's serotype (Gibbons et al. 2007). Symptoms of dengue virus infection range from headache, severe muscle, joint pain, and rashes that usually persists for 7–14 days to potentially life-threatening haemorrhagic fever (bleeding in the skin and gastrointestinal tract) or shock syndrome (Dengue shock syndrome). There is currently no specific treatment available for DENV. Recently, an FDA approved Dengvaxia® (CYD-TDV) dengue vaccine has been developed by Sanofi Pasteur against all four strains of DENV. Dengvaxia® DENV vaccine was first licensed in December 2015 in Mexico. It is recommended for the age group of 9–45 years of individuals in more than 20 countries.
b. **Zika Virus**. The virus is primarily transmitted through the bite of an infected Aedes (Aedes aegypti) mosquito to the human in subtropical and tropical regions. However, viral transmission through sexual contact, blood transfusion, organ transplantation and mother to foetus during pregnancy has also been reported (Wikan and Smith 2016). The virus causing Zika Virus Disease (ZVD), was first discovered in 1947 from the Zika forest in Uganda in rhesus monkeys and was transmitted in humans in 1952 by Aedes aegypti mosquito (Petersen et al. 2016). The first biggest outbreak of Zika virus was reported in in 2007 in Yap Island followed by French Polynesia and Brazil in 2013 and 2015 respectively. By 2018, Zika virus epidemic explosively transmitted in more than 86 countries and territories including America (Musso and Gubler 2016).

In 2016, the WHO declared Zika virusa global public health emergency (McNeil and Shetty 2017). The symptoms of Zika virus disease can last for several days to

weeks that are generally of low-grade fever, rash, joint pain, conjunctivitis, malaise, arthralgia and asthenia. Recent studies have suggested that Zika virus has also been associated with serious sequelae like microcephaly and Guillain-Barre syndrome (GBS) in infants of those mothers who were infected with the virus during pregnancy (McNeil and Shetty 2017). To detect Zika virus infection, nucleic acid amplification testing (NAAT) has been used for various specimens such as serum, amniotic fluid, urine, whole blood, semen, cerebrospinal fluid and tissues. Presently, no specific vaccine or antiviral therapy is available for ZVD. Supportive treatment such as analgesics and antipyretics can be used by clinician for viral infection.

III. **Human filoviruses (HFV)**

Human filoviruses are the members of *Filoviridae* family with non-segmented, lipid enveloped, single-stranded negative-sense RNA (-ssRNA). These viruses were first identified as the infectious pathogens of a haemorrhagic fever outbreak in 1967 in Europe. Filovirus forms filamentous thread-like morphology called virions. There are two members of this family that are namely known as the Ebola virus (EV) and Marburg virus (MV) (Martines et al. 2015). Both EV and MV are most lethal human pathogens with epidemic potential that can cause severe haemorrhagic fever illness in humans and non-human primates (Kuhn et al. 2019a, b). Bats are considered the natural reservoir for both EV and MV zoonotic pathogens (Kuhn et al. 2019a, b). HFV transmission in humans occurs from direct human-to-human contact with it infectious body fluids (vomitus, blood, semen, saliva, breast milk stool and tears) through an infected symptomatic patient. Filoviruses are classified as category A infectious agents due to their high CFR, potential aerosol infectivity, direct human-to-human transmission, and absence of specific antiviral therapy and vaccine.

Ebola virus (EV). This viral infection is a most virulent and deadliest that can causes fatal Ebola virus disease (EVD) or Ebola haemorrhagic fever in humans. The first EV infection outbreak was reported in Zaire (now known as Democratic Republic of the Congo) near the Ebola river in 1976, since then the virus is known as Ebola (Messaoudi et al. 2015; Messaoudi and Basler 2015). EVD is a major global public health concern due to its unprecedented outbreak in sub-Saharan African regions in 2013–2016 with high case fatality rate (Feldmann et al. 2020). In 2013–2016, a total number of EVD confirmed cases were more than 28,000 with 11,000 associated deaths due to this endemic. The impact of EV infection has been also observed in US when infected patients who recently travelled from Liberia, West Africa (Chevalier et al. 2014; McCarthy 2014). Recently, three new cases of EVD were reported in the Democratic Republic of the Congo between10 and 14 April 2020 (Feldmann et al. 2020). It is believed that EV is also an animal-borne virus; however bat is the main reservoir and /or nonhuman primates such as monkeys, chimpanzees and apes may be intermediate, or amplifying hosts for this virus (Messaoudi et al. 2015; Siegert et al. 1967). EVD can get through direct close contact with an infected person or animal infected with Ebola virus. It is primarily

transmitted by human-to-human through direct contact from the infected patients with infected body fluids and causes severe and acute systemic disease. Ebola virus incubation period is 2–21 days and initially the EVD patients showed with non-specific influenza-like symptoms such as high fever, fatigue, body aches, weakness, stomach disorder, nausea, cough, vomiting and diarrhoea and at later stage the persistent infection may cause breathing difficulties, bloodshot eyes, internal-external bleeding, gastrointestinal dysfunction and multiple organs failure. Currently, no specific treatment or vaccines approved by FDA for EVD and only supportive and symptomatic therapy is the line of treatment. Remdesivir may be considered as the best option for its treatment (Warren et al. 2016).

IV. **Human orthomyxoviruses**

Human Orthomyxoviruses (influenza viruses) contain enveloped, 6–8 segments of negative-sense, single-stranded RNA genome. These viruses belong to the family, *Orthomyxoviridae*. This pathogenic virus causes significant types of diseases both in humans and in animals and comprises five genera on the basis of core proteins: Influenza virus A, Influenza virus B, Thogoto virus and Isa virus. Three surface glycoproteins of influenza virus; nucleoprotein, Hemagglutinin (HA) and neuraminidase (NA) are subdivided to differentiate influenza virus types. These viruses are believed to be transmitted primarily through droplets or respiratory secretions and aerosol from an infected person. Based on environmental conditions and factors such as temperature, humid surfaces, the virus can survive up to many hours (Blut 2009; Scholtissek 1985).

Influenza viruses are the most important members of this family that are major determinant of incidence and mortality and its outbreaks and can cause worldwide epidemics (Blut 2009; Scholtissek 1985). These viruses have ability to cause an acute respiratory disease called influenza. Its global prevalence has affected 5 -15% of adult population and 20–30% children. Pneumonia may develop as a complication and may be fatal, particularly in elderly persons with underlying chronic disease. Influenza type A is highly antigenic and responsible for bird flu, worldwide epidemics and pandemics influenza and types B causes recurring regional epidemics.

In the past 100 years, these viruses have been causing three major pandemics, (i) 1918-'Spanish Flu' (H1N1 strain), (ii) 1957-'Asian Flu' (H2N2 strain) and (iii) 1968-'Hong Kong Flu' (H2N3 strain). 1918-'Spanish Flu' was the worst pandemic associated with highest mortality ($\sim$40 million) worldwide (Table 4). In addition, recent outbreaks of avian subtypes such as H5N1, H9N2, H7N7, H7N3 and H10N7 in birds have caused occasional human diseases in distinct parts of the world (Blut 2009). The common signs and symptoms of influenza disease are sudden onset of fever, sore throat, cough, malaise and headache. The preferred definitive diagnosis is based on rapid influenza virus-specific antibodies detection in the serum via immunostaining tests such as immunofluorescence, enzyme immunoassay (ELISA), hemagglutination inhibition test (HIT) and the neutralisation test (Blut 2009). An inactivated vaccine against influenza virus has been used

for ~40 years to prevent the disease. Rimantadine and Amantadine are the choice of drugs being used for treatment of influenza A virus infections.

V. Human Coronaviruses (HCoV) and their diseases

The term Coronaviruses (CoVs) named for crown-like spikes on their surface in 1968 and belong to the family *Coronaviridae* was established in 1975 by ICTV. CoVs are enveloped, positive-sense, single-stranded RNA viruses with largest genome size ranged between 26.4 and 31.7 kb that have the ability to infect different animal species including birds and humans. They are emerging and re-emerging viruses which can cause upper respiratory tract, enteric and central nervous system (CNS) illness ranging from mild (common cold like symptoms) to fatal diseases. Coronaviruses include Severe Acute Respiratory Syndrome coronavirus-1 (SARS-CoV-1), Middle East respiratory syndrome coronavirus (MERS) and Severe acute respiratory syndrome Coronavirus-2 (SARS-CoV-2) which causes Coronavirus disease -2019 (COVID-19). There is now few licenced vaccines and antiviral or repurposed drugs available to prevent or treat infections. India was the first country in the world to introduce two successful indigenously developed Covid-19 vaccines, Covaxin (inactivated virus) and covishield (Coronavirus spike protein in Adenovirus vector) in January, 2021. CoV family consists of four genera, α-CoVs, β-CoVs, γ-CoVs, and δ-CoVs. There are 7 known human coronaviruses (HCoVs) species that can infect humans and can cause mild to severe respiratory illness. Four HCoV variants (HCoV-229E, HCoV-NL63, HCoV-OC43 and HCoV-HKU) can cause common mild cold-like symptoms in immunocompromised persons and other 3 (MER-CoV, SARS-CoV-1 and SARS-CoV-2) of the seven HCoVs caused global pandemic and are highly pathogenic with high transmission and fatality rates (Cui et al. 2018). Coronaviruses particularly SARS-CoV-2 is assumed to have transmitted from bat to human first in the animal meat market in Wuhan, China in 2019 (Zhou et al. 2020b).

a. **Severe acute respiratory syndrome coronavirus-1 (SARS-CoV-1)**. Only 12 animal or human coronaviruses identified before the emergence of SARS-CoV-1 in November 2002. The virus is contagious caused by SARS-CoV-1 which was first identified in China and then spread to 4 other countries. The virus potentially infects epithelial cells of the lungs which results in severe and potentially fatal upper respiratory tract illness (Ksiazek et al. 2003). The fatal SARS cases are mainly dominated by diffuse alveolar damage (Peiris et al. 2003). Following its introduction to Hong Kong in 2003, the virus transmitted to more than 30 countries and over 8,422 people were affected with yielding ~10% a global crude fatality rate (CFR) (Table 4). The virus infects humans and has been detected in palm civets and a raccoon-dog in a Southern China market (Lee et al. 2003). The ACE2 (angiotensin converting enzyme 2) transmembrane protein in humans and bats has been identified as an entry receptor into human cells for the SARS-CoV (Donoghue et al. 2000). It is an airborne virus and has ability to transmit from person-to-person and one country to another through infected person's small respiratory droplets. Currently, no

Table 4 Modes of emergence and re-emergence of most common human respiratory transmitted viruses (RTV) and their key characteristics

Respiratory transmitted viruses	SARS-CoV-2 	SARS-CoV-1 	MERS-CoV 	Influenza Viruses			
				H1N1 	H1N1/pdm09 	H2N2 	H5N1 
Disease(s)	COVID-19	SARS	MERS	Spanish flu	Swine Flu/Mexican flu	Asian Flu	Bird/Avian Flu
Known or suspected reservoir(s)	*Bats, Pangolin*	*Bats*	*Dromedary camels*	*Humans and swine*	*Swine, Turkeys, ferrets*	*Bird*	*Birds*
Genomic material	(+) single-stranded RNA	(+) single-stranded RNA	(+) single-stranded RNA	(−) single-stranded RNA	(−) single-stranded RNA	(−) single-stranded RNA	(−) single-stranded RNA
Incubation period	4–14 days	2–7 Days	6 Days	1–7 days	1–4 days	1–4 days	2–5 days up to 17 days
Basic reproduction number (R_o)	2.2	2.8	0.5	1.8	1.75	1.65	1.89
Transmission route	Direct contact via respiratory droplets or aerosols	Direct contact via respiratory droplets or aerosols	Direct contact via respiratory droplets or aerosols	Direct contact through coughing or sneezing from an infected person	Direct contact through coughing or sneezing from an infected person	Direct contact through coughing or sneezing from an infected person	humans contact with infected bird feces, nasal secretions, or secretions from the mouth or eyes
Common symptoms	Fever, cough, and shortness of breath	Fever, malaise, myalgia, headache	Fever, chills, myalgia, and cough	Sore throat, headache and fever	Fever, cough, headache, muscle or joint pain, sore-throat, chills, fatigue	lose weight, fever, sneezing, nasal discharge, pneumonia and seizures	Fever, cough, sore throat, muscle aches, conjunctivitis, breathing problems and pneumonia
Diagnosis	RT-PCR, Serological testing	RT-PCR	RT-PCR, Serological testing	PCR	RT-PCR, Rapid Influenza Diagnostic and Immunofluorescence	PCR	AVantage A/H5N1 flu test kit and RT-PCR

(continued)

Table 4 (continued)

Respiratory transmitted viruses	SARS-CoV-2 	SARS-CoV-1 	MERS-CoV 	Influenza Viruses			
				H1N1 	H1N1/pdm09 	H2N2 	H5N1 
Treatment Vaccine	Supportive No licenced vaccine	Supportive No licenced vaccine	Supportive No licenced vaccine	Traditional medicine No licenced vaccine	Flu Shot, Nasal Spray flu vaccine and monovalent (H1N1)pdm09 vaccine	Supportive No licenced vaccine	Vaccine AUDENZ is Available No highly effective treatment -oseltamivir
Outbreak periods and origin	2019–2020 Wuhan, China	2002–2004 Guangdong, China	2012, 2015, 2018 Saudi Arabia	1918–1920 Spain	2009–2010 Mexico	1957–1958 Guizhou, China	2003–2019 Southeast Asia and Egypt
Outbreak type	Pandemic	Epidemic	Epidemic	Biggest Pandemic	Pandemic	Pandemic	Pandemic
Estimated global cases and deaths	Cases-21,605,614 Deaths-768,226 (as of 15 Aug 2020)	Cases-8,422 Deaths-774	Cases-2499 Deaths-858	Cases-$\sim$500 million Deaths-$\sim$17–50 million	Cases-0.7–1.4 billion Deaths-151700–575400	Cases-$\geq$500 million Deaths-1–4 million	Cases-861 Deaths-455

approved antiviral drugs against SARS-CoV-1 are available. The rapid spread in the human population with high mortality of SARS-CoV-1, its transient re-emergence, and global economic disruptions led to a rush for research on the epidemiological, pathological, molecular, and immunological aspects of the virus and the disease. Due to non-specific clinical illness caused by SARS-CoV-1, diagnosing, management, development of treatment regimens and controlling future infectious diseases will require urgent global coordination to contain the infection and its future outbreak.

b. **The Middle East respiratory syndrome coronavirus (MERS-CoV)**. MERS CoV is a fatal zoonotic virus that cause MERS disease in humans and was first discovered in 2012 in Saudi Arabia and Jordan (Hijawi et al. 2013). From April 2012 and December 2019, a total of 2499 MERS-CoV infection cases and 858 associated deaths (CFR: 34.3%) were recorded in 27 countries of the world. Out of 2499 cases, the majority (2106 cases and 780 related deaths) of them were reported from Saudi Arabia (Arabi et al. 2014). The actual reservoir for MERS-CoV is presently not known but dromedary camels (*Camelus dromedarius*) are supposed to be the animal source of MERS-CoV infection transmitted to humans (see Table 4). Unlike SARS-CoV-1 infection, which was controlled soon after its outbreak, MERS-CoV infection continued to spread and cause human illness worldwide.

   For MERS-CoV infection the host cell dipeptidyl-peptidase 4 (DPP4, also known as CD26) was recognized as the receptor for the entry of the virus into the cell. The high case fertility ratio (CFR) in hospital-based and family-based cluster outbreaks was noted especially in co-morbid and immunocompromised patients. The route of human-to-human transmission of MERS-CoV infection could be through direct or indirect close contact, oral routes including consumption of contaminated food items. The incubation period of MERS-CoV infection ranges between 2 and 14 days (median 5.2 days). The clinical presentation of MERS-CoV infection varies from asymptomatic infection to acute to chronic respiratory illness with severe pneumonia, ADR (acute respiratory distress syndrome), respiratory and multiorgan failure leading to patient's fatal outcome. MERS-CoV infection can be detected by PCR and serological tests using different specimens (nasal swabs, saliva, urine, serum, and stool etc.) from MERS patients (Memish et al. 2020). Presently, there is no FDA-approved specific anti-MERS-CoV vaccine or drug are available for the treatment of MERS patients. However, supportive care/treatments are the main clinical management for these patients (Memish et al. 2015).

c. **Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)**. Since December 2019, COVID-19 (Coronavirus disease 2019) pandemic has serious ramifications on public health, severely affecting the global healthcare systems, killing millions of people, damaging economy and collapsing of numerous industries. The uncontrollable outbreak of COVID-19 is now wreaking havoc and escalating quickly in nearly 213 countries and territories including the most affected countries: USA, Brazil, India and Russia etc. But now India almost tops

the world with its daily toll of coronavirus infection touching 100,000 new cases per day. The novel coronavirus is now known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which was first originated in Wuhan, Hubei province of China on December 31, 2019, has now pandemic across the globe (https://www.worldometers.info/coronavirus/#countries; Chinazzi et al. 2020). At present (15 September, 2020), the global infection recorded is 29,789,734 and death has reached to 940,362. Cumulative global attempts are ongoing to find effective vaccines to control the viral spread as well treatments to save the life of millions of infected people world over (Table 3) (https://www.worldometers.info/coronavirus/#countries).

COVID-19 has been found to be caused by infection of a very aggressive type of coronavirus; SARS-CoV-2 which has more similarity (88% identity) with two bat-derived SARS-CoVs (bat-SL-CoVZC45 and bat-SL-CoVZXC21) but less sequence homology with SARS-CoV-1 (about 79%) and MERS-CoV (about 50%). (Lu et al. 2020b; Wu 2020). Based on its genomic analysis and phylogenetic relationships, bats have been associated to be most likely primary host for these viruses (Zhou et al. 2020b; Lu et al. 2020a, b; Shang et al. 2020). The virus infection can be asymptomatic, low/mild symptomatic and have strong binding affinity to human respiratory ACE2 receptor (Wan et al. 2020) on the lung epithelial cell surface causing highly lethal pneumonia and acute respiratory distress syndrome (Steben and Duarte-Franco 2007), multi-organs failure and death mainly in elderly people, the majority of whom have co-morbidity factors (Tang et al. 2020).

Genome structure and functions of SARS-CoV-2

SARS-CoV-2 is a spherical, small, enveloped positive-sense single-standard RNA (+ssRNA) virus (see Table 4) with its solar crown-like/club-shaped appearance due to surface spike glycoproteins (Zhou et al. 2020b; Lu et al. 2020a, b; Chan et al. 2020; Wu et al. 2020; Wu and McGoogan 2019). The RNA genome of this virus comprises as many as 29 open reading frames (ORFs) and size of genome is about 29.9 kb. It belongs to the family '*Coronaviridae*' and the genus *Betacoronavirus* (Khailany et al. 2020). SARS-CoV-2 RNA genome contains at least 16 non-structural proteins (nsps) to form the replication-transcription complex (RTC), 4 major structural proteins; nucleocapsid (N) protein, envelope (E) glycoprotein, membrane (M) glycoprotein and spike (S) glycoprotein) encoded by the viral genome on the envelope and 6–7 special structural and accessory proteins (HE protein, 3a/b protein, and 4a/b protein) that are translated from the sgRNAs of virus. Out of four structural proteins, spike (S) glycoprotein is cleaved into two glycosylated subunits (S_1 and S_2) which are responsible for binding to the host human angiotensin-converting enzyme-2 (ACE2) receptor and host-viral cell fusion (Tortorici et al. 2019). The transmembrane S protein has a higher affinity to bind to ACE2 receptor unlike in SARS-CoV-1 allowing the entry of virus into susceptible host cells leading to high chances of human-to-human spread and disease severity (Tortorici et al. 2019). The viral N protein binds to genomic RNA and synthesizes a helical capsid (ribonucleic capsid) which helps in viral genome protection,

replication and assembly of virions and also interacts with membrane and non-structural proteins (specifically nsp3). The M protein facilitates virions assembly and budding through enrolment of other SPs to endoplasmic reticulum-golgi-intermediate compartment (ERGIC) (Harapan et al. 2020). It also helps in the interaction with N protein for packaging of RNA into virion and may involve in mitigation of immune response. The last E SARS-CoV-2 protein localizes to ERGIC and involved in assembly, budding and viral pathogenesis (Hoffmann et al. 2020; Mousavizadeh and Ghasemi 2020). For SARS-CoV-1 and SARS-CoV-2, tissue cell culture models are suitable for characterising viral replication cycle, cell tropism, and virus-induced pathogenesis.

Disease pathogenesis and clinical manifestations

The binding of SARS-CoV-2 spike protein to ACE2 receptor allows the virus to enter and infect respiratory mucosa of the host cell (Hoffmann et al. 2020; Mousavizadeh and Ghasemi 2020). Replication cycle of virus mainly found in mucosal epithelium of upper respiratory tract and later further multiplication causes a severe lower respiratory tract infection (Zou et al. 2020). The virus spike proteins help it for the initial attachment and cellular entry through ACE2 receptor and then the virus hijacks the host cell and gain access into the cytoplasm. Studies have reported that this process is commonly accomplished by the cellular surface transmembrane protease, serine 2 (TMPRSS2) followed by membrane fusion with host cells (Hoffmann et al. 2020). Once the receptors binding and fusion completed, viral RNA is released, its genome is translated into polyproteins. Viral nucleocapsid is assembled from genomic RNA and R protein in the cytosol and formation of mature particles by budding into the lumen of the endoplasmic reticulum (ER) (see Fig. 4) (Shereen et al. 2020; Zhou et al. 2020a). The mature virions are then released from the host's infected cell through exocytosis and are transmitted to infect other organs cells of the body such as liver cells, kidney cells, intestine, and lymphocytes as well as lower respiratory system.

Initially, the majority of COVID-19 patients remain asymptomatic and may transmit infection in vulnerable people. Thus, understanding clinical manifestations and following-up of asymptomatic COVID-19 patients is important during coronavirus infection. The sign and symptoms of COVID-19 in patients appear between 5 and 14 days (Wu and McGoogan 2019; Singhal 2020). In rare cases, the incubation period has been found to be as long as 24 days (Harapan et al. 2020; Huang et al. 2020b). The duration of incubation period is based on a number of factors including patient's age, history of co-morbidity, immune system, but majority of infected patients can show symptoms in 11.5 days after virus exposure (World Health Organization (WHO) 2020a; Lauer et al. 2019). SARS-CoV-2 typically causes mild to moderate upper respiratory tract infections but occasionally it can cause severe pneumonia and lower respiratory tract infections with extrapulmonary clinical manifestations in both immunocompromised and older patients. COVID-19 patients usually experience several common symptoms including fever, cough, myalgia, sore throat in conjunction with some other uncommon respiratory problems such as headache, fatigue, diarrhoea, runny nose, dyspnoea, breathing

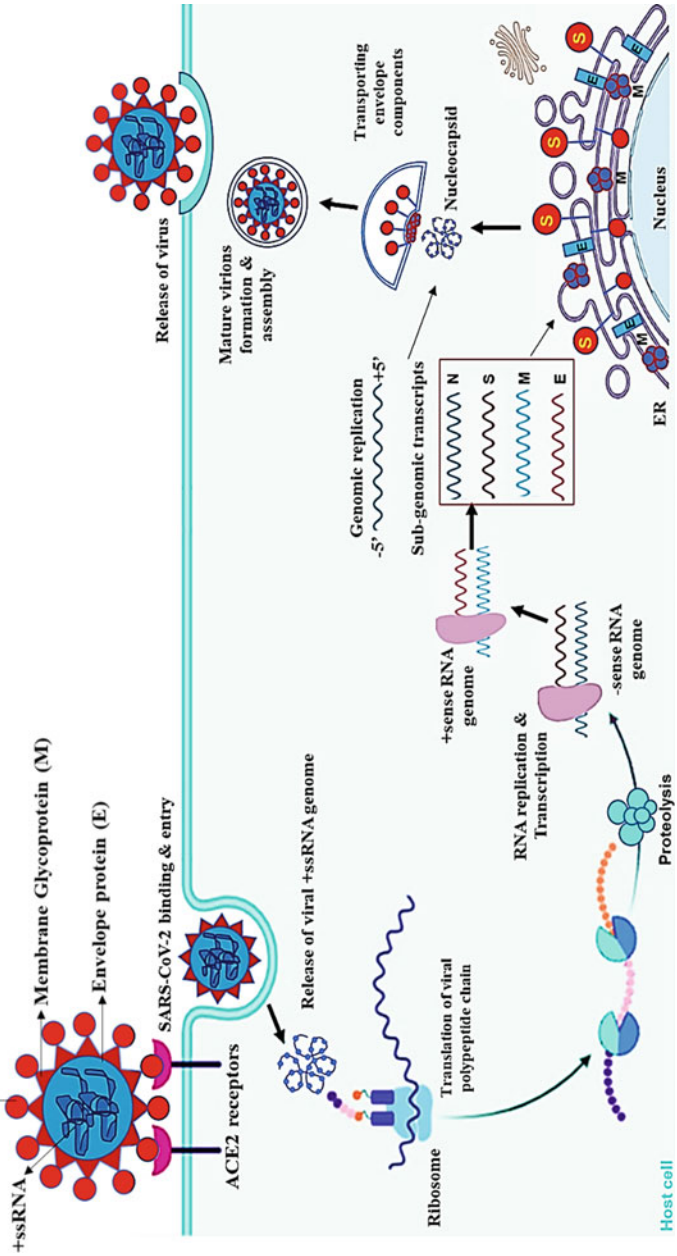

Fig. 4 Novel coronavirus transmission and pathogenesis cycle in the host cell. Spike (S) glycoprotein of SARS-CoV-2 bind to ACE2 receptors on the surface of the target cell membrane allowing virus to enter into the host cell through the endosomal pathway leading to high chances of disease pathogenesis and severity. Next, virus genomic ssRNA unveiled and releases in the cytosol of host susceptible cell. After human ACE2 receptor binding and viral-host cell fusion, virus RNA transcribed and proteins are synthesized in the cytoplasm. Viral helical ribonucleic capsid synthesized, virions assembled at the cell membrane and genomic RNA packaged into virion and mature particle forms by budding into the lumen of the endoplasmic reticulum (ER). The mature virions then released through exocytosis and begin pathogenesis to infect other organ cells

difficulty, pneumonia to acute respiratory distress syndrome (Stebbing et al. 2020), and even death in severe and older patients (Adhikari et al. 2020; Wu et al. 2020; Huang et al. 2020b). The infection of SARS-CoV-2 can be detected in bronchoalveolar-lavage (93%), sputum samples (73%) nasal swab (63%), pharyngeal swab (32%) (Bastola et al. 2020; Wang et al. 2020b, c) and saliva samples (12–50%) (Zhang et al. 2020a, b; To et al. 2020). The overall fatality rate (CFR) depends between country to country but a global rate appears to be around 6.2.% (Abduljalil and Abduljalil 2020). The estimate of reproductive number (R_0) of SARS-CoV-2 varies between 2.2 and 5.7 (Wang et al. 2020a) which is higher than SARS-CoV-1 (Guan and Zhong 2020; Liu et al. 2020).

Potential targets for SARS-CoV-2

Human ACE2 is a surface receptor that protects host from lung injury but it serves as a point of entry for SARS-CoV-2. ACE2 is also identified as binding partner of the SARS-CoV-1 spike (S) protein. Recent functional studies are revealing that SARS-CoV2-ACE2 binding-directed treatment strategies can inhibit the entry of virus into the host cell which can be an ideal antiviral therapeutic target for SARS-CoV2 (Zhang et al. 2020a, b). Cell surface protease enzyme, TMPRSS2 (transmembrane serine protease 2) can cleaves both spike (S) and ACE2 protein of SARS-coronaviruses. Cathepsin L is a lysosomal pH-dependent protease that facilitates SARS-CoV entry via endosomes. Thus, targeting expression and activity of both TMPRSS2 and Cathepsin L may be potential approaches in developing antiviral drug for the treatment of COVID-19 (Lindahl and Li 2020). Furin is a protease enzyme that cleaves envelope proteins of various influenza viruses, HIV, ebolavirus and certain coronaviruses. Furin-like cleavage site has recently been identified in the protein sequence of S glycoprotein of the SARS-CoV-2. Inhibiting Furin can block the cleavage of SARS-CoV-2 S protein and suppress virus production which may serve as a new therapeutic target for SARS-CoV-2. Further, Phosphatidylinositol 3-phosphate 5-kinase (PIKFYVE) is a kinase synthesizes a class of phosphoinositides that are essential for early endosome formation and its activity required for human SARS-CoV-2 infection. Inhibition of PIKfyve kinase using specific inhibitors (Apilimod) have strong antiviral activity and may serve as potential targets for the development of small-molecules against SARS-CoV-2 representing potential COVID-19 therapeutic approach (Bouhaddou et al. 2020; Kang et al. 2020).

Detection, Diagnosis and Treatment of COVID-19

Suspected person can be tested for infection based on the clinical manifestations or who have travelled from COVID-19 affected part of world. Clinical presentation accompanied by radiographic assessment and standard molecular diagnosis are the possible methods for definitive diagnosis. The majority of COVID-19 symptomatic patients show bilateral involvement under chest X-ray and computed tomography (CT) imaging. CT image diagnosis is a non-invasive method that contains a number of X-ray measurements at various angles across a chest to generate cross-sectional images which mainly depends on the stage and onset of symptoms after viral

infection. Furthermore, viral RNA can be detected in various respiratory specimens (nasopharyngeal swabs, sputum, bronchoalveolar lavage fluid, blood, deep throat saliva and fibro-bronchoscope brush biopsy) by qRT-PCR method (Xu et al. 2020). Viral protein testing for SARS-CoV-2 infection can be also used for the diagnosing of COVID-19 patients. Serological testing such as ELISA, neutralization assay, chemiluminescent immunoassay and immunochromatographic assays could also be used to check immunologic reaction and which can detect IgM, IgG, or total antibodies against virus. In addition, genome sequencing may be performed to analyse mutational landscape (World Health Organization 2020b, c).

On the basis of clinical presentation, the clinical stages are categorised into 3 phases; (i) the acute phase (pneumonia) (Katakura et al. 2005), (ii) the chronic phase (viremia) and (iii) the recovery phase. If patient's immune system in pneumonia phase functions effectively, and no other diseases exists, the virus can be successfully suppressed and infection can get cleared and enter the recovery phase. If the patient's immunity is weak or the patients are older or associated with comorbidities, the immune system cannot function effectively to control the virus in pneumonia phase and the patient will become critical or go to viremia phase. During the infection period, total leukocyte count in the early stage of the disease is slightly low (lymphopenia) and may gradually decrease when the disease progresses, which may affect antibody production in infected patients (Wang et al. 2020a; Guan and Zhong 2020). Further, a high level of D-Dimer, C-reactive protein, inflammatory cytokines, blood urea nitrogen, creatinine and high prothrombin time are frequently noted among severe patients or non-survivors (Wang et al. 2020a).

Recommendations for admission to critical care units (oxygen-based therapy), strategies for community transmission control, and measures to reduce health care-associated spread are being established (Wax and Christian 2020). More importantly, a thorough understanding of natural history and biological behaviour of the virus and the disease is urgently needed to develop targeted therapies and/or more effective vaccines.

A number of antiviral drugs that have been used for the treatment of other viral diseases have been tried on COVID-19 patients but only with limited success. A recent study showed that effective concentrations of combinational therapy with remdesivir/lopinavir/Ivermectin (protease inhibitors), homorringtonine and emetine against SARS-CoV-2 are proven to have significant improvement on patient's clinical outcome (Choy et al. 2020). Other studies or case reports indicated that combination treatment with anti-HBV (IFN-alpha) and anti-HIV ritonavir-boosted Lopinavir drugs have anti-SARS-CoV activity (National Health Commission of the People's Republic of China 2020). In addition, remdesivir has been shown antiviral activity against SARS-CoV and MERS-CoV both *in vivo* and *in vitro* studies and now used as a potential drug on a compassionate basis for COVID-19 patients treatment (Wu et al. 2020; Holshue et al. 2020; Sheahan et al. 2020). A number of multicentre clinical trials recently conducted in multiple hospitals in various countries to assess safety and efficacy of chloroquine (CQ) or hydroxychloroquine (HCQ) (antimalarial and antirheumatic drugs) for the treatment of COVID-19

patients and these drugs were found to be safe and effective in treating COVID-19 patients (Gao et al. 2020; Savarino et al. 2003). and have potential to inhibit virus entry into the host cells by interfering with the glycosylation of its ACE2 receptor (Huang et al. 2020a). Recently, combination therapy of HCQ and azithromycin have been found to have a significant synergistic effect in decreasing viral load, effective for acute infection and associated with reduced mortality rate in COVID-19 patients (Gautret et al. 2020; Molina et al. 2020). Furthermore, several other potential drugs such as Arbidol, Favipiravir, Umifenovir (Targeting ACE2/S protein), darunavir/cobicistat, Tocilizumab, Camostat mesylate (TMPRSS2 inhibitor), emtricitabine/tenofovir alafenamide and baloxavir are being assessed in clinical trials and now recommended for treatment of COVID-19 patients in various countries including China, Russia and Japan (Harrison 2020). Favipiravir inhibits the SARS-CoV-2 by targeting the catalytic domain of nsp12 and recommended for the treatment of COVID-19. Other immunomodulatory drugs, herbal or bio-active compounds can act as anti-viral agents and used to improve immunity against SARS-CoV-2 in patients (Ingraham et al. 2020; Panyod et al. 2020). Though, these drugs are potentially effective against COVID-19 patients but at this point these are not routinely recommended as standard treatment for SARS-CoV-2. Hence, there is an urgent need for large-scale global coordination for the development of therapeutic vaccine and/or anti-SARS-CoV-2 drug for an effective treatment and control of COVID-19 pandemic. A large number of patients hospitalized with Covid-19 have developed high level of life-threatening blood clots leading to deadly thromboembolic events. Therefore, patients treated with anticoagulants showed improved survival. It is demonstrated that Covid-19 patients given anticoagulants orally or intravenously can prevent possible deadly events such as heart attack, strokes and pulmonary embolism in Covid-19 patients.

Prevention and vaccine approach

A number of features of SARS-Cov-2, including long incubation period, asymptomatic feature and transmission from asymptomatic subjects and recurrent mutations etc. make prevention and management of the disease difficult. Supportive care strategies are critical for dealing with COVID-19 infected patients. Preventive measures such as self-isolation, social/physical distancing, avoiding unnecessary community gathering and use of face mask are being recommended and are mandatory to prevent and control disease spread. Nearly every government in the world are taking precautionary actions such as partial/complete lockdown; public distancing, self-isolation/quarantine (14 days) and fast testing etc. to reduce and control the spread of highly contagious corona virus and in most cases it is working effectively. Quarantine of suspected people helps in reducing the possibility of infection transmission to healthy population. Community lockdown by several nations at the early onset of the outbreak meant limiting possibility of community transmission. Extensive thermal screening of people remains initial step for identification of COVID-19 symptom and mandatory use of face mask and keeping distance (of no less than 2 m) and regular washing of hands with soap or sensitization of hands especially when coming home from outside are ways to protecting

and control person-to-person transmission of infection. Healthy diet, fresh air and normal amount of exercise have been found to improve immunity and fight against the infection (Fig. 5). Also, prophylactic use of some medicines such as paracetamol, certain herbal preparation including Homeopathic medicines such as Arsenicum, Rhus toxicodendron and Mercurius solubilis are often recommended.

Until such time the virus exists amongst us and as there is no specific treatment available for COVID-19 patients, except vaccine or administration of analgesic and antipyretic drugs, respiratory support through mechanical ventilation and use of pre-existing antibiotic/antiviral drugs are to control the disease. The most effective long-term approach for prevention and elimination of COVID-19 outbreaks would be the development of an effective SARS-CoV-2 specific vaccine which only can provide immunological protection against this virus. However, currently researchers all over the world are battling for the development of effective SARS-CoV-2 vaccine and its universal access to end the pandemic. Currently, ≥ 100 candidate vaccines are under development globally, and amongst them more than ten were at advanced stage of clinical trials on human subjects (Amanat and Krammer 2020). There are atleast 10 vaccines are already placed in immunization program in different countries (see Table 5). In India, two indigenous vaccines were developed, Covaxin (Bharat Biotech and National Institute of Virology, Pune ICMR), an inactivated Corona vaccine while Covishield (Serum Institute of India in collaboration with AstraZeneca, Oxford UK) is a Corona virus spike protein in adenovirus vector called AZD1222 and ChAdOx1. Both vaccines together have been given to more than 60 millions people in India. The data indicate that the Covishield vaccine has an overall efficacy of 70% with vaccine efficacy at 62.1%. while Covaxin has been r reprted 81% effective in an intrim analysis 2,58,000 participants. Both vaccines were found to be safe and triggerd good immune responses.

Conclusion

Persistent Sars Cov-2 infections may induce a number of cellular and biomolecular modifications in the host, which can evolve over time, leading to an increased risk of variety of human diseases including cancer. One of the first approaches could be large clinico-epidemiological studies to obtain a better understanding of the natural history and biological behavior of virus infection and its relationship with specific human diseases. Some studies focused on the increased use of antipyretics and other drugs available over the pharmacy counter without proper medical prescription, that are able to suppress the symptoms of acute infections regardless of possible effects on the immune system, resulting in an increased risk of disease development. Other priority research could be development of vaccines against various infectious agents to control the disease and associated mortalities. As a matter of fact, the development of vaccines against HBV for young children and HPV vaccines for adolescent girls can be considered as an effective prevention strategy for two most prominent cancers (hepatocellular and genital carcinomas). Further studies are needed to fill our knowledge gaps on the link between emerging, re-emerging and pre-existing viral infections both acute and chronic and the

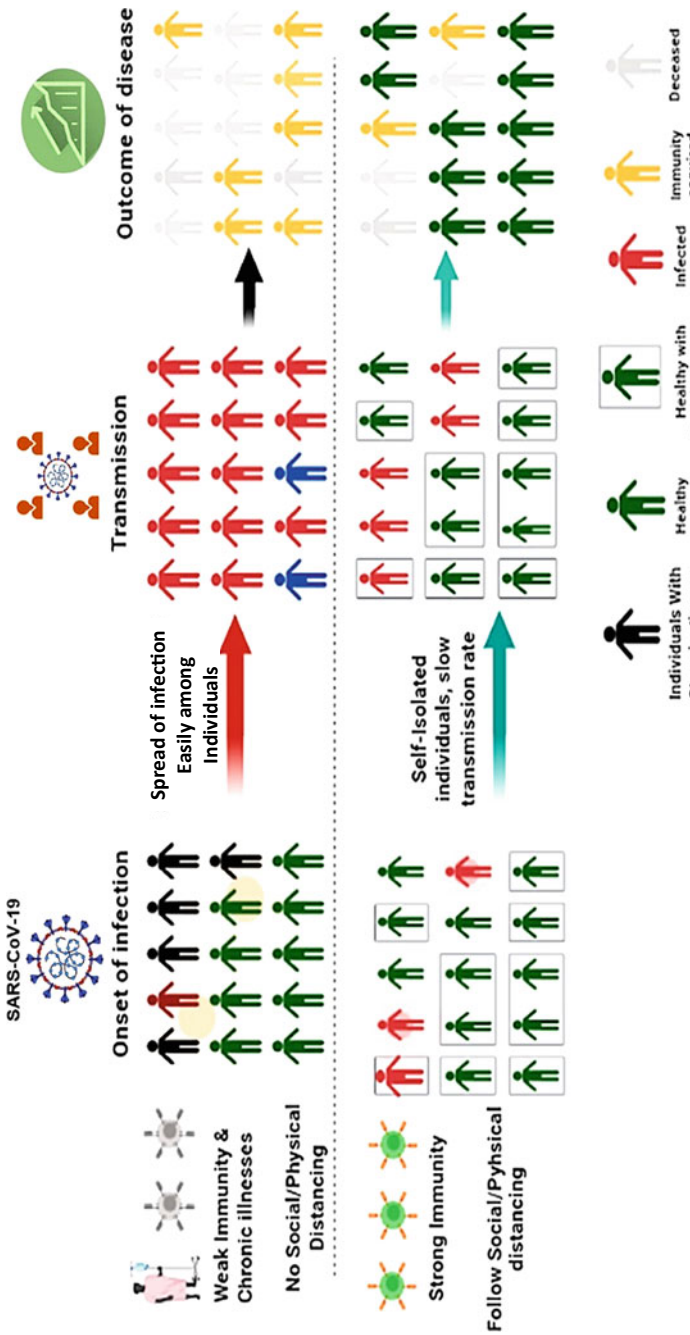

Fig. 5 Social/Physical distancing and strong immunity slow down the rate and extent of community transmission of SARS-CoV-2 infection which eventually leads to reduce disease incidence and mortality

Table 5 List of corona virus vaccines

S. No.	Vaccine Name	Vaccine Type	Primary Developers	Country of Origin
1	Comirnaty (BNT162b2)	mRNA-based vaccine	Pfizer, BioNTech; Fosun Pharma	Multinational
2	Moderna COVID 19 Vaccine (mRNA-1273)	mRNA-based vaccine	Moderna, BARDA, NIAID	USA
3	COVID-19 Vaccine AstraZeneca (AZD1222); also known as Covishield	Adenovirus vaccine	BARDA, OWS	India & UK
4	Sputnik V	Recombinant adenovirus vaccine (rAd26 and rAd5)	Gamaleya Research Institute, Acellena Contract Drug Research and Development	Russia
5	COVID-19 Vaccine Janssen (JNJ-78436735; Ad26.COV2.S)	Non-replicating viral vector	Janssen Vaccines (Johnson & Johnson)	The Netherlands, USA
6	CoronaVac	Inactivated vaccine (formalin with alum adjuvant)	Sinovac	China
7	BBIBP-CorV	Inactivated vaccine	Beijing Institute of Biological Products; China National Pharmaceutical Group (Sinopharm)	China
8	EpiVacCorona	Peptide vaccine	Federal Budgetary Research Institution State Research Center of Virology and Biotechnology	Russia
9	Convidicea (Ad5-nCoV)	Recombinant vaccine (adenovirus type 5 vector)	CanSino Biologics	China
10	Covaxin	Inactivated vaccine	Bharat Biotech, NIV-ICMR	India

development of various viral diseases including cancers in human. The present COVID-19 pandemic has taught us great lesion to conform the continued threat of infectious viral diseases and new infections that may evolve for which world should be prepared to face the future challenges. Whether SARS-CoV-2 or any other

highly pathogenic virus will emerge or re-emerge as an epidemic infection is currently not possible to predict. However, constant awareness and viral surveillance studies on animal species around us including bats, rodents, birds, ticks, mosquitoes and livestock, are essential to understand the pathobiology of potential human pathogenic agents that exist around us in the environment before they can spill-over. Therefore, there is a need for research on these potential emerging viruses and human development associated variation in microbiomes and to develop broad-spectrum prophylactic vaccines and therapeutic approaches to control viral diseases and to remain prepared for the present as well as future emerging and re-emerging pathogenic viruses and other microbes.

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