Emerging and re-emerging viral diseases: risks and controls

M. Khalid Parvez

Department of Pharmacognosy, King Saud University College of Pharmacy, Riyadh 11451, Saudi Arabia

In the present globalized world with overflowing travels and trades, human health has been increasingly threatened due to incidences of emerging or/and re-emerging infectious diseases. The most important sources of novel human pathogens are mainly farm mammals and poultry, and to some extent, wild animals and arthropods. It is estimated that zoonosis constitute about 60% of the 'known', and up to 75% of 'emerging' new human infections. A disproportionate number of such pathogens are viruses, suggesting their potential to evolve and adapt in humans, more rapidly than other infectious microbes. The best examples are the severe acute respiratory syndrome-coronaviruses (SARS-CoV) and influenza A viruses (H5N1 and H1N1 strains) that continue to cause outbreaks, epidemics and occasional pandemics across the globe. The most recent additions to the list include identification of severe fever with thrombocytopenia syndrome virus (SFTV) in China, a novel CoV-EMC in the Middle East and Lujo virus in southern Africa. The key to understand the emergence/re-emergence of novel pathogens, including viruses, is to know the intricate 'host-pathogen-environment' relationship in microbe evolution. The underappreciated aspect of growing human populations, global climate and land-use changes, and the introduction of anthropophilic vectors is the selective pressure on hosts, and pathogen reservoirs. We have however, limited knowledge of such zoonosis and the diversity of these pathogens in their known non-human reservoirs. Nevertheless, while there is little information on some of the domestic animals hosting a few dozen virus species, we have insufficient data on wild mammals that harbor over 5,000 virus species. Despite extraordinary scientific advances during the past two decades, emerging infectious diseases continue to kill about 15 million people every year. The new approach to consumable animal product-safety and to protecting humans against foodborne infections is the most stringent control measure. However, the current biosecurity guidelines appear to have been generally more successful for constraining bacterial pathogens rather than viral infections. With the complete disappearance of smallpox and the near-eradication of polio, with measles on the path to elimination; significant progress in controlling HIV and hepatitis B and C viruses have been made. The unpredictable nature of novel infections and the rare occasions of outbreaks with small number of confirmed cases, severely hamper the control and preventive modalities. Nevertheless, despite substantial effects on global public health and economy, and growing understanding of pathogens biology and etiology, the emergence of novel pandemic viruses remain to be inherently inconclusive.

Keywords Emerging infectious diseases, Emerging pathogens, Emerging or re-emerging viruses

1. Introduction

Incidences of emerging infectious diseases have exerted the greatest toll on human health due to the present globalization process with increased cross-border travels and trades, as well as the steady climate change. The knowledge that human diseases periodically emerge or/and re-emerge, actually goes back millennia when ancient Greek, Roman and Persian philosophers wrote about devastating plagues [1,2]. The unforgettable 1918 'Spanish Flu' or 'La Grippe' pandemic, cited as the deadliest natural disaster in human history, had killed up to 100 million people. The pandemic was repeated in 1956 as 'Asian Flu' (~2 million deaths) and in 1968 as 'Hong Kong Flu' (~1 million deaths), and recently re-emerged in 2009 as 'Swine Flu' (~18000 deaths). A very recent discovery of a 14th century hastily-built cemetery in London in 2013 [3], has refreshed the 'Black Death' pandemic or bubonic plague that devastated England in 1347-1351. John Stow, the 16th century historian had documented the burial of more than 150,000 Black Death victims in London alone, including 50,000 at a site in Farringdon known as 'No Man's Land'. Historically, about 75 million people and up to 60% of the European population are recorded to have died in this four-year global pandemic [3]. During and after the Black Death pandemic, European government officials had quarantined arriving ships and passengers and set up emergency clinics to prevent its importation to the city. In the 15th century again, England was hit by a mysterious disease, the 'Sweating Sickness' that had spread by human-to-human contacts. With the developing scientific knowledge in the late 17th century, Robert Boyle, specifically observed that '*there are ever new forms of epidemic diseases appearing…among (them) the emergent variety of exotic and hurtful…'* [4]. Subsequently by the mid of 19th century, the revolutionary discovery that some microbes cause infectious diseases had led to the development of passive immunization, vaccines, and antimicrobial drugs. These biomedical advances spurred over-estimated optimistic predictions that any such infections would be conquered soon. And thus, physicians and public health workers began to neglect the possibilities of the emergence or re-emergence of novel pathogens. Again, in the late 20th century, the symptoms of the Medieval 'Sweating Sickness' re-emerged that matched with 'Hantavirus pulmonary syndrome (HPS)' caused by Hantavirus (HNV) outbreaks in Latin America [5,6]. Notably, another outbreak of HPS in the Four Corners region in the southwestern United States led to the discovery of Sin Nombre virus (SNV) in 1993. Actually, to a large extent, it was the shocking recognition of human immunodeficiency virus (HIV) in the early 1980s that rekindled awareness of, and research interest in emerging infectious diseases. As a result, the concepts of newly emerging and re-emerging infectious diseases have recently become much more widely appreciated.

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Nevertheless, taking its pandemic course, a novel SARS-CoV infection had affected at least 8,422 people with 916 deaths in Asia-pacific region in 2002-2003 [7]. And very recently in 2013, 'Bird Flu' caused by a novel avian influenza A strain (H7N9) has emerged in China. To remind the readers, the first human cases of 'Bird Flu' (H5N1) outbreak had occurred in Hong Kong in 1997 that subsequently spread through Asia-pacific, Africa, Europe and North America. Currently, despite substantial effects on global public health and economy as well as advancements in understanding of pathogens biology and preventive breakthroughs, the emergence of novel pandemic viruses remains an everlasting puzzle.

2. Emerging or re-emerging viral pathogens

Human emerging or re-emerging pathogens are defined as novel etiological agents that have recently manifested in a population and were not known previously, elsewhere. Over the past several decades, sporadic and often isolated outbreaks of emerging human diseases have led to the discovery of a diverse array of novel, highly pathogenic viruses belonging to, but not limited to *Filoviridae*, *Arenaviridae*, *Annuloviridae Bunyaviridae*, *Paramyxoviridae*, *Coronaviridae* and *Flaviviridae* families (Table 1). The best examples are the major devastating incidences of SARS-CoV and influenza A (H5N1-Bird Flu and H1N1-Swine Flu) infections causing outbreaks, epidemics and occasional pandemics across the globe. These incidences resulted in substantial economic loss across the world, the Asian-Pacific region, in particular. The most recent additions to the list include identification of SFTV in China, a novel human CoV-EMC (hCoV-EMC) in the Middle East and UK as well as Lujo virus in southern Africa.

After the first discovery of the simian virus 40 (SV40) before half a century [8], several pathogenic human polyomaviruses have been identified, including BK virus (BKV) [9] and JC virus (JCV) [10]. Another such pathogen, the Merkel cell polyomavirus (MCV or MCPyV) that is one of the seven known human tumor viruses, was identified in the aggressive form of skin cancer, Merkel cell carcinoma (MCC) [11]. The HNV are a relatively newly discovered genus of human viruses that caused 'Korean hemorrhagic fever (HFRS)' outbreak during the Korean War affecting thousands of United Nations soldiers. In addition to SNV, several other HNV have been implicated as etiologic agents for either HFRS or HPS, discussed above. Recently in September-October 2008, Lujo virus which caused fatal human infections in Southern Africa became the first pathogenic arenavirus discovered in over forty years [12].

Table 1 Summary of some important emerging and re-emerging human viruses

Family	Virus	Zoonosis	Etiology
Filovirideae	Ebola virus	Primates	Ebola hemorrhagic fever
	Marburg virus	Bat	Marburg hemorrhagic Fever
Arenavirideae	Lassa virus	-	Lassa fever
	Lujo virus	-	-
	Junin virus	Mouse	Argentine hemorrhagic fever
	Guanarito virus	-	Venezuelan hemorrhagic fever
	Machupo virus	Mouse	Bolivian hemorrhagic fever
	Sabia virus	Rodents	Brazilian hemorrhagic fever
	Chapare virus	-	-
Bunyavirideae	CCHFV	Ticks	Crimean Congo hemorrhagic fever
	SFTSV	Arthropod	Severe fever with thrombocytopenia
	Andes virus	Rodents	Hantavirus cardiopulmonary syndrome
Paramyxovirideae	Nipah virus	Bat	Nipah disease
	Hendra virus	Bat	Hendra disease
Coronavirideae	Influenza virus	Swine, Bird	Seasonal/Swine/Bird Flu
	SARS-CoV	Bat	Severe acute respiratory syndrome
	hCoV-EMC	-	Severe acute respiratory syndrome
Lyssaviruses	EBLV	Bat	Fatal encephalitic disease
	ABLV	Bat	Fatal encephalitic disease
	IRKV	Bat	Fatal encephalitic disease
Togavirideae	Chikungunya virus	Mosquito	Chikungunya fever
Anellovirideae	TTV	Mammals, Bird	Chronic liver diseases
Hepevirideae	HEV	Swine, Boar	Chronic hepatitis E. Neuropathy

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3. Zoonosis

Infectious microbial diseases account for about 40% of the burden of human mortality and morbidity in developing countries. Approximately 70% of protozoa, 40% of fungi, 50% of bacteria, and 80% of viruses that infect human beings are zoonotic [13]. Of note, majority of known viruses that infect humans, indeed, perpetuate naturally in non-human 'reservoirs' (Figure 1). Most of the identified pathogen reservoirs are mammalian (~80%) or, to a lesser extent, avian and invertebrates vectors or intermediate hosts [13,14,15]. The most important sources of novel human pathogens are mainly farm mammals and poultry, and to some extent, wild animals hunted for game meat. It is estimated that zoonotic infectious agents constitute about 60% of the known human pathogens, and up to 75% of 'emerging' human infections [16]. We have however, limited knowledge of such zoonosis and the diversity of these pathogens in their known reservoirs. Nevertheless, while there is little information on some of the domestic animals hosting a few dozen virus species, we have insufficient data on wild mammals that harbor over 5000 virus species [Cleaveland et al., 2001]. Examples include emerging human viruses like, novel influenza strains, human-CoV (hCoV), Hendra virus, Nipah virus and few others, all linked to zoonosis. Very recently, the alarming outbreak of a novel hCoV-EMC in the Middle East and the United Kingdom has raised the possibility of its zoonotic origin because of its close genetic homology with bat CoV, but not to any other known hCoV [17]. Limited surveillance data show that bats harbor the greatest diversity of CoVs that varies from region-to-region and species-to-species [18]. The lyssaviruses are zoonotic pathogens within the family *Rhabdoviridae* that are of global importance as the cause of a fatal encephalitic disease in humans. Rabies virus (RABV) is the archetypal lyssavirus and historically is one of the most feared viruses known to man and the only virus that is invariably fatal [19]. Of the 12 species of lyssavirus, the majority are predominantly associated with infection in bats. Within Europe, alongwith RABV in terrestrial wildlife populations, European Bat Lyssavirus type-1 and -2 (EBLV-1 and EBLV-2) and Bokeloh Bat Lyssavirus (BBLV) are characterized. In Oceania, Australian bat lyssaviruses (ABLV) isolated from five different bat species, have been implicated in human fatalities [20,21,22]. Very recently, death of an Australian boy bitten by a bat died of ABLV infection. Other lyssavirus strains are also reported to circulate in North American and European bats. Further, four Eurasian lyssaviruses have been described that include Aravan virus (ARAV) in Kyrgystan [23], Khujand virus (KHUV) in Tajikistan [24], Irkut virus (IRKV) in Eastern Siberia [24] and West Caucasian Bat virus (WCBV) in Russia [23]. Fortunately, only IRKV has been related to human , so far [25].

HNV are another example of zoonotic viruses where the reservoir rodents: dear mouse, rice rat and cotton rat become a threat when they enter human habitation in rural and suburban areas of the North, Central and South America [26]. The first avian influenza A virus (H5N1) to infect humans occurred in Hong Kong in 1997, and cases of 'Bird Flu' have since been reported in Asia-Pacific, African and European nations. Moreover, in addition to human and swine, a chain of natural mammalian hosts for hepatitis E virus (HEV) is growing that includes deer, boar, mongoose, rabbit, rat and goat [27]. Another example would be the newly established virus family *Anelloviridae* that includes Torque Teno viruses (TTV) pathogenic to humans, swine, cow, sheep, cat, dog and chicken [28].

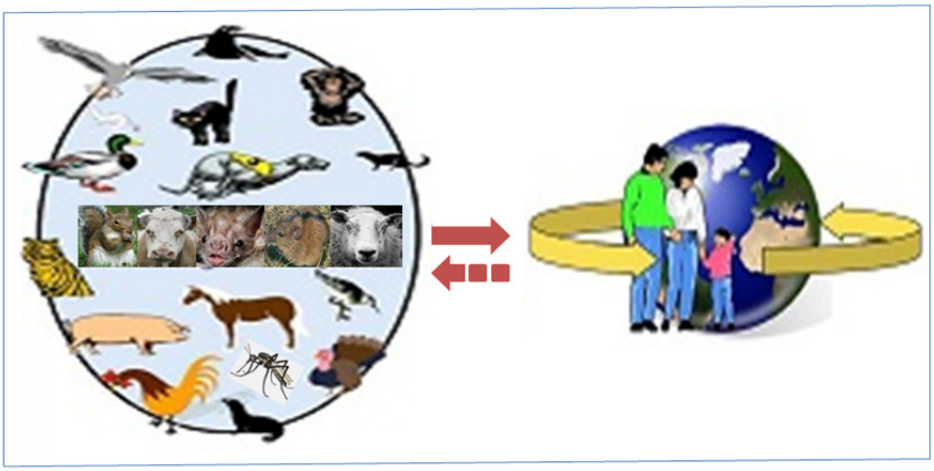

Fig. 1 'Zoonosis' as a potential source of global emerging/re-emerging human health threat at the 'host-pathogen-environment (HOPE)' interface.

Arboviruses are the arthropod vector-borne human pathogens. During 17th to 19th centuries, shipping traffic resulted in the transport of larvae of several important mosquito species, such as *Aedes* (vector of dengue, yellow fever and chikungunya viruses) and *Culex* (vectors of West Nile virus) species. West Nile and chikungunya viruses are among the best understood arboviruses to have emerged in the past two decades. Since the discovery of West Nile virus, the etiological agent of meningoencephalitis in New York in 1999 [29], the failure to identify its vector and the initial control efforts allowed its spread in North America in 2002-2003 [30]. Further, an outbreak of another vector-borne,

Chikungunya virus eventually affected more than a third of the entire population of Réunion Island in 2005-2006 [31,32]. Chikungunya virus has been also reported to cause continuing epidemics in Indian subcontinent, with millions of cases [33]. While Chikunguniya virus has caused smaller outbreaks in Europe, other arboviruses attributed to small outbreaks, including dengue virus in Hawaii and Zika virus in the Micronesian island of Yap [15]. Furthermore, Crimean-Congo hemorrhagic fever virus (CCHFV) is considered to be one of the major emerging disease threats spreading to and within the European nations following an expanding distribution of anthropophilic ticks [34]. Every year more than 1000 cases of CCHF due to human-to-human transmission, are reported from countries of south-eastern Europe, including Turkey. SFTSV, a previously unidentified tick-borne bunyavirus has recently emerged in China with mortality rates as high as 30% [35].

4. Virus evolution and adaptation to humans

A disproportionate number of human emerging or re-emerging infectious agents are viruses, suggesting their potential to evolve more rapidly than other pathogens. A potential pathogen needs to possess the molecular machinery to successfully infect host-in-contact i.e., to enter the tissues or cells, replicate and exit the host to further infect other healthy population. Among the human viruses, DNA viruses, like anelloviruses, papillomaviruses and herpes viruses are believed to have been evolved and diversified within humans for millions of years [28,36]. By contrast, most human RNA viruses are likely to have much more recent evolution and 'human-adaptation' for only thousands of years [37,38]. As per the International Committee on Taxonomy of Viruses (ICTV) data, 158 human RNA virus species with 47 genera and 17 families are recognized; of that only a minority is 'human-adapted' [39]. In the recent six years, at least 20 new 'species' of human RNA viruses have been approved by ICTV. On the other hand, only 91 human DNA virus species consisting of 22 genera and 8 families are described. It is estimated that RNA viruses from 52 (33%) species fall into 'human-adapted' category, and of these 18 have the ability to naturally infect non-human hosts while many more being capable of infecting the same under laboratory conditions. By comparison, nearly 87% of human DNA virus species are human-adapted [39]. In the human-adaptation process, the viral genetic re-assortment or virus-host genetic recombination might lead to the establishment of stable virus lineages in human populations. It is therefore, very much possible that such human-adapted viruses could circulate asymptomatically and remain undetected until its novel clinical manifestations. To further understand, a recently isolated HEV genotype 3 from a chronic hepatitis E patient that contained recombinant virus-host RNA genome was shown to infect cultured human, swine and deer hepatocytes [40]. The human-adapted TTV is associated with autoimmune rheumatic diseases, liver pathologies and respiratory complications [28].

Differential host factors, like age, physiology, immunocompetence and genetics are determinants to human susceptibility to an infection. Host factors often receive less research focus than does pathogen virulence, but improved knowledge of host responses is essential to understand the species-barrier and why some zoonotic pathogens are benign in their natural hosts but lethal to humans. The role of evolutionary adaptation in enabling viruses to establish in human circulation is a subject of active research. Nevertheless, phylodynamics that combines a modeling framework for host, epidemiological, and molecular data, especially for RNA viruses, shows particular promise for understanding of patterns of viral evolution during epidemics [41,42]. Furthermore, our underappreciated aspect of growing human poupulations, global land-use change, and the introduction of anthropophilic vectors is the selective pressure on hosts, and reservoirs. For example, both West Nile and chikungunya viruses evolved rapidly after being introduced to new locations and encountering new vectors. The original genotype of West Nile virus (NY99) was replaced by another mutant strain (WN02) [43] that exhibits increased transmission efficiency in *Cluex pipiens* and *C. tarsalis* [44,45]. Similarly, in Réunion outbreaks (2005-2006), one nucleotide change occurred in chikungunya virus that increased infection in the recently introduced *Ades albopictus* [46]. The same genetic change appeared independently in viruses isolated from Réunion, west Africa, and Italy, but was not identified in mosquitoes from India at the start of the continuing epidemics there in 2006 [47]. When *A. albopictus* rather than *A. aegypti* became the main vector of chikungunya in India from 2007, the same viral strain spread rapidly and the subsequent mutants seem to circulate and persistmore efiiciently [46]. What has been less appreciated is the selective pressure imposed on such zoonotic viruses to be efficiently transmitted by *A. gambiae* and other species where there is a dense human population with increased urbanization and deforestation.

It is assumed that there exists a pool of human virus species which still remains to be discovered completely. The composition of this viral pool is likely to change over time, for example, while some virus species tend to be extinct, others continue to evolve with time. And therefore, two theories would be proposed to explain the ways in which novel virus species may join the existing ones. First, new viruses may appear when humans are exposed for the first time, to an existing virus species. Second, owing to the biological evolutionary process, novel viruses may also emerge from other existing viruses. More commonly, new such virus species arise as a result of jumps from one host to another, thus crossing the species barrier [37]. Humans are therefore, no more than 'incidental' or 'spillover' hosts. Only a minority of such viruses are capable of persisting in human populations (endemics) or spreading through human populations (epidemics) in the absence of a reservoir. Although, significant congruence between phylogenies of HNV and that of their rodent reservoirs have led to the theory of 'long-standing hantavirus-rodent host co-evolution' [48,49], there are

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still some debates. Various HNV have been found to infect multiple rodent species and cases of cross-species transmission (host-switching) have been recorded [50]. Additionally, rates of nucleotide-substitution reveal that HNV clades and rodent subfamilies may not have diverged at the same time [51]. Taking into account the inconsistencies in the theory of co-evolution, it was proposed that the patterns seen in HNV in relation to their reservoirs could be attributed to preferential host-switching directed by geographical proximity and adaptation to specific host types [51]. Based on genetic analysis of mammalian HNV, it has been proposed that the viral evolutionary history consists of a complex mix of both 'host-switching' and 'co-divergence'; suggesting that ancestral shrews or moles rather than cotton rats might be the hosts of ancient HNV [50]. Although other identified HNV have not been shown to cause human infections, their future evolution and disease manifestations cannot be underestimated.

5. The environmental and social drivers

The key to understand the emergence of novel infectious agents, including viruses, is to know the intricate 'host-pathogen-environment (HOPE)' relationship in pathogen evolution. While emergence of infectious diseases in naive regions is caused primarily by pathogen movement due to trade and travel, local emergence is driven by a combination of environmental and social changes. Pathogens introduced into novel regions often cause explosive epidemics followed by declining incidence, whereas pathogens that emerge locally because of land-use or social changes usually show consistent increases. While most of human infections are known to have zoonotic origins, alteration of the environment due to industrialization and urbanization is certainly an important, but completely neglected factor. The origins of most of the human-adapted viruses are not known so far, but the great majority of them fall into the category of 'crowd diseases' that requires relatively high host-densities to persist [38]. To be noted, ample recent incidences have suggested Asia-Pacific region as the global hot-spot for emergence of novel pathogens like, influenza strains, hCoV, Hendra virus and Nipah virus. In this case, an order-of-magnitude estimation of one such event per 100 years is broadly consistent with human demographic history [38]. Pathogen-transmission rates are often higher in dense than in sparse populations, and spread is often greatly enhanced by air travel or human migration. The mathematics of these spreading events is well known today, and a sophisticated array of computational models have been used to back-predict such events accurately, and the best example is the first case clusters of SARS outbreak and its subsequent global spread, including the country-by-country distribution of human cases [52,53].

Multifactorial models of human infections, embodied in the 'HOPE' complex, are now a staple of human-animal epidemiology courses. Of note, the 'HOPE' triangle has been the standard causal model for both animal and plant pathogens. However, these groups hold different perspectives owing to the relative importance of the host, pathogen and environment components in pathogen emergence [52, 54]. While biomedical and vetrenirary research is primarily focused on microbial agents and host-pathogen relationships, in agricultural research, the environment is viewed as the predominant determinant of disease incidence [52]. Moreover, while the human and animal reserch fraternity has been heavily oriented towards 'pathogen' research (particularly vaccines and anti-microbial drugs) to achieve control, the plant fraternity greatly emphasize on host-resistance to pathogens, including environmental factors. As with plants, knowledge of emerging diseases of animals is largely confined to domestic mammals and poultry, and much less is known about wild animals. In animal kingdom, wild populations constitute important but poorly understood reservoirs for known and undiscovered human pathogens, including viruses [54, 55]. Furthermore, the relative importance of an animal species as a source of human infection is a function of the prevalence of zoonotic agents in that species and the probability of close contact (direct or indirect) with susceptible human hosts. Clearly, these factors vary geographically, and changes in patterns of human and animal disease will continue to result from socio-economic and ecological changes at the human-animal interfaces.

6. Potential risk factors and biosecurity measures

The overall balance between exposure and evolution as driving forces of human viruses diversity, is difficult to assess accurately, particularly for those that are not human-adapted and exist primarily in animal reservoirs. If risk is a function of contact frequency and probability of successful adaptation to humans, viruses acquired from non-human primates might already be better adapted to successful transmission than those from other mammals, like bovine, porcine, feline and rodents. Many pandemic zoonoses, such as HIV have already achieved sustained human-to-human transmission without the need for a non-human reservoir. For example, SARS-CoV that originated from the Chinese bats due to bat meat consumption, subsequently spilled over to civets in the wildlife markets of China before infecting humans [56, 57]. Like HEV, many enteric viruses, such as JCV is found in high concentrations in urban sewage worldwide, leading to water contamination in resorce-poor countries [58]. Although person-to-person transmission of BKV is known, a zoonotic origin or else is still not established. Likewise, though MCV is found in respiratory secretions, shedding from healthy skins and gastrointestinal tissues, its precise mode of transmission remains undetermined.

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It is now well known that emerging human viruses can be transmitted through the contacts of infected animals and consumption of animal products, including fresh water and seafood products. The new approach to food-safety and to protecting humans against food-borne health risks is the most stringent control measure to connect animal disease with human illness. However, the vast majority of human infections are not reported to clinicians and therefore, such etiological agents remain unidentified that further contaminate healthy population. As discussed previously, poultry are the high-risk animals for emerging novel influenza A starins. Pork and pig products are another potential sources of Swine Flu and chronic hepatitis E in idustrialized nations. In a public health care initiative, the French health authority has published in its 2009 recommendations to cook swine liver sausages prior to consumption [59]. Precautions and proper care therefore, should be taken while preferring, selecting, purchasing or hunting high risk animals and cooking meats. Nevertheless, the current biosecurity measures appear to have been generally more successful for constraining bacterial diseases but less effective for viral diseases. Surveillance of the human viruses therefore, must include both domestic and wild animal populations as well as their environments at international co-ordination levels. Furthermore, personnel like livestock herders, zookeepers, hunters, rangers and veterinarians working with reservoir or high-risk animals must take hygienic measures.

7. Current advances and challanges

While smallpox, a devastating re-emerging disease for millennia, was eradicated long back in 1980, rinderpest the epizootic measles-related disease was successfully erazed in 2011 [60,61]. With polio close to eradication, with measles on the path to elimination and with significant strides in controlling hepatitis B and C as well as HIV being made, it is now possible to realistically consider eradication as an ultimate means of controlling certain viruses. Effective vaccines have been already developed against human carcinogenic viruses, like HBV and human papilloma virus (HPV). Even though drug-resistance has accelerated alarmingly, new generations of antiviral agents as combinatorial regimen have potential promises against HBV and HIV. However, very recently in 2012, after the tragedy of more than 35 million AIDS deaths, persons treated early with highly active antiretroviral therapy (HAART), although not 'cured' completely, can expect to live normal life spans with only a low risk of transmission. Compared to 1992 data when at least a million children died annually of measles, at present measles eradication with an effective vaccine, is a realistic near-term goal. In 1992 only, it was possible to enter villages in many developing countries to monitor poliovirus circulation by conducting childhood 'lameness surveys'. Despite high fatality rates, for many viruses like CCHFV, there are no vaccine prophylaxis and therapeutic interventions available at present. Although, the outbreak of chikungunya in Europe has died out, its natural interruption due to the arrival of the temperate autumn or mosquito control, is still unclear.

Despite extraordinary progress during the past two decades, infectious diseases still kill 15 million people each year, and deadly new diseases continue to emerge and re-emerge. The perpetual nature of the emergence of infectious diseases therefore, poses a continuing challenge which is volatile and ever-changing. This challenge includes a need for constant surveillance, prompt and efficient diagnosis as well as a need to develop new therapies. There is a further need for ongoing research not only in developing countermeasures but also in understanding the basic biology of new pathogens and our susceptibilities to them. Advances in technologies, such as, molecular diagnostics, deep-sequencing and meta-genomics have enabled to prospectively analyze molecular data to identify potential inter-species human viruses and to assess probable virulence and transmissibility. The predictive value will increase further if the molecular data are correlated with epidemiological and clinical data, and as our understanding of host requisites for transmission and barriers to cross-species improves. In some cases, for example, CoV host range can at least partially be predicted by receptor specificity and other factors [62,63]. Although, some 'laboratory-adapted' viruses can infect cultured human cells and are often unable to infect people, their environmental release is considered as a big threat. Furthermore, viral genetic predispositions enable monkeypox virus (MPV) to infect other animal species across geographic ranges; a challenge to typical eradication measures. Thus, an increased frequency of MPV infections, especially in immunocompromised individuals, may permit the virus to evolve and maintain itself independently in human populations. This could be true for zoonotic strains of HEV that has recently evolved to cause chronic infections in immunosuppressed, solid-organ transplant patients in high-income, developed nations [27,59].

8. Conclusion

The future of human health is ever uncertain, because unimagined new diseases surely lie in wait, ready to explode anytime. After the first human virus, the yellow fever virus (YFV) was discovered in 1901 [64], we have an enormous amount of information on the nature and biology of viruses, their mode of transmission, and the ways they infect hosts and cause diseases. However, we still do not know how many kinds of virus there are, even the most-studied human viruses. And, though we know that a substantial fraction of well identified mammalian viruses is responsible for humans etiology, there are large numbers of evolving viruses, to that humans are yet to be exposed and adapted. The unpredictable nature of novel infections, the rare occasions of outbreaks, the small number of confirmed cases as well

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their further occurrences in remote areas, severely hamper the assessment of control and preventive modalities. Nevertheless, specific geographical regions or interfaces between public, livestock, wildlife and the environment that have been identified as the origins of recent emerging viral diseases, should be the targets for intense surveillance. Further extensive research could therefore, substantially improve our understanding and capacity to predict new pandemics in future, and to prepare control measures in advance.

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