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Review Article

RNA Viruses: A Review on Rapid Adaptation Potential and Globally Emerged Pandemics

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Abstract

Pathogenic RNA viruses continuously evading the human populations, and most prevailing in the last three decades. There are some notably examples as Human Immunodeficiency Virus, Ebola-virus and SARS-CoV2 globally emerged as threatened majorly to the public health concern from more than 180 known RNA virus species that may infect humans. New species and new variants of existing RNA viruses, being reported continuously, on average among these species, 89 percent considered the zoonotic origin. Therefore, we required more scientific understanding of the regular appearance or re-emergence of fatal pathogenic RNA viruses had been a profound impact on human health. The Current review provides the current status of RNA viruses, mainly emphasis on the host-virus relationship mapping, mechanism of adaptation in disease and strategies to control them and available vaccines against them. Conclusively, we required extensive research programs in the specialized antiviral drug programming interfaces would allow us to remain prepared until the next virus appears.

Keywords: SARS-CoV2; Pathogenic RNA Viruses; Vaccines

Introduction

The human population is continuously increasing at the global level and furthermore, habitat fragmentation facilitate the increased interaction between humans, domestic pets and wildlife populations. Human beings also intentionally disturb wild environmental cycles. All these human behaviours increase the risk of transmission of parasites between them. An increasing number of pandemics have been formed as a result of increased human involvement in wild habitats, which are most likely the outcome of animal reservoirs, such as the human immunodeficiency virus (HIV) suspected to be of chimpanzee origin, cause acquired immunodeficiency syndrome (AIDS) pandemic [1]. The swine influenza virus, also known as H1N1 is suspected of spreading across from birds to humans and pigs cause swine flu. The highly pathogenic H5N1 virus or avian influenza suspected to be originate from the wild birds cause Bird Flu. Nipah virus transmitted from fruit bats to pig then humans cause acute respiratory infection and fatal encephalitis. Ebola virus conjecture to be transmitted

to humans through wild animals i.e., fruit bats cause Ebola virus disease (EVD). The middle-east respiratory syndrome coronavirus (MERS-CoV), severe acute respiratory syndrome coronavirus (SARS-CoV) and severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) are all likely to originate from bats and cause viral respiratory disease [1].

An estimated 60% of emerging pathogenic organisms are zoonotic, with more than 71% having wildlife origin [2]. As per the 9th report from the International Committee on Taxonomy of Viruses (ICTV), currently180 known RNA virus species that may infect humans, with two new species being discovered every year on average among these species, 89% are considered zoonotic origin [3]. This type of interspecies leap is possible owing to evolutionary changes, and the RNA virus's evolution is fuelled by a considerably greater rate of mutation than that of its cellular hosts. Per-site level RNA viruses typically have rates of mutation ranging between 10^{-6} to 10^{-4} substitutions/nucleotide/cycle (s/n/c). The mutation rate of DNA viruses is 10^{-8} to 10^{-6} which is less than RNA viruses [4].

Chikungunya (CHIKV) is a new emergent infectious disease endemic/outbreak that was originally identified in Asia throughout the 1950s and has affected millions of people, most recently in America in 2013 [5]. The zika virus (ZIKV) outbreak in 2015, as well as the Ebola virus disease (EVD) epidemic in West Africa in 2014, have emphasized the need for further knowledge of which pathogens are most likely to arise and cause disease in humans. Viruses cause many of these new infectious illnesses, which develop from nonhuman host reservoirs [6]. MERS, SARS, and influenza viruses also were continually evolving new strains, there is a new pandemic of Covid-19 caused by the SARS-CoV-2 virus. Here given some special attention to the zoonotic RNA viruses and problems occurring during control the RNA viral disease.

Molecular mechanism of RNA viruses adaptation

RNA viruses are diverse and rapidly evolving by their fundamental characteristic of the high mutation rate under various circumstances. This conspicuous characteristic is a major cause for viral adaptation to changing environments, and also for the medical issues associated with RNA viruses. Understanding the emergence and new mutations requires an understanding of the host-pathogen relationship. Mutations are the building blocks of most evolution, but the mutation can be harmful and also helpful.

A large portion of mutation is harmful while the small percentage of mutation is helpful. The high rate of background mutation has a clear impact on virus evolution, and adaptation is required for new raw material to adjust to different environments, which includes new hosts, immunological responses and antivirals. As a result, the vaccine is insufficient to control the disease. The increasing rate of mutation is due to replicating RNA viruses lack of proofreading. RNA viruses frequently exhibit mutation rates per site range from 10^{-6} to 10^{-4} s/n/c. The mutation rate of DNA viruses is10^{-8} to 10^{-6} which is less than RNA viruses [4]. As a result, RNA viruses are the most significant class of emerging viruses. In the course of the adaptation process, viral genetic changes, reassortment and genetic recombination of virus-host occurs. All of these factors contribute to the formation of stable viral lineages in the human population. Virus-interacting proteins exhibit increased adaptation throughout all functional domains, along with immune and non-immune functions. When viruses apply selection pressure on a host, interactions between the virus and the host are adapted by detecting virus-interacting proteins (VIPs), which interface with the virus, any new adaptations may be detected [7].

Lack of proofreading of RNA polymerases and recombination accelerate the adaptation

In the specific case of DNA virus replication, DNA polymerases that are DNA dependent have proofreading abilities. Proofreading is accomplished with the help of an enzyme known as an exonuclease. Despite the fact that DNA polymerases can be proofread, they sometimes make errors. However, in the case of RNA virus replication, RNA polymerases are the king of mistakes; this high number of mutations is caused by RNA polymerases lack of proofreading capabilities. As a result, the mutations persist in the newly synthesized RNA. The virus lives as a diversified population of genome mutants or quasi-species due to the high mistake rate or low viral fidelity in RNA virus replication. RNA viruses with low replicative fidelity can adapt to varied selection pressures in replicative situations; it is also linked to viral extinction [8]. This shows that a balance between quasi-species variation and replication fitness "a virus's ability to create infectious progeny in a particular environment" is required for virus virulence and evolution [8].

The most common mechanism is the cross-species transmission for most RNA viruses and other viruses to switch to a new host. The process of recombination may be helpful for viruses because it provides them with direct access to a greater portion of the sequence space than would normally be available through mutation, resulting in an expanded genetic configuration that helps host adaption [9]. In the past few years, a great number of new diseases have been found linked to RNA viruses with active recombination or reassortment. Emerging viruses can also acquire new antigenic combinations through recombination and reassortment, which can help with the cross-species transmission. Hepatitis E virus (HEV) genotype 3 was isolated from a affected person with chronic hepatitis E and was proven to infect human, pig, and deer hepatocytes in vitro, as well as having a virus-host RNA genome recombinant. Influenza A virus gene plasticity is reflected in the continual shuffle between genes encoding hemagglutinin and neuraminidase envelop proteins (a virus that has been related to the start of human pandemics in the past) is a good example of how recombination and reassortment can benefit a virus.

Coronaviruses and their proofreading abilities among RNA Viruses

Because of their extremely rapid mutation and exchange rates, RNA viruses have a unique rate of adaptive evolution, with having a higher rate of substitution than DNA viruses. It is common for RNA viruses not to have RNA polymerase and reverse transcriptase proofreading capabilities. Alternatively, DNA viruses and cellular organisms have replicative DNA polymerases, an exonucleases correct probable nucleotide disincorporation throughout genome replication. Only 10^{-11} to10^{-9} s/n/c occur due to DNA replication mistakes [10]. The fidelity of RNA viruses is almost entirely controlled by RNA-dependent RNA polymerase (RdRp) and retroviral reverse transcriptase (RT). Despite the fact that the inherent fidelity of RdRps is equivalent to that of DNA polymerases, mutations in RNA viruses occur at a rate of 10^{-6} to 10^{-4} s/n/c, because they lack proofreading or post-replicative repair mechanisms [4]. The discovery that SARS-CoV encodes a 3' to 5' endonuclease was the first evidence that coronaviruses could multiply more efficiently than other RNA viruses (ExoN). N-terminal of nonstructural protein 14 (nsp14) encodes the coronavirus ExoN. ExoN-deficient MHV and SARS-CoV have 8 to 12 times higher mutation frequencies than wild-type MHV and SARS-CoV, indicating that they have problems with replication and RNA synthesis. Recombinant versions of HCoV-229E and transmission gastroenteritis virus (TGEV) are not viable in the absence of ExoN. The first known proofreading enzyme nsp14 ExoN, is expressed by RNA viruses and is essential for coronavirus replication [11]. Cooperation has also been discovered in the measles, influenza, and HIV-1 viruses. Restricted tropism and pathogenicity are common in high fidelity forms of several RNA viruses.

Evolution of RNA viruses and their epidemiological characteristics

Evolutionary biology has become one of the imperative determinants explaining the origin of several viruses, because it is a critical aim in virology, particularly for deadly viruses [12]. RNA viruses are the world's most varied collection of biological organisms [13]. RNA viruses account for the majority of known viruses, and they are notorious for having the highest mutation rates of any living creature. Only ssDNA viruses like Phi X174 have a similar substitution rate (10^{-5} to 10^{-4} s/n/c). There are a high number of errors, which are compounded by the lack of proofreading activity in their replicase, have been proposed as important reasons limiting their genome size, which is considerably smaller than that of DNA viruses. Short generation times are another feature of RNA viruses, which results in a large population number in infected individuals. The great genetic heterogeneity and evolutionary pace between host and inter-host virus populations are due to all of these traits, as well as recombination and reassortment [14].

The infection caused by many RNA viruses is the predominant cause of clinically relevant human diseases as demonstrated by their high morbidity and mortality rates. Such viruses include HIV which has led to over 39 million deaths since discovery with about 1.5 million related death cases in 2013 alone [15]. Others include the influenza A virus subtype H1N1, which led to approximately 50 million death in the year 1918 and resulted in about 500 global deaths annually. Ebola virus, which has resulted in over 11 thousand deaths from 2013 to 2016 [16]. Other viruses that have caused clinically significant diseases include Hepatitis B and C virus (HBV and HCV), severe acute respiratory syndrome (SARS) coronavirus, measles virus, and dengue virus amongst many others. SARS-CoV-2 virus causes COVID-19 disease was recently discovered in

December 2019, and new cases are continuously being reported everyday around the world; the total death reported globally till January 2023 is over 6.4 million.

Interspecies transmitted RNA viruses

RNA viruses pose a significant danger to human health. Trade mobility has grown as a result of globalization and the invasion of a natural ecosystem with a rapidly increasing human populations are leading to more interspecies contact, pathogens and parasites interchange: this interspecies transmission is also applied in the case of RNA viruses. Interspecies transmission events are mostly dead ends, however, some virus variations adapt to new host species and promote continuing propagation. Emerging viruses have a stronger capacity for inter-species transmission, because they have RNA genomes, and a higher rate of mutation in them allows for easier adaptation to a new host species.

Influenza virus type A: Evolution and epidemiological characteristics

Despite the fact that influenza viruses may infect a broad variety of avian and mammalian species, studying them is a fascinating subject. The first recorded pandemic case of influenza A virus was 1918 due to the avian influenza A virus subtype H1N1 population and it is called spanish influenza, H1N1 subtype of influenza A virus origin in 2009, other non-H1N1 subtype Influenza A pandemics include 1957 H2N2 subtype and 1968 H3N2 subtype outbreak. In China, a novel influenza virus A strain H7N9 was discovered in 2013 [17]. The influenza virus evolution is essentially controlled by gene segment re-assortment, and its ability to mutate at a faster rate. Gene reassortment occurs when 2 or more Influenza viruses swap matching gene segments leading to the emergence of re-assortment viruses [18]. This is common with Hemagglutinin (HA) and Neuraminidase (NA) genes and when there is a swap of any of these genes, a new influenza subtype may emerge [19]. Also due to the error-prone nature of Influenza RNA polymerase and its absence of proofreading mechanism and viral replication leads to the emergence of new viral genotypes with a unique ability to evade host immunity. The influenza virus HA and NA genes are the most prone to mutation because they are both surface proteins. The mutations develop in the surface proteins of the influenza virus, especially the HA gene most of which occurs at the antibody binding receptor sites, thereby leading to antibody resistance. This process is termed antigenic drift, and the process through which the Influenza virus performs gene segment reassortment is called antigenic shift. Through antigenic shift, the Influenza virus can introduce an entirely different and distinct antigenic variant in the virus population. The antigenic shift can only occur when the host is infected with 2 or more Influenza subtypes [20,21].

In the epidemiology of subtypes of Influenza A virus there is huge variation, Influenza A is further broadly classified into sixteen HA (H1-H16) and nine NA (N1-N9) subtypes based on the combination of these proteins. However, Pandemic illnesses in humans have only been linked to H1-H3 and N1-N2 subtypes. All subtypes of the virus naturally infect avian species and other subtypes of the virus infect pigs, dogs, horses.

Ebola virus

Infection with any of the Ebola virus strains causes Ebola fever, often referred to as Ebola haemorrhagic fever. Ebola fever is extremely debilitating and can be very fatal in humans as well as other primates. It has a mortality rate ranging from 50-100% and has been designated a biosafety level 4 pathogen. The first recorded case of Ebola fever was reported in 1976 when the outbreak of Ebola in Southern Sudan and the Democratic Republic of Congo with a mortality of 53% and 88% respectively [22].

The major outbreak of Ebola ever to occur in West Africa occurred from 2013-2016 with official estimates at greater than 28,000 infections over 11,000 fatalities. Through land borders, the pandemic spread to Sierra Leone, Liberia, and Sierra Leone from Guinea. At that time researchers found genome data of the Zaire Ebola virus and identify high levels of changes in the Ebola virus (EBOV). As a result, obtaining a better grasp of the structural and functional impacts of amino acid substitutions in the virus would help researchers better understand how the virus is evolving.

Ebola virus genus is subdivided into 5 species: Zaire Ebolavirus (EBOV), Sudan Ebola virus (SUDV), Tai Forest Ebola virus (TAFV), Bundibugyo Ebola virus (BDBV), Reston Ebola virus (RESTV). The Zaire Ebola virus species was responsible for the West Africa is experiencing an Ebola virus outbreak from 2013 to 2016. Apart from all species only Reston Ebola virus species affect only nonhuman primates, others cause severe haemorrhagic fevers in humans [16]. Though the natural host of EBOV is not exactly known, fruit bats

are suspected of its natural reservoir. It is transmitted from animals to humans and between humans through body fluids. The source of EBOV has not been fully elucidated but research carried out after the year 2001 outbreaks suggest it may arise from asymptomatic infarction of certain species of fruit bats with confirmed evidence of the virus replicating in the bats [23].

SARS-CoV-2 and wildlife trade

COVID-19 (current coronavirus pandemic) is caused by the SARS-CoV-2, which evolve in Wuhan, China and spread all over the world. SARS-CoV-2 is the seventh coronavirus to be linked to human infection and other coronaviruses SARS-CoV, MERS-CoV, and SARS-CoV-2 can cause serious illness, while HKU1 (Hong Kong University 1), NL63 (NetherLand 63), OC43 (Organ Culture 43), and 229E (specimen coded 229E) are linked with moderate severity [24]. As of yet, SARS-CoV-2's origin is unknown. However, there is significant evidence that the virus was transmitted through the Wuhan wet market [25]. Bats and other wild creatures are routinely sold and housed in close proximity in these marketplaces [24]. Following the emergence of COVID-19, the Chinese government banned the trading and consumption of wild meat in February 2020 [24]. If the human population wants to reduce the risk of another viral spillover, the world needs a fundamental change in how we interact with nature.

In 2020 scientists confirm that the transmission of SARS-CoV-2 is primarily by the droplets and aerosol [26], but furthermore recent reports have proposed that the potential airborne exposures and via various surfaces, the gastrointestinal transmission of the virus reported [27]. With 96.2-98.7% similarity in the complete genome sequence, SARS-CoV-2 most similar to RaTG13, a short RNA-dependent RNA polymerase (RdRp) segment from a bat coronavirus. Comparatively, SARS-CoV and MERS-CoV match 88% of their nucleotides [28]. Furthermore, the pangolin coronavirus (pangolin-CoV-2020) is connected to the SARA-CoV-2, however this phenomena does not support the SARS-CoV-2, which evolved straight from the pangolin-CoV-2020; the pangolin might be natural hosts with an unknown capacity to infect people [29].

Wildlife trade includes the legal and illegal, unregulated harvesting, trade, transportation, and the use of the wildlife as a domestic pet and wildlife products like medicine. In wildlife trade, the multi-level supply chain is involved harvesters, intermediaries, and consumers, According to the International Livestock Research Institute (ILRI) and the United Nations Environment Programme (UNEP), approximately 60% of known infectious illnesses in human beings and 75% of all evolving infectious illnesses are zoonotic [30]. There have been connections between both SARS-CoV and SARS-CoV-2 and traditional unofficial or fresh produce markets (wet markets). They sell live poultry and other farmed animals, as well as aquatic items and dead or live wild animals, in these unlicensed markets. The commodity may be obtained from a variety of locations, including many further corners of the globe [31]. Lin highlighted the six wet market risk variables that can affect human health [32].

- Animals with high disease risk are available at wet markets; some of these animals are more hazardous to human health than others. Among mammals, rodents (order Rodentia), bats (order Chiroptera), primates, carnivores (order Carnivora), and ungulates (mainly Artiodactyla) may all have a high zoonotic capability. Those species most are found in the wet markets except, some unregulated species. Some are captured in the wild, while others are bred in captivity. These wet market species have the potential to spread severe disease to humans and domesticated species. As people come into touch with them, they can help to spread new zoonotic illnesses.
- In wet markets availability of live animals increases the danger of viral disease transmission. Live animal interspecies and intra-species mixing may promote disease dispersal and viral recombination in new hosts, potentially increasing animal virulence to each other and humans. Increased stress in confined animals (for example, owing to high densities in confinement, novel settings, or unexpected interspecies interaction) might weaken immunological response and enhance zoonotic disease transmission and severity.
- In wet markets, poor hygiene is a big threat to human health, because of lax or non-existent biosecurity controls in the markets and because hygiene concerns are amplified over extensive supply chains of livestock. Wet markets without live animals have been associated with parasite and bacterial diseases, often caused by improper handling of corpses, dirty water, or the close presence of other contaminants. Vendor handwashing, normal cleaning methods, and species

isolation can all help to reduce risks, however inappropriate waste disposal and insufficient sanitation steps can intensify deleterious health effects.

- There are various ways to define the market size (such as total trade, market geographical expanse, or multiple customers or transactions), but it is most usually connected with the total population present and things sold. With the consistent density of vendor booths and consumers, larger markets serving larger audiences are more hazardous to human health than smaller markets serving fewer people because food businesses and market attendees are generally the first victims of zoonotic diseases. A significant proportion of SARS patients in early 2003 were food handlers who had no direct animal contact. There were more patients in close proximity to market areas than to farms, which suggests the most likely source of infection was the market, not the farm.
- Wet markets and animal supply chains contribute significantly in the spread of viral diseases. High animal populations can enhance disease transmission within animal species, between animals and people, depending on the structure of a market and the proximity of animals to one another. Interspecies mixing and consequent cross-contamination are more likely with higher animal numbers, which might result in viral spread, adaptability, and the emergence of zoonotic diseases.
- Pathogen transmission and illness hazards might be exacerbated by long supply networks. Longer supply chains allow for increased interspecies mixing of stressed, live animals, and multi-origin animal sourcing (supply chain breadth) increases the possibility of new virus combinations. Viral spillover generally occurs when wild and domesticated species mix in unusual combinations.

As a result, zoonotic infections can transfer from domestic, agricultural or wild animals to people through any point of contact. There are a number of new or unconfirmed pathogens found in some wild animal populations, markets that sell wild animal meat or by-products are particularly dangerous. Additionally, human activities that threaten biodiversity and the sale of endangered or declining species in wet marketplace should be grounds for wildlife protection.

Developing therapeutic approaches to counter the RNA viral diseases

RNA viruses can originate unexpectedly from unexpected origins and cause serious illness in people. To counter these emerging viral diseases, our preparedness and the development of the novel therapies need is urgent. Vaccines can be used to prevent the virus, while small-molecule antivirals or antibody-based therapeutics can be used to treat it. Antiviral medications have been authorized for roughly 10 human viral pathogens over the last five decades, the most of which against the Herpes Simplex virus (HSV), HIV, Influenza virus and Hepatitis C virus (HCV) and most recently, an antiviral against the pathogen SARS-CoV-2 [33].

While vaccines are highly specific for particular viruses, antivirals have an action that extends beyond their initial target, displaying wide activity across virus families [34]. In a perfect scenario, current antivirals with a benign clinical profile and proven efficacy against formerly existing viruses would provide the best foundation for rapid in vitro and in vivo preclinical detailed investigation. Antivirals are currently available to treat developing virus infections as a result of these processes. Furthermore, these antivirals play a critical role in bridging the vaccine development gap.

Antiviral medications are categorised based on their therapeutic target, with direct-acting antivirals (DAAs) originating from viral names and host-directed antivirals originating from cellular components. Both options have their own set of benefits and drawbacks. DAAs are intended to be extremely detailed for a single viral enzyme, to neutralize it with high strength, and to interfere with host processes as little as possible. As a result, the evolution of drug-resistant virus strains causes therapeutic failure of DAAs. DAAs have fewer adverse effects, but they are usually only active against one virus. Some antivirals that target RdRP, on the other hand, are outliers since polymerase is an essential enzyme expressed by all RNA viruses. Remdesivir, Ribavirin, and Favipiravir, antiviral drugs with broad action, represent the “one drug, several viruses” concept. The bulk of licensed antivirals are small-molecule DAAs that primarily target viral genome replication, proteolytic processing, or virus entry [35].

Antivirals that are identified by the host are an alternative to DAAs. Because viruses from various families rely on physiological processes that are similar, host-directed antivirals may inhibit a wide range of viral infections and demonstrate the "one medicine, multiple viruses" principle. Although host-directed antiviral methods are less commonly used in clinical conditions, a few immunomodulators, including such interferons and antimitotic drugs, act by directly targeting host cellular activities rather than viral proteins. [36]. The following are some clinically accessible broad-spectrum medication options-

- **Ribavirin -** A synthetic guanosine analogue is one of the most intensively explored small-molecule antivirals. Ribavirin has a variety of modes of action (MoA) and is effective against a variety of RNA and DNA viruses [37]. A commonly used medication for treating the Hepatitis C (HCV) virus is Ribavirin, when mixed with Type I Interferon. Furthermore, Ribavirin is the only antiviral medicine that is accessible and recommended in order to treat the Lassa virus (LASV) [38]. Ribavirin has both DAA and host-directed antiviral activities. Virus resistance has been reported in several research [39] and adverse side effects as a major drawback of Ribavirin treatment.
- **Remdesivir -** Remdesivir is a prodrug that acts as an adenosine nucleotide analogue and disrupts viral RNA replication by inhibiting RdRp. Remdesivir was used as an antiviral against EBOV in nonhuman primates, with therapeutic efficacy reported in 2015 [40]. Remdesivir's antiviral activity was later verified against a wide variety of RNA virus's, including coronavirus, paramyxoviruses, and other filoviruses, demonstrating broad-spectrum activities and possible contribution against viruses with significant public health consequences [41]. Remdesivir was also included in WHO's multi-national solidarity study aimed at repurposing antivirals to lower SARS-CoV-2 in-hospital mortality [42].
- **Favipiravir -** In Japan, favipiravir, also called as T-705 it is approved to treat severe influenza infections. Favipiravir is a prodrug that's also phosphoribosylated into an active form by cellular enzymes and has the structure of a nucleoside-triphosphate analogue [37]. Favipiravir is perceived by viral RdRp as a purine nucleotide, causing viral RNA replication to be disrupted. Favipiravir's activity is important since it can inhibit Flaviviruses, Alphaviruses, Bunyaviruses, and other RNA viruses in addition to influenza. It appears to have a high resistance development barrier. Overall, Favipiravir seems to be a promising antiviral with wide antiviral activity against new viruses.

Viral resistance

Antiviral resistance, particularly to DAAs, is a serious clinical issue in a variety of viral infections. Viruses, especially those dealing with RNA genome, have a remarkable potential to adapt to antiviral treatment or the host immune system are examples of new habitats, because of their rapid pace of replication, error-prone RdRp, and vast pre-existing genome variety. Antiviral medicines for chronic viral diseases like AIDS do not give a cure, and patients must be treated for the rest of their lives, increasing the chances of resistance developing [43]. With this in mind, scientists are compelled to investigate new and innovative techniques, to bypass resistance mechanisms and find novel treatment targets, such as host-directed antivirals.

Host-directed antiviral approach

Targeting host proteins needed by the virus but not required for host life has been proposed as an alternate and potent antiviral method. Recent research has revealed a number of host cell components implicated in viral infection, showing an active host-pathogen interaction [44]. Host-directed medicines have a higher resistance barrier, but they also have a higher risk of undesirable side effects. As a result, recognizing host-virus interactions and grasping the complex biological process of the disease remain crucial.

Vaccines against RNA viruses

Vaccines are used to control and/or prevent viral infections, and they are very specific for specific viruses. To tackle various diseases caused by RNA viruses, a variety of techniques have been used, including virus-like particles, subunit elements, and recombinant viruses, as well as virus-like particles and nucleic acid based candidates (DNA or RNA), pure inactivated and live attenuated [45].

Inactivated pathogen vaccines

Several years after Pasteur, Salmon, and Smith introduced the attenuated cholera vaccine, the use of heat, gamma-ray, or chemical therapies (i.e., formalin, - propiolactone), in order to counteract these uncommon incidences of severe harmful effects following live-attenuated pathogen injection, it was decided to neutralise pathogen vaccines [46]. A dead version of the pathogen is used in inactivated pathogen vaccinations of and is therefore safer than live attenuated vaccines. Inactivated viruses lose their immunogenicity when chemically, irradiated, or cooked, making this approach less effective than live attenuated pathogen immunisation. As a result, vaccines against inactivated pathogens typically fail to elicit cellular adaptive responses, necessitating the use of adjuvants, which are particular substances that function as immune cell stimulants and amplifiers (Figure 1).

Attenuated pathogen vaccines

In 1880, Pasteur developed the conventional vaccination approach of administering attenuated pathogens to bacteria. After World War II, Enders and colleagues developed methods for attenuating viral strains, which sparked an interest in vaccine production, and some of the mumps, and rubella, poliomyelitis and measles vaccines were developed [46].

Normally, extensive cell or animal cultures are necessary to obtain attenuated strains of a pathogen. The wild-type virus must evolve modifications as a result of reproducing in a new host, acclimate the host to the new environment and eventually decrease its pathogenicity in human hosts, a lengthy procedure that might result in weakly strains with attenuated effects that genetically revert to the wild-type genotype quickly. Attenuated vaccinations induce humoral immunity as well as cell-mediated immunity and are capable of inducing long-lasting immunological responses and increasing cytotoxic T-cell responses [47] (Figure 1).

Figure 1: Showing the overview of strategies used for vaccine development and delivery. A- Debilitating variant of the live pathogen is administered as part of an attenuated live pathogen vaccination strategy. The pathogen's pathogenicity is reduced by long cell culture passaging in non-human cell lines or animals. After a single dosage, this type of vaccination frequently produces powerful and long-term memory immune responses. B- Inactivated pathogen vaccinations include the whole virus that has been inactivated by heat or chemical treatment. C- Subunit vaccines are made by either purifying antigens from pathogens reproduced in cell cultures or using recombinant generated antigens. Adjuvants are frequently added to these vaccinations in order to transmit danger signals to antigen-presenting cells and elicit powerful immune responses. D- Virus-like particles may self-assemble in and be released from recombinant yeast cells, other expression systems like the vaccinia virus expression system, or even tobacco plants infected with tobacco mosaic virus. E- Viral vector vaccines used a genetically modified measles or adenoviral platform to express a foreign antigen, eliciting a strong cellular and humoral response. F and G- Finally, while nucleic acid (DNA and mRNA) vaccines are easy to make, they have yet to be evaluated as effective human vaccination methods. Antigen-presenting cells capture the nucleic acid coding for an immunogenic protein of the pathogen after it has been delivered, and utilise it to produce and present the antigen. Because nucleic acid is rapidly destroyed in the human body, these vaccines are expected to pose little safety concerns. Image adapted from https://media.springernature.com/full/springerstatic/image/art%3A10.1038%2Fs41541-021-00292-w/MediaObjects/41541_2021_292_Fig2_HTML.png?as=webp

Nucleic acid vaccine

Nucleic acid immunisation is a unique and promising technique for the creation of human disease vaccines. There is no approved DNA vaccine for use in humans yet. However, the USDA has granted DNA-based permits for veterinary usage, horses are also vaccinated against West Nile virus and one against canine melanoma [48]. It is simple to make, considering all you need is a viral antigen and a delivery system to produce nucleic acid vaccines that induce humoral and cellular immunity. DNA vaccines can be given in a number of methods. They can be administered intradermal, where cutaneous antigen-presenting cells (APCs) such as dendritic cells, macrophages and monocytes can be found are boosted their absorption by a short electric pulse (electroporation), they are digested and presented to naïve T cells in Secondary lymphoid organs, As a result, cellular adaptive immunity is enhanced. These organs will also be exposed to the newly created antigen, which will activate naive B cells, resulting in antibody production [49]. The mRNA vaccines are administered similarly to DNA vaccines, with the restriction that mRNA can only be converted into protein if it penetrates cytoplasmic or endoplasmic reticulum ribosomes (Figure 1). Thus, Lipid nanoparticle (LNP) vectors can be used to deliver mRNA molecules, which can efficiently encapsulate DNA molecules, the penetration of tissue also allows the transfer of genetic information among host cells and the production of foreign antigen proteins.

Viral-vector vaccine

Vaccination with viral vectors has been used to assess immunogenicity against infectious agents as well as protection against pathogenic organism challenges [50]. Various viruses are modified throughout the creation of viral vector vaccines to lessen their virulence and reproduction potential while maintaining their ability to infect human cells. The use of vectors from adenovirus, measles, or vesicular stomatitis virus (VSV) is common in these designs that prompt strong immune responses after only one treatment. A recombinant vesicular stomatitis virus (rVSV) vector containing the Ebola glycoprotein-coding genetic information. The vaccine called "rVSV-ZEBOV" or Ervebo received approval from FDA in December 2019 [51].

There are two types of viral vectored vaccines used in vaccine manufacturing: replication-defective and replication-competent (Figure 1). To induce strong presentation, replication-competent vectors require a lower dosage. Replication-defective vectors, on the other hand, should be given in higher doses since they lack the ability to self-propagate.

Subunit vaccines

The concept of subunit vaccinations was founded on the idea that an immunogenic component, to generate significant immune responses, rather than the complete pathogen is necessary. There are protein subunit vaccinations, virus-like particle (VLP) vaccines, polysaccharide vaccines and conjugated vaccines are all subunit vaccines administration techniques that different in the chemical characteristics of the antigen provided and the need for an adjuvant to boost the immune system.

The pathogen was cultivated in huge quantities, recombinant protein antigen production or protein extraction and purification processes are used to create protein subunit vaccines. Antigen-presenting cells (APCs) that have been stimulated with an adjuvant absorb the antigen and convey it to the adaptive immune system [52]. The immunogenicity and tolerability of vaccines based on virus-like particles (VLPs) containing many copies of the same antigen on their surfaces trigger robust immune responses against the antigen. Without adjuvants, they effectively crosslink particular receptors on B cells, producing significant B cell responses [53] in addition, it can be triggered by the T-cell response [54]. A variety of VLP-based vaccines against hepatitis B virus (HBV), human papilloma virus (HPV) and hepatitis E virus (HEV) have been approved and are available commercially in many parts of the world [55]. The subunit vaccine strategy in (Figure 1).

Additional efforts to control and prevent viral diseases the "universal vaccine" can play an important role. Scientists have attempted to create a Mutable vaccine against the Influenza virus, which could offer protection against all strains of the virus for more than just one season and perhaps even a lifetime. If this concept truly works, this would be a major paradigm shift in our approach against mutable viruses.

Factors driving the emergence of a viral pandemic

Pandemics are rare events that are influenced by human-made alterations in the natural environment. According to the findings

of a report issued by [56], the following seven primary causes of zoonotic disease development are implicated; several of these variables occur in the very same place and intensify their influence.

Increasing demand for animal protein

The consumption of animal-source meals in high-income countries has been relatively constant during the last four decades. Southeast Asia, on the other hand, has experienced a significant growth: Since the 1960s, the share of protein from animal products in the region's daily food supply has quadrupled to 21%; from fish, it has risen by half to 15% [57]. In many low- and middle-income nations, this increase in per capita animal protein consumption has coincided with large population growth. Over the last 50 years, these factors have combined to drive strong growth in meat production (+260%), milk (+90%), and eggs (+340%) [57]. This pattern is anticipated to prolong in the future decades, with low- and middle-income nations experiencing the greatest increase in consumption of animal-source foods. In comparison to other protein sources, cattle product consumption is fast increasing, whereas pulse consumption remains stable over time.

Unsustainable agricultural intensification

Animal production is being intensified and industrialised in response to the rising demand for animal-source goods. Large numbers of genetically similar animals result from the intensification of agriculture, particularly domestic livestock rearing (animal husbandry). They're frequently developed for increased output levels. However, in recent years, they've been developed for the prevention of disease. Therefore, domestic animals are kept together in close quarters, frequently in less-than-ideal conditions. Because disease-resistant individuals are more likely to be found in genetically varied groups, those genetically homogeneous infections are more likely in host groups. The animals are not physically separated due to a lack of physical separation, factory farming of pigs, for example, aided in the spread of swine flu. In poorer countries, there are extra risk concerns, including livestock establishment being concentrated near cities, biosecurity and basic husbandry standards being lacking, the management of animal waste is ineffective and antimicrobial medications being used to cover bad circumstances or practices. Measures to increase agricultural productivity such as dams and irrigation initiatives have been used since 1940, and industrial farms have been linked to more than 25% of all zoonotic infections that have emerged in humans, and more than 50% of all zoonotic infections [58]. Furthermore, animal feed accounts for roughly one-third of cropland. In some countries, this is driving deforestation [57].

Increased exploitation and use of wildlife

There are a variety of methods in which wildlife is exploited, but the following are the most common-

- Wild animal meat (sometimes known as "bushmeat") is harvested as a source of protein, vitamins, and funds for the needy.
- As a status symbol, recreational hunting and wildlife consumption.
- Live animal trade for pets and zoos, as well as research and medical tests; and
- Animal parts are used to make decorative, medical, and other commercial items.

New roads in rural locations can boost human access to animals and potentially transfer illnesses more quickly across and between countries, facilitating wildlife exploitation. As wild animals grow scarcer, interest has shifted to the cultivation of some wild animal species [59]. While this has the potential to alleviate wildlife pressure, cultivating or "ranching" wildlife is frequently more expensive than shooting or harvesting wild animals, and is less popular among local population; it also may provide a shield for the "laundering" of wild animals.

Unsustainable utilization of natural resources accelerated by urbanization, land-use change, and extractive industries

Rapid urbanisation, particularly when unmanaged and with inadequate infrastructure, is a problem, leads an unexpected and diversified interactions between animals, cattle, and people. Rapid urbanisation causes increased mobility of people, livestock, food, and trade, frequently creates favourable conditions in order to prevent the spread of infectious illnesses, such as zoonosis [60]. Irrigation systems, for example, promote the spread of certain vector-borne zoonosis; Deforestation and ecosystem and animal habitat segmentation, on the other hand, encourage social

interaction somewhere at human-livestock-wildlife environment interface, Domesticated and wild animals' herding and migratory movements are hampered by expanding human settlements and fences. Human settlements near caves and woodland regions, especially those with inferior buildings, may enhance socialization and expose populations to insects, ticks, and other disease vectors. The conversion of natural areas to commercial and retail purposes, as well as other land-use change causes, can all contribute to the loss and fragmentation of wildlife habitats, there has been an upsurge in human-wildlife conflict.

Travel and transportation

Diseases can now spread across the globe in a relatively short time it requires for them to evolve (the period between pathogen exposure and the first clinical symptom of sickness). The growing volume of human movement and trade, as well as the increased handling, transportation [61], Increasing the risk of zoonotic illnesses arising and spreading is the (legal and illicit) trafficking of animals and animal products.

Changes in food supply chains

Especially in low- and middle-income nations, food supply chains are stretching and diversifying. This pattern is being influencing by rising consumption of animal source food, developing industries for wildlife food, and ineffectively controlled expansion of agricultural, which is increasing the potential for disease transmission in wildlife. The following are some of them:

- There are more chances for cross-contamination to occur.
- The spread of zoonotic illnesses can be aided by changes in processing (e.g., biofilm development on the creation of microbial ecosystems in food processing facilities).
- Disease transmission can occur in industrial meat processing factories. Food purchased from modernized retail stores is not always safer than food purchased from street vendors [62].

Climate change

Most zoonosis seem climate-sensitive, and the majority of them will develop in the future warmer, wetter, more disaster-prone planet [63]. Some viruses, vectors, and host animals are likely to fare worse as environmental conditions change, disappearing in some regions and allowing other species to colonise the new ecological niches formed by their absence. Climate change has the ability to increase or reduce the occurrence of sand-fly-transmitted leishmaniosis and Chagas disease as well as other vector-borne and zoonotic diseases, with higher degrees of warmth, generally resulting in more illness [64]. There is some suggestion that the "SARS-CoV-2 may perform much better just outside of the body in colder, drier environments" [65].

Other factors influencing illness onset have included the type of pathogen, pathogenicity, and transmission pathways; the sensitivity of the pathogen's host; and the pathogen's animal reservoir's longevity and range. Because RNA viruses lacking the "proofreading" capabilities that DNA viruses have, they accumulate many more changes over time, some of these changes may help the virus infect a new host. Viruses that transmit through the host's respiratory processes (which are over-represented in the population of people who are acquiring diseases) encounter fewer hurdles to spreading from one host to the next. Some people are more prone to virus infection than others. Health, Age, sex, physiological, nutritional condition, contact history, concurrent infection with several pathogens, immune-competence, inheritance, and underlying disorders all have an impact on an individual person vulnerability to infection. Based on physiological traits, environmental niche, social behaviour, and human relatedness, certain animals are more prone to host zoonotic or potentially zoonotic infections.

Reducing the spread of a viral pandemic

Pandemics were formerly characterised by an extremely high number of severe cases of human mortality. The human fatalities, as well as the social and economic implications of the COVID-19 catastrophe, clearly demonstrate the worth and urgency for increasing investment in a system capable of preventing similar events. An effective surveillance system is essential for providing information for action on priority diseases and public health decision-making. Surveillance offers data that can be utilised for determining priorities, making policy decisions, planning, implementing policies, mobilising and allocating resources, and predicting and detecting epidemics. Disease prevention and control strategies can also be monitored, evaluated, and improved via a surveillance system. Surveillance also gives crucial information

for delivering cost-effective health care. In 2006, the World Health Organization (WHO), Food and Agriculture Organization (FAO), and World Organization for Animal Health (OIE) created the global early warning and response system as standardized tracking and reporting framework for disease outbreaks [66]. The purpose of this early warning system is to integrate the capabilities of three organizations in order to improve human and livestock health early warning signals aimed at reducing the frequency and consequences of rising infectious illnesses in livestock and humans. However, this early warning and response mechanism has been ineffective in preventing occurrences like SARS-CoV-2. The covid-19 pandemic has highlighted the significance of developing global strategies, policies and legal regulations address the various components of disease development in order to enhance our collaborative ability to avoid, recognise, and deal with the threat.

A systematic worldwide surveillance network must be built to avert pandemics. A network like this would undertake viral surveillance to identify spill over from animals to cattle and humans long before it became isolated outbreaks, averting high-impact outbreaks and pandemics [67]. Strategic monitoring of wild animals, humans, and their livestock in defined hotspot zones, according to the network, would reduce the need for global viral surveillance. When new genomic data on zoonotic viruses in wild animals from viral research activities such as the worldwide virome project, as well as related metadata, are stored in global databases, a global viral surveillance network will be more efficient in detecting early viral transmission into humans. These discoveries may also aid in the development of improved diagnostic reagents and their application via the development of new, more widely accessible, and cost-effective pathogen identification and sequencing systems. With the refining of present hotspots, the targeting of suggested viral surveillance would've been improved as well. These analytics, in conjunction with bioinformatics techniques, Artificial intelligence and a big database base might aid in the prevention of pandemics by progressively expanding the capability of a worldwide monitoring system to enhance infection and propagation models that are dynamic and predictions [67].

Possible pandemic threats

Increased urbanisation, international travel, business, and climate change make it more likely that emergent zoonosis will persist, if not worsen, in the long term. Concerns about a future pandemic were further intensified following the COVID-19 pandemic. The rapid expansion around the globe of the COVID-19 disease, the severity of illness associated with infection, and the initial uncertainty about its specific clinical characteristics (e.g., the structure of the virus and transmission routes) presented unprecedented dilemmas concerning the global governance of disease hypothesised that zoonotic risk forecasts are of limited utility and will not reveal which virus will trigger the next pandemic [68]. Instead, we should concentrate our viral surveillance efforts on the human-animal interface. Pandemic dangers are divided into three groups-

- Pathogens that have a high risk of causing major pandemics. This group includes pandemic influenza viruses, which have a high efficiency of human-to-human transmission via respiratory droplets, long incubation periods that allow infected persons to roam around undetected, and an uncommon symptom profile that makes differential diagnosis difficult (this is especially so in the early periods of infection).
- Viruses are a moderately serious global danger. These include the Nipah virus and influenza A viruses H5N1, H5N8, and H7N9, which have not been transferred from person to person but might be transmitted more effectively through mutation or adaptation.
- Ebola, Marburg, and Lassa viruses are examples of pathogens that can generate regional or interregional outbreaks. Extreme poverty, political instability, and a lack of healthcare infrastructure all contribute to the spread of such infections. Nonetheless, because to slow transmission, a high possibility of early discovery and the efficiency of containment measures, the risk of worldwide spread is restricted.

There have been several notable pandemics throughout human history, including smallpox, cholera, plague, dengue, AIDS, influenza, SARS, West Nile illness, TB and most recently SARS-CoV-2. Pandemics are unexpected, but recurrent occurrences that might have serious effects for the human species can be predicted and prepared for, resulting in fewer victims and lowering the likelihood of a second crisis. It is impossible to anticipate when or where the future epidemic or pandemic would occur. The goal is to figure out how to keep breakouts from spreading into widespread pandemics that endanger us all.

The urgency of pandemic preparedness has developed within a broader climate of fear about newly emerging diseases. Effective planning and response are essential for mitigating the effects of any emergency situations, including epidemics. Pandemic preparedness appears to be strongly related to the larger global political and economic contexts under which it is conceptualized, including massive and largely uncontested expenditure in preparedness activities and the probable international disparities caused by such measures. Controlling the condition of infection in animal populations is also considered a crucial response to the potential of pandemics. Global pandemic preparedness has some important flaws and challenges. Multiple outbreaks, most notably the 2014 Ebola epidemic in West Africa, have highlighted shortcomings in illness detection, basic treatment, contact tracing, quarantine and isolation measures, and preparedness beyond the medical sector, including international co - operation and response mobilisation [69]. These gaps are particularly visible in resource-constrained contexts, and they have caused problems with relatively localised outbreaks, with terrifying consequences for what might occur in a Pandemic on a global scale. Antiviral medicine stockpiling and vaccine development are generally presented as part of preparedness, which necessitates significant expansion in global vaccine manufacturing capacity.

Conclusions

Despite incredible advances in scientific understanding, the regular appearance or re-emergence of fatal pathogenic RNA viruses has had a profound impact on human health. Furthermore, RNA viruses are also commonly implicated in zoonotic transmission, making international disease control challenging. Their biological variety and high adaptation rate, which is linked to increased virulence and evaluability, have proven tough to resist and have sparked ongoing pharmacological and medical technology research. To combat the current and future RNA virus epidemics or pandemics, it is critical to expanding the arsenal of available antiviral options. The technological development is specifically designed for understanding how virus interplays with the host during infection and this part is important for drug discovery and the control of RNA viruses. High population density, high animal protein demand, increasing wildlife trade, hosts and disease reservoirs are under pressure due to changing climates and newly emerged anthropophagic vectors, causing pandemics to occur. Preventive survey initiatives, such as the formation of a formal global surveillance network that evaluates the most vulnerable sectors and geographic locations, can be used to predict future pandemic threats. These programs' data also aid in enhancing diagnostics and making plans that ensure that patients have sufficient and adequate access to therapy. There are numerous challenges in pandemic preparedness, including disease detection, availability of basic care, contact tracing, and preparedness outside of the healthcare system, including global coordination. These resource constraints posed a challenge during endemic or full-fledged global pandemics. Controlling the condition of infection in animal populations is also seen as a critical response to pandemic threats.

A single database that collects well-annotated and confirmed virus-host interactions for critical human pathogenic viruses across methodologies, comparable to the Human Protein Atlas resource, would be transformational. Some efforts, such as Viral Zone, Viruses, STRING, and VirHostNet, are off to a good start. However, they all fall short in terms of comprehensiveness and degree of integration. On a variety of levels, this resource would aid research and medicine development. Among other things, the proposed database would make it easy to compare results from TPP, co-IP, and CRISPR-based genetic screenings. In the event of a newly developing infection, such a database would enable the mapping of critical viral-host relationships and, as a result, vulnerabilities based on firmly related viruses.

Finally, in order to become successful in the discovery or repurpose of medications for new viruses, beyond any pandemic or epidemic, research capacities must be established, with the devoted and unambiguous objective of bringing more breakthrough antivirals to market. Because of their occasional onset and acute illness presentation, neglected diseases like ZIKV, DENV, and others sneak under the pharmacology firm's radar. Academic institutions, in particular, must increase their commitment to readiness. More research, specialized antiviral drug programming interfaces, and biosafety facilities will result in innovative antivirals, allowing us to remain prepared until the next virus appears.

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Bibliography

1. Roberts M., *et al*. "Challenges in modelling the dynamics of infectious diseases at the wildlife-human interface". *Epidemics* 37 (2021): 100523.

2. Cutler SJ., *et al*. "Public health threat of new, reemerging, and neglected zoonoses in the industrialized world". *Emerging Infectious Diseases* (2010): 1-7.

3. Kuhn JH. "Virus Taxonomy". *Encyclopedia of Virology* (2021): 28-37.

4. Peck KM and Lauring AS. "Complexities of Viral Mutation Rates. Sullivan CS, editor". *Journal of Virology* (2018): 92.

5. Weaver SC and Forrester NL. "Chikungunya: Evolutionary history and recent epidemic spread". *Antiviral Research* (2015): 32-39.

6. Woolhouse MEJ., *et al*. "Assessing the epidemic potential of RNA and DNA viruses". *Emerging Infectious Diseases* 22 (2016): 2037-2044.

7. Enard D., *et al*. "Ancient RNA virus epidemics through the lens of recent adaptation in human genomes". *The Royal Society* 375 (2020): 20190575.

8. Robson F., *et al*. "Coronavirus RNA Proofreading: Molecular Basis and Therapeutic Targeting". *Molecular Cell* 79 (2020): 710-727.

9. Simon-Loriere E and Holmes EC. "Why do RNA viruses recombine?" *Nature Reviews Microbiology* 9 (2011): 617-626.

10. Smith EC., *et al*. "Thinking Outside the Triangle: Replication Fidelity of the Largest RNA Viruses". *Annual Review of Virology* 1 (2014): 111-132.

11. Saha RP., *et al*. "Repurposing Drugs, Ongoing Vaccine, and New Therapeutic Development Initiatives Against COVID-19". *Frontiers in Pharmacology* (2020).

12. Holmes EC. "What can we predict about viral evolution and emergence?" *Current Opinion in Virology* (2013): 180-184.

13. Holmes EC. "The Expanding Virosphere". *Cell Host Microbe* 20 (2016): 279-280.

14. Trifonov V and Rabadan R. "Frequency Analysis Techniques for Identification of Viral Genetic Data. Lipkin WI, editor". *MBio* (2010): 1.

15. Murray CJL., *et al*. "Global, regional, and national incidence and mortality for HIV, tuberculosis, and malaria during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013". *Lancet* 384 (2014): 1005-1070.

16. Jacob ST., *et al*. "Ebola virus disease". *Nature Reviews Disease Primers* 6 (2020): 13.

17. Peng J., *et al*. "The Origin of Novel Avian Influenza A (H7N9) and Mutation Dynamics for Its Human-To-Human Transmissible Capacity. Stambas J, editor". *PLoS One* 9 (2014): e93094.

18. Marshall N., *et al*. "Influenza Virus Reassortment Occurs with High Frequency in the Absence of Segment Mismatch. Basler CF, editor". *PLoS Pathogens* 9 (2013): e1003421.

19. Lu L., *et al*. "Reassortment patterns of avian influenza virus internal segments among different subtypes". *BMC Ecology and Evolution* 14 (2014): 16.

20. Holmes EC., *et al*. "Whole-genome analysis of human influenza A virus reveals multiple persistent lineages and reassortment among recent H3N2 viruses. Levin S, editor". *PLoS Biology* 3 (2005): 1579-1589.

21. Treanor J. "Influenza Vaccine — Outmaneuvering Antigenic Shift and Drift". *The New England Journal of Medicine* 350 (2004): 218-220.

22. Coltart CEM., *et al*. "The Ebola outbreak, 2013-2016: Old lessons for new epidemics". *Philosophical Transactions of the Royal Society B* (2017): 20160297.

23. Fairhead J., *et al*. "Spillover or endemic? Reconsidering the origins of Ebola virus disease outbreaks by revisiting local accounts in light of new evidence from Guinea". BMJ Global Health 6 (2021): e005783.

24. Andersen KG., *et al*. "The proximal origin of SARS-CoV-2". *Nature Medicine* 26 (2020): 450-452.

25. World Health Organization. "WHO-convened global study of origins of SARS-CoV-2: China Part. COVID-19 Anim". *Interface Food Safety* (2021).

26. Jayaweera M., *et al*. "Transmission of COVID-19 virus by droplets and aerosols: A critical review on the unresolved dichotomy". *Environmental Research* 188 (2020): 109819.

27. Greenhalgh T., *et al*. "Ten scientific reasons in support of airborne transmission of SARS-CoV-2". *Lancet* Elsevier (2021): 1603-1605.

28. Ge H., *et al*. "The epidemiology and clinical information about COVID-19". *European Journal of Clinical Microbiology and Infectious Diseases* (2020): 1011-1019.

29. Liu P., *et al*. "Are pangolins the intermediate host of the 2019 novel coronavirus (SARS-CoV-2)?" *PLoS Pathogen.* Public Library of Science (2020): e1008421.

30. United Nations Environment Programme. "Zoonotic diseases and how to break the chain of transmission: A scientific assessment with key messages for policy-makers". UN Environ. Program. (2020).

31. Petrikova I., *et al*. "COVID-19, wet markets, and planetary health". *Lancet Planet Health* 4 (2020): e213-214.

32. Lin B., *et al*. "A better classification of wet markets is key to safeguarding human health and biodiversity". *Lancet Planet Health* (2021): e386-394.

33. NIH NI of H. "What's New | COVID-19 Treatment Guidelines". Natl. Institutes Heal. USA (2022).

34. Ianevski A., *et al*. "Expanding the activity spectrum of antiviral agents". *Drug Discovery Today* 24 (2019): 1224-1228.

35. Chaudhuri S., *et al*. "Innovation and trends in the development and approval of antiviral medicines: 1987-2017 and beyond". *Antiviral Research* 155 (22018): 76-88.

36. De Clercq E and Li G. "Approved Antiviral Drugs over the Past 50 Years". *Clinical Microbiology Review* 29 (2016): 695-747.

37. Geraghty RJ., *et al*. "Broad-spectrum antiviral strategies and nucleoside analogues". *Viruses* (2021): 667.

38. Eberhardt KA., *et al*. "Ribavirin for the treatment of Lassa fever: A systematic review and meta-analysis". *International Journal of Infectious Diseases* 87 (2019): 15-20.

39. Perales C., *et al*. "Resistance of hepatitis C virus to inhibitors: Complexity and clinical implications". *Viruses MDPI AG* (2015): 5746-5766.

40. Warren T., *et al*. "Nucleotide Prodrug GS-5734 Is a Broad-Spectrum Filovirus Inhibitor That Provides Complete Therapeutic Protection Against the Development of Ebola Virus Disease (EVD) in Infected Non-human Primates". *Open Forum Infectious Diseases* (2015): 2.

41. Lo MK., *et al*. "GS-5734 and its parent nucleoside analog inhibit Filo-, Pneumo-, and Paramyxoviruses". *Scientific Report* 7 (2017): 43395.

42. WHO Solidarity Trial Consortium., *et al*. "Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results". *The New England Journal of Medicine* 384 (2021): 497-511.

43. Little SJ., *et al*. "Antiretroviral-Drug Resistance among Patients Recently Infected with HIV". *The New England Journal of Medicine* 347 (2021): 385-394.

44. Taguwa S., *et al*. "Defining Hsp70 Subnetworks in Dengue Virus Replication Reveals Key Vulnerability in Flavivirus Infection". *Cell* 163 (2015): 1108-1123.

45. Yuan S., *et al*. "SREBP-dependent lipidomic reprogramming as a broad-spectrum antiviral target". *Nature Communication* 10 (2019): 1-15.

46. Barnes K. "Culturing poliovirus in cells". *Nature Research* (2021).

47. Nascimento IP and Leite LCC. "Recombinant vaccines and the development of new vaccine strategies". *Brazilian Journal of Medical and Biological Research* 45 (2012): 1102-1111.

48. Atherton MJ., *et al*. "Cancer immunology and canine malignant melanoma: A comparative review". *Veterinary Immunology and Immunopathology* 169 (2016)15-26.

49. Leitner WW., *et al*. "DNA and RNA-based vaccines: principles, progress and prospects". *Vaccine. NIH Public Access* 18 (1999): 765.

50. Lundstrom K. "RNA viruses as tools in gene therapy and vaccine development". *Genes (Basel)* 10 (2019).

51. Monath TP., *et al*. "rVSVΔG-ZEBOV-GP (also designated V920) recombinant vesicular stomatitis virus pseudotyped with Ebola Zaire Glycoprotein: Standardized template with key considerations for a risk/benefit assessment". *Vaccine X* 1 (2019): 100009.

52. Cate TR., *et al*. "Clinical Trials of Monovalent Influenza A/New Jersey/76 Virus Vaccines in Adults: Reactogenicity, Antibody Response, and Antibody Persistence". *Journal of Infectious Disease* 136 (1977): S450-455.

53. Roldão A., *et al*. "Virus-like particles in vaccine development". *Expert Reviews in Vaccines* 9 (2010): 1149-1176.

54. Buonaguro L., *et al*. "Virus-like particles as particulate vaccines". *Current HIV Research* 8 (2010): 299-309.

55. Jain NK., *et al*. "Formulation and stabilization of recombinant protein based virus-like particle vaccines". *Advanced Drug Delivery Reviews* 93 (2015): 42-55.

56. Nations Environment Programme U, Livestock Research Institute I. A Scientific Assessment with Key Messages for Policy-Makers A Special Volume of UNEP's Frontiers Report Series PREVENTING THE NEXT PANDEMIC PREVENTING THE NEXT PANDEMIC Zoonotic diseases and how to break the chain of transmission (2020).

57. Nepstad D., *et al*. "Slowing Amazon deforestation through public policy and interventions in beef and soy supply chains". *Science (80-). American Association for the Advancement of Science* 344 (2014)1118-123.

58. Rohr JR., *et al*. "Emerging human infectious diseases and the links to global food production". *Nature Sustainability* 2 (2019)445-456.

59. Tensen L. "Under what circumstances can wildlife farming benefit species conservation?" *Global Ecology Conservation* 6 (2016): 286-298.

60. Hassell JM., *et al*. "Urbanization and Disease Emergence: Dynamics at the Wildlife-Livestock-Human Interface". *Trends in Ecology and Evolution* 32 (2017): 55.

61. Muley D., *et al*. "Role of transport during outbreak of infectious diseases: Evidence from the past". *Sustain* 12 (2020): 1-22.

62. Wertheim-Heck S., *et al*. "Food safety and nutrition for low-income urbanites: exploring a social justice dilemma in consumption policy". 31 (2019): 397-420.

63. Evander M and Ahlm C. "Milder winters in northern Scandinavia may contribute to larger outbreaks of haemorrhagic fever virus". *Global Health Action* 2 (2009).

64. Wells K and Clark NJ. "Host Specificity in Variable Environments". *Trends in Parasitology* 35 (2019): 452-465.

65. Khan N., *et al*. "Explanation of Corona Virus Control Novel by Warm and Humid Seasons in the World". *SSRN Electronic Journal* (2020).

66. Zinsstag J., *et al*. "Towards integrated surveillance-response systems for the prevention of future pandemics". *Infectious Diseases of Poverty* 9 (2020): 140.

67. Carroll D., *et al*. "Preventing the next pandemic: the power of a global viral surveillance network". *BMJ. British Medical Journal Publishing Group* 372 (2021): n485.

68. Wille M., *et al*. "How accurately can we assess zoonotic risk?" *PLOS Biology* 19 (2021): e3001135.

69. Jia K and Mohamed K. "Evaluating the use of cell phone messaging for community Ebola syndromic surveillance in high risked settings in Southern Sierra". *African Health Science* 15 (2015): 797.