Emerging Viral Diseases: From the past to the future for an efficient dynamics and control

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Abstract

Almost every year mankind is confronted with the appearance of one or more “new” viral pathogens. Some of these remain below the threshold of becoming self-sustaining pathogenic human infections, either because they do not readily transmit among human beings and/or because they do not cause human disease. Here, we will summarize only some of the major “new” viral infections. We will argue that the emergence of a completely “new” virus is a very rare event, not seen during written history. Instead we see “new” human viruses always zoonotically transmitted from animal species. The major factor leading to these trans-species transmissions appears to be human population growth and expansion, bringing humans in closer contact with wild animals and their infectious agents. Bats, rodents, and non-human primates (NHPs) appear of particular relevance as sources of “new” viruses. As a consequence, we come to the conclusion that the “new” viral infections are predominantly man-made. Maintaining and extending the classic control modalities (surveillance, clinical medicine, and clinical virology) are essential, but new tools (mathematical modelling, remote sensing, and ecologically based approaches) are also important.

Key words: Emerging/Re-Emerging disease, Viral infection, Zoonotically, Viral mutation, Mathematical modelling, Remote sensing, Ecological approach.

Introduction

Human emerging pathogens are defined as novel etiological agents that have recently manifested in a population and were not known previously, elsewhere [1]. They also included re-emerging infectious diseases that had been controlled but were newly active because of the failure of application of established control measures or their ability to evade formerly effective controls [2]. 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 [3]. Two of the most common causes of human
morbidity and, at times, mortality are gastroenteritis and respiratory infections for which viruses are the most common cause of both [2]. In fact, emerging infectious diseases can be seen as part of a historical process. Thus, this review aimed to learn from the past to the future for an efficient dynamics and control of emerging viral diseases.

Molecular basis of cross-species transmission

One of the most devastating viral infections that newly spread among humans during the second half of the 20th century and is still exerting a large death toll particularly in sub-Saharan Africa is HIV/AIDS [4]. It is without any doubt that the current HIV-1 epidemic by type M viruses resulted from the trans-species transmission of a recombinant lentivirus originating in Great Apes [5]. Specifically, a hybrid virus was generated in the Hominidae combining two simian immunodeficiency viruses (SIVs), which each cause persistent asymptomatic infections in lower monkeys [6-7]. These monkeys are hunted by chimpanzees for prey, which in turn became infected by the two viruses and joined the 5’ half of the SIV from red-capped mangabey (Cercocebus torquatus) to the 3’half of the SIV of the greater spot-nosed monkey (Cercopithecus nictians). The recombination event happened right in the middle of the genome in the gene encoding the Vpr protein [8]. Such events probably occurred multiple times in Great Apes indicating that the respective genomic region is vulnerable to recombination [9]. After a long period of clinical latency, chimpanzees develop a disease that mirrors human AIDS [10]. It is believed that the virus eventually transmitted from the Pan troglodytes troglodytes chimpanzee subspecies to humans in the decade following 1920 was the one best adapted to the new host (M or major group virus) and acquired further adaptations to humans through point mutations, eventually causing the world wide pandemic. The subsequent spread among humans can be mainly attributed to social changes in the target population [5]. A likely scenario for the initial transmission event is bush meat hunting activity [4].

It is unknown, but not unlikely, that previous (before 1920) or later transmissions of closely related viruses to humans occurred that did not translate into sustained infections among men (note also that trans-species transmissions to humans of HIV-1 group N, O, and P viruses and HIV-2 took place independently from HIV-1 M group viruses but that compared with group M viruses these infections are far more restricted) [11].

Other top causes of mortality among viruses are the various influenza A (INF A) types. The H1N1 “Spanish Flu” of 1918/1919 with approximately 30-40 million human deaths worldwide is the most severe event caused by a single infectious agent in the last century [1]. However, the threat posed by influenza A viruses was and is by far not over: the so-called H2N2 “Asian Flu” from 1957, the H3N2 1968 “Hong Kong Flu” epidemic, the re-emergence of a variant H1N1 virus during the 1977 “Russian Flu”, or the H5N1 “avian flu” that, although so far causing fewer than 700 human infections since 2003, has a case fatality ratio (CFR) of more than 50%, and the pandemic of 2009, caused by a variant H1N1 and erroneously termed “swine flu”, with a general CFR of approximately 0.1% [12]. A CFR of 0.1 % does not sound very impressive; however, due to the pandemic nature of INF A this easily translates up to several ten thousand worldwide deaths. Furthermore, WHO noticed the spread of an H7N9 virus originating in China that has been detected in less than 200 humans in the first half of 2013 with a CFR of 25% [13]. It is questionable whether this potential epidemic has come to a real halt, since epidemiological and molecular evidence point to human-to-human transmissions, although less effectively than the fully human adapted INF A viruses [12-13].

All of the 16 known types of H (hemagglutinin) proteins and the 9 types of N (neuraminidase) proteins are present in birds, mainly in water fowl [12], in which INF A
causes a gastrointestinal infection and viral particles are excreted with the faeces. Additional H and N types have recently been described in bats [14]. Influenza viruses are RNA viruses with a segmented genome with the genes encoding the surface proteins H and N located on different segments of the eight segments harbouring virus. The segments of at least two different INF A viruses infecting the same cell within one host can be interchanged relatively freely, leading to a phenomenon known as genetic shift, if a new recombinant virus emerges [13].

The gastrointestinal tract infections of wild bird are usually caused by low-pathogenic avian INF A (LPAI), characterized by a trypsin-like cleavage site in the H-protein, which must be cleaved from the H0 precursor into H1 and H2 proteins for the virus to become infectious. Trypsin-like proteases are present in the gastrointestinal tract of birds. If it comes to the infection of domestic fowl (mainly chicken under the condition of industrial mass animal farming), the amplification of this virus can lead to the emergence of high-pathogenic avian INF A (HPAI) strains by point mutations (genetic drift). These mutants are characterized by an extended stretch of basic residues in their H0 protein, allowing cleavage by the ubiquitously present furin-like proteases. Thus, the key difference between LPAI and HPAI appears to be the localized (by LPAI) vs. the generalized (by HPAI) infection in aves [14]. The HPAI virus strain can now be pathogenic even for wild bird species [13].

If either by direct transmission from birds (as supposedly at the origin of the “Spanish Flu”) or by using an alternate intermediate host (e.g. swine that have the “advantage” of bearing the cellular receptors for both avian and human influenza viruses in their upper respiratory tract, whereas humans have cells with receptors for avian viruses only in their lower respiratory tract, and also live in substantial numbers close to human settlements, especially at least in SE Asia) trans-species transmission to humans occurs, subsequent genetic shift and drift may result in a “new” pandemic strain. It is impossible to predict how this strain will behave clinically and epidemiologically in the new human target population.

Another virus is Zika virus (ZIKV). ZIKV belongs to the Spondweni virus serogroup of mosquito-borne viruses in the flavivirus genus. Phylogenies reveal the existence of 2 lineages: the African lineage which has showed no propensity to disseminate outside of Africa, and the Asian lineage which continues to seed in previously unaffected regions of the world [15-17].

All strains having recently disseminated belong to the Asian lineage (with Cape Verde outbreak strain of unknown lineage) [18-21]. ZIKV genomes from patients infected in Surinam and Brazil in 2015 are closely related to the strain that circulated in French Polynesia in 2013, with more than 99.7% and 99.9% of nucleotide and amino acid identity, respectively [21]. Virions of ZIKV are 40–60 nm in diameter, spherical in shape and contain a lipid envelope. Its genome consists of a positive sense RNA of approximately 11 kb. The virions consist of a single capsid (C) and two membrane-associated envelope proteins (M, E). The nonstructural proteins (NS1-NS5) contain sequence motifs characteristic of a serine protease, RNA helicase and RdRp (NS5). The genomic RNA contains a single long ORF flanked by 5' and 3'-terminal non-coding regions (NCRs) that form specific secondary structures required for genome replication and translation. Translation-initiation of genomic RNA is cap-dependent. Viral proteins are synthesized as part of a polyprotein that is co- and post-translationally cleaved by viral and cellular proteases. RNA synthesis occurs in the cytoplasm in association with modified cellular membranes via synthesis of full-length negative-strand intermediates. Virion assembly, including acquisition of the glycoprotein-containing lipid envelope, occurs by budding through intracellular membranes. Viral particles are transported in cytoplasmic vesicles through
the secretory pathway before they are released by exocytosis [15,22,23].

Regarding the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), the using SARS-CoV pseudotyped HIV particles, Nie et al. have shown that the susceptibility of a given cell type to infection correlates well with levels of the SARS-CoV receptor molecule angiotensin-converting enzyme 2 (ACE2) [24]. Bat cells do not support efficient infections of civet or human SARS-CoV strains because of residue changes (e.g. K31N, E35K, and Y41H) in their ACE2. However, given the diversities of bat ACE2 molecules, it is possible that future studies may identify a bat ACE2 that supports SARS-CoV infections. On the other hand, currently known bat SARS-CoV strains cannot jump from bats to civets or humans because of truncations in their receptor-binding motif (RBMs). Significant evolution would be needed for these RBMs to acquire sufficient binding affinity for civet or human ACE2. Once SARS-CoV had jumped from bats to civets, it underwent further mutations in civets. The first K479N mutation allowed SARS-CoV to jump from civets to humans and the second S487T mutation allowed SARS-CoV to transmit from human to human, leading to the severe SARS outbreak in 2002–2003. In the following year, SARS-CoV only acquired the K479N mutation, but not the S487T mutation, leading to the sporadic SARS infections with no human-to-human transmission. Mice supports SARS-CoV infection at low levels because of the K353H residue change in their ACE2, and rats are resistant to SARS-CoV infection because of the K353H and M82N double residue changes. In sum, critical residue changes in animal ACE2 molecules present species barriers for SARS-CoV infections. Through natural evolutions of its receptor-binding domain at key positions, SARS-CoV overcame the species barriers between some animal species (e.g., between bats and civets and between civets and humans), but not others (e.g., between civets and mice or between civets and rats) [25].

About Ebola and Marburg viruses, they are in the Filoviridae family in the order Mononegavirales wich is separated from other Mononegavirales on the basis of morphological, physiochemical, and biological features and more latterly genomic analyses [26]. Filoviruses are non-segmented, negative-strand RNA viruses. The viruses are filamentous enveloped particles of variable length. The filovirus genomes are typically approximately 19 kb in length [27]. The proteins expressed by the filoviruses are: nucleoprotein (NP), glycoprotein (GP), RNA-dependent RNA polymerase (L), and four structural proteins: VP24, VP30, VP35, and VP40 [28]. Ebolavirus is able to express a truncated soluble glycoprotein (sGP) through RNA editing. The ribonucleoprotein is derived from the RNA genome, NP, VP30, VP35, and L protein, though Marburgvirus is reported to be able replicate in the absence of VP30. The VP35 protein is known to block interferon induction in both Marburg and Ebola viruses [29], and the discovery of the open reading frame for this protein integrated into bat genomes is an area for future research exploration to better understand host-virus interactions and immunity [30]. The two proteins VP40 and VP24 form the internal viral membranes and the surface of the viral membranes are spiked with GP trimers. The trimers are formed from GP1 and GP2, which are cleaved from the GP precursor. The GP trimers mediate receptor binding and are the target for neutralizing antibodies [27].

Advances in technologies, such as, molecular diagnostics [31,32], deep-sequencing and meta-genomics [33] have enabled to prospectively analyze molecular data to identify potential inter-species human viruses and to assess probable virulence and transmissibility. The molecular diagnostics is now considered as a gold standard for the diagnosis of infectious diseases caused by fastidious or uncultivable agents. Its impact on diagnosis is irrefutable. Molecular tools have an impact on disease prognosis and response to therapeutic interventions [31].

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Regarding the deep-sequencing and metagenomics techniques, they provide a high speed and throughput that can produce an enormous volume of sequences with many possible applications in research and diagnostic settings. They have been applied to meta-genomics based strategies for the detection of unexpected diseases-associated virus and for the discovery of novel human viruses, including cancer—related viruses [33].

**Animals as reservoirs of human diseases**

In 2003 yet another virus could be identified as the causative agent of the severe acute respiratory syndrome (SARS) pandemic originating in the Chinese province of Guangzhou [34]. SARS was caused by the SARS-coronavirus (SARS-Cov) and resulted in approximately 8000 cases of infection in 31 countries around the globe (with China being the epidemiological hotspot) in the first six months of 2003 [35]. The CFR was roughly 10% [36]. Fortunately only ill patients excreted the virus and had to be considered as further sources of infection [36]. This is in contrast to human influenza where persons during the (asymptomatic) incubation also shed virus [12]. This characteristic was the main reason why the SARS pandemic could be stopped by classical measures of hygiene (such as isolation) without initially knowing the causative agent.

However, the threat to the world by SARS-like coronaviruses is not over. Chinese horseshoe bats (*Rhinolophus spp.*) were identified as original hosts of SARS-Cov [35]. It remains unclear whether raccoon dogs or civet cats, which were sold on Guangzhou markets as delicacies, served as amplifying intermediate hosts [35-37]. Furthermore, SARS-like coronaviruses have been found in bats around the world, which appear to be symptomless infected, indicating that the SARS-thread is not over [36].

One of these is the Middle-East respiratory syndrome (MERS)-Cov. MERS was first recognised in Saudi Arabia, which remains the hotspot of human cases, in summer 2012. Up to 21st March, 2016, WHO has recorded around 1,694 laboratory-confirmed human cases with a CFR of approximately 36% [38]. Current epidemiological data indicate that the agent can be transmitted among humans although not efficiently [39]. At the moment it is unclear what the original host is and how the virus infects human beings: Some researchers have identified the virus in bats [40-42], while others have detected MERS-like CoVs in camels [43]. It may turn out that camels served as amplifying host of an original bat virus [41,42].

Henipaviruses belong to the paramyxoviruses (such as measles virus). These are single-stranded RNA-containing viruses. Without any doubt they have been transmitted to humans and other mammals from their original hosts, the flying foxes (fruit-eating *Chiroptera* species) in SE Asia and Australia [44]. Because the natural habitat of the flying foxes was destroyed by urbanization, they got in increased contact with humans [45]. Now Nipah virus (NiV) appears to be endemic in the swine and human population in SE Asia and Bangladesh, causing from time to time dreaded outbreaks in the pig farm industry among pigs and humans [46]. Since 1998, thousands of humans came down with NiV infections with a CFR of around 75%, as a consequence of severe viral encephalitis [47]. Both peculiarities of their fusion proteins and viral strategies to abrogate the human innate immune (interferon) response, likely contribute to the high pathogenicity of henipaviruses [48,49]. Hendra virus (HeV) appears to be less common than NV with only three reported human and several equine cases since 1994; however, with a high lethality [50]. NiV can be transmitted among humans, although this route is not used frequently [51]. More recently Henipa viruses have been described to occur in *Chiroptera* species from other parts of Asia, in Africa and South and Central America [52].

These few examples illustrate that the majority of “new” human viruses do not arise
spontaneously, but are zoonotically transmitted from animals to the new human target population. After further adaptations by point mutations (drift) a “new” human viral infection is born. The chain of trans-species transmission may involve an intermediate host for the amplification of the virus, before transmission to humans. Also from a more theoretical point of view, the generation of a new virus appears unlikely. There exist three theories on the origin of viruses that are generally agreed upon [53]:

a) Viruses are older than their host cells and derive from replicating-competent entities (the “RNA-world”). Later on they acquired their cell-parasitic nature.

b) Viruses evolved as replicating cellular genetic elements after the development of host cells. The separation of individual genes from the host genome may have occurred at any time after the development of the host species.

c) Viruses were originally something like bacteria, which later lost certain functions (and genetic material).

Probably not one explanation fits to all viruses. Be this as it may, it is however clear that the development of a new virus is almost as rare as the development of a new host species (which on average takes place every 100,000 years [54]). Given the enormous potential of genetic change (in particular in RNA-viruses) this notion appears at odds. Since viral fossils do not exist, it is even impossible in most instances to extrapolate an intermediate evolutionary viral history [55].

However, with the probable exception of pathogenic bovine diarrheal virus (BDV) variants, which regularly require a recombination event between the exogenous virus and an endogenous cellular mRNA to convert into highly pathogenic variants [56], we do not (and never before) witness the appearance of a completely “new” virus.

Instead we are witness of an assumed increased trans-species transmission rate from animals to mankind. By now there are more than 7 billion people populating the globe and the demographic forecasts point to a plateauing at around 10 billion by 2100 and are thus not encouraging [57]. This will without any further doubt lead to more exposure and an enhanced transmission rates among humans of new viral infectious diseases. Once introduced into and established in the human population, modern air traffic guarantees their spread around the world within a few days or weeks [58].

If one closely looks at table 1, one recognizes bats prevail as original source of “new” human viruses. Although rodents outnumber bats (in terms of total individuals and in the number of species) and should transmit viruses more often than bats [59] (68 potentially zoonotic viruses in rodents versus 61 in bats, the vast majority being RNA-viruses [60]), they do not do so very effectively (or it has not been investigated deeply enough). It has been found that the currently relative close association between humans and some rodent species has resulted in transmissions in the past, with only a few virus families remaining for transmission. Like rodents, bats present a very old mammalian order; and they represent roughly 20% of known mammalian species [61]. However, in contrast to some rodent species, bats were until recently less likely to meet humans or other mostly domestic animal species that could likely act as amplifying intermediate hosts. Furthermore, in contrast to rodents, various bat species are known to live in very large colonies [62] and, in addition, the individual life span of a bat is usually longer than that of rodents [63]. These features may result in enhanced viral transmission among animals (on average, each bat species hosts 1.79 zoonotic viruses, while this value is 1.48 for rodent species [60]) and consequently to humans. Some bat species are known to be migratory (for instance the Mexican freetailed bat (Tadarida brasiliensis mexicana) may travel more than 1,300 km between their summer caves in Texas and New Mexico and their
overwintering sites in Mexico [64]). This feature may also result in an enhanced transmission rate.

It could be argued that not all transmitting viruses are derived from mammals (although the majority is and the avian INF A variants are known [12-14]). Furthermore, some mammals (for instance sea mammals) are less likely to transmit zoonotic viruses than others (for instance bats, see discussion above). However, this view does only change the global picture in nuances and not by orders of magnitude.

Technological advances now allow for individual genome sequencing within days or weeks, while the first human genome project took around ten years [31-33]. We therefore, believe that the time to determine (not only) the mammalian host genomes and their parasites (not only viruses) has come and that justifications for this should not use the possibility of detecting “new” viruses with zoonotic potential [65] as an argument because it is appears to be counterproductive.

Zika virus is transmitted by *Aedes* mosquitoes and *Ae. aegypti* is the only species for which transmission outside Africa has been confirmed. In the 2007 Yap island outbreak, *Ae. Hensilii* mosquitoes were implied as vector, but this could never be confirmed by virus detection. The virus has been isolated and/or detected by PCR from *Ae. africanus*, *Ae. aegypti*, *Ae. albopictus*, *Ae. apicoargenteus*, *Ae. luteocephalus*, *Ae. vitattus*, *Ae. taylori*, *Ae. dalzieli*, *Ae. hirsutus*, *Ae. metallicus*, *Ae. unilinaetus*, *Ae. opok* and *Ae. furcifer* species in the field in Africa [15]. In addition ZIKV genomic RNA was detected in *Mansonia. uniformis*, *Culex perfuscus* and *Anopheles coustani* mosquitoes in Senegal [66]. *Ae. albopictus* has shown competence for ZIKV dissemination in laboratory circumstances but has never been implied in ZIKV epidemiology in the field outside Africa [15].

Additional modes of transmission have been identified. Perinatal transmission can occur most probably by trans-placental transmission or during delivery when the mother is infected [15]. ZIKV has been isolated from semen collected 14 days post start of symptoms [67] while detection of ZIKV genomes was described in semen 28 days post onset of symptoms [68]. Sexual transmission was indicated in three case reports [15]. There is a potential risk of ZIKV transfusion-derived transmission [69] and Brazilian authorities announced the first cases of blood-transfusion mediated transmission on 5 February, 2016 [70].

Filoviruses, including Ebola virus and Marburg virus, pose significant threats to public health and species conservation by causing hemorrhagic fever outbreaks with high mortality rates. Since the first outbreak in 1967, their origins, natural history, and ecology remained elusive until recent studies linked them through molecular, serological, and virological studies to bats [27].

**Factors determining emergence**

From experience, we know that many different elements can contribute to the emergence of a new virus disease; these include (see figure 1) virologic determinants [such as mutation, recombination, reassortment (drift and shift), natural selection, fitness adaptation, and evolutionary progression], natural influences (such as ecologic, environmental and zoonotic influences) and factors pertaining to human activity (such as behavioural, societal, transport, commercial and iatrogenic factors) [71]. Perhaps most disturbing elements of these factors are the (a) rise of antimicrobial resistance with a paucity of development of truly new classes of antimicrobials ;(b) increasing resistance of arthropods to control agents and the lack of active development of new ones; and (c) failure of the vaccine industry to translate biotechnological advances to new immunogens for humans[2].

Continuing expansion of human populations and satisfying their needs will accelerate global warning, habitat fragmentation, forest
Table 1: Non-exhaustive examples of zoonotic viruses

<table>
<thead>
<tr>
<th>Virus</th>
<th>Original host</th>
<th>Main human diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human Immunodeficiency Virus</td>
<td>Old World Great Apes</td>
<td>Acquired Immunodeficiency Syndrome</td>
</tr>
<tr>
<td>Influenza A</td>
<td>Birds (swine)</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>Severe Acute Respiratory Syndrome</td>
<td>Bats</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>Middle-East Respiratory Syndrome</td>
<td>Bats, Camel (?)</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>Henipah</td>
<td>Bats</td>
<td>Vasculitis, encephalitis and pneumonia</td>
</tr>
<tr>
<td>Ebola, Reston</td>
<td>Bats, Primates</td>
<td>Haemorrhagic Fever, none</td>
</tr>
<tr>
<td>Hepatitis E Virus</td>
<td>Swine, cattle, boar, bats?</td>
<td>Hepatitis</td>
</tr>
<tr>
<td>Hanta Viruses</td>
<td>Rodents</td>
<td>Haemorrhagic Fever with Renal Syndrome, Hantavirus Pulmonary Syndrome, Haemorrhagic Fever</td>
</tr>
<tr>
<td>Foamy Viruses</td>
<td>Non-Human Primates</td>
<td>None</td>
</tr>
<tr>
<td>Lassa</td>
<td>Rodents</td>
<td>Haemorrhagic Fever</td>
</tr>
<tr>
<td>Rabies</td>
<td>Carnivores, Vampire bats</td>
<td>Encephalitis</td>
</tr>
<tr>
<td>Hendra virus</td>
<td>Bats</td>
<td>Hendra Disease</td>
</tr>
<tr>
<td>European Bat Lyssa Virus</td>
<td>Bats</td>
<td>Fatal encephalitite disease</td>
</tr>
<tr>
<td>Australian Bat Lyssa Virus</td>
<td>Bats</td>
<td>Fatal encephalitite disease</td>
</tr>
<tr>
<td>Irkut Virus</td>
<td>Bats</td>
<td>Fatal encephalitite disease</td>
</tr>
<tr>
<td>Sabia Virus</td>
<td>Rodents</td>
<td>Brazilian Haemorrhagic Fever</td>
</tr>
<tr>
<td>Andes virus</td>
<td>Rodents</td>
<td>Hantavirus cardiopulmonary syndrome</td>
</tr>
<tr>
<td>Zika virus</td>
<td>Aedes, Bats?</td>
<td>Microcephaly, Guillain Barré Syndrome</td>
</tr>
</tbody>
</table>

Figure 1: Different factors contributing to the emergence of viral diseases

clearing, and conversion to conifer plantations, overgrazing, erosion, land exhaustion, and loss of biodiversity. More than 700 known viruses circulating in nature are stirred in this mix [71]. Travel, trade, and transport have rapidly moved human diseases
worldwide and these factors continue to introduce non-native animal and plant species into novel environments, which continue to take hold and flourish with some regularity, most dangerously potential arthropod vectors of diseases. The perturbation of the ecologic balance and subsequent shifts in resident species, as well as take-over by introduced species are not just of concern to those of us who feel we should be good stewards of the planet. These exponentially increasing changes are setting the stage for the emergence of new diseases and new transmission cycles of old diseases [2].

**Prevention and control**

Virus emergence is continuous (Table 1). Development of a global surveillance/diagnostics/communications network is needed, but this, in turn, must be linked to a global action network. This network must be designed to be flexible; capable, for example, in one instance of emphasizing local professional infrastructure development, and in the next of emphasizing global epidemic aid. Given the nature and magnitude of the threat represented by new and emerging virus diseases, the development of a global surveillance/action network is, indeed, a worthy goal for national and international public health authorities.

Given the diversity of emerging viral diseases, it is sometimes helpful to analyze a situation in terms of a simple formula:

\[
[Viral \text{ variation}] + [changing \text{ ecology}] + [travel \text{ and transport}] = [increased \text{ opportunities for viral emergence}] \ [2,72].
\]

This formula can be used to analyse either a situation in which emergence might occur or an actual emerging disease by using a broad definition of ecology. Think of ecology in its broadest sense: for a mosquito borne virus, it could refer to the natural world in the breeding locations; for HIV, however, it could apply to mucous membranes and the human behaviours that bring them into contact. A great source of “new” viruses is the natural world; with a few exceptions, most of the emergences of these viruses are driven by their changing ecology or travel and transport. Viral variation probably is important as well but mainly occurs in an adaptive way [2].

**Prediction of new emergences**

In general, there is no way to predict when or where the next important new viral pathogen will emerge; neither is there any way to reliably predict the ultimate importance of a virus as it first emerges. Given this reality, initial investigation at the first sign of the emergence of a new virus disease must focus on characteristics such as mortality, severity of disease, transmissibility, and remote spread, all of which are important predictors of epidemic potential and societal threat. Clinical observations, pathologic examinations and preliminary virus identification and characterization often provide early clues, since new, emerging viruses often resemble their closest genetic relatives in regard to their epidemiologic and pathogenetic characteristics.

From the incomplete list of emergences in Table 1, we have to learn that emergence is continuous and once the circumstances are propitious for the virus to appear, it will establish itself or it will return; it will rarely disappears. Thus, surveillance and research must continue for periods beyond the patience of most funding agencies. Many emergences come from new taxons [52,73] and some represent viruses that are characteristic of a previously unstudied group of parasites of a group of animals [2,74].

**New tools in the control of re-emerging viral diseases**

Nowadays, for an efficient control of re-emerging viral diseases, new tools are used: mathematical modeling, remote sensing and ecologically based approaches. Mathematical models can project how infectious diseases progress to show the likely outcome of an epidemic and help inform public health interventions. Models use some basic assumptions and mathematics to find
parameters for various infectious diseases and use those parameters to calculate the effects of possible interventions, like mass vaccination programmes [75]. Environmental approach of emerging viral diseases is a particularly complex research [76]. Remote sensing data enable scientists to study the earth’s biotic and abiotic components [77]. The causes underlying the rise of disease are at macro (socio-cultural) and micro (cellular and molecular) levels, but they are indeed acting over the individuals, populations and communities [78, 79]. There are several lines of evidence on the relationship between natural ecosystems intervention and re/emergence of diseases produced by bacteria, parasites and viruses [80, 81]. Specifically, for understanding viral emergence it is important to understand the sylvatic cycle of viruses, the transition to human populations, the relationship between vectors, pathogens and reservoirs in wildlife ecosystems, the change in the distribution of vectors and reservoirs after natural habitat fragmentation, and how these conditions are generating potential new roles and ecological niches for species. Wild ecosystems historically disturbed by agricultural and industrial activities with changes in biotic and abiotic factors (water bodies distribution, soil profiles, plant coverage, breeding microclimate, vertebrate and invertebrate populations, etc.) [82], constitute new selective pressures for pathogens and therefore new opportunities for adaptation [83]. It allows vectors/reservoirs to exploit the new resources, favouring viral contact with potentially new host populations (humans).

Conclusion
Despite extraordinary progress during the past two decades, infectious diseases still kill millions 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.

Competing Interests
The authors declare that they have no competing interests.

Abbreviations
HIV/AIDS: Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome,
SIV: Simian Immunodeficiency Virus,
CFR: Case Fatality Rate,
LPAI: Low-pathogenic avian INF A,
HPAI: High-pathogenic avian INF A,
SARS-Cov: Severe acute respiratory syndrome-coronavirus,
MERS-Cov: Middle-East respiratory syndrome-coronavirus,
NiV: Nipah virus,
HeV: Hendra virus,
BDV: Bovine diarrheal virus,
RNA: Ribonucleic acid,
ZIKV: Zika virus

Authors’ contribution
Gabriel K. Bunduki wrote the review, designed tables and figures. Matala Wafula revised the text, tables and figures. Both authors read and approved the final manuscript submitted.

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