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Review

AIDS, Avian flu, SARS, MERS, Ebola, Zika... what next?

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ABSTRACT

Emerging infections have threatened humanity since times immemorial. The dramatic anthropogenic, behavioral and social changes that have affected humanity and the environment in the past century have accelerated the intrusion of novel pathogens into the global human population, sometimes with devastating consequences. The AIDS and influenza pandemics have claimed and will continue to claim millions of lives. The recent SARS and Ebola epidemics have threatened populations across borders. The emergence of MERS may well be warning signals of a nascent pandemic threat, while the potential for geographical spread of vector-borne diseases, such as Zika, but also Dengue and Chikungunya is unprecedented. Novel technologies and innovative approaches have multiplied to address and improve response preparedness towards the increasing yet unpredictable threat posed by emerging pathogens.

Contents

1. Main text

Ever since the emergence of the human species from the animal world, complex interactions between humans and animals have resulted in human-animal interfaces that promoted cross-species transmission, emergence and evolution of an ever increasing number of human pathogens, originating from animals (review in [1]). In the past centuries, our global environment has changed dramatically as a result of major and unprecedented anthropogenic influences that have had a significant and global impact on the earth's ecosystems [1]. These influences include extreme forms of predatory behavior, domestication, warfare, colonization, travel, agriculture, habitat fragmentation, urbanization and industrialization, collectively leading to what has now been proposed to be the most recent geological period: the 'Anthropocene' [2]. Until the beginning of the last century, infectious diseases were the major cause of human mortality, causing about fifty percent of all human deaths. In the following decades, this burden dramatically decreased to less than a few percent in the industrialized world [3]. Implementation of public health measures such as sewage installment and development of clean drinking water systems, but also to introduction of vaccines and antimicrobials were the major drivers of this spectacular decrease. Successes in this regard were the eradication of smallpox virus and rinderpest virus through orchestrated vaccination campaigns among humans and cattle, respectively. The eradication of smallpox virus led to the abolishment of smallpox vaccination, which created a niche for human infections with other orthopox viruses, leading to increasing incidences of human cowpox and more dramatically monkeypox. The eradication of rinderpest virus from cattle may well bear important lessons for the envisaged eradication of the closely related measles virus from humans through sustained vaccination

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efforts [4]. Both these viruses with a quite similar pathogenesis in their respective species belong to the Morbillivirus genus of which several members have a history of frequent interspecies transmission. This raises the question whether we should continue measles vaccination, even after the eventual eradication of measles virus.

The successful reduction of infectious diseases in the middle of the last century even prompted prominent policymakers and scientists to raise the expectation that infectious diseases of humankind would eventually, at least in the industrialized world, be brought under control. Paradoxically the following decades confronted the world with an ever-increasing number of emerging or re-emerging infectious diseases, some causing true pandemic threats or even pandemics. Viruses spilling over from wildlife reservoirs, either directly or via intermediate hosts, were at the basis of most of these disease outbreaks. Striking examples of emerging viral diseases of mankind that had their origin in wildlife reservoirs and spilled over either directly or via domestic animals, were AIDS from chimpanzees, influenza from wild birds, Ebola, SARS and MERS from bats, and Dengue, Chikungunya and Zika from mosquitoes. This paved the way for the unprecedented spread of infections in humans and animals with dramatic consequences for public and animal health, animal welfare, food supply, economies, and biodiversity.

The **AIDS** pandemic that emerged more than three decades ago, happened after multiple introductions of a simian lentivirus from chimpanzee reservoirs into the human population [5]. To date more than 70 million people have become infected, more than 35 million have died, while more than 1 million die annually [6]. One of the central questions in this tragic series of events is, why did a lentivirus that has been 'locked up' in chimpanzee reservoirs for a long time, suddenly start a human pandemic? A complex mix of predisposing factors linked to major changes in the societal environment and ecology of our globalizing world, collectively created opportunities and niches for HIV to not only cross the animal-human species barrier, but to also spread globally in the new human host. Although huge efforts were made to stop this pandemic, it took more than two years before **HIV** was identified as the causative agent [7], another two years to identify CD4 as its receptor [8], about a decade before an effective antiviral strategy was developed [9], while it is not even clear today if and when a vaccine will become available, despite new hopes making the news [10].

The continuing threat posed by **influenza viruses** in migratory bird reservoirs, that may lead to zoonotic infections via domestic poultry or mammals like pigs, can eventually lead to an influenza pandemic [11]. Humanity has experienced four pandemics in the past century, which have collectively cost the lives of tens of millions of people. During the last pandemic - the Mexican flu - that was relatively mild in spite of causing deaths among relatively young people [12], we for the first time could use specific and effective antivirals and vaccines, although for many countries vaccines came too late or in too low quantities. This was in part due to largely outdated manufacturing practices making use of embryonated chicken eggs for the production of the vaccines (reviewed in [13]). Clinical preparedness was furthermore limited, with relatively few implementations of relevant clinical studies and trials, at the start and during the course of the pandemic [14–18]. Such studies are essential to gather evidence on the efficacy of preventive and therapeutic interventions, to inform clinical management and guide public health response. A wide diversity of avian influenza viruses with zoonotic potential are circulating in poultry and wild bird reservoirs, posing an abiding threat to humanity. Recent outbreaks of highly pathogenic and low pathogenic avian influenza virus infections in poultry and wild birds across Asia, Europe and Africa this winter demonstrate an ever-present Sword of Damocles. Therefore the influenza vaccine community is now concentrating on the development of more universal influenza vaccines, with broader coverage and longer longevity of protection against a wide range of influenza virus strains and subtypes [19].

Ebola was first identified as a disease entity associated with high mortality, in the seventies of the last century [20]. It was eventually recognized that the most likely reservoir of the causative filovirus is bats, based on serology, PCR and experimental infections [21] and that the virus may infect humans upon bat contacts, or upon consumption of e.g. primates that have died as a result of the infection acquired from bats. Since the infection initially occurred in urban regions where human-to-human transmission routes could rapidly be understood and avoided, the annual Ebola death toll was always less than 1000 people during outbreaks. Although efforts to develop a vaccine against Ebola viruses were made, they never went beyond pre-clinical testing in macaques. When during the last and devastating Ebola outbreak that started in 2013, the virus started to spread in urban environments of West Africa and subsequently through air travel to many other countries worldwide, the global death toll rose to more than 11,000 individuals. Limited diagnostic capacity largely contributed to the delayed recognition of the emerging epidemic, with initial cases misdiagnosed as cholera and later as Lassa fever [22]. The delayed recognition of the Ebola outbreak led to overwhelmed health care systems unable to contain the spread of the virus. Halted vaccine development and testing activities were resumed but relatively late during the course of the epidemic, and eventually the epidemic was contained by strict implementation of hygienic and sanitary measures [23]. However, several Ebola vaccine candidates and prime-boost regimens were tested pre-clinically and eventually also clinically in the affected area. The trials were initiated mostly during the tail of the epidemic, but led to at least one effective vaccine [23]. This vaccine may be used in the face of a next Ebola outbreak, to protect healthcare workers and contacts of infected individuals, to control nosocomial and subsequent further spread in the population.

Severe acute respiratory syndrome (SARS) was recognized as a disease entity when clusters of atypical pneumonia were identified in provincial hospitals in China at the end of 2002 from where it spread to Hong Kong. This subsequently led to a global outbreak by dissemination of the virus through air travel. In total, more than 8000 people were infected, with 774 deaths reported in 37 countries [24] (Fig. 1). Once the search for the cause was started by a WHO-coordinated task force consisting of representatives of a dozen laboratories worldwide, within two weeks SARS coronavirus (SARS-CoV) was identified as the etiologic agent and the Koch's postulates were fulfilled [25,26]. Angiotensin converting enzyme 2 (ACE2) was identified as its functional receptor within months after the new virus discovery [27]. The virus most likely originated from bats and spread to humans via live animal markets in China, where Himalayan civet cats and other carnivores sold for human consumption had become infected [28,29]. After identification of the agent, implementation of specific diagnostic tests and isolation of infected individuals halted the spread of the virus. Antiviral strategies, like the use of Interferon-α proved effective [30], and a dozen of SARS vaccine candidates were developed. However as the disease was rapidly controlled after the identification of the agent, further development and clinical testing of vaccine candidates were stopped [31,32]. Collectively the well-coordinated activities that led to the early identification of the virus and the implementation of measures at the global scale limited the death toll of this emerging pandemic.

Ten years after the emergence of SARS-CoV, another coronavirus was identified as the cause of an emerging respiratory disease in the Middle East; the **Middle East Respiratory Syndrome (MERS)** coronavirus (MERS-CoV). Initially the virus was identified as the cause of a fatal respiratory infection in an elderly man in

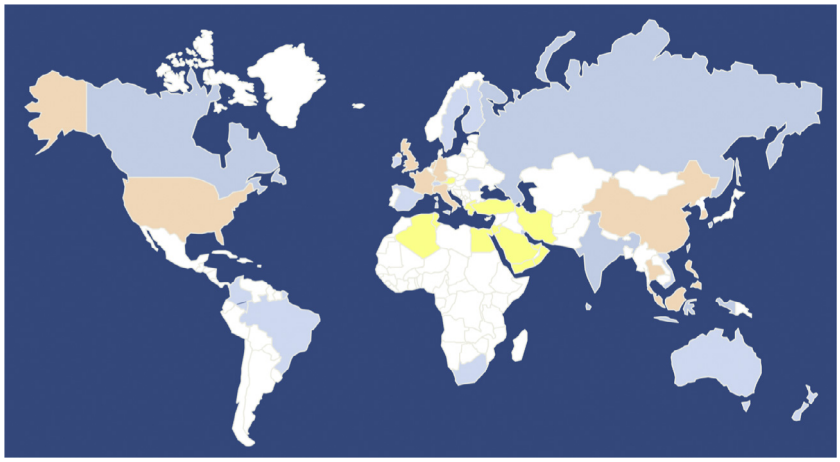

Fig. 1. Global distribution of reported cases of SARS coronavirus infection at the end of the epidemic of 2003 and of MERS coronavirus infection as of January 2017 (at country level); blue: countries that reported cases of SARS coronavirus infection only; yellow: countries that reported cases of MERS coronavirus infection only; orange: countries that reported both cases of SARS and MERS coronavirus infection. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Saudi Arabia [33], and subsequently CD26 was rapidly identified as the receptor [34]. MERS-CoV also likely originated from bats [35], spread via dromedary camels to humans, and proved to cause disease outbreaks in Middle East and Asian hospitals. The total number of confirmed cases is approaching 2000, with a case fatality rate of about 35% [36]. From the Middle East the virus has spread to a total of 27 countries where in some cases also chains of human-to-human infections have taken place, e.g., in the Republic of Korea (Fig. 1). Several vaccine development activities have been initiated and different vaccine candidates have been developed. One of these is an MVA-based vaccine expressing the MERS-CoV glycoprotein. It proved to be efficacious in dromedary camels, while most likely also effective against camelpox [37]. This vaccine has prompted discussions on the advantages of prevention at the source, i.e., in the animal reservoir of the disease, supporting the One Health approach increasingly endorsed by the international community. This vaccine will soon be clinically tested in humans, with the final aim of protecting healthcare workers to prevent nosocomial spread, and protecting contacts of infected individuals.

The mosquito-borne infections **Dengue, Chikungunya and Zika** are imminent threats to humanity, in part due to the expansion of their arthropod vectors, in particular *Aedes aegypti* and (*A.*) *albopictus*, into new geographical areas. This is facilitated by anthropogenic changes including climate change. **Dengue** is one of the most common vector-borne diseases, with four distinct serotypes of dengue flavivirus circulating in more than 110 countries worldwide, mainly in tropical and sub-tropical regions (Fig. 2). Its incidence has increased dramatically in the past decades with half of the world's population now at risk. Infection may cause severe hemorrhagic fever, especially upon subsequent infections with different dengue flavivirus serotypes. Globally, there may be close to 400 million cases of dengue virus infection annually, with about 100 million clinically symptomatic, and half a million requiring hospitalization [38]. It is a leading cause of severe disease and death in children in Asia and South America. Only recently – since late 2015 – was the first dengue vaccine registered (Dengvaxia CYD-TDV by Sanofi Pasteur).

Historically distributed across tropical Africa and Southeast Asia, the **Chikungunya** alphavirus has in recent years expanded its geographical range across the Indian Ocean and lately across South America and the Caribbean. It has also caused outbreaks in more temperate regions, such as Florida (USA), southern France, Italy and Croatia, evolving from a rare and exotic ailment to a disturbing international public health threat. More than 100 countries and territories are affected by sustained local transmission (Fig. 2). In contrast to other arbovirus diseases, chikungunya causes acute symptomatic disease in the majority of patients, with about 30% further developing chronic disabling arthralgias. As for other rare and neglected diseases, attempts for the development of chikungunya virus vaccines have so far not led to the successful implementation of effective intervention strategies against this emerging virus infection. A number of vaccines have been developed up to pre-clinical evaluation, with three vaccine candidates having reached up to phase 2 clinical trials [39].

Until recent outbreaks in the Pacific in 2007 and 2013, and its spread to the Americas in 2015, mainly serologic evidence of **Zika** flavivirus infection had been reported in African and Asian countries [40]. Less than a hundred cases of infection were confirmed in Micronesia in 2007, while the epidemic of 2013 spread across the Pacific, resulted in an estimated 20,000–35,000 cases, with imported cases in New Caledonia, Japan and Germany. In early 2014, autochthonous Zika virus transmission was reported in New Caledonia, as well as on the Cook Islands and Easter Island (Chile). Cases were later imported to Queensland Australia, Germany and New Zealand. In 2015, autochthonous Zika cases continued to occur in the Pacific, before reaching Brazil and Columbia and further spreading across central and Latin America (Fig. 2). Asymptomatic infections are likely common, and clinical manifestations include fever with a rash, conjunctivitis and arthralgia. Zika virus is a cause of microcephaly and other congenital brain anomalies, as well as a trigger of Guillain-Barré syndrome [41]. It may further be associated with other neurological disorders. A number of Zika virus vaccine candidates are currently being developed [42].

Due to the complex and largely interactive nature of the drivers for newly emerging virus infections, it is virtually impossible to predict what the next pathogen threat will be, from where it will come and when it will strike. The recent Ebola and Zika epidemics testify of the unpredictable nature of emerging infections, yet point to a particularly persistent threat by RNA viruses, likely due to their ability to rapidly evolve and adapt to (environmental and host) changes [43]. A better understanding of the underlying processes favoring infectious disease emergence may eventually lead to improved preparedness for outbreaks in humans and animals. Importantly, the increased emergence of viral infections is largely paralleled by medical, veterinary, technological, and scientific progress, continuously spurred by our never-ending drive to combat

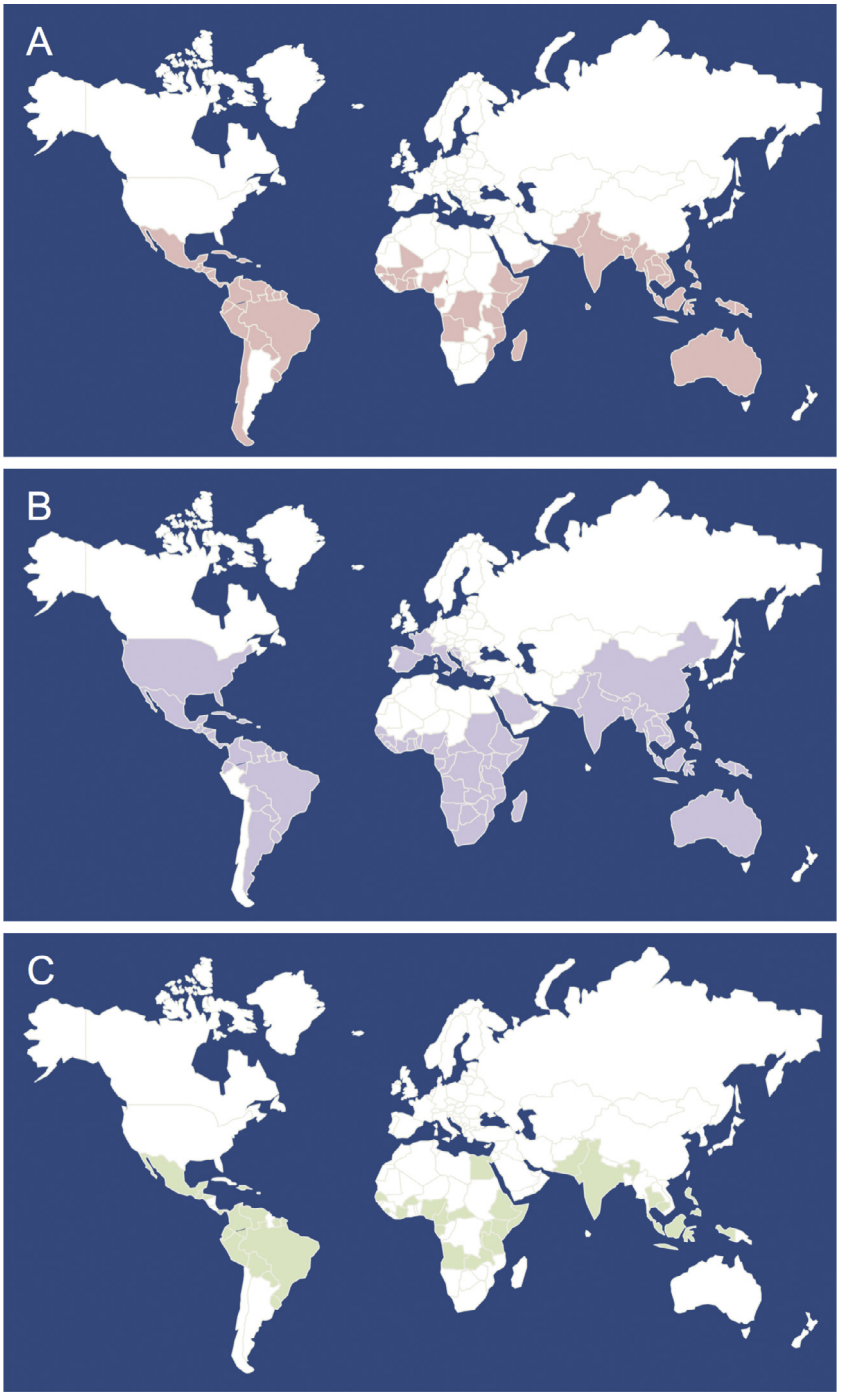

Fig. 2. Current geographical range of sustained transmission of Dengue (A), Chikungunya (B) and Zika (C) virus (at country level).

pathogens. Investment in better understanding the human-animal interfaces will therefore offer a future head start in the never-ending battle against infectious diseases of humans. Comprehensive surveillance programs, based on new high-throughput technologies and improved diagnostic capacity in regions of the world that need them most, constitute the essential foundation upon which preparedness programs can be built. Rapid identification and characterization of novel pathogens and their host-interactions, e.g. with cellular receptors and innate immune responses, is key to allow prompt diagnostic and containment measures, as demonstrated by the emerging SARS pandemic that was essentially nipped in the bud. Prevention at the source and One Health interventions have strong potential to mitigate the threats posed by zoonotic pathogens. Successful examples include the closure of Asian wet-markets, reducing the risk of emergence of zoonotic pathogens, such as influenza A viruses and SARS coronavirus [44]. Protection of date palm sap collection by simple measures like bamboo skirts, reduced bat contacts in Bangladesh, limiting the risk of contamination with Nipah virus and other known or unknown bat pathogens [45]. Emerging epidemics also offer invaluable but often rarely occurring opportunities to carry out clinical research aimed at improved clinical management and better-informed public health responses. Therefore, clinical preparedness with associated adapted policy, regulatory and ethical procedures are urgently needed for timely deployment upon emerging epidemics. Lastly, the establishment of vaccine and

antimicrobial development platforms, widely applicable to both known and still unknown pathogens, while striving towards more universal or broader protective responses, will further contribute to a better R&D based response preparedness towards an ever-increasing threat.

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