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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

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