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Mini Review

Influenza, a One Health paradigm—Novel therapeutic strategies to fight a zoonotic pathogen with pandemic potential

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ABSTRACT

Influenza virus is a paradigm for a pathogen that frequently crosses the species barrier from animals to humans, causing severe disease in the human population. This ranges from frequent epidemics to occasional pandemic outbreaks with millions of death. All previous pandemics in humans were caused by animal viruses or virus reassortants carrying animal virus genes, underlining that the fight against influenza requires a One Health approach integrating human and veterinary medicine. Furthermore, the fundamental question of what enables a flu pathogen to jump from animals to humans can only be tackled in a transdisciplinary approach between virologists, immunologists and cell biologists. To address this need the German FluResearchNet was established as a first nationwide influenza research network that virtually integrates all national expertise in the field of influenza to unravel viral and host determinants of pathogenicity and species transmission and to explore novel avenues of antiviral intervention. Here we focus on the various novel anti-flu approaches that were developed as part of the FluResearchNet activities.

Introduction

Influenza is a prime example of a zoonotic disease and highlights the relevance of a One Health approach, where experts in animal and human health-care and research combine their efforts to solve interrelated problems. Human disease due to pandemic (H1N1) 2009 influenza and avian to human transmission of influenza A/H5N1or A/H7N9 viruses are only recent examples of new zoonoses with significant global impact. Management, prevention and treatment of influenza requires the expansion and continuing support of collaborations between human and animal health experts at the clinical, diagnostic laboratory, public health, research and training levels.

Influenza A/H5N1, first isolated in 1996 from a goose in Guangdong province in China, caused severe poultry losses and occasional human infections in Hong Kong in 1997 (Watanabe et al., 2012). The main human public health response that controlled this outbreak was an aggressive poultry cull. However, from 2003 the virus continued to spread to different other parts of the world. Since then, more than 600 sporadic cases of human infection with influenza A/H5N1 viruses with high lethality have been reported, primarily by 15 countries in Asia, Africa, the Pacific, Europe and the Near East (Watanabe et al., 2012). In January 2014, the first case of a human infection with H5N1 in the Americas was reported from Canada. Fortunately, human-to-human transmission of H5N1 was and is still rare, so far preventing pandemic spread of this potentially devastating pathogen.

Human infections with a new avian H7N9 virus were first reported in China in March 2013 (Liu et al., 2014). Most of these infections are believed to result from exposure to infected poultry or contaminated environments, as H7N9 viruses have also been found in poultry in China. Most patients have had severe respiratory illness, with about one-third resulting in death. The first case outside of China occurred in Malaysia and was reported in February 2014. The frightening feature of this virus is, that it does not belong to the group of highly pathogenic avian influenza viruses according to the structure of its surface glycoprotein hemagglutinin. This not only hampers proper surveillance in poultry but also challenges the general concept of avian virus pathogenicity for humans (Liu et al., 2014). Fortunately also here no evidence of sustained

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person-to-person spread of H7N9 has been found, though some evidence points to limited person-to-person spread in rare circumstances.

Nevertheless, because avian influenza A viruses have the potential to change and gain the ability to spread easily between people, monitoring for human infection and person-to-person transmission of A/H5N1 and A/H7N9 is extremely important for public health.

While most experts were concerned about a pandemic threat due to flu activity in Asia, the first pandemic influenza virus of the 21st century came from a completely different and unexpected region of the world. The first descriptions of pandemic (H1N1) 2009 influenza virus infection occurred in the southwestern United States and Mexico in April 2009 (York and Donis, 2013). This virus was identified to have animal origins, with reassortment of influenza gene segments from North American and Eurasian swine, avian and human viruses (reviewed in Zell et al., 2013). Although seasonal A/H1N1 viruses had been circulating for many years, this novel reassortant A/H1N1 virus was not covered by current seasonal influenza vaccines and could spread very quickly all over the world. Fortunately, this pig borne virus in general caused only relatively mild disease symptoms in humans and did not acquire higher pathogenicity over time.

The emergence of the panH1N1 virus from a yet unidentified pig source is not a unique event. There is a plethora of reports indicating mutual transspecies infections of humans and pigs. In Europe, the prevalent lineages of swine influenza viruses presently comprise avian-like H1N1, human-like H1N2 and human-like H3N2 serotypes (Zell et al., 2013). The avian-like H1N1 lineage emerged in 1979 after transmission of an Eurasian avian H1N1 virus to pigs. This virus strain rapidly spread to pigs in many European countries and replaced the circulating classical swine H1N1 strains. In the following years, numerous reassortants of avian-like H1N1 and the human seasonal H3N2 could be detected but only one achieved to establish a persistent lineage. This human-like swine H3N2 lineage has strain A/Port Chalmers/1/73-like hemagglutinin and neuraminidase genes and six internal genes of the avian-like H1N1. In the UK, seasonal H3N2 and H1N1 reassorted with avian-like H1N1 to yield a human-like swine H1N2 virus which spread to many other European countries. In the following years, the avian-like H1N1 as well as the human-like H3N2 and H1N2 developed distinctive genetic lineages and became prevalent in the major swine-producing countries in Europe but also diffused to several Asian countries (Thailand, China, Hong Kong). It is obscure where and when an avian-like swine H1N1 virus recombined with a North American triple reassortant swine influenza virus to yield the novel swine-origin H1N1 (panH1N1) that caused the 2009 pandemic. During the ongoing pandemic, panH1N1 was repeatedly transmitted to swine as shown by numerous successful isolations from pigs. However panH1N1 failed to establish a stable infection chain in the European pig population. This failure was attributed to a pronounced one-sided antigenic cross-reactivity of the wide-spread avian-like H1N1: panH1N1 refused to propagate in pig herds presenting with antibodies against avian-like H1N1 as shown by the FluResearchNet laboratory Dürrwald (Dessau-Rosslau; Dürrwald et al., 2010). Later, the FluResearchNet laboratory Zell (Jena) demonstrated that a 7+1 reassortant of panH1N1 with the neuraminidase gene of human-like H1N2 exhibited additional six substitutions in the antigenic sites of the hemagglutinin gene (Lange et al., 2013). This reassortant showed no or only little cross-reaction with avian-like H1N1 post infection sera and hence was able to establish a persistent infection chain. Due to the wide distribution of swine influenza viruses with prevalences (on the herd level) of each subtype of 40–50% in Germany (FluResearchNet laboratory Dürrwald, unpublished data), vaccination is recommended to limit the economical losses of pig farmers. However, the virus isolation program and the genetic characterization of the isolates from pigs that were conducted in the recent years by the FluResearchNet laboratories Dürrwald (Dessau-Rosslau) and Zell (Jena) revealed additional novel, persisting virus lineages which complicate both diagnostics and vaccine development (Dürrwald and Zell, unpublished data).

Beside human-to-swine transmission, there is also evidence of swine-to-human infections. In contrast to zoonotic infections with the avian subtypes H5N1, H7N2, H7N3, H7N7, and H9N2 which are often associated with severe diseases and high case fatality rates, swine-to-human infections are believed to be mostly mild. Since 1993, several case reports from the Netherlands, Switzerland, Spain, Germany, Hong Kong and China indicate that close occupational contact to pigs increases the risk of zoonotic infections with the European lineages of swine influenza viruses in exposed pig farm workers and their family members. As most zoonotic swine-to-human infections do not result in severe clinical symptoms and thus may not be diagnosed, seroprevalence studies are considered a suitable approach to describe the general risk of infection. Consistently, serological evidence of frequent zoonotic infections in Germany was demonstrated by the FluResearchNet laboratories Zell (Jena) and Dürrwald (Dessau-Rosslau) in two studies (Krumbholz et al., 2010, 2013). The data demonstrate that direct contact to pigs is associated with higher risk of seroreactivity to swine influenza viruses. This risk is more obvious in the younger participants. Comparable results were obtained in serosurveys from Luxembourg and Italy (Gerloff et al., 2009; De Marco et al., 2013).

The frequent and unpredictable transmissions of influenza from birds and pigs to humans highlight the urgent need of a joint One Health approach integrating human and veterinary medicine in surveillance, communication, pathogen characterization and intervention strategies. Especially the latter point is of major importance. Considering that vaccination is not an option in the very early phase of a pandemic and that there is only a very limited arsenal of licensed antiviral drugs, we urgently need novel therapeutic intervention approaches.

In Germany, three Federal Ministries, the Ministry of Health (BMG), the Ministry of Education and Research (BMBF), and the Ministry of Food, Agriculture and Consumer Protection (BMELV, since 2013 BMEL) have jointly raised a funding scheme for network actions to fight zoonotic diseases in 2006. As part of this action the aforementioned FluResearchNet, (www.fluresearchnet.de) was installed in 2007, which is a first nationwide research network on zoonotic influenza, that integrates virtually all national expertise to meet the One Health challenge. While the network covers several different lines of research activities, a unique strength of the FluResearchNet was and still is the exploration of various novel anti-influenza approaches directed to both viral and host factors, which will be summarized in the following.

State-of the art: currently licensed antiviral drugs

There are two classes of clinically approved antiviral agents against influenza: M2 channel inhibitors (rimantadine and amantadine) and neuraminidase (NA) inhibitors (zanamivir and oseltamivir). M2 inhibitors specifically block an ion channel in the viral envelope formed by the viral M2 protein that is derived from a spliced mRNA from RNA segment 7. These inhibitors are however limited in clinical practice due to their toxicity, lack of activity against influenza B and rapid emergence of drug resistance (Pinto and Lamb, 2006, 2007). High frequency of resistance in clinical isolates in the US have led to the conclusion that M2 inhibitors should not be used for the treatment and prophylaxis of influenza until susceptibility to these drugs has been reestablished among