1918 influenza virus: 100 years on, are we prepared against the next influenza pandemic?

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As we commemorate 100 years since the 1918 pandemic, research has advanced our knowledge of influenza virulence and pathogenesis, and has highlighted the role of animal reservoirs in the emergence of pandemic strains. Future efforts in understanding viral ecology, zoonosis and in integrating human and animal epidemiology should aid pandemic preparedness.

The 1918 influenza A virus (IAV) pandemic was the first well-documented influenza pandemic of the 20th century, having devastating consequences worldwide, with an estimated death toll of ~50 million casualties[1]. The past 3 years have been dramatically marked by the large outbreaks of Ebola, Chikungunya and Zika viruses in various geographical locations, sporadic but persistent human infections with H5N1 and H7N9 influenza viruses in South-East Asia and the widespread H5N2 IAV outbreak in poultry and wild birds in North America. These events highlight and remind us that zoonotic viruses can emerge unexpectedly in nature resulting in the establishment of viral infections with important economic and health burden.

Characterization of the 1918 IAV genome

In the past few decades, owing to the efforts of many scientists, the full RNA genome of the 1918 IAV was sequenced, providing crucial information on the evolution, virulence and antigenic properties of the virus. Following the development of reverse genetics, researchers were able to reconstruct the whole virus[2], which has enabled us to study its pathogenic potential and receptor binding preferences, as well as its transmission requirements and host responses to infection in relevant animal models (for example, mice, ferrets and non-human primates). Although at the time that this work was carried out this was a controversial topic owing to the fear of bringing back to life an extinct virus and to concerns of its potential dual use as a bioweapon, there is no doubt that the benefits of that work have outweighed the risks, providing a greater understanding of the events that occurred during the 1918 pandemic, and a perspective of the pathogenic determinants and virulence markers of this highly lethal virus[3]. Through studies of the 1918 and the other contemporary pandemic viruses, we have learnt, for example, that influenza viruses that cause human pandemics require adaptation of specific residues in the haemagglutinin (HA) glycoprotein for proper binding to receptors containing α-2,6-linked sialic acids expressed in epithelial cells of the mammalian upper respiratory tract (UTR), which are also key for efficient airborne transmission of the virus; that the neuraminidase needs to be complementary to the HA protein for efficient production of progeny virus and that replication competence of the virus in the mammalian URT requires an adaptation in the viral polymerase complex. In fact, this knowledge together with the advances in sequencing technologies and established model systems were crucial for the rapid assessment and characterization of the origin and pathogenic potential of the 2009 H1N1 pandemic IAV, which, within a month of its emergence, had been determined to lack highly virulent markers present in the 1918 H1N1 and the highly pathogenic H5N1 viruses. This information has also been crucial in the evaluation of the pandemic potential of the H7N9 virus, which currently continues to circulate in poultry in China, now as a highly pathogenic strain, producing constant spillover infections in humans. Indeed, direct comparison of some of the virulence markers present in the 1918 virus and the H5N1 and H7N9 avian IAV, have highlighted the latter two as viruses with pandemic potential.

Preparing for the next pandemic

One common characteristic of all influenza pandemic viruses is that they emerge unexpectedly. Although it is well known that birds are the major reservoirs of IAVs in nature, our knowledge is still limited with regard to the factors and potential intermediary hosts and paths that are needed for the genesis of a pandemic virus. One

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open question is how the 1918 virus originated. Current evidence suggests that this virus was not a direct introduction of an avian virus into humans but rather that a number of reassortment events of viruses circulating in humans and swine and an introduced avian virus into humans took place for some years before the pandemic strain was identified[4]. Further clarification of this key question is hampered by the lack of human and swine viral sequences from before, during and after the pandemic.

What information would help us to be better prepared for the next pandemic outbreak? First and most importantly, how pandemic viruses originate, and what factors modulate viral reassortment and transmission in nature. Through retrospective studies of the 1918 pandemic and the in-depth research conducted with the 2009 H1N1 pandemic virus in recent years, it is now clear that swine, presumably as intermediate host, have a major role in the reassortment of viruses of human, avian and swine origin. Like the 1918 strain, the 2009 pandemic precursor viruses were present in swine for long periods of time before it emerged in humans. However, this virus emerged in Mexico where very little animal surveillance was being conducted. Hence, one lesson learned from both pandemic events is the need for integrated surveillance programmes of relevant animal hosts in key geographical locations worldwide.

The emergence of a new influenza pandemic, or the outbreak of other emerging viruses, is a continuous and real threat (Supplementary information S1 (Figure)). The evolution of IAV is dynamic and is likely to continue to change at a fast pace, as is already being seen for the H5N1 viruses in wild birds and poultry in the Middle East, Asia, Europe and Africa, which have a high level of divergence. Moreover, climate change is affecting reservoir populations and avian migration patterns across continents, which is likely to drive avian species to new locations in both hemispheres during winter migration, where they might interact with other avian species. Similarly, human population growth is changing the environment and landscape across the world, which more than ever before is exposing humans to close contact with new animal reservoirs and their viral pathogens (Supplementary information S1 (Figure)).

Population at highest risk

Another key feature of the 1918 pandemic was the high rate of infection and mortality seen in young adults (20–45 years of age), which is a drastically different epidemiological pattern from that usually observed for other pandemics and the seasonal influenza epidemics — in which children and the elderly are usually the highest risk populations. During the 1918 pandemic, the incidence of secondary bacterial infections was a major cause of death, for which there were no antibiotic treatments available at that time. Although the unique virulence markers of the 1918 virus and the high rate of secondary infections might explain the higher rate of severe infections in the general population, it does not explain the age-specific susceptibility to the virus. Thus, additional epidemiological and host factors are likely to explain this phenomenon, including the possibility of pre-existing immunity in the older population, which had considerably lower infection rates, and the role of host innate immune responses, which are likely to modulate disease severity, as has been suggested by *in vivo* studies. Our experience in dealing with the 2009 H1N1 pandemic has revealed that comorbidities (for example, obesity, diabetes or cardiovascular disease) and increased and sustained inflammatory responses contribute to disease severity. Nonetheless, the molecular factors at the basis of disease outcome are still not well understood.

Looking forward

The emergence of a novel pandemic influenza virus is a result of several events that take place in nature[5]. The advance of new research tools has enabled great opportunities to use integrative biological approaches and bioinformatics to obtain molecular epidemiological data in real time and to interrogate complex biological systems in depth. Current technologies enable us to define and dissect the global molecular processes involved in viral infection and thus provide the unique opportunity to design early interventions to control an outbreak at its source. Understanding the ecology of IAV will help us to appreciate viral diversity, evolution and the host barriers that lead to the emergence of novel strains that affect human health (Supplementary information S1 (Figure)). Thus, a major leap forward lies in understanding complex virus–host interactions in their natural reservoir and early on once they establish infection in humans. This will enable us to elucidate the history and genesis of pandemic viruses, and the factors that modulate disease severity in at-risk populations. The integration of human and animal epidemiological data from relevant geographical sites, in the Southern and Northern hemispheres, will aid the development of predictive models of pathogen emergence, which is one important aspect in which great efforts should be placed in the coming years to be better prepared for the next IAV pandemic.

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Competing interests statement

The author declares no competing interests.

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SUPPLEMENTARY INFORMATION

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