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Importance of 1918 virus reconstruction to current assessments of pandemic risk

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ABSTRACT

Reconstruction of the 1918 influenza virus has facilitated considerable advancements in our understanding of this extraordinary pandemic virus. However, the benefits of virus reconstruction are not limited to this one strain. Here, we provide an overview of laboratory studies which have evaluated the reconstructed 1918 virus, and highlight key discoveries about determinants of virulence and transmissibility associated with this virus in mammals. We further discuss recent and current pandemic threats from avian and swine reservoirs, and provide specific examples of how reconstruction of the 1918 pandemic virus has improved our ability to contextualize research employing novel and emerging strains. As influenza viruses continue to evolve and pose a threat to human health, studying past pandemic viruses is key to future preparedness efforts.

1. Introduction

Unlike other viral diseases including smallpox, polio, and measles, which circulate exclusively in humans, influenza A viruses are not a target for eradication (1993). The segmented genome of influenza A viruses, coupled with an error-prone polymerase and high tolerance for mutations, means that antigenic and genetically distinct viruses are constantly generated in both humans and zoonotic reservoirs (Brooke, 2017; Petrova and Russell, 2018), posing a public health risk when humans come into contact (direct or indirectly) with virus shed from these animals. Most zoonotic transmission events are limited, resulting from close contact with infected poultry or swine, and due to both virus and host barriers, do not result in subsequent or sustained human-to-human transmission. Emergence of a pandemic influenza virus is dependent on three criteria: little to no pre-existing immunity to the virus in the human population, the ability for the virus to cause infection in humans, and the capacity for sustained human-to-human transmission throughout the population (Belser et al., 2010). The third criterion is the only one lacking among zoonotic influenza viruses.

Reports of epidemics in humans believed to be caused by influenza viruses date to ancient times (Potter, 1998). However, our current understanding of pandemic influenza viruses has been largely obtained by studying the last four pandemics in human history, which occurred during the 20th and 21st centuries; analyses of pandemic influenza from the 19th century are limited (Valleron et al., 2010). The H1N1 pandemic from 1918-19 is well-known as the most devastating infectious disease event in history, lowering the life expectancy in the United States by more than 10 years and causing an estimated 50 million deaths worldwide (Glezen, 1996; Johnson and Mueller, 2002). Subsequent pandemics in 1957 and 1968, caused by H2N2 and H3N2 strains, respectively, resulted in slightly lower attack rates but dramatically lower case fatality proportions compared with those recorded in 1918–19 (Biggerstaff et al., 2014; Mills et al., 2004). Advances in modern medicine, laboratory science, and public health practices have contributed to our understanding that not all pandemic viruses will pose a uniformly severe threat to human health. Most recently, the 2009 H1N1 pandemic illustrated both the strides made in preparedness efforts during the last century, and the unpredictability of identifying a causative pandemic virus prior to widespread detection in humans.

Given the frequency and diversity of circulating influenza viruses in zoonotic populations (Webby and Webster, 2003), a virus possessing the properties necessary to cause a pandemic could emerge at any time. Understandably, it is difficult to prepare for a target you cannot identify in advance. There are many zoonotic reservoirs from which a pandemic virus could emerge following interspecies transmission, including but not limited to those in avian and swine populations (Yoon et al., 2014). From these reservoirs, select virus subtypes have already demonstrated an enhanced ability to cause human infection. Among these are H5N1 subtype highly pathogenic avian influenza (HPAI) viruses, responsible for > 850 cases with a > 50% fatality rate in the last 15 years (WHO, 2018). H7N9 viruses, first associated with human infection in 2013 as low pathogenic avian influenza (LPAI) viruses but now circulating in

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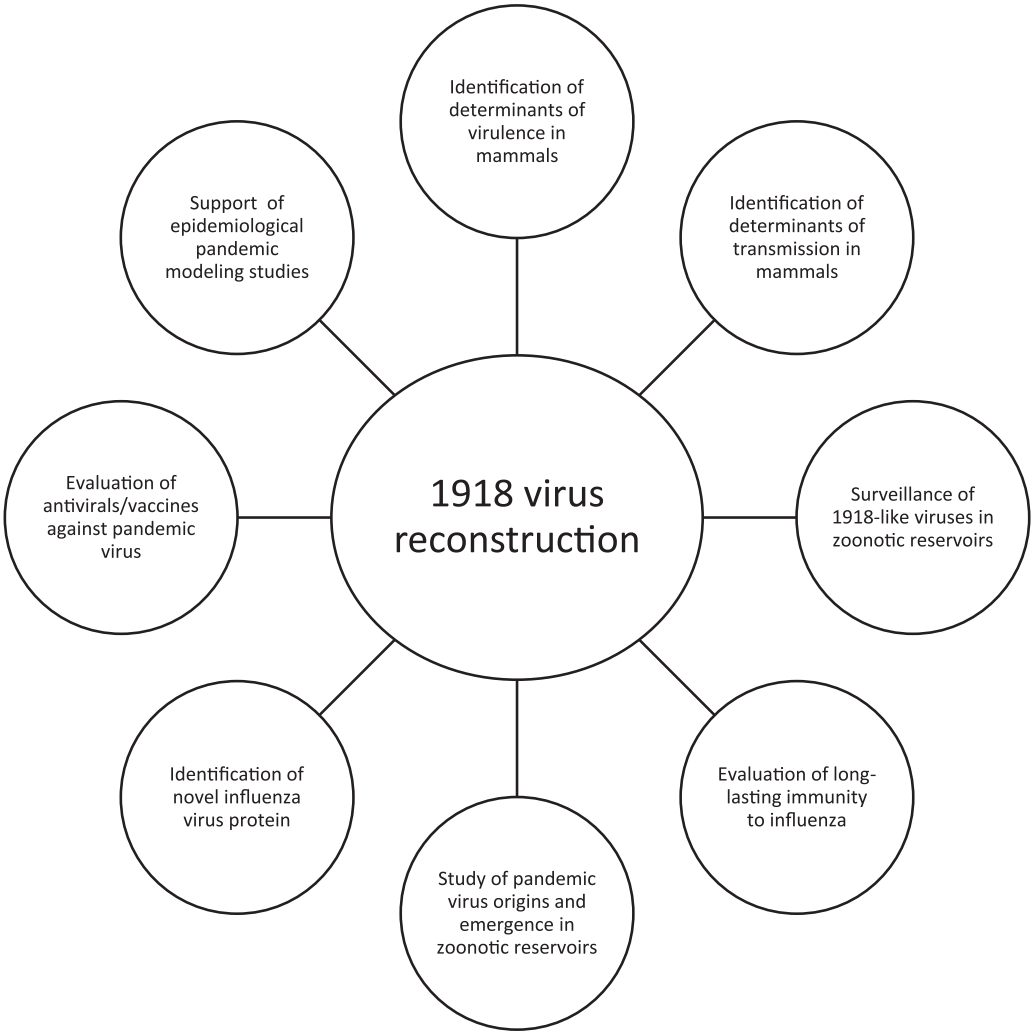

Fig. 1. Selected benefits of 1918 virus reconstruction on contemporary public health pandemic preparedness. Individual studies supporting these and other roles of 1918 virus reconstruction are discussed throughout the text and may be found in (Buhnerkempe et al., 2015; Giles et al., 2012; Jagger et al., 2012; Pearce et al., 2012a; Tumpey and Belser, 2009; Watanabe et al., 2014; Worobey et al., 2014).

both HPAI and LPAI forms, have caused an even greater burden of human disease, with > 1600 human cases detected with a > 30% fatality rate (FAO, 2018). H2 subtype viruses, associated with the 1957 pandemic, have persisted in avian reservoirs (Schafer et al., 1993). Variant H1 and H3 viruses from the swine reservoir have additionally caused human infections over the last decade, and are antigenically distinct from currently circulating strains (Shu et al., 2012). It is clear that there is a multitude of potential candidates for the next influenza pandemic.

The more researchers and public health professionals learn about viruses from past pandemics, the better we will understand which molecular features are associated with a pandemic virus, the scope of mammalian disease elicited by pandemic influenza viruses, and the best ways to mitigate illness and infection via use of vaccination and antiviral drugs. Reconstruction of the 1918 virus has offered an invaluable tool in advancing our knowledge in these areas (Fig. 1). This virus represents in many ways the "worst case scenario" for a pandemic virus: a highly transmissible virus, causing severe disease in many infected individuals (notably in previously healthy, younger individuals) with a high mortality rate. Studying the molecular determinants of virulence and transmission for this virus, in comparison with other pandemic viruses and other contemporary viruses with pandemic potential, has afforded us a window into understanding why the 1918 pandemic was so devastating, and has aided efforts to ensure an event of this magnitude is not repeated. In this review, we describe critical findings obtained from research utilizing the reconstructed 1918 virus, and discuss selected examples of improved understanding of novel and emerging strains due to prior and parallel research with this past pandemic virus, with an emphasis on mammalian pathogenicity and transmissibility.

2. Part 1: Unlocking the mysteries of the 1918 pandemic virus

2.1. 1918 virus reconstruction and mammalian pathogenicity

The causative strain of the 1918 pandemic was initially thought to be lost to time: identification and isolation of influenza virus was not reported until the 1930s (Shope, 1931), at which point no samples containing live virus from the pandemic remained. Accordingly, efforts in 1951 to culture infectious virus from lung biopsies collected from 1918 victims preserved in the permafrost were unsuccessful (Taubenberger et al., 2007). It was only via the use of archaevirology that enabled reconstruction of the 1918 virus (Tumpey and Belser, 2009). Coding sequence of 1918 viral RNA segments was obtained by RT-PCR from either formalin-fixed, paraffin-embedded autopsy tissues taken from victims at the time or isolated from a frozen lung sample of a 1918 victim buried in the permafrost from Brevig Mission, Alaska (Taubenberger, 2006; Taubenberger et al., 1997). Via the use of reverse