Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Recipe for Zoonosis: How Influenza Virus Leaps into Human Circulation

Rebekah Honce1,2 and Stacey Schultz-Cherry1,*

1Department of Infectious Diseases, St. Jude Children’s Research Hospital, Memphis, TN 38105, USA
2Integrated Program in Biomedical Sciences, Department of Microbiology, Immunology and Biochemistry, University of Tennessee Health Science Center, Memphis, TN 38163, USA
*Correspondence: stacey.schultz-cherry@stjude.org
https://doi.org/10.1016/j.chom.2020.09.008

The features that permit or prevent a virus from becoming a zoonotic threat is an ongoing area of investigation. In this issue of Cell Host & Microbe, Herfst et al. and Henritzi et al. help define the molecular and host determinants of influenza virus spillover from animal to human populations.

Humans are continually threatened by the ongoing emergence and circulation of potentially zoonotic viruses in wild and domestic animal populations. Understanding which, if any, of these viruses pose a threat to human health requires understanding of characteristics of the virus, the host, and the species-specific barriers that must be overcome. In this issue of Cell Host & Microbe, two separate groups report key findings that extend our understanding of the molecular and host determinants that could drive influenza virus spillover from animal to human populations (Figure 1).

Zoonotic transmission and establishment of a novel virus in the human population are largely constrained by three features: the opportunity to spill over from the animal host, the capacity to transmit and replicate in the human population, and the ability to escape human immunity. First, spillover from the reservoir or intermediate host must occur through direct or indirect contact between an infected vector and the naive host. Second, the virus must be able to transmit effectively and replicate in a human host. This is constrained by receptor-mediated entry to cells and the replication competence in that new host environment. Third, to successfully establish itself in the human population, successful zoonotic viruses must escape human immunity, including innate...
Figure 1. A Recipe for Zoonosis

Delineating the molecular and host restrictions that permit or prohibit viral spillover from wild, agricultural, and domestic animal species is crucial in understanding the true risk the vast number of viruses that circulate globally pose to humanity. Here, Henritzi et al. (2020) and Herfst et al. (2020) discuss the characteristics in swine and avian-origin viruses that potentially encode their pandemic potential.
(Dornfeld et al., 2019). Only viruses with MxA resistant markers transmitted to contact ferrets, which showed signs of infection and successfully seroconverted. In addition, the European swine viruses are resistant to human memory-recall responses. Many of the swine reassortant viruses showed little cross-reactivity with existing neutralizing antibodies from banked human sera and had significant antigenic distance as measured by antigenic cartography. Together, this suggests the presence of novel swine-origin viruses that can replicate efficiently in mammalian hosts with the ability to escape both innate and memory responses.

The ongoing SARS-CoV-2 pandemic is a stark reminder that a zoonotic virus can spill over anytime from any source, highlighting the need for global and sustained active and passive surveillance programs in animal reservoirs, spillover species, and at the animal-human interface. These programs, highlighted by the cohorts utilized within these two studies, provide a unique opportunity not only to understand the circulating viruses but also, more importantly, to accurately assess the risks they might or might not pose to human and animal health. The works within this issue describe the pandemic potential of currently circulating viruses in mammalian species, focusing on known and novel molecular determinants of binding to human cells, capacity to replicate within this new host, and ability to escape antigenic memory. The culmination of these findings suggests that the breadth of viruses circulating in domestic swine, as well as avian-origin viruses that have adapted to a mammalian host, can in particular harbor genetic signatures, including HA-receptor specificity and stability, escape of human innate immunity, and evasion of human antigenic immune memory, together reading as a recipe for pandemic potential.

Unfortunately, the next flu pandemic is not a matter of if but when. Where the spillover will occur and whether it will be from a bird or mammal is unknown. These studies highlight that influenza viruses from wild birds and swine can gain the molecular determinants needed to successfully infect, replicate, and transmit in mammals including humans. These studies provide important new molecular and host determinants important for spillover infection, which will be invaluable in ongoing and future characterization of emerging influenza viruses.

REFERENCES
Dornfeld, D., Petric, P.P., Hassan, E., Zell, R., and Schwemmle, M. (2019). Eurasian Avian-Like Swine Influenza A Viruses Escape Human MxA Restriction through Distinct Mutations in Their Nucleoprotein. J. Virol. 93, 93.
Henritzi, D., Petric, P.P., Lewis, N.S., Graaf, A., Pessia, A., Starick, E., Breithaupt, A., Strebelow, G., Luttermann, C., Parker, L.M.K., et al. (2020). Surveillance of European Domestic Pig Populations Identifies an Emerging Reservoir of Potentially Zoonotic Swine Influenza A Viruses. Cell Host Microbe 28, this issue, 614–627.
Herfst, S., Zhang, J., Richard, M., McBride, R., Lexmond, P., Bestebroer, T.M., Sprokken, M.J.J., de Meulder, D., van den Brand, J.M., Rosu, M.E., et al. (2020). Hemagglutinin traits determine transmission of avian A/H10N7 influenza virus between mammals. Cell Host Microbe 28, this issue, 602–613.
Karlsson, E.A., Ip, H.S., Hall, J.S., Yoon, S.W., Johnson, J., Beck, M.A., Webby, R.J., and Schultz-Cherry, S. (2014). Respiratory transmission of an avian H5N8 influenza virus isolated from a harbour seal. Nat. Commun. 5, 4791.
Russier, M., Yang, G., Rehg, J.E., Wong, S.S., Mostafa, H.H., Fabrizio, T.P., Barman, S., Krauss, S., Webster, R.G., Webby, R.J., and Russell, C.J. (2016). Molecular requirements for a pandemic influenza virus: An acid-stable hemagglutinin protein. Proc. Natl. Acad. Sci. USA 113, 1636–1641.
Tzarum, N., de Vries, R.P., Peng, W., Thompson, A.J., Bouwman, K.M., McBride, R., Yu, W., Zhu, X., Verheije, M.H., Paulson, J.C., and Wilson, I.A. (2017). The 150-Loop Restricts the Host Specificity of Human H10N8 Influenza Virus. Cell Rep. 19, 235–245.
van den Brand, J.M., Wohlsen, P., Herfst, S., Bodewes, R., Pfankuche, V.M., van de Bildt, M.W., Seehusen, F., Puff, G., Richard, M., Siebert, U., et al. (2016). Influenza A (H10N7) Virus Causes Respiratory Tract Disease in Harbor Seals and Ferrets. PLoS One 11, e0159625.