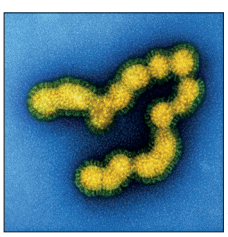
Europe needs a sustainably funded influenza research and response network

Influenza viruses have caused four pandemics during the last century.[1] The 1918 H1N1 pandemic claimed 20–50 million lives, the 1957 H2N2 pandemic and the 1968 H3N2 pandemic claimed 1–4 million lives each, and the 2009 H1N1 pandemic claimed an estimated 280 000 lives.[2,3] Influenza mortality remains high during seasonal epidemics, at 290 000–650 000 global deaths every year.[4] Influenza A has an extensive animal reservoir and enormous genetic diversity. Consistently, all four pandemics were caused by influenza A viruses containing viral genomes derived, at least in part, from strains circulating in animals. Influenza A viruses have two different spike proteins: haemagglutinin and neuraminidase. So far, 19 haemagglutinin subtypes and 11 neuraminidase subtypes have been detected in animals, with wild waterfowl as main hosts. Coinfection of one host with different influenza viruses and exchange of genomic segments can lead to progeny viruses with altered virulence, escape from human pre-existing immunity, and efficient human-to-human transmission. Such reassorted viruses have a very high potential to cause the next pandemic. It is plausible that the next pandemic will be due to an influenza A subtype, as four of the last six pandemics were caused by influenza A viruses, with HIV-1 and SARS-CoV-2 causing the other two.

Influenza A H5N1 viruses originated in wild birds and have been transmitted to domestic poultry, where they evolved towards a highly pathogenic avian influenza (HPAI) phenotype. H5N1 has been recognised as a threat to humans since 1997, when it infected 18 people in Hong Kong and killed six of them.[5] Since then, infection by H5 HPAI viruses (including H5NX viruses) has been a persistent threat for poultry operations, wild birds, carnivores, and humans—leading to 1074 confirmed human cases and 527 deaths.[6] In 2020, a new clade of H5N1 virus started to spread globally, causing mass die-offs in wild birds and mortality among wild carnivores, devastating outbreaks and mass culling in poultry operations, and potential mammal-to-mammal transmission in both wildlife, such as seals,[7] and fur farms in Spain and Finland.[8,9] The virus is now firmly established in wild bird populations globally and continues to evolve due to reassortment with local avian influenza viruses. In March, 2024, H5N1 was detected in dairy cattle in the USA with sustained transmission within the US cattle population.[10] Influenza A had not previously been reported in cattle and mammal-to-mammal spread of avian H5N1 had, so far, only been sporadic. Cow-to-cow spread is highly concerning, given that the barrier to adapt and transmit to humans is potentially reduced with every transmission event within the herds due to potential mammalian adaptations. In addition, close interactions between humans and dairy cattle and consumption of non-pasteurised dairy products increases the risk of transmission to humans. The situation required



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Panel: The role of the US Centers of Excellence for Influenza Research and Response

The Centers of Excellence for Influenza Research and Response (CEIRR; formerly known as Centers of Excellence for Influenza Research and Surveillance; CEIRS) is funded by the National Institute of Allergy and Infectious Diseases (NIAID) at the US National Institutes of Health (NIH) and was established for two key tasks: first, to perform influenza virus research and surveillance in peace time; and second, to rapidly respond to emerging issues, such as the 2009 H1N1 pandemic, the 2013 H7N9 outbreak, and the ongoing cattle H5N1 outbreak. The CEIRR network currently consists of six scientific centres and a data processing centre, which are each generously funded (approximately up to US$109 million/year across the centres, divided into core funding and optional funding) for 7 years. CEIRR investigators are in constant communication with NIAID, have published a sizeable percentage of the global influenza literature, and have generated a large proportion of data that directly influence influenza policy. CEIRR has also provided data to support decision making by the US Food and Drug Administration and the Centers for Disease Control and Prevention during the current H5N1 outbreak.
The programme has a strong One Health focus and is exceptional in training young investigators. CEIRR has also played a crucial role in responding to the COVID-19 pandemic with many of the investigators in NIH's SARS-CoV-2 Assessment of Viral Evolution programme also being CEIRR investigators. The highly successful CEIRR network is now in its third 7-year iteration. A sister programme focused on vaccine development, the Collaborative Influenza Vaccine Innovation Centers, was launched in 2019.

For more on **CEIRR** see https://www.ceirr-network.org

(and still requires) an immediate scientific response to inform policy decisions. The USA has a rapid response research network for influenza, the Centers of Excellence for Influenza Research and Response (CEIRR), which is funded by the National Institute of Allergy and Infectious Diseases and is based on collaborative work among the US influenza research community (panel). CEIRR responded quickly to the H5N1 situation in dairy cattle and provided much needed data for policy decisions within a very short period of time.

Europe has a large number of excellent influenza researchers (with some already contributing to CEIRR) and supports individual research consortia, but they are scattered, their funding is unsteady (due to non-extendable 3-year or 4-year funding cycles), and their research activities fragmented. A tight and sustained network such as CEIRR, with strong ties to national and EU policy makers, is needed in Europe. Given the continued risk of influenza pandemics, particularly with the current panzootic H5N1 situation, a European version of CEIRR would significantly enhance the ability and capacity to respond to infectious disease crises and new pandemics. Building and funding such a network is especially prudent since US infectious diseases research currently faces considerable uncertainties with a new government. In addition, we should remember the economic costs of pandemics, which are estimated to be trillions of Euros.[11] We therefore urge European funders and policy makers—specifically the Directorate-General for Research and Innovation, but also EU member states and non-EU states in Europe—to consider the establishment of a European version of CEIRR, with a focus on building influenza research and response networks across European borders. Such a network would also work synergistically with global initiatives and complement activities of WHO and the European Center for Disease Control, the European Food Safety Authority, the Health Emergency Preparedness and Response Authority, the European Medicines Agency, and the human and animal influenza reference centres and laboratories in Europe. Because solving the global threat to human health will require improved mitigations and control in animals, the activities of such a network would also benefit animal health and organisations such as the Food and Agriculture Organization, World Organisation for Animal Health, and World Organisation for Animal Health/Food and Agriculture Organization Network of Expertise on Animal Influenza. Furthermore, it would also provide training for the next generation of influenza researchers and increase European competitiveness. This step is both urgent and necessary to prepare Europe and the world for the next influenza pandemic.

All authors and their laboratorys could potentially receive funding from European influenza research and response funding. The Icahn School of Medicine at Mount Sinai (New York, NY, USA) has filed patent applications relating to SARS-CoV-2 serological assays, Newcastle disease virus-based SARS-CoV-2 vaccines, influenza virus vaccines, and influenza virus therapeutics that list FK as coinventor, and FK has received royalty payments from some of these patents. Mount Sinai has spun out a company, Kantaro, to market serological tests for SARS-CoV-2 and another company, Castlevax, to develop SARS-CoV-2 vaccines. FK is cofounder and scientific advisory board member of Castlevax and cofounder of Amovir. FK has consulted for Merck, GlaxoSmithKline (GSK), Sanofi, Curevac, Seqirus, and Pfizer and is currently consulting for 3rd Rock Ventures, Gritstone, and Avimex. FK and his team are also collaborating with Dynavax on influenza vaccine development and with VIR on influenza virus therapeutics. RJC is deputy chair of International Society for Influenza and other Respiratory Virus Diseases, acts as an advisor to the European Medicines Agency and WHO. MB is coordinator of the EU Horizon programme-funded project KAPPA-FLU about understanding the connectivity and dynamics of avian influenza. MB is part of a project for the development of SARS-CoV-2 live vaccines where the Friedrich-Loeffler-Institut receives funding from RocketVaxx, Basel, Switzerland. IHB currently leads a UK-funded research consortium addressing emerging issues in relation to H5 high pathogenicity avian influenza in birds and animals. GG is speaker of the Leibniz Lab Pandemic Preparedness funded by the Leibniz Association. AGS' laboratory has received research support from GSK, Pfizer, Senhwa Biosciences, Kenall Manufacturing, Blade Therapeutics, Avimex, Johnson & Johnson, Dynavax, 7Hills Pharma, Pharmamar, ImmunityBio, Accurius, Nanocomposix, Hexamer, N-fold, Model Medicines, Atea Pharma, Applied Biological Laboratories, and Merck. AGS has consulting agreements for the following companies involving cash, stock, or both: Castlevax, Amovir, Vivaldi Biosciences, Contrafect, 7Hills Pharma, Avimex, Pagoda, Accurius, Esperovax, Applied Biological Laboratories, Pharmamar, CureLab Oncology, CureLab Veterinary, Synairgen, Paratus, Pfizer, Virofend, and Prosetta. AGS has been an invited speaker in meeting events organised by Seqirus, Janssen, Abbott, AstraZeneca, and Novavax. AGS is inventor on patents and patent applications on the use of antivirals and vaccines for the treatment and prevention of virus infections and cancer, owned by the Icahn School of Medicine at Mount Sinai. RG is a consortium member of the Vaccine Effectiveness, Burden, and Impact Studies financed by the European Center for Disease Control and is a member of the Portuguese Technical Commission for Seasonal Vaccination (Influenza, COVID-19). PH receives funding from the National Philanthropic Trust for research on influenza. PH is the co-chief investigator of the RECOVERY randomised controlled trial, which is evaluating treatments for severe influenza. F Hoffmann-La Roche has supplied oseltamivir and baloxavir marboxil free of charge for use in this trial. PH has received payment for consulting services to Vir Biotechnology. MK is co-lead of the Humanities in the European Research Area-funded DURABLE preparedness research network. NSL is funded as a principal investigator by the EU Horizon programme-funded project KAPPA-Flu, by The European Food Safety Authority for establishing capacities for active surveillance of highly pathogenic avian influenza in wild birds, by the National Institute of Allergy and Infectious Diseases through the Centers of Excellence for Influenza Research and Response to undertake surveillance risk and response of swine and avian influenza viruses, and receives funding from the National Philanthropic Trust for research on influenza, from International Federation of Pharmaceutical Manufacturers and Associations to support development of potential vaccine strains for influenza and from the Medical Research Council to investigate evolutionarily smart vaccine strain selection for proactive vaccinology for SARS-CoV-2. NSL has been an invited speaker at meetings sponsored by influenza vaccine manufacturers, but has received no honoraria. SM received research and educational grants and personal fees as advisory board member or speaker from GSK, Merck Sharp & Dohme (MSD), Novavax, Pfizer, Sanofi, Viatris, BioNTech, and Moderna. IM is affiliated with the EU Reference Laboratory for Avian Influenza, which receives

funding from the EU to support its activities. HN is a member of the National Immunization Technical Advisory Group of the Finnish Institute for Health and Welfare, and chairman of WHO SAGE. AO is founding director of the Research Center for Emerging Infections and Zoonoses, University of Veterinary Medicine Hannover, coordinator of EU Horizon influenza vaccine projects ISOLDA and ENDFLU, CSO, and co-founder of CR2O, and ad-hoc consultant, invited speaker, and scientific advisory board member to pharmaceutical companies. RP has consulted for MSD, GSK, Sanofi, and Pfizer. GFR is receiving support from the EU Horizon programme-funded projects ISOLDA and ENDFLU. The University of Veterinary Medicine Hannover has filed a patent application regarding an influenza vaccine on which GFR is listed as inventor. XS has received research support from Sanofi. CaT is the director of the EU Reference Laboratory for Avian Influenza, which receives funding from the EU to support its activities. All other authors declare no additional competing interests.

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