

## **It's Not What You Know, But What You Do With What You Know\*\***

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### **Summary**

Two and a half years after the emergence of the first pandemic influenza virus of the 21st century, we are certain there is space for improvement in the area of preparedness, and thus for mitigation. The persistence of a dogmatic approach for controlling factors underlying the emergence of influenza virus strains that are capable of both jumping the species barrier and spreading among human populations has produced negative outcomes. Such consequences range from mistrust of public health authorities to the delayed availability of vaccines. For this reason, our prediction skills must be improved, and the first step in this direction is to be able to comprehensively analyze the pandemic potential of animal influenza viruses. Paradoxically, we have the dataset, but we just do not look at it with the appropriate tools and mindset. What we need is a “One Flu” approach. This approach includes the development of a permanent observatory (either virtual or physical), including analytic tools that can identify and grade animal strains that fulfill some or all the requisites of a pandemic virus before the virus becomes a problem in humans. This would enable us to have a library of “potentially pandemic” strains which can be used as seeds for vaccine manufacture to ensure product availability in a shorter period of time. The creation of an interdisciplinary data library requires an ongoing and timely mechanism to ensure transparency between the veterinary and medical communities on genetic and epidemiological data, which are routinely collected through surveillance efforts worldwide; such a library is in line with the “One Health” vision. This interdisciplinary approach would pave the way for similar methodologies applicable to other emerging and zoonotic infectious diseases, thus complementing other efforts in the fields of preparedness, response, and mitigation.

### **Current realities**

More than two years after the emergence and spread of the first influenza pandemic of the new millennium, we are aware of how our prediction skills need to improve on many fronts. The emergence of the H1N1 virus strain responsible for the 2009 influenza pandemic (PDM 2009 H1N1) was an unexpected event for most influenza scientists. The viral subtype and the geographical and biological origin of the virus were distant from both the geographic regions and the areas of research where significant funds for influenza were invested. The influenza epicenter was deemed to be Southeast Asia, and the epizootic of a highly virulent H5N1, with a previously unseen capacity to jump the species barrier, was believed to be the most likely candidate for the next human pandemic.

In reality, PDM 2009 H1N1 originated from Central America rather than Southeast Asia. Additionally, PDM 2009 H1N1 was of a subtype not included in the pre-pandemic candidate list, was relatively mild (compared to the virulence of H5N1), and emerged from swine rather than birds. In hindsight, the pandemic potential of some animal viruses was underestimated. These examples illustrate the importance of improving our prediction skills.

Until 2009, the real and perceived threat posed by H5N1 viruses had drawn significant resources to issues related to avian influenza viruses, particularly in Eurasia. Influenza infections in mammalian species were neglected, particularly in the Americas. In addition, a rather dogmatic approach suggested that to ignite a pandemic, the virus had to be of a different subtype to those that were circulating in the human population as seasonal strains. These two blind spots impeded the

identification of the emerging risk in Central America.

Possibly the only correct prediction attempt was that a new pandemic virus would very rapidly infect the entire world population, exploiting opportunities offered by globalization. Although PDM 2009 H1N1 is considered a relatively mild pandemic, it resulted in significant mortality data and years of life lost. Had there been a suitable pre-pandemic vaccine available in time, morbidity and mortality could have been greatly reduced.

In addition, “betting on the wrong virus” (i.e., H5N1) has caused a general sense of mistrust of international health organizations and resulted in avoidable damages to the perception of international health policies aimed at preparedness and mitigation.

### **Scientific opportunities and challenges**

Looking to the future, it is important to bear in mind that we may be baffled again by this disease. Although the recent pandemic was not as severe as had been envisaged for a pandemic caused by H5N1, the future occurrence of a severe influenza pandemic cannot be ruled out. Avian viruses (e.g., H5N1) and others with zoonotic potential (e.g., H9N2) are still endemic in large portions of the eastern hemisphere. Swine influenza viruses and other mammalian viruses are also circulating at a global level, and together with viruses of wild and domestic poultry, represent a unique evolving gene pool containing the precursors of the next human pandemic strain.

We have to recognize that vast improvements in capacity building have been achieved as a result of the H5N1 global crisis. Investments in infrastructure and training have yielded a network of scientists with improved influenza diagnostic capacity. Thousands of viral isolates with zoonotic potential have been obtained through surveillance efforts. However, the genetic information has not been fully exploited. An in-depth knowledge of these viruses would allow the scientific community to obtain a better picture of the pandemic potential of selected strains, and enable the development of better prevention and mitigation strategies.

Influenza infections still represent a major threat to mankind, to the livelihood of rural villages, and to the health and productivity of animals. The recent pandemic highlights a need to improve our prediction capacities to enact more efficient prevention strategies through integrated research and surveillance efforts, embracing both animal health and public health. This is in line with, and possibly the best example of, the One Health vision: a multidisciplinary collaborative approach to improve the health of humans, animals, and the environment, endorsed by the Food & Agriculture Organization of the United Nations (FAO), the World Organisation for Animal Health (OIE), and the World Health Organization (WHO). The One Flu initiative would result in international synergies, bridging gaps between medical and veterinary scientists, permanent monitoring of virus evolution and epidemiology, and the best exploitation of investments in capacity building. Above all, it would be a challenge and an opportunity to apply a One Health approach to influenza (i.e., One Flu). Moreover, this approach could possibly act as a model for other emerging zoonotic diseases.

### **Policy issues**

- A permanent observatory, which contains existing genetic and epidemiological information on strains that are collected globally through animal and human surveillance efforts, must be developed. Such an observatory would provide a basis for a more educated approach to assessing the pandemic potential of currently circulating viruses. Furthermore, it would enable the identification of potential pandemic precursors as they exist in nature. Identifying the

pandemic potential of viruses can be achieved by analyzing the wealth of existing genetic and epidemiologic information to determine which risk factors are likely responsible for the transmission and severity of disease in humans.

- International organizations such as FAO, OIE, and WHO should fortify their surveillance efforts through existing mechanisms, particularly in neglected geographical areas and animal species.
- International donors and funding agencies involved in influenza research and surveillance efforts should ensure that data generated through their funding is made readily available to the scientific community in an equitable, ethical, and efficient manner, as recommended by Walport and Brest (2011).
- Full genome sequencing of influenza viruses should be performed on isolates collected through routine and targeted surveillance, and these sequences should be compulsorily made available in the public domain in a timely manner.
- Entities that hold genetic and epidemiological databases for influenza viruses should ensure compatibility with other datasets and invest in software that can screen sequences for relevant mutations.
- An international One Flu effort should be pursued by relevant public health organizations. This effort should include the use of a flexible risk assessment framework, capable of identifying and grading the pandemic risk posed by selected animal influenza viruses.

## References

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\*\* A policy position paper prepared for presentation at the conference on Emerging and Persistent Infectious Diseases (EPID): Focus on Mitigation, convened by the Institute on Science for Global Policy (ISGP) October 23–26, 2011, at the University of Edinburgh, Edinburgh, Scotland.