Will Influenza become the next pandemic and are we ready for it?

Influenza causes seasonal epidemics, with most mild symptom cases, but results in 3-5 million severe cases and 500,000 deaths annually (Iuliano et al., 2018). While many viruses can cause outbreaks, the Influenza virus has unique biological traits that could trigger a future pandemic. Despite global authorities issuing specialized plans, doubts persist about our actual readiness.

Influenza will be the next pandemic

The Influenza virus could escape human immune recognition through structural changes from a high mutation rate (Abbasian et al., 2023) and develop diverse subtype via gene reassortment, the exchange of genetic segments between strains (Bouvier & Palese, 2008). It also has high adaptability to hosts as it binds to sialic acid (SA), a structure common in animals. Swine which live closely with humans, is an ideal host for creating new strains by gene reassortment, facilitating transmission to humans (Figure 1).

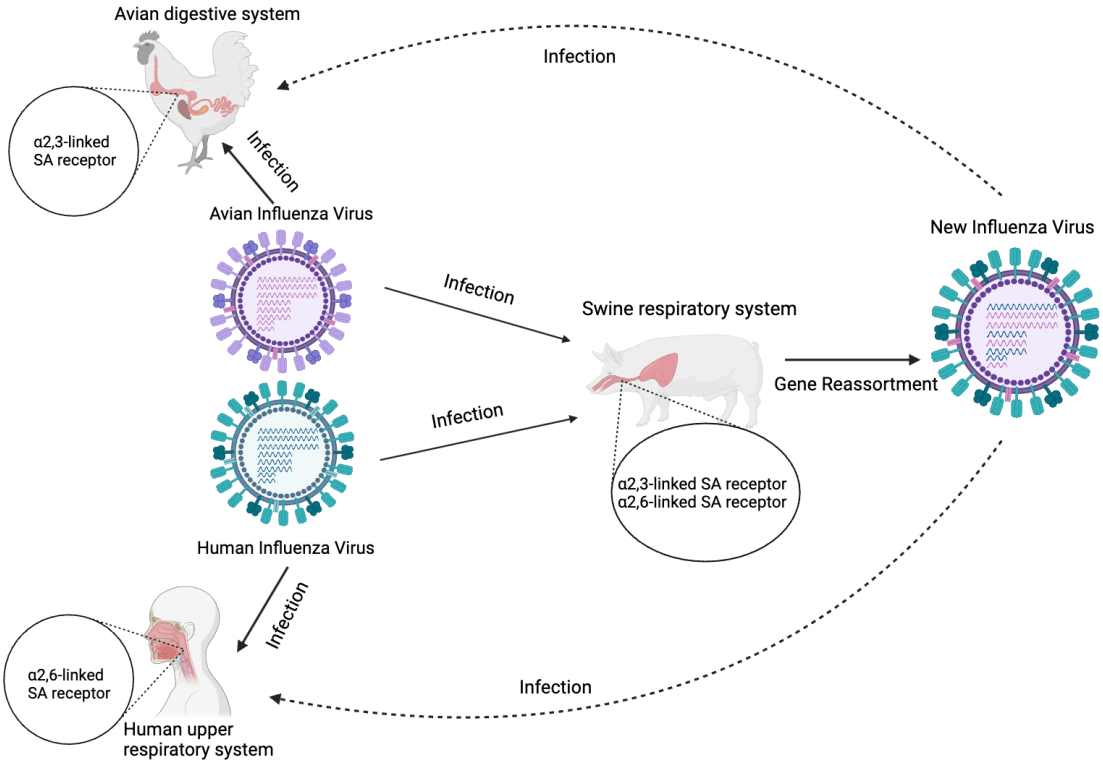


Figure 1: Influenza virus gene reassortment and adaptability to hosts. Avian Influenza virus binds to α2,3-linked SA in avian digestive system, while human Influenza virus prefers α2,6-linked SA in human upper respiratory system (García-Sastre, 2010). Swine, having both receptors (Shao et al., 2017), can be infected by both virus, fostering gene reassortment. This environment may give rise to a virus with a novel genome, capable of binding to human SA receptors, leading to human infections. Figure created by BioRender.

Beyond theories, current emerging cases of avian H5N1 infection is a concern. Since its detection in 1996, the virus rapidly changed subtypes (CDC, 2023). Recently, spillover events of H5N1 clade 2.3.4.4b to humans and mammals, including sea lions in Peru, were reported (Leguia et al., 2023). While no human-to-human transmission is recorded, as an Influenza virus, H5N1 raises concerns about potential fitness improvement. Hence, I believe the Influenza virus, especially H5N1, may cause our next pandemic.

We are not ready

The COVID-19 pandemic emphasizes the necessity to prepare for the next possible Influenza pandemic (Sirleaf & Clark, 2021). Measures and progresses have been made in recent years, **but we are still not ready for combating Influenza virus which possesses such volatile biological feature**.

1) Infodemic

Influenza Infodemic, or rapid spreading of inaccurate information about Influenza related issues, is fueled by Internet's widespread use (WHO, 2023). The freedom to post on social media allows rapid spreading of misleading information, which sways public opinion. Communities with lower education level or elderlies (Shang et al., 2022) will be more susceptible to accepting fraud information.

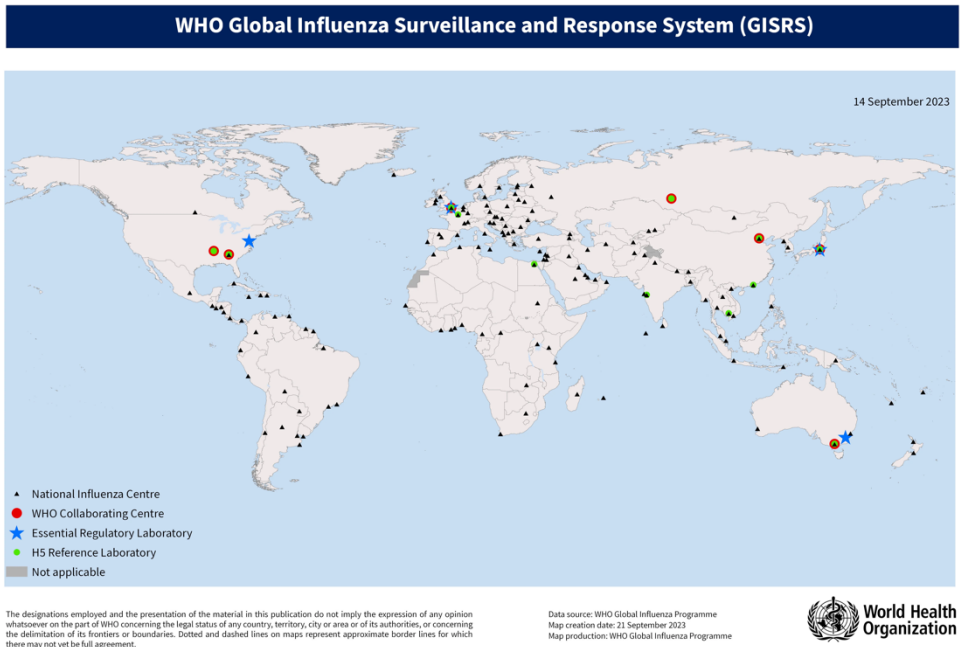
For example, a study on Twitter posts from 1 January 2017 to 1 November 2022 reveals widespread misconception about Influenza vaccines (Ng et al., 2023), especially after COVID-19 pandemic. Common COVID-19 vaccines were made based on mRNA and people developed concern about mRNA vaccines because they did not believe their effectiveness. Because of the Infodemic, more people started to held beliefs that Influenza vaccines also use mRNA which prevent them to be inoculated. However, the truth is most Influenza vaccine are derived from inactivated or weakened virus grown in fertilized chicken eggs (Wong & Webby, 2013). Vaccination is crucial for preventing widespread infections. Therefore, a low vaccination rate increases the risk of outbreaks. Similar misleading information could be found everywhere on the Internet, re-enforcing misunderstandings about Influenza in people's minds, aggravating the Infodemic and impeding community immunity.

2) Limited presence of Global Influenza Surveillance and Response System (GISRS)

The Word Health Organization (WHO)'s GISRS aims to prevent global Influenza pandemic. However, out of 194 WHO member states, only 66% (129 states) have active GISRS (WHO, 2023) (Figure 2 (a)). The National Influenza Centers (NICs) (WHO, 2023), crucial for local virus sample collection and analysis lack designated center in many countries, notably in Africa. This will cause severe delay in pandemic response. African nations without NIC such as

Mali, Niger, Burkina Faso, Ethiopia and Democratic Republic of Congo, experience Influenza outbreak lasting 15-25 weeks annually (Belizaire et al., 2022) (Figure 2 (b)).

(a)



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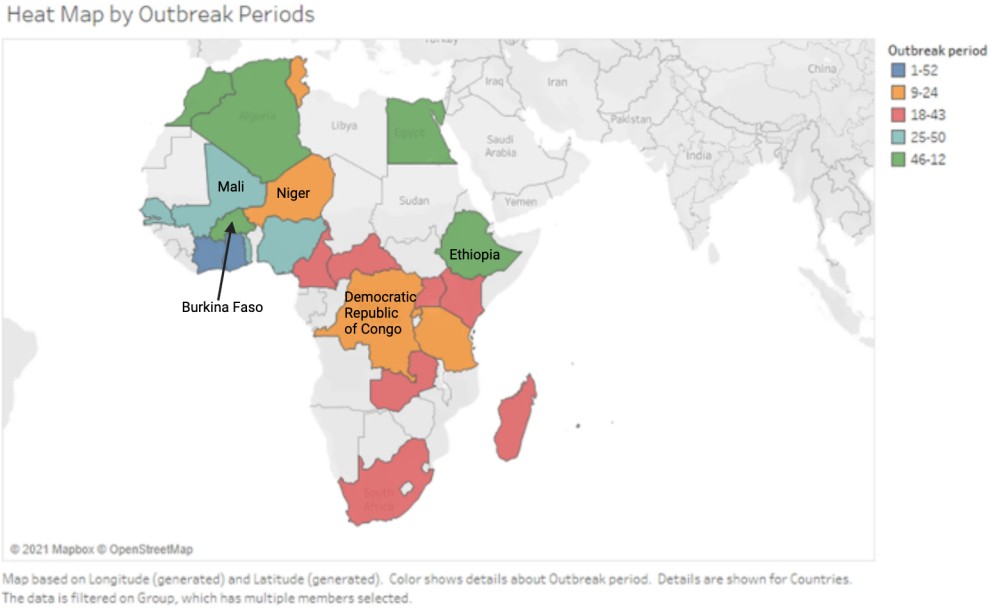

Figure 2: (a) WHO GISRS geographic distribution. The NIC is presented in 66% of all member states. The Collaborating Centre, Essential Regulatory Laboratory, and H5 Reference Laboratory are presented in only 10 countries. (WHO, 2023) (b) **Yearly Influenza outbreak regions and period (weeks) in Africa from 2013-2019.** The colors represent different outbreak periods (Belizaire et al., 2022). The countries with their name written do not have a NIC by 2023.

Large countries (China, Russia, Canada) or counties with scattered islands

(Indonesia) have just one or two NICs, which might also be a concern if outbreak location is far from the NIC, causing delayed sample analysis due to transport. Strict transport requirements along the way, including persistent cold chain storage (4-8°C), present financial challenges for developing countries (Spackman et al., 2013).

Similarly, H5 Reference Laboratories, vital for potential H5N1 outbreaks response, are geographically limited. Countries like Peru which experienced H5N1 spillover to sea lions (Leguia et al., 2023), and some Asian nations with common backyard poultry farming lack H5 Reference Laboratories which will cause delayed response if there will be more severe H5N1 virus transmission.

3) Multisectoral and multilateral collaboration

For effective prevention and control of potential Influenza pandemics, multisectoral collaboration is essential (WHO, 2023). For instance, Public-private partnerships could enhance pandemic control, but our current PPP system is weak. For example, the collaboration required for vaccine production, authorization, and deployment involves pharmaceutical companies, regulators, and public health institutes. However, this collaboration is inefficient for emergency responses, with lengthy authorization and monitoring processes. Concern also arise in whether public and public sectors could coordinate their potential conflicting interests (Díez-Domingo et al., 2022).

International collaboration is crucial during outbreaks, facilitating the timely exchange of virus information and delivery of essential goods such as face masks. Yet, the aftermath of COVID-19, the Ukraine-Russia War, and the Israeli–Palestinian War is fostering de-globalization (Manfredi-Sánchez & Hare, 2021), disrupting information sharing and global supply chains. The length of these impacts is unpredictable, which is a big concern if Influenza virus such as H5N1 seizes the opportunity and causes pandemic in the near future.

The next step

Despite progress in preparedness, including WHO employment of digital methods to monitor the infodemic and 4 new NICs construction in Africa and Eastern Mediterranean from 2014-2021, along with introduction of policies promoting information exchange (WHO, 2023), limitations exist (e.g., a focus on Western social media) and some measures prove ineffective (e.g., ambiguous policies, slow NIC construction). We remain unprepared for a potential Influenza pandemic, particularly H5N1. A more effective, comprehensive management approach is necessary, addressing all issues rather than few aspects. Authorities should soon publish detailed, practical plans with clear quantitative or qualitative goals to assure the public of readiness. For new policies and methods, pilot tests can be used to test their

effectiveness.

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