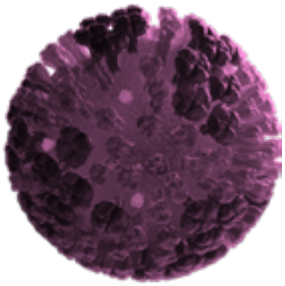
Global Influenza Initiative

InFluNews



The monthly newsletter from the Global Influenza Initiative (GII)

JANUARY 2023 | ISSUE 1

Welcome to the first edition of InFluNews for 2023!

In the previous issue of InFluNews (Issue 7, November 2022), we looked at personalised vaccinology, its challenges, and expectations for the future of these vaccines. If you have missed any of the past issues of InFluNews or would like to find out more about the GII, please visit the ***GII LinkedIn page.***

GII Annual Meeting highlights: Influenza hot topics for 2023

The GII Annual Meeting took place in Berlin, Germany, in November 2022. This was the first face-to-face meeting held in 3 years, bringing together members of the GII Steering Committee and several invited experts from across the globe. Key topics of discussion at the meeting included: unusual patterns of influenza circulation emerging across the globe, the clinical burden of influenza 'beyond flu', the impact of COVID-19 on influenza and influenza surveillance, the future of influenza vaccines and vaccine policy after COVID-19, and influenza communication. The meeting included a mixture of presentations, discussions and workstream activities, enabling the GII to identify key 'hot topics' of interest and set priorities for the coming year.

This month's guest editor and GII co-chair John Paget provides expert commentary.

HIGHLIGHTS THIS MONTH:

Influenza virus image from CDC/Douglas Jordan.

MAT-ES-2300527. V1.0. Marzo 2023

Unusual influenza epidemiology and challenges for surveillance

An early start to the influenza season in Australia

An abnormal rise in cases during the summer in Argentina

Various patterns of activity in Europe

Unusual patterns of influenza circulation have been witnessed globally in 2022. These include an early start to the influenza season in Australia,[1] and an abnormal rise in cases during the summer in Argentina.[2] Various patterns of activity in Europe were also observed, including two peaks of activity or a prolonged influenza season, with SARS-CoV-2 and influenza co-circulating in many countries.[3] Given the unusual and unpredictable nature of influenza circulation in 2022, and the added pressure that co-circulation of SARS-CoV-2 and influenza puts on healthcare facilities and personnel, increasing influenza vaccine coverage rates remains a priority for most regions.

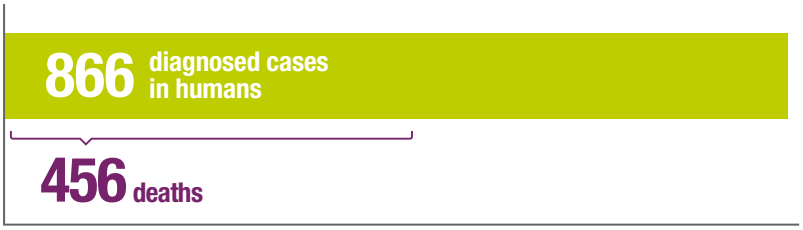
Another outcome of non-pharmaceutical interventions put in place to curb the spread of SARS-CoV-2 has been the global compression of influenza viral diversity and the apparent disappearance of the B/Yamagata lineage.[4] Questions remain as to what actions should now be taken by the global influenza community considering these observations. B/Yamagata could re-emerge in the future, but if it does not re-emerge within the next year or so, it may need to be treated as a high-consequence pathogen and handled under a higher lab biosecurity level (BSL-3). It is currently unclear when and by whom such decisions should be made.

Influenza surveillance has experienced several challenges during the COVID-19 pandemic, including the prioritisation of testing for SARS-CoV-2 to the detriment of testing for influenza. The meeting participants discussed several ongoing challenges for respiratory virus surveillance and proposed some solutions.

Challenges and solutions for respiratory virus surveillance

- A broad case definition for respiratory virus infection should be used to avoid missing patients
- Surveillance should be broad and year-round rather than seasonal to capture out-of-season respiratory virus activity
- Multiplex detection of influenza/COVID-19/respiratory syncytial virus (RSV) will enable better differentiation of respiratory viruses and should be implemented more widely
- Surveillance data should be shared with all relevant stakeholders
- Specific challenges for low- and middle-income countries, such as geographical under-representation, should be addressed

Avian influenza and new vaccine development



HPAI cases in 20 countries over 20 years (2003 to September 2022)

The worldwide outbreak of highly pathogenic avian influenza (HPAI) H5Nx virus is still ongoing at the start of 2023. The rapid spread of the virus around the world is enabled by wild birds – the main transmitter of the virus. HPAI is lethal for domestic poultry, as well as turkeys and some species of ducks, and is therefore having a severe effect on the poultry population, which has already impacted food supplies. The virus could also impact companies that supply eggs for vaccine production, which could affect the supply of vaccines for both animals and humans. Of greatest concern from a One Health perspective is the possibility of the HPAI H5 virus crossing over into humans. This is considered to be possible, although unlikely, as it has occurred only rarely in recent decades, with 866 diagnosed cases in humans and 456 deaths in 20 countries over 20 years (2003 to September 2022). A variety of poultry vaccines have been licensed, while various approaches are being used to develop new vaccines. These include genetic engineering of target antigens to make them more immunogenic in poultry, and the use of computationally optimised broadly reactive antigen (COBRA) technology to generate antigens with potentially broad antigenicity.[5] mRNA vaccines are also in development. Control strategies for avian influenza, however, rely not only on vaccination, but on biosecurity and sanitation processes implemented before, during, and after outbreaks.

The growing evidence base for the burden of influenza 'beyond flu'

Results of the Influenza Vaccination After Acute Myocardial Infarction (IAMI) study[10]

Significantly reduced the risk of the primary composite endpoint of death, acute myocardial infarction and stent thrombosis

Significantly reduced the risk of all-cause death

Multiple studies using different study designs have linked influenza infection with an increased risk of stroke, heart failure and acute myocardial infarction over the past ≈20 years,[6–9] although the mechanisms by which the influenza virus increases the risk of cardiovascular (CV) outcomes remain unclear. Two large studies presented at the GII Annual Meeting demonstrated the effects of influenza vaccination in reducing CV outcomes: the 'Influenza Vaccination After Acute Myocardial Infarction' (IAMI) study showed that vaccination significantly reduced the risk of the primary composite endpoint of death, acute myocardial infarction and stent thrombosis (HR: 0.72; 95% CI: 0.52–0.99; P=0.040) and significantly reduced the risk of all-cause death (HR: 0.59; 95% CI: 0.39–0.89; P=0.010);[10] additionally, a large meta-analysis of randomised controlled trials published between 2000 to 2021 showed that influenza vaccination led to a

statistically significant reduction in major adverse CV events (risk ratio: 0.66; 95% CI: 0.53–0.83; P<0.001) and led to a 56% reduction in CV mortality for patients with recent acute coronary syndrome (risk ratio: 0.44; 95% CI: 0.23–0.85; P-interaction=0.006).[11] Because the effects of influenza vaccination on hard endpoints like death and cardiovascular death are bigger than expected from protection against influenza illness it has been speculated that immune modulation by vaccination may play an important role.[12] A pleiotropic effect of influenza vaccination in CV disease could be investigated in an out-of-season randomized trial with a similar design as the IAMI trial. Immune modulation with influenza vaccination in CV disease could also be investigated using CV imaging.[13]

Influenza can also have serious consequences for people with other chronic conditions such as diabetes and for older people – particularly the frail and elderly. Studies have shown that influenza infection in frail, older adults leads to a significant worsening of functional status,[14] while a 2016 report suggested a link between the peak H3N2 influenza activity in 2014–2015 and a spike in deaths from dementia and Alzheimer's disease.[15] Encouragingly, a recent systematic review and meta-analysis showed a decrease in dementia risk with influenza vaccination.[16]

It is clear that the impact of influenza infection goes beyond 'just getting the flu', but there is a need to communicate these data more widely to increase knowledge regarding the serious effects of influenza and the benefits of vaccination among healthcare professionals and experts across different specialties, in addition to policymakers and the general public.

The future of influenza vaccination

Several influenza mRNA vaccine clinical trials were ongoing at the time of the GII Annual Meeting in November 2022; these include three Phase 1/2 trials to evaluate the safety and immunogenicity of Sanofi's quadrivalent mRNA vaccine and Phase 3 trials conducted by Moderna and Pfizer, evaluating the efficacy of their seasonal influenza vaccines in adults, and one Phase 1/2 trial by Moderna evaluating the safety, reactogenicity, and immunogenicity of their mRNA quadrivalent influenza and COVID-19 combination vaccine (mRNA-1073). Moderna is also evaluating the safety, reactogenicity, and immunogenicity of multi-component vaccines against influenza/RSV, and influenza/COVID-19/RSV in a Phase 1 study.

Experience with the development of pandemic COVID-19 vaccines has enabled the rapid evolution of the mRNA vaccine field. mRNA vaccines against SARS-CoV-2 virus were developed at a record speed and scale and reported to be efficacious with a good benefit-risk profile. However, there are challenges when it comes to developing mRNA vaccines against seasonal influenza viruses. Since mRNA vaccines have been under the spotlight during the COVID-19 pandemic, there is a heightened public awareness of their reactogenicity profile which can be perceived differently outside a pandemic situation and could then negatively impact the vaccination coverage rate for influenza. In addition, the duration of COVID vaccine-induced immunity seems short, the current thermostability of mRNA, but more importantly the efficacy and the added benefit compared to current vaccines are still unknowns. As a result of these challenges, influenza mRNA vaccines may have to be proven significantly more effective with a favourable risk-benefit balance if they are to replace the current flu vaccines.

While vaccine hesitancy has been a known concern before, during and after the COVID-19 pandemic, the pandemic also highlighted vaccination opportunities. For example, some vaccine-hesitant people were motivated to be vaccinated by various factors, such as increased risk perception, and an increased willingness for COVID-19 vaccine uptake among those with a history of receiving the influenza vaccine was observed. In addition, attending a medical facility to receive the COVID-19 vaccine provided an opportunity for healthcare professionals to administer other vaccines, such as the flu vaccine.

To address vaccine hesitancy effectively and increase vaccine coverage, we need to better understand attitudes towards vaccination, dispel mis- and dis-information, micro-target outreach efforts to address differential concerns across different groups, and partner with primary care in addition to community and/or faith-based leaders.

Evaluating influenza vaccine performance

Evaluating influenza vaccine performance can be challenging for several reasons: there is no standard protocol for evaluation, different studies use different endpoints, studies may be subject to bias, evidence may be of low quality, and influenza viruses are constantly evolving, meaning that evaluations must be updated regularly.

The approaches taken by leading public health agencies, such as the Centers for Disease Control and Prevention (CDC), the Advisory Committee on Immunization Practices (ACIP), the European Centre for Disease Prevention and Control (ECDC) and the National Advisory Committee on Immunization (NACI) of Canada, to evaluate influenza vaccine performance, in addition to the use of the GRADE methodology to evaluate quality of evidence, were reviewed and discussed at the meeting and highlighted the many challenges.

The CDC gathers data on influenza vaccine effectiveness from observational studies, but recognises that observational studies have their limitations, such as being particularly susceptible to bias and confounders.[17] NACI noted several methodological concerns during their assessment of influenza vaccine efficacy and effectiveness,[18] and the ECDC made some recommendations for improving the quality of reporting on influenza vaccines.[19]

The GII concluded that there is a need to improve the quality of reporting on influenza vaccines and that a framework to standardise and guide the evaluation of influenza vaccine performance, and to inform policymakers who make differential vaccine recommendations, would be beneficial.

Guest editor and GII co-chair John Paget provides commentary:

We had a wonderful 2-day GII meeting in Berlin where key issues regarding influenza and influenza vaccination were discussed in detail from scientific and policy perspectives. The GII co-chairs thought it was important to share these discussions and findings with a wider audience in this edition of InFluNews. We present the GII's discussions on the epidemiology of influenza, the impact of vaccination beyond only influenza, the current avian influenza activity and its potential impact on humans and the need for standard protocols to evaluate influenza vaccines. There was also a particularly interesting discussion about the new mRNA influenza vaccines, including their advantages, disadvantages and unknowns. For example, the ability to produce influenza vaccines using multiple technologies is considered an advantage, while the need to keep mRNA vaccines frozen is a disadvantage. Importantly, there was a general consensus among the GII experts that these vaccines will need to show higher effectiveness and fewer side effects at delivery if they are to replace existing technologies. We hope you enjoy the overview of these discussions and conclusions in this edition of InFluNews.

GII summary statement

The GII Annual Meeting 2022 provided an opportunity for the GII members and several invited experts to discuss a number of hot topics in the influenza field. Those of particular relevance in 2023 include the unusual patterns of influenza circulation that continue to be observed at the beginning of this year, and the need for greater awareness and understanding of the broader burden of influenza and its impact on those with chronic conditions and the elderly, where the body of evidence continues to grow. Fortunately, there is evidence to support the efficacy of influenza vaccines in these populations, and clinical trials to develop the next generation of influenza vaccines, including mRNA vaccines, are ongoing. Evaluating the performance of influenza vaccines remains a challenge, but it would be made easier by improving the quality of reporting on influenza vaccines and developing a framework to standardise and guide their evaluation.

About the GII

The GII is a global, expert scientific forum that includes international scientists, researchers, and clinicians with expertise in epidemiology, virology, infectious diseases, immunology, health economics, public health, primary care, and geriatrics.

The GII receives financial support from Sanofi, which covers the involvement of Ogilvy Health – a medical communications agency that acts as the secretariat for the GII, as well as coordinating logistics for the annual meetings, managing other GII projects and offering strategic counsel.

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