Global Influenza Initiative

InFluNews

The monthly newsletter from the Global Influenza Initiative (GII)

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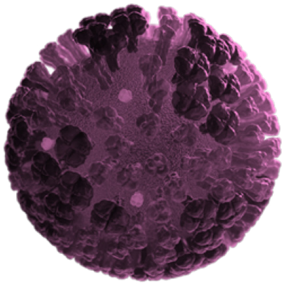


Welcome to the latest issue of InFluNews. This issue is guest edited by the GII co-chairs, John Paget and Bruno Lina.

The last issue of the GII newsletter (Issue 5 2021) examined the impact of the COVID-19 pandemic on influenza surveillance and activity. It also considered how national and international health organizations can best prepare for the forthcoming influenza seasons.

This issue presents highlights from the GII Annual Meeting, 2021 which took place virtually in early November.

How has the COVID-19 pandemic impacted influenza infection rates – and what are the implications for future seasons?

Introducing the FluCov Project

John Paget, Nivel, Utrecht, Netherlands

This 12-month project (March 2021–March 2022) undertakes to understand the impact of COVID-19 on influenza activity by collating global data. It has three key objectives:

1. Establishing a procedure for the dissemination and publication of regular surveillance data for influenza (FluNet) and SARS-CoV-2
2. Implementing a National Influenza Centre (NIC) survey of testing and laboratory practices to assess the impact of the SARS-CoV-2 pandemic on influenza surveillance capabilities
3. Collecting influenza vaccination rates by risk group in selected countries

Influenza virus image from CDC/Douglas Jordan.

FOCUS THIS MONTH: GII ANNUAL MEETING HIGHLIGHTS

IMPACT OF THE COVID-19 PANDEMIC

How has the activity of influenza and other respiratory viruses been affected?

VACCINATION POLICY

What recommendations can be made for the future?

To date, a regular FluCov Epi-bulletin is being published and a website has been established to communicate the findings of the project (www.nivel.nl/en/flucov). A survey of the GII members has been completed and an NIC survey is planned in which data will be collected from 21 countries. In addition, a landscape analysis of modelling activities around the world on the impact of SARS-CoV-2 on influenza activity has been performed and a report will be published in the public domain. The work is the subject of two conference abstracts to date; a research letter describing an increase in influenza vaccine coverage rates during the COVID-19 pandemic has been submitted for publication and further publications are planned.

Impact of NPIs on Seasonal Epidemics

Simon Cauchemez, Institut Pasteur, Paris, France

Non-pharmaceutical interventions (NPIs) were introduced widely to limit the transmission of SARS-CoV-2 in an attempt to lower the reproduction number (R rate) for SARS-CoV-2 from around 3 to below 1. As the seasonal R for influenza is generally between ~1.1 and 1.3, a reduction in transmission of 10–30% might be sufficient to avoid an epidemic in regions where the restrictions remain in place. However, vaccination rates and current levels of restrictions vary widely, even between different countries in the same region (e.g. Europe). This variability will likely result in differing populations of susceptible individuals and widespread heterogeneity in the circulation of influenza and other respiratory viruses. Already, evidence indicates an increased likelihood of respiratory syncytial virus (RSV) outbreaks due to lower virus circulation levels. While recent reductions in influenza virus circulation may dampen antigenic drift and thus mediate the size of the next seasonal outbreak, evidence from modelling indicates a potential for more sizeable influenza epidemics in the future.

Surveillance and Epidemiology – SARS-CoV-2 and Influenza

Sheena Sullivan, WHO Collaborating Centre for Reference and Research on Influenza, Melbourne, Australia

Influenza activity in the northern hemisphere came to a halt at the start of the COVID-19 pandemic. In the southern hemisphere, the impact of travel restrictions, for example border closures in Australia, have had a similar effect. Hospitalizations and mortality have been markedly reduced and almost all cases of influenza confirmed in Australia since April 2020 have been identified in travellers from overseas. A(H3N2) viruses still appear to be circulating in tropical Africa and Asia but the reasons for this are unclear.

However, rhinovirus and RSV activity have been at higher levels than usual in recent months, which may be a consequence of the large number of susceptible children who avoided infection in 2020. A rebound in influenza activity can therefore potentially be anticipated in 2022, although the timing is unpredictable. It currently seems likely, based on the seasonal patterns of other coronaviruses, that SARS-CoV-2 activity may eventually follow a similar seasonal course.

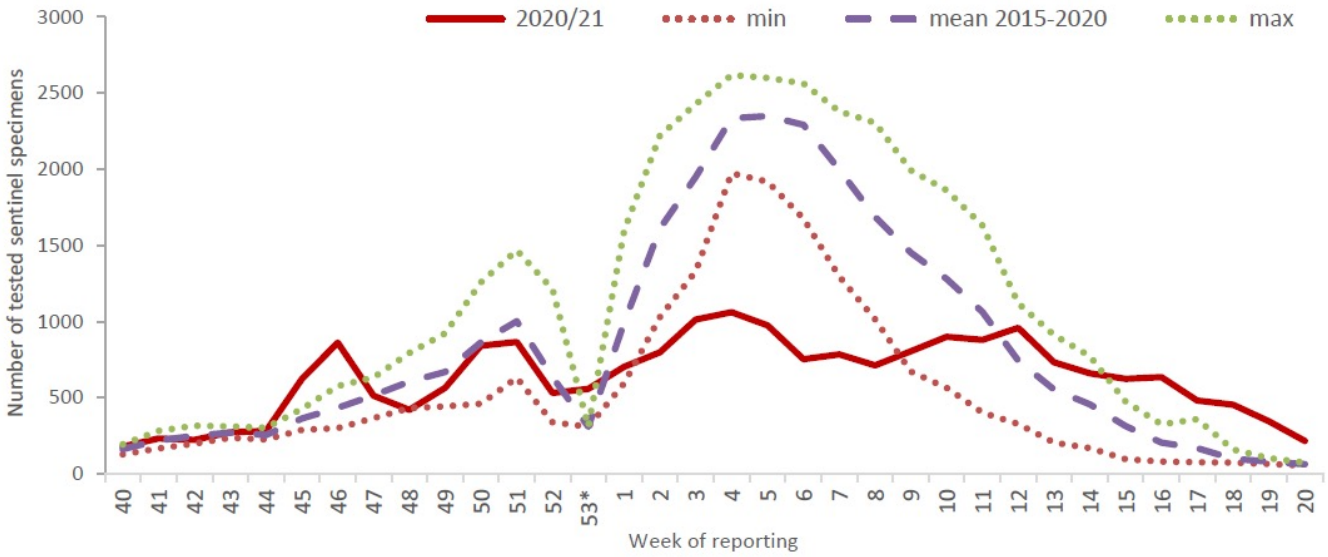
How has the SARS-CoV-2 pandemic affected the circulation of other respiratory viruses?

European Influenza Surveillance Network Update – COVID-19 Surveillance and Circulation

Jan Kynčl, National Institute of Public Health Prague, Czech Republic

The European Influenza Surveillance Network (EISN) reports a sharp decline across Europe in the rates of influenza disease. Based on information from Invasive Respiratory Infection Surveillance laboratories, a similar pattern also applies for diseases caused by pathogens including *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Neisseria meningitidis* following the introduction of travel restrictions and social distancing to combat the COVID-19 pandemic. EISN also reports that influenza activity has remained at baseline levels since the start of the 2020-21 season and the severity of influenza cases has also declined, with few hospitalizations.

Number of tested specimens from sentinel surveillance, week 40/2020 to week 20/2021, compared to minimum, mean and maximum values from seasons 2015-16 to 2019-20, EU/EEA



*Seasons 2014–15 and 2020–21 have 53 weeks of reporting.

Influenza Circulation – Southern Hemisphere Update

Angela Gentile, Hospital de Niños Dr. Ricardo Gutiérrez, Buenos Aires, Argentina

Although influenza activity has remained low across central and southern America during 2021, levels are slightly higher than in 2020. Distinct seasonality patterns could be ascertained for most tropical and subtropical countries.

For example, influenza activity remains at baseline (at EW40 of 2021) in Argentina, where RSV activity is high but decreasing and SARS-CoV-2 levels are low. In Brazil, influenza activity also remains low (to EW40) and there have been some detections of RSV, rhinovirus and parainfluenza, amongst other respiratory viruses, with SARS-CoV-2 at moderate activity levels. Continued surveillance of influenza and RSV will be needed in the post-pandemic period to alert countries to the possibility of outbreaks, identify influenza seasonality patterns and help to inform the timing of vaccination programmes.

Viral Interference: Influenza and SARS-CoV-2

Ben Cowling, University of Hong Kong, Hong Kong, China

Influenza infections have almost disappeared in the 2020–21 season. Several different mechanisms of virus interference may be playing a role in this:

- *Cellular interference* – via blockade or destruction of available receptor sites
- *Immunologic interference* – via virus-induced interferon during a refractory period
- *Behavioural interference* – where reinfection is less likely during the recovery phase

Interactions between viruses are known to impact the activity of influenza and the common cold. A study of influenza vaccination in Hong Kong investigated whether the temporary non-specific immunity to the common cold that results from natural influenza infection is affected in individuals who receive influenza vaccination. Evidence from other studies has been contradictory. It may be that virus interference occurs when there are high rates of one infection. A clearer picture may emerge when both influenza and SARS-CoV-2 infections recur.

How are hospitalization rates for influenza being investigated?

Global Influenza Hospital Surveillance Network (GIHSN) Initiatives

Bruno Lina, University of Lyon, Lyon, France

GISN has been engaged in collecting evidence of confirmed influenza-related hospitalizations during the 2020–21 season. Preferred test methods are PCR for influenza (first priority) and PCR or wet assay for COVID-19, RSV and other respiratory viruses where possible.

Latest updates from GISN include current participant sites and preliminary data. Although data collection is ongoing, the majority of laboratory-confirmed influenza cases have so far come from Kenya and the largest proportion of SARS-CoV-2 cases from the Russian Federation. RSV and other respiratory viruses have been detected in countries doing multiplex testing – predominantly in Brazil, China, the Russian Federation and France, with the greatest diversity of viruses detected in those under 10 years of age.

Worldwide Influenza Hospitalization Rates

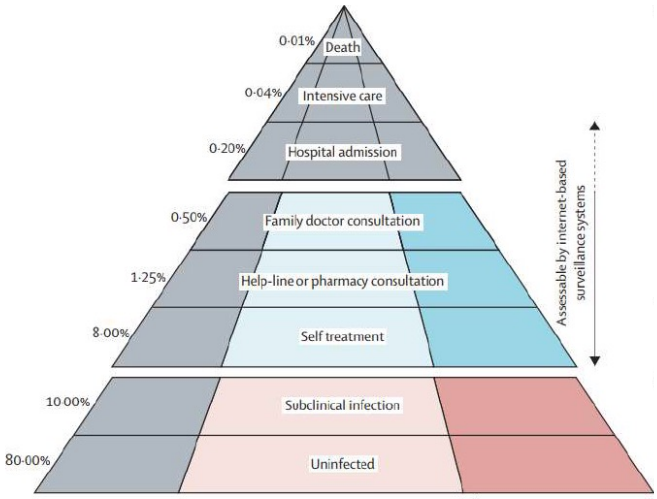
John Paget, Nivel, Utrecht, Netherlands

The Burden of Influenza and RSV Disease (BIRD) study aims to improve understanding of global estimates for influenza-related hospitalizations and to provide both national and international summaries. As part of the study, the Netherlands Institute for Health Services Research (Nivel) has conducted a literature review assessing five factors:

1. Assessment method was based on rate-based or statistical modelling
2. The outcome measure divided into three envelopes (narrow, medium, wide)
3. Whether every hospitalization was laboratory-confirmed or not
4. Whether national or regional (local) data were used
5. If the rates were based on a single year or multiple years

The study identified a standard global influenza-associated hospitalization rate. Rates varied by age, with children having the highest rate in most countries except the US, where elderly patients were most frequently hospitalized.

The study data have led to the refinement of the disease burden pyramid for influenza hospitalizations:



The estimated global hospitalization rate is roughly equivalent to 3 million hospitalizations per year. Further investigation is needed to assess the impact of other factors (such as vaccination rates, predominant strain/s) on hospitalization rates. Greater harmony in estimation methods, which are currently highly diverse, would be helpful for future regional and global estimates.

How effective are SARS-CoV-2 mRNA vaccines – and can they be co-administered with influenza vaccines?

Challenges and Benefits of mRNA Vaccines for SARS-CoV-2 and Influenza

Behazine Combadière, INSERM, Paris, France

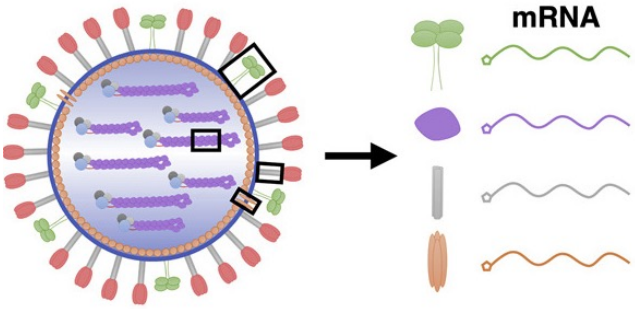
mRNA vaccines are one of four main types of SARS-CoV-2 vaccine that have been studied in clinical trials; other vaccine types include viral vector, inactivated whole virus and subunit vaccines.

Key benefits of SARS-CoV-2 mRNA vaccines are that they incorporate effective delivery systems in the form of liposomes and are able to stimulate both innate and cell-mediated immunity.

Moderna and Pfizer are both in the early stages of developing mRNA vaccines for influenza. In the future, these could eventually incorporate multiple antigens and/or be combined with SARS-CoV-2. mRNA vaccines offer the potential for high efficacy and they avoid the risks of other types of vaccine (e.g. use of live viruses).

mRNA future vaccines

Influenza mRNA vaccine



Choice of antigens ?

- HA (seasonal modification)
- HA conserved region
- NP, Neuraminidase
- T cell antigen / peptide based vaccine

However, there are a number of potential challenges for the development of effective mRNA vaccines against influenza. These include:

- a target population for vaccination that is not naive, therefore influenza mRNA vaccines may be less effective than COVID-19 mRNA vaccines, which initially targeted a naïve population
- the complexity of developing a quadrivalent vaccine using four different types of mRNA
- the need to monitor the safety of annual influenza mRNA vaccine administration
- the difficulty of measuring vaccine efficacy whilst the number of influenza cases is very low, meaning that it will take much longer to demonstrate efficacy in clinical trials
- the potential for local side effects to impact acceptability of the vaccine.

Efficacy and Safety of Pfizer SARS-CoV-2 mRNA Vaccine

Ann Falsey, University of Rochester Medical Center, Rochester, NY, USA

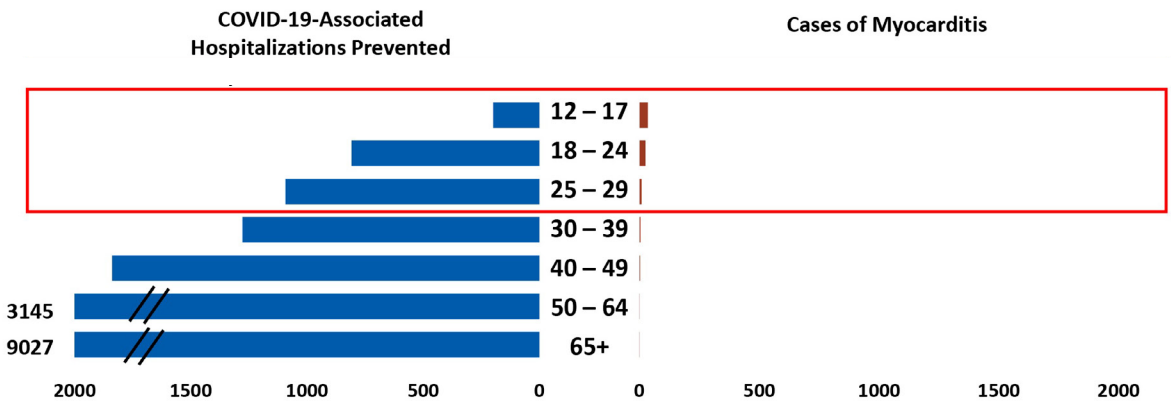
The vaccine has demonstrated high efficacy rates:

- 95% for asymptomatic infections
- 94% in people >65 years of age
- Prevention of severe disease

Efficacy levels in clinical studies have been shown to decline over time – at a rate of approximately 6% every two months.[1] Real-world evidence indicates vaccine effectiveness of around 50% after five months – although high effectiveness against severe disease appears to be retained.

Early evidence from Israel – where there has been widespread primary vaccine uptake – indicates that infection rates, symptomatic and severe disease were reduced in people over the age of 60 who received a booster dose. Severe disease also declined in people between the ages of 40 and 60 who received a booster dose.[2] Although most patients have experienced minor side effects, the US Vaccine Adverse Event Reporting System (VAERS) has identified a small number of cases of myocarditis/pericarditis in the 12–39 age group. Most occurred within the first three weeks following vaccine administration and cases were more frequent after the second primary dose. Overall, however, the benefits of vaccination continue substantially to outweigh the risks in this population.

Benefits/risks after dose 2, by age group: for every million doses of SARS-CoV-2 mRNA vaccine given with current US exposure risk[3]



Based on hospitalization rates from COVID-NET as of May 22nd. Benefit/Risk calculated over 120 days.[3]

Co-administration of Influenza and SARS-CoV-2 Vaccines

Kevin Yin, Sanofi Pasteur

A Phase II study demonstrated the immunogenicity and safety of separate and concomitant administration of a high-dose quadrivalent influenza vaccine (HD-QIV) and the Moderna mRNA SARS-CoV-2 vaccine in people over the age of 65.

At day 22, the co-administration and HD-QIV arms demonstrated similar GMT levels, seroprotection rates and seroconversion rates for each influenza strain. For the SARS-CoV-2-specific immune response, the co-administration and mRNA vaccine arms demonstrated similar GMCs and GMC ratios at day 22.

The safety analysis did not raise any concerns concluding that the vaccines can be safety administered together without evidence of immune interference.

These interim findings support the vaccine co-administration recommendations from both the WHO and national health authorities. These are the first data for co-administration of these vaccines under a 'conservative scenario' involving the use of a full dose (100µg) of the Moderna vaccine (a half dose of the Moderna vaccine (50µg) has now been authorised for use as a booster dose).

What are the broader benefits of influenza vaccination?

Influenza Vaccination for People with Diabetes

Marco Goeijenbier, Erasmus MC, Rotterdam, The Netherlands

Diabetes can be characterized as a highly heterogeneous disease, influenced by genetic, epigenetic, behavioural and environmental factors, and is more prevalent in African-American, Hispanic, Asian-Pacific-Islander and American-Indian people.

People with diabetes have an increased susceptibility to infectious diseases although the reasons for this are poorly understood. The risk of influenza hospitalization is tripled, and the risk of influenza mortality doubled in people who have diabetes:

- Glycaemic variability was recently shown to increase influenza severity
- Obesity is:
  - associated with an increased risk of death from seasonal influenza
  - significantly associated with hospital and intensive care unit admissions and the subsequent need for ventilatory support

WHO and many other organizations typically recommend influenza vaccination for patients with all types of diabetes but uptake is generally low. There are a number of challenges to be overcome in order to increase vaccine uptake in people with diabetes, including:

- tackling vaccine hesitancy and attitudes towards vaccination
- gaining a better understanding of the epidemiology of the disease

What are the implications for future influenza outbreaks – and what policy recommendations can be made?

Influenza Vaccination Policy Recommendations and Uptake

Susanna Esposito, University of Parma, Parma, Italy

Influenza vaccination is currently recommended by the WHO for those ≥6 months of age. While most countries follow these general recommendations, there are local country-by-country variations, for example across Europe. The COVID-19 pandemic has impacted vaccination rates: in Italy, vaccination rates have declined in children with chronic illnesses, adolescents and pregnant women and there have been delays to scheduled vaccinations for children up to the age of 2. The CDC announced in May 2021 that COVID-19 vaccines may be co-administered with other vaccines on the same day, as well as within 14 days. WHO has also provided interim guidance for vaccine coadministration stating that countries can consider administering COVID-19 vaccines and influenza vaccines during the same visit. Co-administration of an inactivated seasonal influenza vaccine and any dose of a COVID-19 vaccine is considered acceptable in terms of safety and efficacy. Coadministration facilitates the implementation of COVID-19, influenza and other vaccines allowing for more robust vaccination programmes.

The impact of reduced population immunity to influenza, resulting from lower infection rates in the 2021–21 season, remains unknown. Accordingly, a robust vaccination programme for influenza will be an important addition to ongoing implementation of COVID-19 vaccinations.

Priorities and Challenges for the Future of Influenza Vaccination

John McCauley, The Francis Crick Institute, London, UK

The Center for Infectious Disease Research and Policy (CIDRAP), with the support of the Wellcome Trust, have developed a roadmap for influenza vaccines which looks towards the future of influenza vaccine development. Moore et al.[4] summarised the major issues and priority areas of research outlined in the roadmap, from which Dr McCauley selected some personal highlights.

The strategic goals selected highlighted the need for:

- improved forecasting of influenza virus strain circulation
- improved understanding of vaccine immunogenicity, including T-cell immunity, mucosal immunity, and correlates of protection for universal vaccines.
- further exploration of the role of neuraminidase, and new adjuvants
- accelerated clinical development for the most promising available universal vaccines.

Questions that remain to be addressed in relation to the development of mRNA influenza vaccines include:

- how a quadrivalent mRNA vaccine would be formulated
- whether multiple mRNAs could cause interference of expression of different HA subtypes
- how best to assess immunogenicity of mRNA vaccines – for example, using T-cell assays and expanded assessment of correlates of protection beyond virus neutralisation assays?

In the future, a broader assessment of vaccine efficacy may be needed that includes the vaccine's impact on more severe disease.

GII Summary Statement

As we approach the end of 2021, a global trend towards an increase in influenza cases is being recorded. Heterogeneity in the circulation of influenza and other respiratory viruses continues to be observed between countries, likely as a result of the wide variations in COVID-19 restrictions. Rebounds in influenza activity are anticipated in 2021/2022, but the timings and geographical locations of these are hard to predict.

Given this unpredictability, influenza vaccination should continue to be recommended and supported by policymakers to avoid adding to the healthcare and economic burden of COVID-19. Additional modelling studies are needed to help us to predict future epidemic peaks of respiratory virus activity.

Surveillance networks such as EISN and GIHSN continue to play an important role during this time. Not only are they helping us to better define the global burden of influenza-related disease and hospitalization but also gathering vital epidemiological data on SARS-CoV-2 during the ongoing pandemic.

We are looking towards the future, encouraged by the rapid development and high efficacy of the COVID-19 vaccines, but with a number of potential challenges to overcome in order to develop more effective influenza vaccines, not least of which are the technical challenges of developing quadrivalent influenza mRNA vaccines and the need for a better understanding of influenza vaccine immunogenicity and potential correlates of protection.

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 Pasteur which covers the involvement of Ogilvy Health, a medical communications agency which acts as a secretariat for the GII as well as coordinating logistics for the annual meeting, managing other GII projects and offering strategic counsel.

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