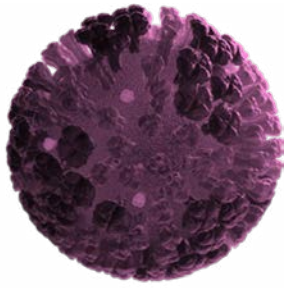
Global Influenza Initiative

InFluNews



The monthly newsletter from the Global Influenza Initiative (GII)

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Welcome to the July issue of InFluNews!

The previous issue of InFluNews summarised the key findings from the recent Nature Communications publication by Dhanasekaran et al. (2022),[1] which considered the short- and long-term implications of COVID-19 control measures on the epidemiology and evolution of seasonal influenza viruses.

*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**.*

Evaluating seasonal influenza vaccine performance

Why is evaluation so challenging?

Although evaluation of seasonal influenza vaccine performance is hindered by a number of factors, the most significant is potentially the lack of a standard protocol. Thus, studies of influenza vaccine efficacy and effectiveness assess different endpoints, may risk bias, have variable and often low-quality evidence and can often lack key details preventing accurate evaluation and comparison between newer and enhanced vaccines. The constant evolution of influenza viruses also requires evaluations of vaccine performance to be updated regularly.

This issue of InFluNews looks at approaches to the evaluation of seasonal influenza vaccine performance taken by three public health agencies: the US Centers for Disease Control and Prevention (CDC), the European Centre for Disease Prevention and Control (ECDC) and Canada's National Advisory Committee on Immunization (NACI) in order to assess recent progress and ongoing challenges.

Prof. Bruno Lina (GII co-chair, University of Lyon), our guest editor this month, provides expert opinion and insight into the topic.

Influenza virus image from CDC/Douglas Jordan.

FOCUS THIS MONTH:

Evaluating seasonal influenza vaccine performance

Approaches taken by key public health agencies

Key challenges and future perspectives

CDC assessment of influenza vaccine effectiveness[2,3]

The CDC monitors how well seasonal influenza vaccines are working in the US every year. It uses observational studies of vaccine effectiveness, which represents the percentage reduction in frequency of flu illness in vaccinated versus unvaccinated individuals who seek healthcare. (The Test-Negative Design, with all cases in the study being laboratory-tested). These studies are conducted across four US networks: the US Flu VE Network, the Influenza Vaccine Effectiveness in the Critically Ill (IVY) network, the New Vaccine Surveillance Network (NVSN) and the VISION VE network. Each focuses on the prevention of different outcomes of influenza infection.[2]

CDC networks for measuring vaccine effectiveness[2]

- **US Flu VE Network** measures vaccine effectiveness in preventing outpatient medical visits due to laboratory-confirmed influenza
- **IVY** estimates vaccine effectiveness in preventing severe flu illness in adult intensive care unit patients – since April 2021, IVY has enrolled adults hospitalised with COVID-19 or influenza
- **NVSN** measures vaccine effectiveness in preventing hospitalisation due to laboratory-confirmed influenza
- **VISION VE Network** collects data on emergency department visits, hospitalisations and ICU admissions

Importantly, these observational studies are conducted in diverse populations including those with underlying medical conditions, different settings and varied real-world conditions in contrast with the controlled environment of a randomised controlled trial (RCT). In addition, vaccine schedules, storage and handling requirements may not be followed as precisely in observational studies compared to RCTs, and thus, observational study results may be subject to biases such as selection and confounding biases. Other factors that affect the results of vaccine effectiveness studies include antigenic drift of influenza viruses, low virus circulation, study design factors and the measurement of non-specific outcomes.[3]

The CDC website currently provides vaccine effectiveness estimates from the 2004/5 to 2019/20 seasons. These estimates are typically adjusted for study site, age, sex, underlying medical conditions and days from illness onset to enrolment. Since 2010, the adjusted overall vaccine effectiveness per season has ranged from 19% to 60%. Vaccine effectiveness could not be measured for the 2020/21 season due to low virus circulation during the COVID-19 pandemic.[2]

Independent systematic review funded by ECDC[4]

The objective of the ECDC systematic review was to assess and synthesise the literature on the efficacy, effectiveness and safety of newer and enhanced seasonal influenza vaccines for the prevention of laboratory-confirmed influenza in adults aged ≥18 years. The vaccines assessed included MF59-adjuvanted, high-dose, cell-based and recombinant haemagglutinin (HA) vaccines. In addition, the review aimed to assess the relative efficacy/effectiveness of newer and enhanced vaccines versus standard vaccines, and the duration of protection of the newer and enhanced vaccines.[4]

An important aspect of the systematic review was a quality assessment of the evidence provided by the studies. Independent reviewers assessed the risk of bias using standardised tools and the certainty of evidence for key outcomes using the GRADE methodology.[4]

GRADE (Grading of Recommendations, Assessment, Development and Evaluations) is "a transparent framework for developing and presenting summaries of evidence and provides a systematic approach for making clinical practice recommendations."
Siemieniuk and Guyatt 2011[5]

The GRADE methodology rates the certainty or quality of evidence as *very low, low, moderate or high*. Factors that can downgrade the rating include *risk of bias, imprecision, inconsistency, indirectness and publication bias*.[5] Rating the evidence is important when deciding whether confidence in an estimated effect is adequate to support a particular recommendation.[6]

Key data highlights* and certainty of evidence[4]

Vaccine type	Relative VE vs standard-dose vaccine, % (95% CI) [age group, study type]	Quality of evidence	Absolute VE vs placebo, % (95% CI) [age group, study type]	Quality of evidence
High-dose trivalent	24 (10–37) [≥65 years, RCT]	Moderate	No data	No data
Quadrivalent recombinant HA	30 (10–47) [≥50 years, RCT]	Moderate	No data	No data
Cell-based trivalent	No data	No data	70 (61–77) [18–49 years, RCT]	Moderate
MF59-adjuvanted trivalent	No statistical difference	No GRADE performed/ limited evidence	45 (23–61) [≥65 years, observational studies]	Low

CI, confidence interval; RCT, randomised controlled trial; VE, vaccine efficacy/effectiveness.
*Key data highlights only – for a full summary of the review findings, see pages 3–5 of the full report: seasonal-influenza-vaccines-systematic-review-efficacy.pdf (europa.eu).[4]

The authors experienced numerous challenges in conducting the review. These included a lack of consistent terminology or clear reporting, for example, lack of reporting of raw vaccine effectiveness data, failure to disaggregate outcomes by vaccine type, lack of reporting of extent of match or mismatch for a given season and use of a wide range of comparators.[4]

As a result, the report provided some considerations for improving the quality of reporting on influenza vaccines. These may be summarised as follows:[4]

- Studies should clearly report the key features of the study in the title and abstract (e.g. types of vaccines included, study design)
- Clearer reporting is needed in terms of how the patient population was selected, whether influenza was laboratory confirmed, the type of adjuvant used and the valency of the included vaccines
- Data should also be reported according to the age groupings for the licensed indications of the included vaccines
- Results should be disaggregated by vaccine type for all included vaccines, where possible
- The degree of matching between vaccine and circulating strains should be explicitly reported as part of the results section, preferably as a percentage
- Vaccine effectiveness should be presented as both an adjusted and unadjusted outcome, with adjusted comparisons explicitly stating the variables included in the final model

The authors concluded that the evidence base for the efficacy and effectiveness of newer and enhanced influenza vaccines is limited, but it is probable that these vaccines provide greater protection than no vaccination, based on the reviewed evidence. Evidence comparing newer and enhanced vaccines with traditional seasonal influenza vaccines was described as uncertain, due to a dearth of available literature, as well as clinical and statistical heterogeneity.[4]

NACI review on the efficacy and effectiveness of high-dose and MF59-adjuvanted influenza vaccines[8]

NACI conducted previous literature reviews on the efficacy, effectiveness, immunogenicity and safety of high-dose and MF59-adjuvanted vaccines to inform their annual recommendations on the use of these vaccines. The purpose of their 2018 review was to identify additional efficacy and effectiveness evidence published since the original literature reviews.

The 2018 NACI review identified five studies of the high-dose vaccine and four studies of the MF59-adjuvanted vaccine that assessed vaccine effectiveness. Key findings from the new studies were that the high-dose vaccine was significantly more effective than standard-dose vaccine in preventing influenza-like illness (ILI), non-laboratory-confirmed influenza-related death and all-cause hospitalization. There was some evidence that high-dose vaccine is likely to provide current season clinical benefit

over standard-dose vaccine, irrespective of vaccination dose in the previous season (high dose or standard dose). There was evidence that high-dose vaccine is more effective than standard dose in preventing possible influenza-related serious cardiorespiratory events. There was also some evidence to suggest that the high-dose vaccine may provide additional benefit in the very elderly. For the MF59-adjuvanted vaccine, new observational studies provided some additional evidence of vaccine effectiveness against hospitalization for influenza or pneumonia and laboratory-confirmed influenza infection compared to no vaccination in adults ≥65 years of age.

The authors noted that despite the included studies receiving good quality ratings (using the US Preventive Services Task Force [USPSTF] grade definitions†), previously noted methodological concerns around the body of efficacy and effectiveness evidence for the two vaccines had not been adequately addressed by the new evidence. These methodological concerns included those related to observational studies, which provided most of the available data in the elderly, for example, being particularly susceptible to residual confounding, selection bias and other biases such as healthy vaccinee bias. It was noted that other factors should be considered when assessing and interpreting study data such as influenza seasonality, vaccine mismatch with circulating influenza strains and indirect protection from vaccination.

Given these concerns, the conclusions of previous reviews did not change. In summary, these were that:

1. There is good evidence that high-dose vaccine provides superior protection including decrease in ILI, influenza-related death and all-cause hospitalization compared with standard-dose trivalent vaccine in the elderly (grade A evidence)
2. There is fair evidence that the MF59-adjuvanted vaccine may be effective at reducing the risk of hospitalisation for influenza and influenza complications in the elderly compared to unvaccinated individuals (grade B evidence)
3. There is insufficient evidence that MF59-adjuvanted vaccine is effective at reducing the risk of hospitalisation for influenza and influenza complications in the elderly compared with those who received unadjuvanted trivalent inactivated subunit vaccine (grade I evidence)
4. There is no identified evidence that directly compares high-dose vaccine with MF59-adjuvanted vaccine (grade I evidence).

Overall, the reviews summarised in this issue of InFluNews illustrate some important points. Data on influenza vaccine efficacy and effectiveness are derived from various study types, which often do not include RCTs, use different endpoints and have varying quality of evidence. It can therefore be difficult for public health agencies, healthcare workers and the general public to know how to interpret these data and what to do when the results of different studies are not aligned. A common forum where these issues can be discussed is needed.

†USPSTF assigns one of five letter grade definitions (A,B,C,D or I) which describe the strength of a recommendation, whereby A or B indicate offer or provide this service, C indicates offer or provide this service for selected patients depending on individual circumstances, D indicates discourage the use of this service and I indicates read the clinical considerations section of USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.[9]

Guest editor Prof. Bruno Lina comments:

Recent reviews of the literature on influenza vaccine effectiveness highlight the need for well-designed and robust evaluations that can provide high quality evidence of a measurable impact of vaccination on the burden of influenza. Ideally, evaluations of influenza vaccine effectiveness should be strain based and compare different vaccine types (i.e. inactivated, adjuvanted, high dose, cell-based or recombinant protein) across a range of outcomes, including influenza infection, hospitalisation and mortality, as well as outcomes related to the exacerbation of chronic conditions such as cardiovascular disease. Study sizes must also be large to avoid large confidence intervals. Lastly, the use of standardised protocols would greatly aid the interpretation and comparison of effectiveness data.

GII Summary Statement

Evaluation of the performance of seasonal influenza vaccines in the real world is challenging. Systematic reviews of the literature are hampered by the fact that publications reporting on influenza vaccine effectiveness often lack critical information and/or include low-quality evidence (often in the absence of RCTs) making evaluation very difficult. The methods used by public health agencies to assess vaccine performance also vary, with no standard protocol. There is therefore a need to improve the quality of reporting on influenza vaccines and to develop a standardised protocol for evaluating influenza vaccine performance in the real world.

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 which acts as the 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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