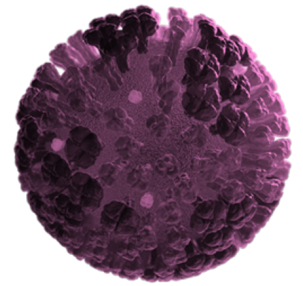


# InFluNews



The monthly newsletter from the Global Influenza Initiative (GII)

SEPTEMBER 2022 | ISSUE 6

Welcome to the September issue of InFluNews!

*The previous issue of InFluNews focused on achievements, challenges and future perspectives for respiratory virus surveillance.*

*If you have missed any of the past issues of InFluNews or would like to find out more about the GI, please visit the [GII LinkedIn page](#).*

## **Influenza in cardiovascular disease (CVD) and the impact of vaccination: Highlights from the European Society of Cardiology (ESC) Congress 2022**

In this month's issue of InFluNews we present highlights from the ESC Congress, focusing on four presentations, which described the impact of influenza on CVD outcomes and the benefits of influenza vaccination. These presentations include: a study of the impact of myocardial injury on mortality and adverse events in hospitalised patients with influenza (Dr Amabile Valotta); an overview of the evidence on influenza as a trigger for cardiovascular events and the impact of vaccination (Dr Ankeet Bhatt); a study of double-dose versus standard dose quadrivalent influenza vaccine on major cardiopulmonary events in patients with acute coronary syndromes (The VIP-ACS trial) (Dr Remo Furtado); and DANFLU-1, a study of the feasibility of a pragmatic randomised trial to assess the relative effectiveness of high-dose versus standard-dose quadrivalent influenza vaccine on severe cardiorespiratory outcomes in elderly adults (Dr Niklas Dyrby Johansen). Note that some of the data included in this issue are new and not yet fully peer-reviewed.

This month's guest editor, Prof. Tor Biering-Sørensen, provides expert commentary.

### **FOCUS THIS MONTH:**

#### **Highlights from the ESC Congress 2022**

Impact of influenza on CVD

Benefits of influenza vaccination in patients with CVD

## Impact of myocardial injury on mortality and adverse events in hospitalised patients with influenza: A prospective cohort study

Presenter: Amabile Valotta

The aim of this study was to assess the short- and mid-term clinical implications of influenza-related myocardial injury in hospitalised patients with influenza. This was a small prospective, multicentre, cohort study (n=145) conducted during the 2018–2019 seasonal influenza epidemic. The primary endpoint was all-cause death at 28 days and the composite secondary endpoint included all-cause death at 28 days, ICU admission, mechanical ventilation or all-cause death at 30 months. A highly sensitive and specific cardiac biomarker (hs-cTnT > 14 ng/L) was used as a measure of

myocardial injury at admission and patients were stratified according to this.<sup>1</sup>

Influenza-related myocardial injury was significantly associated with age, hypertension, COPD, previous cerebrovascular disease, and creatinine level. All-cause death was also more likely in both the short- (28 days, p=0.048) and mid-term (33 months, p=0.003) in patients with influenza-related myocardial injury.<sup>1</sup>

### All-cause death in patients hospitalised for influenza with and without myocardial injury<sup>1</sup>

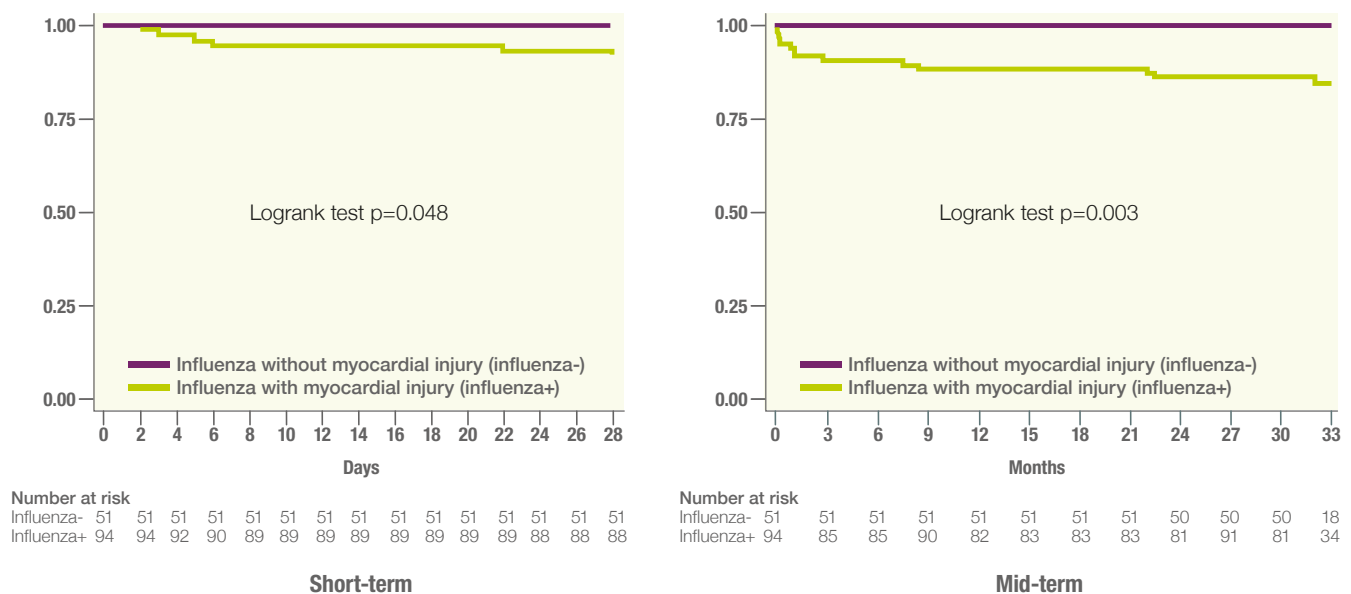


Figure reproduced from Biasco et al. (2022)<sup>1</sup> under a Creative Commons Attribution 4.0 International license: Creative Commons — Attribution 4.0 International — CC BY 4.0.

In conclusion, influenza-related myocardial injury was prevalent in patients in this study, and was associated with a high probability of short- and mid-term adverse events. hs-cTnT is a useful marker to identify patients with

myocardial injury who are at risk of adverse events, and it could help to stratify prognosis.<sup>1</sup>

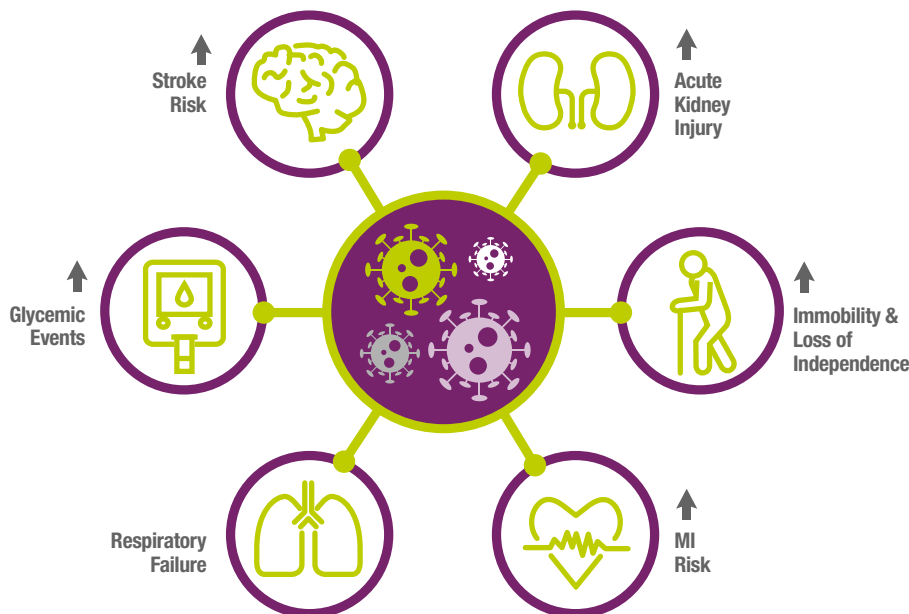
**Evidence on influenza as a trigger for cardiovascular (CV) events and the impact of vaccination (Sanofi-sponsored symposium)**

**Presenter: Ankeet Bhatt**

Dr Bhatt provided an overview of the evidence for a biological link between influenza illness and adverse CV outcomes, described data showing the impact of routine influenza vaccination and provided an update on vaccine coverage rates in patients with CV disease (CVD).

Dr Bhatt described how influenza has an adverse impact on multi-organ systems: it can cause respiratory failure, increase the number of glycaemic events in patients with diabetes, and is associated with an increased risk of stroke, myocardial infarction, acute kidney injury, and immobility and loss of independence in older people.<sup>2-5</sup>

**Influenza multi-organ system involvement<sup>2-5</sup>**



The link between influenza and increased risk of heart failure is well-established and the relationship between viral disease and CVD is more salient than ever since the emergence of COVID-19. Kwong *et al.* (2018)<sup>6</sup> described a 6-fold increase in the risk of myocardial infarction in the 7 days after influenza infection, and Kytömaa *et al.* (2019)<sup>7</sup> showed how heart failure hospitalisations in the US tracked closely with influenza seasons between October 2010 and September 2014. Influenza infection is also associated with increased in-hospital mortality in heart failure patients.<sup>8</sup>

While some relatively small studies have not been able to demonstrate a statistically significant impact of influenza vaccination on CVD outcomes, the body of evidence provides strong support for the impact of influenza vaccination in preventing all-cause death, CV death and other major CV

events. Key evidence includes a large Danish nationwide cohort study reported by Modin *et al.* (2019)<sup>9</sup> two large meta-analyses reported by Udell *et al.* (2013, n=6735)<sup>10</sup> and Behrouzi *et al.* (2022, n=9001)<sup>11</sup> respectively, and the IAMI clinical trial reported by Fröbert *et al.* (2021, n=2531).<sup>12</sup> Furthermore, several major professional societies recommend influenza vaccination in patients with CVD, or state that vaccination may be considered, based on the available evidence.<sup>13-17</sup>

Despite the recommendations, influenza vaccination rates in patients with CVD remain suboptimal across the globe,<sup>18</sup> and have been declining year-on-year in certain patient groups.<sup>19</sup> There is a need for novel vaccine implementation strategies in order to ensure high quality cardiovascular care, including promoting routine yearly influenza vaccination.

## Double-dose versus standard-dose quadrivalent influenza vaccine on major cardiopulmonary events in patients with acute coronary syndromes: The VIP-ACS (Vaccination against Influenza to Prevent cardiovascular events after Acute Coronary Syndrome) trial

Presenter: Remo Furtado

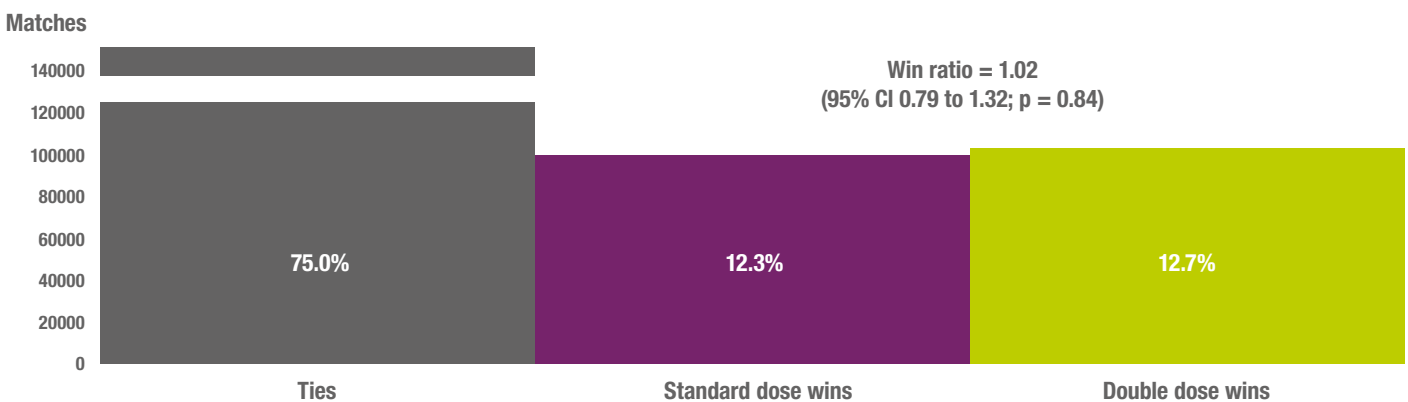
Studies demonstrating the impact of influenza vaccination in reducing the risk of acute coronary syndrome include the meta-analysis conducted by Udell *et al.* (2013)<sup>10</sup> – one of the two meta-analyses mentioned in Dr Bhatt’s presentation, above – and the IAMI study reported by Fröbert *et al.* (2021)<sup>12</sup> which showed that the risk of a primary composite endpoint of all-cause death, MI or stent thrombosis was significantly reduced by influenza vaccination (HR 0.72; 95% CI 0.52–0.99; P=0.04).

The current study aimed to investigate the optimal timing and dosing of influenza vaccination after ACS by assessing whether a double dose of quadrivalent influenza vaccine, (an experimental dosing schedule that is not currently licensed), administered during hospitalisation for ACS, reduces the risk of major cardiopulmonary events when compared with a single-dose influenza vaccine administered 30 days after

discharge. 1801 adult patients with ACS ( $\geq 18$  years) were randomised 1:1 to receive double-dose or standard-dose vaccine and were followed up for 12 months. The primary endpoint was a hierarchical composite of all-cause death, MI, stroke, hospitalisation for unstable angina, hospitalisation for heart failure, urgent coronary revascularisation and hospitalisation for respiratory infections excluding COVID-19.<sup>20</sup>

Due to the COVID-19 pandemic, the Executive Committee decided to stop recruitment in October 2021 and change the primary endpoint measure from time-to-event to win ratio. This methodology compares the number of double-dose to single-dose wins in patient pairs. For example, a double-dose win would be recorded for MI when the single-dose patient had an MI during follow-up and the double-dose patient did not, or both patients had an MI with the single-dose patient at a shorter follow-up time. If neither patient had an MI, or both had an MI at the same time, a tie is recorded.<sup>20</sup>

### Results: Primary endpoint\*<sup>21</sup>



\*Composite of all-cause death, myocardial infarction, stroke, hospitalization for unstable angina, hospitalization for heart failure, urgent coronary revascularization and hospitalization for respiratory infection (excluding COVID-19)

No significant differences were seen when comparing single-dose and double-dose wins for any primary or secondary endpoint. In conclusion, in patients hospitalised for ACS in the VIP-ACS trial, a double-dose quadrivalent vaccine before hospital discharge did not reduce cardiorespiratory events compared with a single-dose vaccine 30 days after

randomisation. Importantly, the author emphasised that these results do not undermine the importance of influenza vaccination in patients with high CV risk, but strategies to improve vaccine coverage and adherence in these patients are needed.<sup>20,21</sup>

## DANFLU-1: Feasibility of a pragmatic randomised trial to assess the relative effectiveness of high-dose (QIV-HD) versus standard-dose quadrivalent influenza vaccine (QIV-SD) on severe cardiorespiratory outcomes in elderly adults

Presenter: Niklas Dyrby Johansen

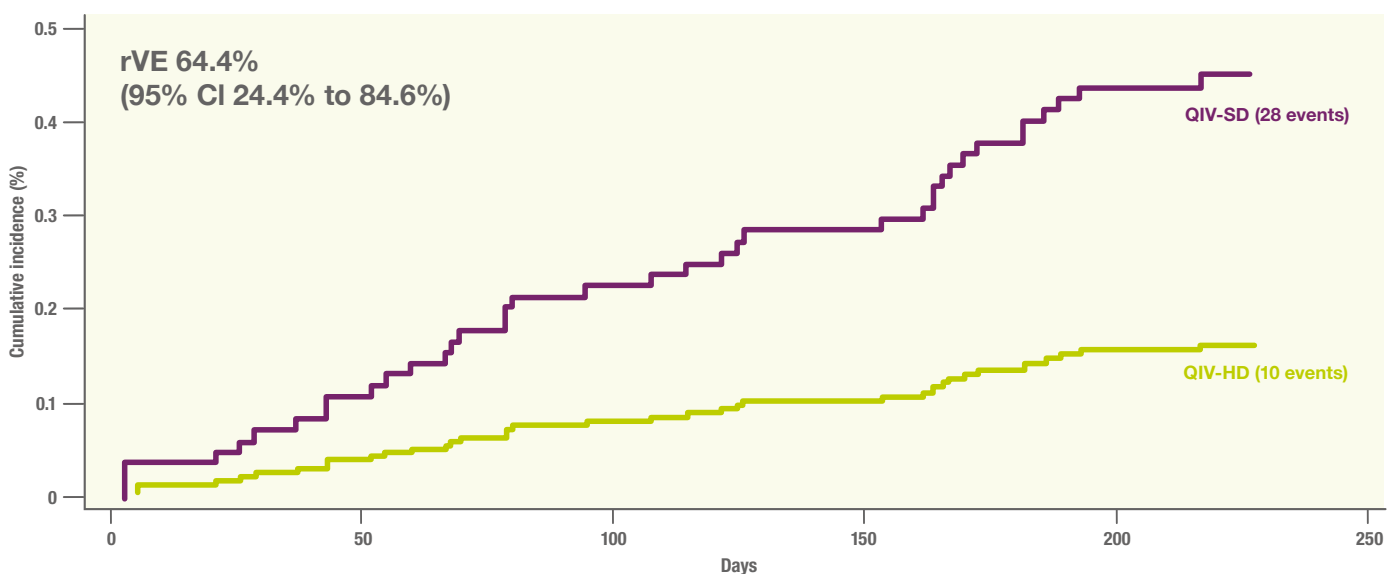
This is the first individually randomised trial to assess the relative vaccine effectiveness (rVE) of QIV-HD versus QIV-SD against CV and respiratory hospitalisations, and mortality in an older adult population. This was a pragmatic, open-label, active-controlled randomised feasibility study conducted in Denmark during the 2021–2022 influenza season. Prof. Tor Biering-Sørensen, GII Steering Committee Member and guest editor of this issue of InFluNews, is Principal Investigator on this trial.<sup>22</sup>

The main objective of this study was to evaluate the feasibility of integrating an individually randomised trial into routine seasonal influenza vaccination practice and using administrative health registries for collection of baseline, outcome and safety data. Feasibility outcomes included participation and inclusion rate, agreement between randomisation group and administered vaccine, balance in baseline characteristics between groups, and comparison of

baseline characteristics between the study population and the general Danish population aged 65–79 years. Based on these outcomes, the authors concluded that a pragmatic, randomised trial of QIV-HD vs QIV-SD using existing infrastructure for recruitment, inclusion, randomisation and vaccination, and relying solely on registry-based data collection, was feasible.<sup>22</sup>

A secondary objective was to descriptively assess the rVE of QIV-HD versus QIV-SD against a range of severe clinical outcomes. Key findings from the pre-specified analyses of rVE were that the incidence of hospitalisation for influenza or pneumonia, and of all-cause mortality, were significantly lower in the QIV-HD versus QIV-SD group (rVEs of 64.4% [95% CI 24.4–84.6%] and 48.9% [95% CI 11.5–71.3%] respectively). These findings require confirmation in a fully-powered future trial.<sup>22</sup>

### Hospitalisation for influenza or pneumonia with QIV-SD versus QIV-HD<sup>22</sup>



## Guest editor Prof. Tor Biering-Sørensen comments:

At this year's ESC conference in Barcelona, the link between heart disease and influenza was underscored yet again. The September issue of InFluNews takes us through the presentations on the topic at this year's conference. The link between influenza infection and cardiovascular morbidity has been known for almost a century. The most common reported cardiovascular complications are cardiovascular death, myocardial infarction, heart failure hospitalization, stroke, myocardial injury, and myocarditis. Supporting these observations, influenza vaccination has been shown to reduce the incidence of cardiovascular events in observational studies and randomized clinical trials. There are multiple proposed mechanisms driving the increased risk of cardiovascular complications, however, the significance of the individual effects is unclear, and thus whether influenza directly or indirectly causes cardiovascular events is unknown. As mentioned previously, the major cardiovascular societies recommend influenza vaccination in patients with cardiovascular diseases, however, influenza vaccination rates in patients with these diseases remain suboptimal. Hence, the main focus should be to increase awareness about the importance of getting our vulnerable patients vaccinated, in addition, I can only echo that it is of the utmost importance that we develop novel vaccine implementation strategies in order to ensure routine yearly influenza vaccination amongst our cardiovascular patients.

## GII Summary Statement

ESC 2022 served to reinforce the link between influenza and an increased risk of CV events and highlight the growing body of evidence in support of the benefits of influenza vaccination in patients with CVD. While awareness of the need to protect vulnerable populations, such as those with CVD, from influenza is increasing amongst specialist medical professionals, vaccine administration remains suboptimal. The GII is working to increase awareness of the impact of influenza 'beyond flu' and the benefits of seasonal influenza vaccination in vulnerable patient groups. We call on healthcare professionals to work together to break down the barriers to influenza vaccination in people with CVD and find new strategies to reach this vulnerable patient group.

## 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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