Effectiveness of the quadrivalent high-dose influenza vaccine for prevention of cardiovascular and respiratory events in people aged 65 years and above: Rationale and design of a real-world pragmatic randomized clinical trial

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Abstract

Background Influenza has been an acknowledged cause of respiratory disease for decades. However, considerable related, and often unappreciated, disease burden stems from cardiovascular complications, exacerbations of underlying medical conditions and secondary respiratory complications, with the highest burden in the elderly. This novel study combines the gold standard method of a randomized controlled trial with real-world data collection through national registries, to assess the relative effectiveness of high-dose (QIV-HD) vs standard-dose quadrivalent influenza vaccine (QIV-SD) in preventing cardio-respiratory hospitalizations in a large cohort of adults aged ≥65 years.

Methods and results This trial (*NCT04137887*) is a Phase III/IV, modified double-blinded, randomized, registry-based trial, conducted by the Finnish Institute for Health and Welfare (THL). Participants (n>120 000) are being enrolled over multiple influenza seasons and randomized (1:1) to receive QIV-HD or QIV-SD. Participant follow-up is based on data collection up to 11 months post-vaccination using Finnish national health registries. The primary objective is to demonstrate the relative superior effectiveness of QIV-HD over QIV-SD in preventing cardio-respiratory hospitalizations up to 6 months post-vaccination. Safety will be assessed using automated online tools throughout the study, with causality assessed using statistical and probabilistic methods; serious adverse reactions and adverse events of special interest will be investigated individually.

Conclusion This large, real-world, randomized study will provide valuable insight into the contribution of influenza in causing severe cardio-respiratory events, and the role of vaccination with QIV-HD in reducing these outcomes compared to the current standard of care.

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Background

Influenza is an acute infectious viral disease that has been an acknowledged cause of annual epidemics of respiratory disease for decades. Seasonal epidemics are visible, impactful on healthcare systems, and cause an esti-

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mated 290,000–650,000 global respiratory deaths annually, mostly in older individuals.[1] Morbidity and mortality stem not from acute influenza infection alone, but through complications and exacerbations of underlying medical conditions and secondary infections leading to bronchitis, pneumonia, sinus and ear infections which result in more complicated, prolonged illness, hospitalization and death.[1-3] Older individuals (aged ≥65 years) have the highest rates of influenza-associated hospitalizations, a result of age-related immune dysfunction and higher prevalence of underlying chronic medical conditions.[4]

There is increasing recognition of the broader cardiovascular manifestations associated with influenza. Initial hypotheses of a causal link followed observations of synchrony in deaths from cardiovascular causes with influenza/pneumonia epidemics, as long ago as 1932.[5] Proving a causal relationship has, nonetheless, been challenging, primarily because of seasonal confounding from cold weather, co-circulation of other respiratory viruses and other factors which preclude direct measurement of the effect of influenza on cardiovascular outcomes. A variety of analytical and design features have been developed and employed to mitigate this challenge, including the development of ever-more-refined, detailed and complex time-series/excess models which account for confounders and isolate the effect of influenza on cause-specific events. However, the interpretation of these population-level studies is not straightforward and the magnitude of reported effects has been variable.[6]

Additional observational studies have been conducted at the individual level: case-control studies have identified an approximately 2-fold higher odds of recent influenza infection in acute myocardial infarction cases than in controls, after adjusting for confounding.[7] And most recently, self-controlled case-series studies, measuring the association between influenza (as a transient exposure) and cardiovascular outcomes, have identified a 4.5- to 10-fold elevated risk of myocardial infarction[8-10], and a 5- to 6-fold elevated risk of stroke up to 1 or 2 weeks after respiratory or influenza infection[9,10], with an elevated risk of stroke persisting up to 1 month after infection in one study.[9]

Vaccination is an effective means of reducing influenza cases. It follows logically that if influenza triggers some cardiovascular events, then the incidence rate of cardiovascular events in vaccine recipients should be lower than in comparable unvaccinated individuals. In a randomized framework, observed differences in outcome incidence between vaccinated and unvaccinated individuals can be causally attributed to the vaccine-preventable pathogen; such studies have been described as 'vaccine probe' studies.[11]

Numerous studies have consistently demonstrated the benefit of influenza vaccination against influenza-related cardio-respiratory events and associated hospitalizations.[12-16] However, these studies have generally been observational rather than randomized controlled trials (RCTs), and are extremely vulnerable to biases including confounding by indication and/or healthy vaccinee bias. Their interpretation is therefore complicated.[17,18] Randomized studies capturing broader cardiovascular endpoints have been conducted, but were powered to assess primary study endpoints related to laboratory-confirmed influenza.[19] As cardiovascular events are rarer than influenza cases, such studies were underpowered for definitive assessment of the wider benefits of influenza vaccination on cardio-respiratory events. As such, it was concluded that higher quality evidence is necessary to confirm the benefits of influenza vaccination in the prevention of cardiovascular disease.[19]

Studies using conventional active surveillance to capture events would necessarily be large and expensive. One meta-analysis, combining events from several RCTs, demonstrated a significantly lower risk of major adverse cardiovascular events among vaccinees vs controls, with an overall relative risk of 0.64 (95% CI, 0.48-0.86).[20] To definitively confirm and quantify the effectiveness of influenza vaccines in preventing broader outcomes, a number of ongoing sufficiently-powered RCTs have been designed to assess cardiovascular events as primary study outcomes (Table 1).[21-23]

A high-dose (HD) influenza vaccine, containing four times the amount of hemagglutinin antigen than standard-dose (SD) vaccines, was developed to provide improved protection among older age groups in whom immune responses to SD influenza vaccines can be suboptimal.[24] The immunogenicity of the trivalent HD vaccine (TIV-HD) was shown to be superior to that of TIV-SD in an RCT (*NCT00391053*), supporting its licensure in the USA.[25] A relative efficacy study, in which approximately 32,000 subjects aged ≥65 years were enrolled in the USA and Canada over two influenza seasons (2011-2012 and 2012-2013), demonstrated the superior efficacy against laboratory-confirmed influenza illness.[26] In that randomized trial, TIV-HD met the FDA-approved, pre-specified criteria for superiority compared with the SD influenza vaccine; TIV-HD was 24.2% (95% CI: 9.7-36.5) more efficacious than TIV-SD.[26] An exploratory analysis of those data also suggested a benefit for TIV-HD for the prevention of serious cardio-respiratory events possibly related to influenza, with an overall relative effectiveness of TIV-HD relative to TIV-SD of 17.7%.[27] Additional RCTs and observational studies have demonstrated the benefits of TIV-HD in comparison with SD influenza vaccines in different populations and settings, and for a variety of different outcomes, with data accumulated over nine influenza seasons for more than 24 million subjects.[14,15] The further development of a quadrivalent formulation (QIV-HD), containing an additional influenza B

Table 1. Ongoing randomized studies assessing impact of influenza vaccination on cardio-respiratory outcomes

Reference	Study	Participants	Design	Countries	Product	Comparator	Primary outcome
Frobert et al[21]	IAMI (NCT02831608)	4400 patients with STEMI or non-STEMI undergoing coronary angiography	Registry-based, multicentre RCT	Sweden, Denmark, Norway, Czech Republic, Scotland, Latvia, Bangladesh	TIV-SD	Placebo	Composite of time to all-cause death, a new acute MI, or stent thrombosis at 1 year
Vardeny et al[23]	INVESTED (NCT02787044)	9300 patients ≥18 years old with HF and post-infarction	Pragmatic RCT	USA and Canada	TIV-HD	QIV-SD	Composite outcome: all-cause mortality and hospitalization from a cardiovascular or pulmonary cause
Loeb et al[22]	IVVE (NCT02762851)	5000 patients ≥18 years with HF	Pragmatic RCT, multicenter, multinational	Cameroon, China, India, Kenya, Lebanon, Mozambique, Nigeria, Philippines, Saudi Arabia, Uganda, UAE, Zambia	TIV-SD	Placebo	Composite outcome: cardiovascular death, non-fatal myocardial infarction, non-fatal stroke and hospitalizations for heart failure
Current study	NCT04137887	>120,000 patients ≥65 years old	Pragmatic registry-based RCT	Finland	QIV-HD	QIV-SD	First occurrences of cardiovascular or respiratory inpatient hospitalizations from ≥ 14 days after vaccination up to 31 May of the season (approximately 6 months), based on discharge diagnosis code

The table lists known pragmatic RCTs that are currently being undertaken to assess the impact of influenza vaccination on cardio-respiratory outcomes.
HD, high-dose; MI, myocardial infarction; QIV, quadrivalent influenza vaccine; RCT, randomized controlled trial; SD, standard dose; STEMI, ST-segment elevation myocardial infarction; TIV, trivalent influenza vaccine

strain lineage, represented an important step in the continued improvement of protection against influenza and its complications among older adults.

A well-designed RCT, allowing causal interpretation of results analogous to a vaccine-probe study, would allow for a more comprehensive assessment of the full benefit of QIV-HD against a range of outcomes. The collection of large sets of health data in national electronic registers renders such an approach feasible, allowing assessment of these health outcomes within a real-world healthcare practice.[28]

By combining the rigour of the gold standard RCT design with real-world data collection through registries, our study assesses the effectiveness of QIV-HD relative to QIV-SD for the prevention of cardio-respiratory hospitalizations in adults aged ≥65 years, representing the first and largest registry-based influenza RCT of its kind in Europe to date.

Research design and methods

Study design

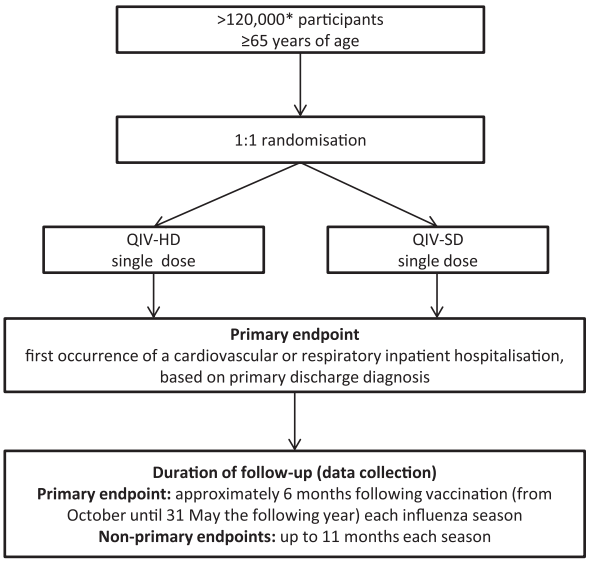
This trial is a pragmatic Phase III/IV randomized, active-controlled, modified double-blinded, registry-based trial conducted in adults aged ≥65 years in Finland (*NCT04137887*). The study is being conducted by the Finnish Institute for Health and Welfare (THL) over multiple influenza seasons beginning in 2019-2020.

Finland has a public healthcare system, with primary healthcare organized by municipalities. Municipal healthcare centers, either alone or jointly with other municipalities, offer a variety of healthcare services at local health stations (including medical or dental consultations, laboratory and x-ray services and, notably, national vaccination campaigns). Specialist healthcare, also organized by the municipalities, is provided across 21 hospital districts. All Finnish citizens and long-term residents are entitled to free national health insurance, allowing equal right to health care for all citizens. Private healthcare, subsidized by the National Insurance Institute (KELA) reimbursements, is also available but inpatient hospitalizations in private hospitals are uncommon. All visits, hospitalizations and reimbursements are recorded in the national health registers.

More than 120,000 participants are planned to be enrolled overall (Figure 1). Participants are randomized (1:1) to receive a single injection of QIV-HD or QIV-SD at over 40 health stations. Enrolment and vaccination are planned to take place between October and December for each year of study. Notably, at the time of study initiation in October 2019, QIV-HD was not licensed in Finland. The post-vaccination follow-up in this study (related to both the effectiveness and safety outcomes) is based on the collection of data from Finnish national health registries over a period of approximately 11 months each year, depending on the study objective. The duration of follow-up reflects the period over which influenza is thought to circulate and exert its effects on the considered outcomes each season. The registries contain population data and health data recorded by healthcare professionals in Finland; our study includes the Finnish Population Information System (Digital and Population Data Services Agency [DVV]), the THL hospital discharge register (Care Register for Health Care), outpatient visits register (Register of Primary Health Care Visits), the THL care register for social welfare, the THL National Infectious Diseases Register, and the Social Insurance Institution of Finland (KELA) registers (Supplementary Methods). All these registries use a permanent, unique personal identity code (PIC) universally used in Finland (including for health records, social services, taxation, banking, driving license and passports). In our study, the PIC will be used by THL to link individual data from the different registries.

The participants, outcome assessors in the hospitals and outpatient care, the investigators, and the sponsor will be blinded to vaccine assignment to avoid bias in reporting and evaluation of illnesses or serious adverse events (SAEs). An unblinded qualified trial staff member will administer the appropriate vaccine at each participating healthcare centre after informed consent and individual randomisation.

Figure 1



Study flow *participants are to be enrolled over multiple years QIV-HD, high-dose quadrivalent influenza vaccine; QIV-SD, standard-dose quadrivalent influenza vaccine

Study endpoints

Vaccine relative effectiveness

The primary study objective is to demonstrate the superior relative clinical effectiveness of QIV-HD compared to QIV-SD among those aged ≥65 years in the prevention of cardiovascular and/or respiratory hospitalizations. First occurrences of cardiovascular or respiratory inpatient hospitalizations based on primary discharge codes from ≥14 days after vaccination and up to 31 May of each year will be recorded. This strategy should capture cardiovascular and/or respiratory events occurring during the influenza transmission seasons only, and will maximize the chance of capturing events that are 'truly' influenza-associated.

Secondary objectives include assessing the relative clinical effectiveness of QIV-HD compared to QIV-SD in the prevention of inpatient hospitalization for selected circulatory and respiratory causes (discharge and admissions data), death (all-cause, cardiovascular or respiratory causes), hospital emergency room visits, primary care visits to physician or major acute cardiovascular events (MACE) from 14 days up to approximately 6 months following vaccination (until 31 May the following year). We will also assess the characteristics of inpatient hospitalization or hospital emergency room visits, or primary care visits to physician in the QIV-HD and QIV-SD groups. These outcomes will be described by age group, specific comorbidities, and different periods of observation.

Our study will allow us to investigate some exploratory endpoints including clinical relative effectiveness over an extended period (up to 11 months post-vaccination), to better understand how long the effects of influenza vaccination might persist, and laboratory-confirmed influenza and invasive bacterial diseases as routinely captured in the registries.

Safety

The safety surveillance for this study was designed to be responsive, timely, and complete to ensure any potential safety concern that might arise during the trial is captured. In this type of registry-based trial with no scheduled follow-up visits, the timely collection of safety data is based on the periodic collection of registry data throughout the study.

Serious adverse reactions (SARs) and adverse events of special interest (AESIs; including new onset of Guillain-Barré syndrome, encephalitis and/or myelitis [including transverse myelitis], Bell's palsy, optic neuritis, and brachial neuritis) are reported to THL by healthcare professionals using paper SAE forms throughout the study (up to 11 months post-vaccination for each influenza season). Data on fatalities are collected by THL online from the Finnish Population Information System. All SARs, AESIs and fatalities are reported by THL to the sponsor within 24 hours of becoming aware of the event.

All unscheduled inpatient hospitalizations (except the primary cardiovascular and respiratory effectiveness endpoints) will be collected from the registry in aggregated form during the blinded follow-up period; causality will be assessed objectively based on statistical methods, comparing the observed frequency with a baseline incidence reflecting aggregated rates of SAEs from both historical data (from 2018-2019) and parallel influenza-vaccinated cohorts (2019-2020) from the same health registry.

An Independent Data Monitoring Committee has been established to monitor participant safety in detail.

Selection of ICD-10 codes

Cardiovascular and respiratory outcomes will be identified using International Classification of Diseases, 10th Revision (ICD-10) codes from the national database. Individual ICD-10 codes were selected from the ICD cardiovascular and/or respiratory sections J and I. We conducted a scoping literature review to assess the events with the highest probability of causal association with influenza and included the respective codes. The remaining ICD-10 I and J codes were assessed by clinical reviewers (among them, cardiologists, geriatricians and epidemiologists). Those with the highest probability of influenza association (eg, likely to result in inflammatory or atherosclerotic processes) were included, whereas those with very specific, non-influenza pathology (eg, acute rheumatic fever) were excluded. The included codes are: I11 and I16 (hypertensive diseases); I20-I25 (ischemic heart diseases); I26 and I27 (pulmonary heart disease and diseases of pulmonary circulation); I30, I31, I33, I38-I42 and I46-I50 (other forms of heart disease); I63-I67 (cerebrovascular diseases); I74-I76 (diseases of arteries, arterioles and capillaries); J00-J06 (acute upper respiratory infections); J09-J18 (influenza and pneumonia); J20-J22 (other acute lower respiratory infections); J40-J47 (chronic lower respiratory diseases); J80 and J81 (other respiratory diseases principally affecting the interstitium); and J85 and J86 (suppurative and necrotic conditions of the lower respiratory tract).

Statistical considerations

With an expected overall attack rate of first occurrence of cardiovascular and/or respiratory hospitalisation (primary endpoint) of approximately 1.8% (over multiple influenza seasons, from 2019-2020), 2200 evaluable cases would provide approximately 90% power (by exact method) to conclude on the primary objective. Based on available evidence[14,15,26,29], we assumed that the true relative vaccine effectiveness of HD over SD would be 13% against prevention of cardiovascular and/or respiratory hospitalisation, with a 0.025 one sided type I error and a lower bound above 0%.

The relative vaccine effectiveness of QIV-HD to QIV-SD will be estimated for the primary endpoint as

follows:

$$\text{rVE} = (1 - (\text{CQIV} - \text{HD}/\text{NQIV} - \text{HD})/(\text{CQIV} - \text{SD}/\text{NQIV} - \text{SD})) \times 100\%$$

where rVE is the relative vaccine effectiveness; CQIV-HD and CQIV-SD are the numbers of participants meeting the primary endpoint definition (first occurrence of cardiovascular and/or respiratory hospitalizations) in the QIV-HD and QIV-SD groups, respectively; and NQIV-HD and NQIV-SD are the numbers of participants in the QIV-HD and QIV-SD groups, respectively.

The superiority of the effectiveness of QIV-HD over QIV-SD will be demonstrated if the lower bound of the CI for the rVE is > 0%. A participant who is enrolled in consecutive study years will be evaluated as an independent participant for each of those years in the main analysis, as re-randomization prevents inflation of type I error.

Other effectiveness endpoints and safety will be summarized per vaccine group, with 95% CI for the main endpoints.

Ethical statement

This study is being undertaken in compliance with the International Conference on Harmonization (ICH) guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki. The protocol and any amendments are subject to approval by applicable Independent Ethics Committees/Institutional Review Boards and the regulatory agency as per local regulations. Informed consent is obtained from the participants or their legal guardians before any study procedures are performed.

Discussion

This study is the first and largest influenza study of its kind that combines an RCT design with real-world registry-based data to assess the effectiveness of QIV-HD compared with QIV-SD in preventing cardiovascular and respiratory outcomes. The study addresses a need to better understand the broader consequences of influenza in the real world and will provide further insight into the benefits of influenza vaccination for public health.

RCTs represent the 'gold standard' in clinical research. Randomized allocation of subjects to interventions minimizes biases arising from differences in participant characteristics and, coupled with well-defined interventions, blinded prospective follow-up, and predefined endpoints, allows the results to be interpreted with a greater level of confidence than other study designs.[30] However, RCTs suffer from a number of limitations, including high costs (which increase with number of participants) associated with planning, recruitment and undertaking required clinical and laboratory assessments. Additionally, the use of narrow inclusion criteria and multiple exclusion criteria to restrict the recruitment to a specific study population can limit the generalizability of results.

The increasing availability of large volumes of digital real-life healthcare data collected over a number of years has led to increasing numbers of studies being conducted using population-based registries.[31] Randomizing participants to a specific intervention and collecting data on outcome events in these registries provides the possibility of nationwide long-term follow-up in a real-world context, thereby increasing generalizability (external validity) to clinical practice. Registry-based data collection also minimizes the risk of losing participants to follow-up or poor compliance.

The use of Finland's national health databases provides a powerful tool for the evaluation of vaccine effectiveness in a large study population.[32] These registries provide access to population-based data on vaccinations and influenza illness that can be linked at the individual level using the PIC.[32] While this is the first individually randomized RCT to systematically evaluate the effect of QIV-HD vs QIV-SD on these outcomes, it should be noted that studies of alternative design have reported additional benefit of HD vaccines for these outcomes.[14,15,26]

Being a registry-based trial with no scheduled follow-up visits, our study combines the active reporting of SARs, AESIs and fatalities to the Sponsor's database, with largely automated data collection from the Finnish registries for evaluation of other non-fatal SAEs. The long-standing nature of the Finnish databases facilitates the analysis of observed vs expected aggregated non-fatal SAEs based on event rates from the current and previous years, strengthening the quantitative safety analysis of this study. Taking into consideration the extensive post-marketing experience with TIV-HD and Phase III clinical trial experience with QIV-HD, demonstrating that TIV-HD and QIV-HD have similar safety profiles[33], a full safety assessment of reactogenicity was not deemed necessary in the current study.

To our knowledge, there is one other ongoing pragmatic RCT (*IAMI; NCT02831608*) using registry-based data from different countries to assess the effect of influenza vaccination on cardiovascular outcomes. The Phase IV study aims to enroll up to 4400 patients with ST-segment elevation myocardial infarction (STEMI) or non-STEMI, randomized to receive a TIV-SD or placebo.[21] Data for the primary endpoint (time to all-cause death, a new myocardial infarction or stent thrombosis up to 1 year) are being obtained from national health registries, hospital records and telephone interviews.

Unlike a classical clinical trial, we collect non-specific cardio-respiratory endpoints, an unknown proportion of which will be triggered by influenza infections and may therefore be preventable through influenza vaccination. The proportion is likely to vary in time due to influenza seasonality and we can therefore expect the relative vaccine effectiveness calculated to vary as a function of influenza seasonality. We may also expect the COVID-19 pandemic, which began in Europe in early 2020, to have

some impact on this study. Indeed, measures such as social distancing imposed to help control SARS-CoV-2 are likely to have also impacted the spread of influenza, while potential changes in health-seeking behavior, particularly those of more vulnerable older adults, may have had some impact on the data reported to the registries.

It should also be noted that the accuracy or quality of the ICD-10 coding may vary between clinicians and/or sites according to experience or knowledge of the illness and the quality framework in place. However, most of the major ICD-10 codes for cardiovascular events have been previously validated.[8,34-36] Moreover, numerous ICD codes have been assigned for confirmed and suspected COVID-19 and COVID-19-related hospitalization, further mitigating the risk of misclassification.

Our study does not assess participants for influenza or systematically record whether a previous influenza-like infection has occurred; thus prior influenza infection in patients who present with cardio-respiratory events will be missed. Nonetheless, given the randomized nature of the study, any differences observed between groups can be attributed to the intervention and the occurrence of influenza reported in the course of normal clinical care will be evaluated as exploratory outcomes. The data generated from our study will thus provide valuable information on the contribution of influenza in causing severe cardio-respiratory events and on the role of QIV-HD in reducing these outcomes.

Author contributions

RH, AP, SP, SS and IDB contributed to the concept or design of the study; SP, MD, JJ, RS and JN contributed to data acquisition; and all authors have been involved with data analysis or interpretation. All authors were involved in drafting or critically revising drafts of the manuscript, and all approved the final draft for submission. All authors accept accountability for the accuracy and integrity of the content of the publication.

Data availability

Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at: https://www.clinicalstudydatarequest.com

Conflict of interest

SP, MD, AS, JN, SS and IDB are employees of Sanofi Pasteur. RH was an employee of Sanofi Pasteur at the time that this work was undertaken. JN and IDB own shares in Sanofi, a company which produces influenza vaccines. AAP, JJ, and RS are investigators at the Finnish Institute for Health and Welfare (THL), which received research funding from Sanofi Pasteur Inc. for the current study and from GlaxoSmithKline SA, and Pfizer Inc. outside of the submitted work.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2021.03.007.

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