High-Dose Quadrivalent vs Standard-Dose Influenza Vaccine Effectiveness using EHR in Portugal

VEBIS EHR Annual Meeting

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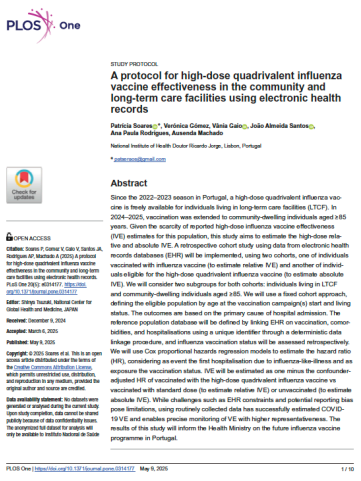

PLOS One

STUDY PROTOCOL

A protocol for high-dose quadrivalent influenza vaccine effectiveness in the community and long-term care facilities using electronic health records

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Data availability statement: No datasets were generated or analysed during the current study. Upon study completion, data cannot be shared publicly because of data confidentiality issues. The anonymized full dataset for analysis will only be available to Instituto Nacional de Saúde

Abstract

Since the 2022–2023 season in Portugal, a high-dose quadrivalent influenza vaccine is freely available for individuals living in long-term care facilities (LTCF). In 2024–2025, vaccination was extended to community-dwelling individuals aged ≥ 85 years. Given the scarcity of reported high-dose influenza vaccine effectiveness (IVE) estimates for this population, this study aims to estimate the high-dose relative and absolute IVE. A retrospective cohort study using data from electronic health records databases (EHR) will be implemented, using two cohorts, one of individuals vaccinated with influenza vaccine (to estimate relative IVE) and another of individuals eligible for the high-dose quadrivalent influenza vaccine (to estimate absolute IVE). We will consider two subgroups for both cohorts: individuals living in LTCF and community-dwelling individuals aged ≥85. We will use a fixed cohort approach, defining the eligible population by age at the vaccination campaign(s) start and living status. The outcomes are based on the primary cause of hospital admission. The reference population database will be defined by linking EHR on vaccination, comorbidities, and hospitalisations using a unique identifier through a deterministic data linkage procedure, and influenza vaccination status will be assessed retrospectively. We will use Cox proportional hazards regression models to estimate the hazard ratio (HR), considering as event the first hospitalisation due to influenza-like-illness and as exposure the vaccination status. IVE will be estimated as one minus the confounder-adjusted HR of vaccinated with the high-dose quadrivalent influenza vaccine vs vaccinated with standard dose (to estimate relative IVE) or unvaccinated (to estimate absolute IVE). While challenges such as EHR constraints and potential reporting bias pose limitations, using routinely collected data has successfully estimated COVID-19 VE and enables precise monitoring of VE with higher representativeness. The results of this study will inform the Health Ministry on the future influenza vaccine programme in Portugal.

Soares P, Gomez V, Gaio V, Santos JA,Rodrigues AP, Machado A (2025) A protocolfor high-dose quadrivalent influenza vaccineeffectiveness in the community and long-termcare facilities using electronic health records.PLoS One 20(5): e0314177. https://doi.org/10.1371/journal.pone.0314177

Background

The case for the High Dose Vaccine

- In most European countries, seasonal influenza vaccination is recommended annually for high-risk individuals. Standard-dose (SD) vaccines may be less effective in older adults, a high-dose (HD) quadrivalent vaccine was developed that shows superior efficacy for older individuals [1, 2, 3].

- In Portugal, the HD vaccine was first introduced in LTCFs for individuals aged ≥ 60 during the 2022/23 season. In 2023/24, eligibility was expanded to community-dwelling individuals aged ≥ 85. Other adults aged ≥ 60 can access the vaccine through medical prescription in community pharmacies [4].

- The Portuguese Ministry of Health has commissioned DEP-INSA a comprehensive report assessing the effectiveness of the HD influenza vaccine since its introduction among adults aged ≥ 60 years.

Objectives

Using a **retrospective cohort** study design using data routinely collected in **EHR** databases for mainland Portugal [4], the primary and secondary objectives of the study are to estimate:

Primary Objectives

- the **relative VE of the HD** quadrivalent influenza vaccine against hospital admission due to influenza-like-illness in individuals with any approved influenza vaccine.
- the **absolute VE of the HD** quadrivalent influenza vaccine against hospital admission due to influenza-like-illness in individuals eligible for vaccination.

Secondary Objectives

- if sample size allows, to estimate **absolute VE** by time since vaccination to **evaluate the presence of waning immunity**.

Each season (2022/23 up until 2025/26) will be analysed from the start of the HD vaccination campaign until 9 months later.

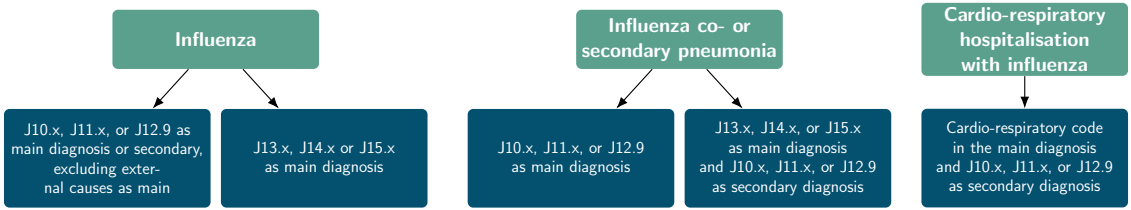
Exposure & Outcome

Definitions

Vaccination Status

Assessment	Exposure	Time Since Vaccination
Relative VE	**Interest:** Vaccinated with High-Dose (14 days after vaccination) **Reference:** Standard-Dose Vaccine	$t = 0$ - Start of vaccination campaign
Absolute VE	**Interest:** Vaccinated with High-Dose (14 days after vaccination) **Reference:** Unvaccinated	Stratified as: - 14–89 days (<13 weeks) - 90–179 days (13–26 weeks) - 180–272 days (26–39 weeks)

Hospitalizations [ICD-10] as Outcome



Methodology

STUDY POPULATION

All registered individuals aged more than 60 years and eligible for influenza vaccination

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INCLUSION CRITERIA

– Eligible for vaccination with HD or SD quadrivalent influenza vaccine
– Individuals living in LTCF or community-dwelling in Mainland Portugal.

↓

EXCLUSION CRITERIA

– Inconsistent/missing vaccination data (status, date, brand, doses)
– Received non-EMA approved vaccine
– Vaccinated between seasons (week 21–39)
– >1 influenza vaccine in the same season

Methodology

Cohort	Season under analysis	Objective	Exposed	Reference group
Individuals living in LTCF aged ≥ 60	2022/23 and 2023/24	Estimate **relative VE** of the HD influenza vaccine	Individuals living in **LTCF vaccinated with HD** influenza vaccine	Individuals living in **LTCF vaccinated with the SD** influenza vaccine aged
Individuals living in the community aged ≥ 85	2023/24 to date	Estimate **relative VE** of the HD influenza vaccine	Individuals living in the **community vaccinated with the HD** influenza vaccine	Matched individuals in the **community vaccinated with the SD** influenza vaccine
Individuals living in the community aged ≥ 85	2023/24 to date	Estimate **absolute VE** of the HD influenza vaccine	Individuals living in the **community vaccinated with the HD** influenza vaccine	Matched individuals from the **community who are unvaccinated but eligible** for the HD influenza vaccine

Data Sources & Confounding Variables

Data Sources

We'll be using the same data sources as in the VEBIS-EHR Study.

- National Health Service User [NHSU] - Reference population database, includes individual records of the study population.
- National Vaccination Registry [VACINAS] - Vaccination registry or vaccination record databases with individual data.
- National Hospital Discharges Registry [BDMH & BIMH] - Public hospital management and centralises data on hospitalisation information.
- Primary Healthcare Data [SIM@SNS] - Diagnoses, chronic conditions, and eligibility for the influenza vaccine.

Confounding Variables

- Age
- Region
- Sex
- European Deprivation Index
- Comorbidities
- Previous COVID-19 vaccination

Analysis Plan

Main Analysis

1. Construction of the cohort.
   - Identification of individuals and characteristics at baseline.
   - Time since vaccination.
   - Identification of outcomes during follow-up.
   - Censoring events (hospitalisation date, at the end of the study, or on the date of death).
2. Descriptive analysis of cohorts.
3. Cox Proportional Hazards Models.
   - Adjusted Hazard Ratio (aHR) for first hospitalisation due to influenza-like-illness and as exposure the vaccination status.
   - Vaccine Effectiveness - $\text{VE} = (1 - \text{aHR}) * 100$

- Spatiotemporal analysis on the vaccination in LTCF (HD vs. SD).
- Propensity score matching for comparability - Given the anticipated high vaccination coverage, there may be a scarcity of unvaccinated individuals.

Risk Assessment

Identified Risk	Contingency Plan / Mitigation
Underascertainment of individuals living in LTCFs	Characterize individuals receiving COVID-19 vaccines in the first season.
Differential administration of high-dose and standard-dose vaccines in LTCFs	Conduct spatio-temporal analysis by ISO week and municipality.
High-dose vaccination outside LTCFs	Exclude these individuals from the analysis, as vaccination outside LTCFs may occur ad-hoc during the 22/23 season.
Incomplete or outdated municipality data	Compare LTCF counts with official statistics to verify accuracy.
Few standard-dose recipients in LTCFs and few high-dose recipients in the community	Use propensity score matching; adjust matching ratio if necessary.
Outcome misclassification from hospital admission registries	Consider alternative outcome definitions with varying sensitivity.

Conclusion

- The protocol outlines a study design and methodology to evaluate the effectiveness of the HD quadrivalent influenza vaccine in reducing hospital admissions due to influenza-like illness and related outocmes among individuals aged 60 and over in LTCFs and people living in the community aged ≥ 85.

- The study will estimate both relative and absolute VE, adjusting for important confounders, using EHR databases.

- This study will address critical gaps in the evidence, particularly for the institutionalised elderly population, where data on the effectiveness of the HD vaccine remain limited, especially in Portugal.

- The results will inform public health strategies to optimise influenza vaccination programmes and improve protection against severe influenza outcomes in vulnerable older adults.

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