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Do COVID-19 and Influenza vaccines influence susceptibility to other respiratory viruses? A population-based study

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INTRODUCTION

- Studies have raised concerns that influenza **vaccination may influence susceptibility to other respiratory viruses** (ORV), potentially modifying the risk of non-targeted infections
- Such influences could reflect temporary changes in immune responsiveness, including **reduced cross-protection from natural infection** or, conversely, **vaccine-induced cross-immunity**, possibly resulting from modulation of host–virus interactions
- This challenges a **key assumption of test-negative** design studies, that **vaccination should not change the likelihood of being infected by other viruses** within the same clinical syndrome
- If such **viral interference occurred**, vaccines might appear more or less effective than they actually are, depending on the direction of the interference and **vaccine effectiveness estimates could be biased**

AIM

Evaluate the association between influenza and COVID-19 vaccination and the risk of non-influenza/COVID-19 respiratory virus infections

METHODS

STUDY DESIGN

Test-negative design (TND) study nested within a larger multicentre case-control study also using a TND design (VEBIS Primary Care study), which was developed to monitor vaccine effectiveness against COVID-19 and influenza across different settings in different European countries

STUDY POPULATION

- Portuguese patients who consulted a general practitioner **AND** meet the Acute Respiratory Infection (ARI) case definition **AND** give their consent to participate in the VEBIS Primary Care study
- Were included patients from seasons 2022-2023, 2023-2024, and 2024-2025 (October 2022 to April 2025)

EXPOSURE

Seasonal influenza and/or COVID-19 vaccination

OUTCOME

RT-PCR positive for non-influenza and non-SARS-CoV-2 respiratory viruses

METHODS

EXCLUSION CRITERIA

- Patients vaccinated against influenza or COVID-19 **less than 14 days before symptoms onset** (excluded 1-13 days)
- Patients tested **more than 7 days after symptom onset** (to avoid false negatives)
- Patients with **laboratory-confirmed influenza/COVID-19 infection**

VARIABLES

- **Demographics** (sex, age groups, onset date), **influenza and COVID-19 vaccination status** and **presence of chronic conditions**
- **Laboratory results** - RT-PCR for influenza, respiratory syncytial virus (RSV), SARS-CoV-2, human rhinovirus (hRV), parainfluenza virus (PIV 1, 2, 3 and 4), human enterovirus (hEV), adenovirus (ADV), human metapneumovirus (hMPV), human coronaviruses (hCOV-OC43, NL63, 229E) and human bocavirus (hBOV)

STATISTICAL ANALYSIS

- Logistic regression estimated adjusted odds ratios (aOR) of being vaccinated among cases (ORV positive) and controls (ORV negative)
- Adjustment variables (sex, age, onset date, and chronic conditions) were selected based on the literature and data availability

RESTRICTION FLOWCHART

2086 patients recruited

(seasons 2022-2023, 20223-2024, 2024-2025)

605 patients

Missing data
- Missing Influenza vaccination information (N = 24)
- Missing COVID-19 vaccination information (N = 10)
- Missing symptom onset date (N=18)
- Missing Influenza, SARS-CoV-2 or others respiratory virus PCR test result (N = 553)

1481 patients with complete data

385 patients

Exclusion criteria
- Vaccinated 1–13 days before symptom onset (N = 44)
- Testing more than 7 days after symptom onset (N = 91)
- PCR positive for Influenza and/or COVID-19 (N = 250)

1096 patients meeting inclusion criteria and complete data

466 controls
(ORV Negative)

630 Cases
(ORV Positive)

RESULTS – Influenza & COVID-19 Vaccination status

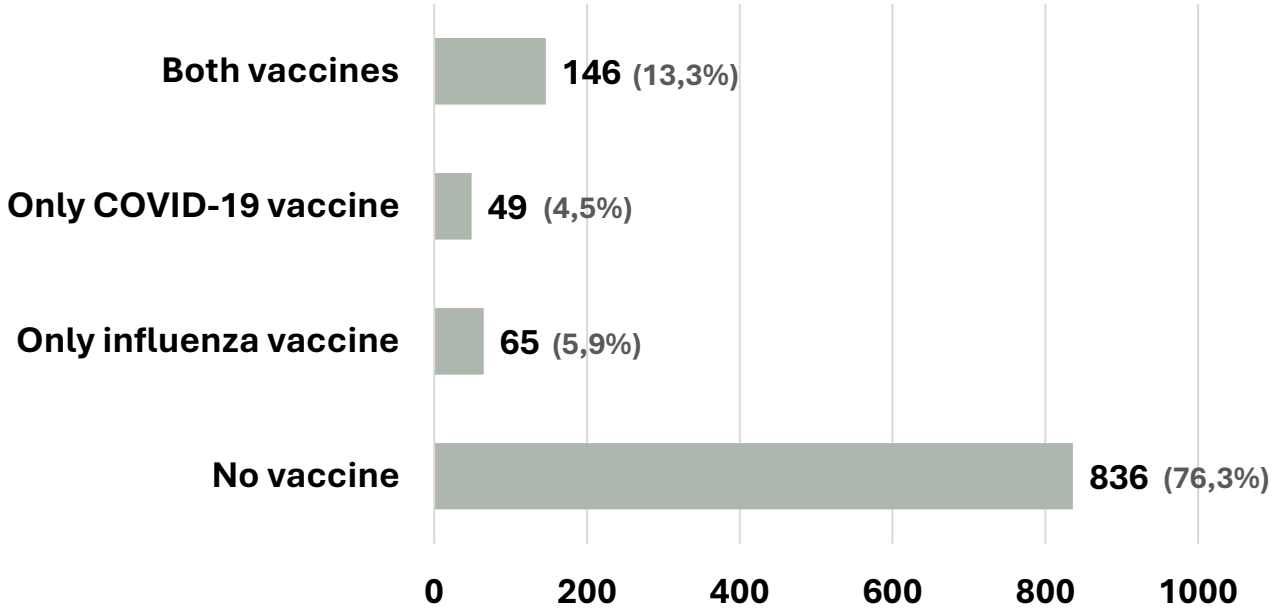

Figure 1, Vaccination status for Influenza and COVID-19 RT-PCR negative patients (n=1096).

Of **1 096 patients with negative** influenza and COVID-19 RT-PCR, **23,7% (n=260) had received** an influenza and/or COVID-19 vaccine

The majority of patients who received **both vaccines** (n=146, 13,3%) received them on the **same day (87,0%)**

Majority of patients were **male** (68,1%), **aged 35-64 years** (51,2%) and with **at least one chronic condition** (49,0%)

RESULTS – Other respiratory virus (ORV)

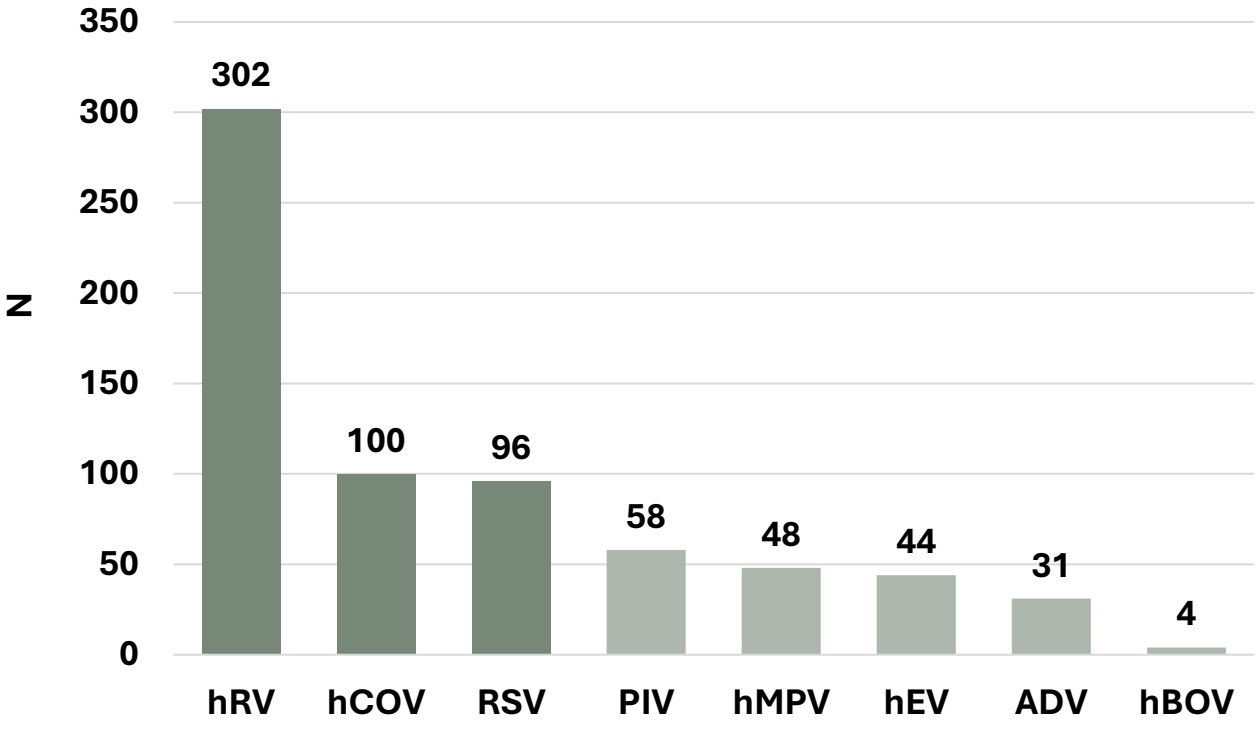

Figure 2, Number of positive RT-PCR for respiratory syncytial virus (RSV), human rhinovirus (hRV), parainfluenza virus (PIV), human enterovirus (hEV), adenovirus (ADV), human metapneumovirus (hMPV), human coronaviruses (hCOV) and human bocavirus (hBOV) (n=630),

Of the patients included in the analysis, **57,5% (n=630) had an infection** with other respiratory virus than influenza or SARS-Cov-2

human Rhinovirus (44,2%), **human Coronavirus** (14,6%), and **respiratory syncytial virus** (14,1%) were the viruses more frequently identified

RESULTS – Vaccination status & ORV

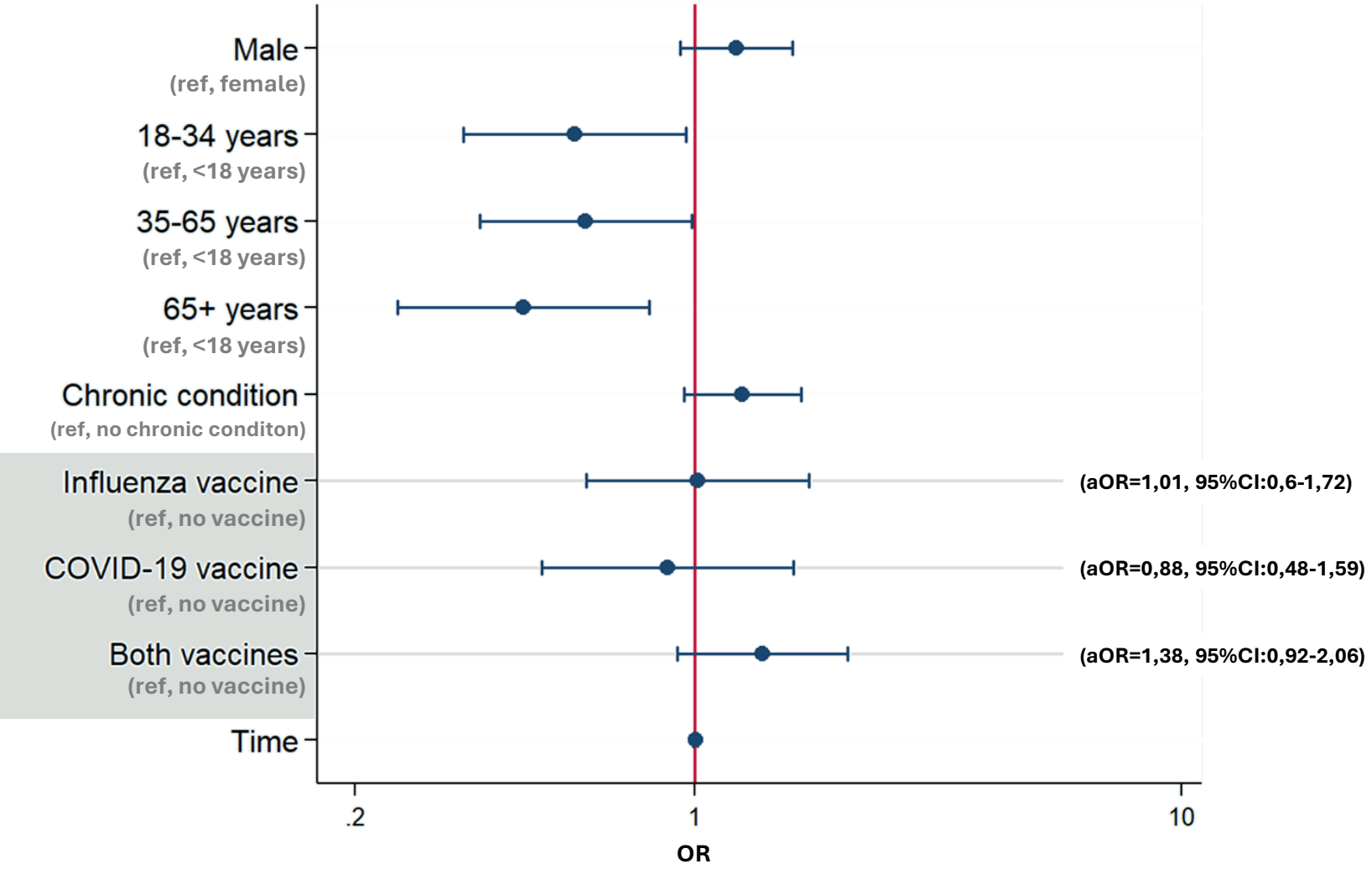

Figure 3. Adjusted Odds ratios (aOR) with confidence intervals (95%CI).

Patients that received

only the influenza vaccine

or

only the COVID-19 vaccine

or

Influenza and COVID-19 vaccines

⇣

were **not associated to a higher risk of infection by other respiratory viruses**

LIMITATIONS

- The present study was conducted under the **same constraints and methodological conditions** that were applied to the **original study** for which the patient recruitment was designed, along with those specific to the current analysis

- Although **not all ARI-causing pathogens were tested**, the **testing panel was comprehensive** and included the **most commonly implicated viral agents** associated with respiratory infections

- **ARI case definition may not capture all respiratory pathogens**, although it is broad enough to detect most prevalent respiratory viral infections

CONCLUSION

- Our results suggest that **vaccination status** - whether for influenza, COVID-19, or both - **was not significantly associated with the risk of other respiratory virus infections**

- This **supports the use of test-negative controls for influenza** and **COVID-19 within the same clinical syndrome**, as it upholds the key test-negative design assumption of **no association between vaccination and risk of non-target infections**

- While mechanisms such as **reduced cross-protection from natural infection** or potential v**accine-induced cross-immunity** have been proposed, **our findings reinforce the validity of the primary methodological assumption** rather than suggesting evidence for these alternative effects

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