Winter 2022-23 influenza vaccine effectiveness against influenza-related hospitalised aLRTD: a test-negative, case-control study

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Background

Influenza activity in the UK started early during the winter 2022-23 season, with most surveillance systems reporting high levels of hospitalisation, intensive care unit influenza admission and GP influenza-like illness (ILI) consultation rates. Laboratory confirmed positivity rates were comparable to those seen pre-pandemic, between the end of November 2022 and the end of January 2023, exceeding 25% as they did during the 2019-2020 season [1,2]. Annual vaccination against influenza is recommended in the UK to eligible higher-risk groups: adults ≥65 years(y); children and adults in at-risk groups (including during pregnancy); and, pre-school, primary and secondary school-aged children[3]. However, in 2022-23 the offer of seasonal influenza immunisation was extended to healthy 50-64y olds[4]. The vaccines used were quadrivalent, containing one influenza A(H1N1) virus, one influenza A(H3N2) virus, one influenza B/Victoria lineage virus, and one influenza B/Yamagata lineage virus[5]. Public health measures aiming to reduce the transmission of SARS-CoV-2 had affected the transmission of respiratory viruses like influenza during the previous two seasons, with the 22-23 season being the first one where social mixing returned to pre-pandemic levels. Systematic monitoring of the effectiveness of the seasonal flu vaccine (VE) is a public health priority as influenza activity returns to pre-pandemic levels.

Methods

VE against hospitalised virologically-confirmed influenza was estimated using a test-negative case-control design (TND), with the study population consisting of patients with signs/symptoms of respiratory infection, aged ≥18y hospitalised with an acute lower respiratory tract disease (aLRTD) between 1st October 2022 and 31st March 2023, in North Bristol and University Hospitals Bristol and Weston NHS Trusts [AvonCAP:

ISRCTN17354061]. Study eligible patients were identified from the medical admission list, and data were collected from medical records using REDCap. Test-positive and test-negative patients were identified using the results of standard-of-care NP swabs tested for influenza by RT-PCR in the local UKHSA clinical microbiology lab using either the Hologic Panther Fusion platform or the BioFire Diagnostics system. Patients hospitalised with aLRTD and a positive admission influenza test result were classified as cases while those with a negative result were classified as controls. To reduce the chance of including potentially false negative admission influenza tests, patients with symptoms starting >10-days prior to admission were excluded. Participants with current or suspected COVID-19 infection or previous proven COVID-19 infection within the last 28 days were excluded from the analysis[6]. Additional subgroup analysis was performed by including patients hospitalised with aLRTD only through the Emergency Department.

Participants who had documented record of seasonal influenza vaccine administration in 22-23 (vaccination between 1 September 2022 and 31 March 2023) were defined as vaccinated, while those without record of vaccination in the 22-23 season were categorised as unvaccinated. We define immunisation as having received the vaccine with >14 days having elapsed between the vaccine and symptom onset, excluding those vaccinated <14 days before their symptom onset.

Under the assumptions of the TND, we estimated the overall VE against influenza A and B combined by comparing the odds of testing positive for influenza among vaccinated versus unvaccinated participants, defining adjusted VE as $(1 - aOR)\times100$, where aOR is the adjusted odds ratio of testing positive among vaccinated participants compared with unvaccinated participants using a multivariable logistic regression analysis adjusting for age, sex, ethnicity, index of multiple deprivations (IMD) decile rank , Charlson comorbidity index (CCI),

smoking status, presence of pre-existing respiratory disease, presence of cardiovascular disease, seasonal covid vaccination (autumn 2022 booster programme: 5 September 2022 - 12 February 2023) and week of admission (spline function).

Results

During the study period, 2,972 adult aLRTD hospitalisations occurred in Bristol, UK and were eligible for this analysis. Among 196 (6.6%) who tested influenza positive, 189 were influenza A virus subtypes and 7 were influenza B. Among the study sample, 47% of influenza-positive patients (cases) had received a seasonal influenza vaccine, compared with 63% of influenza-negative patients (controls). The characteristics of cases and controls are listed in Table 1.The overall adjusted VE against influenza-associated hospitalisation, as shown in Table 2, was 55.9% (95% confidence interval [CI]: 31.4-71.5). Subgroup analysis of aLRTD hospitalisations through the Emergency Department resulted in overall adjusted VE against influenza-associated hospitalisation of 53.8% (95% CI: 24.3-71.6).

Discussion

In this analysis, we consider the effectiveness of seasonal influenza vaccination during the 2022-2023 season when the incidence of flu cases surpassed the levels observed in the COVID-19 pandemic influenza seasons (2020-21, 2021-22). Our findings suggest that the influenza vaccine programme in the UK provided substantial protection, reducing the risk of hospitalised virologically-confirmed influenza by 56% among all adults, mainly against

circulating influenza A viruses and more specifically influenza H3N2 which accounted for the majority of subtyped influenza A according to surveillance data for the UK. Notably, the vaccines administered during this period included the dominant strain of influenza, suggesting that it contributed to its effectiveness. Our estimates demonstrate higher values in comparison to other studies. In a hospital emergency care department setting in England[7], the overall VE has been estimated as 30% (95% CI: 21-38) and UKHSA[2] reported the age-group-specific VE against influenza-associated hospitalisation following an emergency department visit in England to be 32% (95% CI:13-47%) in 18-64y and 28% (95% CI:15-39) in >65y. Primarily, this could be explained by the imperfect sensitivity and specificity of the diagnostic tests used for the detection of influenza in these studies, which results in the underestimation of vaccine effectiveness[8]. Secondly, our study employs a prospective approach with thorough case ascertainment, minimizing the bias by inclusively capturing all patient groups, which may also contribute to higher vaccine effectiveness estimates.

Vaccination remains one of the most effective ways to prevent influenza-associated severe outcomes like hospitalisation.

Ethics and permissions

The Health Research Authority Research Ethics Committee (East of England, Essex), REC20/EE/0157 approved this study, including using Section 251 of the 2006 NHS Act under Confidentiality Advisory Group authorisation.

Role of the funding source

This study was conducted as a collaboration between The University of Bristol (study sponsor) and Pfizer (study funder). The study funder did not undertake any data collection, data analysis or manuscript preparation.

Data Sharing

The data used in this study are sensitive and cannot be made publicly available without breaching patient confidentiality rules. The data dictionary is therefore unavailable.

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Conflict of interest: CH is Principal Investigator of the AvonCAP study which is an investigator-led University of Bristol study funded by Pfizer and has previously received support from the NIHR in an Academic Clinical Fellowship. JO and LD are Co-Investigators

on the AvonCAP Study. AF is a member of the Joint Committee on Vaccination and Immunization (JCVI) and, until December 2022 was chair of the World Health Organization European Technical Advisory Group of Experts on Immunization (ETAGE) committee. In addition to receiving funding from Pfizer as Chief Investigator of this study, he leads another project investigating transmission of respiratory bacteria in families jointly funded by Pfizer and the Gates Foundation. The other authors have no relevant conflicts of interest to declare.

Authors' contributions: AC, CH, RC, RM, LD, JO, and AF generated the research questions and analysis plan. CH, JK, SM and The AvonCAP team were involved in data collection. AC, CH, RM, RC, LD, and AF undertook data analysis. All authors (AC, CH, RC, RM, JK, SM, NM, JO, LD, AF) were involved in the final manuscript preparation and its revisions before publication. The data was verified by CH, JK and SM. AF provided oversight of the research.

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