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José Luis Alonso Bilbao[1]
Alejandro de Arriba Fernández[2, 3]
Alberto Espiñeira Francés[1] Antonio Cabeza Mora[1]
Ángela Gutiérrez Pérez[1] Miguel Ángel Díaz Barreiros[1]

Epidemiological study on the impact of influenza vaccination on the clinical evolution of patients with COVID-19 and COVID-19 co-infection in Gran Canaria, Spain.

[1]Gerencia de Atención Primaria, Área de Salud de Gran Canaria, Servicio Canario de la Salud, Las Palmas de Gran Canaria, Spain
[2]Servicio de Medicina Preventiva, Complejo Hospitalario Universitario Insular Materno Infantil, Servicio Canario de la Salud, Las Palmas de Gran Canaria, Spain.
[3]University Institute of Biomedical and Health Research. University of Las Palmas de Gran Canaria, Las Palmas de Gran Canaria, Spain.

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SUMMARY

Objective. To analyse the frequency of coinfections between influenza viruses and SARS-CoV-2, as well as the differences in the evolution (risk of mortality, hospital admission or intensive care) of patients infected by the SARS-CoV-2 virus according to vaccination or non-vaccination for influenza in the 2021-2022 season.

Method. Retrospective observational population-based study in a cohort of 19,850 patients diagnosed with COVID-19 between 1 June 2021 and 28 February 2022 on the island of Gran Canaria.

Results. A total of 1,789 people were vaccinated against influenza, 9% of the total number of patients diagnosed with COVID-19. 13,676 people (68.9%) had a full COVID-19 vaccination schedule. In the period from 1 June 2021 to 28 February 2022, 8 cases of influenza and COVID-19 co-infection were reported. Hypertension (18.5%), asthma (12.8%) and diabetes (7.2%) were the most frequent co-morbidities. There were 147 deaths (0.7%). Older people ([OR] 1.11 95% CI 1.09-1.13) and those with cancer ([OR] 4.21 95% CI 2.58-6.89) were at higher risk of death from CO- VID-19 (p<0.05). Female sex was considered a protective factor ([OR] 0.61 CI 95% 0.40-0.92).

Conclusions. Older age, male sex and cancer were independent predictors of mortality. Three doses of SARS-CoV-2 vaccine and influenza vaccine were highly effective in preventing COVID-19-related deaths and admissions. These findings suggest that influenza vaccination may help control the pandemic.

Keywords: COVID-19, influenza, vaccines, infection, immunity.

Correspondence:
Alejandro de Arriba Fernández
Servicio de Medicina Preventiva, Complejo Hospitalario Universitario Insular Materno Infantil, Servicio Canario de la Salud, Las Palmas de Gran Canaria, Spain.
E-mail: alejandrodearribafdez@gmail.com

Epidemiological study on the impact of influenza vaccination on the clinical course of patients with COVID-19 and co-infection by both viruses in Gran Canaria, Spain

ABSTRACT

Objectives. To analyze the frequency of influenza and SARS-CoV-2 co-infections, as well as the differences in the course of disease (risk of mortality, hospital and intensive care admissions) in patients infected with the SARS-CoV-2 virus in relation to flu vaccination status in the 2021-2022 season.

Methodology. Population-based observational retro- spective study in a cohort of 19,850 patients diagnosed with COVID-19 between June 1, 2021 and February 28, 2022 on the island of Gran Canaria.

Results. A total of 1,789 patients (9%) diagnosed with COVID-19 had received flu vaccinations. 13,676 people (68.9%) had a full course of COVID-19 vaccinations. In the period be- tween June 1, 2021 and February 28, 2022, 8 cases of flu and COVID-19 coinfection were recorded. Hypertension (18.5%), asthma (12.8%) and diabetes (7.2%) were the most frequent comorbidities. There were 147 deaths (0.7%). Older patients ([OR] 1.11 95% CI 1.09-1.13) and people with cancer ([OR] 4.21 95% CI 2.58-6.89) had a higher risk of dying from COVID-19 (p<0.05). Female sex was noted as a protective factor ([OR] 0.61 95% CI 0.40-0.92).

Conclusions. Old age, male sex and cancer were independent prognostic factors for mortality. Three doses of SARS-CoV-2 vaccines and influenza vaccines were highly effective in preventing COVID-19-related deaths and hospital admissions. These findings suggest that flu vaccination can help control the pandemic.

Keywords: COVID-19, flu, vaccines, infection, immunity.

INTRODUCTION

Since December 2019, coronavirus disease 2019 (COVID-19) has been an international public health emergency [1]. Worldwide, there have been more than 636 million cases of COVID-19 and more than 6.6 million deaths as of 3 November 2022 [2].

Severe acute respiratory syndrome type 2 coronavirus (SARS-CoV-2) mimics influenza virus in terms of clinical presentation, transmission mechanism and seasonal coincidence. Therefore, co-infection with both viruses is feasible [3].

Influenza is a disease of viral aetiology that occurs as annual epidemics in the winter months and occasionally in pandemic form. Although it is generally a mild and self-limiting disease, when it affects elderly or chronically ill people it can increase mortality [4,5].

The most effective strategy to prevent influenza virus disease is vaccination, mitigating the burden on health systems. However, it has been challenging to maintain influenza virus vaccination services during the SARS-CoV-2 pandemic, which has had the potential to disrupt vaccination programmes in many countries [6]. On the other hand, measures to reduce SARS-CoV-2 transmission have also been effective in reducing transmission of other endemic respiratory viruses [7,8].

Vaccine effectiveness against laboratory-confirmed infection was moderate (50-60%) against A(H1N1) pdm09 and B viruses, and low or null, depending on the age group, against A(H3N2) virus. A very positive impact of the influenza vaccination programme in Spain in the 2019-20 season has been estimated among those over 64 years of age. The influenza vaccine was able to prevent 26% of hospitalisations, 40% of ICU (Intensive Care Unit) admissions and 37% of deaths from all influenza-attributable causes occurring in hospitals in this age group [9]. Co-infection with influenza virus was associated with increased likelihood of receiving invasive mechanical ventilation compared to SARS-CoV-2 mono-infection [10].

This study analysed the epidemiological and clinical characteristics of influenza vaccinated COVID-19 cases in Gran Canaria. We analysed the possible differences in the evolution (hospital admission, ICU admission and mortality) of patients infected by SARS-CoV-2 virus vaccinated and non-vaccinated influenza in the 2021-2022 season. The frequency of co-infections between influenza viruses and SARS-CoV-2 was determined.

METHODS

Type of study. Retrospective population-based observational study in a cohort of 19,850 patients aged 12 years or older diagnosed with COVID-19 between 1 June 2021 and 28 February 2021 in Gran Canaria.

Inclusion criteria. Confirmed COVID-19 case: patient who meets clinical criteria for a suspected case with positive PDIA (diagnostic test for active infection), or asymptomatic patient with positive PDIA and negative or absent IgG. Suspect case: patient with acute respiratory infection of sudden onset of any severity with fever, cough or dyspnoea. Other symptoms such as odynophagia, anosmia, ageusia, muscle pain, diarrhoea, chest pain or headache, among others, were also considered suspicious symptoms. The exclusion criterion was age <12 years.

Data collection and source. All patients vaccinated against SARS-CoV-2 in Gran Canaria (period 28 December 2020 to 31 December 2021) were identified using the REGVACU registry (Registro de Vacunación frente al SARS-CoV-2 en España). All COVID-19 cases in Gran Canaria reported to ReVeCa (Red de Vigilancia Epidemiológica de Canarias) in the period between 1 June 2021 and 28 February 2022) were identified. Clinical information on patients diagnosed with CO-IDV-19 and their influenza vaccination status was obtained from the electronic medical record of Primary Care, DRAGO-AP.

Influenza vaccination was defined as a person who has received a dose of influenza vaccine in the indicated seasonal period. The influenza vaccination campaign for the 2021-2022 season started in Can- rias on 28 October 2022. The target groups were: people over 60 years of age, pregnant women, chronically ill people of any age, healthcare workers and carers of vulnerable people.

Variables. The main outcome variable was morbidity. Influenza vaccination was the main dependent variable. Control variables were: age, sex, underlying morbidities (asthma, cancer, dementia, diabetes, coronary heart disease, chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), hypertension (HT) and obesity), immunosuppressive treatment, dates of the first, second and booster doses of the COVID-19 vaccine and type of vaccine (Pfizer, Moderna, Astrazeneca, Janssen).

Definitions. Diabetes was classified as: baseline glycaemia ≥126 mg/dl or with anti-diabetic treatment; obesity: BMI ≥30 $^{kg/m2}$; HTN: systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, or with antihypertensive treatment.

Complete vaccination schedule for COVID-19. Patient who has received 2 doses of vaccine at least 19 days apart if the first dose was BNT162b2 mRNA (Pfizer-BioNTech), 21 days apart for ChAdOx1 nCoV-19 (AstraZeneca-Oxford University) or 25 days apart for mRNA-1273 (Moderna), and at least 7 days since the last dose if the last dose was from Pfizer, or 14 days apart if from Astra-Zeneca or Moderna. Those who received a dose of Ad26 were also considered fully vaccinated. COV2.S (Janssen) more than 14 days ago and those aged ≤65 years were also considered fully vaccinated.

who, having passed the disease, have received a dose of any vaccine, after the minimum period equal to that established for second doses. In the heterologous regimen using AstraZeneca in the first dose and mRNA vaccines in the second dose, the patient was considered fully vaccinated after 7 days if the second dose was with Pfizer, or 14 days if with Moderna [11].

Statistical analysis. Descriptive analysis of the results was performed using frequency measures and percentages for categorical variables. Bivariate analysis for qualitative variables was performed using the χ test[2] , using the Likelihood Ratio when necessary. The level of statistical significance used was 5% ($p<0.05$). The statistical treatment of the data was carried out using the Statistical Package for the Social Scien- ces (SPSS), v28.

Study approved by the Clinical Research Ethics Committee of the Hospital Universitario de Gran Canaria Dr. Negrín (registration number 2021-356-1 COVID19). It was conducted in accordance with local laws and regulations, the Helsinki Declaration, Fortaleza and Good Clinical Practice.

RESULTS

In the period from 1 June 2021 to 31 December 2021, 1,789 people (9.0%) of the total number of patients diagnosed with COVID-19 were vaccinated against influenza. 13,676 people (68.9%) were vaccinated with the full COVID-19 schedule.

In the period between 1 June 2021 and 28 February 2022, 8 cases of influenza and SARS-CoV-2 co-infection were reported. Figure 1 shows the description of these co-infections according to the covariates analysed.

Table 1 shows the bivariate analysis between influenza vaccination and the main study covariates. Female sex, older population groups (≥70 years), people on immunosuppressive treatment and those requiring hospital admission were associated with a higher rate of influenza vaccination.

In the multivariate logistic regression model (table 2) we found that older people, men and those with cancer were more likely to die from COVID-19. Other variables associated with a higher probability of death were hospital admission and requiring mechanical ventilation during admission ($p<0.05$). The third dose of SARS-CoV-2 vaccine was associated with a lower risk of death (Odds Ratio 0.17, 95% CI 0.08-0.35; $p<0.05$), and influenza vaccine was also protective (Odds Ratio 0.36, 95% CI 0.17-0.78; $p<0.05$). No association was found with asthma, COPD, hypertension, obesity, diabetes, complete SARS-CoV-2 vaccination schedule or ICU admission ($p>0.05$).

DISCUSSION

It was observed that the evolution of the 2021-22 influenza season was more similar to the immediately preceding season, 2020-21, than to more distant seasons. From the beginning of the season to 28 February 2022, 142 influenza viruses were found: 136 are influenza A viruses [96 (AH3), 1 (AH3), 1 (AH3) and 1 (AH3)].
(AH3N2), 17 (AH1pdm09), 4 (AH1N1pdm09) and 23 (ANS)]. Only B virus was found [12].

In the 2020-2021 season, 492,889 people were vaccinated in the Canary Islands, 71.8% of the target population [13]. This figure is expected to be similar in the 2021-22 season [14]. As public health restrictions are lifted, co-infections of respiratory viruses, including SARS-CoV-2, are more likely to occur [10]. It has not been possible to demonstrate

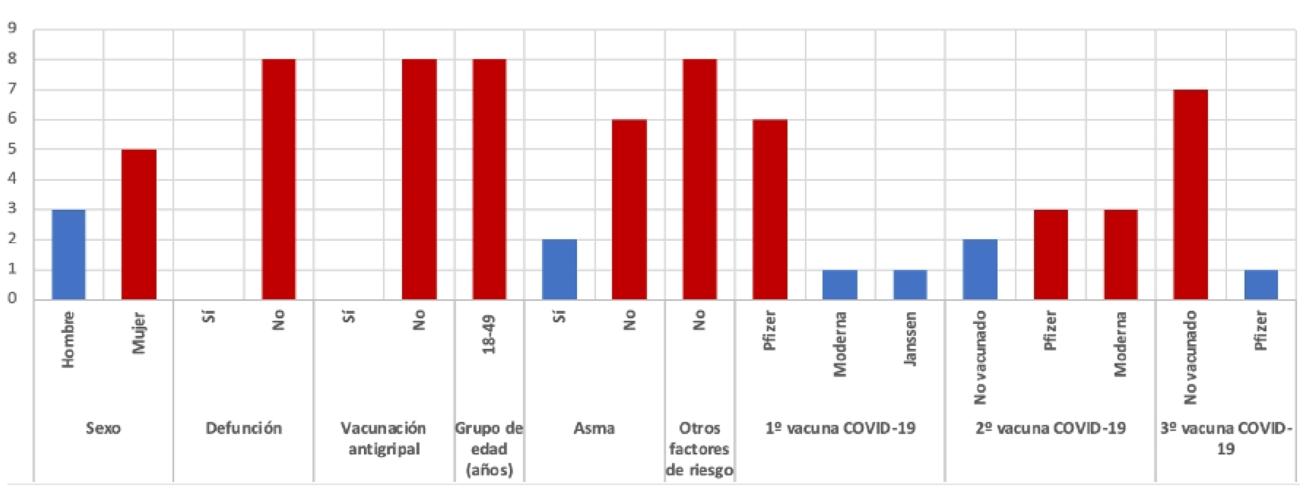

Figure 1 **Description of the frequency of co-infection with influenza virus and SARS-CoV-2 (n=8).**

Table 1 **Bivariate analysis. Associations between the main study covariates and influenza vaccination in 1,789 vaccinated persons out of a total of 19,850 participants.**

Variables	N cases	Influenza vaccination YES (%)	Influenza vaccination NO (%)	Odds Ratio (OR)	P value
Sex					
Male	9.344	727 (7,8)	8.617 (92,2)	1	0,000
Femal e	10.506	1062 (10,1)	9.444 (89,9)	1,33 (1,21 -1,47)	
Deaths Yes					
No	147	11 (7,5)	136 (92,5)	0,82 (0,44-1,51)	0,516
	19.703	1.778 (9)	19.725 (91)	1	
Age groups 18-					
49	13.884	533 (3,8)	13.351 (96,2)	0,01 (0,00-0,01)	0,000
50-69	4.619	712 (15,4)	3.907 (84,6)	0,11 (0,07-0,15)	0,000
>=70	1.347	544 (40,4)	803 (59,6)	1	Ref
Mechanical ventilation					
Yes	60	7 (11,7)	53 (88,3)	1,34 (0,61-2,94)	0,472
No	19790	1782 (9)	18.008 (91)	1	
Admission to Intensive Care Unit Yes					
No	208	22 (10,6)	186 (89,4)	1,20 (0,77-1,87)	0,428
	19642	1767 (9)	17.875 (91)	1	
Hospital admission					
Yes	831	138 (16,6)	693 (83,4)	2,10 (1,73-2,53)	0,000
No	19.019	1.651 (8,7)	17.368 (91,3)	1	
Immunosuppressive treatment					
Yes	330	84 (25,5)	246 (74,5)	3,57 (2,77-4,59)	0,000
No	19.520	1.705 (8,7)	17.815 (91,3)	1	

It is not definitively known whether these co-infections lead to a higher severity of COVID-19. The initial study by Ding et al [15] on mixed SARS-CoV-2/gripe infections showed no worsening or worse prognosis than infection alone. However, a large Public Health Service study showed that, although co-infections are common, patients co-infected with both viruses are 2.4 times more likely to die than those infected with only one virus, especially relevant in those aged >65 years, among whom more than 50% of co-infected patients die [16]. These data support the need to protect the general population, especially at-risk groups, from co-infection ("the perfect storm"), which appears to significantly increase morbidity and mortality [17]. In line with this hypothesis, Marín-Hernández et al [18] have studied the relationship between influenza vaccination in >65 years of age and the evolution of COVID-19 in Italy, finding a strong correlation between a higher vaccination rate and a lower number of COVID-19 deaths. Another large study in Italy shows a significant inverse association between influenza vaccination coverage, population seroprevalence rate against SARS-CoV-2 (spread of infection), prevalence of hospitalised patients, ICU admissions and number of deaths attributable to the virus, estimating that an increase in the number of deaths attributable to the virus is associated with an increase in the number of deaths attributable to the virus.

1% in vaccination coverage in people >65 years would prevent 350 hospital admissions and 2,000 deaths in the country [19]. Another study conducted in Brazil on 90,000 patients diagnosed with COVID-19, 31.1% of whom were vaccinated against influenza, confirmed that those vaccinated before or during the SARS-CoV-2 epidemic had lower mortality and fewer ICU admissions [20].

One possible explanation could be that the flu vaccine partially protects against SARS-CoV-2 infection. This would occur if the vaccine stimulates innate immunity against other respiratory viruses. The local respiratory immune system would elicit a strong and rapid response that would make other respiratory viral infections more difficult [5]. Immunologically, the influenza vaccine is designed to induce a long-lasting adaptive response through the production of neutralising antibodies and T-cell responses. Despite the low genetic similarity between influenza viruses and SARS-CoV-2, it is possible that some T-CD8+ lymphocytes recognise minor epitopes present in them. However, due to the extraordinary antigenic diversity of influenza viruses, the production of neutralising antibodies and T-cells against other RNA viruses, including SARS-CoV-2, seems unlikely [21]. Therefore, according to Fink et al [20], the most likely mechanism for the potential benefits of the vaccine is the production of neutralising antibodies and T-cells against other RNA viruses, including SARS-CoV-2 [21].

Table 2 **Multivariate analysis. Associations of mortality in the 1,789 influenza vaccinees among the population of 19.850**

Variable	Death and logistic regression analysis (95%CI)	P value
Sex		
Female	0,61 (0,40-0,92)	0,000
Male	1 (Ref.)	
Age (years)	1,11 (1,10-1,13)	0,000
Asthma		
Yes	1,17 (0,62-2,20)	0,635
No	1 (Ref.)	
Cancer		
Yes	4,21 (2,58-6,89)	0,000
No	1 (Ref.)	
Diabetes		
Yes	0,92 (0,59-1,45)	0,722
No	1 (Ref.)	
Chronic obstructive pulmonary disease		
Yes	0,67 (0,34-1,34)	0,261
No	1 (Ref.)	
High blood pressure		
Yes	1,05 (0,66-1,65)	0,843
No	1 (Ref.)	
Obesity		
Yes	0,64 (0,13-3,13)	0,585
No	1 (Ref.)	
Full vaccination schedule		
Yes	0,82 (0,52-1,32)	0,419
No	1 (Ref.)	
Booster		
Yes	0,17 (0,08-0,35)	0,000
No	1 (Ref.)	
Influenza vaccine		
Yes	0,36 (0,17-0,78)	0,010
No	1 (Ref.)	
Hospital admission		
Yes	15,95 (9,57-26,56)	0,000
No	1 (Ref.)	
Mechanical ventilation		
Yes	4,30 (1,57-11,82)	0,005
No	1 (Ref.)	
Admission to Intensive Care Unit		
Yes	1.64 (0,88-3,07)	0,122
No	1 (Ref.)	

The main reason for this is the innate immunity induced by vaccination. In addition, some vaccines, probably also the influenza vaccine, induce non-specific immunotherapeutic mechanisms that increase the host response to other pathogens.

through a complex process called "trained immunity" [5].

Another non-virological explanation for the protective effect of the influenza vaccine could be that the higher rates

The correlation may also be due to chance or to the epidemiological behaviour of other respiratory viruses [18]. It is also possible that this correlation is due to chance or to the epidemiological behaviour of other respiratory viruses [18].

Influenza vaccination should continue to be implemented and intensified as it reduces the prevalence of the disease, the severity of its symptoms and reduces hospitalisations and admissions to the ICU, relieving the pressure of care throughout the health care system and allowing better care for patients with other pathologies. Given the limited experience with influenza vaccination of patients with COVID-19, it is recommended that those who present compatible symptoms or laboratory confirmation of SARS-CoV-2 delay influenza vaccination until they have fully recovered, reminding them of the need to join the vaccination programme at a later date [18, 22, 23]. In short, annual influenza vaccination remains the best and perhaps the only cost-effective public health tool with a proven impact on the epidemiology and prevention of seasonal influenza. Other authors propose increasing influenza vaccination rates to prevent influenza co-infection with SARS-CoV-2 [24].

Kuderer NM et al [25] reported an association between cancer and higher mortality rates. Cancer patients may be immunocompromised due to antineoplastic therapy, supportive medications and the immunosuppressive properties of the cancer itself. These findings are consistent with the results of our study in which the prevalence of active cancer as a comorbidity among patients diagnosed with COVID-19 was 3.2%, identified in the multivariate analysis as an independent factor associated with mortality.

Vaccinated patients are older and more comorbid, factors that are associated with higher mortality in COVID-19 patients without influencing influenza vaccination. Multiple studies found age to be an independent risk factor for mortality in COVID-19 patients, which could be explained by immunosenescence [26]. Consistent with other studies, our patients with high comorbidity had significantly higher mortality than those with low comorbidity [27].

Our study has some limitations. We did not include analytical data that could be associated with increased mortality as suggested by several studies [9], but our aim was to assess influenza vaccination and other comorbidities in the risk of mortality in patients diagnosed with COVID-19. Treatments administered during hospital admission were also not taken into account, due to their heterogeneity and low level of evidence in published studies [28]. In addition, the epidemiological situation may have conditioned admission criteria and bed availability and influenced mortality outcomes [29].

In this respect, the Gripometer (a tool for real-time knowledge of influenza vaccination coverage) is a practical and very useful tool that can be used in the field of influenza vaccination.

This may be especially important at times like 2021-2022 and beyond, when influenza could coexist with COVID-19. Influenza vaccination is a key complementary weapon, in the context of the COVID-19 health crisis, to avoid a potential collapse of health care [30].

In conclusion, older age, male sex, absence of COVID-19 booster doses, hospital or ICU admission, absence of influenza vaccination and cancer were independent predictors of mortality which could help clinicians to identify patients with poor prognosis for management and treatment. Further studies on the role of influenza vaccination in the course of COVID-19 disease are warranted and will be vital for research and development of a more effective vaccine. All eligible persons should be offered vaccination, including those with previous SARS-CoV-2 infection, to reduce their risk of future infection.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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