Influenza Vaccination among Multiple Sclerosis Patients during the COVID-19 Pandemic

Ignacio Hernández-García 1,2,*, Moisés Garcés-Redondo 3, Moisés Garcés-Redondo 3, Moisés Garcés-Redondo 3, Judit Espinosa-Rueda 3, Joana Rodríguez-Montolio 3, Irantzu Bengoa-Urrengoechea 1,2 and Carlos Aibar-Remón 1,2,4

1 Department of Preventive Medicine and Public Health, Lozano Blesa University Clinical Hospital of Zaragoza, Calle San Juan Bosco 15, 50009 Zaragoza, Spain
2 Health Services Research Group of Aragon (GRISSA), Aragon Institute for Health Research (IISA), Calle San Juan Bosco 15, 50009 Zaragoza, Spain
3 Department of Neurology, Lozano Blesa University Clinical Hospital of Zaragoza, Calle San Juan Bosco 15, 50009 Zaragoza, Spain
4 Department of Preventive Medicine and Public Health, University of Zaragoza, Calle de Pedro Ceballos 12, 50009 Zaragoza, Spain
* Correspondence: ihernandezgsalud.aragon.es

Abstract: In the context of the COVID-19 pandemic, the co-circulation of influenza and SARS-CoV-2 viruses may have severe complications for vulnerable populations. For this reason, the World Health Organization pointed to the 2020–2021 anti-influenza campaign as being of special relevance. Our aim was to assess the 2020–2021 influenza vaccination coverage, and its associated factors, among patients in a Spanish multiple sclerosis (MS) unit. A cross-sectional study was conducted. People attending the MS unit of the Clinical Hospital of Zaragoza during 2020 were included. Variables were obtained by reviewing records. Associations with 2020–2021 influenza vaccination were analyzed using bivariate analysis and a multiple logistic regression model. A total of 302 patients were studied; 62.6% were women, whose mean age (standard deviation) was 47.3 (11.5) years. The 2020–2021 influenza vaccination coverage was 55.3% (59.8% in women and 47.8% in men). A total of 89.7% had at least one other indication for vaccination (e.g., immunosuppressive treatment in 225 patients). The variables associated with getting vaccinated were being female (adjusted odds ratio (95% confidence interval) (aOR (95%CI) = 2.12 (1.12–3.99)), having received the 2019–2020 influenza vaccine (aOR (95%CI) = 31.82 (14.71–68.86)) and being born in Spain (aOR (95%CI) = 12.91 (1.07–156.28)). Coverage is moderate compared to other countries. It is necessary to develop strategies to improve it, especially in men and those born outside Spain.

Keywords: multiple sclerosis; influenza vaccines; vaccination coverage; associated factors; Spain; COVID-19

1. Introduction

Globally, it is estimated that up to 650,000 people die each year from influenza-related causes [1]. In Spain, during the 2019–2020 season, 619,000 people attended primary healthcare consultations for influenza. There were 27,700 hospitalizations with laboratory-confirmed influenza, 1,800 admissions to intensive care units and 3,900 influenza-associated deaths [2]. The percentage of positive results remained above 40% for 11 consecutive weeks (week 51/2019 through week 9/2020) [3].

In particular, influenza can also cause serious complications in people with multiple sclerosis (MS), such as severe exacerbations of MS symptoms [4,5]. For this reason, public health institutions [6,7], scientific societies [8–10] and expert groups [5,11] recommend annual influenza vaccination for patients with MS. However, the vaccination coverage in this population is low [12–17], with the rates in Europe ranging from 19% in Germany [12] to 63.8% in Ireland [15] (Table 1), while in the Americas, they range from 45.4% in Latin America [16] to 59.1% in the USA [13].
Table 1. Influenza vaccination rate among people with MS in European countries.

| Country     | Influenza Season | Vaccination Rate |
|-------------|------------------|------------------|
| Germany [12] | 2017–18          | 19%              |
| Spain [14]  | 2015–16          | 20.40%           |
|             | 2016–17          | 20.40%           |
|             | 2017–18          | 30.80%           |
|             | 2018–19          | 41.20%           |
|             | 2019–20          | 41.50%           |
| Ireland [15] | 2020–21          | 63.80%           |
| Italy [17]  | 2020–21          | 58.20%           |

In Spain, since the 2014–2015 season, the Ministry of Health has recommended annual flu vaccination for people with MS [18]. For this purpose, inactivated vaccines of proven effectiveness and safety are used. These vaccines are usually administered free of charge at primary healthcare centers [2].

In the context of the novel Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2) pandemic [19], the cocirculation of influenza and SARS-CoV-2 viruses may have severe complications for vulnerable populations and can overload the health systems (in terms of the number of admissions and consultations) [7]. For this reason, the World Health Organization and the Spanish Ministry of Health pointed to the 2020–2021 anti-influenza campaign as being of special relevance [2,7].

This research was carried out with the objective of knowing the coverage of influenza vaccination in 2020–2021 and its associated factors in patients in a Spanish MS unit.

2. Materials and Methods

A cross-sectional study was conducted in Aragon (Spain); about 1,200,000 people live in this Spanish region. Among them, about 1300 have MS [20]. The University Clinical Hospital of Zaragoza (UCHZ) houses one of the two MS units in Aragon; in it, patients with MS are monitored physically and/or remotely at least once every six months. Approximately 25% of MS patients living in Aragon are seen in such unit.

Patients seen in the MS unit of the UCHZ between 1 January 2020 and 31 December 2020 were included. The exclusion criterion was death before the start of the 2020–2021 influenza campaign (15 October 2020).

In October 2021, physicians of the MS unit of the UCHZ obtained the following information by reviewing electronic medical records from both specialized care and primary care: sex, country of birth, date of birth, place of residence (city of Zaragoza or other), allergies, date and age at MS diagnosis, MS type (relapsing–remitting, secondary progressive, clinically isolated syndrome or primary progressive) [21], number of MS outbreaks during 2019, Expanded Disability Severity Scale (EDSS) score [22] during 2020, having received the 2019–2020 flu vaccine, registration of the recommendation to get an annual flu vaccination at a primary healthcare center, date and place of administration of the 2020–2021 influenza vaccine, and belonging to any other influenza vaccination target group according to the recommendations of the Spanish Ministry of Health (e.g., (a) 65 years of age or older, (b) chronic cardiovascular disease, (c) isolated arterial hypertension, (d) chronic respiratory disease, (e) diabetes mellitus, (f) morbid obesity, (g) chronic kidney disease, (h) hemoglobinopathies and anemias, (i) asplenia, (j) chronic liver disease, (k) immunosuppressive treatment, (l) cancer, (m) cochlear implantation or awaiting cochlear implantation, (n) disorders and diseases leading to cognitive dysfunction, (o) cerebrospinal fluid fistula, (p) celiac disease, (q) intestinal inflammatory disease, or (r) pregnant in any gestational trimester) (Table S1) [18]. Moreover, information on pneumococcal vaccination status (pneumococcal conjugated vaccine 13–valent (PCV13) and pneumococcal polysaccharide vaccine 23–valent (PPSV23)) until 31 December 2020 was collected in patients taking immunosuppressive medication.
For the statistical analysis, we used measurements of central tendency (mean or median) and dispersion (standard deviation (SD) or range) for quantitative variables (according to whether or not they presented a normal distribution according to the Kolmogorov–Smirnov normality test) and absolute and relative frequencies (percentages) for qualitative variables. The bivariate analyses considered having received the 2020–2021 flu vaccine as the dependent variable and the others as independent variables using the chi square test or the Fisher exact test.

Subsequently, a multiple logistic regression analysis was performed with the variables for which significant associations were observed in the bivariate analyses. To quantify the associations, the adjusted odds ratio (aOR) was calculated with its 95% confidence intervals (95%CI).

Moreover, in patients taking immunosuppressive medication, bivariate analyses considered having received the 2020–2021 flu vaccine as the dependent variable and having received the pneumococcal vaccination (PCV13 plus PPSV23) as the independent variable in the chi square test.

A value of 0.05 was taken as the alpha probability of error. All of this was carried out using the analysis program SPSS v.24.0 (IBM Corp, Hong Kong, China). This study was approved by the Research Ethics Committee of the Autonomous Community of Aragon (approval code C.P.–C.I. PI21/417).

3. Results

The number of persons included was 302, after excluding 1 patient due to death in July 2020. A total of 62.6% (189/302) were women, with a mean age (SD) of 47.3 (11.5) years during the 2020–2021 influenza vaccination campaign. Of the patients, 96.3% were born in Spain, and 53.6% resided in the city of Zaragoza. The median age (range) at diagnosis of MS was 31 (10–62) years. A total of 75.2% (227/302) had relapsing–remitting MS. During 2019, one or more MS outbreaks were suffered by 9.3% (28/302) of people. None of the patients were allergic to the components of the influenza or pneumococcal vaccines. A total of 89.7% (271/302) had at least one other indication for flu vaccination (the most frequent was immunosuppressive treatment, in 225 patients) (Table 2).

Table 2. Results of the descriptive analysis.

|                          | N = 302 |
|--------------------------|---------|
| **Sex, n (%)**           |         |
| Female                   | 189 (62.6) |
| Male                     | 113 (37.4) |
| **Place of residence, n (%)** |         |
| City of Zaragoza         | 162 (53.6) |
| Other                    | 140 (46.4) |
| **Country of birth, n (%)** |         |
| Spain                    | 291 (96.3) |
| Morocco                  | 2 (0.7) |
| Bulgaria                 | 2 (0.7) |
| Other                    | 7 (2.3) |
| **Multiple sclerosis type, n (%)** |         |
| Relapsing–Remitting      | 227 (75.2) |
| Secondary Progressive    | 53 (17.5) |
| Clinically Isolated Syndrome | 13 (4.3) |
| Primary Progressive      | 9 (3.0) |
| **Expanded Disability Severity Scale score, n (%)** |         |
| 0–1                      | 123 (40.7) |
| 1.5–3                    | 85 (28.2) |
| 3.5–6                    | 46 (15.2) |
| 6.5 or higher            | 46 (15.2) |
| Unknown                  | 2 (0.7) |
The flu vaccination coverage in 2020–2021 was 55.3% (167/302); by sex, the coverage was 59.8% in women and 47.8% in men. Depending on the country of birth, the coverage ranged from 57.1% in those born in Spain to 9.1% in those born outside Spain. All flu vaccines were administered at primary healthcare centers.

In the bivariate analyses, the variables associated with being vaccinated against 2020–2021 flu were: female sex, history of influenza vaccination in 2019–2020, type of MS, EDSS score, having received the recommendation for annual influenza vaccination at primary healthcare centers, having diabetes mellitus and being born in Spain (Table 3).

### Table 3. Results of bivariate analyses.

|                                      | Flu Vaccination in 2020–2021 |  |  |
|--------------------------------------|------------------------------|---|---|
|                                      | Yes (n = 167)                | No (n = 135) |  p  |
| Sex, n (%)                           |                              |              |    |
| Female                               | 113 (67.7)                   | 76 (56.3)    | 0.042 |
| Male                                 | 54 (32.3)                    | 59 (43.7)    |    |
| Age during 2020–2021 campaign, n (%)|                              |              |    |
| 65 years of age or over              | 18 (10.8)                    | 7 (5.2)      | 0.079 |
| Under 65 years of age                | 149 (89.2)                   | 128 (94.8)   |    |
| Country of birth, n (%)              |                              |              |    |
| Spain                                | 166 (99.4)                   | 125 (92.6)   | 0.003 |
| Other                                | 1 (0.6)                      | 10 (7.4)     |    |
| Place of residence, n (%)            |                              |              |    |
| City of Zaragoza                     | 84 (50.3)                    | 78 (57.8)    | 0.195 |
| Other                                | 83 (49.7)                    | 57 (42.2)    |    |
| Multiple sclerosis type, n (%)       |                              |              |    |
| Relapsing–Remitting                  | 120 (71.9)                   | 107 (79.2)   | 0.047 |
| Clinically Isolated Syndrome         | 4 (2.4)                      | 9 (6.7)      | 0.025 |
| Primary Progressive                  | 7 (4.2)                      | 2 (1.5)      | 0.709 |
| Secondary Progressive                | 36 (21.5)                    | 17 (12.6)    |    |
| Multiple sclerosis outbreaks in 2019, n (%) |                    |              |    |
| 1 or more                            | 17 (10.2)                    | 11 (8.1)     | 0.545 |
| None                                 | 150 (90.8)                   | 124 (91.9)   |    |
| Expanded Disability Severity Scale score, n (%) |                          |              |    |
| 6.5 or higher                        | 31 (18.6)                    | 15 (11.3)    | 0.039 |
| 3.5–6                                | 32 (19.2)                    | 14 (10.5)    | 0.02 |
| 1.5–3                                | 43 (25.7)                    | 42 (31.6)    | 0.888 |
| 0–1                                  | 61 (36.5)                    | 62 (46.6)    |    |
| Recommendation for annual flu vaccination, n (%) |                    |              |    |
| Yes                                  | 85 (50.9)                    | 39 (28.9)    | <0.001 |
| No                                   | 82 (49.1)                    | 96 (71.1)    |    |
| Flu vaccination in 2019–2020, n (%)   |                              |              |    |
| Yes                                  | 116 (69.5)                   | 9 (6.7)      | <0.001 |
| No                                   | 51 (30.5)                    | 126 (93.3)   |    |
Table 3. Cont.

| Flu Vaccination in 2020–2021 | p   |
|-----------------------------|-----|
|                             | Yes (n = 167) | No (n = 135) |
| **Immunosuppressive treatment, n (%)** |               |               |
| Yes                         | 124 (74.3)    | 101 (74.8)    | 0.911  |
| No                          | 43 (25.7)     | 34 (25.2)     |       |
| **Cognitive dysfunction, n (%)** |               |               |
| Yes                         | 3 (1.8)       | 0 (0)         | 0.256  |
| No                          | 164 (98.2)    | 135 (100)     |       |
| **Chronic respiratory disease, n (%)** |               |               |
| Yes                         | 6 (3.6)       | 9 (6.7)       | 0.222  |
| No                          | 161 (96.4)    | 126 (93.3)    |       |
| **Chronic kidney disease, n (%)** |               |               |
| Yes                         | 4 (2.4)       | 1 (0.7)       | 0.385  |
| No                          | 163 (97.6)    | 134 (99.3)    |       |
| **Diabetes mellitus, n (%)** |               |               |
| Yes                         | 11 (6.6)      | 2 (1.5)       | 0.03   |
| No                          | 156 (93.4)    | 133 (98.5)    |       |
| **Chronic cardiovascular disease, n (%)** |               |               |
| Yes                         | 5 (3.0)       | 1 (0.7)       | 0.23   |
| No                          | 162 (97.0)    | 134 (99.3)    |       |
| **Isolated arterial hypertension, n (%)** |               |               |
| Yes                         | 25 (15.0)     | 12 (8.9)      | 0.109  |
| No                          | 142 (85.0)    | 123 (91.1)    |       |
| **Pregnancy, n (%)**        |               |               |
| Yes                         | 3 (1.8)       | 0 (0)         | 0.256  |
| No                          | 164 (98.2)    | 135 (100)     |       |
| **Celiac disease, n (%)**   |               |               |
| Yes                         | 2 (1.2)       | 3 (2.2)       | 0.659  |
| No                          | 165 (98.8)    | 132 (97.8)    |       |
| **Inflammatory bowel disease, n (%)** |               |               |
| Yes                         | 4 (2.4)       | 0 (0)         | 0.131  |
| No                          | 163 (97.6)    | 135 (100)     |       |

In the logistic regression analysis, the variables that maintained their significant association were being female (aOR (95%CI) = 2.12 (1.12–3.99)), having received the 2019–2020 flu vaccine (aOR (95%CI) = 31.82 (14.71–68.86)) and having been born in Spain (aOR (95%CI) = 12.91 (1.07–156.28)) (Table 4).

Table 4. Variables included in the multiple logistic regression model.

| Flu Vaccination in 2020–2021 | aOR (95%CI) | p   |
|-----------------------------|-------------|-----|
|                             | Yes (n = 167) | No (n = 135) |
| **Sex, n (%)**              |             |               |
| Female                      | 113 (67.7)  | 76 (56.3)     | 2.12 (1.12–3.99) | 0.02 |
| Male                        | 54 (32.3)   | 59 (43.7)     | 1               |     |
| **Country of birth, n (%)** |             |               |
| Spain                       | 166 (99.4)  | 125 (92.6)    | 12.91 (1.07–156.28) | 0.046 |
| Other                       | 1 (0.6)     | 10 (7.4)      | 1               |     |
| **Flu vaccination in 2019–2020, n (%)** |         |               |
| Yes                         | 116 (69.5)  | 9 (6.7)       | 31.82 (14.71–68.86) | <0.001 |
| No                          | 51 (30.5)   | 126 (93.3)    | 1               |     |

aOR (95%CI): adjusted odds ratio (95% confidence interval).

In patients taking immunosuppressive medication, an association was detected between being vaccinated against influenza in 2020–2021 and a history of pneumococcal vaccination (PCV13 plus PPSV23) (p < 0.001). Thus, 53.2% (66/124) of those vaccinated for influenza in 2020–2021 had a history of vaccination against pneumococcus, while 26.7% (27/101) of those not vaccinated against influenza in 2020–2021 had a history of vaccination against pneumococcus.
4. Discussion

This is, to our knowledge, the first study to evaluate the 2020–2021 influenza vaccination coverage in people with MS in Spain. The rate obtained is moderate with respect to those documented internationally [12,13,15–17,23,24], where, in the 2020–2021 season, coverages of 45.4% [16] to 63.8% [15] and 68.6% [24] were described in persons with MS in Latin America [16], Ireland [15] and Italy [24], respectively.

Likewise, the rate obtained (55.3%) is higher than that described to date in Spain in patients with MS (from 20.4% in the 2016–2017 season to 41.5% in the 2019–2020 season) [14]. However, such rate is lower than that achieved in Spain during the 2020–2021 campaign in other groups targeted for vaccination, such as healthcare personnel (62.0%), those over 65 years of age (67.7%) and pregnant women (61.9%) [25]. Similarly, the rate obtained is lower than that achieved in other countries during the 2020–2021 campaign in healthcare personnel (75.9% in the USA [26] and 58.9% in Italy [27]) or those over 65 years of age (75.2% in the USA [28], 59.9% in France [29] and 73.5% in Greece [29]), although it was somewhat higher than that documented in pregnant women in the USA (54.5%) [30].

The corresponding percentage of unvaccinated patients (44.7%) is relevant given that, in addition, none had an allergy to the vaccine and almost 90% had at least one other indication for influenza vaccination. This could reflect the lack of awareness among people with MS about the importance of receiving this vaccine. In fact, in studies that have evaluated the hesitancy over the flu vaccine among people with MS, the most common reason they stated for not getting vaccinated was a perceived lack of necessity (the reason given by up to 50.0% of those not vaccinated) [15].

In contrast to other studies conducted prior to the coronavirus pandemic (COVID-19) caused by SARS-CoV-2 [14,15], having received the recommendation by healthcare personnel to be vaccinated was not associated with receiving the flu vaccine in 2020–2021. This may indicate that the context of the COVID-19 pandemic has contributed to patients who have not received this advice and who have not been vaccinated to date deciding to get vaccinated in the 2020–2021 season. Whether this change will continue in other seasons, along with the reasons for vaccination and non-vaccination in the new context of the COVID-19 pandemic, should be evaluated in further research in order to plan improvement strategies for this type of patients.

Meanwhile, it is necessary to implement some interventions aimed at improvement, such as facilitating the accessibility of the vaccine by offering it to patients when they come to the hospital. Thus, several authors have described how improving accessibility to the vaccine is a useful strategy to increase influenza vaccination coverage in other vaccination target groups [31].

The association between being vaccinated and having received the influenza vaccine in the previous season is consistent with that described in studies of other types of patients, in which previous vaccination has been described as an important predictor of flu vaccination [32]. The differences detected in influenza vaccination coverage according to sex (59.8% in women and 47.8% in men) represent an important reversal of the gender gap described so far in Spain, given that men tended to be vaccinated against influenza more frequently than women, regardless of their level of education or place of residence [33]. Thus, in the 2014–2015 season, differences in vaccination coverage by sex of up to 13.4 percentage points were documented in Spain among men aged 80 and over compared to women in that age group [33]. Similar differences have been documented in other types of patients [34–36], such as splenectomized patients (with flu vaccination coverage rates of 63.3% in men and 50% in women) [34] or individuals with chronic obstructive pulmonary disease (with vaccination rates of 62.6% in men and 53.6% in women in the 2012–2013 campaign) [36]. A contributing factor to this unexpected finding is perhaps the pandemic of the new SARS-CoV-2, in which influenza vaccination to avoid possible coinfection with the two viruses may have been a particularly important reason for women to be vaccinated.

As in Yap et al. [15], in the bivariate analysis, a higher EDSS score was associated with influenza vaccination. However, those authors only performed a bivariate analysis,
without adjusting for other variables, as we have done in the multiple logistic regression
analysis. Thus, the validity of comparing our results with those is limited.

On the other hand, the finding that those born outside Spain have been vaccinated
significantly less than those born in Spain represents a health inequity (i.e., an unfair
distribution of resources [37]). This inequity has also been described in other countries,
such as Australia [38] and Italy [39], where flu vaccination coverage ranges from 16.9%
among immigrants to 40.2% among Italian citizens [39]. Given the unfair nature of health
inequities [37], it is especially necessary to develop specific strategies to increase vaccination
among people born outside Spain. To this end, a specific investigation should be carried
out to find out the reasons why these people are undervaccinated.

In Spain, since 2018, the Ministry of Health has recommended vaccination against
pneumococcus (PCV13 plus PPSV23) in people taking immunosuppressive treatments [40].
In particular, in our study, among patients with MS who were taking immunosuppressive
treatment, a history of pneumococcal vaccination (PCV13 plus PPSV23) was associated with
influenza vaccination in 2020–2021. A similar association has been described by several
authors in studies performed before the COVID-19 pandemic in other population groups.
Dominguez et al. in Spain [41] and Hottes et al. in Canada [42] described how people
aged 65 years or older who reported having received the influenza vaccination at least
once were significantly more likely to report having received the PPSV23 vaccine. This
may be because patients who follow the pneumococcal vaccination recommendation are
more likely to accept other vaccines, such as the 2020–2021 influenza vaccine. However,
we cannot confirm this, because the study of patient attitudes was not an objective of
our research.

5. Limitations and Strengths

Among the limitations of this study is the sample size (302), which, although larger
than the sample sizes in other studies [15,17,23,24] (from 101 [23] to 194 [17]), may have
led to imprecise results. Nevertheless, the sample size is greater than 291, which is the
minimum number to be studied considering a confidence level of 95%, a precision of 5%, a
population of 1300 people [20] and an expected vaccination rate of 41.5% [14]. Although our
research was conducted in an MS unit, it provides an example of a systematic approach to
the evaluation of flu vaccination coverage in MS patients that could be carried out in other
MS units [14]. Despite the fact that this was a registry study, there were no missing data
about vaccinations because such information is always recorded in the electronic medical
record (in its vaccines section). This is the first study to evaluate 2020–2021 influenza
vaccination coverage in people with MS in Spain.

6. Conclusions

In Spain, in the COVID-19 era, influenza vaccination coverage in people with MS must
be improved. To this end, it is particularly necessary to develop strategies, especially aimed
at men and those born outside Spain.

Supplementary Materials: The following supporting information can be downloaded at: https://
www.mdpi.com/article/10.3390/vaccines10101766/s1, Table S1: 2020–2021 influenza vaccine recom-
endations. Spanish Ministry of Health.

Author Contributions: I.H.-G. and C.A.-R. participated in the design, the analysis of the data and
the interpretation of the results and they drafted the manuscript; M.G.-R., J.E.-R., J.R.-M. and I.B.-U.
collaborated in the collection of the data, the interpretation of the results and the revision of
the manuscript for important intellectual content. All authors have read and agreed to the published
version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: This study was conducted according to the guidelines of
the Declaration of Helsinki and approved by the Research Ethics Committee of the Autonomous
Community of Aragon (protocol code: C.P.–C.I. P21/417; date of approval: 20 October 2021).
Informed Consent Statement: Institutional approval was provided by the Research Ethics Committee of the Autonomous Community of Aragon (protocol code: C.P.–C.I. PI21/417) and the need for informed consent was waived.

Data Availability Statement: The data are contained within the article.

Acknowledgments: Collaborators of the Vaccine Working Group: Rosa Mareca, Purificación Prieto, Javier Moliner, Jose Ignacio García and Cristina Íñiguez.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. World Health Organization. Up to 650,000 People Die of Respiratory Diseases Linked to Seasonal Flu Each Year. Available online: https://www.who.int/news/item/13-12-2017-up-to-650-000-people-die-of-respiratory-diseases-linked-to-seasonal-flu-each-year (accessed on 15 September 2022).

2. Ministerio de Sanidad. Preguntas y Respuestas Sobre la Vacunación frente a la Gripe: Información Para Ciudadanía. Septiembre 2020. Available online: https://www.salud.gob.es/campanas/campanas21/gripecambio.htm (accessed on 3 December 2020).

3. Delgado-Sanz, C.; Oliva, J.; Mazagatos, C.; Larrauri, A.; Pozo, F.; Casas, I. Informe de Vigilancia de la Gripe en España. Temporada 2019–2020; Instituto de Salud Carlos III. Sistema de Vigilancia de la Gripe en España: Madrid, Spain, 2020.

4. Jakimowski, D.; Weinstock-Guttman, B.; Ramanathan, M.; Dwyer, M.G.; Zivadinov, R. Infections, Vaccines and Autoimmunity: A Multiple Sclerosis Perspective. *Vaccines* 2020, 8, 50. [CrossRef] [PubMed]

5. Filippi, M.; Capra, R.; Centonze, D.; Gasperini, C.; Patti, F.; Perini, P.; Pozzilli, C.; Rocca, M.A.; Uccelli, A.; Trojano, M. Therapeutic recommendations and seasonal influenza vaccine for multiple sclerosis patients in treatment with ocrelizumab: An expert consensus. *J. Neurol*. 2021, 268, 1540–1543. [CrossRef] [PubMed]

6. Grohskopf, L.A.; Sokolow, L.Z.; Broder, K.R.; Walter, E.B.; Bresee, J.S.; Fry, A.M.; Jernigan, D.B. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices—United States, 2017–2018 Influenza Season. *MMWR Recomm. Rep.* 2017, 66, 1–20. [CrossRef]

7. World Health Organization. WHO Regional Office for Europe Recommendations on Influenza Vaccination for the 2020/2021 Season During the Ongoing COVID-19 Pandemic (2020). Available online: https://apps.who.int/iris/bitstream/handle/10665/335721/WHO-EURO-2020-1141-4087-55342-eng.pdf?sequence=1&isAllowed=y (accessed on 9 August 2022).

8. Otero-Romero, S.; Rodríguez-García, J.; Vilella, A.; Ara, J.R.; Brieva, L.; Calles, C.; Carmona, O.; Casanova, V.; Costa-Frossard, L.; Eichau, S.; et al. Recommendations for vaccination in patients with multiple sclerosis who are eligible for immunosuppressive therapies: Spanish consensus statement. *Neurología* 2021, 36, 50–60. [CrossRef]

9. Farez, M.F.; Correale, J.; Armstrong, M.J.; Rae-Grant, A.; Gloss, D.; Donley, D.; Holler-Managan, Y.; Kachuck, N.J.; Jeffery, D.; Beilman, M.; et al. Practice guideline update summary: Vaccine-preventable infections and immunization in multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology* 2019, 93, 584–594. [CrossRef] [PubMed]

10. Lebrun, C.; Vukusic, S.; French Group for Recommendations in Multiple Sclerosis (France4MS) and the Société Francophone de la Sclérose En Plaques (SFSEP). Immunization and multiple sclerosis: Recommendations from the French multiple sclerosis society. *Mult. Scler. Relat. Disord.* 2019, 31, 173–188. [CrossRef]

11. Riva, A.; Barcella, V.; Benatti, S.V.; Capobianco, M.; Capra, R.; Cinque, P.; Comi, G.; Fasolo, M.M.; Franzetti, F.; Galli, M.; et al. Vaccinations in patients with multiple sclerosis: A Delphi consensus statement. *Mult. Scler.* 2021, 27, 347–359. [CrossRef]

12. Akmatov, M.K.; Holstiege, J.; Steffen, A.; Bätz, J. Utilization of influenza vaccination among chronically ill individuals in Germany: A nationwide claims-based analysis. *Vaccine* 2021, 39, 952–960. [CrossRef] [PubMed]

13. Marrie, R.A.; Kosowan, L.; Cutter, G.R.; Fox, R.; Saltar, A. Uptake and Attitudes About Immunizations in People with Multiple Sclerosis. *Neurol. Clin. Pract.* 2021, 11, 327–334. [CrossRef] [PubMed]

14. Hernández-García, I.; García-Redondo, M.; Rodríguez-Montolio, J.; Bengoa-Urrungoechea, I.; Espinosa-Rueda, J.; Aibar-Romón, C.; Vaccine Working Group. Influenza Vaccination Coverage among Multiple Sclerosis Patients: Evolution over Time and Associated Factors. *Vaccines* 2022, 10, 1154. [CrossRef]

15. Yap, S.M.; Al Hinai, M.; Gaughan, M.; Callanan, I.; Kearney, H.; Tubriddy, N.; McGuigan, C. Vaccine hesitancy among people with multiple sclerosis. *Mult. Scler. Relat. Disord.* 2021, 56, 103236. [CrossRef]

16. Rojas, J.I.; Henestroza, P.; Giachello, S.; Patrucco, L.; Cristiano, E.; Carnero Contentti, E. Influenza vaccination status in multiple sclerosis patients from Latin America. *J. Neurovirol.* 2021, 27, 750–754. [CrossRef] [PubMed]

17. Ziello, A.; Scavone, C.; Di Battista, M.E.; Salvatore, S.; Di Giulio Cesare, D.; Moreggia, O.; Allegorico, L.; Sagnelli, A.; Barbato, S.; Manzo, V.; et al. Influenza Vaccine Hesitancy in Patients with Multiple Sclerosis: A Monocentric Observational Study. *Brain Sci.* 2021, 11, 890. [CrossRef] [PubMed]

18. Ministerio de Sanidad: Vacunas y Programa de Vacunación. Histórico de Recomendaciones de Vacunación Frente a la Gripe. Available online: https://www.mscbs.gob.es/profesionales/saludPublica/prevPromocion/vacunaciones/programasDeVacunacion/gripe/Historico_RecomendacionesVacunacion.htm (accessed on 18 February 2022).
19. Coronaviridae Study Group of the International Committee on Taxonomy of Viruses. The species Severe acute respiratory syndrome-related coronavirus: Classifying 2019-nCoV and naming it SARS-CoV-2. Nat. Microbiol. 2020, 5, 536–544. [CrossRef]
20. Heraldo de Aragón. Cerca de 1300 Personas Tienen Esclerosis Multiple en Aragón. Available online: https://www.heraldo.es/noticias/aragon/2019/05/30/cerca-1300-personas-tienen-esclerosis-multiple-aragon-126606-300.html (accessed on 18 September 2022).
21. Lublin, F.D.; Reingold, S.C.; Cohen, J.A.; Cutter, G.R.; Sorensen, P.S.; Thompson, A.J.; Wolinsky, J.S.; Balcer, L.J.; Banwell, B.; Barkhof, F.; et al. Defining the clinical course of multiple sclerosis: The 2013 revisions. Neurology 2014, 83, 278–286. [CrossRef]
22. Kurtzke, J.F. Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS). Neurology 1983, 33, 1444–1452. [CrossRef]
23. Auriel, E.; Gadoth, A.; Regev, K.; Karni, A. Seasonal and H1N1v influenza vaccines in MS: Safety and compliance. J. Neurol. Sci. 2012, 314, 102–103. [CrossRef]
24. Mariscalco, G.T.; Scavone, C.; Moreg gia, O.; Di Giulio Cesare, D.; Aiezza, M.L.; Guglielmi, G.; Longo, G.; Maiolo, M.; Raiola, E.; Russo, G.; et al. Flu vaccination in multiple sclerosis patients: A monocentric prospective vaccine-vigilance study. Expert Opin. Drug Saf. 2022, 21, 979–984. [CrossRef] [PubMed]
25. Ministerio de Sanidad. Coberturas de Vacunación. Datos Estadísticos. Available online: https://www sanidad.gob.es/profesionales/saludPublica/prevPromocion/vacunaciones/calendario-y-coberturas/coberturas/home.htm (accessed on 10 May 2022).
26. Centers for Disease Control and Prevention. Flu and Tdap Vaccination Coverage Among Pregnant Women-United States, 2011. Available online: https://www.cdc.gov/flu/fluvaxview/pregnant-women-apr2021.htm (accessed on 19 September 2022).
27. Centers for Disease Control and Prevention. Flu Vaccination Coverage, United States, 2020–2021 Influenza Season. Available online: https://www.cdc.gov/flu/fluuvaxview/hcp-coverage_1920-21-estimates.htm (accessed on 17 September 2022).
28. Dettori, M.; Arghittu, A.; Deiana, G.; Azara, A.; Masia, M.D.; Palmieri, A.; Spano, A.L.; Serra, A.; Castiglia, P. Influenza Vaccination Strategies in Healthcare Workers: A Cohort Study (2018–2021) in an Italian University Hospital. Vaccines 2021, 9, 971. [CrossRef] [PubMed]
29. Centers for Disease Control and Prevention. Flu Vaccination Coverage, United States, 2020–2021 Influenza Season. Available online: https://www.cdc.gov/flu/fluuvaxview/hcp-coverage_2021estimates.htm (accessed on 19 September 2022).
30. Centers for Disease Control and Prevention. Influenza Vaccination Coverage among Health Care Personnel-United States, 2020–2021 Influenza Season. Available online: https://www.cdc.gov/flu/fluuvaxview/pregnant-women-apr2021.htm (accessed on 19 September 2022).
31. De Sarro, C.; Papadopoli, R.; Cautela, V.; Nobile, C.; Pileggi, C.; Pavia, M. Vaccination coverage among health-care workers: Pre-post intervention study to assess impact of an on-site vaccination-dedicated clinic. Expert Rev. Vaccines 2021, 20, 753–759. [CrossRef] [PubMed]
32. Dominguez, A.; Soldevila, N.; Toledo, D.; Godoy, P.; Castilla, J.; Force, L.; Morales, M.; Mayoral, J.M.; Egurrola, M.; Tamames, S.; et al. Working Group of the Project PI12/02079. Factors Associated with Influenza Vaccination of Hospitalized Elderly Patients in Spain. PLoS ONE 2016, 11, e0147931. [CrossRef] [PubMed]
33. García Calvente, M.M.; del Río Lozano, M.; Maroto Navarro, G.; Sánchez-Cantalejo Garrido, C.; Fernández Ruiz, E. Informe Salud y Género en Andalucía 2018; Consejería de Salud, Junta de Andalucía: Sevilla, Spain, 2018.
34. Hernández-García, I.; Chauré-Pardos, A.; Aíbar-Remón, C.; Grupo de trabajo vacunas HCUUL. Influenza vaccination coverages and related factors among splenectomy patients from a health sector in Zaragoza (Spain). Rev. Esp. Salud. Publica 2019, 93, e201911095. [PubMed]
35. Fuentes-Alonso, M.; Jimenez-Garcia, R.; Lopez-de-Andres, A.; Zamorano-Leon, J.J.; Carabantes-Alarcon, D.; Jimenez-Trujillo, I.; Sanz-Rojo, S.; de Miguel-Diez, J. Time Trends (2012–2020), Sex Differences and Predictors for Influenza Vaccination Uptake among Individuals with Chronic Obstructive Pulmonary Disease in Spain. J. Clin. Med. 2022, 11, 1423. [CrossRef]
36. Ruiz Azcona, L.; Román-Rodriguez, M.; Llor Bove, M.; Van Boven, J.F.M.; Santibañez Marguillo, M. Prevalence of seasonal influenza vaccination in chronic obstructive pulmonary disease (COPD) patients in the Balearic Islands (Spain) and its effect on COPD exacerbations: A population-based retrospective cohort study. Int. J. Environ. Res. Public Health 2020, 17, 4027. [CrossRef]
37. Arcaya, M.C.; Arcaya, A.L.; Subramanian, S.V. Inequalities in health: Definitions, concepts, and theories. Glob. Health Action 2015, 8, 27106. [CrossRef]
38. Karki, S.; Dyda, A.; Newall, A.; Heywood, A.; McIntyre, C.R.; McIntyre, P.; Banks, E.; Liu, B. Comparison of influenza vaccination coverage between immigrant and Australian-born adults. Vaccine 2016, 34, 6388–6395. [CrossRef]
39. Fabiani, M.; Riccardo, F.; Di Napoli, A.; Gargiulo, L.; Declich, S.; Petrelli, A. Differences in Influenza Vaccination Coverage between Adult Immigrants and Italian Citizens at Risk for Influenza-Related Complications: A Cross-Sectional Study. PLoS ONE 2016, 11, e0166517. [CrossRef] [PubMed]
40. Limia Sánchez, A.; Pérez Martín, J.J.; Navarro Alonso, J.A.; Urbiztondo Perdices, L.C.; Borràs Ló pez, E.; Armona Aquerreta, J.M.; López Hernández, S.; Soler Soneira, M.; de Viarece Torres de Mier, M. Vacunación en Grupos de Riesgo de Todas las Edades y en Determinadas Situaciones; Ministerio de Sanidad, Consumo y Bienestar Social: Madrid, Spain, 2018.
41. Dominguez, A.; Soldevila, N.; Toledo, D.; Godoy, P.; Torner, N.; Force, L.; Castilla, J.; Mayoral, J.M.; Tamames, S.; Martin, V.; et al. Project PI12/02079 Working Group. Factors associated with pneumococcal polysaccharide vaccination of the elderly in Spain: A cross-sectional study. Hum. Vaccin. Immunother. 2016, 12, 1891–1899. [PubMed]
42. Hottes, T.S.; Skowronski, D.M.; Hiebert, B.; Janjua, N.Z.; Roos, L.L.; Van Caeseele, P.; Law, B.J.; De Serres, G. Influenza vaccine effectiveness in the elderly based on administrative databases: Change in immunization habit as a marker for bias. PLoS ONE 2011, 6, e22518. [CrossRef]