SHORT REPORT

Coverage and predictors of influenza vaccination in patients with cystic fibrosis in a campaign with a mobile phone text messaging intervention

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ABSTRACT
Annual influenza vaccination is considered the best protection against influenza infection. We analyzed the influenza vaccine coverage (IVC) in cystic fibrosis (CF) patients and evaluated the factors associated with the IVC, including the effect of text-message/SMS reminders.

We performed a cross-sectional study in the Community of Madrid (Spain) in 2015. The target population was people with CF older than 6 months of age at the beginning of the flu vaccination campaign. The IVC was calculated according to the study variables.

A total of 445 CF patients were analyzed. In 2015, IVC reached 67.9% and was higher in children and women. The main factor associated with flu vaccination was having been vaccinated in the previous campaign (aOR 14.36; IC95%: 8.48–24.32).

The probability of being vaccinated after receiving the SMS was more than twice than for those who did not receive it, although no statistical significance was reached.

In conclusion the IVC of patients with CF is high, but it still has room for improvement. SMS reminders sent to CF patients might improve influenza vaccine uptake.

Introduction
Cystic fibrosis (CF) is a complex multi-system rare disease, but lung disease accounts for nearly 85% of the mortality. Influenza is strongly associated with pulmonary exacerbations, higher hospitalization, disease progression and increased propensity for bacterial infections.1,2

Annual influenza vaccination is considered the best protection against influenza infection and is recommended for these patients by the European Cystic Fibrosis Society Vaccination Group.3

In the Community of Madrid (CM) influenza vaccination is recommended and administered free of charge to the population aged 60 and over, in the patients with chronic medical conditions, pregnant women, some professional groups and people who live with or care for persons at high risk of serious influenza complications. Flu vaccines are administered in primary care health centers, accredited private medical centers, hospitals, nursing homes, prisons, etc. As in previous years, flu vaccination campaign messages diffusion is tailored to general population and is disseminated via posters, fact sheets and adverts in media. The 2015 campaign also included SMS (short message service) reminders with the recommendation for vaccination against influenza to high risk population.

Text-messaging interventions (SMS) have proved to be cost-effective to improve health and care delivery, reminding appointment attendance, adherence to treatment and better self-management.4 A recent systematic review described that patient’s reminders probably improved receipt of influenza vaccinations based on moderated certainty evidence.5

In 2015 the Madrid Regional Health Authority implemented the information system for Rare Diseases (SIERMA), as part of the Spanish Rare Diseases Registry,6 improving epidemiological information on CF.

The objectives of this study were: 1) to analyze the influenza vaccine coverage (IVC) in CF patients in the CM during the 2015 influenza vaccination campaign; and 2) to evaluate the factors associated with the IVC, including the effect of text-message/SMS vaccination reminders.

Results
A total of 445 CF patients were analyzed, 93.3% Spanish-born, 51.5% women and 34.4% under 15 years old (Table 1). The median age was 22.0 (interquartile range 14.0). The most common comorbidity was diabetes mellitus (19.8%).

In 2015, IVC reached 67.9% (70.7% women and 64.8% men, p-value = 0.18) (Table 2). No statistically significant differences were observed with respect to IVC in 2014 (67.0%; p-value = 0.85). IVC was higher in children (81.0% vs. 61.0% adults, p-value < 0.01) and in autochthonous population (60.9% vs. 40.0% in foreign-born, p-value < 0.01). Cardiopathy was the comorbidity with higher vaccination coverage (100.0%; six cases). In patients vaccinated in three or more previous campaigns the coverage was 91.0%.

Patients who were vaccinated in the previous year had the highest probability of being vaccinated in 2015 (aOR 14.36; IC95%: 8.48–24.32) (Table 2). Women and children under
Two hundred and twenty-one cases were vaccinated within the first four weeks after the beginning of the flu campaign (Figure 1) and 9% of them (CI95% 5.9–13.6%) have not been vaccinated the previous year. Two hundred and five SMS were sent and 77 cases were vaccinated afterwards. Of them, 29.8% (CI95% 20.8–40.8%) had not been vaccinated the previous year. The probability of being vaccinated after receiving the SMS was more than twice than for those who did not receive the SMS, although no statistical significance was reached (cOR: 2.26 CI95% 0.72 to 7.04).

### Discussion

To the best of our knowledge, this is the first report on IVC for CF patients from a population-based registry in Spain. The IVC in 2015 was higher in children. The main factor associated with flu vaccination was having been vaccinated in the previous year. The SMS might encourage vaccination of people who had never received the influenza vaccine before.

The IVC for CF patients in this study was similar to that reported by other authors in other countries. Two studies from the USA described an IVC of 76.4% in 1997, 88.9% in 2010 and 91.0% in 2011. Within Europe, in the United Kingdom, one study reported that 65% of CF patients under 18 years old were vaccinated against influenza in 2003. A multicenter study in France estimated an IVC of 79.9% in 2005 and two more recent studies in that country considering children, described similar IVC in 2007 and 2010 (around 67.0%). A multicenter study from Italy reported for children an IVC of 91.2% in 2009. Comparisons should be made with caution, most of the studies were based in specialized centers and higher coverages have been attributed to the management of this complex disease in these centers.

Several studies have found higher flu vaccination rates in children than in adults with CF reaching more than 80%, and exceeding the coverage seen in children with other risk conditions. Nevertheless, one study described that IVC in children decreased with increasing age, and higher coverages have been attributed to the management of this complex disease in these centers.
It has been observed that children with CF are advised to receive an influenza vaccination more often compared to patients with other chronic diseases. However, an Australian retrospective audit of immunization registers of children with CF aged 6 months to 7 years found that only 27% were given influenza vaccine in 2007, although 92% were up to date with routine immunisations. In our study, the higher coverages in CF children than in adults could be explained at least partially by the fact that parents are responsible for their children’s vaccination. Zindalini et al. suggest that parental supervision plays a major role in adherence to medical management of CF.

The association between influenza vaccination and having received the previous seasonal or pandemic flu vaccine has already been described and highlights the importance of the first uptake to engage with influenza immunization as an usual behaviour.

Although the impact of the SMS reminder on IVC was underpowered to detect statistically significant differences, a very interesting result was the immunization after SMS delivery of unvaccinated people in the previous year (despite the non-feasibility to establish a cause-effect relationship between the SMS reception and the immunization with this type of study). Further studies should ask the patients or their parents in the case of children about the influence of the SMS reminder in the vaccination decision. Studies in the United Kingdom, Australia and the USA have shown that the rate of influenza vaccination may be increased by using mobile phone-based text messages. The use of clinical records avoids potential recall and reporting biases but they have the limitation of a possible lack of registry completeness and quality. The reasons for non-vaccination or for vaccination could not be analysed in this study because this information was not available.
As a strength of this study, it is important to mention that it is a population-based one, and that is even more valuable in studies of rare diseases, due to the scarcity of cases and the lack of knowledge about them.

In conclusion, the IVC of patients with CF is high, but it still has room for improvement. The main factor associated with vaccination was being vaccinated in the previous campaign. To improve the IVC it is critical a health professional recommendation and to enhance patients education. SMS reminders sent to patients might improve influenza vaccine uptake.

Materials and methods
This was a population-based cross-sectional study in the CM, Spain, with 6,436,996 inhabitants in 2015. The information source was SIERMA. All the cases were further ascertained through reviews of electronic medical records. Vaccination data was provided by the regional public health information system, which is maintained from clinical records.

The target study population was all people with CF older than 6 months of age at the beginning of the flu vaccination campaign (October 2015).

The variables studied were sex, age (at 30 September 2015), country of birth, the presence of other comorbidities and information on previous flu vaccinations campaigns.

An SMS reminder of the recommendation for vaccination against influenza was sent to all people with CF or their parents, who had not been vaccinated within the first four weeks after the beginning of the campaign.

A descriptive analysis of the study population was performed. The IVC was calculated according to the study variables. Categorical variables were compared using the Chi-square test. Binary logistic regression was used to identify factors associated with being vaccinated or not. The selection threshold for entry into multivariate analysis was p-value 0.20 or less. Results were expressed as crude (cOR) and adjusted odds ratios (aOR) with 95% confidence intervals (CI). Analyses were undertaken using IBM SPSS Statistics 21.0.

The study was conducted ensuring the confidentiality of the information in accordance with the legislation of SIERMA and the Spanish legislation on data protection. The prior consent of patients and approval by an ethics committee were not required, given the characteristics of the study and that legislation.

Disclosure of potential conflict of interest
The authors report no conflict of interest.

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References
1. Wat D, Gelder C, Hibberts S, Cafferty F, Bowler I, Pierrepoint M, Evans R, Doull I. The role of respiratory viruses in cystic fibrosis. J Cyst Fibros. 2008;7:320–328. doi:10.1016/j.jcf.2007.12.002.
2. Clifton JJ, Kastelik JA, Peckham DG, Hale A, Denton M, Etherington C, Conway SP Ten years of viral and non-bacterial serology in adults with cystic fibrosis. Epidemiol Infect [Internet]; 2008 accessed 2016 Jul 13. 136. http://www.journals.cambridge.org/abstract_S0950268807008278
3. Malfrout A, Adam G, Ciofu O, Döring G, Knoop C, Lang AB, Van Damme P, Dab I, Bush A. Immunisation in the current management of cystic fibrosis patients. J Cyst Fibros. 2005;4:77–87. doi:10.1016/j.jcf.2004.10.003.
4. Varma DS, Hart M, McIntyre DS, Kwiatkowski E, Cotter LB. A research protocol to test the effectiveness of text messaging and reminder calls to increase service use referrals in a community engagement program. JIMIR Res Protoc. 2016;5:e133. doi:10.2196/resprot.5854.
5. Jacobson Vann JC, Jacobson RM, Coyne-Beasley T, Asafu-Adjei JK, Szilagyi PG. Patient reminder and recall interventions to improve immunization rates. Cochrane Database Syst Rev. 2018;1:CD003941.
6. Zoni AC, Domínguez Berjón MF, Barceló E, Esteban Vasallo MD, Abaitua I, Jiménez Villa J, Margolles Martíns M, Navarro C, Posada M, Ramos Aceituro JM, et al. Identifying data sources for a national population-based registry: the experience of the Spanish Rare Diseases Registry. Public Health. 2015;129:271–275. doi:10.1016/j.puhe.2014.12.013.
7. Marshall BC, Henshaw C, Evans DA, Bleyl K, Alder S, Liou TG. Influenza vaccination coverage level at a cystic fibrosis center. Pediatrics. 2002;109:E80–80. doi:10.1542/peds.109.5.e80.
8. Patient Registry. Annual data report 2012. Bethesda (MD): Cystic Fibrosis Foundation; 2012.
9. Wat D, Gelder C, Hibberts S, Bowler I, Pierrepoint M, Evans R, Doull I. Is there a role for influenza vaccination in cystic fibrosis? J Cyst Fibros. 2008;7:85–88. doi:10.1016/j.jcf.2007.05.002.
10. Murris-Espin M, Aubert M, Bosdure E, Dubus J-C. Influenza vaccination coverage in patients with cystic fibrosis followed at 12 care centers in the Greater South Region of France for the season 2005/2006. Vaccine. 2008;26:5612–5618. doi:10.1016/j.vaccine.2008.07.095.
11. Tuppin P, Samson S, Well A, Ricordeau P, Allemand H. Influenza vaccination coverage in France in 2007–2008: contribution of vaccination refund data from the general health insurance scheme. Médecine Mal Infect. 2009;39:780–788. doi:10.1016/j.medmal.2009.08.013.
12. Masson A, Launay O, Delaisi B, Bassinet L, Remus N, Lebourgeois M, Chedevergne F, Bally C, Foucaud P, Corvol H, et al. Vaccine coverage in CF children: A French multicenter study. J Cyst Fibros Off J Eur Cyst Fibros Soc. 2015;14:615–620. doi:10.1016/j.jcf.2015.04.006.
13. Dallapé S, Maniscalco E, Carloni F, Marino MG, Cioffi Degli Atti ML, Gesualdo F, Romano M, Giannattasio A, Guarino A, Carloni R, Borgia P, et al. Immunization coverage and timeliness of vaccination in Italian children with chronic diseases. Vaccine. 2012;30:5172–5178. doi:10.1016/j.vaccine.2011.02.099.
14. Ortiz JR, Neuzil KM, Victor JC, Aitken ML, Goss CH. Predictors of influenza vaccination in the cystic fibrosis foundation patient registry, 2006 through 2007. Chest. 2010;138:1448–1455. doi:10.1378/chest.10-0356.
15. Giannattasio A, Squeglia V, Vecchio AL, Russo MT, Barbarino A, Carломagno R, Guarino A. Pneumococcal and influenza vaccination rates and their determinants in children with chronic medical conditions. Ital J Pediatr. 2010;36:1. doi:10.1186/1824-7288-36-28.
16. Cugley K, Crawford N, Royle J, Elia S, Massie J. Immunisation rates of children with cystic fibrosis using the Australian Childhood Immunisation Register. J Paediatr Child Health. 2010;46:768–771. doi:10.1111/j.1440-1754.2010.01836.x.
17. Zindani GN, Streetman DD, Streetman DS, Nasr SZ. Adherence to treatment in children and adolescent patients with cystic fibrosis. J Adolesc Health Off Publ Soc Adolesc Med. 2006;38:13–17. doi:10.1016/j.jadohealth.2004.09.013.
18. Jiménez-García R, Esteban-Vasallo MD, Rodríguez-Rieiro C, Hernandez-Barrera V, Domínguez-Berjón MF, Carrasco Garrido P, Lopez de Andres A, Cameno HM, Iniesta FD, Astray-Mochales J. Coverage and predictors of vaccination against 2012/13 seasonal influenza in Madrid, Spain: analysis of population-based computerized immunization registries and clinical records. Hum Vaccines Immunother. 2014;10:449–455. doi:10.4161/hv.27152.
19. Herrett E, Williamson E, van Staa T, Ranopa M, Free C, Chadborn T, Goldacre B, Smeeth L. Text messaging reminders for influenza vaccine in primary care: a cluster randomised controlled trial (TXT4FLUJAB). BMJ Open. 2016;6:e010069. doi:10.1136/bmjopen-2015-010069.
20. Regan AK, Bloomfield L, Peters I, Effler PV. Randomized controlled trial of text message reminders for increasing influenza vaccination. Ann Fam Med. 2017;15:507–514. doi:10.1370/afm.2120.
21. Stockwell MS, Kharbanda EO, Martinez RA, Vargas CY, Vawdrey DK, Camargo S. Effect of a text messaging intervention on influenza vaccination in an urban, low-income pediatric and adolescent population: a randomized controlled trial. JAMA. 2012;307:1702–1708. doi:10.1001/jama.2012.502.