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Effect of mobile phone text messaging for improving the uptake of influenza vaccination in patients with rare diseases

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ABSTRACT

Objectives: Influenza vaccine is recommended in some chronic medical conditions, including several rare diseases. The objectives of the study were to assess the effect of text message reminders on influenza vaccination uptake of patients with selected rare diseases and delayed vaccination, and to describe their characteristics.
Methods: Quasi-experimental pre-post intervention study performed along the 2016 influenza vaccination campaign in the Autonomous Community of Madrid. Unvaccinated patients diagnosed with a selected rare disease were targeted for intervention. SMS were sent to them at least one month after the beginning of the campaign, in four consecutive weeks. Those with no mobile phones available or no certainty of message reception, were assigned as controls. The association between the reception of the SMS and vaccination uptake was assessed using multiple poisson regression models.
Results: Of 69.040 patients with delayed vaccination, 87.2% received an SMS reminder in the asigned contact mobile telephone. Global influenza vaccine coverage reached 41.3%. The uptake of influenza vaccine was significantly higher among those receiving the reminder (9.3% vs. 7.1% in the control group, $p < 0.001$). Those who received a SMS reminder were 30% more likely to uptake seasonal influenza vaccine. By sex and age, the reception of the reminder was associated with a significantly higher probability of vaccination in men ≥65 years with at least a concurrent chronic condition (IRR: 1.58, CI95%: 1.25–2.00). Among women, this higher probability was detected in those between 14 and 64 years of age (IRR: 1.41, CI95%: 1.22–1.63), and ≥65 years without concurrent chronic conditions (IRR: 1.40, CI95%: 1.05–1.89).
Conclusion: Although the intervention was modestly effective, it proved beneficial in some cases. It can be an additional strategy to improve vaccine uptake, since it is simple, feasible, affordable and easily scalable, particularly when immunization and target population data are available in population registries.

1. Introduction

Seasonal influenza is a serious public health problem that causes severe illness and death in high-risk populations. In Spain, the disease burden has been recently estimated, with an average of more than 800,000 cases of influenza-like illness attended annually in primary care and, in regards to severe cases, annual average hospitalization rates of 16.5 and 18.9/100,000 habitants in 0–4 years, and ≥65 years, respectively [1]. Influenza vaccination is the most effective way to prevent disease. The Autonomous Community of Madrid recommends and provides free vaccines against influenza in the population aged 60 and over, in the population with chronic medical conditions, pregnant women, some professional groups and persons who live with or care for persons at high risk for influenza-related complications [2].

In Europe, rare diseases are defined as life-threatening or chronically debilitating diseases –mostly inherited– that affect less than 5 in 10,000 of the general population [3]. Many of them affect the cardiovascular, respiratory, nervous and/or immune system, with the consequent increased risk for severe influenza illness and indication for vaccination [4]. In 2015 the Autonomous Community of Madrid implanted the Regional Registry for Rare Diseases (SIERMA), a population based disease registry in the context of the Spanish Rare Diseases Registry [5]. This database allows the identification of these patients, and therefore their selection for

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concrete interventions and subsequent evaluation. Although no specific data on influenza vaccination coverage in these patients are available, it could probably be suboptimal. Vaccination coverage in people with a chronic condition was 39.6% in our region in the 2012 campaign [6]. Health Surveys in Spain show low vaccination coverages with an apparent descending trend since the pandemic season in 2009 [7,8].

In the last years the field of information and communication technologies has greatly developed. Patients can benefit from the use of new media [9]. A recent systematic review estimated that patients reminders probably improved receipt of vaccinations for childhood and adult influenza based on moderated certainty evidence [10]. Mobile telephone text message reminders have become a widely used tool in health interventions, both alone or connected to another comprehensive health intervention system [11]. Text-messaging interventions have proved effective for example at addressing diabetes self-management or medication adherence [12]. They have been identified as an element with potential for improving vaccine uptake [13], although limited evidence exists to determine the most efficacious intervention characteristics.

The General Directorate of Public Health established in the 2016 influenza vaccination campaign a series of measures aimed at promoting vaccination against influenza. These measures included the sending of reminders via Short Messages Service (SMS) to selected patients based on the information collected in SIERMA and in their electronic medical records. The objectives of the study were to assess the effect of text message reminders on influenza vaccination uptake of patients with selected rare diseases and delayed influenza vaccination and to describe the characteristics of this target population.

2. Methods

2.1. Design and study population

This is a quasi-experimental pre-post intervention study. The study population consisted of all patients aged 6 months and over with access to the Madrid Regional Public Health System at the beginning of the influenza vaccination campaign (October 17, 2016) and diagnosed with a rare disease with indication for influenza vaccination identified from the SIERMA. This population-based registry collects sociodemographic and clinical data of patients diagnosed with rare diseases using different sources of information (clinical records, mortality records, laboratory data...) [5]. The selected diagnoses included disorders involving an immune mechanism, neurological disorders, rheumatoid and cardiopulmonary diseases (Table 1).

Table 1
List of rare diseases with indication for influenza vaccination selected for the intervention, with their corresponding codes in the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

Selected rare disease	ICD-9-CM codes
Sarcoidosis	135
Mycosis fungoides/Letterer-siwe disease	202.1/202.5
Polycythemia vera	238.4
Cystic fibrosis	277.0
Amyloidosis	277.30
Deficiency of immunity: humoral/cell-mediated immunity/combined	279.0/279.1/279.2/279.4
Hereditary/hereditary hemolytic anemias	282/283
Aplastic anemia	284
Other deficiency anemias/Other and unspecified anemias	281/285
Coagulation defects	286
Purpura and other hemorrhagic conditions	287
Diseases of white blood cells/Other diseases of blood and blood-forming organs	288/289
Psychoses with origin specified to childhood (autism and others)	299
Other specified mental retardation	318
Cerebral degenerations usually manifest in childhood/Other cerebral degenerations	330/331
Other extrapyramidal disease and abnormal movement disorders	333
Spinocerebellar disease/Anterior horn cell disease/Other diseases of spinal cord	334/335/336
Disorders of the autonomic nervous system	337
Other demyelinating diseases of central nervous system	341
Infantile cerebral palsy	343
Rheumatic chorea	392
Primary pulmonary hypertension	416.0
Other diseases of pulmonary circulation	417
Acute miocarditis/Cardiomyopathy	422/425
Moyamoya disease	437.5
Polyarteritis nodosa and allied conditions	446
Extrinsic allergic alveolitis	495
Coal workers' pneumoconiosis	500
Asbestosis/Pneumoconiosis due to other silicates/other inorganic dust/unspecified	501/502/503/505
Pneumonopathy due to inhalation of other dust	504
Respiratory conditions due to other and unspecified external agents	508
Other alveolar and parietoalveolar pneumonopathy	516
Lung involvement in conditions classified elsewhere/Other diseases of lung	517/518
Chronic hepatitis/Primary biliary cirrhosis	571.4/571.6
Diffuse diseases of connective tissue	710
Felty's syndrome/Polyarticular juvenile rheumatoid arthritis	714.1/714.3
Polymyalgia rheumatica	725
Other congenital anomalies of heart	746
Other congenital anomalies of circulatory system	747

2.2. Information sources and variables

For each person, information on sex, date and country of birth, health centre and contact telephone numbers was obtained from the Individualized Health Card (IHC) database, which collects information from people with access to state-provided healthcare (95% of the population). Other chronic conditions with indication for influenza vaccination were identified in the electronic clinical record in primary care (ECRPC) through their codes in the International Classification of Primary Care (ICPC). In the case of inespecific ICPC codes (chronic hepatopathy and other malignancies), the descriptive clinical text was used to discern the disease. Information on the socioeconomic status (SES) of the person was not included in the ECRPC nor IHC. The SES may be inferred from the general sociodemographic composition of the area of residence using census-derived information. A deprivation index based on census data of 2011 was used to assign SES to each patient. This deprivation index includes 4 indicators, related to work and education [14]. The corresponding quintile of the deprivation index was assigned to each primary care health centre and, by extension, to the patients assisted in it, which mostly live in its vicinity. No parental information for children was obtained.

Individual records of vaccine doses administered during the seasonal vaccination campaign from October 17, 2016 to February 28, 2017 were obtained from the Public Health Information System. This vaccination registry was created in 2005 and it contains nominal information of all the vaccine doses administered in public and private health centres [15]. Similarly, the records corresponding to the four previous anti-influenza campaigns (2012–2015) were obtained.

2.3. Intervention

Patients with an available mobile telephone number and with no record of influenza vaccination between the beginning of the campaign and the date of delivery of the SMS reminder were

considered in a delayed vaccination status and selected as the eligible population for intervention. SMS reminders with the following generic text: "If you or a family member belongs to a risk group, chronic illness or pregnancy, ask for an APPOINTMENT at your HEALTH CENTER to get a FLU VACCINATION. For NO MORE SMS 012', were sent by the General Directorate of Public Health in four consecutive weeks: (1) November 17, 2016: patients between 14 and 64 years of age, (2) November 24, 2016: children between 6 months and 13 years of age, (3) December 1, 2016: patients aged 65 years and over with at least another selected comorbidity, and 4) December 13, 2016: patients aged 65 years and over without concurrent selected comorbidities. Information on the reception of the text message as: 'unknown number', 'pending' or 'delivered', was retrieved. Of the individuals with delayed vaccination status, those with a delivered text message were considered as intervention individuals. Those with a report of 'pending' message, 'unknown number', or without available mobile telephone number were categorized as control group.

2.4. Statistical analysis

A descriptive statistical analysis was performed. Comparisons were performed using the χ^2, *t*-Student and Kruskall-Wallis tests. Multiple poisson regression models, separately by sex and age group, were used to assess the association between the reception of the SMS and the vaccination uptake. Variables with imbalance

Table 2
Sociodemographic, clinical and vaccination characteristics of patients with selected rare diseases with indication for influenza vaccination in the 2016 campaign, Autonomous Community of Madrid.

		Total		Vaccinated pre-intervention		Delayed vaccination		
		N	%	N	%	N	%	*p-value*
		106,987		37,947		69,040		
Sex								
	Men	39,960	37.4	14,827	**39.1**	25,133	36.4	*<0.01*
	Women	67,027	62.6	23,120	60.9	43,907	**63.6**	
Age								
	Mean (SD)	54.9 (25.0)		68.4 (20.3)		47.4 (24.2)		*<0.01*
	Median (IQR)	59 (39–76)		74 (63–82)		48 (32–65)		*<0.01*
Age group	0–13 years	10,930	10.2	1710	4.5	9220	**13.4**	*<0.01*
	14–64 years	50,983	47.7	8858	23.3	42,125	**61.0**	
	>64 years	45,074	42.1	27,379	**72.2**	17,695	25.6	
Origin								
	Autochthonous	96,157	89.9	36,205	**95.4**	59,952	86.8	*<0.01*
	Immigrant	10,825	10.1	1742	4.6	9083	**13.2**	
Socioeconomic status								
	Q1 (richest)	19,016	17.8	6531	17.2	12,485	**18.1**	*<0.01*
	Q2	19,992	18.7	6861	18.1	13,131	**19.0**	
	Q3	25,224	23.6	8768	23.1	16,456	**23.8**	
	Q4	20,295	19.0	7461	**19.7**	12,834	18.6	
	Q5 (poorest)	21,934	20.5	8277	**21.8**	13,657	19.8	
Number of concurrent comorbidities								
	0	55,134	51.5	12,814	33.8	42,320	**61.3**	*<0.01*
	1	30,457	28.5	12,550	**33.1**	17,907	25.9	
	2	13,182	12.3	7446	**19.6**	5734	8.3	
	3	5472	5.1	3366	**8.9**	2106	3.1	
	≥ 4	2744	2.6	1771	**4.7**	973	1.4	
Concurrent comorbidities indicating vaccination *(ICPC codes)*								
Other cardiovascular disease *(K78, K82-4)*		15,478	14.5	8890	**23.4**	6588	9.5	*<0.01*
Diabetes mellitus *(T89-90)*		14,269	13.3	8229	**21.7**	6040	8.7	*<0.01*
Asthma *(R96)*		9731	9.1	3668	**9.7**	6063	8.8	*<0.01*
Chronic bronchitis/COPD *(R79,R95)*		6780	6.3	4114	**10.8**	2666	3.9	*<0.01*
Ischaemic heart disease *(K74-6)*		6749	6.3	4120	**10.9**	2629	3.8	*<0.01*
Other malignancies*		6483	6.1	3396	**8.9**	3087	4.5	*<0.01*
Heart failure *(K77)*		4544	4.2	2766	**7.3**	1778	2.6	*<0.01*
Neuromuscular disease *(N86-7, P70)*		4372	4.1	2358	**6.2**	2014	2.9	*<0.01*
Cerebrovascular disease *(K90)*		3964	3.7	2125	**5.6**	1839	2.7	*<0.01*
Chronic liver disease *(D72, D97)*		3513	3.3	1347	**3.5**	2166	3.1	*<0.01*
Nephropathy *(U88, U99.01)*		2916	2.7	1537	**4.1**	1379	2.0	*<0.01*
Immunodepression *(B72-4, B76, B79)*		2900	2.7	1151	**3.0**	1749	2.5	*<0.01*
Other pulmonary disease *(R84-5, R89)*		1062	1.0	534	**1.4**	528	0.8	*<0.01*
Morbid obesity *(IMC $\geq$ 40 in the last year)*		929	0.9	501	**1.3**	428	0.6	*<0.01*
HIV-infection/aids *(B90)*		735	0.7	227	0.6	508	**0.7**	*<0.01*
Previous influenza vaccination								
2012 campaign		38,532	36.0	28,024	**73.9**	10,508	15.2	*<0.01*
2013 campaign		41,015	38.3	29,807	**78.5**	11,208	16.2	*<0.01*
2014 campaign		41,606	38.9	31,032	**81.8**	10,574	15.3	*<0.01*
2015 campaign		44,278	41.4	33,335	**87.8**	10,943	15.9	*<0.01*
Mobile telephone available		96,988	90.7	33,746	88.9	63,242	**91.6**	*<0.01*

Due to missing values in some variables, the sum can fall short of the overall total.
Bold values represent statistically significant higher proportions ($p < 0.05$).
* International Classification of Primary Care codes: A79, D74-7, F74, H75, K72, L71, N74, S77 (limited to 'melanoma', 'sarcoma'), T71, U75-7, X75-6, Y77.

between the groups at baseline and those that could exert confounding were included in the maximum models. Variables were deemed to be confounders if the estimate of the coefficient of the variable 'reception of the SMS' changed by more than 10% when that variable was removed from the model. A backward strategy was used. Results from Poisson regression analyses were expressed as incidence rate ratios (IRR) with 95% confidence intervals (CI95%). The number needed to test was estimated based on the inverse of the absolute risk difference. Statistical significance was set at p-value < 0.05. Analyses were performed with SPSS 22.0 software.

2.5. Ethical aspects

The intervention was a public health measure, and given the characteristics of the study and the current legislation the prior consent of patients and approval by an ethics committee were not required. Patient information is available for scientific purposes, with the right to privacy fully guaranteed.

3. Results

In October 17, 2016, a total of 106,987 patients suffering from a rare disease with indication for immunization were identified (Table 2). They were mainly women (62.6%) with a mean age of 54.9 years (SD: 25.0), the 89.9% were born in Spain and 48.5% had at least another of the selected concurrent comorbidities for influenza immunization. A mobile phone number was available for 90.7% of them. Up to 35.5% of the population received the influenza vaccine previously to the programmed intervention. Patients with delayed influenza vaccination were younger (mean: 47.4 years vs. 68.4 years, p < 0.001), and they were in a significantly higher proportion women (63.6 vs. 60.9), immigrants (13.2% vs. 4.6%) and residents in areas with higher SES. Another comorbidity indicating influenza vaccination was detected in a lower proportion (61.3% vs. 33.8 with only rare disease, p < 0.001) except HIV-infection/aids, and the compliance with influenza vaccination in the four previous campaigns was worse.

The vaccination coverage before the first text message was sent was 31.9%, reaching a 35.3% after the first reminder, a 37.6% after the second one, a 39.1% after the third one and a final figure of 41.3% (Fig. 1).

Of the 69.040 patients with delayed vaccination, the 87.2% received the text message in the assigned contact mobile telephone (Table 3). Compared to controls they were in a higher proportion women (63.9% vs. 61.6%, p < 0.001), younger (mean: 46.5 years vs. 53.8 years, p < 0.001), autochthonous (87.2% vs. 84.6%, p < 0.001) and residents in areas with middle SES. The presence of asthma and other malignancies was more common among them, meanwhile diabetes mellitus, other cardiovascular diseases, heart failure and neuromuscular diseases were significantly less common. Compliance with the four previous campaigns of influenza vaccination was lower.

Vaccination took place mainly in the first days after the reception of the SMS (Fig. 2). The uptake of influenza vaccine in 2016 was significantly higher among those receiving the text message (9.3% vs. 7.1%, p < 0.001) (Table 4). By sex and age, in men the vaccination was significantly higher in the group under 14 years of age (6.2% vs. 3.9%) and in those of 65 years and over with a concurrent disease with indication for influenza vaccination (15.2% vs 9.7%). Among women, in all groups except that of 65 years and over with a concurrent disease with indication for vaccination the vaccine uptake was significantly higher, with the greatest absolute difference in the group aged 14–64 years (9.1% vs 5.2%, p < 0.001).

Individuals who received a SMS reminder were 30% more likely to receive a seasonal influenza vaccine (IRR: 1.30, CI95%: 1.20–1.41) than controls. The reception of the SMS was associated with a significantly higher probability of vaccination in men of 65 years and over with at least a concurrent chronic condition (IRR: 1.58, CI95%: 1.25–2.00). Among women, this higher probability was detected in those between 14 and 64 years of age (IRR: 1.41, CI95%: 1.22–1.63), and of 65 years of age and over without concurrent chronic conditions (IRR: 1.40, CI95%: 1.05–1.89). Forty-five SMS messages, costing 1.9€ (0.04€/SMS), were required for one additional patient to be immunized.

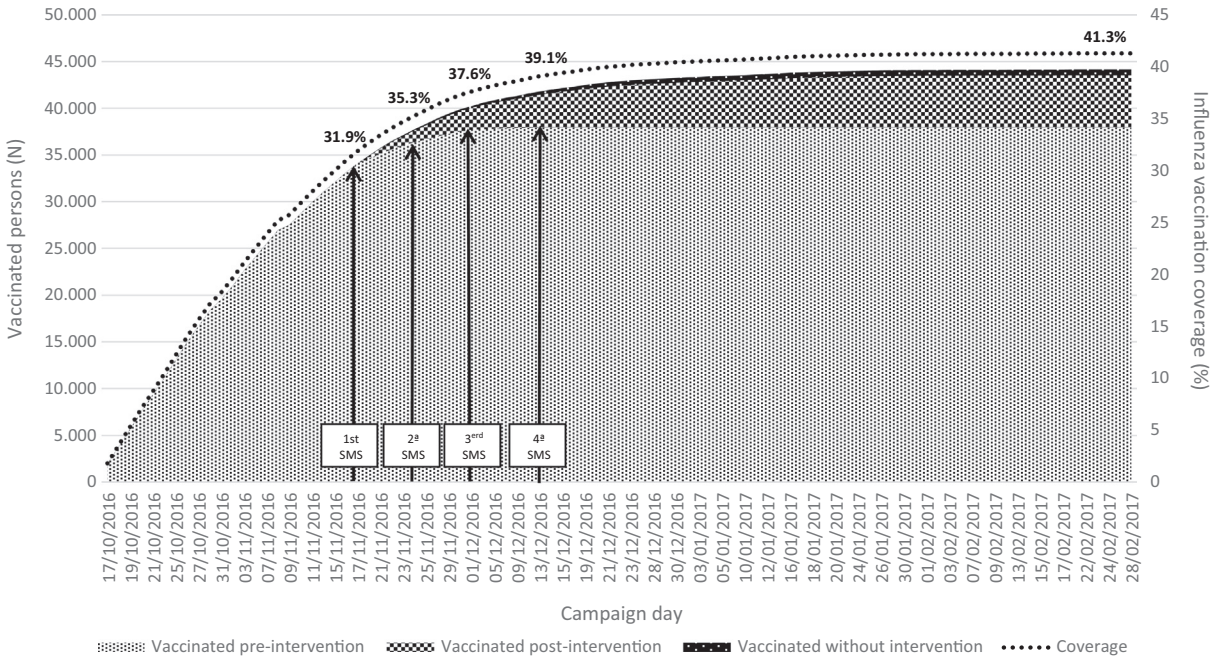

Fig. 1. Patients with selected rare diseases vaccinated and influenza vaccination coverage per day of the 2016 campaign. Autonomous Community of Madrid.

Table 3
Comparison of sociodemographic, clinical and vaccination characteristics of patients with selected rare diseases with indication for influenza vaccination and delayed vaccination in the 2016 campaign, by intervention group. Autonomous Community of Madrid.

		Intervention group (SMS received)		Control group (no SMS received)		
		N	%	N	%	p-value
Total		60,205		8835		
Sex						
	Men	21,739	36.1	3394	**38.4**	<0.01
	Women	38,466	**63.9**	5441	61.6	
Age						
	Mean (SD)	46.5 (23.8)		53.8 (26.0)		<0.01
	Median (IQR)	48 (31–63)		57 (36–76)		<0.01
Age group	0–13 years	8173	**13.6**	1047	11.9	<0.01
	14–64 years	37,789	**62.8**	4336	49.1	
	>64 years	14,243	23.7	3452	**39.1**	
Origin						
	Autochthonous	52,478	**87.2**	7474	84.6	<0.01
	Immigrant	7722	12.8	1361	**15.4**	
Socioeconomic status						
	Q1 (richest)	10,827	18.0	1658	**18.8**	<0.01
	Q2	11,615	**19.3**	1516	17.2	
	Q3	14,547	**24.2**	1909	21.6	
	Q4	11,263	18.7	1571	17.8	
	Q5 (poorest)	11,882	19.7	1775	**20.1**	
Number of concurrent comorbidities						
	0	36,839	61.2	5481	62.0	<0.01
	1	15,754	**26.2**	2153	24.4	
	2	4998	8.3	736	8.3	
	3	1782	3.0	324	**3.7**	
	≥ 4	832	1.4	141	1.6	
Concurrent comorbidities indicating vaccination *(ICPC codes)*						
Other cardiovascular disease *(K78, K82-4)*		5684	9.4	904	**10.2**	0.018
Diabetes mellitus *(T89-90)*		5154	8.6	886	**10.0**	<0.01
Asthma *(R96)*		5473	**9.1**	590	6.7	<0.01
Chronic bronchitis/COPD *(R79,R95)*		2293	3.8	373	4.2	0.060
Ischaemic heart disease *(K74-6)*		2261	3.8	368	4.2	0.060
Other malignancies*		2752	**4.6**	335	3.8	<0.01
Heart failure *(K77)*		1520	2.5	258	**2.9**	0.028
Neuromuscular disease *(N86-7, P70)*		1646	2.7	368	**4.2**	<0.01
Cerebrovascular disease *(K90)*		1586	2.6	253	2.9	0.211
Chronic liver disease *(D72, D97)*		1902	3.2	264	3.0	0.389
Nephropathy *(U88, U99.01)*		1204	2.0	175	2.0	0.905
Immunodepression *(B72-4, B76, B79)*		1536	2.6	213	2.4	0.433
Other pulmonary disease *(R84-5, R89)*		461	0.8	67	0.8	0.941
Morbid obesity *(IMC ≥ 40 in the last year)*		382	0.6	46	0.5	0.203
HIV-infection/aids *(B90)*		443	0.7	65	0.7	0.999
Previous influenza vaccination						
2012 campaign		8917	14.8	1591	**18.0**	<0.01
2013 campaign		9553	15.9	1655	**18.7**	<0.01
2014 campaign		9091	15.1	1483	**16.8**	<0.01
2015 campaign		9501	15.8	1442	16.3	0.194

Due to missing values in some variables, the sum can fall short of the overall total.
Bold values represent statistically significant higher proportions ($p < 0.05$).
* *International Classification of Primary Care codes: A79, D74-7, F74, H75, K72, L71, N74, S77 (limited to 'melanoma', 'sarcoma'), T71, U75-7, X75-6, Y77.*

4. Discussion

SMS reminders for seasonal influenza vaccination significantly increased the proportion of rare diseases' patients who received a seasonal influenza vaccine. The intervention seemed to result in larger absolute differences for children and population aged 65 years and over with other comorbidities. The reception of the reminder was associated to a significantly higher probability of influenza vaccine uptake in men of 65 years of age and over with at least a concurrent chronic condition and in women between 14 and 64 years of age, and of 65 years of age and over without chronic conditions concurrent with the rare disease. Although the absolute increase was modest, it was similar to that observed in randomized controlled trials with text-messaging interventions to enhance influenza vaccination in patients with underlying medical conditions [16–18].

A higher vaccination uptake associated to the SMS reception was observed in women. A trial in UK to determine the effectiveness of text message influenza vaccination reminders among 18–64 years old patients at-risk due to chronic conditions showed a moderate effect, with an absolute 2.62% increase in vaccine uptake in the intervention group, similar to ours, although no differences in the effect of the intervention by sex or age group were detected [17]. Neither differences of effect by sex were observed when the text message was sent to patients older than 6 months with chronic medical conditions and delayed influenza vaccination

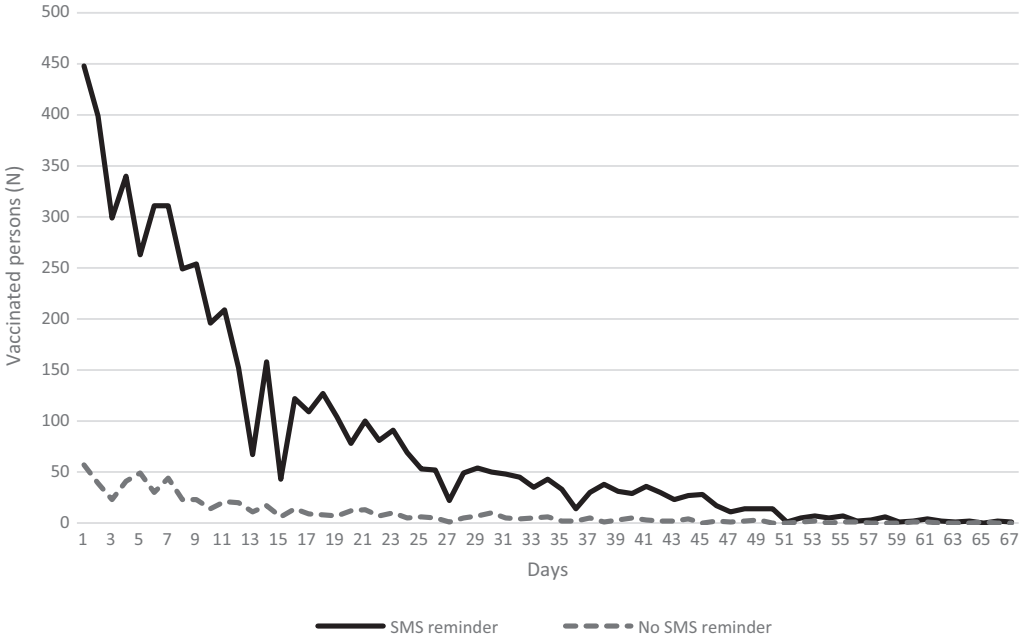

Fig. 2. Time (in days) between the date of short message service (SMS) reminder and 2016 influenza vaccination uptake. Autonomous Community of Madrid.

Table 4
Uptake of influenza vaccine according to study group, 2016 campaign. Autonomous Community of Madrid.

	Intervention group (SMS received)		Control group (no SMS received)		Absolute difference (95%CI)			
	Total N	Vaccinated N (%)	Total N	Vaccinated N (%)	% (95%CI)	p-value	IRR (95% CI)	NNT
Total	60,205	5590 (9.3)	8835	630 (7.1)	**2.2 (1.6–2.7)**	***<0.001***	**1.30 (1.20–1.41)**	45
0–13 years	8173	495 (6.1)	1047	36 (3.4)	**2.6 (1.4–3.8)**	***0.001***	1.29 (0.97–1.71)[a]	38
14–64 years	37,789	3478 (9.2)	4336	300 (6.9)	**2.3 (1.5–3.1)**	***0.000***	**1.33 (1.19–1.49)**	43
> 64 years with only rare disease	4631	298 (6.4)	1429	68 (4.8)	**1.7 (0.4–3.0)**	***0.020***	1.23 (0.96–1.57)	59
> 64 years with concurrent comorbidities	9612	1319 (13.7)	2023	226 (11.2)	**2.6 (1.0–4.1)**	***0.002***	**1.23 (1.08–1.40)**	38
Men								
Total	21,739	2060 (9.5)	3394	275 (8.1)	**1.4 (0.4–2.4)**	***0.010***	**1.17 (1.04–1.32)**	71
0–13 years	4358	272 (6.2)	542	21 (3.9)	**2.4 (0.6–4.1)**	***0.028***	1.16 (0.81–1.66)[a]	42
14–64 years	12,726	1188 (9.3)	1770	167 (9.4)	0.1 (−1.4–1.6)	*0.892*	0.99 (0.85–1.15)	1000
> 64 years with only rare disease	1146	65 (5.7)	358	17 (4.7)	0.9 (−1.7–3.5)	*0.502*	0.78 (0.46–1.32)[b]	111
> 64 years with concurrent comorbidities	3509	535 (15.2)	724	70 (9.7)	**5.6 (3.1–8.0)**	***0.000***	**1.58 (1.25–2.00)**	18
Women								
Total	38,466	3530 (9.2)	5441	355 (6.5)	**2.7 (1.9–3.4)**	***<0.001***	**1.41 (1.27–1.56)**	37
0–13 years	3815	223 (5.8)	505	15 (3.0)	**2.9 (1.2–4.5)**	***0.008***	1.46 (0.92–2.33)[a]	34
14–64 years	25,063	2290 (9.1)	2566	133 (5.2)	**4.0 (3.0–4.9)**	***0.000***	**1.41 (1.22–1.63)**[a]	25
>64 years with only rare disease	3485	233 (6.7)	1071	51 (4.7)	**1.9 (0.4–3.4)**	***0.023***	**1.40 (1.05–1.89)**	53
>64 years with concurrent comorbidities	6103	784 (12.8)	1299	156 (12.0)	0.8 (−1.1–2.8)	*0.411*	1.07 (0.91–1.26)	125

NNT: number needed to text (defined as the inverse of the absolute difference).
Bold values represent statistically significant ($p < 0.05$).
[a] Adjusted by influenza vaccination in the previous campaign (2015).
[b] Adjusted by SMS reception and influenza vaccination in the previous campaign (2015) and by socioeconomic status.

[18]. Possible differences by sex in the clinical characteristics (type of rare disease, severity, comorbidities) could have promoted a higher compliance with vaccination among women.

According to our data, the vaccination uptake was significantly higher in children under 14 years of age whose parents received the text message, but the regression analysis did not attribute a statistically significant effect to the SMS reminder. A randomized controlled trial performed in the US in 2010 among children aged 6 months to 18 years from a low-income urban population showed that a text messaging intervention increased the rate of influenza vaccination [19]. In another study in Australia, the intervention with text messages seemed particularly successful among parents of children younger than 5 years with underlying medical conditions, who were more than twice as likely to have their children vaccinated against influenza [18]. A positive effect attributed to the use of SMS was also found on the compliance with the routinely recommended vaccines in children <12 months of age [20,21], with adolescents vaccines [22–24], and on HPV vaccine completion [25]. In some of these studies, text messages were personalized and sent in the specified parent's preferred language. Moreover, the sending of messages was periodically repeated, which could increase their effect. When immunization communication utilizing text messages was explored from the parents perspective, 98% of them were interested in receiving immunization reminders by text messages [26]. They preferred text message reminders to be brief and personalized [27]. Perceived barriers of

text reminder messages included technology and communication-related issues [26,28]. Theoretically, a greater effect of text messages would be expected when selecting a high-risk population, but in the case of children, parents opinions and attitudes towards vaccines are influencing the decisions on vaccination. A study in children suffering from three rare genetic diseases (specifically Rubinstein-Taybi, Sotos and Beckwith-Wiedemann syndromes) found that the coverage of all the recommended vaccines was poor and significantly lower than in healthy controls, and their parents had negative attitudes toward vaccination more frequently, mainly for fear of the emergence of adverse events or deterioration of the underlying disease [29]. In a survey among caregivers of unvaccinated children with chronic respiratory conditions, the main reason reported for not receiving vaccination was that influenza vaccine was not beneficial [16]. Health professionals that regularly follow-up these children should clearly recommend influenza vaccination, explaining all of the benefits and real risks of vaccines, acknowledging parental concerns and clarifying misconceptions. Healthcare providers' attitudes towards vaccination are among the most important influences on the decision to vaccinate [30].

Despite the use of modern communication methods, the intervention seemed to be effective also in elderly patients, similarly to other study that included aged population [16]. This could be due in part to their acceptance of new technologies [31], and also to the fact that in the cases with difficulties for handling them, the mobile telephone number provided for health records would be that of a close relative more familiar with them. The higher vaccination uptake was reached by the group of patients aged 65 years and over with concurrent clinical conditions for immunization, which can be related with a higher perception of risk, and with more frequent contacts with health facilities, increasing the opportunities for vaccination. In the case of women with no other concurrent chronic conditions, the SMS reminder could have help to identify the risk situation and the convenience of immunization.

In our study, the target population was selected due to vaccination delay, which are probably less aware of their own risk or more hesitant towards vaccination, and therefore less motivated to seek immunization. These determinants can minimize the effect of the reminder. A trial performed selecting children aged 6 months to 17 years with delayed influenza vaccination found no differences in vaccination when a text message including educational content was sent to the parents, compared to children following usual care, and only text message reminders with embedded educational information and options for interactivity had a small positive effect on influenza vaccination [32]. On the contrary, among people with underlying medical conditions, a message sent 6 weeks after the start of the influenza vaccination period in Australia increased vaccination uptake in those under 5 years of age and with 18 years and over [18].

The patients who were not reached by the SMS reminder were in a higher proportion older, immigrant, and in the highest and lowest quintile of SES. These characteristics can be associated with a lower availability of mobile phones or more probably with a worst updating of the number in health databases. A greater effort to update information would be necessary to reduce the possibility of generating inequalities by gap in data.

Among the strengths of this study, it should be noted its population scope, with a large target population. It allowed establishing the feasibility of recruiting eligible patients, developing interventions and ascertaining outcome data using the electronic clinical records and public health registries. This was a simple, easy and low-cost intervention, with good acceptance by the recipients, since very few patients expressed refusal to receive SMS. Moreover, the conduct of these patients in the next vaccination campaigns could be monitored to detect a medium and long-term effect of the SMS reminder. Previous studies in our context showed that those patients incorporated to the influenza vaccination were more likely to get vaccinated in the following campaigns [6].

Among the limitations of this study, the absence of randomization in the assignation of the intervention should be mentioned, although the use of real-world data gives a more accurate vision of the feasibility and effects of the intervention. The heterogeneity of the selected rare diseases and the multisystemic nature of many of them prevented the analysis disaggregated by subgroups. The rare disease could be redundantly registered under the selected ICPC codes (specifically in the generic groups of other cardiovascular or pulmonary diseases) leading to the misclassification of some patients of 65 years and over in the group of patients with a concurrent comorbidity. Anyway, this would minimally affect the results. Other limitations related to the information sources used would be the presence of errors in registration and the fact that it is not possible to evaluate exceptions to the indication, such as adverse events during previous vaccinations.

5. Conclusions

The intervention was modestly effective for the entire intervention cohort, but it proved beneficial in some cases. Text messaging is simple, feasible, affordable and easily scalable, particularly when immunization and target population data are available in population registries. It can be an additional strategy to improve vaccine uptake. However, the global coverage reached in this high-risk group was far from optimal, highlighting the need for additional interventions aimed at improving influenza vaccination.

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Declaration of Competing Interest

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