HUMAN VACCINES & IMMUNOTHERAPEUTICS
2022, VOL. 18, NO. 1, e2025732 (6 pages)
https://doi.org/10.1080/21645515.2022.2025732

Taylor & Francis
Taylor & Francis Group

RESEARCH PAPER

OPEN ACCESS Check for updates

Systemic sclerosis and vaccinations: a three-year register-based cohort study about vaccination rate and uptake from Liguria referral center, northwest Italy

Giuseppe Murdaca[a], Giovanni Noberasco[b], Dario Olobardi[b], Matilde Ogliastro[b], Raffaella Sibilio[b], Giacomo Sambuceti[a], Riccardo Balzano[a], Laura Sticchi[b,c], Giancarlo Icardi[b,c], and Andrea Orsi[b,c]

[a]Departments of Internal Medicine, University of Genova, Genova, Italy; [b]Department of Health Sciences, Vaccines and Clinical Trials Unit, University of Genova, Genova, Italy; [c]Hygiene Unit, "Ospedale Policlinico San Martino IRCCS", Genova, Italy

ABSTRACT

Patients with diffused Systemic Sclerosis (dSSc) are more subject to severe respiratory complications with higher rates of intensive care unit (ICU) admission. Vaccination represents the most effective means of prevention and care for frail patients, such as SSc patients, preventing infections, reducing mortality and morbidity, and granting a better quality of life. Both vaccinations against seasonal influenza and Streptococcus pneumoniae are currently recommended by the European League Against Rheumatism (EULAR) guidelines on vaccination. The aim of this study is to give an updated analysis on *S. pneumoniae* and seasonal influenza vaccination coverage in a cohort of 91 patients with SSc and to investigate demographic and clinical variables significantly related to vaccine acceptance. The correlation between vaccine administration and other factors was investigated using a binomial logistic regression to evaluate the adjusted odds ratio (aOR). The patients followed up in this study reached higher percentages than the general population, passing the 75% target for both influenza and anti-pneumococcal vaccinations and reaching for influenza vaccine coverage rates of 83.8% for subjects undergoing immunosuppressive therapies and 88.9% for elderly subjects. For the latter group, it is important to emphasize the strong correlation between older age groups and vaccination acceptance.

ARTICLE HISTORY
Received 21 July 2021
Revised 15 December 2021
Accepted 31 December 2021

KEYWORDS
Systemic sclerosis; vaccines; flu; influenza; pneumonia; S. Pneumoniae

1. Introduction

Systemic sclerosis (SSc) is a chronic inflammatory disease with a prevalence ranging from 7 to 700 cases per million with a significant difference between countries with peaks in the USA and Australia and lows in Europe and Japan.[1,2] This wide range of prevalence can be caused by differences in medical recordings that can influence overall data availability.

The main pathogenetic effect behind the disease is the continuous cycle of inflammation followed by tissue fibrosis. The main areas affected by this process are the skin, vascular system, and organs, such as lungs, kidneys, heart, and the gastrointestinal tract.[3,4] There are two main subtypes of SSc: limited cutaneous (lSSc) and diffuse cutaneous systemic sclerosis (dSSc) but, due to the great heterogeneity of clinical presentation, the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) developed a new classification system.[1] This different classification approach incorporating autoantibodies commonly tested helped to reduce the time needed for diagnosis.

The disease etiology is only partially understood, as both genetic and environmental factors influence SSc onset and outcome.[5] The main factor clarified is the involvement of T-cell. CD8+ suppressor cells activity is impaired, leading to relapses and disease progression.[6] Patients with dSSc are at a higher rate more subject to severe respiratory complications with higher rates of intensive care unit (ICU) admission. The average time between SSc diagnosis and ICU admission is 78 months and the mainly due to acute respiratory failure.[7]

The disease has a mortality ratio of 2.3–3.5 with a cumulative survival rate from diagnosis of 75% at 5 years and 62.5% at 10 years.[8]

The main causes of death are interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH);[9] endothelial dysfunction and vascular abnormalities often leading to death by cardiac complications,[10,11] and opportunistic infections as the patients are often undergoing therapy with immunosuppressive or biological drugs.[12–16]

Vaccination represents the most effective means of prevention and care for frail patients such as SSc patients preventing infections, reducing mortality and morbidity, and granting a better quality of life.

Both vaccinations against seasonal influenza[17] and Streptococcus pneumoniae are currently recommended by the EULAR guidelines on vaccination to prevent pneumonia, meningitis, and bacterial sepsis.[18] From a clinical and statistical point of view children, the elderly and immunocompromised subjects have the strongest recommendations for vaccination suffering from a higher incidence and a worse outcome associated with said diseases and with mortality rates for the disease's invasive form ranging from 5% to 35%.[19–27]

CONTACT Giuseppe Murdaca giuseppe.murdaca@unige.it Departments of Internal Medicine, University of Genova, Genova 16132, Italy

The aim of this study is to give an updated[28] analysis on *S. pneumoniae* and seasonal influenza vaccination coverage among patients with SSc and to investigate demographic and clinical variables significantly related to vaccine acceptance comparing this year's results with the previous.

2. Materials and methods

All adult patients followed up at the regional referral center for the diagnosis and treatment of systemic sclerosis (SSc): the Immunology Clinic, in the Department of Internal Medicine (DiMI), of the San Martino Polyclinic Hospital in Genoa were recruited for the study.

In September 2018, an informed consent to data acquisition was provided during a clinic visit and signed by the patients involved. Data on gender, age, concomitant immunosuppressive treatment, comorbidities (pulmonary "ILD," cardiovascular, diabetes mellitus "DM," chronic kidney disease "CKD," hematological or solid malignancy), smoking habits, and previous pneumococcal and flu vaccinations were systematically collected by the researchers with a standardized form from both older medical records and by patient self-report.

All procedures were in accordance with the Helsinki Declaration of 1975.

All patients were entrusted to the Department of Hygiene (DISSAL) for a general evaluation and to be offered information about available vaccines. Yearly all patients were recalled to the vaccination center and offered the seasonal influenza vaccine. After the evaluation of the patient's vaccination status from a regional telematic register, both pneumococcal vaccines, Prevenar13 ® (PCV-13) and Pneumovax23 ® (PPV-23), were offered according to the schedule provided on the technical datasheet and to Italian guidelines on immunization (PNPV),[29] first PCV-13, then PPV-23 6 months or a year later.

Since it was not clear what influenced patients the most when deciding to adhere to vaccination schedules or not, the researchers asked them who proposed them the needed vaccinations and how did they motivate such advice (e.g. "who proposed the vaccinations to you? Your GP? A clinician from this hospital? A researcher? Others?" "did he/she provide any information material?" "did you feel motivated by the proposal?"), the answers were then collected and added to the database to be analyzed.

This procedure was repeated over the following 2 years, focusing on patients' clinical status reevaluation, due to possible therapy modifications, and calculating the cohort vaccination coverage over time.

Thanks to the follow-up data, it was possible to evaluate the changes in vaccination acceptance rates of the complete cohort and other subgroups, such as patients with comorbidities, chronic therapies or therapies shifts, and different age groups and link them to factors guiding their decision.

Both quantitative (means and medians) and qualitative (proportions and percentages) variables were analyzed and described. The correlation between vaccine administration and other factors was examined with Fisher's exact test (the result is significant if $p < .05$) and the chi-square test, applying the Yates correction when necessary. The change in vaccination coverage between 2017–18 and 2018–19 seasons was examined with Fisher's exact test (the result is significant if $p < .05$) and the chi-square test, applying the Yates correction when necessary. Statistics version 25 of IBM SPSS (produced by IBM of Armonk, New York) was used to evaluate the binomial logistic regression between vaccinations and investigated characteristics, and to evaluate the adjusted odds ratio (aOR) to investigate independent correlations with vaccination uptake.

3. Results

3.1. Clinical and demographic characteristics

During the first year, 72 patients were recruited, this number grew to 91 in the second year and, despite the death of a patient due to myocardial infarction and consequent fatal heart failure, remained stable during the third year with the addition of a new patient.

All the patients attending our center consented to participate in the study forming the cohort in analysis.

The average age was 63.51 (SD 13.98) years, with a median of 64 (IQR 54–74.5). The female population was just over 80%, and the male-to-female ratio was 1:4, in line with the epidemiology of the disease.

Half of the subjects (46/91, i.e. 50.5%) were afflicted by SS limited form (lcSSc), while 29.7% of the cohort has the disease's diffuse form (dcSSc). 19.8% were afflicted by an overlapping or unspecified form.

The clear majority of patients were affected by comorbidities (85.7%). In order of prevalence pulmonary interstitial disease (ILD) was the most represented with a prevalence of 61.5%, followed by cardiovascular diseases (53.9%), chronic renal failure (CRI) of grade II or higher in 18.7%, and neoplastic disease in 4.4%.

Among the 91 patients, one third (34.1%) had a positive history of smoking and 40.7% were under immunosuppressive treatment mainly with the use of two drugs: mofetil-mycophenolate (called MMF, 27.5%) and methotrexate (MTX, 8.8%).

The precise clinical and demographic data are summarized in Table 1.

3.2. Vaccination rate

Significant changes in vaccination rates between the first year and the last year were pointed out in our study. Changes were evaluated among the entire cohort and different subgroups of patients. No statistical significance was found in vaccination rates between the second year and the last year, although the coverages kept a rising trend across the whole observation time.

Vaccination rate changes are described in Tables 2 and 3.

3.3. Vaccinations uptake

According to the National Vaccination Prevention Plan (PNPV), influenza vaccination is recommended to people affected by several risk factors.

Among the patients 49.5% (45/91) were over 65 years old, 40.7% (37/91) had comorbidities, and 2.2% (2/91) were under the effect of an immunosuppressive treatment

Table 1. Clinical and demographic characteristics of systemic sclerosis patients.

Patient characteristics	Total	Patients vaccinated against flu	Patients not vaccinated against flu	Patients vaccinated against *S. pneumoniae*	Patients not vaccinated against *S. pneumoniae*
Number	91	69	22	70	21
Mean age (years)	63.51 (SD 13.98)	66.39 (SD 13.69)	54.45 (SD 10.88)	65.6 (SD 13.46)	56.5 (SD 13.71)
Median age (years)	64 (IQR 54–74.5)	66 (IQR 59–76)	55 (IQR 47.5–59.25)	66 (IQR 57.25–75.75)	57 (IQR 47–66)
Over 65 years old	49.5%	60.6%	18.2%	55.7%	28.6%
Females	82.4%	70.8%	95.2%	80.0%	90.5%
Comorbidities	85.7%	86.9%	81.8%	88.6%	76.2%
Interstitial Lung Disease	61.5%	62.3%	59.1%	64.3%	52.4%
Cardiovascular	53.8%	55.1%	50.0%	55.7%	47.6%
Neoplastic	4.4%	4.3%	4.5%	4.3%	4.8%
Chronic Kidney Disease	18.7%	17.4%	22.7%	18.6%	19.0%
Diabetes	4.4%	5.8%	0.0%	5.7%	0.0%
Smokers	34.1%	33.3%	36.3%	28.6%	52.4%
Ongoing therapy	40.7%	44.9%	27.3%	47.1%	19.0%
Methotrexate	8.8%	10.2%	4.6%	10.0%	4.8%
Mycophenolate mofetil	27.5%	29.0%	18.2%	30.0%	14.3%
Limited cutaneous Systemic sclerosis	50.5%	55.1%	36.4%	54.3%	38.1%
Diffuse Systemic sclerosis	29.7%	26.1%	40.9%	28.6%	33.3%

Table 2. Changes in *S. Pneumoniae* vaccination coverage between 2017–18, 2018–19 and 2019–2020 seasons.

Patient characteristics	2017–2018	2018–2019	2019–2020	*p*
Total (n)	23.6% (17)	74.7% (68)	76.9% (70)	<.01*
Over 65 years old	24.3%	86.3%	86.7%	<.01*
Males	18.2%	75.0%	87.5%	<.01*
Females	24.6%	82.4%	74.6%	<.01*
Comorbidities	27.8%	78.8%	79.5%	<.01*
Interstitial Lung Disease	30.4%	89.3%	80.4%	<.01*
Cardiovascular	38.5%	85.7%	79.6%	<.01*
Ongoing therapy	35.3%	89.2%	89.2%	<.01*
Methotrexate	40.0%	87.5%	87.5%	.07
Mycophenolate mofetil	26.7%	88.0%	87.5%	<.01*

Statistical significance examined with Fisher's exact test (the result is significant if $p < .05$) and the chi-square test, applying the Yates correction when necessary; * statistical significance.

Table 3. Changes in flu vaccination coverage between 2017–18, 2018–19 and 2019–2020 seasons.

Patient characteristics	2017–2018	2018–2019	2019–2020	*p*
Total (n)	58.3% (43)	69.2% (63)	75.5% (69)	<.01*
Over 65 years old	75.7%	88.6%	88.9%	.08
Males	54.6%	75.0%	93.8%	.04*
Females	59.0%	81.0%	72.0%	.12
Comorbidities	60.4%	75.0%	76.9%	.05*
Interstitial Lung Disease	58.7%	77.4%	76.8%	.07
Cardiovascular	76.9%	75.5%	77.6%	.99
Ongoing therapy	34.9%	83.8%	83.8%	<.01*
Methotrexate	60.0%	87.5%	87.5%	.46
Mycophenolate mofetil	73.3%	84.0%	83.3%	.67

Statistical significance examined with Fisher's exact test (the result is significant if $p < .05$) and the chi-square test, applying the Yates correction when necessary; * statistical significance.

(MTX) that made them eligible for vaccination, 7.7% (7/91) received a yearly direct recommendation from their general practitioner for both influenza and *S. Pneumoniae* vaccinations and only 7.7% (7/91) patients did not have any risk factor.

As emerges from our group data on vaccination coverage rates, although almost every subject was entitled to receive vaccination, only 75.5% of the patients received it.

Pneumococcal vaccination was accepted by 76.9% (70/91) patients and flu by 75.8% (69/91). In more than 85% of cases the immunologist in charge of these patients recommended immunization. General Practitioners proposed the vaccination to just over 10%, while a couple of subjects were advised by other specialists.

Then, we analyzed various individual variables such as age, sex, comorbidities, immunosuppressive therapy, and positive history of smoking, to find a significant correlation (p-value < .05) with the vaccinations carried out by patients. First, the Unadjusted Odds Ratio (UOR) was calculated, later it was corrected and transformed into an Adjusted Odds Ratio (AOR) to exclude the influence of any confounding factor.

Of all the characteristics analyzed, only the age of over 65 is a significant factor that correlates with the carrying out of both vaccinations. For anti-pneumococcal immunization, the AOR is 7.12 (95% CI: 1.69–29.88), while for flu vaccination, it is 43.24 (95% CI: 5.93–315.11), both high values that showed a positive correlation between old age and vaccinations. The patients older than 65yo were 7.11 (95% CI: 1.69–29.88) or 43.24 (95% CI: 5.93–315.11) times more prone to be vaccinated for the corresponding pathogens. A negative correlation was also found: being a woman in the studied cohort was a disadvantage for immunization against influenza with an AOR of 0.04 (95% CI: 0.01–0.63). Tables 4 and 5 present the precise unadjusted and adjusted odds ratios of each factor on flu and pneumococcal vaccine uptake, respectively.

4. Discussion

As the results showed, most patients followed up at our center had at least one factor that made vaccinations recommendable to them. Age represented the factor most positively correlated with vaccine acceptance, while immunosuppression and severe comorbidities had a slightly lower influence. Nonetheless, continuous recommendations led to satisfactory vaccination coverages.

Seasonal flu and pneumococcus are high incidence respiratory infections with significant morbidity and mortality. Many studies have proven that the elderly, subjects

Table 4. Raw and adjusted odds ratios on each factor evaluated for *S. pneumoniae* vaccination over the 3-year period.

Patient characteristics	Raw OR	Adjusted OR	95% Confidence interval	*p*
Age over 65 years old	3.15	7.11	1.69–29.88	.01*
Female sex	0.42	0.21	0.03–1.48	.12
Interstitial Lung Disease	1.64	0.79	0.22–2.90	.73
Cardiovascular	1.38	1.32	0.36–4.82	.68
Smoking	0.36	0.70	0.20–2.37	.56
Chronic Kidney Disease	0.97	0.60	0.15–2.50	.49
Immunosuppressive therapy	3.79	3.49	0.76–6.23	.99
Methotrexate	2.22	0.76	0.27–16.12	.99
Mycophenolate mofetil	2.57	1.93	0.69–6.35	.99

Statistical significance examined with Fisher's exact test (the result is significant if $p < .05$) and the chi-square test, applying the Yates correction when necessary; * statistical significance.

Table 5. Raw and adjusted odds ratios on each factor evaluated for 2019–2020 seasonal flu vaccination.

Patient characteristics	Raw OR	Adjusted OR	95% Confidence interval	*p*
Age over 65 years old	6.59	43.24	5.93–315.11	>.01*
Female sex	0.17	0.04	0.00–0.63	.02*
Interstitial Lung Disease	1.15	0.34	0.07–1.64	.18
Cardiovascular	1.23	0.70	0.17–2.98	.63
Smoking	0.88	0.78	0.20–3.00	.71
Chronic Kidney Disease	0.72	0.28	0.06–1.24	.09
Immunosuppressive therapy	2.18	3.74	0.16–85.09	.41
Methotrexate	2.37	6.61	0.16–275.16	.32
Mycophenolate mofetil	1.84	5.48	0.21–142.62	.06

Statistical significance examined with Fisher's exact test (the result is significant if $p < .05$) and the chi-square test, applying the Yates correction when necessary; * statistical significance.

with comorbidities, and immunocompromised individuals suffer more from complications and have an overall worse prognosis.[21–25]

Subjects affected by SSc are a perfect example, both immunocompromised and with systemic resentment given by the underlying pathology.[10,19] Since flu and anti-pneumococcal vaccinations have a high level of safety and effectiveness even in rheumatic or immunological diseases,[13,27] their coverage rate should be as high as possible.

In 2018, Harrison et al.[30] found that Austrian rheumatology patients were mostly vaccinated by general practitioners. As shown before, the situation in our study group was completely reversed. The high vaccine coverage was reached due to health education provided by the immunologists who followed up the patients.

The first step to achieving a better vaccination implementation and higher coverage rates should start with prevention and vaccination education granted to the general population by general practitioners.

Although at the beginning of the study, the coverage of the Ligurian cohort was far from sufficient, it is essential to underline how a vaccination campaign, actively aimed at this category of subjects, led to a significant increase in immunized subjects in the following 2 years.

During the years of this study, an effective vaccination campaign was carried out which made it possible to exceed the 75% coverage rate target set by 2017–2019 PNPV for pneumococcus and influenza.

The main focus of the campaign was raising awareness about the importance of vaccines in frail subjects. This was carried out by providing constant information and dialogue during each patient's hospital visit to reduce hesitancy and help a conscious choice. The latest data published by the Ministry of Health (updated to 2019)[31] show that only 15.8% of the general Italian population is immunized against seasonal flu, with a level slightly above 50% in the elderly subjects (>65). The patients followed up in this study reached higher percentages than the general population, passing the 75% target and reaching 83.8% for subjects undergoing immunosuppressive therapies and 88.9% for elderly subjects. For the latter group, it is important to emphasize the strong correlation between older age groups and vaccination acceptance.

The results obtained for *S. pneumoniae* show a satisfactory vaccination coverage rate of over 75% with higher rates in the same categories as flu. It is important to point out that over the years, the population protected against pneumonia will grow due to the long-lasting effects of immune memory.

The fact that the other calculated variables do not allow the extraction of different significant correlations expresses how the population is heterogeneous throughout the years of the study. This demonstrates how immunization should not remain addressed to a specific category of patients with SSc, but that, on the contrary, it should be extended to all these patients regardless of their personal and/or clinical characteristics.

The main limitation of this study might be a bias in the selection of our cohort since it is composed of highly followed patients that showed a high compliance with all procedures. This could either be casual or the result of a higher awareness of the importance of vaccination. Another limitation may be linked to the overall different approaches in the management of this frail patient population worldwide. This is both a limit and a strong point of the study, trying to provide more data on an important aspect of prevention. The yearly monitoring grants the possibility to also assess the advantages granted by the continuous communication and monitoring.

5. Conclusions

This study aimed to give an updated analysis of *S. pneumoniae* and seasonal influenza vaccination coverage among patients with SSc and to investigate demographic and clinical variables significantly related to vaccine acceptance.

Although vaccinations are often the safest and most effective means of protection for frail patients, the tendency toward immunization is still too low. The absence of clear and univocal information about vaccines and the different opinions on vaccines provided by health-care workers often fuel vaccine hesitancy. Giving correct information can lead, as shown in our patient group, to satisfactory vaccine acceptance and coverage rates only increasing throughout the years.

Obtaining similar results not only for patients affected by SSc but also for the general population would gradually help to create a herd immunity and further increase the effectiveness of vaccinations giving frail patients such as SSc patients more chances to be protected from high-risk preventable diseases.

This study adds significance to the previous results[28] observed over a two-year observation, emphasizing the importance of the prolonged and vaccine offering campaign.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The author(s) reported that there is no funding associated with the work featured in this article.

ORCID

Giovanni Noberasco http://orcid.org/0000-0001-6827-6191
Laura Sticchi http://orcid.org/0000-0002-7819-7400
Giancarlo Icardi http://orcid.org/0000-0002-8463-8487
Andrea Orsi http://orcid.org/0000-0002-2433-9610

Author contributions

Data curation, G.N., D.O., G.S. and R.B.; Investigation, M.O. and R.S.; Project administration, G.M., L.S., G.I. AND A.O. All authors have read and agreed to the published version of the manuscript.

Informed consent statement

Informed consent was obtained from all subjects involved in the study.

References

1. van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, Matucci-Cerinic M, Naden RP, Medsger TA Jr, Carreira PE, et al. 2013 classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative. Ann Rheum Dis. 2013 Nov;72(11):1747–55. PMID: 24092682. doi:10.1136/annrheumdis-2013-204424.
2. Elhai M, Avouac J, Walker UA, Matucci-Cerinic M, Riemekasten G, Airò P, Hachulla E, Valentini G, Carreira PE, Cozzi F, et al. A gender gap in primary and secondary heart dysfunctions in systemic sclerosis: a EUSTAR prospective study. Ann Rheum Dis. 2016 Jan;75(1):163–69. Epub 2014 Oct 23. PMID: 25342760. doi:10.1136/annrheumdis-2014-206386.
3. Thompson AE, Pope JE. Increased prevalence of scleroderma in southwestern Ontario: a cluster analysis. J Rheumatol. 2002 Sep;29 (9):1867–73. PMID: 12233880.
4. Gazi H, Pope JE, Clements P, Medsger TA, Martin RW, Merkel PA, Kahaleh B, Wollheim FA, Baron M, Csuka ME, et al. Outcome measurements in scleroderma: results from a delphi exercise. J Rheumatol. 2007 Mar;34(3):501–09. Epub 2007 Feb 1. PMID: 17299843.
5. Filaci G, Fravega M, Negrini S, Procopio F, Fenoglio D, Rizzi M, Brenci S, Contini P, Olive D, Ghio M, et al. Nonantigen specific CD8+ T suppressor lymphocytes originate from CD8+CD28- T cells and inhibit both T-cell proliferation and CTL function. Hum Immunol. 2004 Feb;65(2):142–56. PMID: 14969769. doi:10.1016/j.humimm.2003.12.001.
6. Manetti M, Pratesi S, Romano E, Bellando-Randone S, Rosa I, Guiducci S, Fioretto BS, Ibba-Manneschi L, Maggi E, Matucci-Cerinic M. Angiogenic T cell expansion correlates with severity of peripheral vascular damage in systemic sclerosis. PLoS One. 2017 Aug 10;12(8):e0183102. PMID: 28797111; PMCID: PMC5552290. doi:10.1371/journal.pone.0183102.
7. Pène F, Hissem T, Bérezné A, Allanore Y, Geri G, Charpentier J, Avouac J, Guillevin L, Cariou A, Chiche JD, et al. Outcome of patients with systemic sclerosis in the intensive care unit. J Rheumatol. 2015 Aug;42(8):1406–12. Epub 2015 Jul 1. PMID: 26136487. doi:10.3899/jrheum.141617.
8. Rubio-Rivas M, Royo C, Simeón CP, Corbella X, Fonollosa V. Mortality and survival in systemic sclerosis: systematic review and meta-analysis. Semin Arthritis Rheum. 2014 Oct;44 (2):208–19. Epub 2014 May 14. PMID: 24931517. doi:10.1016/j.semarthrit.2014.05.010.
9. Chaisson NF, Hassoun PM. Systemic sclerosis-associated pulmonary arterial hypertension. Chest. 2013 Oct;144(4):1346–56. PMID: 24081346; PMCID: PMC3787920. doi:10.1378/chest.12-2396.
10. Nikpour M, Baron M. Mortality in systemic sclerosis: lessons learned from population-based and observational cohort studies. Curr Opin Rheumatol. 2014 Mar;26(2):131–37. PMID: 24441644. doi:10.1097/BOR.0000000000000027.
11. Murdaca G, Colombo BM, Cagnati P, Gulli R, Spanò F, Puppo F. Endothelial dysfunction in rheumatic autoimmune diseases. Atherosclerosis. 2012 Oct;224(2):309–17. Epub 2012 May 18. PMID: 22673743. doi:10.1016/j.atherosclerosis.2012.05.013.
12. Landemaine A, Petitcollin A, Brochard C, Miard C, Dewitte M, Le Balc'h E, Grainville T, Bellissant E, Siproudhis L, Bouguen G. Cumulative exposure to infliximab, but not trough concentrations, correlates with rate of infection. Clin Gastroenterol Hepatol. 2021 Feb;19(2):288–295.e4. Epub 2020 Mar 19. PMID: 32200087. doi:10.1016/j.cgh.2020.03.018.
13. Murdaca G, Spanò F, Contatore M, Guastalla A, Penza E, Magnani O, Puppo F. Infection risk associated with anti-TNF-α agents: a review. Expert Opin Drug Saf. 2015 Apr;14(4):571–82. Epub 2015 Jan 29. PMID: 25630559. doi:10.1517/14740338.2015.1009036.
14. Murdaca G, Spanò F, Contatore M, Guastalla A, Magnani O, Puppo F. Efficacy and safety of etanercept in chronic immune-mediated disease. Expert Opin Drug Saf. 2014;13 (5):649–61. doi:10.1517/14740338.2014.899579.
15. Almaaitah S, Highland KB, Tonelli AR. Management of pulmonary arterial hypertension in patients with systemic sclerosis. Integr Blood Press Control. 2020 Mar 23;13:15–29. PMID: 32280271; PMCID: PMC7125406. doi:10.2147/IBPC.S232038.
16. Papadopoulos CG, Gartzonikas IK, Pappa TK, Markatseli TE, Migkos MP, Voulgari PV, Drosos AA. Eight-year survival study of first-line tumour necrosis factor α inhibitors in rheumatoid arthritis: real-world data from a university centre registry. Rheumatol Adv Pract. 2019 Mar 14;3(1):rkz007. PMID: 31431995; PMCID: PMC6649942. doi:10.1093/rap/rkz007.
17. Rondaan C, Furer V, Heijstek MW, Agmon-Levin N, Bijl M, Breedveld FC, D'Amelio R, Dougados M, Kapetanovic MC, van Laar JM, et al. Efficacy, immunogenicity and safety of vaccination in adult patients with autoimmune inflammatory rheumatic diseases: a systematic literature review for the 2019 update of EULAR recommendations. RMD Open. 2019;5(2):e001035. PMID: 31565247; PMCID: PMC6744079. doi:10.1136/rmdopen-2019-001035.
18. Aguilar-Guisado M, Jiménez-Jambrina M, Espigado I, Rovira M, Martino R, Oriol A, Borrell N, Ruiz I, Martín-Dávila P, de La Cámara R, et al. Spanish network for research in infectious diseases. Pneumonia in allogeneic stem cell transplantation recipients: a multicenter prospective study. Clin Transplant. 2011 Nov-Dec;25 (6):E629–38. Epub 2011 Aug 21. PMID: 22150886. doi:10.1111/j.1399-0012.2011.01495.x.
19. Ghebrehewet S, MacPherson P, Ho A. Influenza. BMJ. 2016;355:1733–45.
20. Hak E, Nordin J, Wei F, Mullooly J, Poblete S, Strikas R, Nichol KL. Influence of high-risk medical conditions on the effectiveness of influenza vaccination among elderly members of 3 large managed-care organizations. Clin Infect Dis. 2002 Aug 15;35 (4):370–77. Epub 2002 Jul 19. PMID: 12145718. doi:10.1086/341403.

21. Blumentals WA, Arreglado A, Napalkov P, Toovey S. Rheumatoid arthritis and the incidence of influenza and influenza-related complications: a retrospective cohort study. BMC Musculoskelet Disord. 2012 Aug 27;13(1):158. PMID: 22925480; PMCID: PMC3495205. doi:10.1186/1471-2474-13-158.
22. Murdaca G, Orsi A, Spanò F, Puppo F, Durando P, Icardi G, Ansaldi F. Influenza and pneumococcal vaccinations of patients with systemic lupus erythematosus: current views upon safety and immunogenicity. Autoimmun Rev. 2014 Feb;13(2):75–84. Epub 2013 Sep 14. PMID: 24044940. doi:10.1016/j.autrev.2013.07.007.
23. Vila-Córcoles A. Vaccinate your child and save its grandparents from a heart attack? Current perspectives in antipneumococcal vaccination. J Intern Med. 2009 Nov;266(5):432–44. Epub 2009 Aug 21. PMID: 19754854. doi:10.1111/j.1365-2796.2009.02149.x.
24. Glück T, Müller-Ladner U. Vaccination in patients with chronic rheumatic or autoimmune diseases. Clin Infect Dis. 2008 May 1;46 (9):1459–65. PMID: 18419456. doi:10.1086/587063.
25. van Assen S, Elkayam O, Agmon-Levin N, Cervera R, Doran MF, Dougados M, Emery P, Geborek P, Ioannidis JP, Jayne DR, et al. Vaccination in adult patients with auto-immune inflammatory rheumatic diseases: a systematic literature review for the European League against rheumatism evidence-based recommendations for vaccination in adult patients with auto-immune inflammatory rheumatic diseases. Autoimmun Rev. 2011 Apr;10 (6):341–52. Epub 2010 Dec 20. PMID: 21182987. doi:10.1016/j.autrev.2010.12.003.
26. Bijl M, Agmon-Levin N, Dayer JM, Israeli E, Gatto M, Shoenfeld Y. Vaccination of patients with auto-immune inflammatory rheumatic diseases requires careful benefit-risk assessment. Autoimmun Rev. 2012 Jun;11(8):572–76. Epub 2011 Oct 22. PMID: 22037116. doi:10.1016/j.autrev.2011.10.015.
27. Martens P, Worm SW, Lundgren B, Konradsen HB, Benfield T. Serotype-specific mortality from invasive Streptococcus pneumoniae disease revisited. BMC Infect Dis. 2004 Jun 30;4:21. PMID: 15228629; PMCID: PMC455681. doi:10.1186/1471-2334-4-21.
28. Murdaca G, Noberasco G, Battaglini A, Vassallo C, Giusti F, Greco M, Schiavi C, Sticchi L, Icardi G, Orsi A. Systemic sclerosis and vaccinations: a register-based cohort study about seasonal influenza and streptococcus pneumoniae vaccination rate and uptake from Liguria Regional Center, Northwest Italy. Vaccines. 2020;8:204. doi:10.3390/vaccines8020204.
29. Piano Nazionale Prevenzione Vaccinale (PNPV). 2017–2019. [accessed 2019 Mar 19]. www.salute.gov.it/imgs/C_17_pubblicazioni_2571_allegato.pdf .
30. Harrison N, Poeppl W, Miksch M, Machold K, Kiener H, Aletaha D, Smolen J, Bahrs C, Burgmann H, Lagler H. Predictors for influenza vaccine acceptance among patients with inflammatory rheumatic diseases. Vaccine. 2018;36(32):4875–79. doi:10.1016/j.vaccine.2018.06.065.
31. Ministero della Salute. Vaccinazioni per categoria. [accessed 2021 Mar 22]. http://www.salute.gov.it/portale/influenza/dettaglioOpuscoliInfluenza.jsp?lingua=italiano&id=356.