

**Perception and awareness of vaccinations in
Autoimmune Inflammatory Rheumatic Diseases**

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To my family, with a special dedication to my parents and Celine

Abstract

Vaccines provide effective protection against diseases which can otherwise result in morbidity and mortality to the general population. This is even more relevant to patients suffering from autoimmune disease with a dysregulated immune system who are therefore more vulnerable, especially if on immunosuppressive therapy. The aim of the research is to provide information regarding vaccinations within immunocompromised patients suffering from autoimmune inflammatory rheumatic diseases (AIIRD). The methodology consisted of three phases. Phase 1 focused on a gap analysis to capture differences and similarities between practice guidelines in vaccination status recommendations issued by two main authorities in the field namely EULAR (European Alliance of Associations for Rheumatology) and American College of Rheumatology (ACR). Phase 2 consisted of the development, and validation of two separate questionnaires to rheumatologists and AIIRD patients respectively. Phase 3 focused on the dissemination of the questionnaires. The “Rheumatologists vaccination questionnaire” intended for rheumatologists captured the national experts practice on vaccinations in Maltese AIIRD patients. The “AIIRD vaccination perception and awareness questionnaire” aimed for AIIRD patients captured the perception and awareness of vaccination in a cohort of AIIRD patients. Study findings from Phase 1 indicate that the EULAR and ACR guidelines agree on recommendations put forward for vaccinations related to influenza, Pneumococcal vaccine, Hepatitis A and B and vaccinations against Covid-19 in AIIRD patients. There is a difference in the age range recommendation for Human Papilloma Virus vaccine whilst a lack of agreement for varicella zoster vaccine where EULAR suggests avoid during immunosuppression and ACR strongly recommends the vaccine in patients over 18 years of age whilst on immunosuppressive therapy.

Study findings from Phase 2 indicate that Maltese rheumatologists (n=3) follow EULAR guidelines and recommend that patients get their yearly influenza and COVID-19 vaccinations. Despite this, patients are still hesitant, fearful and not fully compliant as can be seen in Phase 3 of this study, with 10 out of the 13 who answered the questionnaire suggesting a need for more information about vaccine side effects for this cohort and are currently not satisfied with the information provided to them by health care professionals.

The research highlights a gap between patient and rheumatologist views, that could indicate the need for educational informative campaigns to address patient fears and concerns regarding vaccines. Pharmacist-led education can be relevant since pharmacists are highly accessible within the community and trained to bridge this gap to educate AIIRD patients by providing correct and up to date information without payment and address any queries and concerns.

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Table of Contents

| | |
|---|-----------|
| Abstract | iii |
| Acknowledgments | iv |
| List of Figures | viii |
| List of Appendices | ix |
| List of Abbreviations..... | x |
| | |
| Chapter 1 Introduction..... | 1 |
| 1.1. The multifacet of rheumatology conditions | 2 |
| 1.1.1 Aetiology and pathophysiology | 4 |
| 1.2 Relevance of vaccination in rheumatology | 7 |
| 1.3 Aim of the study | 10 |
| | |
| Chapter 2 Methodology..... | 11 |
| 2.1 Study design | 12 |
| 2.2 Phase 1: Gap analysis of EULAR and ACR guidelines..... | 12 |
| 2.3 Phase 2: Development and validation of tools..... | 12 |
| 2.3.1 <i>Validation of developed questionnaires.....</i> | <i>15</i> |
| 2.4 Phase 3: Dissemination of developed questionnaires..... | 15 |

| | |
|--|-----------|
| Chapter 3 Results..... | 17 |
| 3.1 Phase 1: Gap analysis of EULAR and ACR guidelines recommendations..... | 18 |
| 3.2 Phase 2: Validation of the developed questionnaires..... | 19 |
| 3.3 Phase 3: Study findings from disseminated questionnaires..... | 20 |
| 3.3.1 <i>Responses from rheumatologists on vaccination for AIIRD patients.....</i> | <i>20</i> |
| 3.3.2 <i>Responses from AIIRD patients on vaccination.....</i> | <i>21</i> |
| 3.5 The 'AIIRD vaccination perception and awareness questionnaire' responses | |
| Chapter 4 Discussion..... | 26 |
| 4.1 The importance of vaccinating AIIRD patients..... | 27 |
| 4.2 Challenges to patient vaccination adherence..... | 28 |
| 4.3 Limitations..... | 30 |
| 4.4 Recommendations for further studies..... | 30 |
| 4.5 Conclusion..... | 31 |
| References..... | 32 |
| Appendices..... | 37 |

List of Figures

| | |
|--|----|
| Figure 3.1 <i>Current rheumatology related medications indicated by responders</i> | 22 |
| Figure 3.2. <i>Vaccines taken by the responders</i> | 23 |

List of Appendices

| | |
|--|----|
| Appendix 1- Ethics Approval..... | 38 |
| Appendix 2 - The Rheumatologists AIIRD vaccination Questionnaire | 39 |
| Appendix 3- AIIRD vaccination perception and awareness Questionnaire | 42 |
| Appendix 4- The Rheumatologists AIIRD Questionnaire Validation..... | 46 |
| Appendix 5- AIIRD vaccination perception and awareness validation..... | 51 |
| Appendix 6- Study Information Sheet for Consultants | 56 |
| Appendix 7- Intermediary consent form | 57 |
| Appendix 8- Patient Informed Consent..... | 58 |

List of Abbreviations

Autoimmune Inflammatory Rheumatic Disease - AIIRD

European Union- EU

American College of Rheumatology- ACR

European League Against Rheumatism- EULAR

Systemic Lupus Erythematosus – SLE

Rheumatoid Arthritis- RA

Major Histocompatibility Complex – MHC

Antigen Presenting Cells – APC

Conventional Synthetic Disease Modifying Antirheumatic Drugs – cDMARDs

Targeted Biological Disease Modifying Antirheumatic Drugs - bDMARDs

Chapter 1
Introduction

1.1 The multifacet of rheumatology conditions

Rheumatology is an umbrella term which captures conditions where pain and stiffness in the musculoskeletal system are the prominent features (Mallia and Coleiro, 2016). Rheumatology conditions, also known as autoimmune inflammatory rheumatic diseases (AIIRDs), often lead to involvement of organs such as heart, lungs and eyes and lead to complications, co-morbidities and extra-articular manifestations (Goldblatt and O'Neill, 2013; Giles, 2019). This consequently leads to a substantial global burden on the health systems, the clinicians and the patients themselves (Shapira et al, 2010; Nikiphorou et al, 2018; An et al, 2019; Hsieh et al, 2020). In a report published in 2019 by the EULAR Task Force, it is stated that AIIRDs affect approximately 25% of European Union (EU) population equating to roughly 120 million individuals¹. According to the American College of Rheumatology, over 7 million American people suffer from AIIRD². AIIRD is shown to be the number one cause of disability in the United States of America with approximately 60% of patients suffering from AIIRDs experiencing limitations especially in their work life². Examples of autoimmune inflammatory rheumatic diseases include rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) psoriatic arthritis, to mention a few. Rheumatoid arthritis is an autoimmune inflammatory disease which affects the synovial tissues, this is caused by interaction of T lymphocytes, B lymphocytes and synovial fibroblasts which dysregulate the inflammatory cascade.

¹ EULAR Taskforce. RheumaMap: A research roadmap to transform the lives of people with Rheumatic and Musculoskeletal Diseases. [Internet] 2019 [cited November 2023]. Available from: <https://www.eular.org/web/static/lib/pdfs/web/viewer.html?file=https://www.eular.org/document/download/184/9ad4d185-1db2-4018-b3437668837ffdab/188>

² American College of Rheumatology. Rheumatic diseases in America: the problem, the impact, and the answers. [Internet] 2012 [cited November 2023]. Available from: https://www.bu.edu/enact/files/2012/10/ACR_Whitepaper_SinglePg.pdf

The disruption of the inflammatory cascade generally leads to dysregulation of tumour necrosis factor- α and interleukin-6 damaging bone, cartilage and joints through continuous inflammation and increased vascularity (Clunie et al, 2018). Symptoms of rheumatoid arthritis include pain, stiffness, swelling, warmth and redness in joints, lethargy, fever, poor appetite and weight loss with patients suffering from these symptoms even more after periods of rest (Mallia and Coleiro, 2016; Guo *et al.*, 2018). Women are three times more at risk to be diagnosed with rheumatoid arthritis (Akil and Veerapen, 2004). Systemic lupus erythematosus (SLE) is another example of an autoimmune rheumatic disease which involves a number of organs and tissues. Although the full aetiology of SLE is still not yet fully understood, factors such as genetic, immunological and environmental contribute to development of the condition (Tsokos et al, 2020). Patients with systemic lupus erythematosus suffer from lethargy, rash, fever, pain and stiffness and swelling in the joints, xerophthalmia, headaches and skin lesions which worsen with UV exposure, and is highly associated with cardiovascular, pulmonary, renal, haematological and neural systems involvement implying that patients can suffer from multiple co-morbidities (Fortuna and Brennan, 2013). Females have a risk of 10 times more than males to suffer from systemic lupus erythematosus. This has serious implications considering that lupus in pregnancy can be challenging with potential risks of pre-eclampsia to the mother and complications in the baby (Lateef and Petri, 2013; Do et al, 2019; Pastore et al, 2019). Psoriatic arthritis develops in 40% of patients that suffer from psoriasis. Psoriasis and psoriatic arthritis are heavily link with hereditary, the HLA-B and HLA-C genes have the strongest genetic risk factors and the familial factors can be as high as 80%, HLA genes are the ones that help the immune system identify the body's own proteins (Veale and Fearon, 2018).

The age group where symptoms generally manifest is between 20 and 40 years of age with cytokines IL-23 and IL-17 being implicated in the development of psoriatic arthritis (Clunie et al, 2018).

1.1.1 Aetiology and pathophysiology

The aetiology and pathophysiology of AIIRDs is complex. Commonly AIIRDs are chronic and progressive which result in the degradation of joints affecting younger and older patients depending on the respective condition within AIIRDs (O'Sangha, 2000). Autoimmune disease occurs when the immune system targets and attacks self-proteins and tissues leading to damage. Dysregulation in the immune system causing immune imbalance also plays a role in AIIRD as it promotes inflammation whilst reducing the immunity (Punt et al, 2018). Autoimmunity occurs when the body's defense mechanism that recognises infectious and malignant cells breaks down and produces antibodies and T-cells that attack the body. At this point there is no differentiation between self or non-self, giving rise to autoreactive T-cells which are unregulated causing destruction to tissue or cells with harmful effect (Rosenblum et al, 2015). T-lymphocytes (T-cells) respond to surface proteins known as major histocompatibility complex (MHC) which are split into two, class I proteins which present antigens to cytotoxic T-cells and class II, known as antigen-presenting cells, that present to helper T-cells. Cytotoxic T-cells are the CD8⁺ and helper T-cells are the CD4⁺, these two types characterize the T regulatory cells and a particular feature which distinguishes them is the Foxp3 transcription factor, a protein that regulates the function and development of regulatory T cells and is heavily involved in immune system response. The cytotoxic CD8⁺ cells have the ability to destroy infected cells whilst CD4⁺ helper T-cells should be able to coordinate

signals and even help other immune cells, the MHC class I molecules have to be present on all cells so that there can be antigen presentation to CD8⁺ cells and MHC class II proteins are expressed on the antigen presenting cell surface for CD4⁺ cell (Lleo et al, 2010). T-regulatory cells suppress immune response of T-cells, B-cells and antigen presenting cells (APCs) resulting in central tolerance which is the elimination of self-reacting lymphocytes generated in either the bone marrow or the thymus. A decreased number or reduced function of T-regulatory cells is implicated in autoimmune diseases (Denyer et al, 2011). Negative selection also plays an important role where thymocytes having receptors that can potentially bind to self-MHC or autoreactive clones and disrupt central tolerance are removed by apoptosis in the thymus, when negative selection does not function properly it can also result in autoimmune disorders. Laboratory tests are used to help in diagnosing AIIRDs, rheumatoid arthritis and systemic lupus erythematosus are classified as seropositive which means there is the presence of antinuclear antibodies and rheumatoid factor and in some cases like psoriatic arthritis, the auto antibodies are negative meaning that this is classified as seronegative (Punt et al, 2018).

Smoking, heavy metals and pesticides are also associated with autoimmune disease but exposure to micro-organisms such as bacteria, viruses and carcinogens can either damage DNA or interfere with polyclonal activation resulting in T- or B- cell clones and dysregulating the immune system, potentially causing the development of an autoimmune disease (Lleo et al, 2018; Manasson et al, 2020). Viruses, in particular, have the ability to trigger the process of an immune system malfunction in the natural defense mechanism (Punt et al, 2018). According to Punt et al, recent studies have suggested an association with the body's microflora, patients having in the early stage of rheumatoid arthritis have a decreased or absent bacteria that are specifically found in the intestines. This means that microflora in the gastrointestinal tract have an important role in homeostasis and immune system regulation,

it is now known that our microbiota, which are our microorganisms found in the internal environment have a two-way communication boosting our immunity to exogenous organisms. It is also being suggested that any nutrition changes and the increased use of antibiotics can dysregulate immune tolerance through disruption of the microflora in the gut (Punt et al, 2018). A study carried out by Sultan et al. in 2019 have concluded that patients who used antibiotics had a 60% more likelihood of developing RA but the class of antibacterial therapy and the type of infection varied the risk with respiratory pathogens having the strongest association with RA. This study also concluded that although different classes have different risk, still all carry a risk for RA development with clindamycin being the highest.

Studies have implicated various viruses such as Epstein-Barr and cytomegaloviruses in the pathophysiology of autoimmune diseases (Perl, 1999, Ercolini and Miller, 2008; Barzilai et al, 2017). In cases of AIIRD, the gut epithelial barrier is known to be compromised and the imbalance of the microflora can invoke inflammatory pathways which can lead to an inflammatory reaction especially in those who are pre-disposed to an AIIRD. A proposed mechanism of the association between gut microflora and AIIRD is molecular mimicry. This mechanism provides a possible theory because there is similarity between bacterial antigens and self-antigens, resulting in an activation of autoreactive T lymphocytes. It is also stated that this molecular mimicry is unlikely to be the only mechanism causing autoimmune disease and there are still unknown mechanisms at play in AIIRD with the suspected role of genetics still being evaluated (Rojas et al, 2018).

1.2 Relevance of vaccination in rheumatology

As mortalities and severe morbidities are of a high risk for patients suffering from AIIRD, vaccine preventable diseases are key in protecting this cohort of vulnerable patients (Colmegna and Libman, 2023). The goal of management of AIIRD is to suppress the immune response leading to AIIRD patients being administered immunosuppressive therapy (Mazzone et al, 2019). Common mainstay immunosuppressive therapy includes corticosteroids, conventional synthetic disease modifying antirheumatic drugs such as methotrexate, leflunomide and hydroxychloroquine (cDMARDs) and the ever-increasing armamentarium of the potent and targeted biological disease modifying antirheumatic drugs (bDMARDs) such as TNF alpha inhibitors, IL-1 inhibitors and IL-6 inhibitors, these treatments aim at suppressing the patients' immune system and prevent it from attacking healthy tissues and organs. DMARDs are important mainstays as they target the inflammatory process whilst also slowing down the disease progression and prevent joint deformities which proves that early use of DMARDs is a must as this can result in better patient prognosis and quality of life (Cohen et al, 2022). Patients with AIIRDs are at an increased risk towards infections including those which nowadays can be prevented through the administration of vaccines (Furer et al, 2019). This is because a reduced immune response due to immunosuppressive therapy being administered and an immune system that is not functioning properly, the risk of contracting an infection from an exogenous pathogen is higher with a study by Ranjan et al putting it as twice as likely to die from infections (Ranjan et al, 2015). This increased risk of infection highlights the relevance of vaccines in providing immunity in this high-risk cohort of patients (Papadopoulou et al, 2015). However, despite the acknowledged statement that vaccination is beneficial to safeguard AIIRD patients, there are a few challenges which must be taken into consideration towards safety of vaccines in these patients (Friedman and Winthrop, 2017).

One of these challenges focuses on the efficacy of vaccines since it is argued that patients on immunosuppressive therapy will mount a lower immune response towards the pathogen and therefore will result in a potential suboptimal effect. There is also the question on whether AIIRD patients who are not on immunosuppressive therapy can also generate an adequate response to the vaccine, their dysregulated immune system can hinder antibody formation and this in turn will also provide suboptimal protection (Ranjan et al, 2015, Puges et al, 2016, Subesinghe et al, 2018). Another challenge in terms of vaccination in AIIRD patients is the timing of administration of the vaccine especially if biological DMARDs are being administered or being considered for administration (Friedman et al, 2017). In order to ensure vaccine safety in these patients, there are different timing schedules for certain vaccines and taking into consideration disease activity status, type of vaccine (live attenuated versus inactivated) and patient general health status.

Live-attenuated vaccines use viruses or bacteria which have been cultured repetitively making them much weaker and a small dose of this weakened virus or bacteria is administered to the patient. The pathogen will then replicate enough to cause an immune response in the patient. This usually does not cause any ailment and any reaction or disease which is caused is generally considered an adverse event, but severe and life-threatening infections can happen in patients with a weakened immune system and that is why live attenuated vaccines are not recommended in AIIRD patients on immunosuppressive therapy as their immune response would be suboptimal which will result in uncontrolled proliferation of the pathogen³. Inactivated vaccines cannot cause disease in an immunosuppressed patient as the pathogen is killed or an antigen is used. Although inactivated vaccines are safer in immunosuppressed patients, it does not provide life-long immunity and a protective immune response is only achieved after a second or third immunization. As inactivated vaccines produce antibodies,

unlike the live-attenuated vaccines which mount a very similar response to the infection, an additional dose is needed periodically so there is an increase in antibodies³. A study carried out by Hannech et al. in 2022 concluded that there was lack of awareness on the importance of vaccination in rheumatology patients.

The World Health Organisation attributes vaccine hesitancy as one of the ten health threats which needs to be addressed in relation to safe immunization⁴. This vaccine hesitancy is shown in a study carried out by Krasselt et al. in 2016 where a German outpatient clinic reported low vaccination rates for vaccines which are strongly recommended like Pneumococcal and influenza vaccine. Only 33% of rheumatoid arthritis patients got vaccinated with Pneumococcal vaccine and 53% for the influenza. Another finding in this study was that for Pertussis vaccine, only 12% of rheumatoid arthritis patients got vaccinated. One method on how to increase the rate of vaccinations is to include vaccination records for assessment by the rheumatologist and the need for further vaccination should be reviewed yearly. The number of consultation hours per patient to be increased as physicians can pay more attention to the vaccination status of the AIIRD patients. Electronic records will also help in keeping track of patient vaccination (Moon, 2023).

³ Principles of Vaccination. [Internet] Centres for Disease Control and Prevention; 2021 [cited December 2023]. Available from: <https://www.cdc.gov/vaccines/pubs/pinkbook/prinvac.html#acknowledgements>

⁴ WHO. Ten threats to global health in 2019. [Internet] 2019 [cited November 2023]. Available from: <https://www.who.int/news-room/spotlight/ten-threats-to-global-health-in-2019>

The European Alliance for Associations for Rheumatology (EULAR), Europe's leading organisation in the field of rheumatology and AIIRDs published clinical guidelines on immunization within AIIRD patients in 2019. Its American counterpart, the American College of Rheumatology also published guidelines in 2022 which were further revised in February 2023. Both guidelines are intended to assist clinicians in recommending and administering appropriate vaccinations to patients suffering from AIIRDs for protection against preventable disease taking into consideration the latest Covid-19 pandemic.

1.3 Aim of the study

The aim of this study is to provide information regarding vaccinations to immunocompromised patients specifically suffering from AIIRDs. The objectives of the study are to:

- i. capture the adherence of the national scenario with European recommendations on vaccines
- ii. undertake a gap analysis on recommendations at international and national level
- iii. assess the perception and concerns of AIIRD patients in terms of vaccines.

Chapter 2

Methodology

2.1 Study design

The study was divided in three phases. Phase 1 consisted of undertaking a gap analysis between the recommendations of European Alliance of Associations for Rheumatology (EULAR) and American College of Rheumatology (ACR) to identify differences, if any, and similarities between the two main authoritative guidelines in the field of rheumatology. Phase 2 aimed at developing tools to capture i) the national experts practice on vaccination in the Maltese AIIRD patients and ii) the awareness and perception of Maltese AIIRD patients on vaccinations. Phase 3 focused on the dissemination the questionnaires developed from Phase 2. Ethical approval was granted by the University of Malta Faculty of Medicine and Surgery Research Ethics Committee with reference number MED-2023-00063 (Appendix 1).

2.2 Phase 1: Gap Analysis of EULAR and ACR guidelines

A literature review was undertaken to identify latest versions of vaccination guidelines put forward by EULAR and ACR respectively. The guidelines were analysed to identify the similarities and differences, findings were summarised in a table format. Data in the table consisted of the respective vaccines in both guidelines and the recommendations given by each authority.

2.3 Phase 2: Development and validation of tools

Two separate questionnaires for rheumatologists and AIIRD patients were developed and validated in this Phase. The '*Rheumatologists AIIRD vaccination questionnaire*' (Appendix 2) was developed with the aim to identify the current clinical practice in Malta in terms of vaccination recommendations in AIIRD patients and compare to the recommendations to the EULAR and ACR guideline recommendations. The '*Rheumatologists vaccination questionnaire*' was

disseminated in the English language but a professional translation by a certified proofreader was made into Maltese for both ethics approval and also in case a clinician preferred to answer in the Maltese language.

The '*Rheumatologists AIIRD vaccination questionnaire*' consisted of 12 questions focusing on i) identifying the vaccines that are routinely recommended to AIIRD patients, ii) the reference source is used by clinicians in their practice for decision making, iii) the occurrence of vaccine adverse reactions in this high-risk cohort, iv) whether patient education on vaccinations in this cohort is readily available and v) whether patients in Malta have enough knowledge regarding vaccine use within their condition. The questionnaire takes approximately 5-10 minutes to complete and was anonymous (Appendix 2).

Questions 1 and 2 focused on advice given to AIIRD patients in terms of vaccines and captured whether their experience the patients usually take the rheumatologist's advice and get vaccinated. Questions 3 and 4 focused on which guidelines do the clinicians follow for vaccination recommendations in AIIRD patient and if the commonly used guidelines do not specify, which sources do they refer to make a decision. Question 5 asked clinicians if they are aware whether vaccine manufacturer offers advice for administration in their summary of product characteristics for AIIRD patients whilst Question 6 asked which vaccines were routinely recommended where a list of 17 vaccines was given as options to choose from. For the ones they do not recommend, rheumatologists were asked to state the reason why. Question 7 focused on the increased risk of AIIRD patients with respect to vaccine related adverse reactions and used a Likert Scale from highly unlikely to highly likely (1 to 5). Questions 8 till 12 focused on recommendations of seasonal influenza vaccine, SARS-CoV2 (Covid-19) vaccine, suggestion of adding vaccines to be given free of charge, educational information to patients and the knowledge that patients have in terms of safety and relevance with respect to vaccines.

Questions 8, 9, 11 and 12 had a 'Yes' or 'No' option whilst in question 10 rheumatologists were asked to indicate which vaccines they suggest to be free to AIIRD patients.

The second questionnaire, titled the '*AIIRD vaccination perception and awareness questionnaire*' (Appendix 3) was developed with the aim of assessing the perception and concerns of AIIRD patients in relation to vaccines. The '*AIIRD vaccination perception and awareness questionnaire*' consisted of 4 sections. Section A captured the demographics. Section B gathered information on the type of rheumatology conditions, where 15 options of rheumatic diseases were given for patients to choose from for ease of reference. In case of patients having another condition which was not listed, they were asked to specify the condition. Section B asked patients how many years since their diagnosis. Section C identified the current anti-rheumatic medication, 14 options were given to patients. These included the standard treatment for AIIRD and if their treatment was not listed, patients were asked to specify. Section D looked at the patients' vaccination status, identifying the vaccines taken by patients, the question has 16 options of vaccines for patients to choose from and their compliance to vaccines recommended and the recommendations given by their clinicians with the list of vaccines given are according to the national immunisation schedule. Section D assessed concerns patients may have in relation to vaccines, whether enough educational information on vaccines in AIIRD is available for patients to make an informed decision or understand the recommendations given by their rheumatologist and capturing references sources patients refer to in order to gather information regarding vaccinations. The final question of Section D specifically asked the patients from which healthcare professional they are most comfortable seeking information. The questionnaire was anonymous, available in both English and Maltese and takes approximately 10 minutes to complete.

2.3.1 Validation of developed questionnaires

The '*Rheumatologists AIIRD vaccination questionnaire*' was validated by an expert panel consisting of 3 pharmacists and a medical doctor (N=4). A Google form sheet was compiled for validation (Appendix 4) and disseminated to the expert panel via google form link, where each question had a 5-point Likert Scale for clarity and relevance. All responses from the validation panel were anonymous.

The '*AIIRD vaccination perception and awareness questionnaire*' was validated in the same manner as the '*Rheumatologists vaccination questionnaire*' by an expert panel consisting of three pharmacists, a medical doctor and an AIIRD patient (N=5). A Google form sheet was compiled (Appendix 5) and disseminated via google form link to the expert panel where each question had a 5point Likert-Scale for clarity and relevance. All responses from the validation panel were anonymous.

2.4 Phase 3: Dissemination of developed questionnaires

Following ethics approval, dissemination of the developed and validated questionnaires was undertaken. Both the '*Rheumatologists vaccination questionnaire*' and the '*AIIRD vaccination perception and awareness questionnaire*' were developed via Google form sheets. However the '*Rheumatologists AIIRD vaccination questionnaire*' was distributed in paper format via the secretary of the Rheumatology department at Mater Dei Hospital for easier access to the rheumatologists in an attempt to facilitate response rate. The '*AIIRD vaccination perception and awareness questionnaire*' was distributed to patients within the Arthritis and Rheumatism Association Malta, in electronic format via the President of the Arthritis and Rheumatism Association Malta (ARAM) who acted as intermediary. The responses which were anonymous

were collected through Google Forms for analysis. For both questionnaires, a study information was attached to the questionnaire.

Chapter 3

Results

3.1. Phase 1: Gap analysis of EULAR and ACR guidelines recommendations

Study findings from Phase 1 focused on the gap analysis undertaken to compare the guidelines from the two main authorities in the field of rheumatology. It was noted that EULAR and ACR agree on vaccinating AIIRD patients for Influenza, Pneumococcal and Hepatitis A and B. EULAR provides recommendations for Haemophilus influenzae, Tetanus toxoid, Yellow Fever and Measles, Mumps and Rubella (MMR), Yellow fever and MMR are live-attenuated vaccines. EULAR recommends that AIIRD patients can be vaccinated with Haemophilus influenzae vaccine even during treatment. For the Tetanus toxoid, the recommendation is to administer according to general population guidelines and patients who are on B-cell depleting therapy such as rituximab can be given passive immunisation. EULAR also puts forward recommendations for Yellow Fever and MMR. This authority advises that Yellow Fever vaccine should be generally avoided in these patients. The MMR vaccine can be given with caution under special circumstances although this must be timed for 4 weeks prior starting treatment. The varicella zoster vaccine can be considered and given with caution in special circumstances in patients suffering from AIIRD. During immunosuppressive therapy the varicella zoster vaccine should be avoided and can be timed for 4 weeks prior to beginning immunosuppressive treatment. ACR strongly recommends vaccinating patients over 18 years and less than 50 years of age during immunosuppressive therapy. With respect to the Human Papilloma Virus vaccine (HPV), EULAR recommends vaccinating patients up to 26 years of age and for patients between the ages of 27-45 years, a discussion is recommended as per general population guidelines. ACR recommends the vaccinating AIIRD patients for HPV between the ages of 26-45 who are on immunosuppressive therapy. Both EULAR and ACR recommend the vaccination of the COVID-19 vaccine in AIIRD patients and that the timing should be appropriate with regards to the patient therapy in order to optimize vaccine use.

3.2. Phase 2: Validation of the developed questionnaires

In this section, the validation results of both the ‘Rheumatologists AIIRD Vaccination Questionnaire’ and the ‘AIIRD vaccination perception and awareness questionnaire’ are presented.

The *‘Rheumatologists AIIRD Vaccination Questionnaire’* was disseminated and validated by three pharmacists and one medical doctor (N=4). All expert panel members agreed that in general the questionnaire was clear and relevant. For question 2 looking at whether patients follow the rheumatologists’ advice on vaccine recommendation, a general comment put forward was to add the response option of ‘Do not Know’ in addition to ‘Yes’ and ‘No’. This comment was also put forward for question 5 asking whether clinicians are aware if the vaccine manufacturer gives advice for administration in AIIRD patients in the summary of product characteristics. Upon general comments received by the expert panel a further 2 questions namely: ‘Do you suggest changes in the availability of vaccines free of charge to AIIRD patients?’ and ‘Do you think that AIIRD patients have enough knowledge on vaccine use in AIIRD in terms of safety and relevance’ were added to the *‘Rheumatologists AIIRD Vaccination Questionnaire’*.

The *‘AIIRD vaccination perception and awareness questionnaire’* was disseminated and validated by three pharmacists, a medical doctor and an AIIRD patient (N=5). All expert panel members agreed that in general the questionnaire was clear and relevant. Following the expert panel recommendations, a question focusing on whether patients took the seasonal influenza vaccine and if they do not to kindly indicate why was added. The reason for the

addition of this question is to identify the reason AIIRD patients avoid getting vaccinated with the influenza vaccine. At the end of the *'AIIRD vaccination perception and awareness questionnaire'* on recommendation of the expert panel, the patients were invited to extra comment or suggest what they would like to improve regarding vaccines for rheumatology patients.

3.3 Phase 3: Study findings from disseminated questionnaires

This section presents the study findings of the responses related to the disseminated *'Rheumatologists AIIRD Vaccination Questionnaire'* and the *'AIIRD vaccination perception and awareness questionnaire'*

3.3.1 Responses from rheumatologists on vaccination for AIIRD patients

The *'Rheumatologists AIIRD Vaccination Questionnaire'* was disseminated to a total of six rheumatologists out of whom three responded.

All three rheumatologists agreed that they recommend their AIIRD patients to get vaccinated and that they themselves as rheumatologists follow the recommendations put forward through EULAR. When asked for sources which they used in addition to EULAR guidelines one rheumatologist indicated UpToDate, another one indicated the Arthritis UK as source whereas the third rheumatologist did not answer. All three rheumatologists answered 'Do Not Know' for question 5, which asked if the vaccine manufacturer provides advice for administration in AIIRD patients in the summary of product characteristics. The routine vaccine recommendations given by the three rheumatologists to AIIRD patients were Pneumococcal, Influenza and COVID-19 vaccines. One rheumatologist stated that live vaccines are not recommended in AIIRD patients on immunosuppressive therapy and that some of the

vaccines, such as Yellow Fever vaccine are of no clinical use, as risk of infection is insignificant if not travelling to high-risk areas. All three rheumatologists agreed that the Polio, Diphtheria, Pertussis, Tetanus, Haemophilus influenzae type b (Hib), Hepatitis A and B, MMR, Rotavirus and Meningitis are not routinely recommended. All three rheumatologists recommended the yearly influenza and yearly COVID-19 vaccines to AIIRD patients. All three rheumatologists suggested that the Pneumococcal vaccine should be given free of charge to patients suffering from AIIRD.

When rheumatologists were asked to score between 1 (highly unlikely) and 5 (highly likely) whether AIIRD patients are at increased risk of developing vaccine related adverse drug reactions when administered at the recommended time, all three rheumatologists indicated that this was unlikely. When asked whether in their opinion, there was enough educational information available for AIIRD patients and if whether this information can be used by health care professionals, all three answered 'Yes'. For the final question in the '*Rheumatologists AIIRD Vaccination Questionnaire*', rheumatologists were asked if in their opinion, AIIRD patients have enough knowledge on vaccine use in AIIRD in terms of safety and relevance to which all three rheumatologists (N=3) answered Yes.

3.3.2 Responses from AIIRD patients on vaccination

13 patients answered the 'AIIRD vaccination perception and awareness questionnaire' which was disseminated via the intermediary despite several reminders.

Six patients were in the age range of 41-60 years, another 6 were in the age range between 61-75 years and 1 patient was over 75 years. Eight patients indicated that they suffered from rheumatoid arthritis, three suffered from osteoarthritis, one from ankylosing spondylitis,

another patient had osteoporosis and one (n=1) had Palindromic Rheumatoid arthritis.

Six patients stated that they have had the condition for less than 5 years, two had the condition between 5-10 years, three had the condition between 10-20 years and another two patients had the condition for over 20 years. Four patients stated that they were on methotrexate, two were on hydroxychloroquine and rituximab respectively whereas prednisolone, etanercept, leflunomide and naproxen were indicated as being taken by one patient each respectively. Seven patients chose 'other' as treatment option. Out of these 7, two indicated that they were on calcium supplements, whilst glucosamine and chondroitin supplements, ibuprofen, paracetamol and Ixekizumab were indicated by one patient respectively.

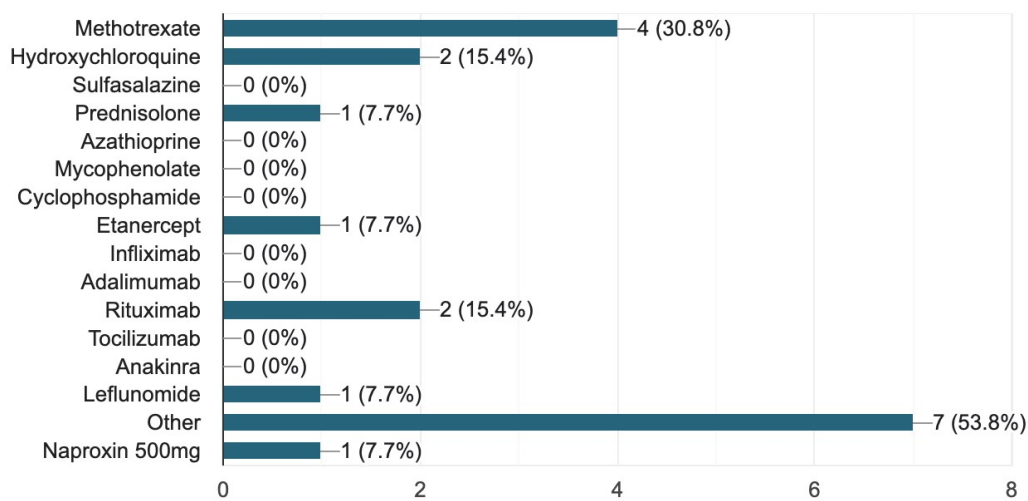


Figure 3.1. Current rheumatology related medications indicated by responders (N=13 patients)

A total of 10 patients claimed that they took the COVID-19 vaccine and 9 patients stated that they take the influenza vaccine yearly. Six patients had been administered the tetanus vaccine and five the MMR. Five patients had been administered the Polio, four patients have been

administered the Pneumococcal, three patients the Varicella and Hepatitis A respectively. Two of the patients who answered the questionnaire stated that they have been administered the diphtheria, pertussis, Haemophilus influenza type b and Hepatitis B respectively. One patient was administered the yellow fever and smallpox.

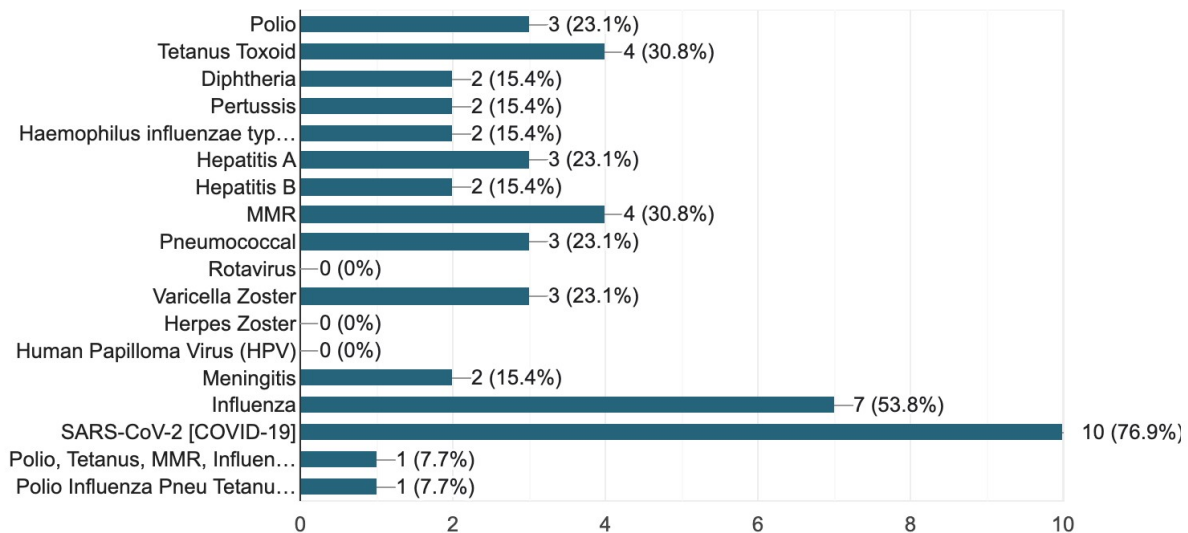


Figure 3.2. Vaccines taken by the responders (N=13 patients)

Out of 13 patients, 9 indicated that they take the seasonal influenza vaccine on a yearly basis and that they feel safe in taking it on a yearly basis. Three patients stated that they sometimes miss taking it and 2 patients stated that they never took this vaccine. Out of the 5 patients who either never took the vaccine or do not take it on a yearly basis, two patients stated that following the vaccine they had an inflammatory response with joint pains, one patient stated fear as the reason for not taking it, another patient stated that vaccination is always followed by a period of sickness due to flu itself immediately after taking it and another patient stated that the vaccine is not taken because the influenza season did not effect this patient. All 13

patients stated that they took the first dose of COVID-19 vaccine, but only 8 stated that they felt safe taking it.

When patients were asked if they always follow their health care professional's advice regarding recommendations on vaccinations, the majority (n=10) answered 'Yes'. Out of the 3 patients who answered 'No' one patient reported that they did some research online and took the decision based on that, one patient mentioned that they disliked vaccinations, and one patient reported fear as being the primary reason for not following the advice given by the rheumatologist. One patient reported feeling bad after the second Covid-19 vaccine and decided to stop taking any more boosters. Out of 13 patients who answered the questionnaire, 6 patients stated that they follow or read any studies regarding vaccination in rheumatology. Out of these 6 patients, 5 follow the EULAR published documents on vaccinations in rheumatology. A total of 10 patients stated that there is not enough information available for patients to make informed decisions on getting vaccinated or not. Seven patients reported that they are most comfortable seeking information from their hospital consultant, 4 from their general practitioner, 1 from the pharmacist and 1 patient relied on information available on the internet.

For the final question of the 'AIIRD vaccination perception and awareness questionnaire', which asked the patients for suggestions in order to improve vaccinations in AIIRD patients, 7 patients wished to have access to more information regarding vaccines and their side effects in their condition with more awareness and informative programmes including the risk and benefits associated with taking or not taking the vaccines. One patient suggested more timely assistance from the rheumatology helpline and one patient recommended a vaccination review and the subsequent administration of missing vaccinations prior to initiation of

immunosuppressive therapy. One patient stated that the Pneumococcal vaccinations should be given free of charge to AIIRD patients.

Chapter 4

Discussion

4.1 The importance of vaccinating AIIRD patients

Guidelines from both EULAR and ACR agree that AIIRD patients need to be vaccinated with the seasonal influenza vaccine, COVID-19, Pneumococcal and Hepatitis A and B. These vaccines are safe in patients and will prevent them from life-threatening infections and their importance was highlighted in a study conducted by Vazquez et al. in 2024. This study reports that the pathogens who had more fatal and serious consequences in AIIRD patients were COVID-19, *P. aeruginosa* and pneumococci which clearly shows the need for patient vaccination. Maltese rheumatologists who participated in answering the questionnaire also agreed in patients getting vaccinated yearly with the Influenza and COVID-19 vaccines whilst also taking the Pneumococcal vaccination. Pneumonia affects 17% of patients per year with those on prednisone being at a higher risk of infection and a risk of morbidity and mortality being a consequence of these infections with the lungs are particularly a common target of infections (Di Franco et al, 2017). This is also a reason why the Pneumococcal vaccine should be given free of charge, as currently the price stands at around €63.00, and this might improve compliance and has been given as a suggestion by both Maltese rheumatologists and by AIIRD patients. Maltese rheumatologists do not recommend the administration of live vaccines in AIIRD patients on immunosuppressive therapy, live vaccines are attenuated which means they are made weaker and less virulent, but they are still active and for patients who have a dysregulated immune system might be at an increased risk of a fatal infection due to the live pathogen replicating itself without control. EULAR provides the timing for MMR and varicella zoster to be given 4 weeks prior to therapy initiation to prevent complications, this will provide enough time for their immune system to provide the necessary antibodies whilst also

controlling the viral replication.

4.2 Challenges to patient vaccination adherence

Study findings from the AIIRD vaccination perception and awareness questionnaire, 5 patients have commented that they are afraid of taking the yearly influenza and COVID-19 vaccines, reasons given by these patients is because of fear of side effects. One of the side effects reported by patients is a flare of their rheumatology condition which involves inflammation and joint pains, even when patients are under control with their treatment. A study regarding flares in autoimmune patients was conducted by Jagtap et al. in 2023 and reported that 1 in 10 AIIRD patients reported flares including pain and fatigue. However one has to note that myalgia was one of the prominent adverse effects of any COVID-19 vaccination even in non-AIIRD population and which could be easily mistaken for a flare in these patients. The low hospitalisation rates following vaccinations which are documented in literature continues to bolster the argument that vaccines do prevent severe illness but patients who are not in remission or are at the beginning of treatment will require monitoring (Fong et al, 2023). Study findings indicate that in line with EULAR and ACR recommendations, Maltese rheumatologists recommend patients to get vaccinated with the COVID-19 vaccine yearly, as this will prevent complications which can result in further morbidity and mortality. In total the majority of the respondents, 10 out of 13 stated that they followed the rheumatologists' recommendations for COVID-19 vaccine. There seems to be more hesitancy when it comes to the yearly seasonal influenza vaccine. This hesitancy and fear of side effects could be targeted through strategies that involve education and informative sessions to patients which is also what some patients have indicated to be a way forward.

A perhaps hidden challenge is this issue of education. Responses from rheumatologists answering the Rheumatologists AIIRD vaccination questionnaire, the rheumatologists have commented that in their opinion, the AIIRD patients have enough knowledge on vaccine use in their conditions with regards to safety and efficacy and that there is enough educational information for patients which can be used in order to make an informed decision. However, the patients feel there is not enough information for them to make an informed decision regarding vaccinations. Patients who look up information cited reliable sources such as EULAR but a random search on internet was also mentioned. This raises serious issues regarding the reliability of accessible information which is available on the internet especially considering random searches. Patient education led by pharmacists could be a strategy to address and resolve gaps in knowledge for patients on vaccinations. As health care professionals and most importantly as pharmacists, who are constantly accessible and can provide advice free of charge play an important role in educating patients on vaccines, address their concerns and try to improve their compliance whilst also explaining the need for them to get vaccinated due to their AIIRD condition. Pharmacists have always been at the forefront in providing patient care and medication review with patients also looking for advice and asking for information to their pharmacist of choice both for information and for minor ailments. This can be an opportunity in providing patients with the correct and most recent information on vaccines, during the opening hours of the pharmacy and at no cost (Lisenby 2021; Terrie, 2021). Pharmacists providing information regarding vaccinations is carried out on a day-to-day basis, but training can be given in order to improve the knowledge of vaccinations in AIIRD patients and also to be aware of the type of treatment the patient is taking and if there is the need for any modifications regarding to the timing of vaccinations. This method can also ease the workload on the consultant rheumatologists and patients do not have to wait for their

appointment to ask any questions or pay a fee to their GP with respect to any queries they have on vaccines (Lisenby 2021; Terrie, 2021). Pharmacists could also provide education to patients especially the younger generations who are more apt toward digital information on how to do their research online and to read articles and studies from scientific websites like PubMed or the British medical journal which are peer-reviewed and provide evidence of their findings. This ensures that patients will know what to look for and be able to identify good sources of information, minimise the exposure of unfounded information without evidence and myth and can also be encouraged to ask anything they do not understand about articles or studies (Ullrich Jr et al, 2002).

4.3 Limitations

The main limitation of this study was the patient responses for the 'AIIRD vaccination perception and awareness questionnaire'. Only 13 responses were obtained despite constant communication with the intermediary of the study for more responses by patients who are members in the ARAM. The intermediary did not provide the total number of members to calculate the percentage response of the said members. Reminders were sent via email but were not answered by the intermediary. An attempt at recruiting another intermediary was made via email and was not acknowledged or answered.

4.4 Recommendations for further studies

It would be recommended to increase the robustness of the study by gathering responses to the 'AIIRD vaccination perception and awareness questionnaire' maybe through the

Rheumatology Clinic, although one understands the limitation in time for such a busy clinic. A more robust study would be able to support the prospective study of establishing a pharmacist-led vaccination informative campaign for AIIRD patients thus reducing patient hesitancy towards vaccination, ensuring correct and adequate vaccination status during AIIRD treatment and allowing timely communication between patients and pharmacists on concerns of vaccinations. On a final note, it is to be highlighted that this study was intended for adults suffering from AIIRD (patients had to be 18 years of age). It would be interesting to gather scientific data on concerns of parents whose children suffer from AIIRDs and who fall within the range where most of the recommended standard vaccines are to be administered. This data could contribute towards closing gaps and assist parents in their decision making.

4.5 Conclusion

The data gathered from both questionnaires have indicated that more communication with patients is needed to address their concerns regarding adverse effects of vaccines and to provide evidence-based information. The importance of vaccines has long been proven but we also need to remember that communication can be a solution for fear and hesitancy. The underuse of the contribution of pharmacists in this aspect is greatly highlighted and should be addressed by pharmacists with the aim of providing a more holistic and beneficial service to our patients.

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Appendices

Appendix 1 – Ethics Approval



**L-Università
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Ref No: MED-2023-00063

16 May 2023

Mr Jonathan Joseph Attard
Entrance D Flat 5 Triq il-Vaguni
Binja tas-salib,
Birkirkara, BKR4820

With reference to your application submitted to the Faculty Research Ethics Committee in connection with your research entitled:

Vaccinations in Rheumatology

The Faculty Research Ethics Committee is granting ethical approval for the above-mentioned application.

A handwritten signature in blue ink, appearing to read 'A Serracino'.

Professor Anthony Serracino Inglott
Chair
Faculty Research Ethics Committee

Appendix 2- The Rheumatologists AIIRD vaccination Questionnaire

1. In general, as a clinician, do you advise AIIRD patients to get vaccinated?

- Yes
- No
- Not Always

If No or not always please state reason: _____

2. From your experience do patients usually take your advice and get vaccinated?

- Yes
- No

If No, what do you think is the reason for non-compliance?

3. Which guidelines do you follow for vaccine recommendation in AIIRD patients?

- European Alliance of Associations for Rheumatology (EULAR)
- American College of Rheumatology (ACR)
- Other

If you selected Other, Please Specify which guidelines: _____

4. In cases where guidelines do not specify whether a vaccine is recommended for AIIRD patients, what sources do you refer to make a decision?

5. Does the vaccine manufacturer give advice for administration in AIIRD patients in the SPC?

- Yes
- No
- Do not Know

6. Which vaccines do you **routinely** recommend in AIIRD patients?

- Polio
- Diphtheria
- Tetanus Toxoid
- Pertussis

Haemophilus influenzae type b (Hib)
 Hepatitis A
 Hepatitis B
 MMR
 Pneumococcal
 Rotavirus
 Varicella Zoster
 Herpes Zoster
 Yellow Fever
 Human Papilloma Virus (HPV)
 Meningitis
 Influenza
 SARS-CoV-2 Covid-19

For the ones you do not recommend, can you please state the reason why?



7. From your experience, please rate the following: Rheumatology patients are at an increased risk of developing vaccine related adverse drug reactions when these are administered at the recommended time i.e taking into consideration biologics doses. 1. Highly Unlikely 2. Unlikely 3. Do Not know 4. Likely 5. Highly Likely

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| | | | | |

8. Do you generally recommend seasonal yearly influenza vaccine to AIIRD patients?

Yes
 No

9. Did you recommend Covid-19 vaccine to AIIRD patients?

Yes
 No

10. Do you suggest changes in the availability of vaccines free of charge to AIIRD patients?

11. Do you think that there is enough educational/information resources available on vaccines for AIIRD patients which can be used as source of information by healthcare professionals?

Yes

No

12. Do you think that AIIRD patients have enough knowledge on vaccines use in AIIRD in terms of safety and relevance?

Yes

No

Appendix 3 - AIIRD vaccination perception and awareness Questionnaire

Section A: Demographics

- i) Age:
- 18- 25 years
 - 26 – 40 years
 - 41 – 60 years
 - 61 – 75 years
 - Over 75 years

Section B: Rheumatology medical history

- i) Please indicate your rheumatology condition:
- Rheumatoid arthritis
 - Psoriatic arthritis
 - Systemic lupus erythematosus
 - Ankylosing spondylitis
 - Adult Still's disease
 - Sjorgen's syndrome
 - Anti-phospholipid syndrome
 - Systemic sclerosis
 - Polymyositis
 - Dermatomyositis
 - Giant cell arteritis
 - Vasculitis
 - Bechet's disease
 - Familial Mediterranean Fever
 - Polyarteritis nodosa
 - Other: _____
- ii. How long have you been suffering from the rheumatology condition?
- less than 5 years
 - 5 to 10 years
 - 10 to 20 years
 - More than 20 years

Section C: Rheumatology medication history

- i) Currently I am on the following medications:
You may tick more than one
- Methotrexate
 - Hydroxychloroquine
 - Sulphasalazine
 - Leflunomide

Prednisolone
Azathioprine
Mycophenolate
Cyclophosphamide
Etanercept
Infliximab
Adalimumab
Rituximab
Tocilizumab
Anakinra
Other, Kindly indicate your medication: _____

Section D: Vaccination status

i. Which of the following vaccines have you had? You can choose more than one option.

- Polio
- Diphtheria
- Tetanus Toxoid
- Pertussis
- Haemophilus influenzae type b (Hib)
- Hepatitis A
- Hepatitis B
- MMR
- Pneumococcal
- Rotavirus
- Varicella Zoster
- Herpes Zoster
- Human Papilloma Virus (HPV)
- Meningitis
- Influenza
- Covid-19 vaccine

ii. With respect to the seasonal influenza vaccine, do you take it:

- Every year, and go to iib
- Not every year, and go to iic
- Never took it, and go to iic

iib. As a rheumatology patient I feel safer taking the seasonal influenza vaccine

- Yes
- No

ii. If you never took the seasonal influenza vaccine or you take it but not on a yearly basis, kindly indicate why:

- Fear
- Accessibility of the vaccine
- Other

iii. With respect to the Covid-19 vaccine, please indicate if you took it or no:

Yes and go to iiib No
and go to iiic.

iiib. As a rheumatology patient I feel safer taking the Covid-19 vaccine

- Yes
- No

iiic. If you never took Covid-19 vaccine, kindly indicate why:

- Fear
- Accessibility of the vaccine
- Other

iv. Who recommends to you to get vaccinated for the yearly seasonal vaccine?

- General Practitioner
- Rheumatologist
- Pharmacist
- Other, please specify: _____

v. Who recommended to you to get vaccinated for the Covid-19 vaccine?

- General Practitioner
- Rheumatologist
- Pharmacist
- Other, please specify: _____

vi. Do you always followed your healthcare professional's advice regarding vaccine recommendations?

- Yes
- No

If No, please state reason

vii. Do you read and/or follow studies regarding vaccinations in rheumatology patients?

Yes

No

If Yes, which studies?

American College of Rheumatology (ACR)

European Alliance of Associations for Rheumatology (EULAR)

Other Studies

If you selected Other studies, kindly specify _____

viii. Do you think there is enough information, either from medical sources or from health care professionals, to make an informed decision whether to get vaccinated or not?

Yes

No

ix. From where are you most comfortable seeking information and advice regarding vaccines:

Hospital specialist/consultant

Hospital specialist nurse

General practitioner

Pharmacist

Other sources

If you opted for Other Sources, kindly specify the source:

Comments or suggestions on what you would like to improve in terms of vaccines for patients like yourself

Appendix 4- The Rheumatologists AIIRD vaccination Questionnaire Validation

Questionnaire Validation

1 is the lowest score

5 is the highest score

You can add comments below each respective question.

* Indicates required question

1. 1. Currently, are there any finalised or ongoing studies regarding vaccinations * in AIIRD patients?

Mark only one oval per row.

| | 1 | 2 | 3 | 4 | 5 |
|-----------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Clarity | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| Relevance | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

2. Comment

3. 2. As a clinician/physician, do you advise AIIRD patients to get vaccinated? *

Mark only one oval per row.

| | 1 | 2 | 3 | 4 | 5 |
|-----------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Clarity | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| Relevance | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

4. Comments

5. 3. If yes in 2, Do these patients take your advice and get vaccinated? *

Mark only one oval per row.

| | 1 | 2 | 3 | 4 | 5 |
|-----------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Clarity | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| Relevance | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

6. Comment

7. If No, what do you think is the reason for non-compliance? *

Mark only one oval per row.

| | 1 | 2 | 3 | 4 | 5 |
|-----------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Clarity | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| Relevance | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

8. 4. Do you think that there is enough education locally in the rheumatology

* community regarding vaccinations?

Mark only one oval per row.

| | 1 | 2 | 3 | 4 | 5 |
|-----------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Clarity | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| Relevance | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

9. Comments

10. 5. Which guidelines do you follow for vaccine recommendation in

* rheumatology patients?

Mark only one oval per row.

| | 1 | 2 | 3 | 4 | 5 |
|-----------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Clarity | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| Relevance | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

11. Comments

12. 6. Are the available guidelines sufficient for you to make a decision whether vaccinated? * an AIIRD patient should get

Mark only one oval per row.

| | 1 | 2 | 3 | 4 | 5 |
|-----------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Clarity | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| Relevance | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

13. Comments

14. 7. When guidelines do not specify, how do you make your decision? *

Mark only one oval per row.

| | 1 | 2 | 3 | 4 | 5 |
|-----------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Clarity | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| Relevance | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

15. Comment

16. 8. Does the vaccine manufacturer give advice for administration in Rheumatology/AIIRD patients in the SPC?
Mark only one oval per row.

| | 1 | 2 | 3 | 4 | 5 |
|-----------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Clarity | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| Relevance | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

17. Comment

18. 9. Is there a need for local vaccine recommendations in these patients? *
Mark only one oval per row.

| | 1 | 2 | 3 | 4 | 5 |
|-----------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Clarity | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| Relevance | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

19. Comment

20. 10. Which vaccines do you recommend in these patients? The ones you do not recommend, can you state the reason?
Mark only one oval per row.

| | 1 | 2 | 3 | 4 | 5 |
|-----------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Clarity | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| Relevance | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

21. Comment

22. When do you recommend AIIRD patients to take their vaccinations? *

Mark only one oval per row.

| | 1 | 2 | 3 | 4 | 5 |
|-----------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Clarity | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| Relevance | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

23. Comment

24. 12. In your opinion, is there a question regarding the efficacy of vaccination in these patients due to their immune system being imbalanced, dysregulated and ultimately harmful to the patient?

Mark only one oval per row.

| | 1 | 2 | 3 | 4 | 5 |
|-----------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Clarity | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| Relevance | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

25. Comment

26. 13. Are rheumatology patients at an increased risk in developing vaccine related adverse drug reactions?

Mark only one oval per row.

| | 1 | 2 | 3 | 4 | 5 |
|-----------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Clarity | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| Relevance | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

27. Comment

Appendix 5 - AIIRD vaccination perception and awareness Questionnaire validation

Questionnaire Validation

1 is the lowest score

5 is the highest score

You can add comments below each respective questions

* Indicates required question

1. Medical History and Current Treatment *

Mark only one oval per row.

| | 1 | 2 | 3 | 4 | 5 |
|-----------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Clarity | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| Relevance | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

2. Comment *

3. Currently I am on the following medications *

Mark only one oval per row.

| | 1 | 2 | 3 | 4 | 5 |
|-----------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Clarity | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| Relevance | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

4. Comments

5. 1. How long have you been suffering from the rheumatology condition? *

Mark only one oval per row.

| | 1 | 2 | 3 | 4 | 5 |
|-----------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Clarity | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| Relevance | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

6. Comments

7. 2. Have you been administered the following Vaccines *

Mark only one oval per row.

| | 1 | 2 | 3 | 4 | 5 |
|-----------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Clarity | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| Relevance | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

8. Comments

9. 3. I take the yearly seasonal influenza vaccine? *

Mark only one oval per row.

| | 1 | 2 | 3 | 4 | 5 |
|-----------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Clarity | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| Relevance | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

10. Comments

11. 4. I feel safe taking the seasonal influenza vaccine *

Mark only one oval per row.

| | 1 | 2 | 3 | 4 | 5 |
|-----------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Clarity | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| Relevance | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

12. Comments

13. 5. I feel safe taking the Covid-19 vaccine *

Mark only one oval per row.

| | 1 | 2 | 3 | 4 | 5 |
|-----------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Clarity | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| Relevance | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

14. Comments

15. 6. Does your Physician encourage you to get vaccinated? *

Mark only one oval per row.

| | 1 | 2 | 3 | 4 | 5 |
|-----------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Clarity | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| Relevance | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

16. Comments

17. 7. Have you always followed your Physicians' advice regarding vaccine * recommendations?

Mark only one oval per row.

| | 1 | 2 | 3 | 4 | 5 |
|-----------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Clarity | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| Relevance | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

18. Comments

19. 8. Do you read and/or follow studies regarding vaccinations in rheumatology * patients

Mark only one oval per row.

| | 1 | 2 | 3 | 4 | 5 |
|-----------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Clarity | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| Relevance | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

20. Comments

21. 9. Do you think there is enough information, either from medical sources or * from health care professionals, to make an informed decision whether to get vaccinated or not?

Mark only one oval per row.

| | 1 | 2 | 3 | 4 | 5 |
|-----------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Clarity | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| Relevance | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

22. Comments

23. 10. From where are you most comfortable seeking information and advice * regarding vaccines:
Mark only one oval per row.

| | 1 | 2 | 3 | 4 | 5 |
|-----------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Clarity | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| Relevance | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

24. Comments

Appendix 6- Study Information Sheet for Consultants

Dear Consultant,

My name is Jonathan Attard, a Pharmacy student currently reading for Master of Pharmacy at the Department of Pharmacy, Faculty of Medicine and Surgery, University of Malta. As part of my M.Pharm requirements, I am carrying out a study entitled: *Vaccinations in Rheumatology* under the supervision of Dr Louise Grech (Email: louise.grech@um.edu.mt)

I would like to distribute a questionnaire titled: *"The Rheumatologists AIIRD Vaccination Questionnaire"* to Rheumatologists willing to complete it on a voluntary and anonymous basis. The aim of the questionnaire is solely to capture the current clinical practice in Malta in terms of vaccination recommendations in Autoimmune Inflammatory Rheumatic Disease (AIIRD) patients.

The questionnaire is on a voluntary basis and takes about 10 minutes to complete.

Thank you

Yours sincerely,

Jonathan Joseph Attard jonathan.attard.15@um.edu.mt

ID No: 3695M

Contact No: +35679908408

I, _____, consent to fill in the questionnaire on a voluntary basis.

Signature and Warrant Number:

Date:

Appendix 7- Intermediary consent form

President
Arthritis and Rheumatism Association Malta Mgarr,
Malta

7th February 2023

Dear [XXXX] ,

I am Jonathan Attard, a pharmacy student currently reading for my pharmacy degree at the Department of Pharmacy, Faculty of Medicine and Surgery, University of Malta. As part of my degree requirements I am carrying out a study entitled: *Vaccinations in Rheumatology* under the supervision of Dr Louise Grech. I would like to distribute a questionnaire titled: *"AIIRD vaccination perception and awareness Questionnaire"* to patients willing to complete it on a voluntary and anonymous basis. The aim of the questionnaire is solely to capture vaccination status of AIIRD patients and their concerns and perception of vaccines. I would like to ask you if you, if you could act as intermediary and could disseminate the questionnaire to patients aged over 18 years in your ARAM group. If you consent, I will send you the questionnaire google form link which you could disseminate to your patient group. The questionnaire is on a voluntary basis and takes about 10 minutes to complete.

Thank you
Yours sincerely
Jonathan Joseph Attard
ID No: 3695M
Contact No: +35679908408

I, [XXXX], consent to act as intermediary and disseminate the questionnaire google link to the patients aged 18 years and over in the ARAM group.

Signature and ID No:

Date:

Appendix 8- Patient informed consent

Dear Participant,

My name is Jonathan Joseph Attard, currently reading for the Master of Pharmacy in the Department of Pharmacy at University of Malta. For my dissertation I am conducting a research study titled 'Perception and awareness of vaccinations in Autoimmune Inflammatory Rheumatic Diseases' under the supervision of my tutor Dr. Louise Grech from the Department of Pharmacy. This is an invitation to participate in this study through the questionnaire 'Vaccinations In Rheumatology- AIIRD vaccination perception and awareness Questionnaire'. Below you will find information about what your involvement would entail, should you decide to take part. Please note that this study will be conducted in English only.

The aim of this study is to provide information regarding vaccinations to immunocompromised patients specifically suffering from AIIRDs. The objectives are to:

- i. capture the adherence of the national scenario with European recommendations on vaccines
- ii. recommend a national framework for vaccination within the AIIRD patients
- iii. assess the perception and concerns of AIIRD patients in terms of vaccines.

Data collected from the questionnaire will remain completely anonymous.

Participation in this study is entirely voluntary; you are free to accept or refuse to participate, without needing to give a reason. You are also free to withdraw from the study at any time, without needing to provide any explanation and without any negative repercussions for you.

If you choose to participate, please note that there are no direct benefits to you, however participation would contribute towards research in the field of rheumatology.

Any data collected from this study will not include personal or identifiable information.

Thank you for your time and consideration. Should you have any questions or concerns, please do not hesitate to contact me via e-mail on jonathan.attard.15@um.edu.mt or my study supervisor on louise.grech@um.edu.mt

If you agree - proceed to answer the questionnaire

if you disagree- exit the questionnaire