A protocol to differentiate the COVID-19 infection and vaccine experiences of patients with systemic, single site and overlap immune-mediated inflammatory disease (IMID)

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Abstract

Background: Patients with immune-mediated inflammatory disease (IMID), including autoimmunity, fared significantly worse than the general population during the COVID-19 pandemic both in terms of infection outcomes and levels of life disruption. Despite this, COVID-19 vaccine uptake has not been universal. The absence of IMID patients from clinical trials and the subsequent lack of precision in vaccine safety profiling adds to vaccine hesitancy in this high-risk group.

Objective: The present protocol sets out an investigation that aims to address this by enhancing COVID-19 vaccine pharmacovigilance for patients with IMID. Combining the international data and knowledge assets of the COVID-19 Vaccination in Autoimmune Diseases (COVAD) 1 Study and the electronic Delphi Study to Define and Risk-Stratify Immunosuppression (DESTINIES), its objective is to differentiate patient-reported COVID-19 infection and vaccine outcomes between systemic, single site and overlap IMID patients and general population controls.

Methods: The COVAD 1 Study successfully collected data on the demographic, health, COVID-19 infection and COVID-19 vaccination outcomes of a broad range of IMID patients between March and December 2021. The present protocol expands on this initial analysis, utilising IMID expertise within the DESTINIES Consortium to allocate survey respondents into single site and systemic categories and thereby produce comparative vaccine benefit-risk profiles between these and general population controls. Due to respondents' ability to self-declare multiple diagnoses, an overlap group was introduced for those affected by both single site and systemic diagnoses. Descriptive statistics, Chi-squared tests of independence, incidence rate ratios and multivariable logistic regressions will be utilised to test for significant differences in COVID infection rates, severity, duration and vaccine side effects between populations.

Results: We anticipate that more severe COVID-19 infection outcomes (hospitalisation with and without Oxygen support) and vaccine side effects (mild and major) were reported amongst systemic patients than single site IMID patients. We expect this will be moderated by factors including age, prior health status and medication, however. The multimorbidity of the overlap IMID

category is also expected to result in increased adverse COVID-19 infection and vaccine outcomes compared to exclusively single site patients.

Conclusions: Advocating for direct-to-patient vaccine reporting pathways, this study intends to provide more precise vaccine safety profiles of IMID patients. It seeks to address current gaps in pharmacovigilance and potentially remedy vaccine hesitancy in high-risk groups by doing so.

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Abstract:

Introduction:
Patients with immune-mediated inflammatory disease (IMID), including autoimmunity, fared significantly worse than the general population during the COVID-19 pandemic both in terms of infection outcomes and levels of life disruption. Despite this, COVID-19 vaccine uptake has not been universal. The absence of IMID patients from clinical trials and the subsequent lack of precision in vaccine safety profiling adds to vaccine hesitancy in this high-risk group. The present protocol sets out an investigation that aims to address this by enhancing COVID-19 vaccine pharmacovigilance for patients with IMID. Combining the international data and knowledge assets of the COVID-19 Vaccination in Autoimmune Diseases (COVAD) 1 Study and the electronic Delphi Study to Define and Risk-Stratify Immunosuppression (DESTINIES), its objective is to differentiate patient-reported COVID-19 infection and vaccine outcomes between systemic, single site and overlap IMID patients and general population controls.

Methods:
The COVAD 1 Study successfully collected data on the demographic, health, COVID-19 infection and COVID-19 vaccination outcomes of a broad range of IMID patients between March and December 2021. The present protocol expands on this initial analysis, utilising IMID expertise within the DESTINIES Consortium to allocate survey respondents into single site and systemic categories and thereby produce comparative vaccine benefit-risk profiles between these and general population controls. Due to respondents' ability to self-declare multiple diagnoses, an overlap group was introduced for those affected by both single site and systemic diagnoses. Descriptive statistics, Chi-squared tests of independence, incidence rate ratios and multivariable logistic regressions will be utilised to test for significant differences in COVID infection rates, severity, duration and vaccine side effects between populations.

Results:
We anticipate that more severe COVID-19 infection outcomes (hospitalisation with and without Oxygen support) and vaccine side effects (mild and major) were reported amongst systemic patients than single site IMID patients. We expect this will be moderated by factors including age, prior health status and medication, however. The multimorbidity of the overlap IMID category is also expected to result in increased adverse COVID-19 infection and vaccine outcomes compared to exclusively single site patients.

Discussion:
Despite the international nature of COVAD data collection and the nuance of information made available through self-report, we acknowledge that this planned investigation could be criticised for small sample sizes, time elapsed since initial data collection and its dependence on patient recall.

Conclusion:
Advocating for direct-to-patient vaccine reporting pathways, this study intends to provide more precise vaccine safety profiles of IMID patients. It seeks to address current gaps in pharmacovigilance and potentially remedy vaccine hesitancy in high-risk groups by doing so.

Introduction:
The COVID-19 pandemic has had a disproportionate impact on the lives of those with immune-mediated inflammatory diseases (IMID), including autoimmunity [1]. By virtue of their

immunosuppressed state, these patients were incorporated into shielding programmes where possible and were prioritised for novel medical supplies including COVID-19 antivirals and vaccines [2]. Such measures were necessary given the heightened rates of hospitalisations, respiratory complications and mortality observed in IMID patients who contracted COVID-19 [3, 4].

Despite this, COVID-19 vaccine uptake was not universal amongst IMID patients and the immunosuppressed more broadly [5]. The absence of these patients from vaccine development trials [6] coupled with the lack of observational studies on their specific vaccine tolerance [7] has generated notable hesitancy in this group [8]. This is visible in comparisons of vaccine refusal rates between key risk groups: work by Gaur and colleagues (2023) saw autoimmune patients lead chronic risk groups with 19% COVID-19 vaccine refusal versus 17.8% and 13.4% seen amongst chronic lung and cancer patients, respectively [9]. More precise assessments of vaccine risk in the IMID population are urgently needed to reassure these patients about the safety and suitability of these products [10].

One solution is to enhance pharmacovigilance surveillance. Current methods, including the analysis of computerised medical records (CMRs) or data from centralised reporting mechanisms (Yellow Card, Vaccine Adverse Events Reporting System etc.) are primarily clinician-facing and select for major adverse events [11]. It is hypothesised that direct-to-patient vaccine side effect surveys may deliver the detailed and differentiable data high-resolution pharmacovigilance requires.

The first iteration of the COVID-19 Vaccination in Autoimmune Diseases (COVAD) Study, COVAD 1 [12], was established to test this hypothesis, initially identifying whether a patient COVID-19 vaccine survey could provide sufficient data to compare safety profiles between patients with a diverse range of immune-mediated inflammatory disorders – with a special emphasis on autoimmunity - and general population controls. The present protocol, however, describes a follow-on study that will enhance this initial analysis, assessing whether the COVAD dataset can also test for internal heterogeneity in the COVID-19 infection and vaccine experience of the IMID population. To do so, this work will allocate COVAD IMID respondents into single site and systemic IMID categories, as per the directive of the electronic Delphi Study to Define and Risk-Stratify Immunosuppression (DESTINIES) phenotype [13]. Ratified by 64 world-leading experts at the intersection of immunology and clinical risk prioritisation, this COVID-19 risk hierarchy separates the IMID population into diagnoses with single organ involvement versus those with diffuse sites of impact. Surveys responses involving comorbidity between these groups will be assigned to an overlap category.

As per DESTINIES study evaluations, we are anticipating that single site IMID patients will report milder COVID-19 infections and fewer vaccine side effects than their systemic counterparts. We also hypothesise that the multimorbidity of the overlap category will also increase the likelihood of adverse COVID-19 infection and vaccine outcomes in this group compared to exclusively single site IMID patients.

Methods:

COVAD 1 Study design, ethical approvals, recruitment, data collection and initial results have been described elsewhere [12]. The DESTINIES eDelphi protocol is also publicly available [13], and its results are in review for publication. As a secondary analysis of COVAD 1 data, this work adheres to existing COVAD 1 ethical approvals and has the oversight and participation of the COVAD steering group.

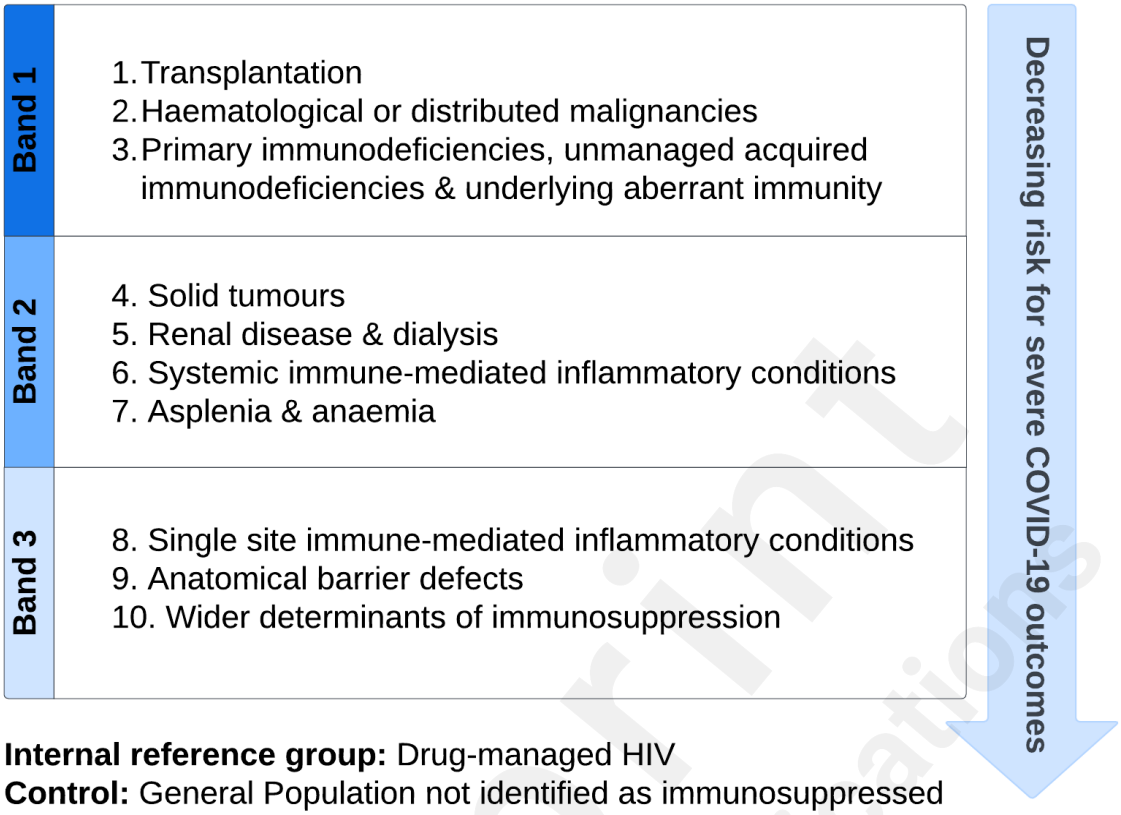
Between March and December 2021, the COVAD 1 Study collected the following information from vaccine surveys presented to an international cohort of IMID patients and population-based controls: demographic details, IMID type, treatment details, current symptoms, COVID-19 infection history (inclusive of symptoms, duration and complications), COVID-19 vaccine details, 7-day COVID-19 adverse events of interest and specific patient-reported outcome measures (health, pain,

activity, fatigue, physical function status). In total, 19,200 patients with IMID or population-based controls responded to the survey [14].

Self-identified by survey respondents, the following IMIDs were represented in this study set: ankylosing spondylitis or psoriatic arthritis, anti-synthetase syndrome, Crohn's disease or ulcerative colitis (Inflammatory bowel disease/IBD), dermatomyositis, haemolytic anaemia/ idiopathic thrombocytopenic purpura (ITP), inclusion body myositis, juvenile dermatomyositis, mixed connective tissue disease, multiple sclerosis, myasthenia gravis, necrotising myositis, overlap myositis with lupus or Sjögren's or systemic sclerosis or rheumatoid arthritis, pernicious anaemia, polymyalgia rheumatica, polymyositis, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic lupus erythematosus, thyroid (hypothyroid or hyperthyroid), type 1 diabetes and vasculitis. Respondents were able to indicate when they had multiple diagnoses. All survey respondents were over 18 years of age, ensuring congruence between this study set and the DESTINIES Study's primary output, the DESTINIES phenotype.

Visualised below and ratified by the DESTINIES panel, the DESTINIES phenotype COVID-19 risk-stratifies the conditions agreed to confer immunosuppression into ten risk levels. Here, IMIDs are demarcated into single site and systemic categories, the latter of which is considered at higher risk for severe COVID-19 outcomes. In the present study (to be conducted between November and December 2024), the conditions just cited will be allocated into these categories by relevant experts within the DESTINIES panel. As per DESTINIES protocol, multiple rounds of consensus building will take place if necessary. However, consensus will only be set as 75% agreement for the first round of allocations. Due to time constraints, the diagnoses that do not meet this threshold will be allocated into single-site and systemic categories by majority vote in the second round.

Figure 1: The DESTINIES Phenotype



Internal reference group: Drug-managed HIV
Control: General Population not identified as immunosuppressed

Survey respondents that report having both single site and systemic disorders will have their data allocated into a third, overlap category for analysis. As per the COVAD 1 protocol [12], incomplete surveys or unvaccinated respondents will be removed from the study set. Surveys will be considered incomplete if they do not indicate their IMID status. Efforts will be made to preserve usable data where possible, imputing 'No response' if questions are skipped. Free text data, such as that clarifying 'Other' selections, will be removed. This includes immune-mediated conditions that fall outside of the 22 diagnoses specified. Google Translate (Alphabet, Inc.) will be used to ensure eligible diagnoses provided in other languages are not omitted.

To investigate our hypothesis that systemic and overlap IMID patients experience worse COVID-19 infection and vaccine outcomes than their single site counterparts, the following analyses will be conducted:

Cohort profiling will tabulate and compare IMID categories and the control population by age, sex, gender, ethnicity, country economic status and self-reported health, activity, fatigue, pain and physical function levels. Country economic status will be operationalised using World Bank Country classifications [15], whereby 'Higher' will refer to countries identified as high-income, and 'Lower' will refer to those classified as either low, lower-middle or upper-middle income. IMID data will be compared to general population controls as an aggregate before being differentiated into systemic, single site and overlap categories. To assess the significance between continuous and categorical data, descriptive statistics will be reported alongside chi-square tests of independence.

COVID-19 infection incidence, severity (self-limiting, hospitalised, hospitalised with oxygen support) and average duration will be tabulated and differentiated by number of vaccine doses received and country economic status. Vaccine uptake and side effects will also be tabulated (separately for severe and mild) and differentiated by number of doses received, vaccine type (mRNA vs non-mRNA), medication status prior to vaccination (concurrent or discontinued) and country economic

status. As before, IMID data will be compared to population-based controls as an aggregate before being differentiated into single site, systemic and overlap categories; incidence rate ratios will be used IRR and 95% CI (obtained via Poisson regression) to assess the significance between populations.

Multivariable logistic regressions will be used to quantify the relative contributions of demographic, health and vaccination variables on the likelihood of reporting i) severe COVID-19 (hospitalisation or hospitalisation with oxygen support) and ii) vaccine side effects (mild or severe) for each population. The following models will be run separately for IMID (aggregated and categorised) and general control cohorts:

- Model 1 (demographics): age, sex, ethnicity and country economic status
- Model 2 (demographics + prior health): age, sex, ethnicity, country economic status, health status and medication status
- Model 3 (demographics + prior health + vaccination): age, sex, ethnicity, country economic status, health status, medication status and vaccine dose.

Results:

As a collective, this analysis will identify key demographic differences between IMID categories and general population controls, quantify differences in the COVID-19 infection and vaccine experiences of these groups and delineate the contributions of numerous demographic and health variables to each group's likelihood of being hospitalised for COVID-19 or of experiencing a side effect post-inoculation.

At the time of writing, seven IMID experts within the DESTINIES Consortium have already been enlisted and successfully categorised respondents' diagnoses into their study categories (single site, systemic or control). Two rounds of consensus building were necessary for this process; the first round attempted to obtain over 75% consensus on each diagnosis, as per DESTINIES conduct. However, seven diagnoses did not meet this threshold and were entered into the second round of consensus building that made allocations by majority vote. The results of these two rounds and final categorisation are provided in Table 1 and 2 below.

Table 1: Round 1 of Consensus Building, n = 7

Diagnosis	Single site (n)	Single site (%)	Systemic (n)	Systemic (%)	Categorisation
Ankylosing Spondylitis or Psoriatic arthritis	1	14.29	6	85.71	Systemic
Anti-synthetase syndrome	0	0	7	100	Systemic
Crohn's disease or ulcerative colitis (Inflammatory bowel disease/IBD)	2	28.57	5	71.43	Contested
Dermatomyositis	0	0	7	100	Systemic
Haemolytic anaemia/ idiopathic thrombocytopenic purpura (ITP)	4	57.14	3	42.86	Contested
Inclusion Body Myositis	4	57.14	3	42.86	Contested
Juvenile dermatomyositis	0	0	7	100	Systemic
Mixed Connective	0	0	7	100	Systemic

Tissue Disease					
Multiple sclerosis	3	42.86	4	57.14	Contested
Myasthenia gravis	3	42.86	4	57.14	Contested
Necrotizing myositis	3	42.86	4	57.14	Contested
Overlap Myositis with lupus or Sjögren's syndrome or Systemic sclerosis or Rheumatoid arthritis	0	0	7	100	Systemic
Pernicious anaemia	4	57.14	3	42.86	Contested
Polymyalgia rheumatica	0	0	7	100	Systemic
Polymyositis	0	0	7	100	Systemic
Rheumatoid arthritis	0	0	7	100	Systemic
Scleroderma	1	14.29	6	85.71	Systemic
Sjögren's syndrome	0	0	7	100	Systemic
Systemic lupus erythematosus	0	0	7	100	Systemic
Thyroid (hypothyroid or hyperthyroid)	7	100	0	0	Single site
Type 1 diabetes	7	100	0	0	Single site
Vasculitis	0	0	7	100	Systemic

Table 2: Round 2 of Consensus Building

Diagnosis	**Single site (n)**	**Single site (%)**	**Systemic (n)**	**Systemic (%)**	**Categorisation**
Crohn's disease or ulcerative colitis (Inflammatory bowel disease/IBD)	2	28.57	5	71.43	Systemic
Inclusion Body Myositis	4	57.14	3	42.86	Single site
Multiple sclerosis	5	71.43	2	28.57	Single site
Haemolytic anaemia/ idiopathic thrombocytopenic purpura (ITP)	7	100.00	0	0.00	Single site
Myasthenia gravis	6	85.71	1	14.29	Systemic
Necrotizing myositis	2	28.57	5	71.43	Systemic
Pernicious anaemia	6	85.71	1	14.29	Single site

Final allocations are provided in Table 3. This will direct data cleaning and analysis as specified within Methods. Respondents who self-identify as having both single site and systemic diagnoses according to these categorisations will be allocated into the overlap group.

Table 3: Final single site and systemic IMID allocations, n = 7

Single Site IMID	Systemic IMID
• Type 1 diabetes • Thyroid (hypothyroid or hyperthyroid) • Myasthenia gravis • Multiple sclerosis • Pernicious anaemia • Haemolytic anaemia/ idiopathic thrombocytopenic purpura (ITP) • Inclusion Body Myositis	• Scleroderma • Rheumatoid arthritis • Sjögren's syndrome • Systemic lupus erythematosus • Overlap Myositis with lupus or Sjogren or Systemic sclerosis or Rheumatoid arthritis • Polymyalgia rheumatica • Ankylosing Spondylitis or Psoriatic arthritis • Vasculitis • Mixed Connective Tissue Disease • Anti-synthetase syndrome • Juvenile dermatomyositis • Dermatomyositis • Polymyositis • Crohn's disease or ulcerative colitis (Inflammatory bowel disease/IBD) • Necrotizing myositis

Discussion:

Irrespective of whether our data is consistent with the hypotheses specified, analysis such as this provides valuable insights for clinicians, policymakers and pharmaceutical firms. For example, any indications of elevated vaccine side effects amongst specific IMID types, even historic, require closer examination. Alternatively, indications that the COVID-19 vaccine was universally well-tolerated amongst IMID patients should be made known to patients concerned with taking up this offering going forwards. Such evidence would be especially pressing in a context of repeat vaccination where risks of experiencing adverse events can accumulate [16].

This direct-to-patient reporting pathway holds immense promise for pharmacovigilance going forwards. The COVAD study group has already utilised this data set to interrogate multiple longstanding questions in the vaccine benefit-risk remit for those with IMIDs [17]. It is unique in its amplification of the patient voice that is currently missing from pharmacovigilance; by enhancing the granularity of this data, as we intend, this patient survey offers intelligence that could not be procured through routine surveillance alone.

We acknowledge the following limitations in this dataset. Firstly, the COVID-19 vaccine landscape has changed considerably since this data was collected. At time of writing, vaccine uptake in certain immunosuppressed categories has since exceeded 6 doses, for example [18]. Two doses are the maximum within this COVAD 1 dataset, by comparison. Secondly, this data was not collected in real-time with vaccination; respondent recall is depended on for an accurate picture of 7-day side effects. To prevent false recall, prospective data would have been preferable. Finally, despite the international nature of this work, sample size is still relatively low – especially once non-completes and the unvaccinated are excluded from the study set. Differentiating survey respondents into three IMID categories and a general population control also affects statistical power. Until survey data is fully cleaned and prepared for analysis, we cannot know if the disproportionate number of diagnoses in the systemic IMID category will undermine planned comparisons.

Conclusion:

At this moment in time, IMID patients are not provided with vaccine safety data that is relevant to their diagnosis. This opacity has been seen to create vaccine hesitancy despite the well-established vulnerability of these patients. This investigation seeks to enhance COVID-19 pharmacovigilance for the IMID population. If successful, this work will corroborate the value of direct-to-patient reporting

pathways for vaccine benefit-risk surveillance in complex groups.

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Supplementary Files

Figures

The DESTINIES Phenotype.